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Aims and scope

Journal of Yeungnam Medical Science is a peer-reviewed and open access journal in the medical field published in English four times a year (January 31, April 30, July 31, and October 31). The journal's publishers are the Yeungnam University College of Medicine and Yeungnam University Institute of Medical Science. The abbreviated title is *J Yeungnam Med Sci* (*JYMS*).

JYMS aims to deliver new medical information to health professionals of various disciplines as well as the general public, and to facilitate the advancement of medicine by publishing high-quality evidence-based articles.

JYMS covers all fields of medical science, including clinical research, basic medical science, and medical education. *JYMS* is especially interested in medical education for learners of all levels, from residents and fellows to medical students. Its regional scope is primarily Korea but we welcome submissions from researchers all over the world.

JYMS publishes editorials, review articles, original articles, case reports, image vignettes, communications, resident fellow section (RFS; clinical vignette, teaching images), and imagery. All manuscripts should be creative, informative, and helpful for the diagnosis and treatment of diseases and for the communication of valuable information about all medical fields.

JYMS was first published in 1984. The original Korean title was "*Yeongnam yidae hagsulji*" (print ISSN 1225-7737). The Journal was renamed "*Yeungnam University Journal of Medicine*" (online ISSN 2384-0293) in 2015 and "*Journal of Yeungnam Medical Science*" (online ISSN 2799-8010) in 2022.

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"UNESCO Global Geoparks Baekseoktan Valley in Cheongsong, Korea"

Photograph by Yeung Man Kim, Daegu, Korea

The "Imagery" section of *Journal of Yeungnam Medical Science* (*JYMS*) is devoted to the artistic and imaginative qualities of our readers. *JYMS* invites you to submit your drawings, illustrations, or photographs, along with appropriate explanatory information, for publication within this section. Please forward electronic images via e-mail to: jyms@yu.ac.kr.

Editorial

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Journal of Yeungnam Medical Science is now indexed in Scopus, a great step closer to a journal's goal

So-Young Park

Department of Physiology, Yeungnam University College of Medicine, Daegu, Korea

Congratulations! *Journal of Yeugnam Medical Science* (JYMS) was finally accepted for indexing in Scopus. On the evening of March 11, 2023, I received a call from the managing editor of JYMS with this great news. I checked through the e-mail and verified that the Scopus Content Selection and Advisory Board (CSAB) had reviewed the application and approved JYMS for coverage. The

Table 1. The history of the *Journal of Yeungnam Medical Science* development

Date	Key milestones
Dec 1984	The inaugural issue was published in Korean with 15 articles, and its name was *Yŏngnam Ŭidae haksulji* in Korean
Jul 1994	International standard serial number was assigned (pISSN 1225-7737)
Jun 1996	The journal joined as a member of the Korean Association of Medical Journal Editors (KAMJE)
Dec 2004	The journal was indexed in KoreaMed
Mar 2012	The journal was indexed in KoreaScience
Jun 2012	The journal's English name was added as *Yeungnam University Journal of Medicine* (pISSN 1225-7737, eISSN 2234-8042)
Feb 2013	The journal was indexed in KoreaMed Synapse
Jan 2014	The journal became a member of the Korean Council of Science Editors (KCSE)
Jun 2015	The journal began publishing articles online only The journal name remained the same (*Yeungnam University Journal of Medicine*) and a new ISSN was issued (eISSN 2384-0293)
Dec 2016	The journal was indexed as a candidate journal in Korea Citation Index (KCI)
Jun 2018	The journal adopted an English-only policy and online submission and review systems were introduced
Oct 2018	The journal was indexed as an accredited journal in KCI
Jun 2019	The journal was indexed in the Directory of Open Access Journals (DOAJ)
Oct 2019	The journal was indexed in PubMed Central (PMC) and became searchable through PubMed
Jan 2020	International-level manuscript editing was implemented through professional manuscript editing by InfoLumi (Seoul, Korea)
Oct 2020	The journal was indexed in Chemical Abstracts Service (CAS)
Jan 2022	The journal's name was changed to *Journal of Yeungnam Medical Science* (eISSN 2799-8010) The journal expanded the types of articles published: imagery, image vignette, and resident fellow section were launched
Dec 2022	The journal was indexed in ScienceCentral
Mar 2023	The journal was accepted to Scopus[a]

[a]The reviewer's comment was as follows: "This institutional English language journal from South Korea is publishing 20–30 items per annum from all health disciplines, with a substantial increase in citation activity (>600) since last reviewed. The editors have responded constructively to the previous Scopus evaluation in 2019, and on balance, there are no obvious contraindications to accession to Scopus at this point."

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news was too good to believe.

Now, I am delighted to share this great news with the readers, authors, and reviewers of JYMS. This achievement would not have been possible without their contributions and help. I also thank the past and present editorial board members for their dedication to JYMS.

Since the inaugural issue of JYMS in 1984, there have been milestones that greatly contributed to the acceptance of JYMS to Scopus. The chronological details of JYMS until its indexation in Scopus are presented below to help the editors of other journals understand the process (Table 1).

JYMS is currently awaiting evaluation for Emerging Sources Citation Index (ESCI) listing by Clarivate Analytics. If JYMS is accepted for ESCI, Journal Citation Reports (JCR) impact factor (IF) is very important for JYMS to be listed in Science Citation Index Expanded (SCIE). To increase the JCR IF, JYMS will try to publish high-quality articles that can be cited in SCIE-listed journals. JYMS will also recruit eminent editors from various countries to improve the quality of the journal. Our editorial team will do its best to make JYMS an internationally renowned journal.

Notes

Conflicts of interest

So-Young Park has been the editor-in-chief of *Journal of Yeungnam Medical Science* since 2021. Otherwise, no potential conflict of interest relevant to this article was reported.

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Review article

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Hepatic ischemia-reperfusion injury with respect to oxidative stress and inflammatory response: a narrative review

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Hepatic ischemia-reperfusion injury is a major complication of liver transplantation, trauma, and shock. This pathological condition can lead to graft dysfunction and rejection in the field of liver transplantation and clinical hepatic dysfunction with increased mortality. Although the pathological mechanisms of hepatic ischemia-reperfusion injury are very complex, and several intermediators and cells are involved in this phenomenon, oxidative stress and inflammatory responses are the key processes that aggravate hepatic injury. This review summarizes the current understanding of oxidative stress and inflammatory responses and, in that respect, addresses the therapeutic approaches to attenuate hepatic ischemia-reperfusion injury.

Keywords: Inflammation; Ischemia; Liver; Oxidative stress; Reperfusion injury

Introduction

Ischemia-reperfusion injury (IRI) is characterized by initial organ underperfusion (ischemia), followed by restoration of blood flow (reperfusion) [1]. Although restoration of oxygen delivery to an ischemic organ is needed to prevent hypoxic cellular damage, reperfusion may accentuate organ injury in excess of the stress produced by ischemia itself [1]. IRI can occur in diverse clinical settings including organ transplantation, trauma, shock, cardiopulmonary bypass, and thrombolytic therapy. Hepatic IRI is a major complication of hepatic resection surgery (e.g., the Pringle maneuver) and liver transplantation. This pathological condition can lead to liver cellular damage and clinical hepatic dysfunction, and may even predispose to distant organ failure.

Pathophysiology

Various pathophysiological mechanisms have been proposed for hepatic IRI, but the actual mechanisms remain unclear. Hepatic IRI occurs in two main settings. First, ischemia can follow temporary vascular occlusion of the hepatic pedicle or various forms of shock and trauma, whereby hypoxic injury occurs. Second, reperfusion injury can be added to hepatic ischemic injury. This phenomenon is a dynamic process that leads to metabolic acidosis, intracellular calcium overload, mitochondrial damage, Kupffer cell

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activation, oxidative stress, inflammatory responses, and necrotic or apoptotic cell death (Fig. 1) [2].

1. Metabolic acidosis

Metabolic acidosis is the basic mechanism underlying hepatic IRI [3]. It results from anaerobic glycolysis during ischemia, which leads to depletion of adenosine 5′-triphosphate (ATP) from organs, consequently producing lactate. During reperfusion, the tissue pH increases, leading to the activation of phospholipases and proteolytic enzymes, which in turn cause cell damage, necrosis, and apoptosis, resulting in IRI [3].

2. Intracellular calcium overload

Intracellular calcium homeostasis is maintained by the Na^+/K^+ and H^+/Ca^{2+} exchange systems. During ischemia and reperfusion, ATP depletion leads to a decrease in ATP-dependent Na^+/K^+ ATPase activity in the cell membrane. This results in increased intracellular Na^+ concentrations, leading to the inward flux of calcium ions [4]. In addition, increased ischemia-induced permeability of cell membranes causes further movement of calcium ions into the cell, and a large number of calcium ions are released from the endoplasmic reticulum and damaged mitochondria. Intracellular calcium overload occurs, which in turn interferes with cellular metabolic pathways [5].

3. Mitochondrial damage

Mitochondria act as pathological triggers, mediators, and effectors of hepatic IRI [6]. Mitochondrial functions normally involve several processes, including energy production, cell survival, and programmed cell death [7]. However, the dysfunction in pathological ischemia and reperfusion is initiated by mitochondrial permeability transition (MPT) pore opening [8]. ATP depletion, calcium ion overload, and toxic oxidant release promote MPT onset, which follows depolarization of the mitochondrial membrane potential, matrix swelling, and membrane rupture [9]. Moreover, MPT opening can lead to apoptosis by mitochondrial swelling and the subsequent release of cytochrome C [10].

4. Oxidative stress

1) Reactive oxygen species

Reactive oxygen species (ROS) normally exist as by-products of cellular metabolism in proteins, lipids, nucleic acids, and other biologically active molecules. However, the nature and amount of

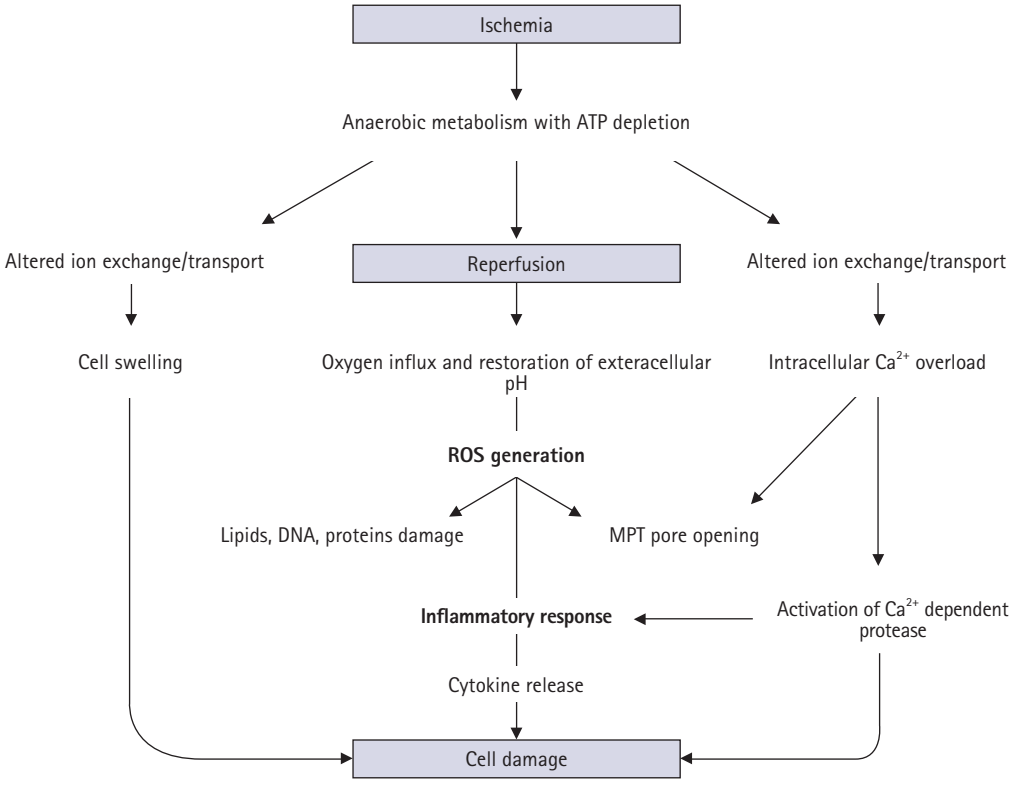

Fig. 1. Pathologic cascade contributing to ischemia and reperfusion injury. Adapted from Kalogeris et al. [2] with permission of Elsevier. ATP, adenosine 5′-triphosphate; ROS, reactive oxygen species; MPT, mitochondrial permeability transition.

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ROS change during IRI. Aerobic cells use molecular oxygen to remove electrons during oxidative catabolism (from O_2 to H_2O) in the mitochondrial respiratory chain. However, small amounts of oxygen (1%–3%) are reduced through the univalent pathway, forming reactive intermediate species, including superoxide anion ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($^{\bullet}HO$) [11,12]. Metal ions such as iron and copper react with hydrogen peroxide via the Fenton reaction, producing the toxic hydroxyl radical [13]. Superoxide anion and these reactive intermediates are known as ROS [12].

Many metabolic processes, including the enzymatic activities of xanthine oxidase (XO) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, for example, and mitochondrial respiration produce large amounts of ROS [14]. Although XO is known to be an important mediator of ROS formation, mitochondria have recently been suggested as the main production site for large amounts of superoxide, leading to the formation of MPT pores that can cause cell death [15].

2) Reactive nitrogen species

Nitric oxide (NO), nitrogen dioxide, and peroxynitrite ($ONOO^-$) are biologically important reactive nitrogen species (RNS), the last two of which result from the interaction of NO with molecular oxygen [16]. Among these, $ONOO^-$, a strong oxidizing agent generated from superoxide anion and NO, can attack basic cell constituents, such as DNA and proteins [17]. NO, a gaseous signaling molecule is produced by the enzymatically catalyzed reaction between L-arginine and oxygen [18]. During hepatic IRI, two main NO synthases (NOS), endothelial (eNOS) and inducible (iNOS), synthesize NO, which can either prevent or promote cell injury [19]. eNOS is constitutively expressed in sinusoidal endothelial cells, whereas iNOS is stimulated by numerous cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-1 (IL-1) [19]. NO exerts a protective effect on parenchymal hepatocytes by preventing the action of TNF-α and apoptotic factors, blocking MPT onset, and preventing sinusoidal obstruction by inducing vasodilatation, neutrophil accumulation, and platelet adhesion [20-22]. However, overproduction of NO during the late reperfusion period can result in high levels of injurious ROS and the accumulation of inflammatory cytokines by increased iNOS expression and decreased eNOS expression [18]. In addition, NO can be converted into the toxic $ONOO^-$, which can cause tissue injury through multiple pathways, including lipid peroxidation, inhibition of the mitochondrial respiratory chain, and modification of protein nitrotyrosine levels [23-25]. Thus, NO can promote or prevent cell survival, depending on its concentration, activation time, and NO-superoxide radical ratio.

Therefore, ROS and RNS directly react with numerous biological molecules, leading to tissue toxicity. The above effects damage sinusoidal endothelial cells, increasing permeability of the microvasculature and promoting neutrophil and platelet adhesion to these cells, followed by subsequent disruption of the microcirculation [26]. Moreover, these oxygen radicals lead to hepatocellular apoptosis by influencing intracellular signaling pathways via effects on gene expression and direct oxidation of nuclear DNA structure in the hepatic parenchyma [27].

3) Antioxidant systems

In contrast to the generation of ROS and RNS, the presence of endogenous antioxidant enzymes attenuates further hepatic injury. When present at low concentrations, antioxidant enzymes can prevent oxidative damage and detoxify ROS [28]. Hepatocytes contain high levels of intracellular antioxidant enzymes, including superoxide dismutase (SOD), glutathione peroxidase, and catalase; however, during IRI, an imbalance between ROS and endogenous antioxidant enzymes occurs, consequently leading to damage to nucleic acids, proteins, and lipids [27]. SOD catalyzes the dismutation of superoxide anion to hydrogen peroxide and oxygen [27]. Hydrogen peroxide can be decomposed via three main systems. First, catalase breaks down hydrogen peroxide into oxygen and water [27]. Second, glutathione peroxidase removes hydrogen peroxide via glutathione oxidation to glutathione disulfide [27]. Finally, peroxiredoxins reduce hydrogen peroxide to water [29].

5. Inflammatory responses

1) Inflammatory cells

Hepatic IRI is characterized by inflammatory responses in the postischemic tissue. During ischemia, a lack of ATP causes failure of the Na^+/K^+ ATPase and subsequent intracellular Na^+ accumulation with cellular swelling in hepatocytes, Kupffer cells, and sinusoidal endothelial cells. Here, increased endothelin and decreased NO (a vasoconstrictor and vasodilator, respectively) levels induce cellular swelling, which in turn leads to sinusoidal narrowing [30]. During reperfusion, the attachment of neutrophils and platelets to the sinusoid with increased adhesion molecules leads to defects in hepatic microcirculation and even the complete absence of blood flow and reflow [26].

Kupffer cells, the resident hepatic macrophages, play a pivotal role in initiating hepatic cellular damage in IRI [31]. During ischemia and the early reperfusion period, Kupffer cells release proinflammatory mediators, such as TNF-α, IL-1, platelet-activating factor, and ROS, which activate a cascade of inflammatory responses [32]. These inflammatory cytokines, chemokines, and small mole-

cule mediators recruit neutrophils and induce ROS production and further inflammation, exacerbating tissue damage during the late reperfusion period [33]. In addition, Kupffer cells activate $CD4^+$ T lymphocytes in the early reperfusion period, preceding neutrophil accumulation induced by the chemotactic agent IL-17. Reciprocally, $CD4^+$ T cells release interferon-gamma, which activates Kupffer cells to generate TNF-α and IL-1 [34,35]. Over a time scale similar to that of the $CD4^+$ T cells, natural killer cells, another leukocyte subset, are recruited to the liver; they produce interferon-gamma, aggravating IRI [36].

2) Complement and cytokines

The complement system and cytokines are important humoral factors involved in hepatic IRI. Once activated in IRI, complement can damage either directly by lysing hepatocytes through the membrane attack complex or indirectly by activating Kupffer cells and neutrophils [26]. Among the complement components, C5a is the most potent inflammatory mediator that releases proinflammatory cytokines, including TNF-α, IL-1, and IL-6 [37]. In addition, C5a inhibits endothelium-dependent relaxation and alters vascular tone, which further compromises the blood flow to ischemic tissues [37].

Numerous cytokines can play one of two roles, either proinflammatory or anti-inflammatory. TNF-α is a crucial proinflammatory cytokine in the hepatic inflammatory response during ischemia and reperfusion. Although various cells in the liver release TNF-α, its production by Kupffer cells is the most prominent [38]. Upregulation of TNF-α during ischemia and reperfusion results in ROS activation, expression of various adhesion molecules such as intercellular adhesion molecule 1 and P-selectin, and thus recruitment of neutrophils into the liver [39]. Similarly, IL-1 can induce ROS production and promote leukocyte aggregation [40]. Conversely, IL-6 produced by Kupffer cells has a protective effect that is mediated by the downregulation of oxidative stress markers and increase in glutathione, an antioxidant, thus reducing hepatocyte damage [41].

3) Endogenous danger signals

One question that arises is how immune cells are stimulated by pathogens in surgical settings. The answer begins with hepatic oxidative stress. During ischemia and reperfusion, ROS and RNS generated by mitochondrial respiration threaten hepatocyte viability [42]. Damaged hepatocytes and other immune cells (e.g., Kupffer cells and neutrophils) release pathogenic endogenous molecules and danger-associated molecular patterns (DAMPs) that overactivate innate immune responses [43]. DAMPs and self-antigens are normally physiological constituents of healthy cells; however, they become immunostimulators in the extracellular environment. Consequently, DAMPs stimulate Kupffer cells, which results in the production of inflammatory mediators, such as cytokines, chemokines, and ROS. This process induces reperfusion injury via intense neutrophil infiltration [32]. In other words, oxygen-free radicals and proinflammatory cytokines released by activated Kupffer cells can promote the infiltration of neutrophils and platelets into sinusoidal endothelium, thereby disrupting hepatic microcirculation and further aggravating hepatic injury [44]. Among the various DAMPs in hepatic IRI, high-mobility group box-1 is the best characterized. It is released by damaged hepatocytes and interacts with toll-like receptors (TLRs), particularly TLR-4 [45]. In this instance, several signaling transcription factors mediate TLR-4 activation, including nuclear factor-kappa B, activating protein-1, and mitogen-activated protein kinases (ERK, JNK, and P38), which modulate gene expression correlated with inflammatory progression [45,46]. Thus, DAMP-derived danger signals mediate the contribution of leukocytes to the severity of liver damage-induced ischemia and reperfusion.

Protective strategies for hepatic ischemia-reperfusion injury

1. Modulation of oxidative stress

Oxidative stress occurs when oxidants are overproduced or antioxidant levels are reduced. Therefore, treatment strategies for oxidant modulation include the inhibition of ROS formation, scavenging of ROS, and potentiation of endogenous antioxidant capacity. As mentioned above, XO, NADPH oxidase, and MPT collectively contribute to ROS formation. Many studies have demonstrated the protective effects of inhibition of these enzymes in hepatic IRI. For example, known inhibitors are allopurinol [47] and apocynin [48] for XO and NADPH oxidase, respectively. Additionally, edaravone, a mitochondria-specific antioxidant with protective effects against hepatic IRI, has been experimentally confirmed as an MPT inhibitor. It exerts its effect by blocking the MPT and maintaining an adequate ATP concentration [49]. Moreover, cyclosporin A inhibits MPT pore opening in the mitochondrial matrix; however, its clinical use remains limited [50].

Normally, the antioxidant defense system controls ROS production. Various antioxidant defenses have been demonstrated to have beneficial effects, both experimentally and clinically, in hepatic IRI. Antioxidants are a heterogeneous family of molecules that can be classified according to their site of action as follows: intracellular, membrane, and extracellular. Representative intracellular antioxidant enzymes are SOD, glutathione peroxidase, and catalase [51-53]. Alpha-tocopherol and coenzyme Q are the main membrane

antioxidants [54], whereas metal-binding proteins, such as transferrin and ceruloplasmin, are major extracellular antioxidants that sequester free iron and copper ions that can promote oxidative damage, respectively [55]. In addition, many low-molecular-weight substances that are synthesized *in vivo* [56] (e.g., melatonin, coenzyme Q, and uric acid) or dietary constituents (e.g., vitamins C and E) exert antioxidant properties [57,58]. These antioxidants have a systematic relationship in the antioxidant network, and they counteract and exhibit synergism [59].

1) Ischemic preconditioning

Among the many interventions against oxidative stress, ischemic preconditioning has been shown to have beneficial effects against hepatic IRI. This preconditioning requires pre-exposure of the liver to brief ischemic episodes to increase its tolerance against subsequent detrimental insults [60]. The underlying molecular mechanism of this intervention is that mild burst oxidants, especially hydrogen peroxide, generated during ischemic preconditioning trigger specific biochemical pathways that ultimately protect against further oxidative damage and lead to adaptation [61]. However, the clinical implications of ischemic preconditioning may be limited because of its invasive properties. Remote ischemic preconditioning is less invasive and more clinically relevant [62]. Remote ischemic preconditioning comprises signal generation from remote organs, signal transfer to target organs, and subsequent protective effects in the target organs. Various neural and humoral factors, such as autonomic ganglion, bradykinin, and adenosine, have been implicated in the pathophysiologic mechanisms of remote ischemic preconditioning [62]. A practical technique has been proposed, which encompasses several brief episodes of ischemia and reperfusion in a remote organ that protects distant targets.

2. Modulation of inflammatory response

As previously mentioned, activation of the immune system is a crucial factor in hepatic IRI, and Kupffer cells and chemoattracted neutrophils are important culprits. Consequently, the cytokine network connected to DAMP contributes to the severity of hepatic IRI via a wave of ROS generation. Consistent with this finding, anti-inflammatory therapy, through various biochemical intersections that inhibit the inflammatory cascade, can attenuate leukocyte recruitment and ROS generation. First, inhibition of DAMP can prevent inflammation and oxidative stress [63]. In addition, administration of a mitochondria-selective S-nitrosylating agent during the acute reperfusion period could prevent mitochondrial ROS bursts and the resulting DAMP release [64]. Further downstream, direct inhibition of Kupffer cells and neutrophils is a promising strategy to treat hepatic IRI [65,66]. In liver transplantation, Kupffer cells are primed in cold ischemic solutions. Subsequently, the primed Kupffer cells exhibit progressive rounding, vacuolization, and degranulation [67]; hence, modulation of Kupffer cell activation plays an important role in reducing IRI in liver transplantation. In contrast, therapeutic modalities to prevent neutrophil recruitment are more diverse due to their multistep processes: chemokine production, expression of adhesion molecules to attach to endothelial cells, and release of effector molecules such as ROS [68]. In a similar context, inhibition of inflammatory cytokines (e.g., TNF-α and IL-1) could be a worthwhile treatment option [38,67].

As TNF-α is a key inflammatory mediator, its neutralization with an antibody and inhibition of its production attenuate hepatic IRI involving neutrophil infiltration [38,69]. Anti-inflammation reduces oxidative stress; conversely, inhibition of ROS and RNS is also a potential therapeutic method for relieving inflammation because these oxidants can activate Kupffer cells and neutrophils, followed by a second wave of ROS and RNS generation. Moreover, inhibition of the complement cascade attenuates hepatic injury [70].

Conclusion

Hepatic IRI occurs in various clinical settings and is a major cause of morbidity and mortality. Although numerous interactions and mediators are involved in its pathophysiology, oxidative stress and inflammatory responses are the main mechanisms. Several therapeutic methods that limit oxidative stress and inflammatory responses have been suggested and applied to attenuate hepatic IRI. If based on a basic understanding of the aforementioned main pathological mechanisms and therapeutic modalities that could improve patient care, our knowledge of these complex hepatic IRI mechanisms remains incomplete.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: EKC, DGL; Data curation, Methodology: EKC; Formal analysis, Supervision, Validation: DGL; Writing-original draft: EKC; Writing-review & editing: EKC, DGL

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Home mechanical ventilation in children with chronic respiratory failure: a narrative review

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Advances in perinatal and pediatric intensive care and recent advances in mechanical ventilation during the last two decades have resulted in an exponential increase in the number of children undergoing home mechanical ventilation (HMV) treatment. Although its efficacy in chronic respiratory failure is well established, HMV in children is more complex than that in adults, and there are more considerations. This review outlines clinical considerations for HMV in children. The goal of HMV in children is not only to correct alveolar hypoventilation but also to maximize development as much as possible. The modes of ventilation and ventilator settings, including ventilation masks, tubing, circuits, humidification, and ventilator parameters, should be tailored to the patient's individual characteristics. To ensure effective HMV, education for the parent and caregiver is important. HMV continues to change the scope of treatment for chronic respiratory failure in children in that it decreases respiratory morbidity and prolongs life spans. Further studies on this topic with larger scale and systemic approach are required to ensure the better outcomes in this population.

Keywords: Child; Home mechanical ventilation; Long-term mechanical ventilation; Noninvasive ventilation; Respiratory insufficiency

Introduction

Advances in perinatal and pediatric intensive care have led to an increasing number of patients with complex medical conditions surviving. For instance, the number of children with chronic respiratory failure requiring long-term mechanical ventilation has increased exponentially worldwide [1-3]. In addition, recent advances in home mechanical ventilation (HMV) during the last two decades have enabled children who would previously have been confined to living in the hospital to return home and participate in family and community activities [4-7]. Moreover, the diseases requiring long-term mechanical ventilation have expanded from respiratory diseases such as chronic lung disease to neuromuscular disease, craniofacial abnormalities, spinal cord injuries, and central hypoventilation syndromes [8,9].

There are two major types of ventilators, namely regular intensive care unit (ICU) ventilators and HMVs. While regular ICU ventilators are more powerful and have more parameters that can be controlled according to the patient's needs (e.g., trigger type, trigger sensitivity, slope of pressurization, and cycling criteria) as well as monitoring functions, they are large and expensive and require more knowledge and skills to operate. In contrast, HMVs are portable devices that are easier to use and require fewer resources but have more technical limitations because they cannot support a higher level of pressure (>20 cmH_2O) and cannot maintain a higher oxygen fraction (FiO_2 of $>60\%$). Therefore, HMVs are more suitable for patients with chronic respiratory failure than for patients with hypoxemic respiratory failure [10]. Although HMV

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is now accepted as a standard treatment option for patients with chronic respiratory failure, patient selection and HMV management vary substantially among countries [11]. Moreover, for children, HMV in children has more considerations than for adults because children are still developing physically and mentally. This review outlines patient selection and special considerations for HMV in children, its modes and technical setup, follow-ups, monitoring and weaning, and potential risks of HMV before finally describing caregiver burden and education.

Diagnosis and patient selection for home mechanical ventilation

Cellular metabolism in humans requires continuous oxygen supply and carbon dioxide removal. The respiratory system comprises two independent subsystems: the gas exchange system (the lungs) and the ventilatory system (the respiratory pump) [12]. Respiratory failure is defined as a problem in either (or both) of these systems and often arises from an imbalance between the respiratory workload and ventilatory strength [13]. Its diagnosis is based on the arterial blood gases (ABGs), arterial partial pressure of oxygen (PaO_2) less than 60 mmHg, and alveolar partial pressure of carbon dioxide ($PaCO_2$) greater than 50 mmHg, which correspond to the hypoxemic (or type I) respiratory failure and hypercapnic (or type II) respiratory failure, respectively [14]. Hypoxic respiratory failure is treatable with oxygen therapy, whereas hypercapnic respiratory failure requires ventilatory support. Cases of multiple disorders or many acute respiratory failures require a combination of ventilatory support and oxygen supplementation.

The respiratory pump is a complex system. Breathing is regulated by the respiratory center of the medulla oblongata. Respiratory signals are transmitted via the central and peripheral neural tracts to the neuromuscular endplate of the respiratory muscles, including the diaphragm and intercostal muscles, sternocleidomastoid, and pectoral muscles, and generate inhalation by the negative pressure in the chest wall. In contrast, exhalation is normally passive, caused by the elastic recoil of the chest wall and the lung parenchyma. As respiratory failure results from the imbalance between the respiratory workload and ventilatory strength (Fig. 1) [15], diseases for which HMV is necessary in children can be classified into three categories, according to the physiological abnormalities they cause (Table 1) [9,16].

Collecting the medical history and performing clinical examinations are the first steps in the diagnosis of chronic respiratory failure. The signs and symptoms suggestive of chronic respiratory failure include sleep disturbances such as frequent awakening during sleep, unrestful sleep, daytime somnolence, and nightmares; worsening of accompanying symptoms of the underlying disease such as weight loss, dyspnea, and decreased exercise capacity; polycythemia; signs of carbon dioxide-associated vasodilation, such as conjunctival injection, leg edema, and morning headache; tachypnea; tachycardia; and anxiety or personality change [16]. In addition, respiratory muscle strength should be measured as an instrument-based assessment; however, this is not always possible, especially in small children or older children with mental retardation. Consequently, the ventilation and gas exchange status must be directly assessed using the arterial PCO_2 via blood gas analysis or continuous monitoring using transcutaneous PCO_2 monitoring ($PTcCO_2$), alternatively. $PTcCO_2$ better captures the complete ventilation trend, despite the possible deviation of individual values from those obtained by the ABG analysis, which is the gold-standard diagnostic test [17].

Chronic respiratory failure can only be treated with ventilator support using a mechanical ventilator, either noninvasively or invasively. Fig. 2 shows the application algorithm for noninvasive and invasive ventilation in children [11]. The goal of HMV in children with chronic respiratory failure is to correct alveolar hypoventilation and maximize development, as possible [18]. The effects of long-term mechanical ventilation, including improving alveolar ventilation, alleviating subjective symptoms of chronic respiratory failure, improving blood gases, reducing morbidity and mortality, and enhancing the quality of life of the affected children, are well established in the previous studies; however, these studies were largely observational and limited to certain disease entities (e.g., congenital central hypoventilation syndrome or progressive neuromuscular diseases such as Duchenne muscular dystrophy) [19-29]. However, in other diseases for which HMV might be required, similar effects can be expected, provided that there is no parenchymal lung disease component in the chronic respiratory failure [16].

Special considerations for home mechanical ventilation in children

HMV in children is much more complex than that in adults. First, smaller children and older children with mental retardation might not be able to communicate or cooperate with assessment and/or treatment. In addition, there is a risk of accidental removal of the tracheostomy tubes. Second, children requiring HMV often have various comorbidities; therefore, they should ideally be cared for by a multidisciplinary team for the underlying conditions. Third, the airway diameters are smaller than those in adults, which makes children more vulnerable to airway obstruction due to secretion when airway clearance is compromised.

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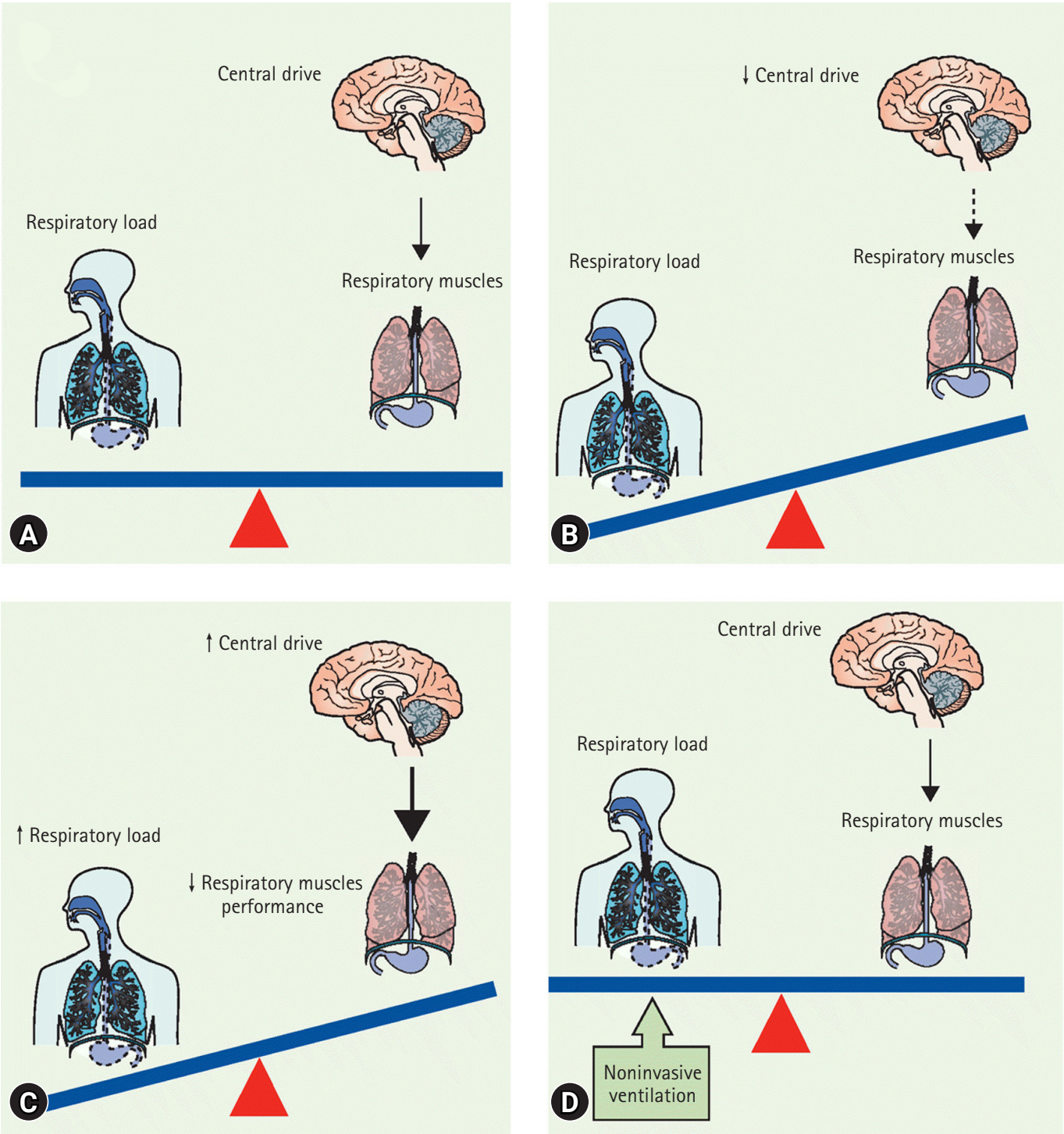

Fig. 1. Respiratory balance. (A) Normal respiratory balance, in which the load imposed on the respiratory system, the capacity of the respiratory muscles, and the central drive are in equilibrium. (B) A decrease in central drive (dotted line) causes a decrease in respiratory muscle activity and, subsequently, a reduced alveolar ventilation. (C) A weakness of the respiratory muscles or an increase in respiratory load causes an increased central drive (bold arrow). Alveolar ventilation occurs when the imbalance exceeds a specific threshold. (D) Noninvasive ventilation can correct disequilibrium in the respiratory balance by replacing the central drive, unloading (in case of an increase in respiratory load, as shown), or assisting the respiratory muscles (in case of respiratory muscle weakness). Reprinted from Amaddeo et al. [15] with permission from Elsevier.

Table 1. Diseases that may benefit from home mechanical ventilation

Increased respiratory load	Ventilatory pump failure	Failure of neurologic control of breathing
Obstructive sleep apnea	Spinal muscular atrophy	Congenital central hypoventilation syndrome
Laryngomalacia	Muscular dystrophies	Acquired central hypoventilation through brain stem affection (e.g., tumor, trauma, bleeding, or encephalitis)
Mucopolysaccharidoses	Myasthenia gravis	Degenerative diseases or central nervous system tumors
Tracheobronchomalacia	Diaphragmatic dysfunction	Stenoses of the craniocervical transition (e.g., Arnold-Chiari malformation)
Bronchiectasis	Motor neuron disease	Syringomyelia
Bronchiolitis obliterans	Congenital muscular dystrophy	
Kyphoscoliosis	Metabolic myopathies	
Chest wall deformities	High-level spinal cord transection	
Lung hypoplasia		
Interstitial lung diseases		
Bronchopulmonary dysplasia		
Heart failure		

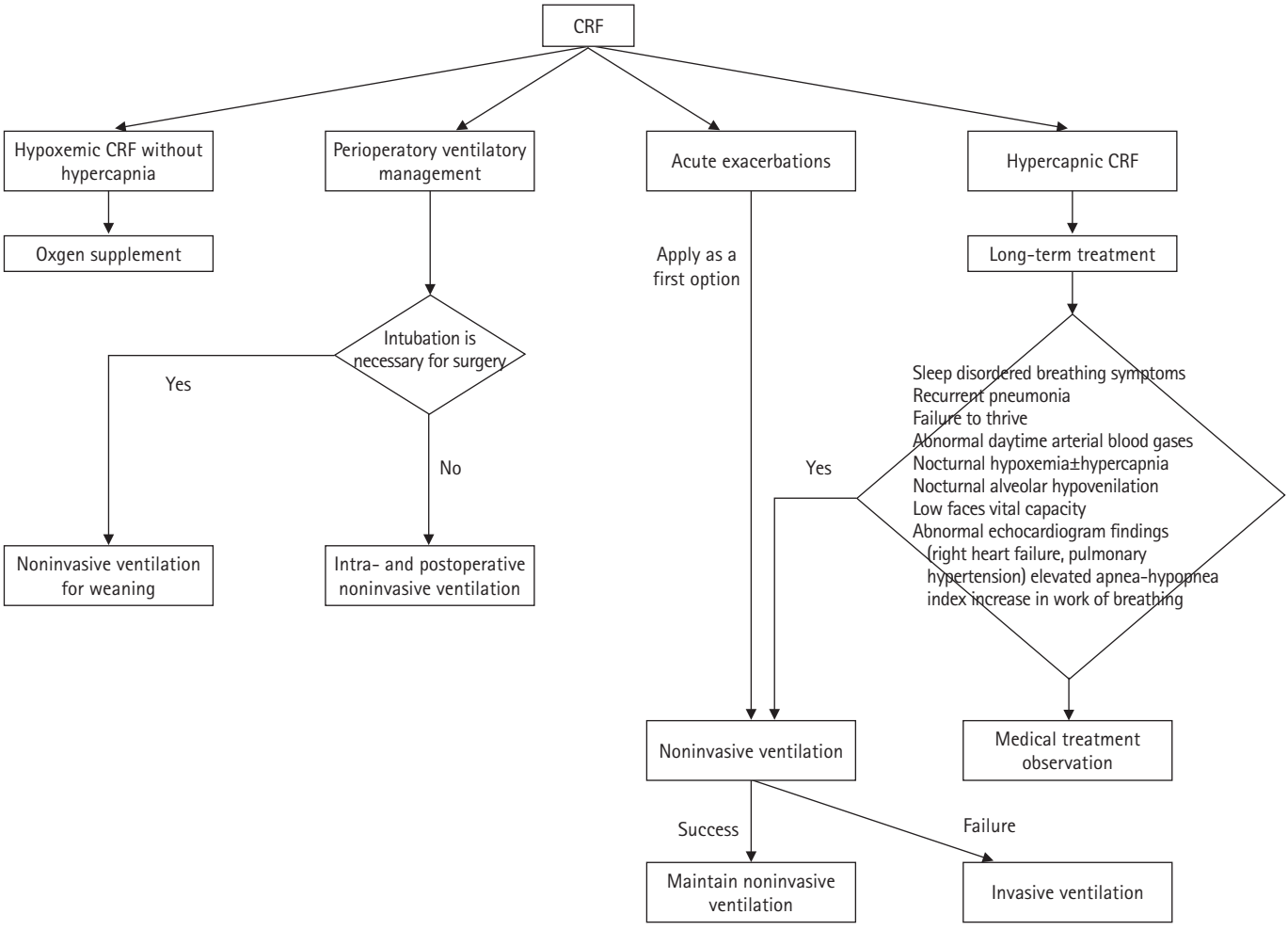

Fig. 2. Application algorithm for noninvasive and invasive ventilation in chronic respiratory failure (CRF) in children.

Fourth, when using noninvasive ventilation (NIV), children unable to remove the ventilation mask themselves might be endangered in cases of vomiting or equipment errors. Finally, care should be taken to ensure that the child can develop normally to the possible extent in terms of speech/language development as well as facial bone growth. Poorer developmental outcomes have

been reported in children on HMV compared to those in healthy controls [30,31], which may arise from a combination of factors including skeletal muscle weakness due to underlying diseases or prolonged bed rest in the acute phases of illness, reduced functional status due to ventilator dependency, increased metabolism due to chronic respiratory distress, and prolonged supine positioning during infancy [30]. Although rehabilitation strategies have been proposed [31,32], no clinical study has examined the effectiveness of rehabilitation therapy in this population. Further studies that focus on the developmental aspect of children on HMV are warranted to facilitate the normal development of these children as far as possible. In infants and small children who have undergone tracheostomy, cannulae with adequate leakage via the glottis should be selected for vocalization, and speaking aids should be implemented where possible. A recent study conducted in a developing country setting reported that having parents as the primary caregiver was related to better speech and language skills in these children [30], which may underscore the importance of the role of primary caregivers in development. As facial bone growth occurs in the early years of life, NIV may hinder the normal facial bone growth, resulting in mid-facial deformity (flattening of mid-face and maxilla retrusion) due to the high pressure applied on the facial bone for a relatively large part of the day in young children, even though NIV is only used during sleep; to reduce this risk, alternative use of different masks that apply pressure to different parts of the face can be considered [33]. In addition, a higher contact pressure is associated with an increased risk of facial deformity, thus, masks of young children should be monitored for optimal fit.

In addition, several technical issues are associated with HMV in children. Because small children might not generate sufficient inspiratory flow to trigger a ventilator, HMV for children should have a sensitive trigger. In addition, ventilation volumes can be very low in infants and small children, and the breathing patterns of the children can be irregular in terms of the frequency and depth of breathing. Therefore, home mechanical ventilators for children should be able to generate a low tidal volume, and HMV with pressure presets may be more appropriate than HMV with volume presets because they can better adapt to irregular breathing patterns [16].

Modes of home mechanical ventilation in children

HMV can be delivered either noninvasively or invasively. NIV uses nasal masks, oronasal masks, full-face masks, or mouthpieces, whereas invasive ventilation requires tracheostomies. The choice of these modes does not depend on a particular disease but rather on the type and severity of the respiratory failure. In general, obstructive sleep apnea syndrome, central respiratory regulation disorder, chronic alveolar hypoventilation, and other chronic respiratory failures are all candidates for NIV. Tracheostomies may result in significant complications, such as granuloma, infection, obstruction of the cannulae, and accidental decannulations, which are more common in children than in adults [34]. Moreover, tracheostomy may lead to impaired language development and negatively impact the body image of children. Therefore, NIV should always be considered before tracheostomy, as is also the case for adults. However, several conditions require tracheostomy insertion, including congenital malformation syndromes with obstruction of the upper airways, vocal cord paralysis, subglottic stenosis, tracheomalacia, progressive neurological diseases with bulbar palsy, bronchopulmonary dysplasia, pulmonary hypoplasia, and a ventilation duration of > 16 hours per day [35]. In some of these conditions, such as some of the congenital malformation syndrome, subglottic stenosis, tracheomalacia, and bronchopulmonary dysplasia, tracheostomy may be closed later in childhood [36]. The advantages and disadvantages of NIV are summarized in Table 2 [37,38]. In cases of NIV failure, tracheostomy is the only alternative and the ultimate therapeutic option [11].

Table 2. Advantages and disadvantages of noninvasive ventilation

Advantage	Disadvantage
Can avoid tracheostomy-related complications such as tracheostomy tube obstruction, infection, tracheoesophageal fistula, tracheocutaneous fistula, tracheal stenosis, granuloma, dysphagia, etc.	Airway protection is suboptimal
	Risk of aspiration
Preservation of communication ability	Pressure ulcers over nasal bridge
	May cause claustrophobia
	Aerophagia
	Cannot access to tracheobronchial tree (tracheal suction is not possible)

1. Noninvasive ventilation

1) Unintentional air leakage

While a certain degree of air leakage is inevitable in NIV because it is not a completely closed system, and it does not necessarily compromise the effectiveness of NIV if the amount of air leakage is small [37]. However, a large amount of air leakage compromises the ventilation effectiveness and may result in nasal mucosal drying and asynchrony between the patient and the ventilator as the ventilator perceives it as an attempt to inhale and continues to dispense breath even though the patient has completed inhalation and is ready to exhale [37]. Therefore, monitoring the delivered tidal volume and air leakage is important in patients undergoing NIV, and most home ventilators have leakage compensation mechanisms [39].

2) Interfaces for children

Various types of ventilation masks are used for NIV, but none can be perfectly sealed, at least intermittently. Therefore, the ventilators must generate a high flow to compensate for leakage to reach preset pressure. Arguably, the most important factor determining successful NIV application is the choice of an appropriate mask that minimizes leakage and maximizes patient's comfort [40]. The masks currently being used in children include follows: nasal pillows or nasal plugs that occlude the nostrils; nasal masks, which cover the nose; oronasal masks, which cover the mouth and the nose; full-face masks, which cover the mouth, the nose, and the eyes; mouthpieces or oral masks; and the helmet, which cover the entire head. Nasal masks provide greater patient comfort and cause fewer skin injuries, making them the most commonly used masks [41]. Nasal masks are preferred in small children because there is less static dead space, they cause less claustrophobia, and they allow communication and expectoration. Oronasal masks and full-face masks must be reserved for use only when nasal masks are not effective due to oral leakage during sleep as they have potential risks of aspiration in cases of gastroesophageal reflux or nausea/vomiting. Mouthpieces can be used for children with neuromuscular disease requiring extended ventilation support in daytime, in addition to nocturnal ventilation [42]. Helmets are effective interfaces for small children, and they are commonly used in the pediatric ICU (PICU). However, their large dead space and the risks of asphyxia in case of technical failure of the ventilator make them unsuitable for HMV [43-45]. The following should be considered when selecting an appropriate mask: (1) patient age and weight, (2) facial bone and the skull anatomy, (3) the presence of mouth breathing, (4) patient's ability to remove the mask by himself/herself, (5) patient comfort and the level of unintentional leakage, and (6) the patient tolerance regarding skin injury or facial deformity [46].

