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