2. Invasive ventilation

1) Tracheostomy and tracheal cannulae

Tracheostomy should be stable when starting HMV; therefore, elective surgical tracheostomy for HMV is always preferred to percutaneous dilatational tracheostomy. Once the tracheostomy stoma is healed, it can be exchanged by a trained nurse alone and even by trained nonprofessional caregivers [47]. In cases of sudden cannulae blockage or a difficult cannulae change, spare cannulae of the same size and smaller should always be prepared. Before discharge from the hospital, parents or caregivers should learn how to manage a tracheostomy, identify complications, and perform cardiopulmonary resuscitation in case of an emergency [47].

2) Humidification and warming

During invasive ventilation, humidification and warming of the inhaled air are necessary to prevent drying of the bronchial mucosa and thickening of secretions [48]. In addition, children tend to have relatively high respiratory rates and, therefore, a higher fluid loss via the airway, which increases the importance of sufficient level of humidification in this population.

Humidification and warming can be achieved either through heat and moisture exchanger (HME) filters or via active humidification. The use of HME filters has the advantage of simplicity; however, they may increase the work of breathing and negatively impact CO_2 elimination. In particular, when using speaking aids, uncuffed cannulae, or fenestrated tracheal cannulae, HME filters are ineffective because air escapes to the larynx, thus requiring active humidification, although this is less convenient [49,50]. Active humidification during the night and HME filters during the day are generally considered to be acceptable [16].

Technical setup of home mechanical ventilator

1. Tubings and circuits

There are two types of tube systems: single-tube systems (single-limb circuits) and double-lumen tube systems (double-limb circuits). While double-lumen tube systems (one tube for inspiration and the other for expiration) are mostly used in acute care settings, such as ICUs, single-tube systems are most commonly used in HMV because they are less cumbersome. When using single-tube systems, unintentional leaks and tidal volumes are estimated instead of measured; therefore, if it is necessary to measure

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expiratory volume accurately, a double-lumen tube system should be used, which is rarely the case in this population [51-53].

2. Pressure versus volume preset

Pressure-preset mechanical ventilation is more widely used than volume-preset ventilation. Pressure-preset mechanical ventilation delivers airflow according to a predefined positive pressure in the airways for a given time. In contrast, volume-preset ventilation provides a fixed volume during a given time regardless of the airway pressure. The advantage of volume-preset ventilation is the delivery of a constant tidal volume, assuring that the desired minute ventilation is achieved; however, the major disadvantage of this mode is the fixed ventilatory support that does not allow changes with the varying demands of the patient. Although the two modes do not differ in terms of NIV effectiveness, pressure-preset ventilation is associated with fewer side effects, such as flatulence and gastric distension [54-56]. In addition, as stated earlier, pressure-preset ventilation is preferred in children because it can better adapt to their irregular breathing patterns.

If a patient experiences problems under a particular ventilation mode, another ventilation mode should be attempted during hospitalization and close monitoring.

3. Ventilator alarms

Alarms in NIV are based on clinical practice rather than scientific evidence due to the lack of studies examining their clinical utility, especially for HMV [57]. Mask interfaces in NIV cannot be completely sealed, which may cause frequent and often spurious alarms. Therefore, careful setting of the alarm system is necessary to ensure that it functions only when there is a genuine need [57,58]. An alarm system is mandatory in invasive ventilation because the blockage of cannulae may lead to a significant risk to the patient. Patients with a speaking valve, uncuffed cannulae, or fenestrated cannulae require an alarm setting that can detect the disconnection and/or hypoventilation, as recommended in adults [58].

Home mechanical ventilation follow-up and monitoring

1. Pulse oximetry

A pulse oximeter is necessary during the invasive ventilation; continuous pulse oximetry monitoring is mandatory in children with tracheostomy, as well as in children using full-face masks or oronasal masks, who cannot remove the masks by themselves. Because frequent false alarms might distract caregivers from concentrating on real alarms, the use of appropriate adhesive sensors and an oximeter with an artifact-minimizing function should be adopted to minimize false alarms.

Oxygen saturation may decrease in cases of airway infection, increased secretion, coughing, dyspnea, and enforced breathing. When the SpO_2 is greater than 95%, no intervention is required; for SpO_2 values are between 90% and 95%, readjusting interfaces and/or secretion clearance should be attempted, after which further treatment can be sought in an outpatient setting; and if SpO_2 is less than 90% despite HMV, immediate action must be taken (e.g., visiting emergency department or calling for the ventilation center, etc.) [16].

Of note, oxygen alone should not be used to correct decreased SpO_2 values in children with alveolar hypoventilation due to neuromuscular diseases because it can worsen hypercapnia, mask the progression of underlying problems, and delay diagnosis and appropriate treatment [59,60].

2. Follow-ups for home mechanical ventilation in children

Regular follow-ups are required to ensure successful HMV in children as HMV treatment should be adapted to the growth of the child and the progression/improvement of the underlying disease. Despite marked heterogeneity in the provision of HMV services, costs, and healthcare system across countries as well as in the individual factors such as underlying disease, medical stability, the age of the child, and socioeconomic status, follow-up in-hospital assessment including nocturnal CO_2 monitoring and synchronization of ventilation is generally recommended to be performed 1 to 3 months after commencing HMV for the first time [61]. Subsequently, repeating these assessments at 6-month intervals is recommended.

Tracheoscopy should be performed at least once annually in invasively ventilated children to adjust the tube size and assess for complications such as tracheal granuloma or ulcers [16]. The follow-up assessment of HMV should include the tests summarized in Table 3.

Any changes made to the ventilators and their setup, including ventilator machine (even from the same manufacturer), ventilation interface (masks and circuits), oxygen application system, humidification system, ventilation parameters, and tracheal cannulae models, can substantially influence ventilation efficacy and should only be performed under thorough monitoring of the attending physician in in-hospital settings [62-66].

Weaning

A recent international consensus statement by the European Respiratory Society indicated weaning from continuous positive airway pressure (CPAP) or NIV in 6% to 40% of children [10]. Suc-

Table 3. Tests that should be performed during the initial diagnosis, commencement of HMV, and follow-up in-hospital assessment of children undergoing HMV

Essential tests in the initial diagnosis and commencement of HMV	Additional tests that might be required in selected patients	Essential test for follow-up in-hospital assessment
Electrocardiogram	Continuous nocturnal CO_2 measurements (e.g., $PTcCO_2$)[a]	Adherence to HMV
Diurnal and nocturnal arterial blood gas analysis	Change of vital capacity between sitting and supine position[a]	Assessment of clinical success of HMV (e.g., alleviation of symptoms)
Pulmonary function test (spirometry, respiratory muscle function test)	Assessment of coughing ability[b]	Side effects (e.g., skin injury, mask issues, nasal mucosal problem, pneumophagia)
Basic laboratory tests	Laryngoscopy/bronchoscopy[c]	Inspection of ventilator system (ventilation setting, humidification unit, ventilation interface, accessories)
Chest X-ray	Swallowing evaluation[d]	Screening of nocturnal ventilation efficacy

HMV, home mechanical ventilation; CO_2, carbon dioxide; $PTcCO_2$, partial pressure of transcutaneous CO_2.
[a]Patients with neuromuscular diseases (ventilatory pump failure). [b]Patients whose coughing ability might be impaired (e.g., neuromuscular diseases, cerebral palsy, traumatic brain injury, central nervous system tumor). [c]Patients with possible laryngeal or bronchial pathologies (e.g., congenital anomalies of the larynx, laryngeal and/or bronchial stenosis). [d]With suspected impairment of swallowing ability (e.g., clinical signs of swallowing difficulty, frequent chest infection, malnutrition).

cessful weaning is attributable to the physiological growth, weight loss, or interventions such as adenotonsillectomy, upper airway surgery, maxillofacial surgery, or orthodontic treatment [67-70]. Successful weaning in children with NMD is less common than that in children with other conditions [71-73]; however, this is expected to be changed along with the development of new therapeutic options, particularly in children with spinal muscular atrophy [11]. Currently, there are no established weaning criteria; however, a recent study by Mastouri et al. [73] proposed respiratory criteria for weaning from CPAP/NIV, including four major criteria and three minor criteria; all four major criteria must be fulfilled with at least two minor criteria for considering weaning from CPAP/NIV. The major criteria were: (1) resolution of nocturnal and daytime symptoms of sleep-disordered breathing after several nights without CPAP/NIV, (2) < 2% of the recording time spent with a SpO_2 of ≤ 90%, (3) < 2% of recording time spent with a $PTcCO_2$ of ≥ 50 mmHg, and (4) obstructive apnea-hypopnea index of < 10 events/hr on a polysomnography or polygraphy. The minor criteria were: (1) minimal SpO_2 of > 90%, (2) maximal $PTcCO_2$ of < 50 mmHg, and (3) 3% oxygen desaturation index of ≤ 1.4 events/hr [73]. Even after successful weaning, recurrence of chronic respiratory failure is possible, depending on the underlying condition; therefore, continuous follow-up is necessary [73].

Potential risks of home mechanical ventilation

Despite the advances in newer ventilators and monitoring devices, children on HMV are still exposed to potential risks, with mortality in this group as high as 43% and medical complications occurring in up to 70% of children [74-76]. In addition, a recent study conducted in the United States analyzing rapid-response (RR) events and code events in children on HMV via tracheostomies in a non-ICU respiratory unit found that children on invasive ventilation via tracheostomy had 8.73 RR events per 1,000 patient days compared to 4.61 RR events per 1,000 patient days in all other hospitalized children. Similarly, children on HMV had 3.14 code events per 1,000 patient days compared to 0.74 in all other hospitalized children [77]. The causes of mortality have not been evaluated systemically; however, a previous study reported that only 34% of mortalities resulted from the progression of underlying diseases and 49% of mortalities were unexpected [75]. The potential risks in children on HMV include ventilator failure, airway obstruction by secretion, tracheostomy-related complications (accidental decannulation, bleeding, infection, etc.), acute lower respiratory tract infection, feeding problems, seizures, dehydration, and electrolyte imbalance [78,79]. A retrospective study reported that children with invasive mechanical ventilation were 16 times more likely to visit hospitals before scheduled visits than children with NIV (odds ratio, 16.3; 95% confidence interval, 2.1–127.4, $p = 0.008$) [78]. Other risk factors for unscheduled hospital admissions were a shorter duration of caregiver education before discharge, a change in the management of the child within 7 days before discharge, and younger age [78-80]. A recent study in Germany evaluating differences in the incidences of complications between children with invasive ventilation at home and children with invasive ventilation at specialized nursing facilities found that children on invasive ventilation at home were more likely to experience tracheostomy-related incidents and infection compared to children with tracheostomy and long-term ventilation support at

specialized nursing care facilities, while there was no difference in the incidence of potentially life-threatening severe adverse events with rapid deterioration of vital signs requiring immediate medical intervention, and may require resuscitation and hospital admission [81]. To reduce preventable adverse events in this population, well-organized caregiver education, providing home nursing services, and monitoring patients using telemedicine were proposed, in addition to training staff caring for children on home mechanical ventilators in the respiratory care unit [74,76-78,80,82].

Caregiver burden and education

1. Caregiver burden

Although HMV allows a more normal lifestyle compared to formal institutionalized (or hospital-based) ventilation treatment, it places significant burdens on patients and their caregivers, ranging from physiological and psychological to social, and existential issues. A recent systematic review of qualitative studies on users' experiences of HMV reported that the users (namely, the patients and their caregivers) perceived that HMV increased their quality of life and permitted a more community- and home-based lifestyle. However, they also experienced continued worries and uncertainty as well as undermined autonomy and self-determinism. The caregivers also expressed difficulties in the collaboration between home-care assistants, including nurses, social-care assistants, and healthcare assistants [83]. Children on HMV and their caregivers have a significantly lower quality of life than healthy controls [30,31,84]. Nevertheless, a recent questionnaire survey revealed that although children with neuromuscular diseases on long-term ventilation treatment experienced a lower health-related quality of life and mental health, ventilator use did not show an additional negative impact on the quality of life [85]. Thus, care should be taken to enable a patient-centered treatment and care in this population and to reduce caregiver burden.

2. Patient and caregiver education

To ensure effective HMV in children, education for the patients (if possible) and caregivers is of critical importance. Although HMV enables a more normal daily life for the children compared to the formal institutionalized or hospital-based ventilation treatment, HMV presents many psychological, physiological, and social challenges to children and their families. In particular, children on HMV are dependent on support for up to 24 hours a day; thus, training for the caregivers and family members is very important. The essential topics for caregiver education are summarized in Table 4 [11,58,86]. Caregiver education totaling < 14 days was associated with higher chances of nonscheduled hospital admissions in children on HMV [78]. The American Thoracic Society clinical practice guidelines recommend training periods of "several weeks before discharge" for children with invasive ventilation [86], while the Canadian Thoracic Society clinical practice guidelines recommend ≥ 2 weeks for patients with invasive ventilation and 48 hours for patients with NIV [87].

Conclusion

HMV continues to change the scope of treatment for chronic respiratory failure in children in that it decreases respiratory morbidity and prolongs life span. However, there remains a gap in the clinical practice and scientific evidence regarding the validated criteria for the initiation of HMV, optimal follow-up, and monitoring, and weaning criteria in different underlying diseases. Therefore, future studies are much needed. In addition, considering that the ultimate goal of HMV in children is not only to correct alveolar hypoventi-

Table 4. Essential educational topics before commencing home mechanical ventilation

No	General considerations	Ventilator care	Tracheostomy care
1	Understand underlying disease	Basic knowledge of how the ventilator works	Understand basic anatomy and physiology regarding tracheostomy
2	Signs and symptoms that require immediate medical attention	How to check ventilator and humidifier	Safe performance of daily activities of living
3	Nutrition/feedings	Mask fitting and interface	Communication/speech issues
4	Chest physiotherapy techniques	Basic troubleshooting	Cleaning and sterilization of tracheostomy site and all supplies
5	Airway clearance techniques	Cleaning and sterile management of all supplies and accessories	Suction technique
6	Immunization	Safe home environment	Tracheal cannulae and tie change
7	Emergency management/cardiopulmonary resuscitation	Battery/power supply	How to respond to accidental decannulation
8	Emergency contact number	Use of self-inflating bag	Transportation
9	Follow-up appointment		

lation but also to maximize development as much as possible, future research should focus on the strategies to promote normal child development in every aspect, as well as provide optimal patient-centered care for the children and their caregivers.

Clinicians should select the best option for HMV according to the patient's age, underlying disease, and HMV tolerance. Training for parents and caregivers is an essential part of HMV, and regular follow-up and good multidisciplinary care should be ensured.

Notes

Conflicts of interest

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Hepatic encephalopathy on magnetic resonance imaging and its uncertain differential diagnoses: a narrative review

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Hepatic encephalopathy (HE) is a severe neuropsychiatric abnormality in patients with either acute or chronic liver failure. Typical brain magnetic resonance imaging findings of HE are bilateral basal ganglia high signal intensities due to manganese deposition in chronic liver disease and hyperintensity in T2, fluid-attenuated inversion recovery, or diffusion-weighted imaging (DWI) with hemispheric white matter changes including the corticospinal tract. Low values on apparent diffusion coefficient mapping of the affected area on DWI, indicating cytotoxic edema, can be observed in acute HE. However, neuropsychological impairment in HE ranges from mild deficits in psychomotor abilities affecting quality of life to stupor or coma with higher grades of hepatic dysfunction. In particular, the long-lasting compensatory mechanisms for the altered metabolism in chronic liver disease make HE imaging results variable. Therefore, the clinical relevance of imaging findings is uncertain and differentiating HE from other metabolic diseases can be difficult. The recent introduction of concepts such as "acute-on-chronic liver failure (ACLF)," a new clinical entity, has led to a change in the clinical view of HE. Accordingly, there is a need to establish a corresponding concept in the field of neuroimaging diagnosis. Herein, we review HE from a historical and etiological perspective to increase understanding of brain imaging and help establish an imaging approach for advanced new concepts such as ACLF. The purpose of this manuscript is to provide an understanding of HE by reviewing neuroimaging findings based on pathological and clinical concepts of HE, thereby assisting in neuroimaging interpretation.

Keywords: End stage liver disease; Hepatic encephalopathy; Magnetic resonance imaging

Introduction

Hepatic encephalopathy (HE) is a severe neuropsychiatric abnormality in patients with either acute or chronic liver failure [1,2]. Typical magnetic resonance imaging (MRI) findings of chronic liver failure are high signal intensity in bilateral basal ganglia high signal intensities (BGH) due to manganese deposition, and high signal intensity in fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) images with hemispherical white matter changes including the corticospinal tract. In acute HE, low apparent diffusion coefficient (ADC) values in the affected area reflect cytotoxic edema. However, neuropsychological im-

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pairment in HE manifests as a spectrum ranging from mild deficits in psychomotor abilities affecting quality of life to stupor or coma with higher grades of hepatic dysfunction [2]. In particular, the long-lasting compensatory mechanism for the altered metabolism in chronic liver disease (CLD) makes HE imaging findings very variable. Therefore, the clinical relevance of imaging findings is questionable, and it is difficult to differentiate HE from other metabolic diseases. The recent acceptance of new clinical concepts such as " acute-on-chronic liver failure (ACLF)" has led to a change in the clinical view of HE. Accordingly, there is a need to reevaluate existing paradigms in the field of neuroimaging diagnosis. The purpose of this manuscript is to provide a comprehensive review of HE through neuroimaging based on the pathological and clinical understanding of HE, thereby assisting in the interpretation of neuroimaging findings.

Typical neuroimaging of hepatic encephalopathy

Ethical statements: Written informed consent was obtained from the patient for publication of this review article and any accompanying images.

MRI is a very useful tool to better understand the pathophysiology of HE and provide direct evidence for the pathogenesis of HE due to severe liver dysfunction. In particular, magnetic resonance spectroscopy (MRS) provides information on the pathophysiological changes in HE at the molecular level.

1. Basal ganglia high signal intensity

The most frequent MRI finding in the brains of patients with CLD is BGH on T1-weighted imaging without mass effect, which results from paramagnetic manganese deposition [3-5]. Manganese crosses the blood-brain barrier and accumulates in the globus pallidus in chronic liver failure, which may be the cause of extrapyramidal symptoms [6]. BGH is thought to be caused by the severity of liver dysfunction and is reversible when liver function returns to normal levels after liver transplantation [7]. Manganese plays an essential role in the normal function of several enzymes, including glutamine synthetase and mitochondrial superoxide dismutase. Manganese has a neurotoxic effect, sparing the nigrostriatal system and causing selective neuronal death in the basal ganglia, structures, and reactive gliosis. This cell death is more apparent in the globus pallidus and substantia nigra reticulata, and less apparent in the striatum and bilateral internal capsules (Fig. 1). Clinically, early gait and balance dysfunction, the relative absence of resting tremors, the presence of mild cognitive impairment at the time of presentation, and little or no response to levodopa distinguish Parkinsonian manifestations in HE from idiopathic Parkinson disease.

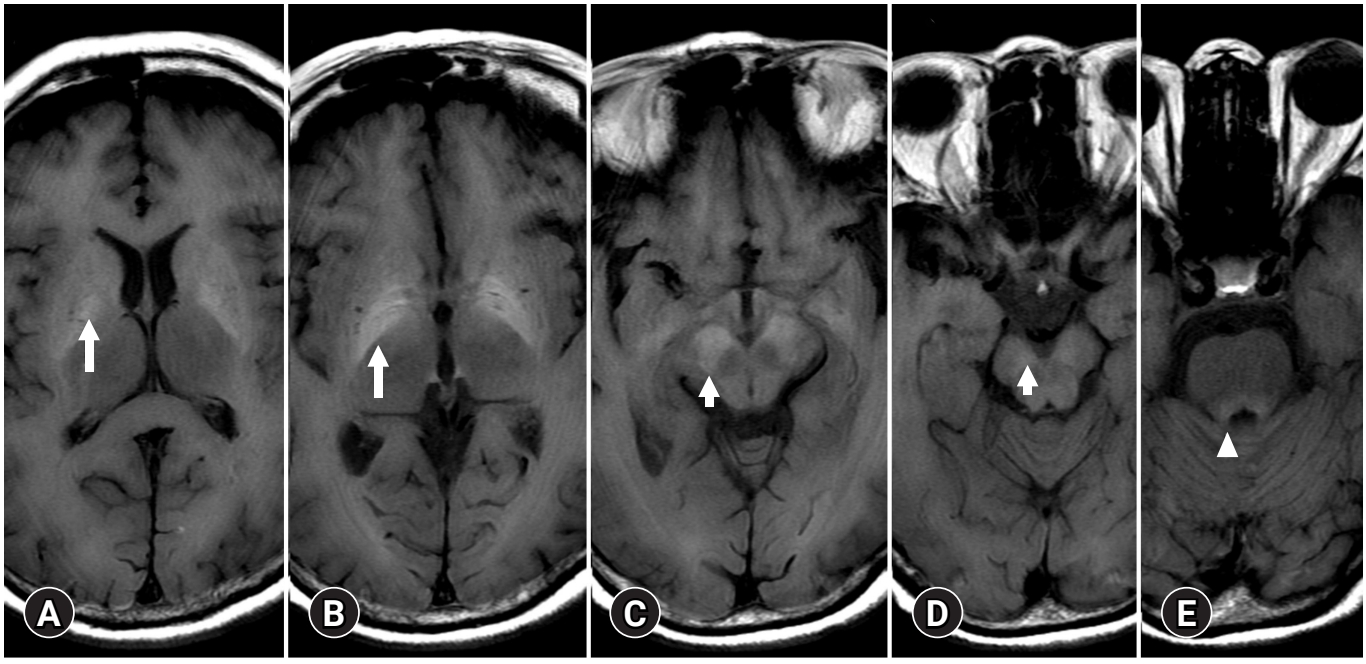

Fig. 1. A 57-year-old male with hepatic encephalopathy. (A–E) T1-weighted imaging shows high signal intensity in the basal ganglia, which is more prominent in the globus pallidus (arrows) and substantia nigra reticulata (short arrows), and to a lesser extent, striatum, portions of the bilateral internal capsules, and cerebellar peduncle (arrowhead).

The pallidal index, used as a semiquantitative parameter to evaluate manganese accumulation in the brain, is a relative value calculated as the ratio of the signal intensity in the globus pallidus to the subcortical frontal white matter in axial T1-weighted images. The pallidal index correlates with clinical indices such as whole blood manganese, Child-Pugh score, and total bilirubin level, which reveals the severity of the portal-systemic shunt [8,9].

2. White matter involvement

Due to minor brain edema that is beyond the threshold for detection on conventional MRI, hyperintensity along the white matter in the cerebral hemisphere or near the corticospinal tract on FLAIR or T2-weighted imaging has been described, mimicking the MRI features of amyotrophic lateral sclerosis [10] (Fig. 2). Transcallosal white matter involvement, so-called Marchiafava-Bignami disease (MBD), is a typical form of white matter involvement in patients with HE [11]. It was believed that MBD was specific to those who resided in central Italy and drank a lot of inexpensive red wine from the Chianti region. However, it is now known worldwide that the cause of MBD is closely related to alcohol consumption. The mechanism of white matter involvement in acute HE is not completely understood. The lack of integrity of the transcallosal connections between motor cortices is the consequence of axonal degeneration of transcallosal fibers. According to another hypothesis, arylsulfatase A (ASA) activity is reduced in patients with alcoholic cirrhosis similar to metachromatic leukodystrophy, which alters sphingomyelin metabolism [12].

Focal white matter T2-weighted lesions (WMLs) may also be observed in liver cirrhosis with or without overt HE. These lesions look like different types of small-vessel disease and white matter hyperintensity in healthy people who are elderly. However, focal WMLs in HE can be partially reversible with HE recovery or after liver transplantation, unlike other WMLs [13].

3. Cortical changes

On T2-weighted and FLAIR images, acute HE is characterized by diffuse cortical, overt brain edema, while cortical-restricted diffusion has a high signal intensity on DWI and low signal intensity on ADC maps, indicating cytotoxic edema (Fig. 3) [14]. The cingulate gyrus and insular cortex were symmetrically involved in the brain MRIs of all patients, with additional cortical involvement being more variable and asymmetrical. However, involvement of the parietal, frontal, temporal, or occipital cortex is unusual [15].

4. Magnetic resonance spectroscopy

Currently, there is agreement on the characteristic triad of proton magnetic resonance spectroscopy (^{1}H-MRS) results in HE, including depletion of intracellular choline (Cho) and myoinositol (mIns) as well as accumulation of glutamine (Gln), all of which are associated with neuropsychiatric dysfunction (Fig. 4) [16]. Signals of glutamate and Gln are increased to compensate for glial Gln accumulation to maintain osmotic homeostasis [17]. However, the decompensation of these volume-regulatory mechanisms may result in neuroglial disturbance and astrocyte swelling. Among these ^{1}H-MRS variables, mIns appears to be a more sensitive biomarker in the early detection of HE [18]. Diminished mIns, which contributes to ion flux, may act as an organic osmolyte and is critical for controlling astrocyte volume. Cho is a component of phosphocholine, which is related to cell membrane activation. Cho is a necessary component in the synthesis of acetylcholine, which is a neurotransmitter associated with memory, awareness, and feelings. A reduced ratio of Cho to creatinine may underlie cognitive impairment in HE. In patients with cirrhosis, the majority of MRS studies found no significant changes in *N*-acetylaspartate, which may

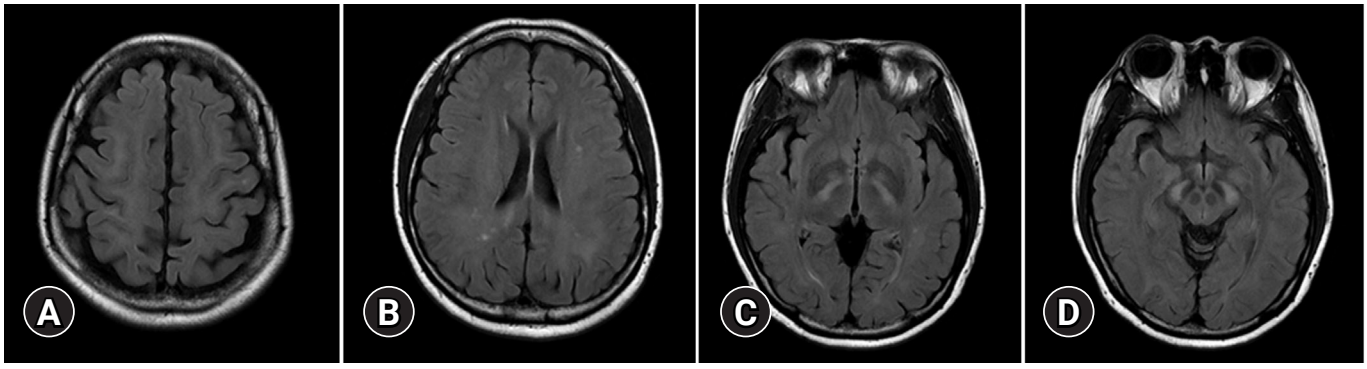

Fig. 2. A 49-year-old male with general weakness. (A) Fluid-attenuated inversion recovery imaging shows diffuse high signal intensity lesions involving subcortical white matter, (B) periventricular white matter, (C) internal capsule, and (D) midbrain crus cerebri in a patient with chronic liver disease.

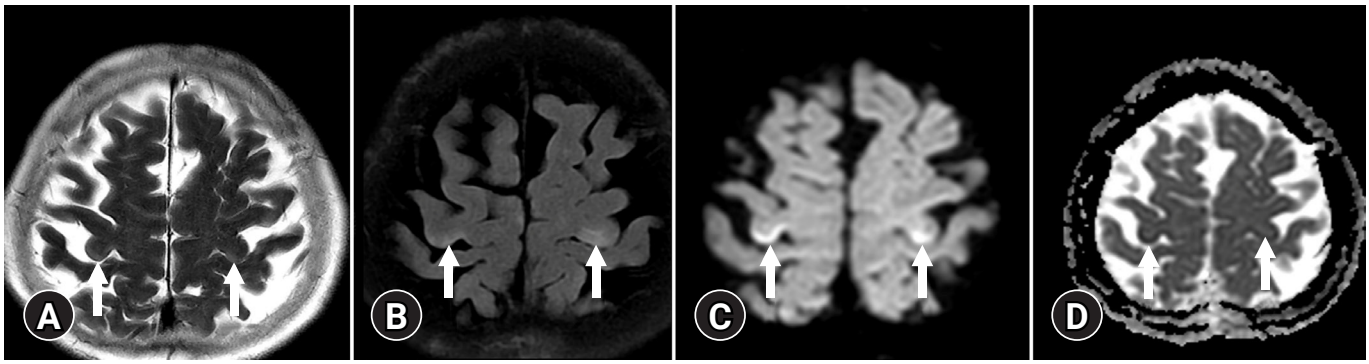

Fig. 3. A 52-year-old male with weakness of upper extremities. (A) Magnetic resonance imaging sequences of T2-weighted imaging, (B) fluid-attenuated inversion recovery, (C) diffusion-weighted imaging, and (D) apparent diffusion coefficient map show signal changes in cortex of precentral gyrus of both frontal lobes (arrows) in a patient with chronic liver disease.

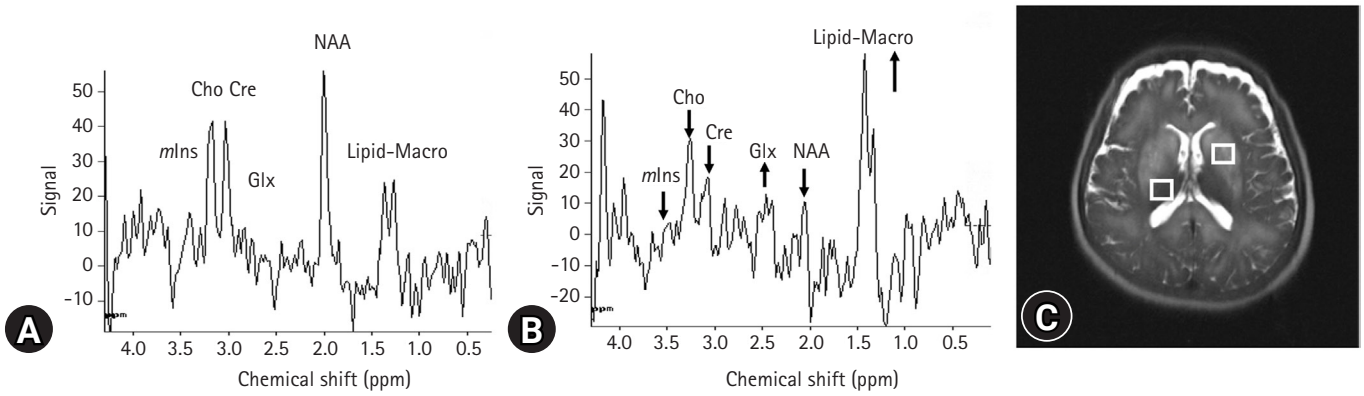

Fig. 4. Magnetic resonance (MR) spectroscopy of a 61-year-old male with liver cirrhosis. Compared with (A) the spectrum from the relatively spared right thalamus, (B) the proton MR spectrum of a patient with hepatic encephalopathy shows significant increases (upward pointing arrows) in lipid macromolecular content (Lipid-Macro) and glutamate/glutamine (Glx), and marked decreases in choline (Cho) and myoinositol (mIns) (downward pointing arrows). (C) On a T2-weighted image, MR shows increased signal intensities at the basal ganglia and corpus callosum with periventricular white matter extension with a relatively spared thalamus. Cre, creatine; NAA, *N*-acetylaspartate.

indicate no discernible neuronal impairment as HE progressed [19]. In the past, it was believed that neuronal changes in HE were either absent or unimportant in explaining the neuropsychiatric abnormality. However, a neuropathological study subsequently showed significant neuronal cell loss in the brains of patients with HE. Dopaminergic and serotoninergic neuronal systems, as well as Purkinje cells, have also been shown to decline in HE [20].

Pathophysiology of hepatic encephalopathy

We have summarized the pathophysiology of HE associated with neuroimaging in Fig. 5. It is essential for radiologists to understand the biological mechanisms to understand this figure. First, it is necessary to understand why patients with HE are vulnerable to osmotic damage and how metabolic changes affect magnetic resonance signals.

1. Metabolites

Ammonia is believed to play an important role in the cause of HE. The liver detoxifies and converts the majority of ammonia absorbed from the small intestine through the portal vein into urea. Thus, HE may result from hepatic dysfunction, defects in urea circulation, or portocaval shunts that increase blood ammonia levels. Skeletal muscle and brain astrocytes contribute to the detoxification of ammonia by converting it to Gln in cases of hepatic dysfunction. Under the catalysis of glutamine synthase, elevated ammonia and Glu are converted to abundant levels of Gln, which contribute to elevated osmotic pressure. Although the mechanism of brain edema in acute hepatic failure is not fully understood, ammonia is generally assumed to play a critical role. In addition, reduced urea cycle activity in chronic liver dysfunction leads to an increase in cerebral Gln synthesis by brain astrocytes [21].

Hyponatremia causes not only rapid loss of intracellular electro-

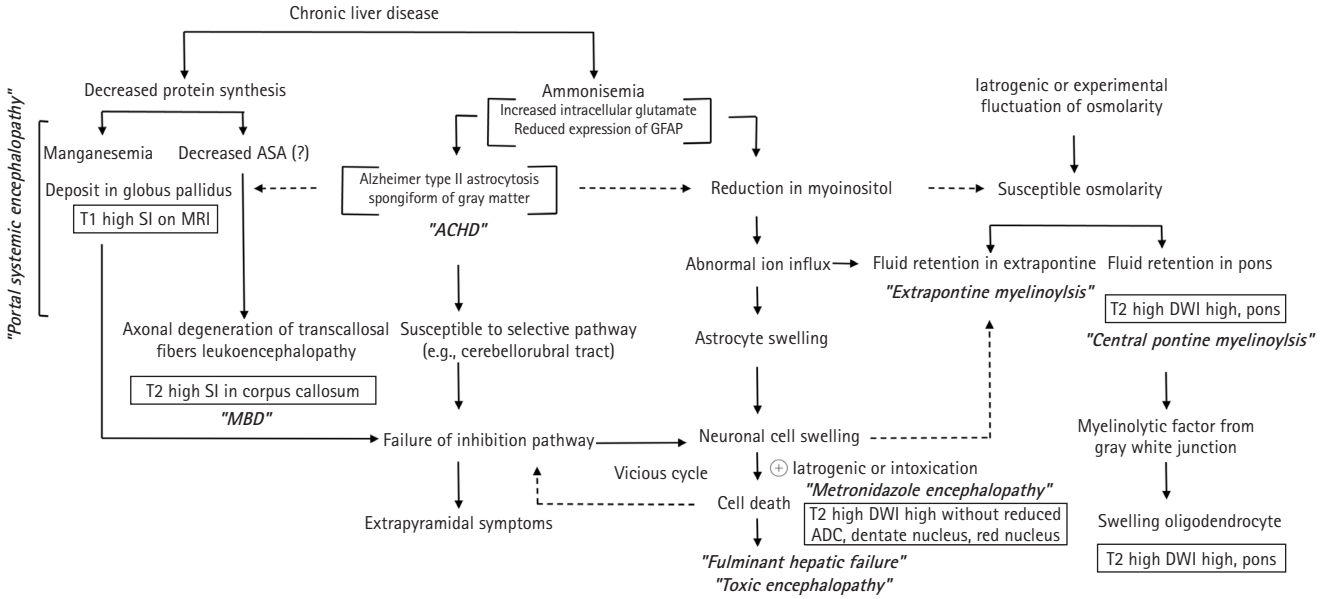

Fig. 5. Proposed pathway of pathophysiology in hepatic encephalopathy. There are two major axes of the pathophysiology pathway: decreased protein synthesis and ammonemia in chronic liver disease. Decreased protein synthesis causes impaired manganese chelation, resulting in manganemia, manganese deposition in globus pallidus, and high T1 signal intensity (SI) observed on brain magnetic resonance imaging (MRI). Arylsulfatase A (ASA) depletion is also believed to trigger axonal degeneration of transcallosal fibers in a metachromatic leukodystrophy-like mechanism, consequently Marchiafava-Bignami disease (MBD). On pathology, ammonemia causes Alzheimer type II astrocytes and spongiform gray matter, which cause acquired chronic hepatocerebral degeneration (ACHD) symptoms. In addition, ammonemia causes a decrease in intracerebral myoinositol, which makes brain cells, especially astrocytes, sensitive to external osmotic pressure changes, resulting in osmotic demyelinating syndrome of central pontine or extrapontine types depending on the anatomical location. Since abnormalities in ion influx eventually lead to edema and death of nerve cells, metronidazole encephalopathy occurs when drugs such as metronidazole are used in these vulnerable patients. GFAP, glial fibrillary acidic protein; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient.

lytes such as potassium but also low-molecular-weight organic osmolytes including mIns and Cho [22]. The decreased mIns contributing to ion flux may serve as an organic osmolyte and plays a more important role in the volume regulation of astrocytes than intracellular electrolytes in such situations [23]. During hyperglycemia in unmanaged diabetes and ethanol intoxication, extracellular osmolality may increase despite normal or decreased extracellular Na^+ concentrations. Astrocyte swelling may not be visible until compensatory osmoregulatory mechanisms, such as loss of intracellular osmolytes, disappear. For this reason, there were cases in which Na^+ concentration changes related to central pontine myelinolysis (CPM) could not be found in the presence of metabolic diseases. Since the pons and lateral geniculate body appear to be the exclusive anatomical locations associated with osmotic demyelination syndrome, deep gray matter involvement is highly likely to result in the osmotic injury related to acquired chronic hepatocerebral degeneration (ACHD). This is expected to be revealed in a detailed study on whether extrapontine myelinolysis (EPM)/CPM-like lesions occur in patients with ACHD and those with HE.

2. Pathology

Pathologically, HE may be classified into portal-systemic encephalopathy (PSE) and HE in fulminant hepatic failure (FHF) [24]. PSE is a complication of portal-systemic shunting of venous blood, which can develop either spontaneously as a result of portal hypertension or after surgical intervention. Astrocytes, a type of neural cell, are most susceptible to the effects of liver failure [25]. Critical astrocytic proteins, such as the structural glial fibrillary acidic protein (GFAP), a cytoplasmic filamentous protein that makes up a significant portion of the cellular component in mature astrocytes, are downregulated when the brain is exposed to ammonia [26]. Diminished GFAP expression causes morphological changes in astrocytes that favor extracellular space diffusivity. The presence of the astrocytic pathology known as Alzheimer type II astrocytosis, in which astrocytes acquire a characteristic swollen shape with a large pale nucleus, a prominent nucleolus, and margination of the chromatin, was shown in histopathologic studies of brain sections of patients with cirrhosis [27]. At autopsy, a subset of patients with hepatocerebral degeneration may have band-like or patchy central nervous system (CNS) myelin vacuolization that is not related to

myelin breakdown or macrophage influx. In nearby astrocytes, typical changes indicative of chronic liver failure were observed [25]. Neurologically, PSE develops slowly; the onset is often insidious starting with personality changes. ACHD occurred in patients with portocaval shunts or liver cirrhosis resulting from a number of causes, but not Wilson disease [25].

Unlike PSE, cytotoxic edema rather than vasogenic edema is visible in the brain tissue of FHF, according to electron microscopic studies [28]. Characteristically cytotoxic brain edema and especially swelling of astrocytes and astrocytic endfeet, among several brain cell types, have been most frequently observed in acute liver failure [28]. Mortality rates are higher in FHF than in PSE; brainstem herniation caused by increased intracranial pressure as a consequence of brain edema is the most common cause of death. In contrast to PSE, patients with FHF progress through states of altered mental capacity and confusion to stupor and coma within a few hours or days.

3. Neurotransmission

Impairment of neuronal communication in HE can result from changes in numerous neurotransmitter systems. High concentrations of ammonium ions have been shown to obstruct glutamatergic excitatory transmission. Increased serotonin turnover caused by chronic hyperammonemia may be the cause of the altered sleep patterns in HE [29]. Ammonia is also known to damage brain energy metabolism and blood flow autoregulation. Recent studies have shown that ammonia exposure causes cultured astrocytes to undergo a process known as mitochondrial permeability transition, which is linked to mitochondrial failure and subsequent cellular dysfunction and has similar mechanisms to those of Wernicke encephalopathy [30].

Acute liver failure results in altered expression of several genes in brain, some of which code for proteins such as the glucose (glucose transporter 1) and glutamate (glutamate transporter-1, GLT-1) transporters, the astrocytic structural protein GFAP the "peripheral-type" benzodiazepine receptor and the water channel protein, aquaporin IV. Loss of expression of GLT-1 results in increased extracellular brain glutamate [29]. In chronic liver dysfunction, reduced urea cycle activity causes astrocytes to increase synthesis of cerebral Gln.

Evolution of clinical staging

1. Classic staging

There are several clinical classifications and a grading system for HE according to cause and severity. According to the underlying disease, HE is subclassified into type A (acute liver failure), type B (bypass or shunt), and type C (cirrhosis). Type C HE is subcategorized into episodic (acute), recurrent, and persistent HE, depending on the time course. According to the existence of precipitating factors, episodic HE is subdivided into spontaneous (non-precipitated), precipitated, or recurrent HE (when two episodes of episodic HE occur in 1 year). Precipitating factors can be identified in almost all cases of episodic hepatic type C [31]. Based on the clinical severity from subclinical alterations to severe coma or death, HE may be subclassified by West Haven Criteria (WHC) into grades 0 to IV [32]. To overcome the limited interobserver reliability of the criteria, the International Society for Hepatic Encephalopathy and Nitrogen Metabolism classification was proposed. Patients with minimal HE and WHC grade I would be classified as having covert HE. Other patients with WHC grades II to IV would be classified as having overt HE, a counterpart of covert HE [33].

2. Acute-on-chronic liver failure

Acutely decompensated cirrhosis and ACLF share two important clinical features: known CLD with acute decompensation. ACLF, a term proposed by Jalan and Williams [34], originated from studies that revealed a syndrome related to a high risk of short-term death (death < 4 weeks after admission) in patients with acutely decompensated cirrhosis. Three major clinical features of ACLF are intense systemic inflammation, frequent association with proinflammatory precipitating events (such as infections or alcoholic hepatitis), and single- or multi-extrahepatic organ failure (e.g., function of kidney, brain, blood coagulation, circulation, and respiration) (Fig. 6) [35,36].

Uncertain differential diagnoses

1. Osmotic demyelination

A few cases of HE show T2 or diffusion high signal intensities of basal ganglia mimicking EPM, or uremic encephalopathy (Fig. 7). HE shares common clinical features with other metabolic diseases such as osmotic demyelination or uremic encephalopathy. There are two possible explanations for the symmetric and synchronous involvement of deep gray matter. One is the concept of ACHD and the other is EPM [37].

As a CPM, a symmetrical solitary, midline lesion in the basis pontis with myelin breakdown, macrophage influx, relative preservation of axis cylinders, and minimal inflammatory response was first described in 1959 as a "hitherto undescribed disease" [38]. CPM is regarded as a disease occurring in alcoholic and malnourished patients with chronic renal failure or hepatocellular dysfunction [39]. In 58 autopsy cases of CPM, EPM was observed more

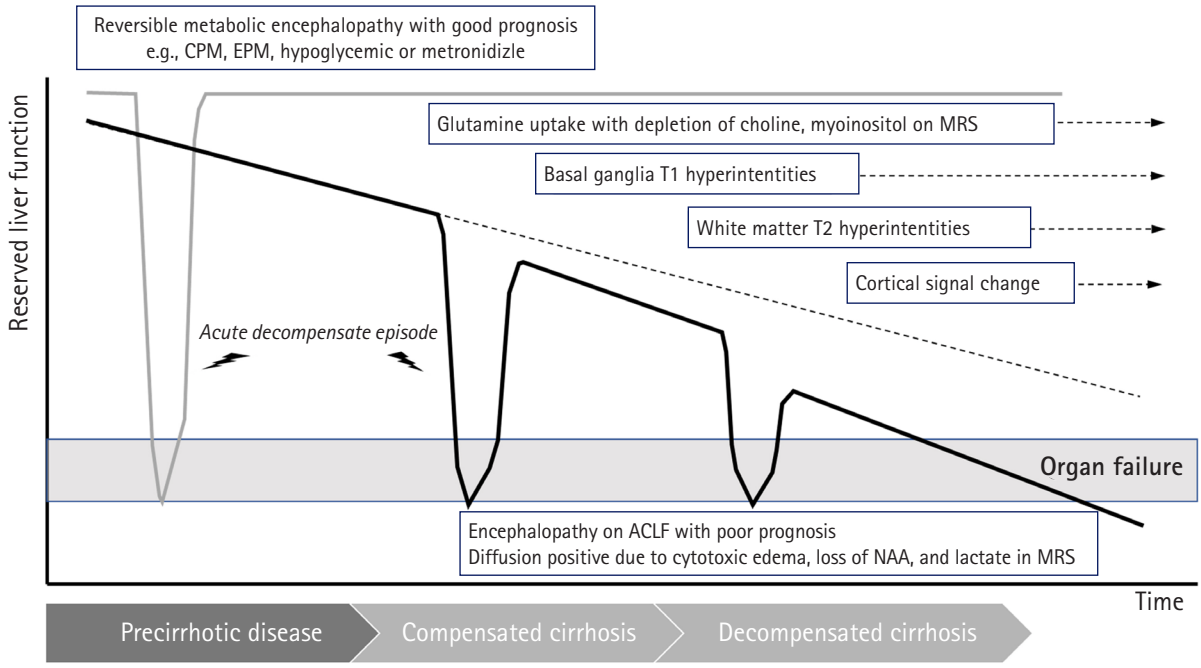

Fig. 6. Clinical manifestation of hepatic encephalopathy. In both chronic liver disease and liver cirrhosis, residual liver function declines over time. Acute decompensation episodes occur recurrently due to the existence of precipitating factors. In the period of precirrhotic disease, reversible metabolic encephalopathy shows good prognosis due to full recovery after a temporary decrease in liver function. As residual liver function gradually declines into compensatory cirrhosis, intracellular glutamine accumulation and deficiency of choline and myoinositol are observed. When an acute decompensation episode occurs from this period onward, returning liver function to its initial state is challenging. With disease progression, basal ganglia T1 hyperintensity related to manganese accumulation is observed, and after entering decompensated cirrhosis, white matter T2 hypersensitivity is observed on magnetic resonance imaging. Finally, this damages the cortex and induces signal changes in the cortex. If organ failure is accompanied by acute decompensation episodes, it can be clinically classified as acute-on-chronic liver failure (ACLF), with increased mortality with a number of organ failures. CPM, central pontine myelinolysis; EPM, extrapontine myelinolysis; NAA, *N*-acetylaspartate; MRS, magnetic resonance spectroscopy.

frequently than a solitary pontine lesion [40]. Through clinical and experimental studies, the onset of CPM and EPM was demonstrated to occur concomitantly with a rapid correction in hyponatremia and osmotic shift. Especially with chronic liver dysfunction, the decreased urea cycle activity causes astrocytes to increase synthesis of cerebral Gln and decrease mIns, which plays an important role in the regulation of astrocytic volume [37]. Therefore, the MRI signal intensity of deep gray matter in patients with HE can be viewed as sensitive to osmotic disease based on organic changes rather than simple osmotic demyelinating disease.

2. Deep gray matter and connectivity

Bilateral involvement of the dentate nucleus was initially thought to be specific to metronidazole encephalopathy (Fig. 8) [41]. However, many case reports of metronidazole encephalopathy reported synchronous involvement of the red nucleus and dentate nucleus [41], which are components of the Guillain-Mollaret triangle [42]. In addition, there may be bilateral T2 intensities in the dentate nucleus in HE related to methyl bromide poisoning, enteroviral encephalomyelitis, and maple syrup urine disease [43-45]. Therefore, there is a limit to associating the cause of metabolic brain disease with the onset of specific anatomical lesions, and understanding the functional connection between various brain responses and toxic substances is necessary.

Conclusion

We used this review to clarify the similarities and differences between HE and lesions belonging to other similar disease entities and to address the uncertainties surrounding their potentially overlapping features by scrutinizing the literature, especially the original descriptions of these entities. We hypothesized that disease progression with varying degrees of corpus callosum and deep cerebral gray matter involvement and the worsening of HE conceptually overlapped. However, EPM and ACHD are pathologically different. EPM may show severe demyelination and macrophage-me-

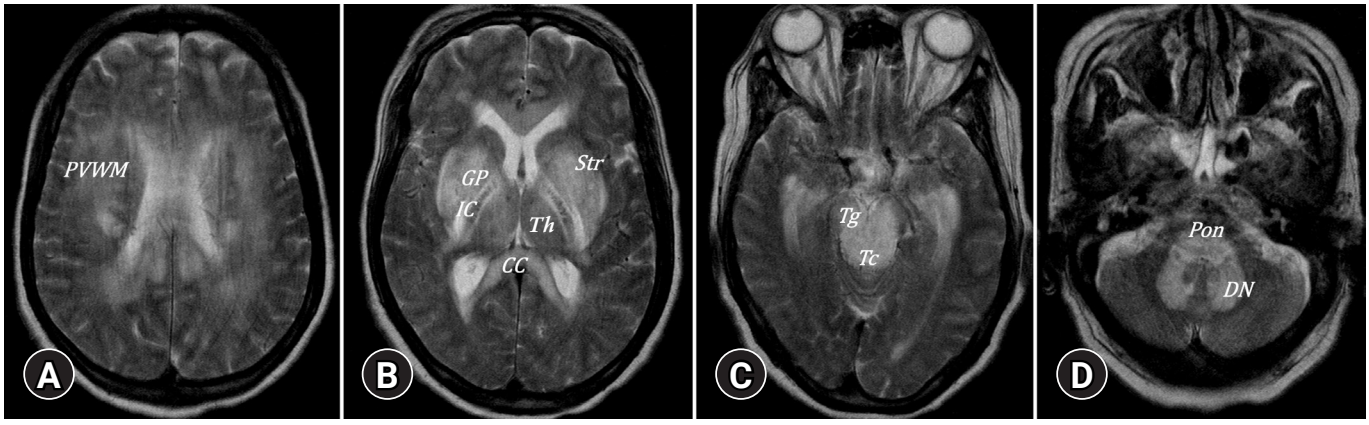

Fig. 7. A 52-year-old male with stuporous mentality. (A–D) Extensive involvement of deep gray matter, including globus pallidus (GP), striatum (Str), thalamus (Th), and dentate nucleus (DN) as well as involvement of white matter such as periventricular white matter (PVWM), corpus callosum (CC), internal capsule (IC), tegmentum (Tg), tectum (Tc), and pons, mimicking central pontine myelinolysis and extrapontine myelinolysis.

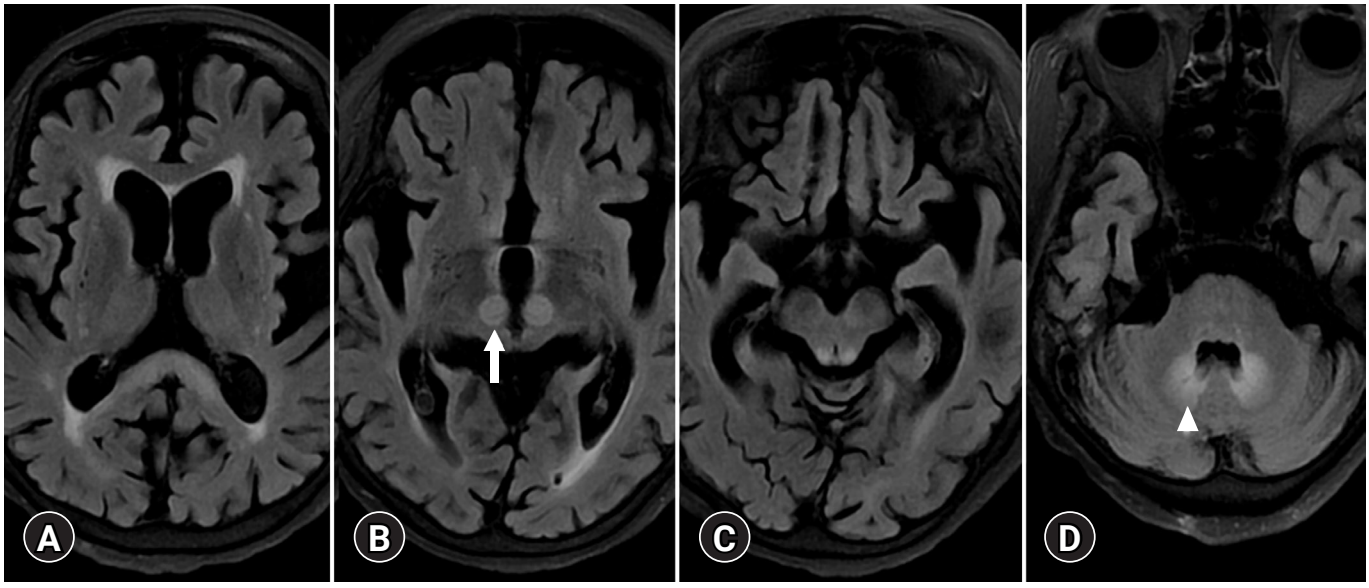

Fig. 8. A 52-year-old male with stuporous drowsy mentality. (A–D) Fluid-attenuated inversion recovery imaging shows reported synchronous involvement of red nucleus (arrow) and dentate nucleus (arrowhead) in a patient with metronidazole encephalopathy.

diated destruction, while ACHD shows band-shaped or speckled vacuolization of CNS myelin without demyelination or macrophage influx. Therefore, the neuropsychiatric abnormality of HE originates from a combination of several synergistic facilitating factors, and CLD induces a state sensitive to injury from osmotic imbalances or external toxic substances through changes in ACHD, resulting in brain lesions similar to those diseases, such as osmotic demyelination syndrome or toxic encephalopathy. To understand the pathophysiological mechanism of HE, multimodality MRI is a useful and practical research tool. It will also become increasingly vital in the early diagnosis, prognosis, and monitoring of HE.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization, Resources: all authors; Data curation: CGL, MHH; Formal analysis: CGL, HJL; Investigation, Software, Vali-

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Association of advanced chronic kidney disease with diabetic retinopathy severity in older patients with diabetes: a retrospective cross-sectional study

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Background: Despite the recent increasing trend in the prevalence of type 2 diabetes among older individuals, the relationship between diabetic retinopathy (DR) and chronic kidney disease (CKD) in these patients remains unclear. This study investigated the severity of renal dysfunction according to the degree of DR in older patients with type 2 diabetes.
Methods: A total of 116 patients with diabetes and CKD stage ≥3 who visited both the nephrology and ophthalmology outpatient departments between July 2021 and January 2022 were screened. There were 53 patients in the no DR group, 20 in the nonproliferative DR (NPDR) group, and 43 in the proliferative DR (PDR) group.
Results: DR severity was related to the deterioration of renal function. The proportion of patients with advanced CKD significantly increased with DR severity (p for trend <0.001). In the multivariate regression model adjusted for age of ≥80 years, male sex, poorly controlled diabetes, macroalbuminuria, insulin use, diabetes duration of ≥10 years, cerebrovascular accident, hypertension, hyperlipidemia, and cardiovascular disease history, the odds ratio compared with the no DR group was approximately 4.6 for the NPDR group and approximately 11.8 for the PDR group, which were both statistically significant ($p=0.025$ and $p<0.001$, respectively).
Conclusion: DR severity in older patients with diabetes may be associated with deterioration of renal function and high prevalence of advanced CKD. Therefore, periodic examination for DR in older patients with diabetes is important for predicting renal function deterioration and CKD progression.

Keywords: Aged; Chronic renal insufficiency; Diabetes mellitus; Diabetic retinopathy

Introduction

Diabetic nephropathy and diabetic retinopathy (DR) are major microvascular complications of diabetes mellitus (DM) with a similar pathogenesis. They also share risk factors such as smoking, poorly controlled blood glucose levels, hypertension (HTN), and hyperlipidemia [1,2]. As a microvascular complication of type 1 DM, the correlation between DR and chronic kidney disease (CKD) has been well established; however, in type 2 DM, the correlation between these two conditions remains relatively unclear [3,4].

Meanwhile, with global increases in life expectancy and long-

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term exposure to metabolic risk factors, there has been a rapid increase in the prevalence of DM among older adults [5,6]. The global prevalence of type 2 DM in this population was reported to be approximately 22% in 2017 [5]. Korea is also an aging society, and a survey conducted from 2016 to 2018 reported a DM prevalence of approximately 28% among individuals aged >65 years, which is higher than the global average [7]. Furthermore, aging itself is associated with the pathogenesis of DM owing to a decrease in pancreatic beta cell function and impaired regulation of various hormones [8].

Despite the recent increasing trend in the prevalence of DM among older individuals, the relationship between DR and CKD in older patients with DM is still uncertain. A recent large cohort study indicated that the severity of DR is also related to CKD progression [9]. However, these large-scale studies were not conducted exclusively in older patients with DM. Therefore, to confirm the relationship between DR and CKD in this subpopulation, a follow-up analysis of older individuals in a large-scale study or additional studies tailored to those greater than a cutoff age are needed. The present study was conducted to investigate renal function and the proportion of advanced CKD cases with respect to the degree of DR in older patients with DM. The present study also examined whether there are additional factors influencing the relationship between advanced CKD and the degree of DR, and in particular, whether the degree of DR and proteinuria have an additive effect on advanced CKD.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Daegu Catholic University Hospital (IRB No: CR-22-022) with an exemption from informed consent. Personal data related to patient information were used and personally identifiable information was protected. This was a retrospective cross-sectional study that did not include personally identifiable information. All study methods were performed in compliance with relevant guidelines and regulations.

1. Study design

A total of 272 patients with DM and CKD stage ≥3 who visited both the nephrology and ophthalmology outpatient departments from July 2021 to January 2022 were screened. Patients with a follow-up period of fewer than 6 months and those who were not screened periodically were excluded. Patients aged <60 years and those with overt or past cancer, autosomal dominant polycystic kidney disease (ADPKD), or solid organ transplantation were also excluded. The World Health Organization has defined old age as ≥60 years [10]. In this study, an older patient was considered at least 60 years old; therefore, the inclusion and exclusion criteria for the study were established. Laboratory test results, such as those assessing renal function and albuminuria, were examined in all patients who met the inclusion criteria. Patients were also evaluated for DR by dilated fundus examination with wide-field fundus photography.

Basic patient information, including age, sex, insulin use, DM duration, HTN, hyperlipidemia, past cerebrovascular accident (CVA), and history of cardiovascular disease (CVD), was collected through an electronic chart review. CVD was clarified as myocardial infarction (MI), acute coronary syndrome (ACS), congestive heart failure (CHF), arrhythmia, or valvular heart disease (VHD). CVD history was diagnosed by a cardiologist. If echocardiography was performed within 6 months, relevant reports were reviewed. Data pertaining to creatinine (Cr), glycated hemoglobin (HbA1c), cholesterol, and serum albumin levels and random urine albumin-Cr ratio were collected from laboratory tests. Albuminuria included both microalbuminuria (30 mg/g Cr ≤ random urine albumin-Cr ratio < 300 mg/g Cr) and macroalbuminuria (random urine albumin-Cr ratio of ≥ 300 mg/g Cr).

We compared renal function and the distribution of CKD stages according to the degree of DR. Cr levels and the estimated glomerular filtration rate (eGFR) were used to compare renal function. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [11]. CKD stage was defined according to the CKD Evaluation and Management criteria reported in 2012 in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Moreover, we investigated whether there were risk factors for advanced CKD, including the degree of DR. Advanced CKD was defined as CKD stages 4 and 5. To analyze the impact of DR on the prevalence of advanced CKD, we used several factors, such as very old age, male sex, poorly controlled DM, macroalbuminuria, insulin use, DM duration of ≥10 years, history of CVA, HTN, hyperlipidemia, CVD, MI, ACS, CHF, arrhythmia, and history of VHD. In previous research, including the 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) blood pressure guidelines, age of ≥80 years was defined as very old, and we adopted this definition in our study [12]. Although the definition of poorly controlled DM differs among studies, we defined it as an HbA1c level of ≥8% in our study.

2. Fundus examination

Patients who visited the ophthalmology department underwent

wide fundus photography and fundus examination after pupil dilation. Fluorescein angiography was performed on all patients suspected of having a new vessel in the fundus examination to distinguish proliferative DR (PDR) from severe nonproliferative DR (NPDR). No DR, NPDR, and PDR were classified according to the Early Treatment Diabetic Retinopathy Study severity scale, and all patients who had undergone panretinal photocoagulation or pars plana vitrectomy for treatment of PDR were included in the PDR group [13,14]. In this examination, even if one eye was normal and the contralateral eye was diagnosed with NPDR, the patient was included in the NPDR group. If only one eye was diagnosed with PDR, the patient was included in the PDR group.

3. Statistical analysis

The three groups classified according to the degree of DR were compared using independent two-sample *t*-tests or one-way analysis of variance (ANOVA) for continuous variables and chi-square or Fisher exact tests for nominal variables. Bonferroni and Tukey methods were used for *post-hoc* analysis of one-way ANOVA results. Receiver operating characteristic (ROC) curve analysis was used to confirm the cutoff value of renal function for NPDR or PDR. The cutoff value was defined as the value that maximized the sensitivity and specificity of the ROC curve (Youden index). The trend in the proportion of advanced CKD according to the degree of DR was analyzed using a linear-by-linear association. The forward conditional method and binary logistic regression analysis were used to select variables regarding risk factors to compare advanced CKD among the three groups. Very old age, male sex, poorly controlled DM, macroalbuminuria, insulin use, DM duration of ≥ 10 years, past CVA, HTN, hyperlipidemia, CVD, MI, ACS, CHF, arrhythmia, and history of VHD were considered confounding variables in the multivariate analysis. As mentioned in the introduction, these confounding factors are widely known risk factors for diabetic nephropathy [1,2]. In the next section, we present the results of multivariate binary logistic regression using the three models. CVD is a broad term for many diseases, including MI, ACS, CHF, arrhythmia, and VHD; when CVD was used for adjustment, the individual diseases were not considered confounding factors. Even when individual CVD diseases were used as confounding factors, regression analysis was not performed by selecting duplicates because MI is a subset of ACS. In addition, a hierarchical regression analysis was conducted using Baron and Kenny method for mediation to analyze the interaction between the degree of DR and level of proteinuria in advanced CKD [15]. The level of statistical significance was set at $p < 0.05$. All statistical analyses were performed using IBM SPSS version 19.0 (IBM Corp., Armonk, NY, USA).

Results

1. Basic characteristics

Of the 272 patients, 33 who had a follow-up period of fewer than 6 months or for whom serial laboratory tests were not performed were excluded. Of the remaining 239 patients, 81 aged < 60 years, 14 with cancer, three with ADPKD, 15 who received liver transplantation, and 10 who received kidney transplantation were excluded, and 116 patients were finally analyzed. Based on the degree of DR, these 116 patients were classified into the no DR group (53 patients), NPDR group (20 patients), and PDR group (43 patients) (Fig. 1).

The basic characteristics of the patients included in this study are summarized in Table 1. No significant difference was observed in age and sex among the three groups classified according to the degree of DR. A significant difference was detected in the serum albumin concentration between the no DR and PDR groups. However, the respective mean levels were 4.10 and 3.95 g/dL, which were higher than the standard hypoalbuminemia cutoff level of 3.5 g/dL. The prevalence of albuminuria was significantly higher in the PDR group than in the other two groups. In particular, the prevalence of macroalbuminuria was significantly higher in the PDR group than in the other two groups, whereas that of microalbuminuria was not statistically different. Insulin use was significantly higher in the NPDR and PDR groups than in the no DR group. The NPDR group showed the highest rate, but no significant difference was observed between the NPDR and PDR groups. The duration of DM was longer in the NPDR and PDR

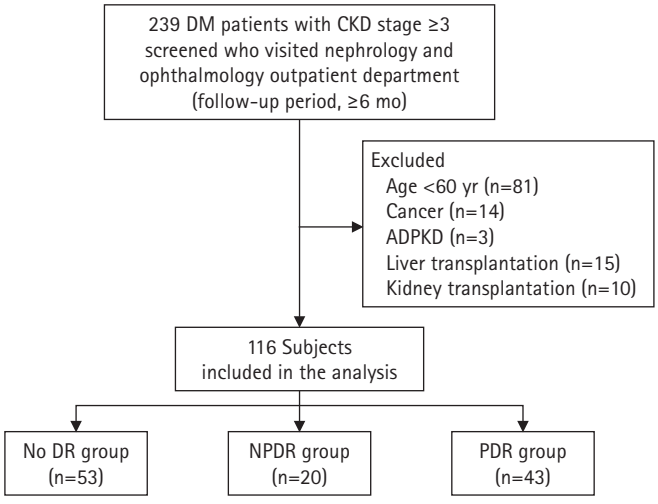

Fig. 1. Distribution of patients included in this study. DM, diabetes mellitus; CKD, chronic kidney disease; ADPKD, autosomal dominant polycystic kidney disease; DR, diabetic retinopathy; NPDR, nonproliferative DR; PDR, proliferative DR.

Table 1. Basic characteristics of the three groups classified according to the degree of DR

Characteristic	No DR group	NPDR group	PDR group	*p*-value		
				No DR vs. NPDR	No DR vs. PDR	NPDR vs. PDR
No. of patients	53	20	43			
Age (yr)	71.62±8.743	70.65±8.887	68.95±8.679	0.906	0.301	0.754
Very old age[a]	12 (22.6)	5 (25.0)	7 (16.3)	>0.999	0.437	0.496
Male sex	23 (43.4)	11 (55.0)	15 (34.9)	0.375	0.396	0.131
HbA1c (%)	7.281±1.343	7.660±1.515	7.781±1.934	0.645	0.290	0.958
Total cholesterol (mg/dL)	147.360±40.484	151.150±28.722	147.910±38.531	0.924	0.997	0.947
Serum albumin (g/dL)	4.098±0.459	4.000±0.511	3.851±0.473	0.710	0.033	0.478
Albuminuria[b]	26 (49.1)	14 (70.0)	40 (93.0)	0.109	<0.001	0.023
Microalbuminuria[c]	3 (5.7)	2 (10.0)	3 (7.0)	0.177	<0.001	0.012
Macroalbuminuria[d]	23 (43.4)	12 (60.0)	37 (86.0)	0.177	<0.001	0.012
Insulin use	11 (20.8)	17 (85.0)	19 (44.2)	<0.001	0.014	0.002
DM duration (yr)	13.496±7.726	17.810±8.644	20.230±8.320	0.110	<0.001	0.514
Hypertension	39 (73.6)	18 (90.0)	36 (83.7)	0.205	0.232	0.706
Hyperlipidemia	39 (73.6)	18 (90.0)	24 (55.8)	0.205	0.068	0.007
Past CVA	5 (9.4)	6 (30.0)	12 (27.9)	0.060	0.018	0.864
CVD	30 (56.6)	10 (50.0)	14 (32.6)	0.613	0.019	0.185
MI	6 (11.3)	6 (30.0)	4 (9.3)	0.077	>0.999	0.061
ACS	14 (26.4)	6 (30.0)	6 (14.0)	0.759	0.135	0.172
CHF	24 (45.3)	10 (50.0)	9 (20.9)	0.719	0.012	0.019
Arrhythmia	9 (17.0)	2 (10.0)	4 (9.3)	0.716	0.274	>0.999
VHD	2 (3.8)	2 (10.0)	4 (9.3)	0.301	0.403	>0.999
CABG history	5 (9.4)	0 (0)	2 (4.7)	0.314	0.454	>0.999

Values are expressed as number only, mean±standard deviation, and number (%).
DR, diabetic retinopathy; NPDR, nonproliferative DR; PDR, proliferative DR; HbA1c, glycated hemoglobin; DM, diabetes mellitus; CVA, cerebrovascular accident; CVD, cardiovascular disease; MI, myocardial infarction; ACS, acute coronary syndrome; CHF, congestive heart failure; VHD, valvular heart disease; CABG, coronary artery bypass graft surgery.
[a] ≥80 years. [b]Albuminuria includes both microalbuminuria and macroalbuminuria. [c]Microalbuminuria is defined as 30 mg/g Cr≤random urine albumin-creatinine ratio<300 mg/g Cr. [d]Macroalbuminuria is defined as random urine albumin-creatinine ratio of ≥300 mg/g Cr.

groups than in the no DR group, but the difference was significant only between the no DR and PDR groups. Past CVA incidence was significantly higher in the PDR group than in the no DR group.

2. Comparison of renal function according to degree of diabetic retinopathy

In the comparison of renal function among the three groups, the mean serum Cr level was 2.13 mg/dL in the no DR group, 3.19 mg/dL in the NPDR group, and 3.71 mg/dL in the PDR group. With the severity of DR, the mean serum Cr level tended to be higher, and it was significantly higher in the NPDR and PDR groups than in the no DR group. Among the three groups, the mean eGFR was 34.0 mL/min/1.73 m^2 in the no DR group, 24.5 mL/min/1.73 m^2 in the NPDR group, and 20.3 mL/min/1.73 m^2 in the PDR group. Corresponding to the trend in serum Cr levels, the mean eGFR decreased with the severity of DR, and a significant difference was observed when comparing the NPDR and PDR groups to the no DR group. However, no significant difference was observed in the mean eGFR between the NPDR and PDR groups (Fig. 2).

3. Cutoff value of renal function to predict comorbidities of nonproliferative and proliferative diabetic retinopathies

In the ROC curve analysis of renal function for NPDR, the area under the curve (AUC) was statistically significant at 0.732 for Cr level and 0.716 for eGFR ($p=0.002$ for Cr and $p=0.005$ for eGFR). The cutoff value of Cr and eGFR predicting NPDR were 2.25 mg/dL and 27.41 mL/min/1.73 m^2, respectively, and the sensitivity and specificity for NPDR were 70.0% and 71.7%, respectively, at a Cr level of 2.25 mg/dL and 70.0% and 73.6%, respectively, at an eGFR of 27.41 mL/min/1.73 m^2. In the ROC curve analysis of renal function for PDR, the AUC was 0.771 for Cr level and 0.769 for eGFR, and the cutoff values were 2.65 mg/dL and 21.27 mL/min/1.73 m^2 for Cr and eGFR, respectively. The sensitivity and specificity for predicting PDR were 79.1% and

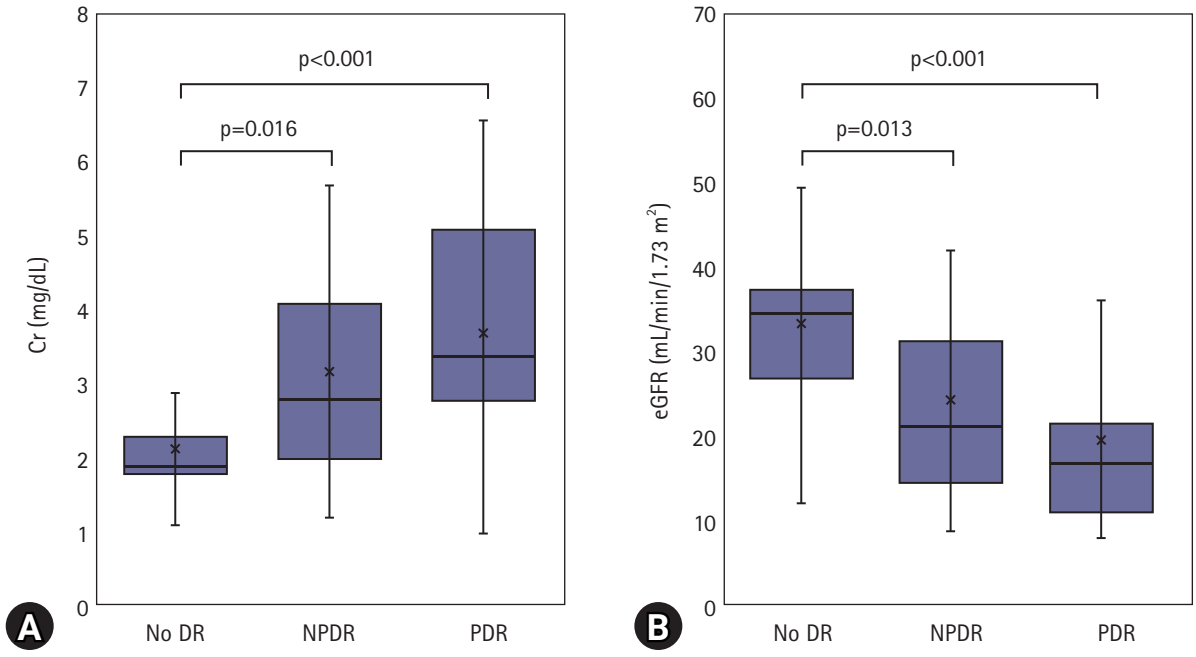

Fig. 2. Comparison of renal function according to the degree of DR in older patients with type 2 diabetes mellitus. As the degree of DR progresses, the mean Cr level increases and the mean eGFR tends to decrease. However, in the *post-hoc* analysis, there is a significant difference only between the no DR and NPDR groups and between the no DR and PDR groups. Meanwhile, in the Spearman correlation analysis, Cr level and eGFR show positive and negative correlations with the degree of DR, respectively. (A) Comparison of Cr according to the degree of DR. (B) Comparison of eGFR according to the degree of DR. Cr, creatinine; eGFR, estimated glomerular filtration rate; DR, diabetic retinopathy; NPDR, nonproliferative DR; PDR, proliferative DR.

26.0%, respectively, at a Cr level of 2.65 mg/dL and 72.1% and 75.3%, respectively, at an eGFR of 21.27 mL/min/1.73 m^2 (Fig. 3).

4. Comparison of the distribution of chronic kidney disease stages and proportion of advanced chronic kidney disease cases

Regarding the distribution of CKD stages ≥ 3 in the no DR group, 64.2%, 30.2%, and 5.7% of patients were categorized as stages 3, 4, and 5, respectively, with the proportions being statistically significantly different between CKD stages 3 and 5. The distribution of CKD stages in the PDR group was as follows: CKD stage 3, 14.0%; CKD stage 4, 44.2%; and CKD stage 5, 41.8%. A statistically significant difference was detected between CKD stages 3 and 5 in the PDR group, as observed in the no DR group. When the trend in the proportion of advanced CKD was analyzed according to DR severity via linear-by-linear association, the proportion of advanced CKD was found to significantly increase with the severity of DR (p for trend < 0.001) (Fig. 4).

5. Association between diabetic retinopathy degree and proportion of advanced chronic kidney disease

In the univariate binary logistic regression analysis, the proportion of patients with CKD stage ≥ 3 having advanced CKD was approximately 4.2 times higher in the NPDR group and approximately 11.0 times higher in the PDR group than in the no DR group, and both differences were statistically significant. Moreover, in the same analysis, the odds ratio for the advanced CKD proportion was approximately 4.4 for macroalbuminuria, 5.5 for DM duration of ≥ 10 years, 3.0 for HTN, 5.5 for MI, and 2.3 for CHF. These results were found to be statistically significant. These results of the univariate binary logistic regression analysis of the proportion of patients with advanced CKD are summarized in Table 2.

Even in the multivariate binary logistic regression analysis, the odds ratio for advanced CKD proportion was higher than that in the no DR group as the degree of DR progressed, even after adjusting for various factors. Multivariate regression model 1 was adjusted for the following factors: very old age, male sex, poorly controlled DM, macroalbuminuria, insulin use, DM duration of ≥ 10 years, past CVA, HTN, hyperlipidemia, and history of CVD. The odds ratio compared with the no PDR group was approximately 4.6 for the NPDR group and approximately 11.8 for the PDR group, and both differences were statistically significant. Next, multivariate regression model 2 was adjusted for the following factors: old age, male sex, poorly controlled DM, macroproteinuria, insulin use, DM duration of ≥ 10 years, past CVA, HTN, hyperlipidemia, MI, CHF, arrhythmia, and history of VHD. The odds ratio com-

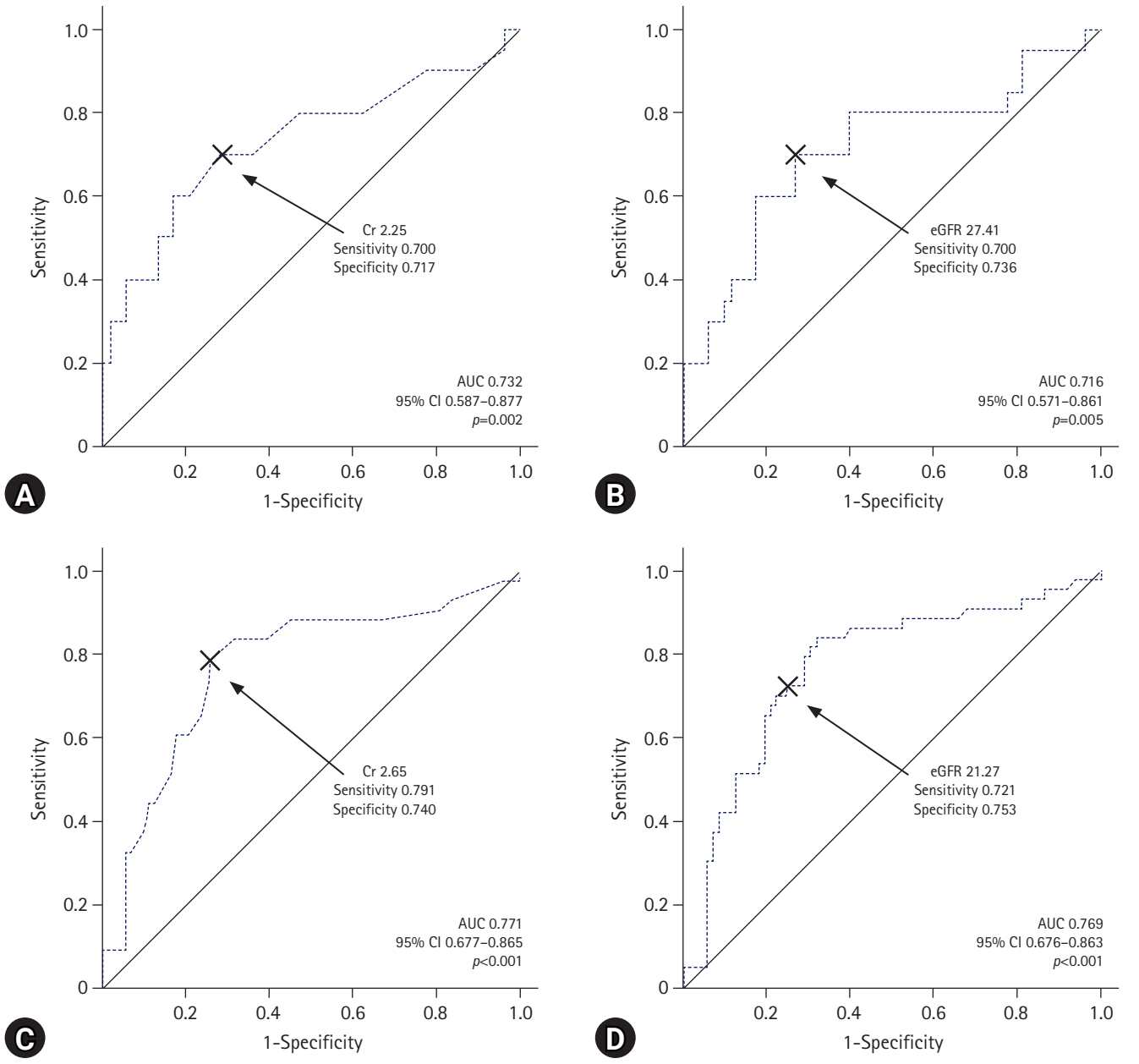

Fig. 3. ROC curves of renal function for NPDR and PDR in older patients with type 2 diabetes mellitus (DM). The degree of renal function deterioration in older patients with type 2 DM may be helpful in predicting the presence of NPDR or PDR. (A) ROC curve of Cr level for NPDR. (B) ROC curve of eGFR for NPDR. (C) ROC curve of Cr level for PDR. (D) ROC curve of eGFR for PDR. AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic; Cr, creatinine; eGFR, estimated glomerular filtration rate; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

pared with the no PDR group was approximately 9.4 for the NPDR group and approximately 25.7 for the PDR group, and both differences were statistically significant. Finally, multivariate regression model 3 was adjusted for the following factors: old age, male sex, poorly controlled DM, macroproteinuria, insulin use, DM duration of ≥ 10 years, past CVA, HTN, hyperlipidemia, ACS, CHF, arrhythmia, and history of VHD. The odds ratio compared with the no PDR group was approximately 5.5 for the NPDR group and approximately 20.2 for the PDR group, and both differences were statistically significant. The results of the multivariate binary logistic regression analysis of the proportion of patients with advanced CKD are summarized in Table 3.

Discussion

Previous studies have documented that the natural course of dia-

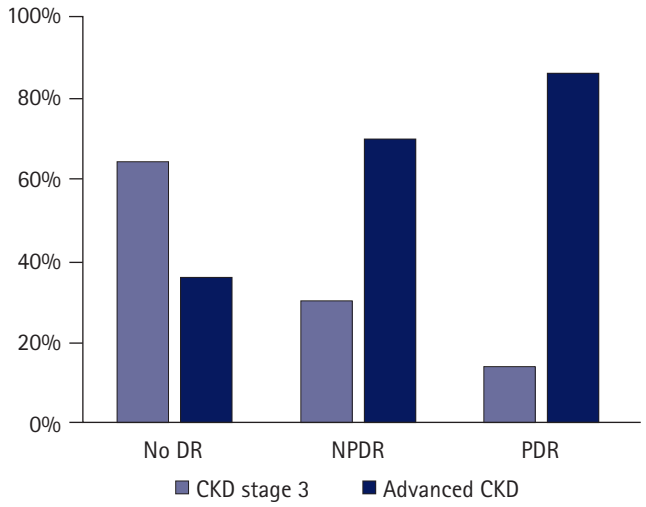

Fig. 4. Comparison of advanced CKD proportion according to the degree of DR among older patients with type 2 diabetes mellitus (DM) and CKD stage ≥3. The proportion of advanced CKD cases among older patients with type 2 DM and CKD stage >3 increases significantly with the severity of DR. DR, diabetic retinopathy; NPDR, nonproliferative DR; PDR, proliferative DR; CKD, chronic kidney disease.

Table 2. Univariate binary logistic regression analysis of advanced chronic kidney disease

Variable	Univariate regression model	
	OR (95% CI)	*p*-value
No DR	Reference	
NPDR	4.175 (1.377–12.657)	0.012
PDR	11.035 (3.943–30.885)	<0.001
Very old age[a]	2.308 (0.809–6.347)	0.105
Male sex	0.591 (0.278–1.256)	0.172
HbA1c ≥8%	1.500 (0.671–3.353)	0.323
Macroalbuminuria[b]	4.430 (1.987–9.878)	<0.001
Insulin use	1.740 (0.802–3.779)	0.161
DM duration ≥10 yr	5.454 (2.127–13.984)	<0.001
Hypertension	2.965 (1.158–7.594)	0.023
Hyperlipidemia	0.721 (0.316–1.647)	0.438
Past CVA	1.295 (0.500–3.358)	0.594
CVD	1.421 (0.671–3.011)	0.359
MI	5.500 (1.187–25.484)	0.029
ACS	2.667 (0.978–7.268)	0.055
CHF	2.252 (1.002–5.061)	0.049
Arrhythmia	1.357 (0.435–4.293)	0.593
VHD	1.103 (0.250–4.855)	0.897
CABG history	1.692 (0.314–9.115)	0.540

OR, odds ratio; CI, confidence interval; DR, diabetic retinopathy; NPDR, nonproliferative DR; PDR, proliferative DR; DM, diabetes mellitus; CVA, cerebrovascular accident; CVD, cardiovascular disease; MI, myocardial infarction; ACS, acute coronary syndrome; CHF, congestive heart failure; VHD, valvular heart disease; CABG, coronary artery bypass graft surgery.
[a] ≥80 years. [b] Macroalbuminuria is defined as a random urine albumin-creatinine ratio of ≥300 mg/g Cr.

betic nephropathy in most cases of type 1 DM is consistent and typical [16-20]. In type 1 DM that is not appropriately treated, microalbuminuria commonly appears 10 to 15 years after disease onset and overt proteinuria appears 20 years after disease onset, resulting in a decrease in glomerular filtration rate [16]. Furthermore, the natural course of DR in type 1 DM occurs in approximately half of patients 7 years after disease onset. It has also been reported that DR precedes diabetic nephropathy in most cases [21,22].

In contrast, in type 2 DM, the natural course of diabetic nephropathy is atypical and inconsistent; therefore, it is common to have a varied range of proteinuria at the time of diagnosis [17,23]. Moreover, it is controversial whether DR precedes diabetic nephropathy in type 2 DM, and in some reports, diabetic nephropathy was confirmed by renal biopsy, even in the absence of DR [24,25]. In previous large cohort studies, the overall prevalence of diabetic nephropathy in patients with type 2 DM was reported to be approximately 17% to 58% [26,27]. In particular, a multinational multicenter cohort study indicated that the prevalence of diabetic nephropathy in patients with type 2 DM tended to be higher in Asia than in Europe, and in Korea, it was 58%, the highest prevalence in Asia [27]. Furthermore, it is important to consider the significantly higher prevalence of type 2 DM than type 1 DM [5,28]. The Diabetes Prevalence Trend Report indicated that the global prevalence of DM is expected to increase from 8.4% in 2017 to 9.9% in 2045, with the prevalence of DM in older individuals reaching almost 20% as of 2017 [29]. Therefore, we focused on the correlations between various microvascular complications in older patients with type 2 DM.

In addition, studies have established that DR and diabetic nephropathy can act as risk factors for each other in patients with type 1 DM [3,18,30]. Relatively few studies have investigated the relationship between DR and diabetic nephropathy in type 2 DM, but there have been reports that the mutual effect of DR and diabetic nephropathy is small compared with that in type 1 DM [3,31,32]. El-Asrar et al. [32] reported that the risk of diabetic nephropathy was higher in patients with type 2 DM according to the severity of DR, but lower than the increased risk in patients with type 1 DM. Parving et al. [31] also reported that the rate of DR was higher in patients with overt proteinuria than in patients without proteinuria. In our study, the degree of DR was associated with deterioration of renal function in older patients with type 2 DM and CKD stage ≥3. Moreover, the proportion of patients with advanced CKD was significantly higher when the degree of DR was higher. These results are consistent with those of previous studies. Nevertheless, previous studies did not target older individuals exclusively or they set the exclusion criterion for age to ≥66 years;

Table 3. Multivariate binary logistic regression analysis of advanced chronic kidney disease

Variable	Multivariate regression model 1		Multivariate regression model 2		Multivariate regression model 3	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
No DR	Reference		Reference		Reference	
NPDR	4.643 (1.211–17.792)	0.025	9.375 (1.514–58.048)	0.016	5.461 (1.313–22.718)	0.020
PDR	11.479 (3.294–40.001)	<0.001	25.668 (5.339–123.414)	<0.001	20.228 (5.332–76.737)	<0.001

Multivariate regression model 1 is adjusted for the degree of DR, very old age, male sex, poorly controlled DM, macroalbuminuria, insulin use, DM duration of ≥ 10 years, history of CVA, HTN, hyperlipidemia, and history of CVD. Multivariate regression model 2 is adjusted for the degree of DR, very old age, male sex, poorly controlled DM, macroalbuminuria, insulin use, DM duration of ≥ 10 years, history of CVA, HTN, hyperlipidemia, MI, CHF, arrhythmia, and history of VHD. Multivariate regression model 3 is adjusted for the degree of DR, very old age, male sex, poorly controlled DM, macroalbuminuria, insulin use, DM duration of ≥ 10 years, history of CVA, HTN, hyperlipidemia, ACS, CHF, arrhythmia, and history of VHD.
Poorly controlled DM is defined as an HbA1c level of ≥ 8.0%. Macroalbuminuria is defined as a random urine albumin-creatinine ratio of ≥ 300 mg/g Cr.
OR, odds ratio; CI, confidence interval; DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; DM, diabetes mellitus; HTN, hypertension; CVA, cerebrovascular accident; CVD, cardiovascular disease; MI, myocardial infarction; CHF, congestive heart failure; VHD, valvular heart disease; ACS, acute coronary syndrome; HbA1c, glycated hemoglobin.

therefore, these studies cannot explain the relationship between DR and diabetic nephropathy in older patients with type 2 DM. Our study was different from these previous studies, as we targeted older patients with type 2 DM aged ≥ 60 years.

Meanwhile, by analyzing 1,583 patients with CKD in the Chronic Renal Insufficiency Cohort (CRIC) Study, Grunwald et al. [9] reported that exacerbation of retinopathy was related to the severity of CKD. However, in their study, the mean age was 60 years, and there were 680 patients with DM (43.0%). Moreover, when only the patients with DM were analyzed, the exacerbation of retinopathy did not significantly affect CKD severity [9]. Although these results are inconsistent with our results, it may be essential to consider the age difference of subjects between the two studies and that their study included patients without DM. Hence, there is a need for larger, well-designed studies investigating the relationship between DR and CKD in older patients with type 2 DM in the future.

Finally, in the univariate regression analysis, we found that the degree of DR in older patients with type 2 DM was associated with a high proportion of advanced CKD cases. Interestingly, these effects were consistent even after adjusting for various factors such as very old age, sex, poorly controlled DM, macroalbuminuria, insulin use, DM duration of ≥ 10 years, and various underlying diseases such as past CVA, HTN, hyperlipidemia, and CVD. These are widely reported risk factors for diabetic nephropathy in several previous studies [1,2,33]. Our results suggest that DR is associated with a higher rate of advanced CKD as well as well-known risk factors in older patients with type 2 DM. It has been reported that the relationship between DR and diabetic nephropathy in patients with insulin-treated type 2 DM was similar to that in patients with type 1 DM [34,35]. Among our study participants, the rate of insulin use was 40.5%, and a higher insulin-use rate in patients with DR or advanced CKD might have affected the results of this study.

Recently, retinal vessels have been identified noninvasively in the ophthalmic field using optical coherence tomography angiography (OCTA). Studies have confirmed the relationship between retinal microvascular changes in DR and diabetic nephropathy. Cankurtaran et al. [36] reported that vessel densities in the superficial capillary plexus, whole disc, and peripapillary area were significantly different depending on the presence of diabetic albuminuria, even in the absence of DR. In other studies, patients with either type 1 or type 2 DM showed a decrease in the quantitative parameters identified by OCTA in diabetic nephropathy [37,38]. Although our study did not evaluate OCTA quantitative parameters and simply confirmed the relationship between DR severity and diabetic nephropathy, meaningful results can be expected if such OCTA parameters are used in the analysis in future studies.

This study has several limitations. First, a selection bias may have occurred. Since the participants were patients who presented at both the nephrology and ophthalmology departments at a tertiary medical institution, the basic characteristics of older patients with type 2 DM in the real world may be different, and there may be differences in treatment adherence. Second, owing to the retrospective cross-sectional study design, changes over time were not reflected. In particular, the rate of severity of DR or CKD can vary among people; therefore, even if they are classified in the same category cross-sectionally, their prognosis may vary over time. Therefore, retrospective or prospective longitudinal observational studies are required to evaluate follow-up changes. Third, this was a small-scale, single-institution study, and the results must be interpreted carefully considering the basic characteristics of the study.

In conclusion, the severity of DR in older patients with type 2 DM may be associated with deterioration of renal function and a higher proportion of advanced CKD. However, this study was small, and it is difficult to clearly elucidate the relationship between DR and CKD in older patients with DM. Therefore, larger,

well-designed, longitudinal studies are needed in the future. Nevertheless, ophthalmology and renal function follow-up tests may be underestimated due to reduced mobility or lack of independence in older individuals; therefore, attention may be required to address this potential shortcoming.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Pediatricians' perception of factors concerning the clinical application of blockchain technology to pediatric health care: a questionnaire survey

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Background: Interest in digital medical information has increased because it allows doctors to easily access a patient's medical records and provide appropriate medical care. Blockchain technology ensures data safety, reliability, integrity, and transparency by distributing medical data to all users over a peer-to-peer network. This study attempted to assess pediatricians' thoughts and attitudes toward introducing blockchain technology into the medical field.

Methods: This study used a questionnaire survey to examine the thoughts and attitudes of 30- to 60-year-old pediatricians regarding the introduction of blockchain technology into the medical field. Responses to each item were recorded on a scale ranging from 1 (never agree) to 7 (completely agree).

Results: The scores for the intentions and expectations of using blockchain technology were 4.0 to 4.6. Pediatricians from tertiary hospitals responded more positively (4.5–4.9) to the idea of using blockchain technology for hospital work relative to the general population (4.3–4.7). However, pediatricians working in primary and secondary hospitals had a slightly negative view of the application of blockchain technology to hospital work ($p=0.018$).

Conclusion: When introducing the medical records of related pediatric and adolescent patients using blockchain technology in the future, it would be better to conduct a pilot project that prioritizes pediatricians in tertiary hospitals. The cost, policy, and market participants' perceptions are essential factors to consider when introducing technology in the medical field.

Keywords: Blockchain; Pediatricians; Pediatrics; Personal health records; Tertiary care centers

Introduction

Medical technology has facilitated remarkable advances in various fields. With the development of healthcare technology, the quality of life and longevity of humans have improved. Interest in the exchange of medical information has also increased [1].

Currently, the medical records of patients are fragmented and stored in different hospitals. Fragmented medical records lead to several problems [2,3]. First, it is difficult for a doctor to check the medical records. Second, because not all medical records are acces-

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sible by every doctor, tests performed at another hospital may be duplicated. Third, although medical records can be digitally stored, patients or guardians copy and transport medical records to other hospitals using paper or compact disks (CDs). Fourth, the medical records stored in the hospital may be hacked or lost due to the hospital's closure. Thus, there may be unnecessary damage and a waste of time and human resources.

Blockchain technology ensures data safety, reliability, integrity, and transparency by distributing and documenting data over a peer-to-peer network [4]. This technology is different from traditional methods that store transactions on a central server [5].

Different perspectives on the application of blockchain technology in the healthcare industry are presented in this paper. Currently, the proposed clinical application will help facilitate the exchange of medical records and will be applied to the Internet of Things (IoT) system to manage patients with chronic diseases such as diabetes [6-10].

Pediatrics is also a field with many subfields that can benefit from blockchain technology. This study aims to assess pediatricians' thoughts and attitudes toward introducing blockchain technology into the medical field.

Methods

Ethical statements: This study was conducted according to the guidelines of the Declaration of Helsinki of 1975 and approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: YUMC 2019-04-041). At the time of receiving the questionnaire from the study participants, consent was obtained verbally, and a process was approved by the IRB.

1. Survey

Based on widely used theories concerning new technology acceptance, we investigated various factors related to using new technologies, such as blockchain, in our survey. In more detail, our study's factors, such as expected performance and ease of use, theoretically stem from the technology acceptance model [11]. Intention, attitude, and perceived behavioral control of using blockchain for hospital work originate from the theory of planned behavior [12].

We conducted a questionnaire survey among pediatricians aged between 30 and 60 years. A paper questionnaire and Google questionnaire were used. Before the participants responded to the questionnaires (Supplementary material 1), they watched a video about blockchain medical applications. The authors do not have any associations or relationships with the company that produced the video [13].

The items that were used to measure intentions, attitudes toward using blockchain for hospital work, expected performance, ease of use, and perceived behavioral control were adopted from validated measures that were used in Venkatesh et al. [14]. Responses to each item were recorded on a scale that ranged from 1 (never agree) to 7 (completely agree). Higher scores were indicative of a higher degree of consent, whereas lower scores were indicative of a lower degree of consent.

The attitudes toward using blockchain technology to manage medical information were adapted from Venkatesh et al. [14] and Min and Kim [15]. Replies to these items were gauged on a 7-point scale, ranging from 1 (very negative) to 7 (very positive). Higher scores denoted more positivity, and lower scores indicated more negativity.

Based on Choi [16] and Kim et al. [17], the types of services that could be implemented through blockchain concerning hospital business were classified.

2. Statistical analysis

The collected data were analyzed using IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA). The demographic characteristics and attitudes of the medical doctors, stratified by their characteristics, were compared using the Mann-Whitney *U*-test. Statistical significance was denoted by $p < 0.05$.

Results

1. Study population

A total of 23 pediatricians were enrolled in this study (Table 1). Most of them were in their 30s (n = 16, 69.6%), five were in their 40s (21.7%), and two were in their 50s (8.7%). There were 10 men (43.5%) and 13 women (56.5%). The average career duration of the participants was 12 ± 9 years (Table 1). Regarding the hospital type, two were primary hospitals (8.7%), five were secondary hospitals (21.7%), and one was tertiary hospital (65.2%). Regarding job titles, eight of the pediatricians were employed (34.8%), six were residents (26.1%), eight were university professors (34.8%), and one was allocated to the "other" category (4.3%).

2. Thoughts about the use and adoption of blockchain

The participants' perspectives on the use and adoption of blockchain are shown in Table 2 and Fig. 1. The average score for the participants' intentions to use blockchain technology was 4.0 to 4.6. Those working at tertiary hospitals provided slightly more

Table 1. Characteristics of the study population

Variable	Data
No. of participants	23
Age (yr)	
31–40	16 (69.6)
41–50	5 (21.7)
51–60	2 (8.7)
Sex	
Male	10 (43.5)
Female	13 (56.5)
Career year (yr)	12 ± 9
Hospital type	
Primary	2 (8.7)
Secondary	5 (21.7)
Tertiary	15 (65.2)
Others[a]	1 (4.3)
Type of worker	
Employed	8 (34.8)
University professor	8 (34.8)
Resident	6 (26.1)
Others[a]	1 (4.3)

Values are presented as number only or number (%).
[a]One is serving as a doctor in the military.

positive answers about their attitudes toward blockchain technology.

Regarding the attitudes toward and perspectives on blockchain technology, the participants expressed only a few positive opinions about the use of blockchain for hospital work (4.3–4.7). Those working at tertiary hospitals provided slightly more positive answers related to the attitudes toward blockchain technology. However, those working in primary and secondary hospitals had slightly negative perspectives on applying blockchain technology to hospital work ($p = 0.018$).

The expectations of the effectiveness of blockchain technology were generally neutral. The participants in tertiary hospitals had positive expectations. Those in tertiary hospitals believed that it would improve productivity, processing speed, quality, and convenience. Participants from primary and secondary hospitals expressed neutral opinions, but these were not statistically significant.

The participants expressed neutral opinions about the ease of using blockchain technology. Participants working in primary and secondary hospitals expressed slightly more negative views regarding the ease of use and learning curve of the technology.

All participants expressed relatively negative opinions of their environment when using blockchain technology. Participants from primary and secondary hospitals expressed more negative views than those from tertiary hospitals. They thought that the information technology resources necessary to use blockchain technology were insufficient and believed they lacked knowledge of blockchain technology. They also considered blockchain incompatible with the hospital work support system they were using.

3. Attitudes toward using blockchain technology to manage medical information

Regarding the benefits of blockchain technology, the most preferred was exchanging medical information between hospitals (Table 3, Fig. 2).

With blockchain technology, when a patient visits another hospital, there is no need to print out the chart from the prior hospital or transfer image information to a CD and deliver it to the new hospital, thereby facilitating the exchange of medical information between the hospitals. Blockchain technology can reduce repetitive tests, thus reducing patient treatment costs and shortening treatment time. Blockchain technology makes it possible to use standardized medical big data for precision medical care and customized medical care.

In addition, the participants found that blockchain technology reduced repetitive examinations, medical expenses, and treatment hours, and it facilitated the use of standardized medical big data. However, the participants expressed neutral opinions about the inability to modify medical records without patient consent, patients managing medical information by themselves, the transmission of all patient medical information to medical staff, and patient access to medical records at any time.

4. Necessity and feasibility of blockchain technology related to hospital business

All participants expressed positive opinions about the need for services that could be implemented through blockchain. Regarding the feasibility of the services that could be implemented through blockchain, positive views were expressed for all services other than patient-centered medical data management services, about which the participants expressed a neutral opinion (Table 4). There were no differences according to the hospital type.

Discussion

This study aimed to clarify the opinions and attitudes of pediatricians related to the adoption of blockchain technology in the medical field. The study findings revealed that pediatricians expressed only a few positive opinions about blockchain, and pediatricians working in tertiary medical institutions were found to have more positive attitudes toward this technology. Pediatricians working in primary and secondary hospitals expressed neutral opinions about

Table 2. Perspectives on the application of blockchain technology in the medical field

Domain	Question	Score by hospital type			*p*-value
		Total	Tertiary hospital	Others	
Intention to use blockchain technology					
	I intend to use blockchain technology for my hospital work	4.6±1.7	4.9±1.4	4.4±1.9	0.283
	I plan to use blockchain technology for my hospital work	4.0±1.8	4.5±1.5	3.8±1.9	0.062
	I expect to use blockchain technology for my hospital work	4.2±1.8	4.8±1.4	3.8±1.8	0.005
	I will try to use blockchain technology in my hospital work	4.2±1.7	4.7±1.5	3.9±1.9	0.036
Attitudes toward blockchain technology					
	It is desirable for me to use blockchain technology to handle hospital work	4.6±1.7	5.0±1.3	4.4±1.8	0.104
	It's a good idea for me to use blockchain technology to do hospital work	4.7±1.7	5.0±1.4	4.5±1.8	0.154
	It is wise for me to use blockchain technology to do hospital work	4.7±1.7	5.0±1.3	4.5±1.8	0.099
	I like to use blockchain technology to do hospital work	4.3±1.7	4.7±1.5	3.9±1.8	0.018
Expected performance from using blockchain					
	The use of blockchain technology will increase the productivity of my hospital business processing	4.8±1.6	5.0±1.2	4.6±1.8	0.328
	The use of blockchain technology will speed up my hospital business processing	4.8±1.6	5.0±1.4	4.6±1.7	0.352
	The use of blockchain technology will improve the quality of my hospital business results	4.8±1.7	5.0±1.4	4.6±1.9	0.054
	Through the use of blockchain technology, my hospital work will be handled more easily	4.7±1.8	5.0±1.5	4.5±1.9	0.166
Ease of use of blockchain technology					
	It will be easy for me to use blockchain technology to handle the hospital work I am currently doing	4.0±1.7	4.3±1.7	3.8±1.7	0.120
	It will be easy for me to learn how to use blockchain technology to handle my hospital business	4.0±1.7	4.2±1.7	4.0±1.7	0.511
	It will be easy for me to use blockchain technology to handle the hospital work I intend to do in the future	4.1±1.7	4.3±1.6	3.9±1.7	0.323
Perceived behavioral control of using blockchain technology					
	I have the information technology (IT) resources (ex: IT devices, experts) needed to use blockchain technology	2.6±1.7	2.9±1.8	2.4±1.7	0.080
	I have the necessary knowledge to use blockchain technology	2.6±1.6	2.7±1.7	2.5±1.6	0.798
	Blockchain technology is well compatible with the hospital work support information system that I am using	2.6±1.7	3.0±1.8	2.3±1.6	0.009

blockchain technology and somewhat negative opinions about its introduction into hospitals.

In our previous study, medical doctors demonstrated significantly more negative attitudes toward blockchain technology than did patients [2]. Furthermore, self-employed doctors demonstrated more negative attitudes than employed doctors and university professors [2]. We attempted to understand these findings using the expectancy theory of psychological motivation [18,19], which suggests that people are motivated to pursue positive outcomes and avoid adverse effects.

Blockchain technology has various applications in pediatrics. Even simple invasive procedures such as obtaining blood samples are often difficult to perform in infants. Using blockchain technology to deliver medical information can lower medical expenses and lessen the inconvenience for children by eliminating redundant examinations.

Children may have to move frequently, sometimes against their will, depending on the circumstances of their parents. Therefore, it is highly possible that finding past records will be difficult. Although a system where the government manages vaccination records has been introduced in Korea, medical records other than vaccination records should be checked by relying on the memory of the guardian.

With blockchain technology, patients do not need to maintain their medical records. Instead of waiting to receive medical information from the guardian of a child, the hospital staff can access the medical history because the technology allows the transmission of the appropriate medical information. Additionally, there is no risk of record loss or distortion. It is essential to share the medical records of patients across different hospitals following their wishes; this is also important for the security of personal data.

In a study of medical record keeping in a summer camp setting

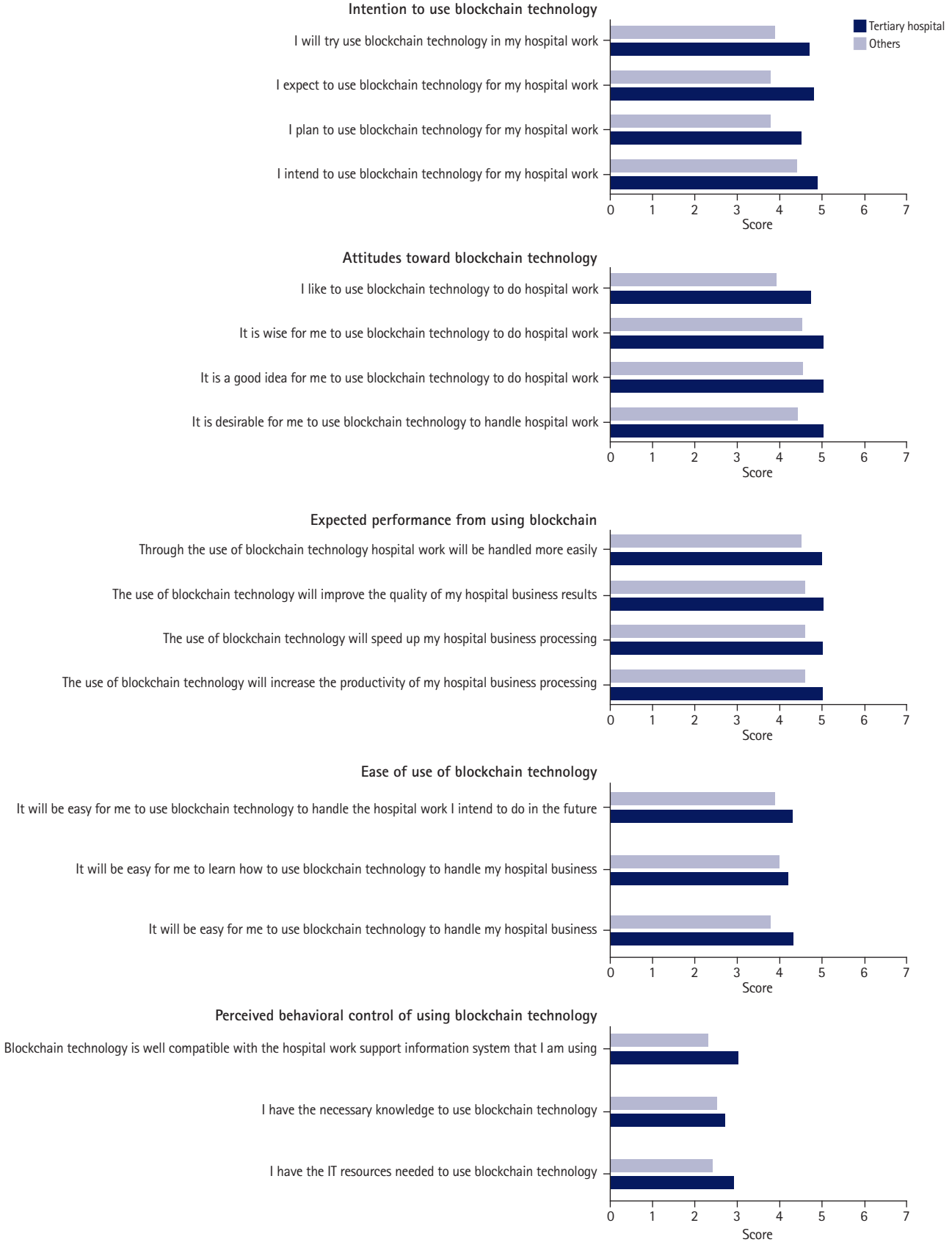

Fig. 1. Perspectives on the application of blockchain technology in the medical field according to hospital type. IT, information technology.

Table 3. Attitudes toward using blockchain technology to manage medical information

Characteristics of blockchain technology	Score by hospital type			*p*-value
	Total	Tertiary hospital	Others	
Through blockchain technology, all the medical information of a patient can be delivered to the medical staff	4.7±1.8	5.0±1.5	4.5±2.0	0.315
Since hacking is impossible using blockchain technology, the security of the patient's medical information can be strengthened	4.6±1.8	4.8±1.7	4.5±1.9	0.561
Once entered by the doctor, the medical chart cannot be modified without the consent of the patient if blockchain technology is used	4.1±1.9	4.2±1.8	4.0±2.1	0.736
Blockchain technology allows patients to freely access their medical information anytime, anywhere	4.6±1.8	4.9±1.6	4.4±1.9	0.173
With blockchain technology, when a patient goes to another hospital, there is no need to print the chart of an existing hospital on paper or put image information on a compact disc and deliver it to other hospitals, thereby facilitating exchange of medical information between hospitals	5.2±1.8	5.5±1.3	5.0±2.0	0.418
Blockchain technology can reduce repetitive tests, thus reducing patient treatment costs and shortening treatment time	5.1±1.8	5.4±1.5	4.8±2.0	0.179
Blockchain technology makes it possible to use standardized medical big data for precision medical care and customized medical care	5.0±1.9	5.3±1.6	4.7±2.1	0.238

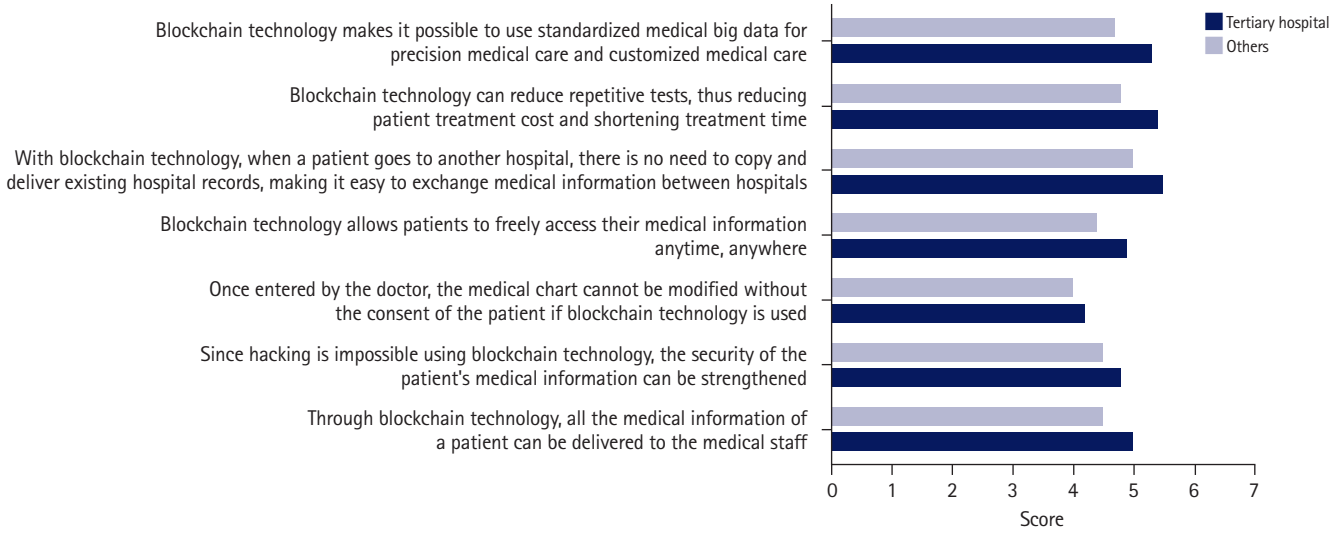

Fig. 2. Attitudes toward using blockchain technology to manage medical information according to hospital type.

Table 4. Necessity and feasibility of services related to hospital business that can be implemented through blockchain technology

Domain	Necessity	Feasibility
Patient-centered medical data management service	4.7±1.6	4.6±1.7
Personal lifelog data integrated management service	4.5±1.7	4.6±1.6
Simplified insurance payment service	4.7±1.8	4.7±1.7
Pharmaceutical safety distribution service	4.8±1.6	4.7±1.6
Integrated medical data management service	5.0±1.7	4.7±1.7
Clinical trial data sharing service	4.9±1.7	4.7±1.7
Genome analysis data safe transaction service	4.6±1.7	4.6±1.7
Integrated management of medical device licensing	4.7±1.8	4.7±1.8
Clinical research data sharing service between countries	4.8±1.6	4.5±1.7

by Kaufman et al. [20], approximately one-fifth of school-aged children were found to spend their time at residential summer camps in the United States. Many of these children had chronic medical conditions. In such a situation, the delivery of medical information for the special pediatric settings of a healthcare provider is said to be necessary. The study noted that standard software for documenting summer camp healthcare practice was needed, along with network and technical support. The delivery of medical records using blockchain technology with the approval of an authorized guardian may be helpful in this field.

The Korea Disease Control and Prevention Agency manages Korea's national immunization program, and vaccinations can be checked online [21,22]. Since a child's vaccination record is maintained from birth, this information is a good starting point for ap-

plying blockchain technology in the medical field. The immunization registration management information system may contain various errors that occurred during data entry. Owing to the nature of blockchain technology, access and modification are possible only with the individual patient's consent, and a potential solution needs to be formulated.

The study findings revealed that pediatricians in tertiary hospitals expressed more positive views about blockchain technology than those in primary and secondary hospitals. A previous study reported similar results for doctors who were not pediatricians [2], which was not related to their direct compensation; there is relatively limited information about individual income levels. The availability of information technology support in tertiary hospitals also could have led to more positive answers.

In the future, the integration of blockchain technology with the medical record systems of pediatric and adolescent patients may be preceded by a pilot project that prioritizes pediatricians in tertiary hospitals. Blockchain technology has various applications in pediatric healthcare management. First, it can be used to deliver medical information securely, transparently, and cost-effectively. For example, it can be used for a national vaccination schedule registry. Blockchain technology can also facilitate a national interoperability framework, eliminate the need to manage different immunization records for each hospital, and lower the overall cost of vaccinations in the country. Second, blockchain technology can be helpful in conducting clinical trials involving children with rare hereditary diseases. Third, blockchain can be used for data sharing without compromising or leaking personal information in big data collected by a monitoring device—a wearable device that continuously monitors medical parameters using the IoT network.

After the coronavirus disease 2019 (COVID-19) outbreak, telemedicine use has increased dramatically in the United States [23]. Telemedicine sessions increased by 683% between March and April 2020. In response to COVID-19, the virtual urgent care system has expanded. Considering the increasing attention given to "untact" technology after COVID-19, the use of blockchain technology for medical record management has garnered interest.

In addition, blockchain technology plays a role as a means of delivering medical information, but digitalization of medical care, telemedicine, and smooth information delivery cannot be fully realized with only blockchain. To use medical blockchain technology, preliminary work such as standardization of medical databases will be required. The standardization of different medical databases for each hospital will facilitate the activation of information sharing between hospitals, which will require policy support from the government.

The limitations of this study are that the survey population was small, and patient and guardian surveys were not obtained. It seems that additional large-scale surveys are needed in this area.

It appears that there is adequate scope for the application of blockchain technology to pediatric healthcare management. With the introduction of blockchain technology to the medical industry, the technology, cost, policies, and the perception of market participants are important. We hope that the reported perceptions of pediatricians, who are important market participants in the introduction of blockchain to the medical industry, will help stimulate active discussions on the introduction of blockchain technology to the field of pediatrics in the future.

Supplementary materials

Supplementary material 1 can be found via https://doi.org/10.12701/jyms.2022.00241.

Notes

Conflicts of interest

Min Cheol Chang has been Associate editor of *Journal of Yeungnam Medical Science* (*JYMS*) since 2021. Jae Min Lee has been editorial board member of *JYMS* since 2021. They were not involved in the review process of this manuscript. Otherwise, there is no conflict of interest to declare.

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Author contributions

Conceptualization, Methodology, Data curation, Formal analysis, Project administration: YSH, JCP, MCC, JML; Investigation, Funding acquisition: JML; Supervision: all authors; Writing-original draft: JML; Writing-review & editing: all authors.

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Effect of prehydration solution on hearing threshold after chemotherapy in patients with head and neck cancers: a retrospective study

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Background: The study aimed to evaluate the effect of prehydration solution on hearing thresholds after cisplatin chemotherapy.
Methods: In this retrospective cohort study, we reviewed the data of patients who underwent ≥3 courses of cisplatin-based chemotherapy for locally advanced head and neck cancers at a tertiary referral center (n=64). The dextrose solution (DW) group (n=26) received 2 L of normal saline and 1 L of 5% dextrose. The Hartmann solution (HS) group (n=38) received 2 L of normal saline and 1 L of HS. Hearing data were measured 1 day before starting the first course of chemotherapy, and again 20 days after the first, second, and third courses of chemotherapy. The severity of hearing loss was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE).
Results: Thresholds at all frequencies after chemotherapy were greater in the DW group than in the HS group. The increase in thresholds in 1 to 4 kHz after the third course of chemotherapy was greater in the DW group than in the HS group. CTCAE grades after the second and third courses of chemotherapy were greater in the DW group than in the HS group. Logistic regression showed that the odds ratio for CTCAE grade 3 or 4 after the third course of chemotherapy in the DW group was 4.84 on univariate analysis.
Conclusion: Prehydration using a solution with salt was associated with a decrease in change in hearing thresholds after cisplatin chemotherapy in patients with head and neck cancers.

Keywords: Cisplatin; Drug therapy; Hearing; Solutions

Introduction

Cisplatin is a classic chemotherapeutic drug discovered by Rosenberg et al. [1] in 1965. It is currently one of the most commonly used chemotherapeutic drugs in locally advanced head and neck cancers. Nephrotoxicity and ototoxicity are considered the most important complications associated with cisplatin use as a chemotherapeutic drug; cisplatin induces or leads to oxidative stress, inflammation, and outer and inner hair cell apoptosis [2-4]. Consequently, cisplatin is associated with progressive and irreversible sensorineural hearing loss. Breglio et al. [4] showed that approximately 40% to 80% of patients who underwent cisplatin chemotherapy experienced permanent hearing loss. Previous studies have investigated the protective effects of several agents on cisplatin-in-

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duced ototoxicity (CIO). However, despite their promising effects in experimental studies, strong evidence regarding the favorable effects of these agents in clinical studies is scarce [5].

Nephrotoxicity is another complication of cisplatin-induced tubular injury. Clinical practice guidelines strongly recommend vigorous hydration to reduce the cisplatin-induced nephrotoxicity [6]. Hydration is associated with volume expansion, leading to an increase in the rate of cisplatin excretion. In addition, the prehydration solution with salt has a high concentration of chloride and prevents the dissociation of the chloride ions from the platinum molecule, thereby reducing the formation of the reactive species of cisplatin [7,8]. Previous studies have revealed that prehydration plays a role in decreasing cisplatin-induced nephrotoxicity and prehydration solutions with salts are more protective in preventing toxicity. This evidence suggests that prehydration using a salt fluid is strongly recommended to reduce nephrotoxicity. These hypotheses may be applicable to CIO, and prehydration using a salt fluid may be associated with protection of CIO. The aim of our study was to evaluate the effect of prehydration solution on hearing thresholds after cisplatin chemotherapy in patients with head and neck cancers.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Kyungpook National University Hospital (IRB No: KNUH 2020-04-009), and the requirement for informed consent was waived.

1. Study population and treatment

In this retrospective cohort study, we reviewed the data of patients who underwent at least three courses of cisplatin-based chemotherapy for locally advanced head and neck cancers at a medical center between May 2014 and September 2019. Among the initial 162 patients, the exclusion criteria included the following: having chronic otitis media or otitis media effusion, or missing data for hearing thresholds at the baseline or after the first, second, or third course of chemotherapy (n = 98). None of the enrolled participants were undergoing any additional therapy associated with ototoxicity during the follow-up period. In addition, other than cisplatin, none of the chemotherapeutic drugs were associated with ototoxicity.

The dose of cisplatin was modified as described in a previous study [9]. Briefly, cisplatin was injected every 3 weeks at doses of 50 to 100 mg/m^2. The cisplatin dose administered in each cycle was determined based on individual patient conditions (age, comorbidities, Eastern Cooperative Oncology Group performance status, and treatment-related toxicities) and tumor status (stage and early treatment response). All patients received concomitant radiotherapy at a dose of 60 to 70 Gy; the doses of radiotherapy were similar among the patients. Prehydration solution (3 L) was administered immediately before cisplatin injection. The dextrose solution (DW) group (n = 26) received 2 L of normal saline and 1 L of 5% dextrose. The Hartmann solution (HS) group (n = 38) received 2 L of normal saline and 1 L of HS. Selection of prehydration was randomly determined regardless of the clinician's decision.

2. Study variables

Clinical and laboratory data collected during the examination included the following: age, sex, hemoglobin (g/dL), serum albumin (g/dL), serum creatinine (mg/dL), body mass index (kg/m^2), location of cancer, cumulative dose of cisplatin, and hearing thresholds. Hearing data were measured 1 day before starting the first course of chemotherapy, and again at 20 days after the first, second, and third courses of chemotherapy. The hearing thresholds were measured using an automatic audiometer at 0.5, 1, 2, 3, 4, 6, and 8 kHz. Hearing thresholds at each frequency were averaged using both ears of each patient. The difference after chemotherapy was defined as postchemotherapy values minus the baseline. The severity of hearing loss was evaluated using the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0), as previously described [10]. Briefly, grade 1 was defined as a threshold shift of 15 to 25 dB at two frequencies in at least one ear. Grade 2 was defined as a threshold shift > 25 dB at two contiguous frequencies. Grade 3 was defined as a threshold shift > 25 dB at three contiguous frequencies. Grade 4 was defined as non-serviceable hearing, > 80 dB at 2 kHz and above.

3. Statistical analysis

The data were analyzed using IBM SPSS ver. 25 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed as counts (percentage), and continuous variables were expressed as means ± standard deviations (expressed as means ± standard errors for multivariate analysis). Pearson chi-square or Fisher exact test was used to analyzing the categorical variables. For continuous variables, means were compared using a Student *t*-test or a paired *t*-test. Logistic regression analyses were used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs), which were then used to determine the correlation between prehydration solution and high CTCAE grade. Multivariate analyses were adjusted for age, sex, baseline hearing thresholds, and cumulative dose of cisplatin and performed using a forward selection method. The *p*-values

< 0.05 were considered statistically significant.

Results

1. Clinical characteristics

The mean age values in the DW and HS groups were 59.4 ± 8.0 and 59.8 ± 11.6 years, respectively ($p = 0.873$) (Table 1). The proportion of male sex in the DW and HS groups was 96.2% and 81.6%, respectively. There were no significant differences in age, sex, hemoglobin, albumin, creatinine, body mass index, and location of cancer between the two groups. The cumulative dose of cisplatin was similar at the first course of chemotherapy, but the cumulative dose of cisplatin at the second and third courses was higher in the DW group than in the HS group.

2. Changes in hearing thresholds after chemotherapy according to prehydration solution

Fig. 1 shows the trends of hearing thresholds according to chemotherapy. Baseline 0.5 and 3 kHz values were greater in the DW group than in the HS group ($p = 0.027$ for 0.5 kHz and $p = 0.017$ for 3 kHz). There were no significant differences in 1, 2, 4, 6, and 8 kHz at baseline between the two groups. However, thresholds at all frequencies after chemotherapy were greater in the DW group than in the HS group. In the DW group, the thresholds in all frequencies after the third course of chemotherapy were greater than each baseline value. In the HS group, those in 3, 4, 6, and 8 kHz after the third course of chemotherapy were greater than each baseline value, but there were no significant differences in 0.5, 1, and 2 kHz between values on baseline and after the third course of chemotherapy.

Table 2 shows the difference between values on baseline and after chemotherapy. The increase in thresholds in 0.5, 1, 2, 3, and 6 kHz after the first course of chemotherapy was greater in the DW group than in the HS group. Those in 0.5, 1, 2, 3, 4, and 6 kHz after the second course of chemotherapy were greater in the DW group than in the HS group. Those in 1, 2, 3, and 4 kHz after the third course of chemotherapy were greater in the DW group than in the HS group. Multivariate analysis showed the same trend for those after the first or second course of chemotherapy. Those after the third course of chemotherapy were greater in the DW group than in the HS group, but statistical significance was not obtained.

We have divided the two groups according to median cumulative dose (260 mg/m^2) in the third chemotherapy. The numbers of patients with median cumulative dose of < 260 mg/m^2 (low dose group) were 9 and 24 in the DW and HS groups, respectively. The numbers of patients with median cumulative dose of ≥ 260 mg/m^2 (high dose group) were 17 and 14 in the DW and HS groups, respectively. In the low dose group, patients with grade 3 or 4 after the third chemotherapy were 3 (33.3%) and 3 (12.5%) in the DW and HS groups, respectively ($p = 0.309$). In the high dose group, patients with grade 3 or 4 after the third chemotherapy were 8 (47.1%) and 2 (14.3%) in the DW and HS groups, respectively

Table 1. Participant clinical characteristics according to hydration solution

Characteristic	DW group (n = 26)	HS group (n = 38)	*p*-value[a]
Age (yr)	59.4 ± 8.0	59.8 ± 11.6	0.873
Male sex	25 (96.2)	31 (81.6)	0.128
Hemoglobin (g/dL)	13.2 ± 1.5	13.4 ± 1.9	0.765
Albumin (g/dL)	4.1 ± 0.4	4.3 ± 0.3	0.094
Creatinine (mg/dL)	0.9 ± 0.3	0.8 ± 0.2	0.115
Body mass index (kg/m^2)	22.9 ± 3.3	23.0 ± 2.7	0.851
Location of cancer			0.955
Nasal cavity, nasopharynx	6 (23.1)	7 (18.4)	
Oral cavity (tonsil, tongue, BOT), oropharynx	8 (30.8)	11 (28.9)	
Larynx	10 (38.5)	17 (44.7)	
The others (LN, EAC, unknown primary)	2 (7.7)	3 (7.9)	
Cumulative dose of cisplatin (mg/m^2)			
First chemotherapy	94.4 ± 12.6	91.1 ± 17.1	0.393
Second chemotherapy	182.7 ± 23.2	168.4 ± 28.2	0.037
Third chemotherapy	262.1 ± 34.8	235.0 ± 34.5	0.003

Values are presented as mean ± standard deviation or number (%).
DW, dextrose solution; HS, Hartmann solution; BOT, base of tongue; LN, lymph node; EAC, external auditory canal.
[a]The continuous variables were compared using Student *t*-test and the categorical variables were compared using Pearson chi-square or Fisher exact tests.

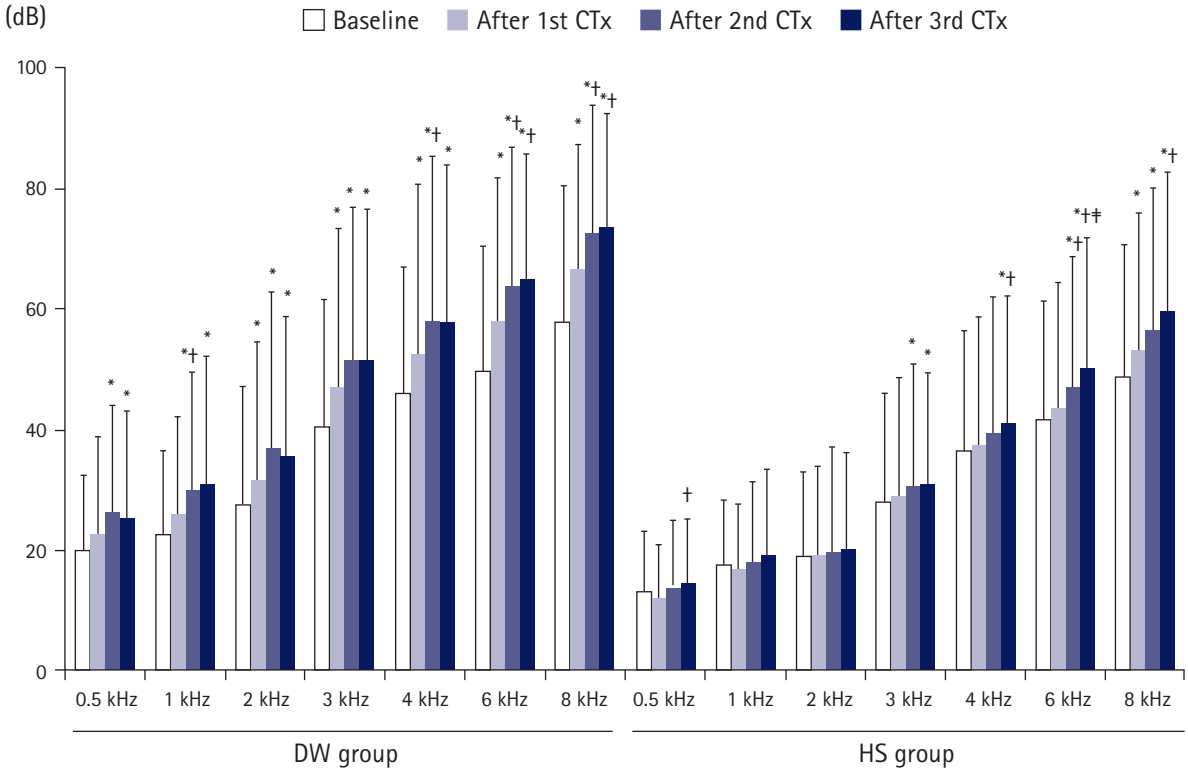

Fig. 1. Hearing thresholds after CTx according to prehydration solution. The mean 0.5 kHz values at baseline, and after the first CTx, second CTx, and third CTx were 19.8±12.6, 22.5±16.3, 26.2±17.7, and 25.3±17.7 dB for the DW group and 13.0±10.0, 11.8±9.2, 13.5±11.5, and 14.5±10.7 dB for the HS group, respectively. The mean 1 kHz values at baseline, after the first CTx, second CTx, and third CTx were 22.9±13.5, 25.8±16.3, 29.8±19.7, and 30.8±21.4 dB for the DW group and 17.4±10.8, 16.6±11.1, 17.9±13.3, and 19.0±14.3 dB for the HS group. The mean 2 kHz values at baseline, after the first CTx, second CTx, and third CTx were 27.4±19.8, 31.5±23.0, 36.9±25.9, and 35.4±23.2 dB for the DW group and 18.9±14.0, 18.9±15.1, 19.5±17.6, and 20.1±16.0 dB for the HS group. The mean 3 kHz values at baseline, after the first CTx, second CTx, and third CTx were 40.5±21.0, 47.0±26.2, 51.4±25.4, and 51.3±25.3 dB for the DW group and 28.0±18.1, 28.7±19.9, 30.4±20.5, and 30.8±18.5 dB for the HS group. The mean 4 kHz values at baseline, after the first CTx, second CTx, and third CTx were 45.9±21.0, 52.4±28.4, 57.9±27.4, and 57.6±26.3 dB for the DW group and 36.4±19.9, 37.3±21.3, 39.3±22.6, and 40.9±21.2 dB for the HS group. The mean 6 kHz values at baseline, after the first CTx, second CTx, and third CTx were 49.4±21.0, 57.8±23.9, 63.7±23.2, and 64.7±21.0 dB for the DW group and 41.6±19.6, 43.5±20.8, 46.9±21.7, and 50.2±21.6 dB for the HS group. The mean 8 kHz values at baseline, after the first CTx, second CTx, and third CTx were 57.9±22.5, 66.6±20.6, 72.2±21.5, and 73.4±18.8 dB for the DW group and 48.8±21.8, 53.3±22.7, 56.3±23.6, and 59.4±23.3 dB for the HS group. CTx, chemotherapy; DW, dextrose solution; HS, Hartmann solution. *$p<0.05$ vs. the value at baseline; †$p<0.05$ vs. the value after the first CTx; ‡$p<0.05$ vs. the value after the second CTx.

($p=0.068$). Although the differences were not statistically significant, the development of grade 3 or 4 in the HS group was lower than that in the DW group in both the low- and high-dose groups.

Lesions owing to radiotherapy can influence hearing impairment more than that with cisplatin or prehydration. In our study, there were 32 and 27 patients with nasopharyngeal or oropharyngeal cancer (NOPCa) and glottic or laryngeal cancer (GLCa), respectively. The numbers of patients with grade 3 or 4 after the third chemotherapy were 10 (31.3%) and 5 (18.5%) in the NOPCa and GLCa groups, respectively ($p=0.263$). There was no significant difference in the development of grade 3 or 4 between the two groups; however, the trend showed a greater proportion of grade 3 or 4 in patients with NOPCa than that in patients with GLCa. Patients with NOPCa were more prone to high risk for radiation than those with GLCa, which may be associated with a greater proportion of hearing impairment in patients with NOPCa.

3. Change in CTCAE grades after chemotherapy according to prehydration solution

CTCAE grade after the first course of chemotherapy in the DW and the HS groups was 15 (57.7%) and 29 (76.3%) in grade 0, 5 (19.2%) and 6 (15.8%) in grade 1, 1 (3.8%) and 1 (2.6%) in grade

Table 2. Change in hearing thresholds after chemotherapy according to hydration solution

Analysis	After the first chemotherapy from baseline			After the second chemotherapy from baseline			After the third chemotherapy from baseline		
	DW group	HS group	*p*-value[a]	DW group	HS group	*p*-value[a]	DW group	HS group	*p*-value[a]
Univariate									
0.5 kHz	2.7 ± 8.0	−1.3 ± 4.5	0.014	6.3 ± 11.1	0.5 ± 5.6	0.007	5.5 ± 13.0	1.5 ± 5.8	0.102
1 kHz	2.9 ± 8.3	−0.7 ± 4.7	0.031	6.9 ± 12.1	0.5 ± 5.9	0.007	7.9 ± 14.4	1.6 ± 7.6	0.028
2 kHz	4.1 ± 10.1	0.1 ± 5.7	0.045	9.5 ± 19.3	0.6 ± 7.5	0.012	8.0 ± 17.2	1.2 ± 7.9	0.036
3 kHz	6.5 ± 15.0	0.7 ± 7.0	0.041	11.0 ± 17.8	2.4 ± 6.9	0.009	10.8 ± 18.4	2.8 ± 8.5	0.023
4 kHz	6.5 ± 14.8	0.9 ± 5.6	0.060	12.0 ± 17.2	2.9 ± 9.8	0.009	11.7 ± 15.8	4.5 ± 12.7	0.048
6 kHz	8.4 ± 14.4	1.9 ± 8.3	0.026	14.2 ± 15.9	5.3 ± 10.6	0.009	15.3 ± 15.2	8.6 ± 13.4	0.069
8 kHz	8.8 ± 15.3	4.5 ± 9.6	0.181	14.3 ± 15.6	7.6 ± 13.4	0.068	15.5 ± 15.7	10.7 ± 16.8	0.251
Multivariate									
0.5 kHz	3.2 ± 1.3	−1.6 ± 1.0	0.009	6.3 ± 1.8	0.5 ± 1.4	0.018	5.2 ± 2.1	1.7 ± 1.7	0.221
1 kHz	3.4 ± 1.2	−1.0 ± 1.0	0.010	6.6 ± 1.8	0.7 ± 1.5	0.019	7.0 ± 2.3	2.2 ± 1.9	0.129
2 kHz	4.5 ± 1.4	−0.2 ± 1.1	0.014	10.0 ± 2.8	0.2 ± 2.3	0.012	7.9 ± 2.7	1.2 ± 2.1	0.070
3 kHz	6.8 ± 2.2	0.6 ± 1.8	0.042	10.6 ± 2.7	2.7 ± 2.2	0.037	9.4 ± 2.8	3.8 ± 2.3	0.152
4 kHz	6.2 ± 2.1	1.1 ± 1.7	0.078	11.1 ± 2.7	3.5 ± 2.2	0.041	10.1 ± 2.9	5.7 ± 2.3	0.263
6 kHz	8.4 ± 2.1	1.9 ± 1.8	0.026	13.3 ± 2.6	6.0 ± 2.1	0.038	13.4 ± 2.8	9.9 ± 2.2	0.349
8 kHz	9.2 ± 2.3	4.2 ± 1.9	0.110	13.6 ± 2.8	8.1 ± 2.2	0.143	13.7 ± 3.0	11.8 ± 2.4	0.647

Values are presented as mean ± standard deviation for univariate analysis and mean ± standard error for multivariate analysis. Values were calculated from values obtained after each chemotherapy minus baseline.

DW, dextrose solution; HS, Hartmann solution.

[a]The *p*-values were tested by Student *t*-test for univariate analysis and analysis of covariance for multivariate analysis. All regimens of chemotherapy were the same excluding doses of cisplatin and radiotherapy. Changes in hearing thresholds after the first, second, and third chemotherapy were compared between the DW and HS groups. The dependent variable was difference in hearing threshold between the baseline and after each cycle of chemotherapy. Covariates were age and baseline hearing thresholds before first chemotherapy, sex, and cumulative dose of cisplatin at the time of audiogram.

2, 2 (7.7%) and 2 (5.3%) in grade 3, and 3 (11.5%) and 0 in grade 4 ($p = 0.241$), respectively. CTCAE grade after the second course of chemotherapy in the DW and the HS groups was 10 (38.5%) and 27 (71.1%) in grade 0, 5 (19.2%) and 5 (13.2%) in grade 1, 0 and 1 (2.6%) in grade 2, 4 (15.4%) and 5 (13.2%) in grade 3, and 7 (26.9%) and 0 in grade 4 ($p = 0.007$), respectively. CTCAE grade after the third course of chemotherapy in the DW and the HS groups was 9 (34.6%) and 22 (57.9%) in grade 0, 4 (15.4%) and 7 (18.4%) in grade 1, 2 (7.7%) and 4 (10.5%) in grade 2, 5 (19.2%) and 4 (10.5%) in grade 3, and 6 (23.1%) and 1 (2.6%) in grade 4 ($p = 0.007$), respectively. CTCAE grades after the second and third courses of chemotherapy were greater in the DW group than in the HS group.

Logistic regression showed that the OR for CTCAE grade 3 or 4 after the third course of chemotherapy in the DW group was 4.84 (95% CI, 1.43–16.41; $p = 0.011$) on univariate analysis. Multivariate analysis was performed using a forward selection method with age, sex, all hearing thresholds, and cumulative dose of cisplatin. The analysis showed that, among the covariates, only prehydration solution was statistically significant. The results of multivariate analysis matched those of univariate analysis.

Discussion

Our study showed that prehydration with a salt solution alone was more effective in protecting the increase in hearing thresholds in patients who received cisplatin chemotherapy for head and neck cancers. All hearing thresholds after cisplatin chemotherapy increased compared with values on the baseline. The amount of increase in hearing thresholds after chemotherapy was greater in the DW group than in the HS group. CTCAE grade as a categorical variable after chemotherapy was higher in the DW group than in the HS group. Logistic regression analyses showed similar trends.

CIO is a well-known complication that appeared in early clinical studies of cisplatin. Previous studies demonstrated that factors such as old age, noise exposure, male sex, hypertension, and high cumulative dose of cisplatin are associated with the incidence of hearing impairment after cisplatin chemotherapy [11]. Various experimental studies have investigated mechanisms of CIO. Previous studies showed that cochlear influx of cisplatin is developed by the copper transporter 1, which results in the production of reactive oxygen species [12-14]. These lead to injuries to various cells in the auditory systems and irreversible hearing impairment. Many

interventional drugs targeting these mechanisms have been investigated for the protection of CIO. Experimental studies have shown favorable results of sulfhydryl compounds (alpha-lipoic acid, amifostine, sodium thiosulfate) or antioxidant/anti-apoptotic agents (NOX inhibitor, allicin, epicatechin, dexamethasone, and vitamin E) for protection of CIO [5]. Meta-analysis has shown a trend toward decreased ototoxicity in patients receiving amifostine, but statistical significance was not obtained [15]. Sodium thiosulfate has shown consistently favorable results in non-metastatic hepatoblastoma, but the data were available for children or adolescents alone [16]. In addition, many clinical studies for mechanism-targeted therapies showed inconsistent results regarding the protective effect, and there is no otoprotective agent routinely recommended for the prevention of CIO [17,18].

The association between vigorous hydration and protection of nephrotoxicity is well known. Although there have been few randomized trials, vigorous hydration (≥ 3 L/day) during cisplatin administration is strongly recommended to maintain a balance between benefits and risks. A previous study has shown that fluid with salt is superior to osmotic agents such as mannitol [19]. The difference between HS and 5% DW should be considered. HS or DW is the two most used crystalloid solutions. HS includes 130 mEq/L of sodium, 109 mEq/L of chloride, 28 mEq/L of bicarbonate, 4 mEq/L of potassium, and 3 mEq/L of calcium in water. The 5% DW includes 50 g/L of glucose in water. The increase in intravascular volume by 1 L supplementation was approximately 85 mL for 5% DW and 250 mL for HS, respectively. The effect of volume expansion is 2.9 times greater in HS than in the 5% DW. The renoprotective effect by volume expansion may be an extension of difference in otoprotective effect according to hydration solution. In addition, fluid therapy with salt influences chloride entrapment for platinum above volume expansion. Therefore, prehydration using fluid with salt may be superior to fluid with glucose alone. However, there are few data regarding association between fluid types and ototoxicity.

In this study, hearing thresholds in two frequencies (0.5 and 3 kHz) were greater in the DW group than in the HS group. This was an inherent limitation of our study. The changes in hearing thresholds after chemotherapy would be influenced by the sensitivity of chemotherapy beyond prehydration fluid. Therefore, our results should be carefully interpreted due to difference in baseline hearing thresholds. However, we tried to attenuate this limitation using multivariate analysis or comparison of delta values in hearing thresholds between two groups. These results revealed favorable trends for the HS group compared to that of the DW group. Our study is a pilot rather confirmative design and insufficient to confirm between prehydration solution and hearing, and the generalization of our results. Therefore, further studies with larger sample size and similar hearing threshold are needed to overcome this limitation. If baseline hearing was different despite large sample size, propensity score-matched cohort would be useful in matching hearing levels.

Our results showed that the change in hearing threshold was increased as frequency increased. The preservation of the hearing threshold by prehydration was better in low-frequency lesion than in high-frequency lesions. The preventive effect by prehydration was attenuated as cycles of chemotherapy increased. Cisplatin ototoxicity can cause cochlear injury. This injury initiates from outer hair cells adjacent to the cochlear base and progresses to the apical cells with increasing dose [20]. Therefore, hearing impairment progresses from high frequency to low frequency, and becomes worse with the increasing cumulative dose of cisplatin. In our study, only 1 L of the total 3 L of hydration solution was different, and this small difference may be difficult to induce a large difference in preventive effect. This small difference between the two groups would be associated with less improvement in high-frequency lesion (highly injurious lesion) than in low-frequency lesions (low injurious lesion). In addition, toxicity accumulates according to the cycle of chemotherapy, which would attenuate preventive effect.

The change in hearing thresholds after the third chemotherapy was lesser than those after the first or second chemotherapy. Two issues were associated with these changes. First, it may be associated with a decreased dose of cisplatin according to cycles of chemotherapy. The dose of cisplatin according to cycles were 93.1 ± 14.8 mg/m^2 in the first, 83.4 ± 15.7 mg/m^2 in the second, and 73.1 ± 16.7 mg/m^2 in the third cycles. The dose of cisplatin decreased as the cycles of chemotherapy increased. A decrease in the dose of chemotherapy may be associated with attenuated ototoxicity of cisplatin despite increase in cumulative dose. Second, activation of resistant mechanism would be associated with decreased ototoxicity according to the cycles of chemotherapy. Resistance can be developed by decreased influx or increased efflux of drug, activation of antioxidant mechanisms, or drug detoxification [21]. Normal hair cells after chemotherapy may have improved resistance to cisplatin compared to that before chemotherapy, although information remains limited in this regard.

Cumulative dose of cisplatin would be a confounding factor for the effect of prehydration on hearing. In our study, based on 100 mg/m^2 as the standard dose, the initial dose of cisplatin was modified according to a patient's performance status. The second or third doses of cisplatin were modified according to toxicity grade, changes in a patient's performance status, and tumor response. Therefore, a low cumulative dose of the HS group may be associat-

ed with higher toxicity grade, changes in a patient's performance status, and poorer tumor response during cycles compared to that in the DW group. Our study did not include these data or adjust for these variables due to limitation of sample size. Adjustment for these variables would be helpful in identifying the independent effect of prehydration on hearing.

This study had several limitations. First, it was a retrospective, single-center study. Prehydration solutions were selected without randomized controlled methods. Second, baseline characteristics, including hearing thresholds and cumulative dose of cisplatin, were different between the two groups. Third, the number of participants was small and statistical significance was weak. In addition, other modifiable factors were not considered because of the small number of participants in our study. Fourth, causal relationship was obscure. In our study, the two groups were distinguished by solution type of 1 L within total 3 L of fluid in both groups. It is not clear whether these small differences can lead to significant changes in clinical outcome. Randomized controlled studies including a larger number of participants are warranted to overcome these limitations.

In conclusion, prehydration using a solution with salt was associated with a decrease in change in hearing thresholds after cisplatin chemotherapy in patients with head and neck cancers. Therefore, vigorous prehydration with a solution of salt may be helpful to prevent CIO in patients with head and neck cancers, except in circumstances in which overhydration would be a hazard.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: DJJ, MO, BJ; Investigation, Resources: EO, KYL; Data curation: DJJ, DA; Methodology: EO, DJJ; Formal analysis: DJJ, BJ; Supervision, Validation: MO; Funding acquisition: BJ, DA; Writing-original draft: DJJ; Writing-review & editing: KYL,DJJ, DA.

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Comparison of the efficacy of erector spinae plane block according to the difference in bupivacaine concentrations for analgesia after laparoscopic cholecystectomy: a retrospective study

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Background: Laparoscopic cholecystectomy (LC) is a noninvasive surgery, but postoperative pain is a major problem. Studies have indicated that erector spinae plane block (ESPB) has an analgesic effect after LC. We aimed to compare the efficacy of different ESPB anesthetic concentrations in pain control in patients with LC.

Methods: This retrospective study included patients aged 20 to 75 years scheduled for LC with the American Society of Anesthesiologists physical status classification I or II. ESPB was administered using 0.375% bupivacaine in group 1 and 0.25% in group 2. Both groups received general anesthesia. Postoperative tramadol consumption and pain scores were compared and intraoperative and postoperative fentanyl requirements in the postanesthesia care unit (PACU) were measured.

Results: Eighty-five patients were included in this analysis. Tramadol consumption in the first 12 hours, second 12 hours, and total 24 hours was similar between groups ($p>0.05$). The differences between postoperative numeric rating scale (NRS) scores at rest did not differ significantly. The postoperative NRS scores upon bodily movement were not statistically different between the two groups, except at 12 hours. The mean intraoperative and postoperative fentanyl requirements in the PACU were similar. The difference in the requirement for rescue analgesics was not statistically significant ($p=0.788$).

Conclusion: Ultrasound-guided ESPB performed with different bupivacaine concentrations was effective in both groups for LC analgesia, with similar opioid consumption. A lower concentration of local anesthetic can be helpful for the safety of regional anesthesia and is recommended for the analgesic effect of ESPB in LC.

Keywords: Analgesia; Erector spinae plane block; Laparoscopic cholecystectomy; Postoperative pain; Ultrasound

Introduction

Although laparoscopic cholecystectomy (LC) is noninvasive, pain in the immediate postoperative period is one of the most common patient concerns [1,2]. Patients undergoing LC may experience somatic pain originating from port-entry wounds and visceral pain

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caused by gallbladder resection, abdominal insufflation, and peritoneal distention and damage [3]. The multimodal analgesic approach is a balanced and effective method for perioperative pain management and is important for regional anesthesia [4]. Multimodal treatments include regional anesthesia, regional analgesia, and analgesic medications for postoperative pain relief [5]. Regional anesthesia during surgery reduces the use of systemic medications, including opioids, for postoperative pain [6]. Regional anesthesia for postoperative pain in LC includes epidural, paravertebral, and fascial plane blocks [3,7-14]. However, epidural and paravertebral blocks have the potential risk of complications such as hematoma, pneumothorax, and epidural abscess [15]. Fascial plane blocks, such as the transversus abdominis plane (TAP) block, rectus sheath block, and erector spinae plane block (ESPB), can reduce postoperative pain during abdominal surgeries [3,9-14]. Sympathetic block, hypotension, and epidural hematoma in patients with coagulopathy can be avoided using fascial plane blocks instead of epidural blocks [16].

ESPB is a peri-paravertebral fascial plane block that has been demonstrated to be an effective regional anesthetic intervention for analgesia following various types of surgery. ESPB is a safe and easy-to-perform fascial plane block. Several studies have demonstrated the analgesic effect of ESPB on post-cholecystectomy pain [3,9-14]. Despite a growing number of publications related to ESPB, the appropriate dose of local anesthetics for ESPB in LC remains unclear. In the present study, we compared the efficacy of ESPB using the same volume of different bupivacaine concentrations for postoperative analgesia in patients with LC.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of St. Vincent's Hospital (IRB No: VC22RISI0096). Due to the retrospective nature of the study, informed consent was waived. All procedures involving human participants were performed according to the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

1. Patients

The medical records of patients who underwent LC and ESPB with different doses of bupivacaine for postoperative analgesia between March 2019 and May 2020 were retrospectively analyzed. The inclusion criteria were patients 20 to 75 years of age who underwent LC and had American Society of Anesthesiologists physical status classification I or II. The exclusion criteria were as follows: patients with cognitive impairment, allergies to anesthetic agents, coagulation disorders, renal failure, hepatic failure, chronic opioid intoxication, and body mass index of > 35 kg/m^2.

2. Anesthesia

Electrocardiography, peripheral oxygen saturation, noninvasive blood pressure, and bispectral index monitoring (BIS) were performed immediately after each patient entered the operating room (OR). Intravenous propofol (2–3 mg/kg), fentanyl (1 μg/kg), and rocuronium bromide (0.6 mg/kg) were administered for anesthesia. General anesthesia was induced with a mixture of 60% air and 4% to 6% desflurane in oxygen. The desflurane concentration was maintained at a BIS value of 40 to 60.

3. Block procedures

After obtaining written informed consent for the procedure, the patients in both groups were placed in a sitting position before general anesthesia. In the first group (group 1), a high-frequency linear ultrasound probe (Philips Ultrasound, Bothwell, WA, USA) was placed longitudinally at the level of the T7 spinous process by the anesthesiologist. The T7 transverse process and erector spinae muscle were confirmed. An 80-mm 21-gauge block needle (Tuohy Needle, Taechang, Gongju, Korea) was inserted using an in-plane approach at an angle of 30° to 40° in the cranial-to-caudal direction using an aseptic procedure. The needle was advanced until the tip contacted the T7 transverse process. Twenty milliliters of 0.375% bupivacaine solution was injected deep into the erector spinae muscle by the anesthesiologist. The same procedure was performed with 20-mL 0.375% bupivacaine on the opposite side. In the second group (group 2), the ESPB procedure was performed as described above with 20-mL 0.25% bupivacaine solution. The same procedure was repeated with 20-mL 0.25% bupivacaine solution on the contralateral side. After the block procedure, the patients were placed in the supine position.

4. Postoperative analgesia

At the end of surgery, the patients were provided with a patient-controlled analgesia (PCA) device for postoperative pain control. The patients received a 10-mg bolus of tramadol with a lockout time of 20 minutes without basal injection by the PCA device. Numeric rating scale (NRS) scores were recorded at 15 minutes and 1, 2, 6, 12, and 24 hours postoperatively. The patients received intravenous tramadol (50 mg) as a rescue analgesic when their NRS score was ≥ 4.

5. Outcome measures

Total tramadol consumption 24 hours postoperatively, intraoperative fentanyl requirements in the OR, postoperative fentanyl requirements in the postanesthesia care unit (PACU), NRS scores at each time point (0.5, 1, 2, 6, and 12 hours), and total rescue analgesic consumption in the first 24 hours postoperatively were included as outcome measures. Surgery time was defined as the time from the beginning of surgery to skin-suture closure. The patients were monitored for procedure-related complications such as pneumothorax, infection, hematoma, and nerve injury. We also monitored postoperative nausea and vomiting (PONV) and shoulder pain during the first 24 hours postoperatively.

6. Statistical analysis

Statistical analyses were conducted using IBM SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA). Quantitative data are expressed as mean ± standard deviation and median (range), whereas qualitative data are expressed as counts (percentages). Data normality was assessed using the Shapiro-Wilk test. The Mann-Whitney U test or independent *t*-test was used to compare continuous variables in the outcomes between the groups. Categorical variables were analyzed using the chi-square test or Fisher exact test, as appropriate. A *p*-value of < 0.05 was deemed significant for all comparisons between the groups.

Results

We identified 95 patients who underwent ESPB for pain control after LC. The medical records of six patients were insufficient, and PCA was discontinued in four patients (Fig. 1). Eighty-five patients were included in this retrospective analysis. The demographic data of the patients are presented in Table 1. There were no significant differences in age, sex, ASA score, or other demographic characteristics such as height and weight between the groups. The duration of surgery was 42.35 ± 6.76 minutes in group 1 and 42.18 ± 7.21 minutes in group 2 ($p = 0.784$).

The pain scores for each group are shown in Table 2. The NRS scores at rest were not significantly different at each postoperative time point between the two groups. The postoperative NRS scores upon movement were similar between the groups at 15 minutes, 1 hour, 2 hours, 6 hours, and 24 hours, but were significantly different at 12 hours. Specifically, the postoperative NRS score at 12 hours was 2 in group 1 and 3 in group 2 ($p = 0.035$). However, the median NRS score remained < 3 for the first 24 hours after surgery.

Table 3 shows the total analgesic use during the first 24 hours postoperatively. Although fentanyl consumption in the OR and PACU was greater in group 2 than in group 1, the difference was not significant ($p = 0.291$ and $p = 0.841$, respectively). Tramadol consumption in the first 12 hours, second 12 hours, and total 24 hours did not differ significantly between the groups ($p > 0.05$).

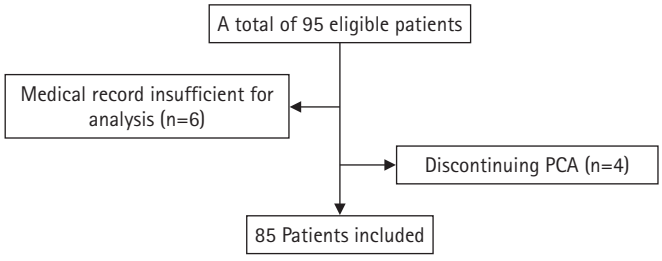

Fig. 1. Flow diagram describing patient selection. PCA, patient-controlled analgesia.

Table 1. Descriptive variables of groups

Variable	Group 1	Group 2	*p*-value
No. of patients	40	45	
Sex, male:female	15:25	19:26	0.825
ASA PS classification I/II	17/23	20/25	>0.999
Age (yr)	51.58 ± 14.16	51.36 ± 14.13	0.943
Height (cm)	163.30 ± 7.94	162.56 ± 9.33	0.819
Weight (kg)	65.22 ± 12.04	66.74 ± 17.47	0.764
Surgical duration (min)	42.35 ± 6.76	42.18 ± 7.21	0.784

Values are presented as number or mean ± standard deviation.
Group 1, 0.375% bupivacaine group; group 2, 0.25% bupivacaine group.
ASA, American Society of Anesthesiologists; PS, physical status.

Table 2. Average NRS scores at rest and upon movement/coughing during the first 24 hours after surgery

Time after operation	NRS score		*p*-value
	Group 1	Group 2	
At rest			
15 min	2 (1–2)	2 (2–2)	0.210
1 hr	2 (2–2)	2 (2–2)	0.410
2 hr	2 (2–2)	2 (2–3)	0.056
6 hr	2 (2–2)	2 (2–3)	0.135
12 hr	2 (2–3)	2 (2–3)	0.132
24 hr	2 (1–2)	2 (1–2)	0.496
On movement			
15 min	2 (2–3)	2 (2–3)	0.305
1 hr	2 (2–3)	2 (2–3)	0.395
2 hr	2 (2–3)	2 (2–3)	0.427
6 hr	2 (2–3)	3 (2–3)	0.054
12 hr	2 (2–3)	3 (2–3)	0.035
24 hr	2 (1–2)	2 (2–3)	0.090

Values are presented as median (interquartile range).
Group 1, 0.375% bupivacaine group; group 2, 0.25% bupivacaine group.
NRS, numeric rating scale.

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Table 3. Intraoperative and postoperative analgesic requirements

Variable	Group 1	Group 2	*p*-value
Average fentanyl use (μg)			
Operative room	91.25 ± 45.13	93.78 ± 31.50	0.291
Recovery room	34.38 ± 39.50	36.11 ± 40.08	0.841
Tramadol PCA (mg)			
First 12 hr	62.38 ± 13.40	63.11 ± 11.93	0.600
Second 12 hr	68.63 ± 20.19	70.22 ± 14.77	0.399
Full 24 hr	130.88 ± 26.33	133.22 ± 19.83	0.470
Rescue analgesic requirements (mg)			
First 12 hr	17.50 ± 26.68	17.78 ± 28.52	0.944
Second 12 hr	12.50 ± 21.18	14.44 ± 25.83	0.928
Full 24 hr	30.00 ± 41.68	32.22 ± 51.57	0.788

Values are presented as mean ± standard deviation.
Group 1, 0.375% bupivacaine group; group 2, 0.25% bupivacaine group.
First 12 hr, 0–12 hr; second 12 hr, 12–24 hr; full 24 hr, 0–24 hr.
PCA, patient-controlled analgesia.

Table 4. Incidences of shoulder pain, nausea, and vomiting

Variable	Group 1	Group 2	*p*-value
Shoulder pain			> 0.999
Yes	4 (10.0)	5 (11.1)	
No	36 (90.0)	40 (88.9)	
Nausea			0.813
Yes	11 (27.5)	14 (31.1)	
No	29 (72.5)	31 (68.9)	
Vomiting			0.679
Yes	2 (5.0)	4 (8.9)	
No	38 (95.0)	41 (91.1)	

Values are presented as number (%).
Group 1, 0.375% bupivacaine group; group 2, 0.25% bupivacaine group.

The average tramadol consumption (mg) in the first 24 hours was 130.88 ± 26.33 mg for group 1 and 133.22 ± 19.83 mg for group 2 ($p = 0.470$). The requirement for rescue analgesics in the ward was 32.22 ± 51.5 mg in group 2 and 30.00 ± 41.68 in group 1 at 24 hours postoperatively; the difference was not significant ($p = 0.788$).

Postoperative right shoulder pain was reported in four patients in group 1 and five patients in group 2 (Table 4). The frequency of PONV was comparable between the groups. No block-related complications, such as infection, bleeding, or pleural puncture, were reported in either group. No opioid-related side effects, such as pruritus, respiratory depression, and urinary retention, were reported in either group.

Discussion

To the best of our knowledge, the present study is the first to compare the efficacy of ESPB using two concentrations of bupivacaine (0.25% and 0.375%) in patients undergoing LC with respect to postoperative pain scores, dose of rescue analgesics required in the postoperative period, and total tramadol consumption at 24 hours postoperatively.

Tramadol consumption was similar at both lower and higher concentrations of bupivacaine. The intraoperative fentanyl requirements and rescue analgesics after surgery were comparable between the two groups. The NRS scores of group 1 were similar to those of group 2 at rest. The NRS scores during movement were similar in both groups, except at 12 hours. The NRS score at 12 hours during movement was 2 in group 1 and 3 in group 2; however, both scores are considered clinically analgesic. In our study, ultrasound-guided ESPB with two concentrations of bupivacaine (0.25% and 0.375%) was effective for managing postoperative pain after LC.

Pain following LC includes both somatic and visceral components, and multimodal analgesic methods have been used to reduce postoperative pain. A previous study demonstrated that the development of chronic pain in LC is related to early visceral pain [17]. Several analgesic approaches, such as regional anesthesia, regional analgesia, and analgesic medications, can reduce the risk of chronic pain development and are recommended during the perioperative period [5]. Multimodal therapy has been widely used for postoperative analgesia to decrease opioid-related side effects [18]. Regional anesthetic techniques such as epidural block, paravertebral block, TAP block, quadratus lumborum block, and ESPB have been developed for analgesia after LC [3,7-14].

Since 2016, ESPB has been used for pain control in various surgeries. Several studies have examined the use of ESPB for pain control in LC. A systematic review and meta-analysis conducted by Daghmouri et al. [19] showed that bilateral ultrasound-guided ESPB could be an effective treatment to reduce opioid consumption and the time to the first use of rescue analgesia. However, the concentration and volume of local anesthetics used to perform ESPB differ among reports [9-14]. There is no consensus on the use of anesthetics. The optimum volume and concentration of local anesthetic agents for ESPB remain unclear.

Tulgar et al. [11] evaluated bilateral ultrasound-guided ESPB for postoperative analgesia in patients with LC. Twenty milliliters of 0.375% bupivacaine was injected. The procedure was repeated on the contralateral side. Altıparmak et al. [9] performed ultrasound-guided ESPB versus oblique subcostal TAP block for postoperative analgesia in LC using 20-mL 0.375% bupivacaine. The same procedure was repeated with 20-mL 0.375% bupivacaine on the contralateral side. Cesur et al. [12] compared bilateral and uni-

lateral ESPB for postoperative analgesia in patients with LC. Twenty milliliters of 0.25% bupivacaine was injected on the right side in the unilateral group and bilaterally in the bilateral group. Postoperative analgesia after LC was more effective in bilateral ESPB than in unilateral ESPB [12]. Vrsajkov et al. [13] reported that ESPB reduces pain after LC. Bilateral ESPB was performed with 20 mL of 0.25% levobupivacaine plus 2 mg of dexamethasone per side. Aygun et al. [10] performed bilateral ESPB or bilateral quadratus lumborum block and used a local anesthetic mixture consisting of 30-mL 0.5% bupivacaine, 10-mL 2% lidocaine, and 20-mL normal saline, with half of the mixture administered to each side. Ozdemir et al. [14] compared ESPB and subcostal TAP blocks for postoperative analgesia after LC. A local anesthetic mixture (10-mL 0.25% bupivacaine and 10-mL 2% prilocaine) was administered into the target space. The same procedure was repeated on the contralateral side.

Several studies have indicated that different local anesthetics at various concentrations and doses are effective for postoperative analgesia following LC [9-14]; however, no trials have been conducted to compare the efficacy of ESPB using different concentrations of these agents in LC. The allowable dose of bupivacaine is 150 to 175 mg [20]. We determined the comparative doses of bupivacaine as 20 mL of 0.375% and 0.25% because side effects can occur with systemic absorption. The dose of local anesthetic should be chosen by carefully weighing the risks and benefits of analgesia and associated side effects. Although regional anesthesia is safer than general anesthesia, overdosage and toxicity of local anesthetics are associated with severe mortality and morbidity, occurring in approximately 1 in 1,000 patients [21]. Local anesthetic systemic toxicity (LAST) can occur when local anesthetics are administered, and is related to the serum concentration of the drug absorbed into the circulation [20]. This serum concentration is affected by the dose, site, and method of drug administration. Ultrasound has been reported to decrease the risk of LAST by 60% to 65% compared with peripheral nervous stimulation alone [22]. However, LAST continued to occur even with ultrasound, and ultrasound guidance did not affect the risk of LAST due to the systemic absorption of local agents. Advances in regional anesthesia, such as the advent of high-volume fascial plane blocks, have contributed to the continued risk of LAST [23,24]. Fascial plane blocks require large-volume (> 20 mL) injections of local anesthetics into the fascial plane between muscles. Since muscles usually have abundant vascular supply, there is a significant risk of LAST due to systemic absorption of local agents [25,26]. Toju et al. [26] demonstrated that administration of ropivacaine at 3 mg/kg for subcostal TAP block rapidly increased the plasma concentration of the anesthetic during the first 2 hours after the block. The peak plasma concentration nearly reached the threshold of systemic toxicity. Other factors, such as the patient's age and condition, including renal dysfunction, liver dysfunction, heart failure, and pregnancy, should be considered prior to regional anesthesia. Old age and renal, hepatic, and cardiac dysfunction reduce the clearance of local anesthetics from the body [6]. The metabolism and excretion of local anesthetics are important determinants of serum drug concentrations [20]. The decrease in clearance of local anesthetics associated with renal, liver, and heart diseases is the most important reason for dose reduction during repeated or continuous anesthetic administration. In hepatic or renal dysfunction, clearance is reduced with the retention of local anesthetics and certain metabolites in the body [20]. Older people have reduced organ function. Therefore, lower concentrations of regional anesthetics should be cautiously selected for older individuals. Doses should be modified according to age- and disease-related effects on the pharmacodynamics and pharmacokinetics of local anesthetics. Limiting the drug dose may contribute to a lower risk of LAST [27]. Lower concentrations and doses of local anesthetics should also be used if epinephrine is omitted [28].

In the literature, most studies did not indicate significant complications after ESPB in LC [19]. A case of pneumothorax after ESPB has been previously reported [29]. An alternative approach using a transverse view of the vertebra and an in-plane lateral-to-medial approach can reduce pneumothorax during ESPB at low thoracic level [30]. ESPB has been used for only several years. Thus, with the increased use of ultrasound-guided ESPB, more complications will occur.

With an increase in the concentration of local anesthetics in the systemic circulation, various signs and symptoms of effects on the cardiovascular and central nervous systems can occur. The immediate management of LAST includes general safety and resuscitation. Early lipid emulsion therapy, prompt seizure management, and supportive cardiovascular pharmacotherapy are necessary [27].

In this study, 0.25% bupivacaine was found to have a clinical effect on postoperative pain. Similarly, several studies have also performed ESPB using 20 mL of 0.25% bupivacaine and obtained effective postoperative analgesia after LC [12,13]. Low concentrations of local anesthetics may have a more positive effect than high concentrations. Bilateral ESPB following LC provides more effective analgesia than unilateral ESPB [12] but requires more volume due to the two sides of treatment, which can cause systemic toxicity. Therefore, the use of lower concentrations of local anesthetics can reduce the risk of systemic toxicity and potential complications of local anesthetics [31]. Furthermore, body weight is important for local anesthetic concentrations. If the body weight of a patient

receiving ESPB is low, the risk of toxicity increases [20]. The minimum dose of a local anesthetic agent with maximal effect can increase the safety of regional anesthesia [20].

PONV is one of the most common and painful postoperative adverse effects. The main risk factors for PONV are a history of motion sickness or PONV, postoperative opioids, female sex, and non-smoking status [32]. The use of regional analgesia usually reduces the need for systemic medications such as opioids [6]. In the present study, the incidence of PONV was comparable between groups.

In our study, the incidence of postoperative shoulder pain was similar between groups. However, the mechanisms underlying shoulder pain after LC remain unclear. Shoulder pain occurs because of irritation of the diaphragm and referred pain from the phrenic nerve [33]. Postoperative shoulder pain may increase with high-pressure pneumoperitoneum and has been shown to be reduced by removal of the remaining gas [34]. Cesur et al. [12] reported that bilateral ESPB decreased shoulder pain postoperatively compared to unilateral ESPB.

This study has some limitations. First, we performed block intervention while the patient was conscious before intubation for general anesthesia. Thus, we did not check the sensory dermatome of the block or risk of block failure. However, we performed ESPB to observe how the drug spreads to the erector spinae plane at the proper target area using ultrasound in real time. Second, we compared the effects of ESPB using different concentrations of local anesthetics within the first 24 hours after surgery. We were unable to study the long-term effects of each block on the chronic phase of cholecystectomy pain. Furthermore, this study did not include control or sham groups, and the placebo effect was unclear.

Ultrasound-guided ESPB using different concentrations of bupivacaine provided clinical analgesic effects and led to similar opioid consumption in both groups. A lower concentration of local anesthetic may reduce the risk of local anesthetic toxicity and can be recommended for safe postoperative analgesia during ESPB following LC.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: SC, JDJ; Data curation, Investigation: SC; Formal analysis, Supervision: JDJ; Methodology: YJP; Writing-original draft: YJP; Writing-review & editing: EY.

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Experience of operating a medical humanities course at one medical school during the COVID-19: a retrospective study

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Background: This study summarizes the experience of operating a 'Medical Humanities' course, which was taught remotely to maintain activities and discussions at medical schools in Daegu, Korea during the sudden and unexpected coronavirus disease 2019 (COVID-19).

Methods: The subjects of this study were 73 first- and 79 second-grade medical students who took the medical humanities (1) and (2) courses among first- and second-grade students of Yeungnam University College of Medicine in 2020. Of the 152 students who agreed to the online survey, 123 completed the survey. Self-, environmental, and program evaluations were conducted on the study subjects, and differences according to grade and gender were analyzed.

Results: As a result of the study, a significant difference between self-evaluation and environmental evaluation was confirmed. Self-evaluation was determined to be higher in the first grade than in the second grade. The environmental evaluation showed that male students were more satisfied than female students and students generally had difficulties in the classroom environment. Of the applications used in class, the highest satisfaction was observed with KakaoTalk (Kakao Corp.) and Zoom (Zoom Video Communications Inc.). At the end of COVID-19, the students preferred online classes.

Conclusion: If the learning environment for online classes is well prepared and systematic provisions are made, such as class operations that are suitable for the subject, effective education and learning can be achieved by taking advantage of both face-to-face and online classes.

Keywords: COVID-19; Medical education; Medical humanities; Medical students; Online classes

Introduction

In 2020, the world was experiencing a pandemic due to the rapid spread of coronavirus disease 2019 (COVID-19). The COVID-19 pandemic is considered the most powerful pandemic since the Spanish flu of 1918, which was recorded as the first pandemic of humankind [1]. Outbreaks of 2002 to 2003 severe acute respiratory syndrome and 2015 Middle East respiratory syndrome showed high mortality rates, but are not considered pandemics. As the first pandemic since the 2009 swine flu, COVID-19 caused fear and

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confusion around the world due to its rapid infection and mortality rates.

Previous outbreaks of infectious diseases have also caused great losses to individuals, society, and the economy; however, these effects are difficult to compare with those of COVID-19. The COVID-19 pandemic is rated as the world's largest medical catastrophe, causing the largest economic loss since World War II. COVID-19 quickly spread to more than 200 countries on five continents within a few months, completely changing the lives of people around the world, including their economies, societies, and cultures [2]. One of the biggest changes was a change in communication, which appeared the fastest in the education field [3].

During COVID-19, online education, which had been provided previously by educational facilities with special purposes, such as cyber universities, was adopted by all universities across the country, and each school had no choice but to undergo trial and error to provide high-quality online education in the absence of preparation [4]. With the transition from face-to-face to online classes, both students and professors were faced with the task of adapting to online teaching and learning within a short period of time.

In particular, because of the nature of the curriculum dealing with human life, medical school education has a large number of subjects and a large amount of material to learn. Classes are centered on practice and case studies, increasing the impact of forced remote learning [4].

In the last decade, medical school education has been transforming education by implementing team-facilitated, active, and self-directed learning. In most medical schools today, discussion-oriented problem-based learning, small-group activities, clinical practice, and academic projects occupy a large part of medical school education, and the educational effectiveness of these practices has been recognized [5].

Prior to COVID-19, medical education was based on meetings in physical space, and this rapidly changed due to the COVID-19 pandemic. The entire process of medical education shifted online through platforms, and this phenomenon was common in all countries, including the United States, the United Kingdom, Canada, and other countries with advanced education. Medical school students around the world had to adapt quickly to home-based learning, and some medical school students lost sight of their educational goals during the transition to online courses [6-9].

Korea was no exception to this change. Korea was classified as a country with entry restrictions by almost all other countries due to an explosive increase in the number of confirmed cases since the first confirmed case of COVID-19 in February 2020. In particular, in the Daegu and Gyeongbuk regions, the COVID-19 situation was so serious that 82% of all confirmed cases in Korea occurred in these regions as of March 30, 2020, resulting in the declaration of a special disaster area [10]. Under these circumstances, medical colleges in Daegu and Gyeongbuk had no choice but to utilize non-face-to-face online curricula.

In Korea's medical education, medical humanities education aims to cultivate competence in affective areas necessary for future doctors, rather than to simply transfer knowledge. Activity-oriented educational methods, such as team-facilitated, active, and self-directed learning, have been widely applied for this purpose. Yeungnam University College of Medicine operates a series of subjects called 'Medical Humanities' for integrated humanities education.

This study summarizes the experience of operating the 'Medical Humanities' course, which had been operated mainly in person at a medical school in the Daegu area, in an online classes setting during the COVID-19 pandemic.

Yeungnam University College of Medicine's 'Medical Humanities' series courses are offered in all grades. The students are divided into 12 groups for each grade, and group guidance professors are assigned. This subject consists of activity-oriented topics, discussion-oriented topics, peer evaluation, and portfolio evaluation, with the guidance of professors and students at the center. This course is designed and operated as a learning method in which interactions between professors and students and between students and students are important. Before COVID-19, all class activities in the 'Medical Humanities' subject were conducted face-to-face, but due to COVID-19, all meetings and activities had to be conducted online classes. Accordingly, students' experiences with online classes medical humanities subjects were studied.

1. Yeungnam University College of Medicine: Medical Humanities course

Yeungnam University College of Medicine's 'Medical Humanities' course series is a unique subject of the College of Medicine for the education of integrated medical humanities. With the underlying principles of coordination and integration of basic medicine, clinical medicine, and medical humanities, currently, medical humanities (1), medical humanities (2), medical humanities (3), and medical humanities (4) courses corresponding to the first, second, third, and fourth grade of medicine are being offered, respectively.

This medical school operated a four and six grades School of Medicine in parallel, but closed the School of Medicine in 2015 and switched in 2017 to a full-scale College of Medicine system of six grades from freshmen level. Accordingly, the College tried to design a curriculum that connects the premedical department to

the medical department through curriculum reform. In addition, to operate a curriculum for the harmonization and integration of basic medicine, clinical medicine, and medical humanities, medical humanities-related subjects from the second semester of the second grade of the premedical department, where the basic medical curriculum begins, to the fourth grade of the medical department, were linked and integrated.

In particular, to establish an integrated medical humanities school in the Department of Medicine, where studying as a full-fledged medical student begins, medical humanities (1), medical humanities (2), medical humanities (3), and medical humanities (4) courses correspond to the first, second, third, and fourth grades of medicine were newly established. Medical humanities courses were taught from freshmen year in 2017 and were then offered sequentially in subsequent years; currently, medical humanities (1) to (4) are offered.

Classes in medical humanities (1) and (2) consist of special lectures, discussions, and group cultural activities. In the special lecture, the same subject is taught in every other grade, and the first- and second-grade students of the medical department are required to take the same subject. The evaluation method consists of portfolio professor, peer, and absolute evaluations, and group activity experiences are shared through a comprehensive presentation at the end of the semester.

The subject of medical humanities (3) is medical humanities education within the clinical practice curriculum, and important major tasks within medical humanities are selected and experienced directly through third-grade clinical practice subjects of the medical department. Medical humanities (4) comprehensively practices previous medical humanities topics, and the Good Work Project is implemented. An outline of the 'Medical Humanities' subject series at Yeungnam University College of Medicine is shown in Table 1.

Methods

Ethical statements: Prior to the survey, a consent form was provided and an online test was designed so that only students who agreed to voluntarily participate could respond. The survey was designed such that it could be stopped immediately if desired, and these matters were disclosed. This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: 2020-10-037-004).

1. Subjects

The subjects of this study were 73 first- and 79 second-grade medical students who took the medical humanities (1) and (2) courses among the first- and second-grade medical students of Yeungnam University College of Medicine in 2020. Thus, a total of 152 students were enrolled in the study.

The first-grade medical students took the 'medical humanities' course for the first time and experienced the online classes medical humanities (1) course without having experienced the face-to-face course. The second-grade medical students had experienced the face-to-face medical humanities (1) course in 2019 and the online classes medical humanities (2) course in 2020.

2. Instruments

The previously developed and implemented Yeungnam University College of Medicine education program questionnaire was revised and supplemented with questions suitable for medical humanities subjects, and online classes-centered medical humanities class-related questions were developed. Three medical education experts and two pedagogical experts participated in questionnaire development. The questionnaire consisted of self-, environmental, and program evaluations. The self-evaluation consisted of participation

Table 1. Yeungnam University College of Medicine humanities courses outline

Subject name	Medical humanities course			
	(1)	(2)	(3)	(4)
Grade	Department of Medicine 1	Department of Medicine 2	Department of Medicine 3	Department of Medicine 4
Core contents	Medical humanities in basic medical curriculum	Medical humanities in basic medical curriculum	Medical humanities in the clinical practice curriculum	Medical humanities as a prospective doctor
Main activities	Medical humanities special lectures and discussions, cultural activities	Medical humanities special lectures and discussions, cultural activities	Important medical humanities task by clerkship	Good work project during clerkship
Assessment methods	Portfolio, peer evaluation, professor evaluation	Portfolio, peer evaluation, professor evaluation	Portfolio, peer evaluation, professor evaluation	Performance plan and process evaluation, peer evaluation, professor evaluation
	Pass/Fail	Pass/Fail	Pass/Fail	Pass/Fail
Course duration	Semester 1, 2	Semester 1, 2	Semester 1, 2	Semester 1

and sincerity components, and the environmental evaluation focused on difficulties in the class environment, discussion places in the class, satisfaction with applications used for class discussions, and satisfaction with professors in charge of each group. The program evaluation emphasized satisfaction with online classes medical humanities classes, application satisfaction, preferred teaching methods after COVID-19, and evaluation-method satisfaction.

3. Data collection

From January 5, 2021 to January 30, 2021, when the medical humanities (1) and (2) courses were completed, an online survey was conducted with the research subjects, including the announcement of research participant recruitment and the consent form. The survey site address was sent to the students' mobile phones, and the research purpose, method, and content were explained in detail in the recruitment notice prior to the survey. Then, by accessing the address of the online survey site, the students were asked to complete the online consent form and survey.

4. Statistical analysis

The collected data were analyzed using IBM SPSS ver. 25.0 (IBM Corp., Armonk, NY, USA) as follows. First, an independent sample *t*-test was conducted to verify the differences in medical school years and genders for the self-evaluation, 'classroom environment and satisfaction with the guidance of the professor in charge' for the environmental evaluation, and 'teaching method and evaluation method' for the program evaluation. Second, a cross-analysis was conducted to confirm the preference according to grade and gender for the 'discussion places in the class' and 'applications used for class discussions' in the learning environment.

Results

1. Characteristics of research participants

A total of 152 people who completed medical humanities (1) and medical humanities (2) were asked to respond, and 123 students (response rate, 80.9%) who agreed to participate in this study were selected as research subjects. Of the 123 final study participants, 77 (62.6%) were men and 46 (37.4%) were women. There were 48 first-grade medical students (40.0%) and 72 second-grade medical students (60.0%) (Table 2).

Table 2. The gender and medical course grade of the subjects

Gender	Medical course grade		Total
	1	2	
Male	31 (40.3)	46 (59.7)	77 (100)
Female	17 (37.0)	29 (63.0)	46 (100)
Total	48 (39.0)	75 (61.0)	123 (100)

Values are presented as number (%).

2. Differences in satisfaction with self-evaluation, classroom environment evaluation, and program evaluation according to gender and grade

Independent sample *t*-tests were conducted to determine whether there were differences in 'participation and sincerity' in the self-evaluation, 'satisfaction with the classroom environment and guidance of the professor in charge' in the environmental evaluation, and 'satisfaction with the teaching method and evaluation method' in the program evaluation according to gender. A statistically significant difference was confirmed in the 'difficulty of the classroom environment' in the environmental evaluation, and it was found that male students were more satisfied than female students (2.25 vs. 1.76, $p < 0.05$) (Table 3).

To determine whether there were differences in 'degree of participation and sincerity' in the self-evaluation, 'difficulty in the class environment, satisfaction with the guidance of the professor in charge' in the class environmental evaluation, and 'online classes medical humanities class satisfaction, and satisfaction with evaluation method' in the program evaluation according to medical school grade, independent sample *t*-tests were performed. A statistically significant difference was found in the degree of participation and the sincerity of self-evaluation ($p < 0.05$). Both participation and sincerity were higher in the first grade of medical school than in the second grade of medical school (Table 4).

3. Differences in application satisfaction levels by gender and grade

To confirm the difference in satisfaction with applications used in class discussions during the COVID-19 pandemic in the classroom environmental evaluation, independent sample *t*-tests were conducted on KakaoTalk (Kakao Corp., Jeju, Korea), Zoom (Zoom Video Communications, San Jose, CA, USA), Google Classroom (Google Inc., Mountain View, CA, USA), Google Form (Google Inc.), face-to-face meetings, and others. Satisfaction with KakaoTalk and Zoom was the highest, and satisfaction with Google Form was the lowest. A statistically significant difference was found in Google Form satisfaction according to gender ($p < 0.05$); female students scored 3.52, which was significantly higher than the score of male students (2.92) (Table 4).

To confirm the difference in satisfaction with the applications used during the COVID-19 pandemic according to medical school grade, independent sample *t*-tests were conducted on KakaoTalk, Zoom, Google Classroom, Google Form, face-to-face meetings, and others. The results showed that satisfaction with Ka-

Table 3. Differences in satisfaction with self-evaluation, classroom environment evaluation, and program evaluation according to gender and medical course grade

Division	No.	Self-evaluation		Classroom environment evaluation		Program evaluation	
		Participation	Sincerity	Difficulty in the class environment	Guidance of the professor in charge	Online classes medical humanities	Evaluation method
Gender							
Male	77	4.00±0.87	3.91±1.02	2.25±1.23	3.92±0.89	4.08±0.96	3.92±0.89
Female	46	3.80±0.81	4.11±0.71	1.76±0.99	4.09±0.81	4.33±0.73	4.09±0.81
p-value		0.219	0.202	0.025	0.305	0.133	0.305
Grade							
1	48	4.19±0.79	4.02±0.86	2.00±1.13	4.02±0.86	4.21±0.92	4.02±0.86
2	75	3.76±0.85	3.96±0.86	2.11±1.19	3.96±0.86	4.15±0.87	3.96±0.86
p-value		0.006	0.002	0.622	0.703	0.708	0.703
Total	123	3.93±0.85	3.98±0.91	2.07±1.16	4.23±0.77	4.17±0.88	3.98±0.86

Values are presented as mean±standard deviation.

Table 4. Application satisfaction by gender

Application	Male		Female		*p*-value
	No. of subjects	Mean±SD	No. of subjects	Mean±SD	
KakaoTalk	73	4.14±0.82	42	4.29±0.74	0.335
Zoom	65	3.42±0.98	33	3.64±1.14	0.322
Google Classroom	48	2.85±1.07	24	3.00±0.98	0.577
Google Form	48	2.92±1.07	21	3.52±0.93	0.027
Face-to-face meeting	49	2.71±1.15	22	2.45±1.01	0.366
Others	42	3.31±0.90	22	3.32±0.99	0.972

SD, standard deviation.
KakaoTalk, Kakao Corp., Jeju, Korea; Zoom, Zoom Video Communications, San Jose, CA, USA; Google Classroom, Google Inc., Mountain View, CA, USA; Google Form, Google Inc.

kaoTalk and Zoom was the highest, and a statistically significant difference was found in satisfaction with Zoom according to the school grade level ($p<0.01$). The satisfaction of first-grade students was 3.88, which was found to be significantly higher than that of second-grade students (3.20) (Table 5).

4. Preferred discussion places and class methods post-COVID-19 pandemic by gender and grade

To confirm the preference for discussion places that were mainly used in the medical humanities class after the COVID-19 pandemic ended, the students were allowed to choose home, cafe, reading room, or 'others.' In addition, face-to-face, online classes, or 'it does not matter' could be selected as the preferred teaching method.

Most of the students preferred to discuss at home. After the COVID-19 pandemic was over, 55 students (44.7%) preferred online classes, 48 students (39.0%) had no preference, 17 students (13.8%) preferred face-to-face classes, and three students (2.4%) preferred some other situation.

A cross-analysis was conducted to confirm the difference in the preferred discussion place and teaching method after COVID-19 by gender, but no statistically significant difference was found ($p<0.05$). In addition, a cross-analysis was conducted to confirm the difference in the preferred discussion place and teaching method after COVID-19 by medical school grade, but no statistically significant difference was found ($p<0.05$) (Table 6).

Discussion

This study examined the experiences with online classes medical humanities courses of medical students who faced sudden changes due to COVID-19. Some of these students had already experienced active activity-centered medical humanities classes before COVID-19. The recommendations based on the research results are as follows.

First, despite the sudden situation caused by COVID-19, medical students were found to be highly satisfied overall with online medical humanities classes according to self-evaluation and program evaluation; however, it was found that difficulties in the class environment were great.

The difficulties in the classroom environment due to suddenly

Table 5. Application satisfaction according to medical course grade

Application	Grade 1		Grade 2		*p*-value
	No. of subjects	Mean ± SD	No. of subjects	Mean ± SD	
KakaoTalk	45	4.36 ± 0.77	70	4.09 ± 0.79	0.075
Zoom	42	3.88 ± 0.92	56	3.20 ± 1.03	0.001
Google Classroom	29	3.14 ± 1.06	43	2.74 ± 1.00	0.115
Google Form	29	3.28 ± 1.13	40	2.98 ± 1.00	0.247
Face-to-face meeting	31	2.81 ± 1.25	40	2.50 ± 0.99	0.252
Others	28	3.50 ± 0.88	36	3.17 ± 0.94	0.154

SD, standard deviation.
KakaoTalk, Kakao Corp., Jeju, Korea; Zoom, Zoom Video Communications, San Jose, CA, USA; Google Classroom, Google Inc., Mountain View, CA, USA; Google Form, Google Inc.

Table 6. Preferred discussion places and class methods after the COVID-19 pandemic end according to gender and medical course grade

Variable	Gender			Grade			Total
	Male	Female	*p*-value	1	2	*p*-value	
Discussion place							
Home	65 (60.2)	43 (39.8)	0.137	45 (41.7)	63 (58.3)	0.107	108 (100)
Others	12 (80.0)	3 (20.0)		3 (20.0)	12 (80.0)		15 (100)
Total	77 (62.6)	46 (37.4)		48 (39.0)	75 (61.0)		123 (100)
Teaching method							
Face-to-face	13 (76.5)	4 (23.5)	0.621	7 (41.2)	10 (58.8)	0.701	17 (100)
Online classes	34 (61.8)	21 (38.2)		21 (38.2)	34 (61.8)		55 (100)
Does not matter	28 (58.3)	20 (41.7)		20 (41.7)	28 (58.3)		48 (100)
Others	2 (66.7)	1 (33.3)		0 (0)	3 (100)		3 (100)
Total	77 (62.6)	46 (37.4)		48 (39.0)	75 (61.0)		123 (100)

Values are presented as number (%).
COVID-19, coronavirus disease 2019.

adopting online classes can be considered to be caused by changes resulting from COVID-19. The biggest change caused by COVID-19 was a change in communication, and it first appeared in the education field [3]. As schools rapidly shifted from in-person to online classes, medical school students were reported to experience problems due to ill-prepared classes and learning environments resulting from the sudden change in online class structure [11]. Due to COVID-19, the learning space called 'school' disappeared for students, and medical students, in particular, were reported to have difficulties due to the loss of the learning space where they spent most of their time studying [12,13].

In this study, it was found that most students attended medical humanities classes and had discussions at home. In the sudden transition to online classes, despite providing the students with basics such as a medium and space for classes and learning, the students had to prepare by themselves, and there were many difficulties due to the sudden pandemic situation. In addition, medical school students had problems adjusting to online classes due to ill-prepared online education and professors who had no experience in preparing online lectures [2].

Second, when comparing various applications such as Zoom, Google Classroom, Google Forms, and face-to-face meetings, it was found that students preferred Zoom and KakaoTalk.

It has already been reported that Zoom is the application with which college students are most satisfied in practice classes because it enables instant conversation and chatting with other parties in real time [14]. Because KakaoTalk also allows real-time conversations, student satisfaction should be high. Various studies and methods have been proposed to solve the problems of real-time conversations in situations where online classes are inevitable. In online classes, a virtual whiteboard that enables mutual communication, collaborative thinking, and an interactive pad for stimulating learner participation has been developed and presented [15]. Therefore, in online classes, professors should apply a teaching method that allows interaction in various ways, and research on this topic should continue.

Students preferred Zoom or KakaoTalk to face-to-face meetings, even though face-to-face meetings are the most active way to com-

municate. This shows the fear of safety caused by the pandemic that students were aware of at the time [16].

Although there are many concerns about online classes, research results on positive aspects have recently been reported. One of the biggest advantages of online classes is that they can help self-directed learning and provide intrinsic motivation for learning [15]. Due to the nature of medical school education, self-directed learning and intrinsic motivation are important; therefore, it is necessary to prepare for effective learning by exploiting the advantages of online classes.

Finally, even after the COVID-19 pandemic ended, medical students preferred online medical humanities classes. It can be seen that there are several advantages if the learning environment for online classes is adequately prepared, and a positive effect has been reported, especially in activity-oriented classes [17-19]. In the lecture-centered online class, the students were passive, had reduced concentration, and experienced boredom; however, in the activity-centered online class, the students demonstrated active class participation and interest. In online classes centered on discussion and participation, students experienced more active participation and interaction than in face-to-face classes, and it was reported that the students demonstrated free expression [18]. Although there is a negative emotional impact of online classes, they have been shown to strengthen student agency and have a positive effect on cooperation and overcoming challenges [19]. As such, online classes have the advantage of improving students' self-directed learning, intrinsic learning, class participation, and interest through online teaching methods.

An opportunity arose during the COVID-19 pandemic for the development and application of online education. If one can enjoy the advantages of both online and in-person lectures, one can aim for a learning outcome that is superior to the teaching and learning that occurred before the pandemic. Now is the time to build know-how and move beyond trying and preparing for online lectures; analyses of member perceptions and needs for online education must be continued. It is expected that the present study will serve as useful basic data to understand the perceptions of changes in the educational environment in such a situation and to improve deficiencies.

COVID-19 has also taught us about the need for flexibility and adaptability. This should be extended to governments, medical institutions, and students [20]. Our experiences from COVID-19 will undoubtedly help the education and development of medical schools. It is also necessary to reflect on how these experiences and reorganized medical education programs can be integrated [21].

In response to such a rapidly changing situation, difficulties such as adapting to different methods and learning new technologies were highlighted. In contrast, the situation can be interpreted differently in that changes that would normally be made relatively slowly were accelerated during the pandemic. In other words, it can be said that the pandemic shortened the time to change, which normally would have been delayed slightly, and thus, innovation was hastened faster than the existing speed of social change. In addition, an opportunity was provided to discuss changing teaching and learning methods and to move forward in a positive direction.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Outcomes after repair of complete atrioventricular canal with a modified single-patch technique: a retrospective study

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Background: This study aimed to present the short- and midterm outcomes after complete atrioventricular canal defect (CAVC) repair using a single-patch technique.
Methods: This study included 30 children who underwent surgical correction of the CAVC using a single-patch technique.
Results: The median age of the patients was 5.7 months (interquartile range [IQR], 5.0–7.5 months), and 23 patients (76.7%) had type A CAVC. Fourteen patients (46.7%) were female and 17 (56.7%) had been diagnosed with Down syndrome. The in-hospital mortality rate was 0%. No deaths were observed during a median follow-up of 4 years (IQR, 3.5–5.0 years). Patients without Down syndrome were associated with late moderate mitral regurgitation (MR) ($p=0.02$). Late MR less than moderate degree was observed in 96.6%, 78.5%, and 50% of patients after 2, 4, and 5 years of follow-up, respectively, while late tricuspid valve regurgitation less than moderate degree was observed in 96.7%, 85.9%, and 59.0% of patients after 2, 4, and 6 years of follow-up, respectively. After a median follow-up of 4 years, only one patient had required surgical repair of a left ventricular outflow tract obstruction, which occurred 26 months after the first operation. Multivariable logistic regression analysis adjusted for the type of CAVC, sex, Down syndrome, age, and weight revealed that the absence of Down syndrome was a risk factor for late moderate MR (MR-2) (odds ratio, 0.05; 95% confidence interval, 0.006–0.50; $p=0.01$).
Conclusion: A single-patch technique for CAVC surgical repair is a safe method with acceptable short- and midterm results.

Keywords: Atrioventricular canal; Congenital heart defects; Outcomes; Surgery

Introduction

Atrioventricular (AV) septal defects include a spectrum of cardiac malformations characterized by varying degrees of incomplete development of the inferior portion of the atrial septum, inflow portion of the ventricular septum, and AV valves. This group of defects

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can be further subdivided into partial, intermediate, and complete forms. In the complete AV canal (CAVC) form of AV septal defects, the key element is the presence of a single AV valve that is common to the right and left AV chambers. The central aspect of this orifice is usually contiguous, with an ostium primum type of atrial septal defect above and a defect in the ventricular septum below [1]. Rastelli et al. [2] classified complete AV septal defects into types A, B, and C and highlighted the variable degree of bridging by the left superior leaflet in a continuous spectrum of leaflet and chordal anatomies. Since the first successful repair of a complete AV septal defect by Lillehei in 1955, three different techniques have been employed. The modified single-patch technique was introduced by Wilcox et al. [3] and Nicholson et al. [4]. All techniques (double-patch, single-patch, and modified single-patch) are in use today; but, until now, there has been no comparison between them. Comparing outcomes between the modified single-patch and double-patch surgical techniques seem difficult since the disease is heterogeneous and rare, and the surgeon may have a preference for the technique used. Although the double-patch technique seems to be a more thorough anatomical repair, the modified single-patch technique has an easier and faster learning curve, and uses a simplified approach [5,6].

Patients with repaired CAVCs represent a substantial percentage of grown-up congenital heart disease cases, and the efficacy of these techniques has been verified over the years. Herein, we present the midterm results from one center after CAVC repair using the modified single-patch technique.

Methods

Ethical statements: The study was performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by the Institutional Review Board and Ethics Committee of Onassis Cardiac Surgery Center (No. 705/15.01.2021). Informed consent for surgery was obtained preoperatively from the relatives of the children.

1. Study population

The study included 30 children who underwent CAVC repair using the single-patch technique from 2015 to 2022 in a single cardiac surgery center. The surgical procedure was performed by three surgeons. All patients were preoperatively evaluated by a cardiologist and transthoracic echocardiography (TTE). The classification of CAVC was based on the Rastelli classification [2]. Type B CAVC was not observed in any patient. All perioperative and follow-up data were recorded in our database. Postoperative length of stay in the intensive care unit and in the hospital was recorded.

The patients were followed up in the outpatient clinic with routine clinical examinations and TTE. TTE was performed during the hospital stay, 1 week after hospital discharge, and every 6 months thereafter. AV valve function postoperative and at follow-up was evaluated using TTE. The last follow-up date was the date when TTE was performed. Currently, there are no clear criteria for grading mitral regurgitation (MR) in children. New echocardiographic indices and classification systems for semiquantitative and quantitative evaluations have been proposed for adults; however, their validity and reproducibility in children are unknown. Quantitative assessment is often important to guide the management of children with MR [7]. Postoperative MR and tricuspid valve regurgitation (TR) were initially classified as follows: without, mild, moderate, and severe [7]. Furthermore, for the purpose of this study and data analysis, the postoperative and follow-up MR and TR were divided into two groups based on degree (trivial-to-mild regurgitation MR and mild-to-moderate regurgitation MR). MR-1 and TR-1 were defined before discharge, while MR-2 and TR-2 were defined at follow-up.

2. Surgical technique

All patients underwent midline sternotomy. In cases of previous pulmonary artery banding (PAB), redo midline sternotomy was performed. Fresh pericardium was used in all cases. Standard aortic and bicaval venous cannulation was performed by placing the patient on cardiopulmonary bypass with the superior vena cava cannula first. A vent was placed in the left heart through the right superior pulmonary vein. The patient was cooled to 34°C. Histidine-tryptophan-ketoglutarate solution was used for cardioplegia. The modified single-patch technique was used in all cases [1,3,4]. In cases where PAB had caused pulmonary artery stricture, pulmonary artery plasty was also performed using a piece of bovine pericardium. In one case, the sternum was left open after leaving the theater and was closed the next day uneventfully.

3. Statistical analysis

Continuous variables are presented as median (interquartile range [IQR]) and the rest as number (percentage). The normality of variable distribution was tested using the Shapiro-Wilk test, histograms, and Q-Q plots. The Student *t*-test, Mann-Whitney test, chi-square test, or Fisher exact test were used for data analysis. Correlations between variables were examined using Spearman (r_s) or Pearson (r) correlation coefficients. Binary logistic regression analysis was implemented to identify the possible risk factors for post-

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operative MR and TR, and the effect size was presented as the odds ratio (OR). The confidence interval (CI) was set at 95%. Statistically significant differences were considered if $p < 0.05$. IBM SPSS ver. 25 for Windows (IBM Corp., Armonk, NY, USA) was used for data analysis.

Results

Of the 30 patients who underwent surgery, 23 (76.7%) had type A CAVC. The median age of the patients was 5.7 months (IQR, 5.0–7.5 months). There were 14 female patients (46.7%) and 17 patients (56.7%) with Down syndrome (trisomy 21).

None of the patients had other genetic abnormalities. Regarding defect size, the ventricular component ranged from 12 to 16 mm, and the atrial component ranged from 11 to 21 mm. Previous PAB was recorded in six patients (20.0%). The median aortic cross-clamp (ACC) time was 92 minutes (IQR, 74–105 minutes). Other perioperative details are listed in Table 1. No difference in cardiopulmonary bypass and ACC times was observed between patients with and without previous PAB ($p > 0.05$ for both; *t*-test and Mann-Whitney test, respectively) (Table 2). Postoperative MR-1 (mild-to-moderate) and TR-1 (mild-to-moderate) were not associated with the type of CAVC, previous PAB, sex, or presence of trisomy 21 (all $p > 0.05$) (Table 3). In addition, patient age and weight at the time of surgery were not associated with MR-1 and TR-1 (all $p > 0.05$) (Table 3). In contrast, patient weight at the time of surgery was closely associated with TR-1 ($p = 0.06$), while age was not ($p = 0.27$) (Table 3). In two cases, postoperative chylothorax was observed, which was treated medically. The median in-hospital length of stay was 8 days (IQR, 7–9 days), while the 30-day mortality and in-hospital mortality were both 0%. Early or late pacemaker implantation was not required in any patient.

The median follow-up of patients was 48 months (IQR, 42–60 months). No deaths were observed during follow-up. The degree

Table 1. Perioperative details

Variable	Data
No. of patients	30
Type of CAVC	
A	23 (76.7)
C	7 (23.3)
Female sex	14 (46.7)
Down syndrome	17 (56.7)
Age (mo)	5.7 (5.0–7.5)
Weight (kg)	6.8 (5.8–8.2)
Previous PAB	6 (20.0)
Aortic cross-clamp time (min)	92 (74–105)
Cardiopulmonary bypass time (min)	122.5 (98–132)
Degree of postoperative AV regurgitation	
Postoperative MR	
Trivial	4 (13.3)
Mild	9 (30.0)
Moderate	17 (56.7)
Postoperative TR	
Trivial	3 (10.0)
Mild	19 (63.3)
Moderate	8 (26.7)
Postoperative chylothorax	2 (6.7)
Open chest and delayed chest closure	1 (3.3)
Intensive care unit stay (day)	2 (2–3)
Length of stay in hospital (day)	8 (7–9)
30-Day mortality and in-hospital mortality	0 (0)

Values are presented as number only, number (%), or median (interquartile range).
CAVC, complete atrioventricular canal; PAB, pulmonary artery banding; AV, atrioventricular; MR, mitral valve regurgitation; TR, tricuspid valve regurgitation.

Table 2. Association of cardiopulmonary bypass and aortic cross-clamp time with previous pulmonary artery banding

Variable	Previous pulmonary artery banding		*p*-value
	Yes	No	
Cardiopulmonary bypass time (min)	110.0 ± 22.0	120.6 ± 20.0	0.30
Aortic cross-clamp time (min)	78.0 (72.0–90.0)	93.5 (82.0–105.0)	0.32

Values are presented as mean ± standard deviation or median (interquartile range).

Table 3. Association of preoperative characteristics of patients with postoperative mild-to-moderate MR and TR before discharge

Variable	Postoperative MR			Postoperative TR		
	No (n = 23)	Yes (n = 7)	*p*-value	No (n = 22)	Yes (n = 8)	*p*-value
Type of CAVC			0.70			0.14
Type A	18	5		15	8	
Type C	5	2		7	0	
Previous PAB	4	2	0.60	6	0	0.15
Female sex	10	4	0.67	11	3	0.68
Down syndrome	15	2	0.19	13	4	0.69
Age (mo)	5.5 (4.7–6.5)	6.1 (5.5–10.5)	0.19	5.7 (5.0–9.0)	5.7 (4.8–6.0)	0.27
Weight (kg)	6.2 (5.7–7.8)	7.2 (6.9–8.8)	0.11	6.9 (6.0–8.0)	5.8 (4.8–7.3)	0.06

Values are presented as number only or median (interquartile range).
MR, mitral valve regurgitation; TR, tricuspid valve regurgitation; CAVC, complete atrioventricular canal; PAB, pulmonary artery banding.

of AV valve regurgitation during follow-up was recorded by TTE. The follow-up TTE findings and data are presented in Table 4. The type of CAVC and sex were not associated with late moderate MR-2 ($p > 0.05$), while not having trisomy 21 was associated with late moderate MR-2 ($p = 0.02$, Fisher exact test) (Table 5). The type of CAVC, sex, and trisomy 21 was not associated with late moderate TR-2 ($p > 0.05$, Fisher exact test) (Table 5). In addition, age and weight at the date of surgery were not associated with late moderate MR-2 and TR-2 ($p > 0.05$, Mann-Whitney test) (Table 5). Left ventricular outflow tract (LVOT) obstruction was observed in one patient 26 months after surgery. During follow-up, MR less than moderate degree was observed in 96.6%, 78.5%, and 50% of patients at 2, 4, and 5 years, respectively (Fig. 1), while TR less than moderate degree was observed in 96.7%, 85.9%, and 59% of patients at 2, 4, and 6 years, respectively (Fig. 2). After a median follow-up of 4 years, one patient had undergone surgery for LVOT obstruction 26 months after the first operation. Multivariable logistic regression analysis adjusted for type of CAVC, sex, Down syndrome, age, and weight revealed that the absence of trisomy 21

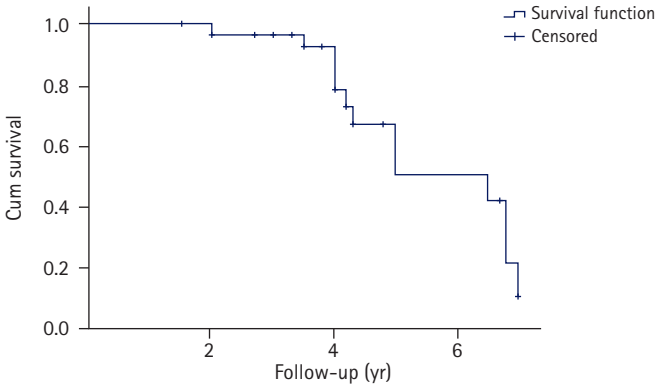

Fig. 1. Disease free from moderate mitral valve regurgitation during follow-up.

Table 4. Transthoracic echocardiography follow-up details

Variable	Data
No. of patients	30
Follow-up (mo)	48 (42–60)
Degree of AV regurgitation at follow-up	
MR	
Trivial	2 (6.7)
Mild	15 (50.0)
Mild to moderate	13 (43.3)
TR	
Trivial	1 (3.3)
Mild	20 (66.7)
Mild to moderate	9 (30.0)
Reoperation for left ventricle outflow obstruction	1 (3.3)

Values are presented as number only, median (interquartile range) or number (%).
AV, atrioventricular; MR, mitral valve regurgitation; TR, tricuspid valve regurgitation.

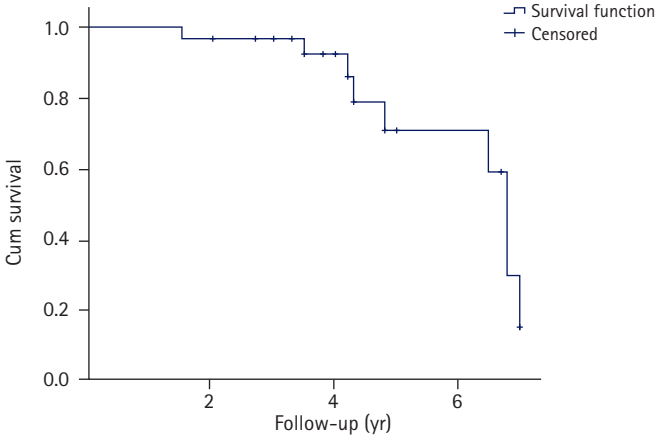

Fig. 2. Disease free from moderate tricuspid valve regurgitation during follow-up.

Table 5. Association of preoperative characteristics of patients with late (at follow-up) mild-to-moderate MR and TR

Variable	MR at follow-up			TR at follow-up		
	No (n = 17)	Yes (n = 13)	*p*-value	No (n = 21)	Yes (n = 9)	*p*-value
Type of CAVC			0.10			> 0.99
A	11	12		16	7	
C	6	1		5	2	
Female sex	8	6	> 0.99	9	5	0.69
Down syndrome	13	4	0.02*	13	4	0.44
Age (mo)	6.0 (5.5–6.5)	5.5 (5.0–9.0)	0.99	6.0 (5.0–9.0)	5.5 (5.2–6.0)	0.26
Weight (kg)	6.8 (5.8–7.8)	7.1 (6.8–8.2)	0.78	7.1 (6–8.2)	5.8 (5.8–6.3)	0.06

Values are presented as number only or median (interquartile range).
MR, mitral valve regurgitation; TR, tricuspid valve regurgitation; CAVC, complete atrioventricular canal.
*$p < 0.05$.

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Table 6. Multivariable logistic regression analysis of risk factors for moderate mitral regurgitation at follow-up

Variable	OR (95% CI)	*p*-value
Type of CAVC, C	0.05 (0.003–1.26)	0.07
Female sex	1.03 (0.08–11.90)	0.98
Down syndrome	0.05 (0.006–0.49)	0.01*
Age	0.92 (0.36–2.39)	0.87
Weight	1.51 (0.42–5.48)	0.52

OR, odds ratio; CI, confidence interval; CAVC, complete atrioventricular canal.
*$p<0.05$.

was a risk factor for late moderate MR (MR-2) (OR, 0.05; 95% CI, 0.006–0.50; $p=0.01$) (Table 6).

Discussion

The modified single-patch repair technique for CAVC is a well-established technique [5-8,9]. However, division of the bridging leaflets is often required, and this process may cause some issues during the long-term follow-up of these patients. Nevertheless, survival rates after CAVC repair with the modified single-patch technique have been reported to be 98.8%, 96.3%, and 96.3% at 5, 10, and, 20 years, respectively [5,10]. Our intermediate results indicated a mortality rate of 0%. Our patients were children and experienced an excellent quality of life.

AV valve function during follow-up, especially the left AV valve, has always been an issue, and the modified single-patch technique has been associated with this complication [5]. However, in a large study, moderate regurgitation of the left AV valve was reported in 15% of patients, and that finding did not correlate with trisomy 21, history of PAB, cleft management, or age [5]. Freedom from reoperation for left AV valve regurgitation has been reported to be as low as 62% after 10 years [11]. Reynen et al. [5] described reoperation for left AV valve regurgitation in 6% of cases. Most investigators did not find any relationship between left AV valve regurgitation and trisomy 21 [5]. Backer et al. [12] performed a meta-analysis of the three repair techniques and found that the rate of reoperation for left AV valve regurgitation was 2% in the modified single-patch, 7% in the two-patch, and 9.7% in the classic single-patch technique. In our study, moderate left AV valve regurgitation was observed in 23.3% of patients, but none of them required left AV valve reintervention. In addition, in our study, there was no requirement for pacemaker implantation as a postoperative procedure. Pacemaker reoperations have been described in patients previously, varying between 2% and 12% [10,13].

LVOT obstruction is a well-described mid- to long-term complication of CAVC repair [14]. In 4% to 5% of patients, LVOT obstruction may require reoperation. In our study, one patient required reoperation for LVOT obstruction, which was diagnosed 2 years after initial repair. The pathology was consistent with the development of a discrete subaortic membrane, and reoperation was successfully performed. During the latest follow-up, the patient was free of recurrence.

This study was a retrospective analysis of patients who underwent CAVC correction using the modified single-patch technique. The small number of patients in this study may have affected our analysis (short-, mid-, and long-term results). Furthermore, the patients underwent surgery in a single department of a tertiary Cardiac Surgery Hospital. This study included only infants and children. In addition, the study did not include a comparison of the two techniques (single- versus double-patch technique) to draw reliable conclusions about the effectiveness and benefits of the single-patch technique.

The single-patch technique for CAVC surgical repair is a method with acceptable short- and midterm results considering that it is a simplified approach. However, long-term assessment is warranted, and prospective randomized studies are needed to compare the advantages and disadvantages between the double-patch and modified single-patch techniques.

Notes

Conflicts of interest

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Case report

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Septic arthritis of the hip joint caused by *Klebsiella pneumoniae*: a case report

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Klebsiella pneumoniae is an uncommon cause of septic arthritis in adults. However, late detection can cause serious complications, including joint destruction and immobility. The purpose of this study was to report a case of successfully treated septic arthritis of the hip joint (SAHJ) caused by *K. pneumoniae*. A 49-year-old female patient presented to our hospital with fever and progressive severe pain in the right hip area. Although there was no abnormality on plain radiographs, ultrasonography revealed diffuse swelling of the right hip joint. Under ultrasonography guidance, the hip joint fluid was aspirated, and Gram staining and culturing were performed. The patient's pain was significantly reduced after the joint aspiration. The Gram staining and culturing revealed gram-negative bacilli, which were subsequently identified as *K. pneumoniae*. According to the results, systemic intravenous antibiotic (ceftriaxone) was administered without complications, and the patient was discharged on oral antibiotic (ciprofloxacin). Clinical cases of septic arthritis of the knee or sacroiliac joint have been occasionally reported in adults, but cases of SAHJ are rare. Moreover, *K. pneumonia*-induced SAHJ has not been reported to date. Therefore, we report this very rare case and its successful treatment.

Keywords: Hip; Infectious; *Klebsiella pneumoniae*; Septic arthritis

Introduction

Septic arthritis is a bacterial, mycobacterial, or fungal joint infection. It is associated with significant morbidity and mortality [1,2]. Clinical cases of septic arthritis of the knee joint have occasionally been reported. However, cases of septic arthritis of the hip joint (SAHJ) are rarely reported, and all previous reports involved immunocompromised patients [2,3]. SAHJ presents a diagnostic challenge because it mimics other musculoskeletal conditions, such as degenerative hip joint disease or tendonitis (Table 1) [4]. Septic arthritis is most commonly caused by gram-positive bacteria, including *Staphylococcus aureus*, *Staphylococcus epidermidis*, and streptococci [1]. *Klebsiella pneumoniae*, a gram-negative bacillus of the family Enterobacteriaceae, is an uncommon cause of septic arthritis in adults [3]. Herein, we describe a case of acute SAHJ caused by *K. pneumoniae* in a patient with no primary lesions or underlying medical conditions. Informed consent for publication of the patient's clinical details and clinical images was obtained from the patient.

Case

Ethical statements: This study was exempted from review by the Institutional Review Board (IRB) of Sahmyook Medical Center (IRB No: 116286-202111-HR-02). Written informed consent was obtained from the patients to participate in the study.

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Table 1. Differential diagnosis of septic arthritis of the hip joint and other musculoskeletal disorders in adults

Differential diagnosis	Clinical feature
Lumbar radiculopathy	Pain in the posterior buttock or radiating pain down the thigh, which may be a burning sensation
Sacroiliac joint disease	Pain in the posterior buttock
Piriformis syndrome	Pain in the posterior buttock with activity, sciatic pain radiating down the leg as a result of nerve compression, tenderness over the piriformis tendon and muscle
Osteonecrosis	Pain in the hip or groin, gradually progresses
Occult femoral neck fracture	Pain in the hip or groin, can be traumatic, associated with accompanying injury, or atraumatic, resulting in a stress fracture
Meralgia paresthetica	Pain in the hip or groin, radiating down the thigh's anterolateral side
Psoas tendinopathy	Pain in the groin, associated with resisted hip flexion
Trochanteric bursitis	Pain localized to greater trochanter, palpable tenderness, minimal pain in the groin
Abductor tendon tear	Pain localized to greater trochanter, minimal pain in the groin
Neurogenic claudication	Back pain is more severe than leg pain, radiating down the leg; it is worse when standing upright and improves when seated bent forward
Vascular claudication	Leg pain is more severe than back pain, is aggravated by walking and any movement, and improves with rest
Iliac avulsion fracture	Pain in the hip following trauma or unexpected muscle activation
Traumatic synovitis, hemarthrosis	Recent trauma history
Gout	Pain caused by polyarthralgia, aggravated by particular foods
Pseudogout	Pain caused by polyarthralgia, more prevalent among those who are elderly
Rheumatoid arthritis flare	Pain caused by polyarthralgia, patient may be on immunosuppressive medication
Osteoarthritis exacerbation	Pain that has recently worsened as a result of increased activity

A 49-year-old housewife presented to our rehabilitation department with a 12-hour history of sudden-onset, progressively worsening pain in the right hip area, with concomitant fever that developed 2 hours after pain onset. She complained of severe pain with a numerical rating scale (NRS) score of 8 when bending her right hip and was unable to ambulate because of severe pain when bearing weight on her right leg. She had no comorbidities or history of trauma. She mentioned high levels of stress for personal reasons, which had persisted for 6 months.

Upon arrival at the hospital, her vital signs were as follows: body temperature, 37.8°C; pulse rate, 93 beats/min; respiratory rate, 20 breaths/min; and blood pressure, 128/80 mmHg. Physical examination revealed tenderness of the right medial thigh and painful limitation of movement, especially internal rotation. Laboratory tests revealed a white blood cell (WBC) count of 14,200/μL with neutrophilic predominance (87.6%), a hemoglobin level of 13.3 g/dL, and a platelet count of 295,000/μL. Plain radiographs showed no abnormalities, except for mild degenerative changes in both hip joints. Ultrasonography revealed diffuse swelling of the right hip joint (Fig. 1A). Under ultrasonographic guidance, 12 mL of yellow, cloudy, moderately viscous fluid was aspirated from the right hip joint, and joint fluid analysis, Gram staining, and culturing were performed (Fig. 1B). The patient's hip pain was significantly reduced (4 on the NRS) after hip joint fluid aspiration; she was able to walk but had general myalgia. Since the patient's clinical signs and symptoms had improved rapidly, and the results of Gram staining and culturing were not yet available, she was discharged with an outpatient appointment scheduled for 4 days thereafter.

Four days later, the patient was admitted to the hospital. Laboratory tests showed a WBC count of 6,229/μL with neutrophilic predominance (67.5%), a hemoglobin level of 14.1 g/dL, and a platelet count of 356,000/μL. The joint fluid showed a WBC count of 8,979/mm^3 with neutrophilic predominance (78%) and a red blood cell count of 1,000/mm^3; septic arthritis was suspected. The Gram staining and culturing revealed gram-negative bacilli, which were subsequently identified as *K. pneumoniae*. Susceptibility test results indicated sensitivity to all antibiotics, including cefepime, meropenem, piperacillin/tazobactam, ceftazidime/avibactam, ceftriaxone, colistin, ertapenem, tigecycline, amikacin, ampicillin/sulbactam, cefazolin, ceftazidime, ciprofloxacin, gentamicin, imipenem, and trimethoprim/sulfamethoxazole, but not ampicillin alone. The patient was hospitalized for antibiotic treatment and underwent further evaluation. Ceftriaxone (2 g, once a day) was administered intravenously for 3 days. A whole-body bone scan was performed to identify complications of SAHJ and revealed no abnormal uptake anywhere in the body, including the right hip joint (Fig. 2). Computed tomography of the abdomen and pelvis to investigate primary lesions of *K. pneumoniae* infection showed no specific abnormalities except for a 6-cm, unilocular, cystic lesion at the right adnexa suspected of being a benign ovarian cyst or a mucinous cystic neoplasm. The patient had no underlying medical conditions that could lead to an immunocompromised state,

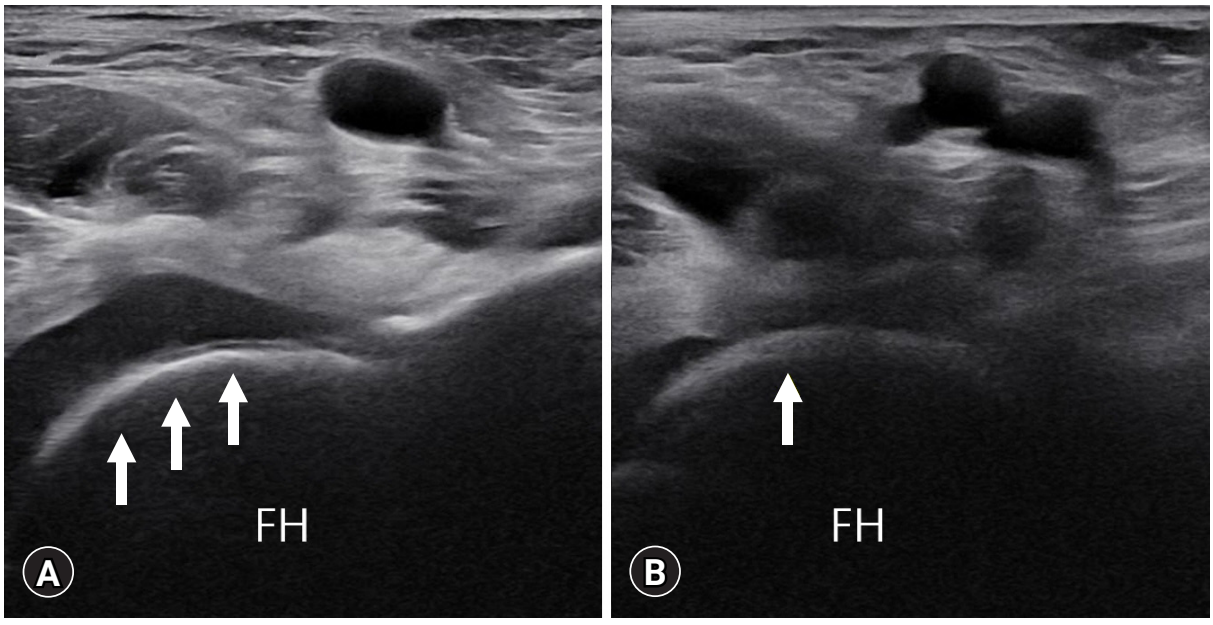

Fig. 1. Pre- and post-aspiration ultrasonography images of the right hip joint. (A) Mild fluid collection and diffuse swelling of the right hip joint (arrows) are seen in the pre-aspiration image. (B) A decrease in the fluid collected in the right hip joint (arrow) is seen in the post-aspiration image. FH, femoral head.

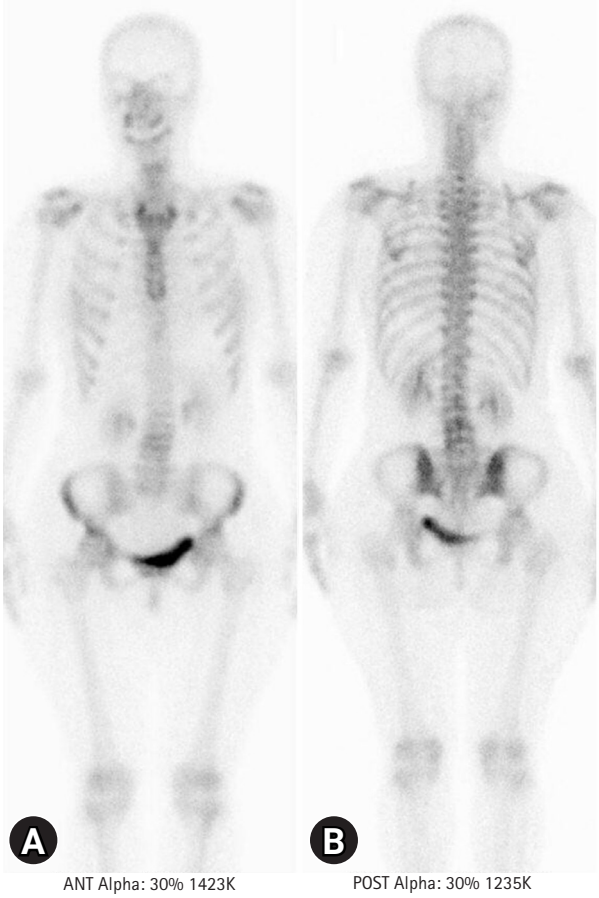

Fig. 2. (A) Anterior and (B) posterior views of a whole-body bone scan. No abnormal findings such as hot or cold spots are observed throughout the body including the right hip joint.

such as diabetes, chronic renal failure, malignancy, alcoholism, or acquired immunodeficiency syndrome. She was uneventfully discharged 3 days later while receiving oral antibiotics (ciprofloxacin, 500 mg, twice daily for 7 days). At her 6-month follow-up, she complained of no hip pain and showed no specific features on review of systems.

Discussion

To the best of our knowledge, this is the first report of a case of acute SAHJ caused by *K. pneumoniae* in a patient with no primary lesion or underlying disease.

It is difficult to estimate the incidence of SAHJ in adults, which has mostly been reported in case reports [1]. Numerous prior studies have dealt with all sites of septic arthritis collectively, despite significant variance in clinical manifestations among joints. The incidence of septic arthritis in the general population of industrialized countries is 2 to 6 cases per 100,000 people [5] and 5 to 12 cases per 100,000 children [6,7]. However, the overall incidence appears to be increasing, and this increase is associated with an aging population, an increasing number of invasive procedures being performed, and the increased use of immunosuppressive therapies [6,8].

Organisms that cause septic arthritis differ according to patient age. The most common causative agent of bacterial arthritis in adults is *S. aureus*, with an incidence between 37% and 67% [9].

Following this, 9% to 20% of bacterial arthritis is caused by gram-negative bacteria such as *Escherichia coli* [10]. In children, the most frequently observed causal organisms are methicillin-sensitive *S. aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* [11]. *K. pneumoniae* rarely causes septic arthritis in all age groups. It is known to cause septic arthritis as a secondary infection through hematogenous transmission after primary infections, such as liver abscesses, pneumonia, and urinary tract infections [12]. *K. pneumoniae* infection of other organs rarely occurs in the absence of a liver abscess, although it may occur in special clinical situations, including trauma, intravenous drug abuse, and immunosuppression following organ transplant or human immunodeficiency virus infection [2,12,13]. In this case, a 49-year-old woman with no known underlying disease developed SAHJ caused by *K. pneumoniae* in the absence of any primary lesion, such as a liver abscess.

Magnetic resonance imaging or surgical intervention was not performed to determine whether the bones and muscles surrounding the hip joint were affected. The reason for this decision was that the patient's clinical symptoms of fever and hip pain improved rapidly after hip joint fluid aspiration, and the subsequent laboratory test after 4 days also improved. In addition, a whole-body bone scan revealed no abnormal uptake throughout the body. Based on these findings, we concluded that an appropriate antibiotic was sufficient to control her SAHJ.

Generally, septic arthritis is treated with drainage, cleaning of the joint abscess, and systemic antibiotic therapy based on the results of susceptibility testing. Appropriate drainage is essential for the management of purulent infections in enclosed spaces. There have been prior cases of children undergoing high-volume lavage and irrigation, and cases of adults undergoing open arthrotomy and ultrasonography-guided irrigation. Arthroscopic lavage and debridement can be performed to drain and clean intraarticular abscesses [14]. Goldenberg et al. [15] compared needle aspiration with surgical intervention, and no evidence was available to recommend one treatment strategy over the other. In our case, the hip joint fluid was sufficiently aspirated under ultrasonographic guidance, and ceftriaxone-susceptible *K. pneumoniae* was identified by Gram staining and culture of the joint fluid. According to the guidelines for treating septic arthritis, it is important to immediately remove the purulent material from inside the joint and administer systemic antibiotics that are effective against the causative organism [16]. Accordingly, in this case, immediate pus aspiration and antibiotic treatment based on the results of susceptibility testing were sufficient to treat the disease and resulted in complete recovery without sequelae, such as residual impairment due to hip joint destruction.

Considering the pathophysiology of joint destruction in septic arthritis, it is known that the synovium in the joint is an abundantly vascularized structure without a restricting base plate, and bacteria have easy access [17]. Extracellular virulence agents produced by bacteria are critical for the progression of erosive joint destruction associated with septic arthritis [18]. As the infection progresses, an effusion forms in the joint, increasing the intraarticular pressure and preventing blood supply to the joint. The reported fatality rates for monoarticular septic arthritis vary by report, but are estimated to be ~11% [1]. Patients with acute septic arthritis often present with fatigue, erythema, edema, discomfort, and limited range of motion in a single joint over a period of 1 to 2 weeks [19].

Septic arthritis in children under the age of 2 years may go undiagnosed due to the absence of typical indications of infection; thus, caution should be exercised when examining them. Anxiety, irritability, tachycardia, and anemia are all possible clinical indications and symptoms [20].

We report a very rare case of SAHJ caused by *K. pneumoniae* that developed in a relatively young patient with no medical history. SAHJ should be considered during the differential diagnosis of patients with acute hip pain despite the absence of plain radiographic abnormalities.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: BJR; Visualization: JBM, JHL; Writing-original draft: JBM; Writing-review & editing: BJR.

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Case report

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Invasive sphenoid sinus aspergillosis with normal findings on initial diagnostic tests that mimics Tolosa-Hunt syndrome—a diagnostic dilemma: a case report

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Invasive sphenoid sinus aspergillosis can mimic Tolosa-Hunt syndrome (THS), leading to frequent misdiagnoses and potentially fatal consequences. We report a case of invasive sphenoid sinus aspergillosis initially misdiagnosed as THS. A 79-year-old man presented with right periorbital pain, ophthalmoplegia, and loss of vision. Initial evaluations including magnetic resonance imaging (MRI), were normal. He was first diagnosed with THS based on clinical features. The disease progressed despite high-dose intravenous steroid treatment, and an enhancing mass-like lesion was found in the right orbital apex, cavernous sinus, and sphenoid sinus on follow-up MRI. Aspergillosis was eventually confirmed by sphenoid sinus biopsy. The patient developed cerebral infarction and finally died despite being treated with amphotericin B. Given that invasive sphenoid sinus aspergillosis may initially resemble THS, high suspicion and rapid histological examination are important for diagnosis.

Keywords: Aspergillosis; Painful ophthalmoplegia; Sphenoid sinus; Tolosa-Hunt syndrome

Introduction

Tolosa-Hunt syndrome (THS) is characterized by painful ophthalmoplegia caused by idiopathic granulomatous inflammation in the orbit and/or cavernous sinus. However, other conditions, such as cavernous sinus lymphoma, can mimic various features of THS, resulting in misdiagnoses [1]. Therefore, repeated neuroimaging studies and histopathologic confirmation are required to exclude other possible causes of painful ophthalmoplegia, specifically when the clinical course and radiologic findings are unusual for THS. We report a case of invasive sphenoid sinus aspergillosis initially misdiagnosed as THS.

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of the Korea University Anam Hospital (IRB No: 2022AN0044), and the requirement for informed consent from the patient was waived by the IRB.

A 79-year-old previously healthy man was experiencing periorbital pain in the right eye with visual impairment of counting fingers and binocular diplopia that worsened rapidly over the course of 7 days. He had a history of hypertension but did not have diabetes

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mellitus or thyroid disease. Nine months earlier, he had undergone craniotomy in the bilateral temporal region because of traumatic subdural hematoma from falling and had recovered without neurological sequelae. On admission, his body temperature was 36.8°C, and no jaw claudication or temporal artery tenderness were present. Neurological examination revealed ptosis and complete ophthalmoplegia with a normal pupillary response to light in the right eye. The rest of his neurological examination was unremarkable. Initial head magnetic resonance imaging (MRI) performed 7 days after symptom onset revealed no abnormalities except for postoperative changes associated with the previous subdural hematoma in the bilateral temporal areas and evidence of left maxillary sinusitis (Fig. 1A). Visual evoked potential showed low amplitude and delayed P100 wave at 188 ms after right eye stimulation. Laboratory findings were within normal ranges, except for erythrocyte sedimentation rate (32 mg/L) and C-reactive protein (82.52 mg/L). Cerebrospinal fluid (CSF) analysis revealed clear color, normal cell count, and normal protein and glucose levels. Immunologic serum markers, such as antinuclear antibody, antineutrophil cytoplasmic antibody, C3, C4, immunoglobulin G (IgG), IgA, IgM, and IgE concentrations, were within the normal range.

With the provisional diagnosis of THS, the patient was treated with intravenous high-dose methylprednisolone (1,000 mg/ day) for 5 days. He experienced significant relief from orbital pain within 24 hours. On admission day 8, the patient was discharged with only mild ptosis and slight limitation of adduction in the right eye; however, he was readmitted 1 month later because the severe right-sided headache and periorbital pain recurred. Seven days after readmission, he developed a left-sided hemiparesis (Medical Research Council [MRC] grade 4) followed by mild drowsiness.

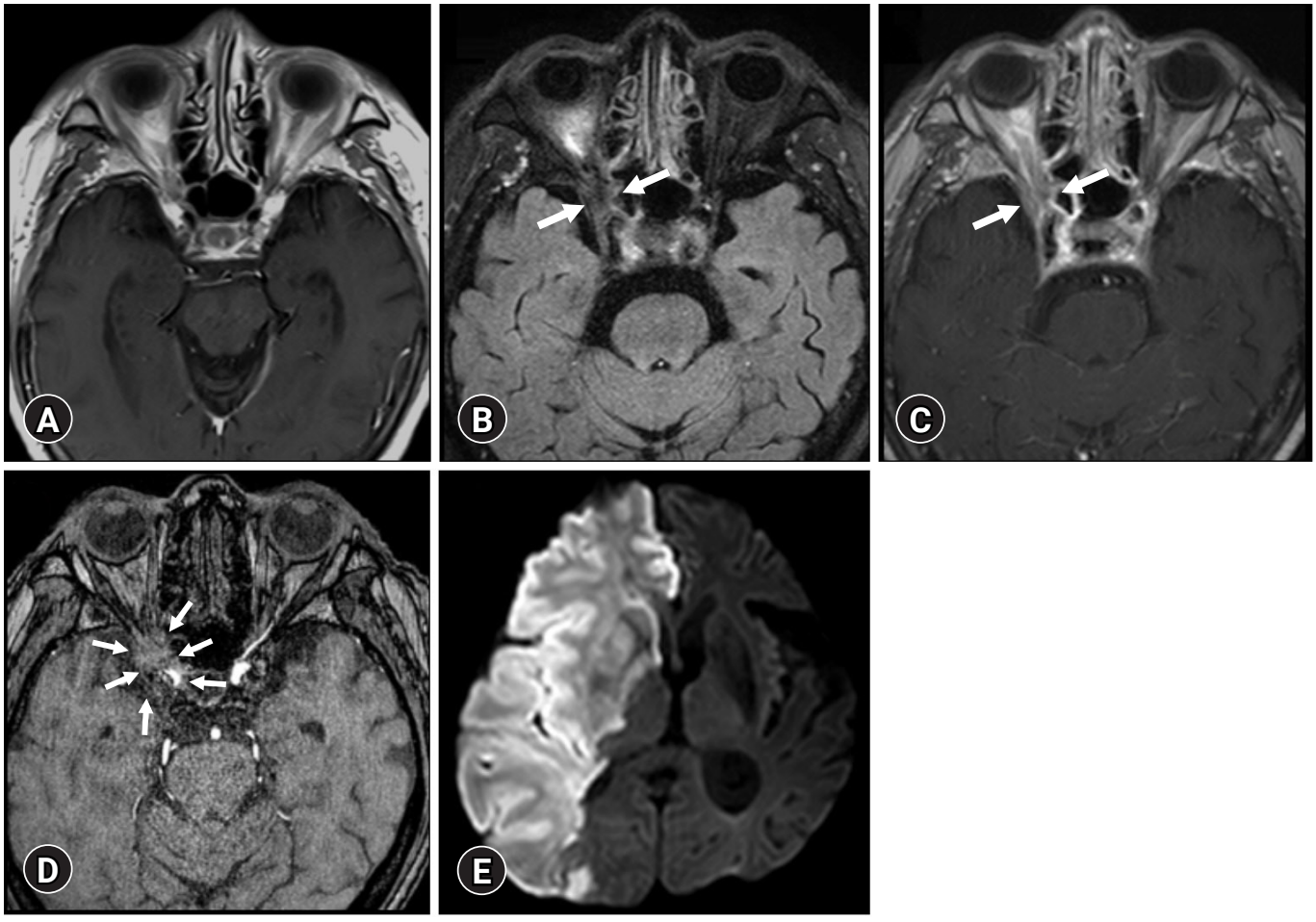

Fig. 1. (A) Initial gadolinium-enhanced T1-weighted magnetic resonance imaging (MRI) shows no abnormalities. (B) T2 fluid-attenuated inversion recovery and (C) T1-weighted (contrast-enhanced) imaging of follow-up gadolinium-enhanced MRI show thickening and enhancement of the right optic nerve, cavernous sinus, sphenoid sinus soft tissue with partial bony destruction, and spread of enhancing tissue into the right orbital apex (arrows). (D) The source image of magnetic resonance angiography shows encasement of the right internal carotid artery (ICA) as well as ipsilateral optic canal invasion (arrows). (E) Diffusion-weighted MRI reveals acute infarction in the right ICA territory.

Diffusion-weighted MRI (DWI) of the brain revealed acute ischemic infarcts in the borderzone of the right middle/anterior cerebral arteries. In addition, a gadolinium-enhanced follow-up brain MRI revealed a diffuse and enhancing mass-like lesion involving the right orbital apex, cavernous sinus, and sphenoid sinus (Fig. 1B, 1C). Encasement of the ipsilateral internal carotid artery (ICA) in the cavernous sinus was suspected (Fig. 1D). On readmission day 9, his mental status deteriorated to a deep drowsy state. Follow-up CSF findings revealed a white blood cell count of 330 cells/μL (lymphocytes 47%, neutrophils 43%), an elevated protein concentration of 96.4 mg/dL (range, < 45 mg/dL), and a reduced CSF/serum glucose ratio, suggesting central nervous system (CNS) infection. A sphenoid sinus biopsy was performed. Although direct microscopy with potassium hydroxide mount and fungal culture was negative, histopathological examination of the resected right sphenoid sinus tissue revealed inflammation and fungal balls with *Aspergillus* organisms (Fig. 2). The patient was treated with amphotericin B. On readmission day 21, left-sided weakness progressed (MRC grade 1), and the consciousness worsened to stupor. Repeated brain DWI revealed infarction in the right ICA territory (Fig. 1E). Brain computerized tomography on readmission day 23 showed a right-to-left shift of the hemisphere due to significant brain swelling. The patient died shortly afterward the same day.

Discussion

Imaging, particularly MRI, and CSF studies play a crucial role in diagnosing invasive aspergillosis involving the orbit, paranasal sinus, and CNS. Our patient was initially diagnosed with THS based on clinical features of unilateral painful ophthalmoplegia and good steroid response after excluding other disease processes through normal findings in initial diagnostic tests, including MRI and CSF studies. Although decreased visual acuity observed in our patient is not a common symptom of THS, it can occur in THS if the inflammatory process extends to the orbital apex [2]. Invasive aspergillosis with normal initial MRI and CSF findings poses a diagnostic dilemma and is often confused with other diseases, as in the present case.

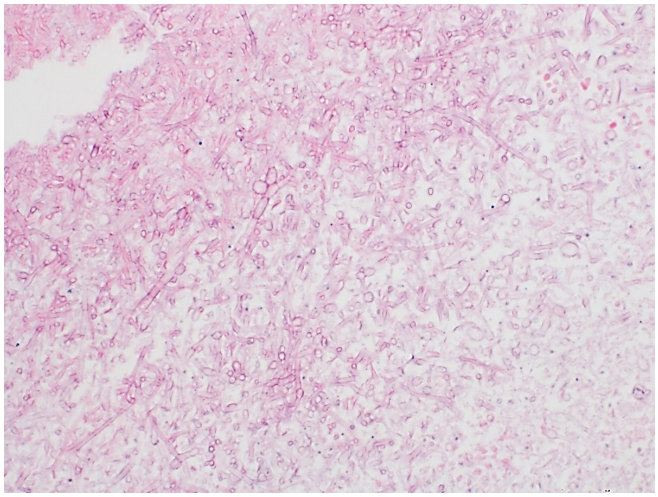

Fig. 2. Histopathology of the resected tissue shows abundant *Aspergillus* organisms with typical branching septate hyphae with a bulbous appearance that branch at 45° (hematoxylin-eosin stain, ×400).

Aspergillosis, particularly of the sphenoid sinus, may have variable clinical manifestations mimicking THS according to the involvement of orbital apex structures and cavernous sinus. In addition, the paucity of this pathology makes diagnosis extremely difficult in a clinical setting. Aspergillosis usually occurs as an opportunistic infection in immunocompromised patients [3]. However, as in our case, orbital or CNS aspergillosis has rarely been reported in immunocompetent patients [4,5]. In addition to the fact that the initial evaluations were normal, the symptoms of invasive sphenoid sinus aspergillosis being similar to THS, the immunocompetent status of our patient, and the rarity of invasive aspergillosis were factors that made initial diagnosis difficult.

The limitations in the diagnosis of invasive fungal disease are widely recognized. Conventional methods such as direct microscopy, fungal culture, and histopathologic examination remain the gold standard for diagnosing invasive fungal diseases. However, these methods lack sensitivity and specificity, and in particular, the duration of obtaining fungal culture results is lengthy, which limits rapid decision-making in clinical practice [6]. Recent studies have suggested new noninvasive methods such as antigen detection tests (galactomannan, beta-D-glucan) and molecular amplification methods, which provide more rapid, sensitive, and accurate results [6,7]. While conventional methods are still needed for a definitive diagnosis of invasive fungal disease, new diagnostic methods facilitate the early detection of pathogenic fungi.

Aspergillus species are angioinvasive, leading to occlusive thrombosis, embolism, and eventual infarction with hemorrhagic transformation [8]. In particular, cavernous sinus invasion and consequent ICA encasement are common in aspergillosis due to concomitant paranasal sinus disease, resulting in major territorial infarcts [9,10]. The present patient also showed cavernous extension and ICA encasement that resulted in ICA thrombosis with a malignant ICA infarct. In the present case, corticosteroid therapy may have exacerbated the *Aspergillus* infection and facilitated the resulting infarction despite improving the symptoms initially.

This study emphasizes that invasive aspergillosis can occur in

immunocompetent patients with orbital or CNS involvement. The diagnosis could be delayed because initial signs, symptoms, and radiologic findings could mimic THS. Invasive sphenoid aspergillosis is a potentially fatal condition if not treated early or aggressively. A high degree of suspicion about the possibility of aspergillosis and repeated neuroimaging studies, specifically with atypical clinical course, is the only way to expect a good prognosis by early treatment after prompt histological confirmation.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: all authors; Investigation: JC, HYS; Data curation: YHJ, JC; Formal analysis: JC, BJK, HYS; Supervision: HYS; Writing-original draft: YHJ, JC; Writing-review & editing: BJK, HYS.

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Case report

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Laparoscopic excision and repair of a cesarean scar pregnancy in a woman with uterine didelphys: a case report

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Cesarean scar pregnancy (CSP) is a rare complication that occurs in less than 1% of ectopic pregnancies, and uterine didelphys is one of the rarest uterine forms. We report a successful laparoscopic excision and repair of CSP in a woman with uterine didelphys and a double vagina. A 34-year-old gravida one, para one woman with a history of low transverse cesarean section presented to our hospital with a suspected CSP. She was confirmed to have uterine didelphys with a double vagina during an infertility examination 7 years earlier. Magnetic resonance imaging showed a 2.5-cm gestational sac-like cystic lesion in the lower segment of the right uterus at the cesarean scar. We decided to perform a laparoscopic approach after informing the patient of the surgical procedure. The lower segment of the previous cesarean site was excised with monopolar diathermy to minimize bleeding. We identified the gestational sac in the lower segment of the right uterus, which was evacuated using spoon forceps. The myometrium and serosa of the uterus were sutured layer-by-layer using synthetic absorbable sutures. No remnant gestational tissue was visible on follow-up ultrasonography one month after the surgery. This laparoscopic approach to CSP in a woman with uterine didelphys is an effective and safe method of treatment. In women with uterine anomalies, it is important to confirm the exact location of the gestational sac by preoperative imaging for successful surgery.

Keywords: Cesarean section; Laparoscopy; Uterine disease

Introduction

Cesarean scar pregnancy (CSP) is a rare complication of pregnancy, occurring in less than 1% of ectopic pregnancies [1]. A CSP is defined as implantation of the blastocyst at the myometrium through dehiscence of a previous cesarean scar [2]. There are two types of CSP using imaging modalities. Type 1 (endogenic type) develops in the myometrium and progresses toward the uterine cavity, and type 2 (exogenic type) deeply invades in the scar defect and progresses toward the uterine serosa with possible uterine rupture [3]. CSPs have increased in prevalence with increasing cesarean section deliveries and advances in ultrasonography [4]. However, CSPs are not easy to diagnose, with a misdiagnosis rate of 70% to 80% during the first examination [5]. Upon ultrasonography, CSPs can be misdiagnosed as threatened and incomplete abortions and cervical pregnancies, depending on the gestational sac's location and shape. Moreover, the diagnosis of CSP may be more difficult if there is a uterine malformation, such as uterine didel-

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phys. Uterine didelphys is one of the rarest uterine forms, accounting for 8.3% of all Müllerian anomalies [6]. Uterine didelphys arises from failure of the Müllerian ducts to fuse resulting in two separate endometrial cavities, two cervices, and often a longitudinal vaginal septum. We report a successful laparoscopic treatment of a very rare case of CSP in a woman with uterine didelphys.

Case

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Keimyung University Dongsan Hospital (IRB No: 2022-02-062) and written informed consent from the patient was waived by the IRB due to retrospective nature of this case study.

A 34-year-old woman, gravida two, para one, with a history of low transverse cesarean section, was initially referred to Keimyung University Dongsan Hospital for a suspected CSP at 7 weeks gestation. Her serum β-human chorionic gonadotropin (β-HCG) concentration was 30,626 mIU/mL at her first visit to our hospital. During a fertility examination performed at another hospital 7 years earlier, she was diagnosed with uterine didelphys, two cervices, and a longitudinal vaginal septum. This pregnancy was confirmed as naturally conceived without infertility procedures. Upon pelvic examination, the left vagina was narrow and inaccessible. The pelvic examination was performed entirely through the right vagina and included vaginal ultrasonography. Based on vaginal ultrasonography, a CSP with active cardiac activity was suspected in the right uterus, and magnetic resonance imaging (MRI) was performed for an accurate diagnosis. A fetal pole (crown-rump length, 20 mm) in a gestational sac was located at the right lower uterine segment with a 41-mm sized intramural myoma at the uterine anterior wall (Fig. 1). There was no evidence of hemorrhage in the endometrial cavity or free fluid in the cul-de-sac. The patient was counseled about the medical treatment of CSP, which had a high probability of failure based on the high level of β-HCG. Because of the risk of uterine bleeding during the pregnancy, we decided to remove only the gestational sac through laparoscopic surgery without removing the uterine myoma, with the patient's consent.

The patient underwent CSP laparoscopic excision with repair based on a stepwise approach. A uterine manipulator was used to facilitate the surgery by easily moving the uterus, which was entered through the right cervix. During the laparoscopy, it was noted that the bladder had adhered to the uterine anterior wall due to the previous cesarean section, and the focus of the ectopic pregnancy was presumed to be a lump protruding outwards from the uterine lower segment (Fig. 2). As the first step, both uterine arteries were clamped to reduce bleeding risk during the surgery. A small transverse incision was made in the lower segment of the uterus, just above the adherent bladder to differentiate it from the bladder flap after the uterus was positioned as far as possible into the abdominal cavity using the uterine manipulator. Careful dissection was performed using monopolar diathermy within the areolar tissue at the vesicouterine plane. As the second step, the focus of

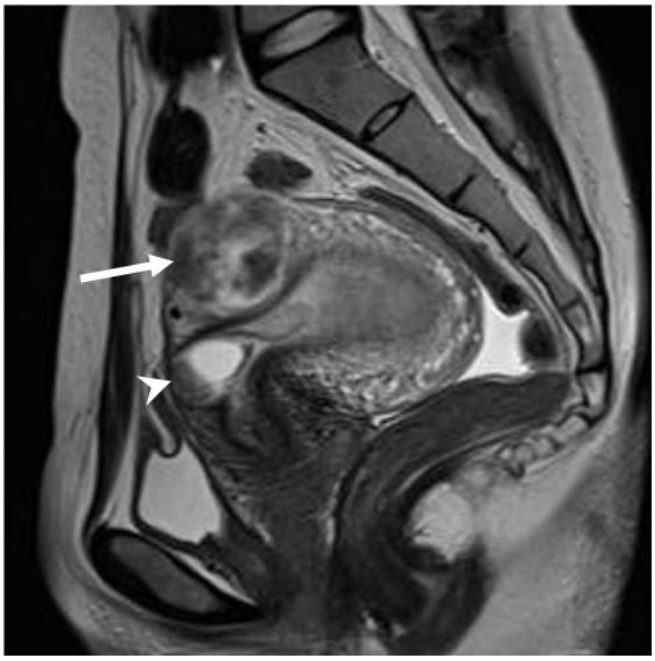

Fig. 1. A gestational sac and intramural myoma on magnetic resonance imaging (T2, sagittal plane). It shows a 41-mm intramural myoma (arrow) at the uterine anterior wall and a 25-mm gestational sac (arrowhead) on the right lower uterine segment.

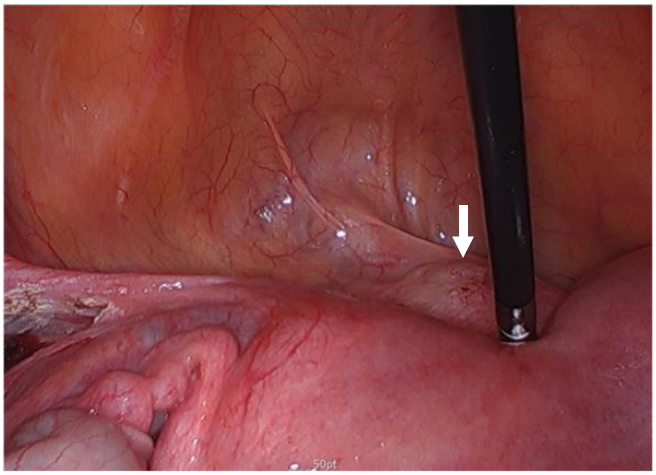

Fig. 2. Focus of the ectopic pregnancy (arrow) protruding outwards from the uterine lower segment.

the ectopic pregnancy was verified at the uterine lower segment and excised without residual lesion. The products of conception on the lower anterior myometrium were removed using spoon forceps (Fig. 3). No massive bleeding occurred from the implantation site while removing the gestational sac. After complete excision, clear bifurcated endocervical canals could be identified without residual lesion (Fig. 4). As a final step, the uterus was repaired layer-by-layer. The defective myometrium was sutured using VICRYL sutures (Ethicon, Somerville, NJ, USA) to prevent occlusion of the bifurcated endocervical canals. The uterine serosa was sutured with 2-0 barbed monofilament sutures.

The patient's postoperative condition was uneventful, and she was discharged home on day 2 after surgery. The histological analysis of the extracted tissue confirmed that it was gestational tissue. Ultrasonography was performed and β-HCG level was assessed 2 weeks later during her follow-up at the outpatient clinic. The ultrasonography showed that the CSP had completely resolved and endometrial thickness was approximately 15 mm without myometrial defect; the β-HCG level also decreased to 88 mIU/mL. She is currently being followed up for 28 months with no surgery-related problems noted to date.

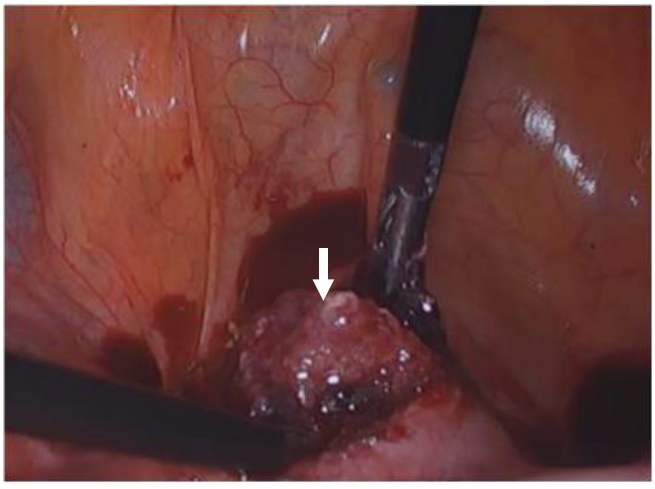

Fig. 3. Products of conception (arrow) on the lower anterior myometrium.

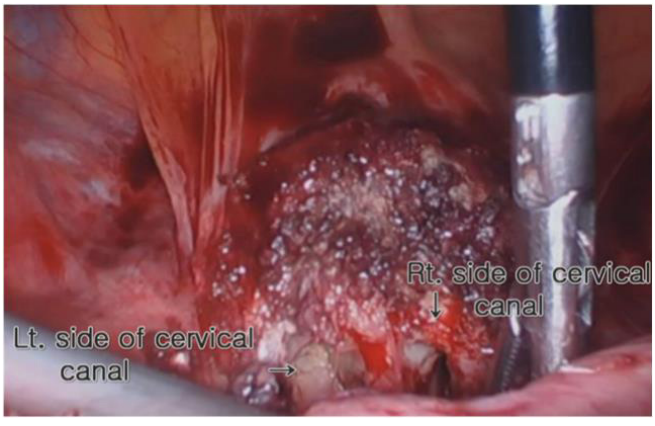

Fig. 4. Bifurcated endocervical canals. Lt, left; Rt, right.

Discussion

We presented a 34-year-old patient who had been diagnosed with uterine didelphys during a fertility test and had previously undergone a cesarean section. She was asymptomatic at 7 weeks gestation with suspected CSP detected by imaging. Although we successfully finished the laparoscopic surgery by excising and repairing the myometrial defect, we performed the surgery under anatomical uncertainty. Moreover, as in our patient's case, CSP in patients with uterine malformations, such as uterine didelphys, can make treatment decisions more difficult. Due to limited reports and varying clinical circumstances involving CSPs, the treatment decision is made by clinical judgment and a clinician's preference among various treatment options. Options range from expectant management, medical management (systemic or gestational sac injections), and surgical approaches. Regardless, early diagnosis and treatment can provide the best outcome because delayed treatment due to misdiagnosis is associated with severe maternal morbidity and mortality due to bleeding risks [7].

Methotrexate (MTX) is a common treatment for ectopic pregnancy and has traditionally been considered an option for ectopic pregnancies with β-HCG values less than 10,000 mIU/mL. In a review report, systemic MTX treatment for CSPs was found to be effective when the serum β-HCG levels were less than 12,000 mIU/mL and fetal cardiac activity was negative [8]. Unlike tubal pregnancies, exposure of the gestational sac to MTX is limited with CSPs due to the fibrous tissue surrounding the gestational sac. This means that local MTX injection is considered an alternative [7]. However, Peng et al. [9] reported the results of a randomized trial comparing local versus systemic injection of MTX in 104 patients with CSP, and success rates were similar for local and systemic injections (69.2% vs. 67.3%, respectively). A surgical approach was our inevitable option because the fetus had active cardiac activity and the β-HCG level was above 30,000 mIU/mL at the first visit. Surgical treatment with a success rate of over 95% is the most obvious option for gestational sac removal and uterine defect repair while maintaining fertility [10]. The main advantage of a surgical approach is that if the gestational sac is completely removed during surgery, the treatment itself can be terminated and the outpatient follow-up time can be shortened.

A variety of surgical methods can be performed, including laparotomy, laparoscopy, hysteroscopy, and dilation and curettage, de-

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pending on various circumstances, such as the patient's condition at the time of diagnosis, location of the gestational sac, and surgical skills of the attending physician. Hysteroscopy for gestational sac access can be considered in patients with normal anatomy, but it would have been difficult in our case with uterine anomalies. We chose the laparoscopic approach in consulting the patient, despite her having uterine didelphys. The first reason was that the patient's condition was hemodynamically stable. Second, as the gestational sac was presumed to be type 2 CSP (exogenic type), protruding into the abdominal cavity by MRI, it was thought that the gestational sac would be easily accessible through laparoscopy. In related literature, it was reported that laparoscopic surgery in CSP is suitable when the gestational sac is growing toward the abdominal cavity [11,12]. Third, surgeons are more likely to choose the procedure they are most familiar with, especially in difficult circumstances involving patients with CSP and uterine didelphys. Finally, since laparoscopic resection of CSP has been reported at up to 11 weeks gestation, the gestational sac was considered sufficiently accessible [13].

There are several case reports of laparoscopic bilateral ligation of the uterine arteries during surgical management of CSP, and we also removed the gestational sac after bilateral ligation of the uterine arteries [14,15]. Ligating both uterine arteries prior to removal of the gestational sac is a very useful procedure, as it can minimize bleeding risk and enables the surgeon to perform the operation under stable conditions. In randomized clinical trials, permanent uterine artery ligation was an effective method for blood loss reduction in surgeries for excision and myometrial defect repair [16,17]. Although there have been reports that permanent uterine artery ligation is associated with early miscarriage, intrauterine growth restriction, and preterm birth [18,19], if the patient wishes no future pregnancy, it is a surgical procedure that can be fully considered, as in our case.

As cesarean delivery increases, clinicians will have more clinical experience with CSPs, but CSPs are still rare to date and those with uterine malformations are even rarer. To our knowledge, this is the first case report of CSP in a woman with uterine didelphys in the medical literature. Therefore, it is important for clinicians to identify this rare condition, such as with uterine didelphys, and to make an accurate diagnosis for prompt treatment. The optimal management of CSP in a patient with uterine didelphys remains unclear. The choice of treatment modality can be influenced by various clinical conditions, including the type of CSP, gestational week, hemodynamic stability, level of β-HCG, possibility of future pregnancy, clinician expertise, and surgical proficiency. Surgical treatment has a high success rate. However, the surgeon must be skilled, especially in laparoscopic surgery, and the surgical risk itself must be discussed with the patient.

In summary, this case is the successful treatment of a woman with CSP and uterine didelphys through a laparoscopic approach. We demonstrated that a laparoscopic stepwise approach can ensure a safe and efficient surgical treatment of CSP. Although the surgical approach selected in our report is one of various treatment methods for CSP, it can be a useful reference for similar cases in the future.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization, Project administration: TKJ; Writing-original draft: all authors; Writing-review & editing: all authors.

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Case report

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Cerebral fat embolism syndrome: diagnostic challenges and catastrophic outcomes: a case series

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Fat embolism syndrome is a rare but alarming, life-threatening clinical condition attributed to fat emboli entering the circulation. It usually occurs as a complication of long-bone fractures and joint reconstruction surgery. Neurological manifestations usually occur 12 to 72 hours after the initial insult. These neurological complications include cerebral infarction, spinal cord ischemia, hemorrhagic stroke, seizures, and coma. Other features include an acute confusional state, autonomic dysfunction, and retinal ischemia. In this case series, we describe three patients with fat embolism syndrome who presented with atypical symptoms and signs and with unusual neuroimaging findings. Cerebral fat embolism may occur without any respiratory or dermatological signs. In these cases, diagnosis was established after excluding other differential diagnoses. Neuroimaging using brain magnetic resonance imaging is of paramount importance in establishing a diagnosis. Aggressive hemodynamic and respiratory support from the beginning and consideration of orthopedic surgical intervention within the first 24 hours after trauma are critical to decreased morbidity and mortality.

Keywords: Brain; Fat embolism syndrome; Injuries; Trauma

Introduction

Fat embolism syndrome is a rare but alarming, life-threatening clinical condition attributed to fat emboli entering the circulation [1]. The first animal model of this syndrome was described over 350 years ago by Lower, who intravenously injected milk into dogs. Magendie performed more elaborate studies in the early 19th century and observed that intravenous injection of oil led to pulmonary edema and the mechanical obstruction of small vessels by fat globules. The first human cases of fat embolism syndrome were described by Zenker in 1862 in patients with severe traumatic crush injuries. He reported the presence of fat droplets in the lung capillaries of railroad workers who died following crush injuries [2]. Since then, fat embolism syndrome has become an interesting research topic, and theories of its pathophysiology and diagnostic criteria have been described [3]. In this case series, we describe

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three patients with fat embolism syndrome who presented with atypical symptoms, signs, and neuroimaging findings. We also review other atypical neurological presentations of this disorder.

Cases

Ethical statements: This study was approved by the Institutional Review Board (IRB) of King Abdullah International Medical Research Center (IRB No: NRJ22J/143/05). Informed consent was obtained according to the Declaration of Helsinki.

1. Case 1

A 23-year-old male presented to the emergency department with polytrauma sustained during a road traffic injury. He had a thoracic vertebral fracture (T6), left humeral shaft fracture, left femoral shaft fracture, right leg crush injury, and right comminuted femoral fracture. At presentation, his vital signs were normal, and he was awake, alert, and communicating. Two days after admission, he developed confusion, drowsiness, and altered sensorium with a drop in his Glasgow Coma Scale (GCS) score to 9/15. Although a detailed neurological examination was challenging due to confusion and agitation, there were no apparent focal or lateralizing signs. The patient was sedated, intubated, mechanically ventilated, and transferred to the intensive care unit. An urgent brain computed tomography (CT) scan revealed generalized edema with no signs of infarction or hemorrhage. He was administered quetiapine (150 mg twice daily) and clonazepam (0.5 mg once daily). On the sixth day of admission, urgent brain magnetic resonance imaging (MRI) revealed extensive bilateral symmetrical punctate foci of nearly the same size with abnormal signal intensities. These foci affected both the cerebral and cerebellar hemispheres with restricted diffusion, decreased signals in susceptibility-weighted imaging (SWI) indicative of microbleeds, and mottled fluid-attenuated inversion recovery (FLAIR) signals (Fig. 1). The MRI appearance suggested a diagnosis of cerebral fat embolism. The patient endured a stormy course in the intensive care unit for two additional months before being transferred to the orthopedic ward, where he underwent surgery for his fractures. The patient was discharged in a stable condition with follow-up at a multidisciplinary clinic and rehabilitation program.

2. Case 2

A 30-year-old male presented to the emergency department 3 hours after a road traffic injury with a right comminuted femoral fracture, left proximal tibial fracture, and left fibular fracture. A few hours later, his level of consciousness started to decline, and he became unresponsive, with a GCS score of 8/15. He also developed oxygen desaturation (O_2 of 92%) and was sedated and intubated with subsequent transfer to the intensive care unit. A plain CT scan of the brain was unremarkable, with no ischemia or hemorrhage. Three days later, the patient showed no improvement in the level of consciousness when sedation was stopped. Due to this unexplained drop in his level of consciousness, brain MRI was ordered on the fifth day of admission and revealed extensive small high-signal-intensity lesions of the whole brain, resembling a starfield pattern in T2-weighted and FLAIR images with restricted diffusion and microhemorrhages in SWI (Fig. 2). The patient endured a stormy course in which he remained in the intensive care unit for 1 month with no significant neurological improvement. He underwent orthopedic fixation surgery and was transferred with a tracheostomy to a rehabilitation floor. He continued to improve slowly with the help of a multidisciplinary team and rehabilitation.

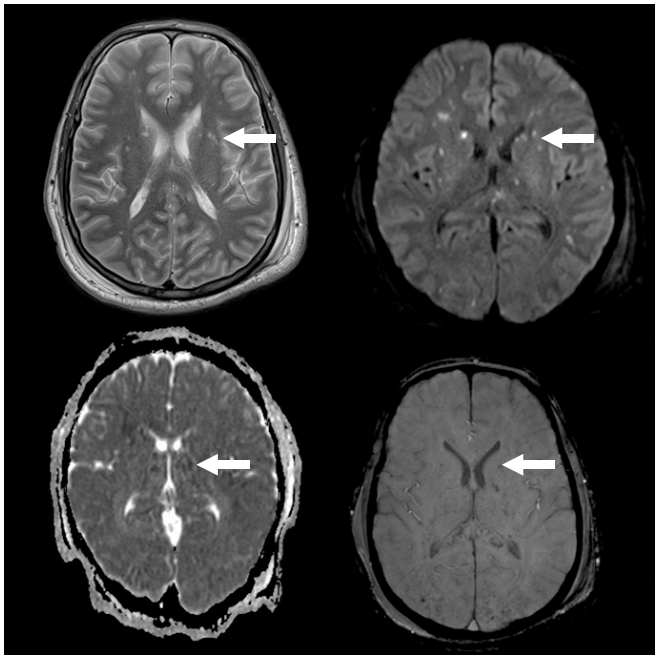

Fig. 1. Brain magnetic resonance images show extensive bilateral, symmetrical punctate foci of nearly the same size and abnormal signal intensities affecting both cerebral and cerebellar hemispheres with diffusion restriction and decreased susceptibility-weighted imaging (microbleeds) and mottled fluid-attenuated inversion recovery signals. Arrows indicate one of the foci as an example.

3. Case 3

A 19-year-old male was admitted after a road traffic injury with multiple fractures (right proximal tibial and right femoral fractures). The patient was conscious, alert, and communicating, with

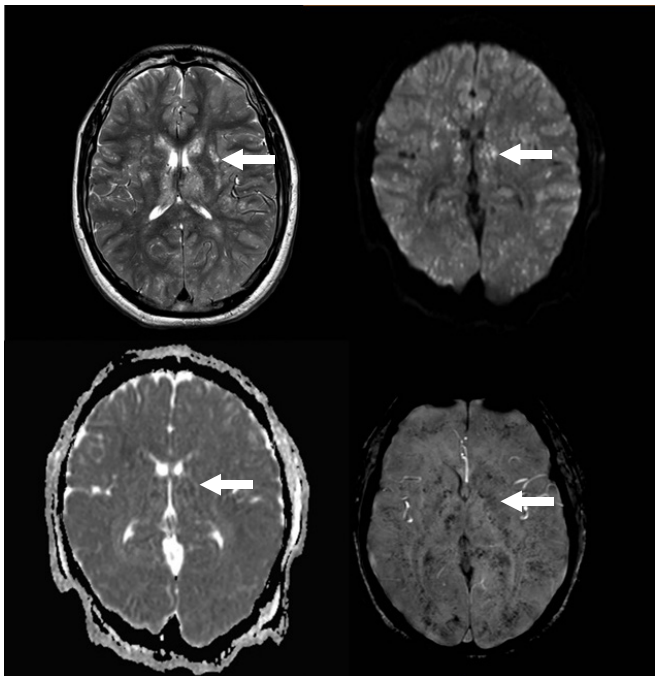

Fig. 2. Brain magnetic resonance images show extensive small high-signal intensity lesions involving the whole brain giving the appearance of a starfield pattern on T2-weighted images with restricted diffusion and profuse microhemorrhages in susceptibility-weighted imaging. Arrows indicate one of the lesions as an example.

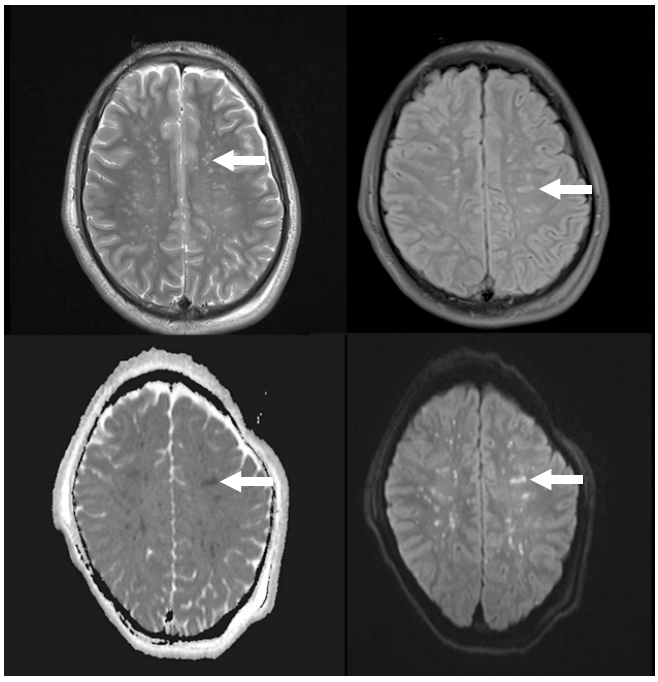

Fig. 3. Brain magnetic resonance images show innumerable deep-white-matter, high-signal foci on T2-weighted images and low-signal foci on T1-weighted images showing restricted diffusion on diffusion-weighted imaging. Some images show blooming artifacts on susceptibility-weighted imaging consistent with multiple small infarctions and some show hemorrhagic components consistent with fat embolism. Arrows indicate one of the foci as an example.

a normal GCS score. A few hours later, he developed acute onset loss of consciousness (GCS score of 3/15) with subsequent sedation, intubation, and mechanical ventilation with immediate transfer to the intensive care unit. One day later, he developed convulsive status epilepticus with repeated episodes of generalized tonic-clonic seizures. He was administered phenytoin and valproic acid and maintained on maintenance therapy with three antiepileptic drugs (phenytoin, valproic acid, and levetiracetam). His electroencephalogram (EEG) showed generalized slowing of the background with frequent generalized epileptiform discharges. Despite treatment, the patient remained in refractory status epilepticus, after which he was fully sedated with midazolam. On the third day, MRI of the brain showed innumerable deep-white-matter, high-signal foci on T2-weighted images and low-signal foci on T1-weighted images showing restricted diffusion on diffusion-weighted imaging. Some foci showed blooming artifacts on SWI, consistent with multiple small infarctions, and some foci showed hemorrhagic components consistent with fat embolism (Fig. 3). The patient continued to have refractory generalized tonic-clonic seizures, and workups for other differential diagnoses, including central nervous system infection and autoimmune encephalitis, were negative. He eventually improved and was transferred to the orthopedic ward, where he was managed conservatively. The patient was subsequently discharged and received multidisciplinary care, including rehabilitation.

Discussion

Fat embolism syndrome is characterized by the classic triad of respiratory compromise, neurological impairment, and petechial skin rashes [4]. Neurological manifestations usually occur 12 to 72 hours after the initial insult. These neurological complications include cerebral infarction, spinal cord ischemia, hemorrhagic stroke, seizures, and coma. Other features include an acute confusional state, autonomic dysfunction, and retinal ischemia. These neurological symptoms and signs are usually nonlocalized with variable severity, which may present a diagnostic challenge, especially in the absence of simultaneous pulmonary and/or dermatological manifestations [5]. None of our patients had a petechial skin rash; one patient experienced oxygen desaturation but showed no radiographic lung changes. The final diagnosis was established mainly by classical neuroimaging findings and exclusion of mimickers

such as brain hemorrhage or ischemia following head trauma, metabolic encephalopathy, and drug toxicity. MRI of the brain is the diagnostic modality of choice for cerebral fat embolism syndrome.

Neurological involvement occurs as a result of the migration of fat globules to the central nervous system following adipose tissue damage and the passage of fat globules into open-ended ruptured venous channels. This physical mechanism is augmented by additional biochemical mechanisms incorporating plasma intermediaries that promote fat embolization from storage, with subsequent formation of fat globules in the intravascular compartment. Severe hypoxia due to respiratory failure is another contributing factor [6].

Although neurological manifestations may occur in up to 65% of patients with fat embolism syndrome, seizures occur in only 20% of cases [7]. Seizures could be focal, with or without secondary generalization, or generalized tonic-clonic seizures from the onset. There have been only three previous reports of nonconvulsive status epilepticus secondary to fat embolism [8]. The third patient in our series appears to be the first case of super-refractory convulsive status epilepticus secondary to cerebral fat embolism reported in the literature. Seizures and status epilepticus from cerebral fat embolism are treated in the same manner as those from any other cause, utilizing the available protocols practiced in the treatment center. EEG, especially continuous EEG monitoring, is a necessary tool for the diagnosis, response to antiepileptic therapy, and detection of nonconvulsive status epilepticus.

MRI is the most sensitive tool for demonstrating changes in the brain related to fat embolism syndrome. Most lesions are distributed in specific areas of the brain, including the centrum semiovale, subcortical white matter, ganglionic regions, and thalamus. In addition, five distinct brain patterns have been reported in the literature, namely starfield-scattered cytotoxic edema, confluent cytotoxic edema in white matter, vasogenic edema lesions that may enhance, petechial hemorrhage of white matter, and chronic sequelae patterns [9]. The neuroimages in our case were fascinating; the diagnoses were suspected and confirmed based on these images. We recommend performing MRI of the brain in any patient with long-bone fractures who develops unexplained deterioration in the level of consciousness and seizures.

The mainstay treatment for fat embolism syndrome is preventive and supportive measures with no specific treatment guidelines. The use of steroids is controversial, although the hypothetical benefit may be justified by their anti-inflammatory role and capacity to reduce capillary permeability [10]. Based on observations from the patients reported in our case series, early and adequate hemodynamic and respiratory support and prevention of sepsis are major steps to avoid morbidity and mortality. In addition, early surgical intervention performed within 24 hours after trauma may reduce the risk of cerebral fat embolism.

Cerebral fat embolism is a rare syndrome that is potentially devastating and has poorly elucidated pathophysiological mechanisms. It usually occurs as a complication of long-bone fractures and joint reconstruction surgery. Cerebral fat embolism may occur without any respiratory or dermatological signs. In these cases, diagnosis is established after excluding other differential diagnoses. Neuroimaging using brain MRI is of paramount importance in establishing a diagnosis. Early aggressive hemodynamic and respiratory support and consideration of orthopedic surgical intervention within the first 24 hours after trauma are critical to decreasing morbidity and mortality.

Notes

Conflicts of interest

No potential conflicts of interest relevant to this article was reported.

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Author contributions

Conceptualization: HAA, SAA; Data curation: HAA, NA, FA, WA; Formal analysis: HAA, BHS, NA, FA, WA; Validation: SAA; Resources, Supervision, Project administration: HAA; Visualization: HAA, WA; Writing-original draft: all authors; Writing-review & editing: all authors.

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Case report

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Transient osteoporosis of the hip with a femoral neck fracture during follow-up: a case report

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We report a case of transient osteoporosis of the hip with a femoral neck fracture found during follow-up. A 53-year-old man presented with left hip pain without trauma. The pain did not improve after 2 weeks and he was brought to our hospital by ambulance. Magnetic resonance imaging (MRI) of the left hip joint showed diffuse edema in the bone marrow, which was identified by low signal intensity on T1-weighted images, high signal intensity on T2-weighted images, and increased signal intensity on short tau inversion recovery. This edema extended from the femoral head and neck to the intertrochanteric area. He was diagnosed with transient osteoporosis of the left hip. Rest gradually improved his pain; however, 3 weeks later, his left hip pain worsened without trauma. X-ray, computed tomography, and MRI results of the hip joint demonstrated a left femoral neck fracture, and osteosynthesis was performed. Differential diagnoses included avascular necrosis of the femoral head, infection, complex regional pain syndrome, rheumatoid arthritis, leukemia, and other cancers. Transient osteoporosis of the hip generally has a good prognosis with spontaneous remission within a few months to 1 year. However, a sufficient length of follow-up from condition onset to full recovery is necessary to avoid all probable complications such as fractures.

Keywords: Complications; Femoral neck fractures; Magnetic resonance imaging; Surgery; Osteoporosis

Introduction

Transient osteoporosis of the hip (TOH) is a rare disease that was first reported in 1959 in three pregnant women who had strong unilateral or bilateral hip pain [1]. TOH generally occurs in middle-aged men and pregnant women in their last trimester [2-4]. Its etiology is unknown; however, it is suspected that ischemia in the femoral head could be involved in the onset of TOH [5-7]. Differential diagnosis includes avascular necrosis of the femoral head, infection, complex regional pain syndrome, rheumatoid arthritis, leukemia, and other cancers. TOH is conventionally a disease with a good prognosis and spontaneous remission within a few months to 1 year. We report a case of TOH where a femoral neck fracture later occurred without trauma, and osteosynthesis was performed.

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Case

Ethical statements: Written informed consent was obtained from the patient for this case report. This study was approved by the Institutional Review Board (IRB) of Musashino General Hospital (IRB No: 12).

A 53-year-old man presented with left hip pain without trauma that had persisted for 2 weeks. After the pain did not subside, he was brought to our hospital by ambulance. He had schizophrenia and epilepsy resulting from a previous head injury. He drank approximately 1.5 L of beer every day and had smoked 20 cigarettes per day for 37 years.

On the first admission, he had difficulty walking due to severe left hip pain. The blood examination was normal. His left hip joint demonstrated painful limitations in passive range of motion. Patrick's test was positive.

X-ray and computed tomography (CT) revealed no obvious fracture (Fig. 1). Magnetic resonance imaging (MRI) showed diffuse edema in the bone marrow, which was identified by low signal intensity on T1-weighted images, high signal intensity on T2-weighted images, and increased signal intensity on short tau inversion recovery (STIR). This edema extended from the femoral head and neck to the intertrochanteric area (Figs. 2, 3).

We prescribed rest and non-weight bearing for him; however, he did not follow our instructions due to his psychological condition. His pain gradually improved and he was discharged from our hospital using crutches.

Three weeks later, his left hip pain worsened without trauma and he visited our hospital again. X-ray, CT scan, and MRI of the hip joint demonstrated a left femoral neck fracture (Garden stage II) (Figs. 4–6), and osteosynthesis (Prima Hip Screw System, Japan Medical Dynamic Marketing, Inc., Tokyo, Japan) was performed (Fig. 7).

Discussion

TOH generally affects middle-aged men and pregnant women in their last trimester [2-4]. It is usually bilateral in pregnant women and unilateral in middle-aged men [8]. The cause and pathogenesis of TOH remain unclear; however, the most dominant theory implicates femoral head ischemia due to venous obstruction as the cause [5-7]. On examination, bone biopsies of patients with TOH showed increased numbers of erythrocytes, suggesting the presence of venous stasis [5]. Furthermore, Orth and Anagnostakos [9] reported that decreased concentrations of fibrinolytic agents and increased concentrations of thrombophilia markers in TOH patients could potentially cause venous obstruction. Risk factors for TOH include trauma, a history of steroid use, consumption of

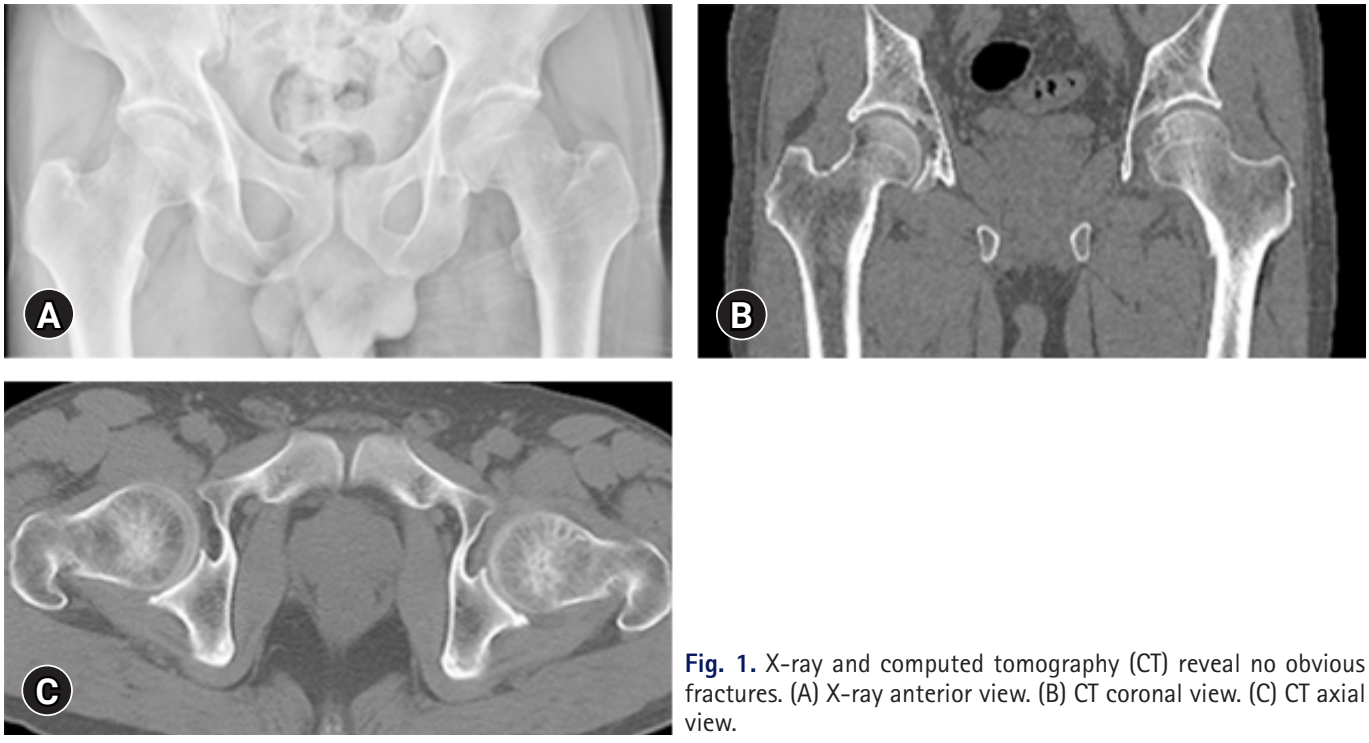

Fig. 1. X-ray and computed tomography (CT) reveal no obvious fractures. (A) X-ray anterior view. (B) CT coronal view. (C) CT axial view.

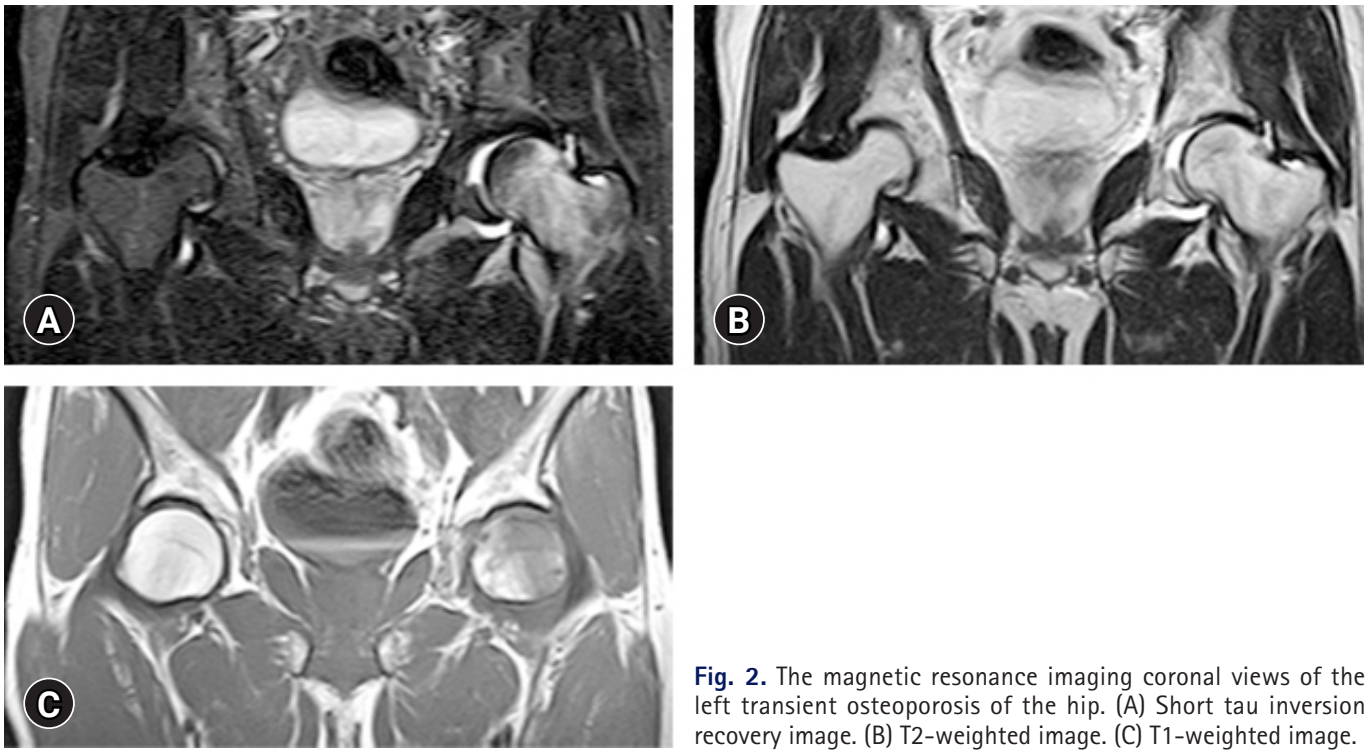

Fig. 2. The magnetic resonance imaging coronal views of the left transient osteoporosis of the hip. (A) Short tau inversion recovery image. (B) T2-weighted image. (C) T1-weighted image.

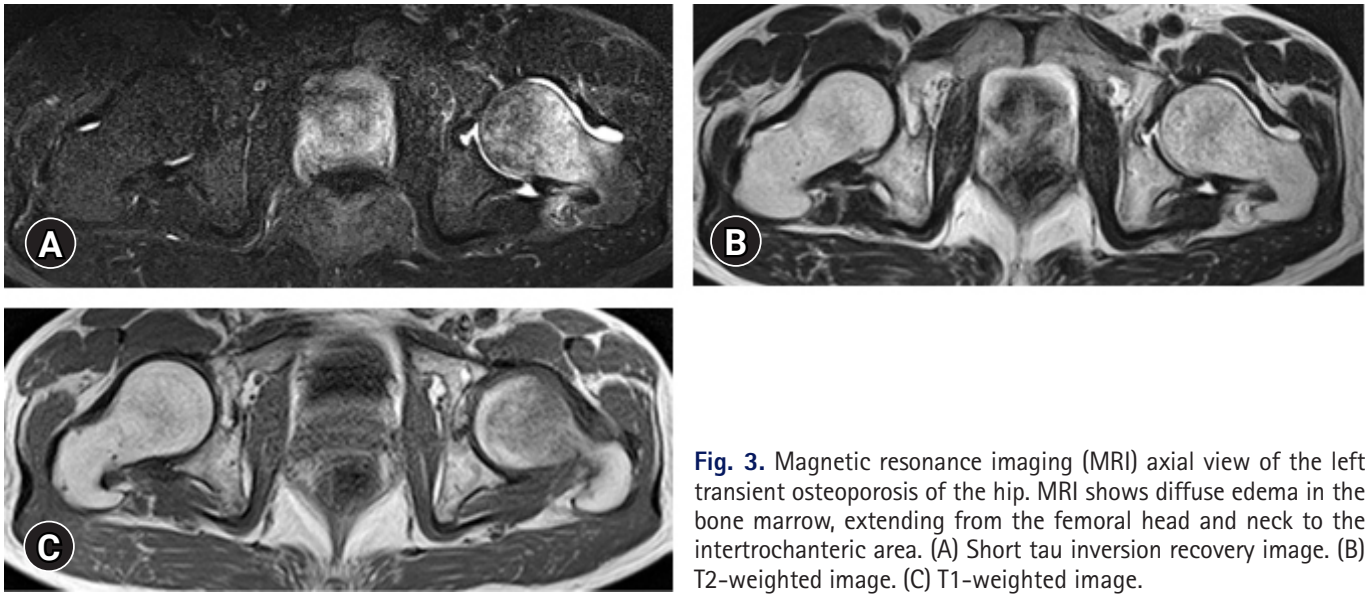

Fig. 3. Magnetic resonance imaging (MRI) axial view of the left transient osteoporosis of the hip. MRI shows diffuse edema in the bone marrow, extending from the femoral head and neck to the intertrochanteric area. (A) Short tau inversion recovery image. (B) T2-weighted image. (C) T1-weighted image.

alcohol, smoking, low testosterone levels, low vitamin D levels, osteogenesis imperfecta, hypothyroidism, and hypophosphatasia [10-13]. In this case, smoking and alcohol were mentioned as risk factors.

MRI is the most powerful tool for the diagnosis of TOH and usually shows low signal intensity on T1-weighted images, high signal intensity on T2-weighted images, and increased signal intensity on STIR, reflecting bone marrow edema.

TOH typically has a good prognosis with spontaneous remission occurring within a few months to 1 year. Methods for joint preservation, including restricted weight bearing, are the first-line therapy. As alternative treatments, the use of bisphosphonates to inhibit bone resorption and the use of teriparatide as an osteoanabolic agent were reported to provide successful outcomes [14-17].

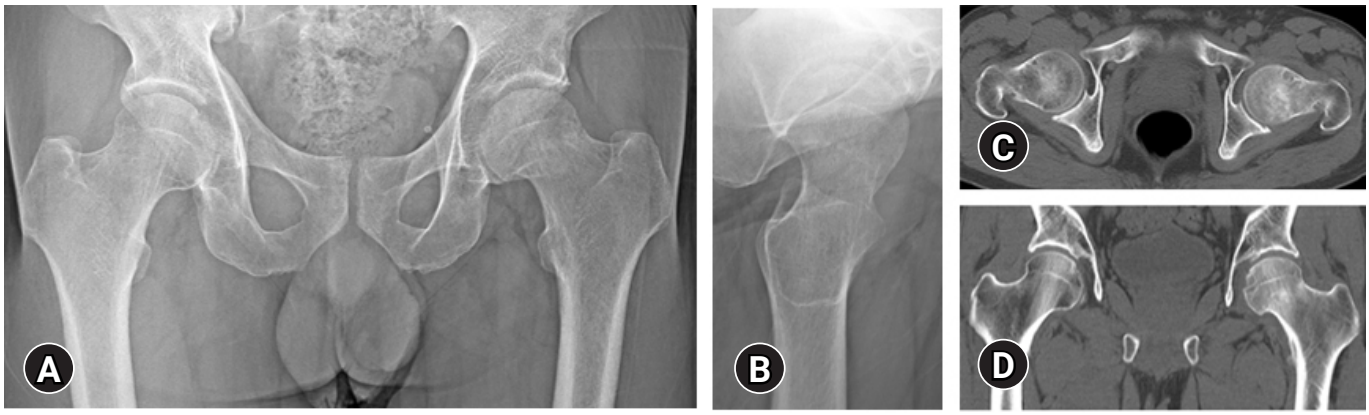

Fig. 4. The left femoral neck fracture. It is difficult to find the fracture line of the femoral neck, by either X-ray or computed tomography (CT). (A) X-ray anterior view. (B) X-ray lateral view. (C) CT axial view. (D) CT coronal view.

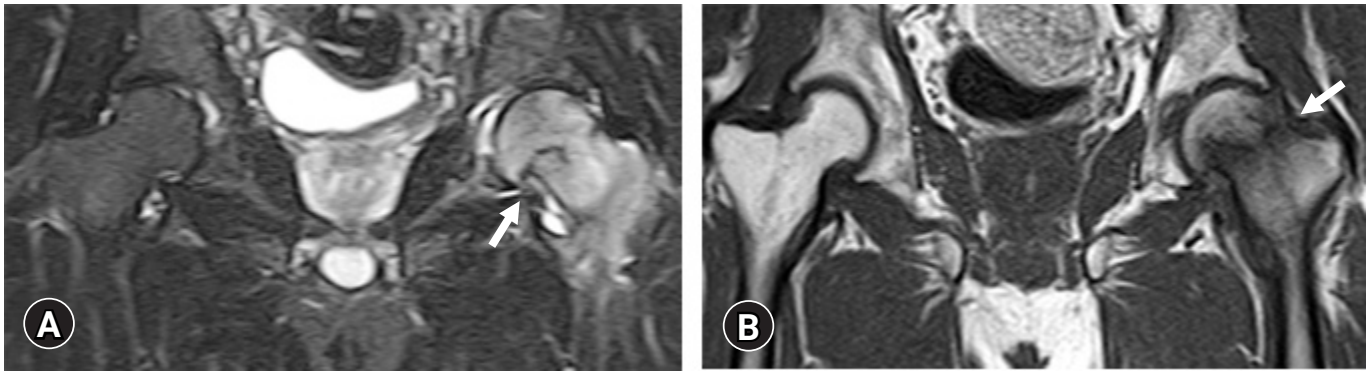

Fig. 5. Magnetic resonance imaging coronal view of the left femoral neck fracture (arrows). (A) Short tau inversion recovery image. (B) T1-weighted image.

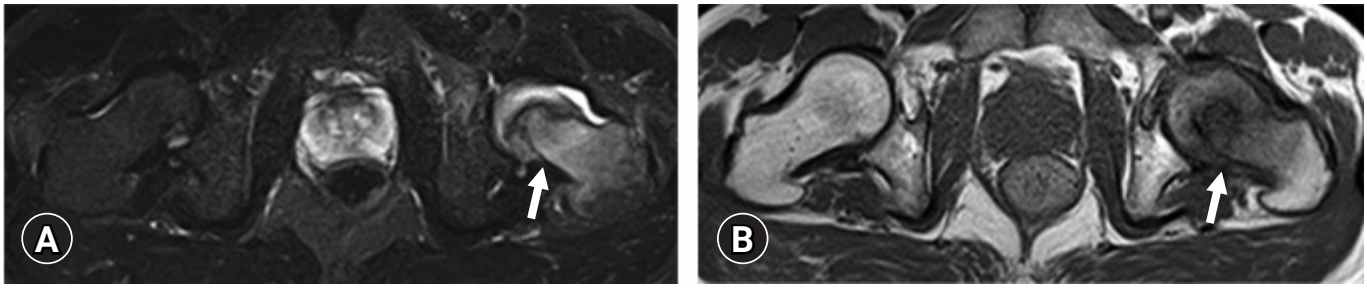

Fig. 6. Magnetic resonance imaging (MRI) axial view of the left femoral neck fracture (arrows). MRI shows a clear fracture line in the left femoral neck. (A) Short tau inversion recovery image. (B) T1-weighted image.

Additionally, hyperbaric oxygen therapy was reported to potentially accelerate recovery in TOH patients, although the effects were not statistically significant [18]. More recently, out of 15 TOH cases, 10 underwent hip drilling for core decompression while five underwent conservative therapy. An investigation of the time to full recovery revealed that hip drilling required a median of 5.8 weeks while conservative therapy required 48.3 weeks, demonstrating the validity of hip drilling as a treatment modality [19].

In the present case, regarding our recommendations to avoid bearing weight, the patient was nonadherent due to his poor mental health; therefore, it was assumed that the constant stress of weight bearing caused the femoral neck fracture. In fact, the fracture pattern in this case originated in the lower part of the femoral neck and is considered to be a pathological condition similar to insufficient fracture secondary to TOH. Interestingly, Hadji et al. [20] demonstrated that out of 52 TOH patients, 12.1% sustained a

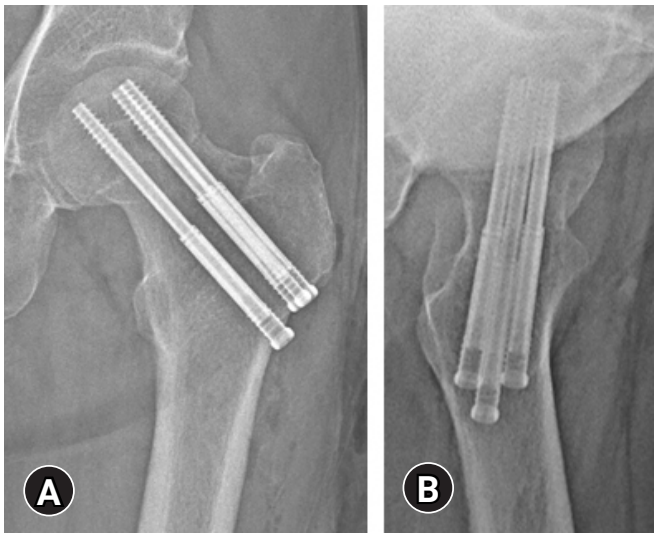

Fig. 7. Osteosynthesis with three Prima Hip screws (Japan Medical Dynamic Marketing, Inc., Tokyo, Japan). (A) X-ray anterior view. (B) X-ray lateral view.

hip fracture. Therefore, for patients with a high likelihood of fracture, it is necessary to provide thorough education, such as instructions not to apply a load to the lower limbs during a specified period. Prophylactic osteosynthesis may also be considered for patients expected to have a high likelihood of fracture. Considering these factors, a sufficient follow-up period from condition onset to full recovery is necessary to avoid as many complications as possible.

Notes

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization, Supervision: YT, TM; Data curation: YT, SM, MM; Formal analysis: SM, MM, KO, YT, TM; Investigation: YT; Writing-original draft: YT; Writing-review & editing: all authors.

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Communication

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The art of diabetes care: guidelines for a holistic approach to human and social factors

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A holistic approach to diabetes considers patient preferences, emotional health, living conditions, and other contextual factors, in addition to medication selection. Human and social factors influence treatment adherence and clinical outcomes. Social issues, cost of care, out-of-pocket expenses, pill burden (number and frequency), and injectable drugs such as insulin, can affect adherence. Clinicians can ask about these contextual factors when discussing treatment options with patients. Patients' emotional health can also affect diabetes self-care. Social stressors such as family issues may impair self-care behaviors. Diabetes can also lead to emotional stress. Diabetes distress correlates with worse glycemic control and lower overall well-being. Patient-centered communication can build the foundation of a trusting relationship with the clinician. Respect for patient preferences and fears can build trust. Relevant communication skills include asking open-ended questions, expressing empathy, active listening, and exploring the patient's perspective. Glycemic goals must be personalized based on frailty, the risk of hypoglycemia, and healthy life expectancy. Lifestyle counseling requires a nonjudgmental approach and tactfulness. The art of diabetes care rests on clinicians perceiving a patient's emotional state. Tailoring the level of advice and diabetes targets based on a patient's personal and contextual factors requires mindfulness by clinicians.

Keywords: Chronic disease; Communication; Diabetes mellitus; Psychology; Self-management

A holistic approach to diabetes

As a long-term illness affected by lifestyle, diabetes requires a holistic approach [1-3]. Holistic care in clinical medicine may be defined as a focus on overall health and well-being [4]. It is humane, compassionate, service-oriented, and relationship-based. Its vision encompasses clinical, human, and societal contexts. This high-level perspective is based on the contextual mindfulness of clinicians [5].

Context of the illness

Factors such as health literacy, access to care, family support, and living conditions can influence diabetes outcomes [6]. Issues such as the availability of whole foods, home-cooked meals, and support from household members can affect nutrition [7]. Access to parks, safe walking paths, and clean neighborhoods supports an active lifestyle. Clinicians should ask about, document, and consider these nonmedical factors (social determinants of health) in treatment planning (Table 1). Children, women who are pregnant, ethnic minorities, those who are older, individuals with extreme obesity, rural residents, and those with comorbid mental health conditions require special consideration regarding these contextual factors [8,9].

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Emotional health

Psychosocial stress due to family dysfunction and work pressure can profoundly impact diabetes. Patients experiencing stressors may experience difficulties following diabetes self-care instructions [10]. Diabetes can cause distress, which is the emotional stress associated with living with diabetes [11]. Emotional stress is important in patients with diabetes and should be considered in clinical care. Diabetes imposes a relentless burden of daily medications and dietary restrictions. Diabetes distress is more common in patients with type 1 diabetes and insulin-treated type 2 diabetes [12]. Higher diabetes distress correlates with worse glycemic control and lower overall well-being [13]. However, a normal glycated hemoglobin (HbA1c) level does not rule it out. Diabetes distress is more common than and can be confused with depression [14].

Increasing pill burden and frequent glucose monitoring worsen distress. Clinicians should explore patients' feelings about living with diabetes.

Patient-centered communication

Patient-centered communication is the foundation of a trust-based relationship [15]. Core skills include eliciting the patient's agenda and priorities, asking open-ended questions, active listening, responding with empathy and non-verbal gestures (concerned facial expression and head nodding), and exploring the patient's per-

Table 1. Eliciting contextual factors in diabetes

Domain	Item	Clinical interview question
Social	Diabetes distress	Are you feeling overwhelmed by diabetes?
		Is it difficult to keep track of all your medicines?
		How many tablets and injections do you take in a day?
	Cost of care	Do you feel you are in financial stress?
		How much do you spend on medicines every month?
	Access to care	Is it difficult for you to come to the clinic?
	Stress	Are you under stress?
		Has something stressful happened to you recently?
	Family support	Who lives with you?
		Who do you rely on if you are sick?
Lifestyle	Physical activity	What are your options for exercise?
		What can you do to be more active?
		What do you enjoy doing outdoors?
	Nutrition	Tell me about the food you eat.
		Do you buy food and cook for yourself?
		What can you do to eat healthier?
Patient's perspective	Ideas	What problems do you face in managing diabetes?
		What has caused you to have diabetes?
	Concerns	What are you worried about that might happen to you?
		Do you worry about blood sugar becoming very low?
	Expectations	Is there something specific that you need from us today?
		Are you satisfied with your diabetes care?
		What can we do to serve you better?
Motivational	Goal setting	Where do you see yourself five years from now?
		What are your life goals for the long term?
	Affirmation	I admire your commitment to ...
		Good work with sticking to your ...
		Nice work! I'm proud of you.
		You look younger than your age!
	Rephrasing/summarizing	So, what you're saying is ...
		Let me summarize ...
	Change talk	While you enjoy ... but one of your goals is to ...
		How do you reconcile ... while hoping to ...

spective. The patient's ideas about disease causation, concerns about the impact on daily living, and unexpressed expectations influence diabetes self-care.

Individuals with diabetes may fear its impact on their lives. Such fears include the risks of blindness, amputation, dialysis, and painful neuropathy. Initiating insulin injections is a common concern. Additionally, individuals may be worried about hypoglycemia, leading to loss of consciousness, social embarrassment, reduced mental acuity, and sudden death. They may hide these fears from health professionals because of reticence or concerns regarding restrictions on driving and independent living. It is important to alleviate a patient's fears and concerns through patient-centered communication.

Cost burden

Physicians should be more mindful of the costs borne by patients and their healthcare systems. Overburdened care can lead to the discontinuation of essential interventions. The cumulative long-term burden can be prohibitive for many individuals [16,17]. As the diabetes care paradigm shifts from glycemic control to patient-oriented outcomes such as reducing macrovascular complications, medication selection needs to be more transparent. A thoughtful discussion on drug prices, co-pays, and the expected benefits of treatment can empower patients.

Frequent laboratory requests, such as HbA1c, electrolytes, and renal and liver function tests, may be burdensome without altering medical management. Excessive fingerstick glucose testing may be less useful in patients with stable type 2 diabetes receiving oral medication [18]. Simply informing patients about their HbA1c results, without discussing behavioral issues, does not seem to improve lifestyle choices [19]. Monitoring clinical parameters, such as blood pressure, waist circumference, vision (fundoscopy, visual acuity, and peripheral vision), and foot sensation, may be more useful in resource-constrained settings. Although less effective than an in-person interaction, follow-up via telephone can reduce the burden of clinic visits.

Glycemic goals

The target HbA1c level for many individuals must be tailored according to context. Factors such as frailty (but not necessarily age), the risk of hypoglycemia, support from household family members, and food security may need to be considered. An aggressive target may not be justifiable in an individual who is frail with a limited life expectancy. A high pill burden (number and frequency per day) can negatively affect patient morale and quality of life, sometimes leading to complete nonadherence. Patients should be asked about the burden of treatment (especially insulin). Insulin treatment may become inevitable; however, it requires the patient's commitment to be safe and successful. Respect for a patient's decision to defer insulin demonstrates epistemic humility on the part of the clinician and concern for personal autonomy. To achieve a reasonable chance of treatment adherence, the patient must feel in control. Open-ended questions ("Tell me more about your…") shift the locus of control toward the patient (Table 1). Well-designed educational resources empower patients and enable richer conversations regarding diabetes goals (Table 2).

Table 2. Selected resources for diabetes care

Domain	Resource
Websites	https://familydoctor.org/condition/diabetes/
	https://medlineplus.gov/diabetes.html
	https://www.niddk.nih.gov/health-information/diabetes
	https://www.diabetes.org.uk/diabetes-and-me
	https://www.diabetesaustralia.com.au/
	Korean
	https://diabetes.or.kr/general/
	https://www.ndss.com.au/about-diabetes/information-in-your-language/korean/
	https://a1cguide.com/what-korean-food-can-diabetics-eat/
Apps	A list of selected apps for use by patients
	https://diabetesed.net/apps-for-diabetes/
Printable	Handouts, worksheets, and self-care records
	https://dtc.ucsf.edu/learning-library/resource-materials/
	https://www.scripps.org/services/metabolic-conditions/diabetes/diabetes-professional-training/handouts
	https://integrateddiabetes.com/diabetic-logsheets/
Videos	Videos by U.S. Centers for Disease Control and Prevention
	https://youtube.com/playlist?list=PLvrp9iOILTQYNH9x0hv-Oub4_5PT9JAmc
	Animated videos about diabetes
	https://youtube.com/playlist?list=PLST_q-QNT8SIICig-JWDOs_A8U-xnW-oEa
Meal plans	A comprehensive set of resources on meal plans
	https://www.cdc.gov/diabetes/managing/eat-well/meal-plan-method.html
	A useful overview of diabetic diet with examples
	https://www.mayoclinic.org/diseases-conditions/diabetes/in-depth/diabetes-diet/art-20044295
Online communities	A list of forums, blogs, and shared resources
	https://diatribe.org/diabetes-blogs-and-forums
Decision aids	Medication choice
	https://diabetesdecisionaid.mayoclinic.org/index
Calculators	Cardiovascular risk calculator
	https://cvdcalculator.com/
	Unit converter for HbA1c and blood glucose
	https://professional.diabetes.org/diapro/glucose_calc

HbA1c, glycated hemoglobin.

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Lifestyle focus

Type 2 diabetes can be considered a lifestyle condition [20]. Despite widespread awareness, many patients are unable to adopt lifestyle recommendations [8,21]. Psychological, household, and societal obstacles form a frustrating structural barrier for these well-intentioned individuals [22]. The art of motivational interviewing lies in creating a nonthreatening space for patients to express their issues. The clinician's role mimics that of a coach. Patients' choices are not judged as good or bad but rather as congruent or in conflict with self-expressed goals. Mini-lectures on diet and exercise cannot be considered effective patient counseling. Simplistic advice disregards patients' understanding of their complex social situations and dismisses their prior attempts at change. Clinicians should avoid assigning blame for poor disease outcomes on patients. In contrast, motivational interviewing uses non-directive techniques such as patient engagement, nonjudgmental listening, exploring ambivalence about behavioral change, encouraging patient-led goal setting, and evoking patient motivation to change. Instead of a series of dreaded reminders, the clinician engages in what appears to be friendly conversation. Not all clinic visits should include lifestyle counseling. Physicians should be mindful of the patient's emotional state when handling conversations about change. Emotionally distressed patients may not be able to assimilate detailed instructions. In these situations, the physician takes a "backseat" and lets the patient express his/her ideas, fears, desires, and hopes. This awareness of the patient's emotional state and social context is based on mindfulness of the clinician [23]. The art of diabetes care relies on reflective mindfulness.

Notes

Conflicts of interest

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Resident fellow section:
Teaching images

A 40-year-old man with neuropathic pain in the entire left foot

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A 40-year-old man with no medical history visited our clinic because of pain in the entire left foot that had persisted for 1 year. The pain was aggravated by sitting, walking, running, and climbing stairs. The pain was stabbing, burning, and tingling and was rated at 7 on a numeric rating scale. In addition to left foot pain, he reported mild left buttock pain with no history of left lower limb or pelvic injury. Physical examination revealed no motor or sensory deficits, and deep tendon reflexes were normal in all four limbs. His straight leg raise test results were negative. Tinel sign over the left tibial nerve in the tarsal tunnel was negative and his foot pain was not aggravated by ankle inversion/eversion.

Differential diagnoses included lumbosacral radicular pain due to spinal disorders, tarsal tunnel syndrome, and sciatic neuropathy. Lumbar magnetic resonance imaging (MRI) showed a diffuse bulging disc on L4–L5 and L5–S1 with a high-intensity zone. No pain reduction was observed on diagnostic blocks of the left L5 and S1 nerve roots and left tibial nerve within the tarsal tunnel with 1 mL of 2% lidocaine. A nerve conduction study and electromyography of the left lower limb revealed no abnormalities.

Further investigation was conducted. On pelvic axial fat-saturated T2-weighted MRI, high signal intensity was found in the left quadratus femoris muscle (Fig. 1). Additionally, the ischiofemoral space was narrower on the left than on the right side. The sciatic nerve was located over an area with high signal intensity. The patient was diagnosed with left ischiofemoral impingement. For the injection procedure, the patient was placed in a prone position, and the left buttock was scanned with a 6-MHz curved probe (LOGIQ P6, General Electric, Seoul, Korea) to acquire axial images. A mixed solution of 20-mg

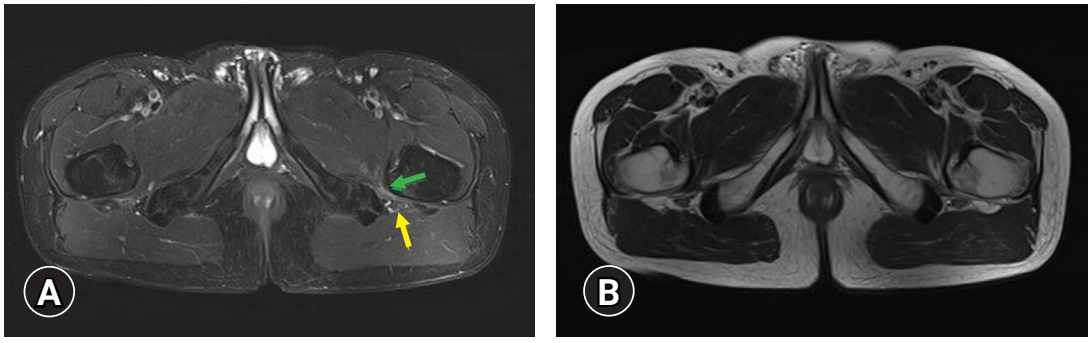

Fig. 1. (A) Pelvic axial fat-saturated T2-weighted and (B) T2-weighted magnetic resonance imaging (MRI) reveal that the ischiofemoral space is narrower on the left side than on the right side. Additionally, on the pelvic axial fat-saturated T2-weighted MRI (A), high signal intensity is found on the left quadratus femoris muscle (green arrow), indicative of muscle edema. Over the area of high signal intensity in the left quadratus femoris muscle, the left sciatic nerve is visible (yellow arrow).

triamcinolone, 1-mL 1% lidocaine, and 3.5-mL normal saline was administered via ultrasound-guided injection to the left sciatic nerve and quadratus femoris muscle. The patient's pain was alleviated by 80% at the 3-week follow-up examination.

Ischiofemoral impingement is an uncommon cause of buttock pain due to impingement of the quadratus femoris muscle between the lesser trochanter and lateral border of the ischium [1-3]. Most patients with ischiofemoral impingement experience buttock pain [1-3]. Neuropathic pain radiating towards the posterior aspect, calf, and foot can occur due to irritation of the adjacent sciatic nerve. There are only a few reports on the diagnosis and treatment of this condition. When conservative treatments with activity modification, stretching of the hip muscles, and ischiofemoral space injection are ineffective, surgical treatment (resection of the lesser trochanter) can be considered [1-3].

In the present case, pain throughout the left foot was caused by ischiofemoral impingement. Clinicians should consider this possibility in patients with neuropathic pain radiating to the area innervated by the sciatic nerve, combined with buttock pain and aggravated by hip motion.

Learning points

- Ischiofemoral impingement can cause buttock pain with or without sciatica due to irritation of the adjacent sciatic nerve, which is caused by impingement of the quadratus femoris muscle between the lesser trochanter and lateral border of the ischium.
- Edema and a narrowed ischiofemoral space identified by pelvic MRI indicate ischiofemoral impingement.
- For ischiofemoral impingement, conservative treatment with activity modification and ischiofemoral space injection can be attempted. In cases that are refractory to conservative treatment, surgical treatment should be considered.

Notes

Ethical statements

This study was approved by the Institutional Review Board (IRB) of Yeungnam University Hospital (IRB No: 2022-07-029). Written informed consent was obtained for the publication of this report.

Conflicts of interest

Mathieu Boudier-Revéret has been editorial board member of *Journal of Yeungnam Medical Science* (*JYMS*) since 2021. Min Cheol Chang has been Associate editor of *JYMS* since 2021. They were not involved in the review process of this manuscript. Otherwise, there is no conflict of interest to declare.

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Author contributions

Conceptualization: MBR, MCC; Data curation, Formal analysis, Methodology, Visualization, Investigation, Resources, Supervision, Validation: MCC; Writing-original draft: all authors; Writing-review & editing: all authors.

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3. Wilson MD, Keene JS. Treatment of ischiofemoral impingement: results of diagnostic injections and arthroscopic resection of the lesser trochanter. J Hip Preserv Surg 2016;3:146–53.

Instructions to authors

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Conflicts of interest

The corresponding author must inform the editor of any potential conflicts of interest that could influence the authors' interpretation of the data. Examples of potential conflicts of interest are financial support from or connections to companies, political pressure from interest groups, and academically related issues. In particular, all sources of funding applicable to the study should be explicitly stated.

Statement of human and animal rights

Clinical research should be done in accordance of the Ethical Principles for Medical Research Involving Human Subjects, outlined in the Declaration of Helsinki of 1975 (revised 2013) (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Clinical studies that do not meet the Declaration of Helsinki will not be considered for publication. Human subjects should not be identifiable, such that patients' names, initials, hospital numbers, dates of birth, or other protected healthcare information should not be disclosed. For animal subjects, research should be performed based on the National or Institutional Guide for the Care and Use of Laboratory Animals, and the ethical treatment of all experimental animals should be maintained.

Statement of informed consent and Institutional Review Board approval

Copies of written informed consent documents should be kept for studies on human subjects, which includes identifiable information or sensitive information. For clinical studies of human subjects, a certificate, agreement, or approval by the Institutional Review Board (IRB) of the author's institution is required. If necessary, the editor or reviewers may request copies of these documents to resolve questions about IRB approval and study conduct.

Process for managing research and publication misconduct

When the journal faces suspected cases of research and publication misconduct, such as redundant (duplicate) publication, plagiarism, fraudulent or fabricated data, changes in authorship, an undisclosed conflict of interest, ethical problems with a submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and so on, the resolution process will follow the flowchart provided by the Committee on Publication Ethics (COPE, https://publicationethics.org/resources/flowcharts). The discussion and decision on the suspected cases are carried out by the Editorial Board.

Process for handling cases requiring corrections, retractions, and editorial expressions of concern

Cases that require editorial expressions of concern or retraction shall follow the COPE flowcharts (https://publicationethics.org/guidance/Flowcharts). If correction needs, it will follow the ICMJE Recommendation for Corrections, Retractions, Republications, and Version Control (https://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/corrections-and-version-control.html) as follows:

Honest errors are a part of science and publishing and require the publication of a correction when they are detected. Corrections are needed for errors of fact. The minimum standards are as follows: (1) it shall publish a correction notice as soon as possible detailing changes from and citing the original publication on both an electronic and numbered print page that is included in an electronic or a printed Table of Contents to ensure proper indexing; (2) it shall post a new article version with details of the changes from the original version and the date(s) on which the changes were made through CrossMark; (3) it shall archive all prior versions of the article. This archive can be directly accessible to readers; (4) previous electronic versions shall prominently note that there are more recent versions of the article via CrossMark.

Editorial responsibilities

The Editorial Board will continuously work to monitor and safeguard publication ethics: guidelines for retracting articles; maintenance of the integrity of the academic record; preclusion of business needs from compromising intellectual and ethical standards; publishing corrections, clarifications, retractions, and apologies when needed; and excluding plagiarism and fraudulent data. The editors maintain the following responsibilities: responsibility and authority to reject and accept articles; avoiding any conflict of interest with respect to articles they reject or accept; promoting the publication of corrections or retractions when errors are found; and preservation of the anonymity of reviewers.

Author qualifications, language requirement, and reporting guideline

Author qualifications

Any researcher throughout the world can submit a manuscript if the scope of the manuscript is appropriate.

Language

Manuscripts should be submitted in good scientific English.

Reporting guidelines for specific study designs

For specific study designs, such as randomized controlled trials, studies of diagnostic accuracy, meta-analyses, observational studies, and non-randomized studies, we strongly recommend that authors follow and adhere to the reporting guidelines relevant to their specific research design. For case reports, authors should follow the CARE guidelines (https://www.care-statement.org). Authors should upload a completed CARE checklist (https://www.care-statement.org/checklist) for the appropriate reporting guidelines during original submission. Some reliable sources of reporting guidelines are EQUATOR Network (https://www.equator-network.org/) and NLM (https://www.nlm.nih.gov/services/research_report_guide.html).

Submission and peer review process

Submission

All manuscripts should be submitted via e-submission system (https://submit.e-jyms.org). If any authors have difficulty in submitting via e-submission system, please send a manuscript to jyms@yu.ac.kr.

Peer review process

JYMS reviews all manuscripts received. A manuscript is first reviewed for its format and adherence to the aims and scope of the journal. If the manuscript meets these two criteria, it is checked for plagiarism or duplicate publication with Similarity Check. After confirming its result, it is sent to two (or more) relevant investigators available for review of the contents. The editor selects peer referees by recommendation of editorial board members or from the board's specialist database.

JYMS adopts a double-blind review, which means that the reviewers and authors cannot identify each other's information. The authors' names and affiliations are removed during peer review. Assuming the manuscript is sent to reviewers, *JYMS* waits to receive opinions from at least two reviewers. In addition, if deemed necessary, a review of statistics may be required. The acceptance criteria for all papers are based on the quality and originality of the research and its scientific significance. Acceptance of a manuscript is decided based on the critiques and recommended decisions of the reviewers.

An initial decision is normally made within 4 weeks of receipt of a manuscript, and the reviewers' comments are sent to the corresponding author by e-mail. The corresponding author must indicate the alterations that have been made in response to the reviewers' comments item by item. Failure to resubmit the revised manuscript within 12 weeks of the editorial decision is regarded as a withdrawal. A final decision on acceptance/rejection for publication is forwarded to the corresponding author from the editor.

We neither guarantee acceptance without review nor very short peer review times for unsolicited manuscripts. Solicited manuscripts are also reviewed before publication.

Peer review process for handling submissions from editors, employees, or members of the editorial board

All manuscripts from editors, employees, or members of the editorial board are processed the same way as the other unsolicited

manuscripts. During the review process, submitters do not engage in the decision process. Editors will not handle their own manuscripts, although they are commissioned ones.

Manuscript preparation

General requirements

The main document with manuscript text and tables should be prepared in an MS Word (docx) format.

The manuscript should be double spaced on 21.6×27.9 cm (letter size) or 21.0×29.7 cm (A4) paper with 3.0 cm margins at the top, bottom, right, and left margin.

All manuscript pages are to be numbered at the bottom consecutively, beginning with the Title as page 1. Neither the author's names nor their affiliations should appear on the manuscript pages.

We recommend using the manuscript template provided by *JYMS* (https://e-jyms.org/authors/authors.php).

The authors should express all measurements according to International System (SI) units with some exceptions such as seconds, mmHg, or °C.

Only standard abbreviations should be used. Abbreviations should be avoided in the title of the manuscript. Abbreviations should be spelled out when first used in the text—for example, extensible markup language (XML)—and the use of abbreviations should be kept to a minimum.

The names and locations (city, state, and country only) of manufacturers should be given.

When quoting from other sources, a reference number should be cited after the author's name or at the end of the quotation.
Manuscript preparation is different according to the publication type, including editorials, review articles, original articles, case reports, image vignettes, communications, resident fellow section (RFS; clinical vignette, teaching images), and imagery.

Review article

All review articles will undergo peer review. An abstract is required whereas Methods section and a Results section are not required (no more than 250 words). The length of review articles is limited to 6,000 words with a maximum of 100 references.

Original article

Original articles should begin with the title page followed by an abstract; a list of key words; an Introduction, Methods, Results, Discussion, References (up to 40 references), and tables and/or illustrations.

1) Title page

The tile page should contain the following information: (1) title (less than 150 characters, including spaces); (2) author list (first name, middle name, and last name); (3) name of the institutions at which the work was performed; (4) acknowledgement of research support; (5) name, address, telephone, fax number, and e-mail address of the corresponding author; (6) running title (less than 50 characters, including spaces).

2) Abstract

Abstract must be organized and formatted according to the following headings: Background, Methods, Results, and Conclusion. The abstract length is typically no more than 250 words.

3) Keywords

List 3-6 keywords from the list provided in Index Medicus under "Medical Subject Heading (MeSH)."

4) Text

The text of manuscripts must have the following sections: Introduction, Methods, Results, and Discussion. The body of the manuscript should be written as concisely as possible. All pages of the manuscript should be numbered.

Introduction

This should provide a context or background for the study and states the specific purpose or research objective of or hypothesis tested by the study. This may include mention of papers most closely related to the article, and of the problem.

Methods

Explanation of the experimental methods should be concise but sufficient to allow other workers to reproduce the results. This provides the technical information, apparatus (the manufacturer's name and brief address) and procedures. Give references and brief descriptions for the methods that have been published. Describe statistical methods with enough detail to enable a reader with access to the original data to verify the reported results. Define statistical terms, abbreviations, and most symbols.

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex or gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases

(e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

Results

This should include a concise textual description of the data presented in tables and figures.

Discussion

This section includes the new and important aspects of the study and the conclusions. The data should be interpreted concisely. Speculation is permitted, but it must be supported by the data presented by the authors.

References

References should be numbered consecutively in the order in which they are first mentioned in the text, with numbers in square brackets before any closing punctuation. They should be listed on a separate document under the heading "References," and double-spaced. Reference format should conform to that set forth in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals. 5th ed." (JAMA 1997;277:927-34). Titles of journals should be abbreviated according to the Index Medicus style.

Reference style:

Journal articles

- List all authors when six or less; when seven or more, list the first six and add et al. Vega KJ, Pina I. Heart transplantation is associated with an increased risk for pancreatobiliary disease. Ann Intern Med 1996;124:980-3.
- Verbalis JG. Renal physiology of nocturia. Neurourol Urodyn 2014;33(Suppl 1):S6-9.

Book

- Ringsven MK, Bond D. Gerontology and leadership skills for nurses. 2nd ed. Albany (NY): Delmar Publishers; 1996.
- Luzikov VN. Mitochondrial biogenesis and breakdown. Galkin AV, translator; Roodyn DB, editor. New York: Consultants Bureau; 1985. p. 362

Book chapter

- Phillips SJ, Whisnant JP. Hypertension and stroke. In: Laragh JH, Brenner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd ed. New York: Raven Press; 1995. p. 465-78.

Web resources

- Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT, Chen YY, David S, et al. Risk factors for groin wound infection after femoral artery catheterization: a case-control study. Infect Control Hosp Epidemiol [Internet]. 2006 [cited 2007 Jan 5];27:34-7. http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf.
- Testa J. The Thomson Reuters journal selection process [Internet]. Philadelphia: Thomson Reuters; 2012 [cited 2013 Sep 30]. http://wokinfo.com/essays/journal-selection-process.

5) Tables

Tables should fit within a single page. The Table's legend may include any pertinent notes and must include definitions of all abbreviations and acronyms that have been used in the Table. For footnotes, the following symbols should be used in this sequence: a), b), c), d), e), f), g), h), etc. Authors are obligated to indicate the significance of their observations by appropriate statistical analysis.

6) Illustrations

Authors must submit illustrations as electronic files. Acceptable figure file formats are JPEG, TIFF, and PPT/PPTX. Each figure needs to be prepared in a resolution higher than 300 dpi with good contrast and sharpness. The file size of each submitted figure should not exceed 10 MB per figure. If the patient's photograph is presented in a paper, it should be manipulated to make it difficult to recognize. Patients introduced in the manuscripts should be informed and aware that their photographs, videotapes, and other images (imaging records) will be released by the authors, and the authors should attach the Authorization and Release Form available at the *JYMS* website (https://e-jyms.org/authors/ethics.php) including each patient's signature. If the patient is a minor, a written consent of the guardian must be submitted.

7) Legends for tables and illustrations

Typed legends that use double-spacing should start on a separate page with Arabic numerals corresponding to the Tables or Illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the Tables or Illustrations, they should be individually identified and explained clearly in the legend.

8) Abbreviations

Authors should limit the use of abbreviations to an absolute

minimum. Abbreviations are not to be used in titles. Abstracts may contain abbreviations for terms mentioned many times in the abstract section, but each term must be identified the first time it is mentioned.

9) Unit of measurement

Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples. Temperature should be in degrees Celsius. Authors must consult the information for authors for the particular journal and should report laboratory information in both the local and International System of Units (SI).

Case report

Case reports should consist of an Abstract (no more than 250 words), Keywords, Introduction, Case, Discussion, and References (no more than 20). Case reports should have fewer than nine authors and follow the CARE guidelines.

Image vignette

Image vignette should be organized in the following sequence: a summary of the presentation, imaging features and discussion. No abstract is required for this manuscript. There should be no more than five references and no more than two figures. Total length should be no longer than 500 words (excluding figure legends, ethical statements, conflicts of interest, author contributions, ORCID, and references).

Communications

Although communication articles are not limited in the format, they should contain a self-standing abstract and references. The abstract should be concisely written and not exceed 250 words.

Resident fellow section

RFS is designed to provide clinical cases and images that are informative for resident or fellow trainees. We encourage article submissions where the primary author(s) are prepared by trainees under the supervision of their attending physicians. We require a statement to be provided within the cover letter of any article submitted to this section that confirms the primary author(s) are residents or fellows. The following categories of articles will be included in the RFS:

1) Clinical vignette

Interesting clinical cases focused on developing clinical reasoning skills of resident or fellow trainees. Authors should follow the CARE guidelines.

Cases may focus on either diagnosis or management. Vignettes should progress logically and be divided into the following sections:

- Brief history and physical exam. Include pertinent history of present illness, medical history, and physical exam findings.
- Differential diagnosis or potential approaches to management. Include discussion regarding reasons for selected differential or potential management approaches.
- Diagnostic results including lab results/imaging (if relevant).
- Diagnosis and discussion of management and outcomes. Include a discussion of the relevant literature related to the vignette.

Clinical vignette should be maximum of 1,500 words, 1-2 tables or 1-2 figures and maximum of 10 references.

2) Teaching images

Previously unpublished magnetic resonance images, computed tomography scans, ultrasound images, X-rays, patient photographs/videos, or other pictorial/videographic material. These pictorials should clearly demonstrate distinct examples of either rare, conventionally common, or uniquely pathognomic observations, techniques, or findings intended to further the education of the trainee audience. The title of the article should be brief and include the patient's age and sex, accompanied by a succinct 5-10 words description of the patient's presentation. Up to two labeled images or figures should be provided with a short description and/or legend. The case description should be written in 500 words or less and directly address the image provided while detailing the clinical significance of the presented findings and correlation with the patient's symptoms. Intended for trainees, teaching images should progress through a patient's history and physical exam while focusing on differential diagnoses, the clinical reasoning for selecting the particular diagnostic study, and the appropriate interpretation, subsequent treatment strategies, and achieved outcome. Finally, 2-3 bulleted learning points should accompany the submission to advance trainee knowledge (will not count toward word limit).

Imagery

This is a regular section of *JYMS*, featured at the beginning of issue and devoted to the artistic and imaginative qualities of the readers. *JYMS* invites your drawings, illustrations, or photographs with a brief explanation. Please send electronic images via e-mail to: jyms@yu.ac.kr. These contributions will not be returned.

Final preparation for publication

Final version

After the paper has been accepted for publication, the author(s) should submit the final version of the manuscript. The names and affiliations of the authors should be double-checked, and if the originally submitted image files were of poor resolution, higher resolution image files should be submitted at this time. Color images must be created as CMYK files. The electronic original should be sent with appropriate labeling and arrows. The JPEG, TIFF, and PPT/PPTX formats are preferred for submission of digital files of photographic images. Symbols (e.g., circles, triangles, squares), letters (e.g., words, abbreviations), and numbers should be large enough to be legible on reduction to the journal's column widths. All of the symbols must be defined in the figure caption. If the symbols are too complex to appear in the caption, they should appear on the illustration itself, within the area of the graph or diagram, not to the side. If references, tables, or figures are moved, added, or deleted during the revision process, they should be renumbered to reflect such changes so that all tables, references, and figures are cited in numeric order.

Manuscript corrections

Before publication, the manuscript editor may correct the manuscript such that it meets the standard publication format. The author(s) must respond within 2 days when the manuscript editor contacts the author for revisions. If the response is delayed, the manuscript's publication may be postponed to the next issue.

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The author(s) will receive the final version of the manuscript as a PDF file. Upon receipt, within 2 days, the editorial office (or printing office) must be notified of any errors found in the file. Any errors found after this time are the responsibility of the author(s) and will have to be corrected as an erratum.

Article processing charge

No page charge or article processing charge applies. There is also no submission fee.

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Research and publication ethics

JYMS
JOURNAL OF YEUNGNAM MEDICAL SCIENCE

Enactment May 22, 2012

Research ethics

The journal adheres to the ethical guidelines for research and publication described in Guidelines on Good Publication (https://publicationethics.org/resources/guidelines) and the International Committee of Medical Journal Editors (ICMJE) Guidelines (https://www.icmje.org).

Authorship

Authorship credit should be based on (1) substantial contributions to the conception and design, acquisition of data, and/or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Every author should meet all of these four conditions. After the initial submission of a manuscript, any changes whatsoever in authorship (adding author(s), deleting author(s), or re-arranging the order of authors) must be explained by a letter to the editor from the authors concerned. This letter must be signed by all authors of the paper. A copyright assignment must also be completed by every author.

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- Correction of authorship after publication: *JYMS* does not correct authorship after publication unless the editorial staff has erred. Authorship may be changed before publication but after submission when an authorship correction is requested by all of the authors involved with the manuscript.

Originality, plagiarism, and duplicate publication

Submitted manuscripts must not have been previously published or be under consideration for publication elsewhere. No part of the accepted manuscript should be duplicated in any other scientific journal without permission from the Editorial Board. Submitted manuscripts are screened for possible plagiarism or duplicate publication by Similarity Check using the 'Turnitin' program (iParadigms, LLC, Oakland, CA, USA). If plagiarism or duplicate publication is detected, the manuscript may be rejected, the authors will be announced in the journal, and their institutions will be informed. There will also be penalties for the authors.

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for the Care and Use of Laboratory Animals, and the ethical treatment of all experimental animals should be maintained.

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Process for managing research and publication misconduct

When the journal faces suspected cases of research and publication misconduct, such as redundant (duplicate) publication, plagiarism, fraudulent or fabricated data, changes in authorship, an undisclosed conflict of interest, ethical problems with a submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and so on, the resolution process will follow the flowchart provided by the Committee on Publication Ethics (COPE, https://publicationethics.org/resources/flowcharts). The discussion and decision on the suspected cases are carried out by the Editorial Board.

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Honest errors are a part of science and publishing and require the publication of a correction when they are detected. Corrections are needed for errors of fact. The minimum standards are as follows: (1) it shall publish a correction notice as soon as possible detailing changes from and citing the original publication on both an electronic and numbered print page that is included in an electronic or a printed Table of Contents to ensure proper indexing; (2) it shall post a new article version with details of the changes from the original version and the date(s) on which the changes were made through CrossMark; (3) it shall archive all prior versions of the article. This archive can be directly accessible to readers; (4) previous electronic versions shall prominently note that there are more recent versions of the article via CrossMark.

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Research and publication ethics form

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Affiliation: _____

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All authors pledges that we follow the basic standards of research and publication ethics in the submission process to *Journal of Yeungnam Medical Science*

Check Yes if Research subject, research object and size, setting of controls, and the methods of data collection are suitable for the research ethics.	☐ ***Yes*** ☐***No***
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Check Yes if This study is conducted in compliance with the Declaration of Helsinki and this comment is written in the method section of the manuscript.	☐ ***Yes*** ☐***No***
Check Yes if All Authors must disclose all relationships that could be viewed as potential conflicts of interest. This relationship also includes any potential conflicts of interest with all material, products, and companies in the manuscript.	☐ ***Yes*** ☐***No***
Check Yes if Authors should confirm that the submitted work is not under consideration or accepted for publications elsewhere, and would not be submitted in any other journals after acceptance.	☐ ***Yes*** ☐***No***
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If the rationale provided by the authors remains unsatisfactory in the judgment of the editors, the manuscript will be rejected or retracted. The authors will not be allowed to subsequently submit their research to *Journal of Yeungnam Medical Science*. The authors should keep the above mentioned disadvantages in mind.

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Patient photographic and videographic consent, authorization and release form

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I am informed and aware of photographs, videotapes and other images (imaging records) taken by Dr. _____ or his designee(s) of myself or any parts of my body regarding surgical procedures carried out by Dr. _____ . I understand and consent that such imaging records may and will be used by Dr. _____ as reference in diagnosing and treating other patients in the future. I further consent to the release and transfer of copyright ownership by Dr. to *Journal of Yeungnam Medical Science* of such imaging records.

I understand that by consenting on release of my imaging records, these may and will be used in upcoming issue or issues of the journal, as well as on the journal website, or any other print or electronic media for the purpose of informing medical professionals or other readers about surgical methods. I understand that when these imaging records are included in any articles, medical information regarding sex, age, operative date and treatment results may and will be included together. But I, nor any member of my family, will be identied by name in any publication, and any information that may aid in identifying me or my family will not be exposed. (In case of facial photographs, the photo is cropped to only necessary parts in order to make individual identication impossible.) I understand that whether I consent on this form or not, it bears no consequences whatsoever on any future actions, and that there will be no eect on the medical treatment I receive from Dr. _____ or any subordinates.

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I hereby transfer in above-mentioned terms, the copyright of my imaging records to

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20 . . .

Name: _____ **Signature:** _____

Hospital: _____ **Department:** _____

Designated Doctor: _____ **Signature:** _____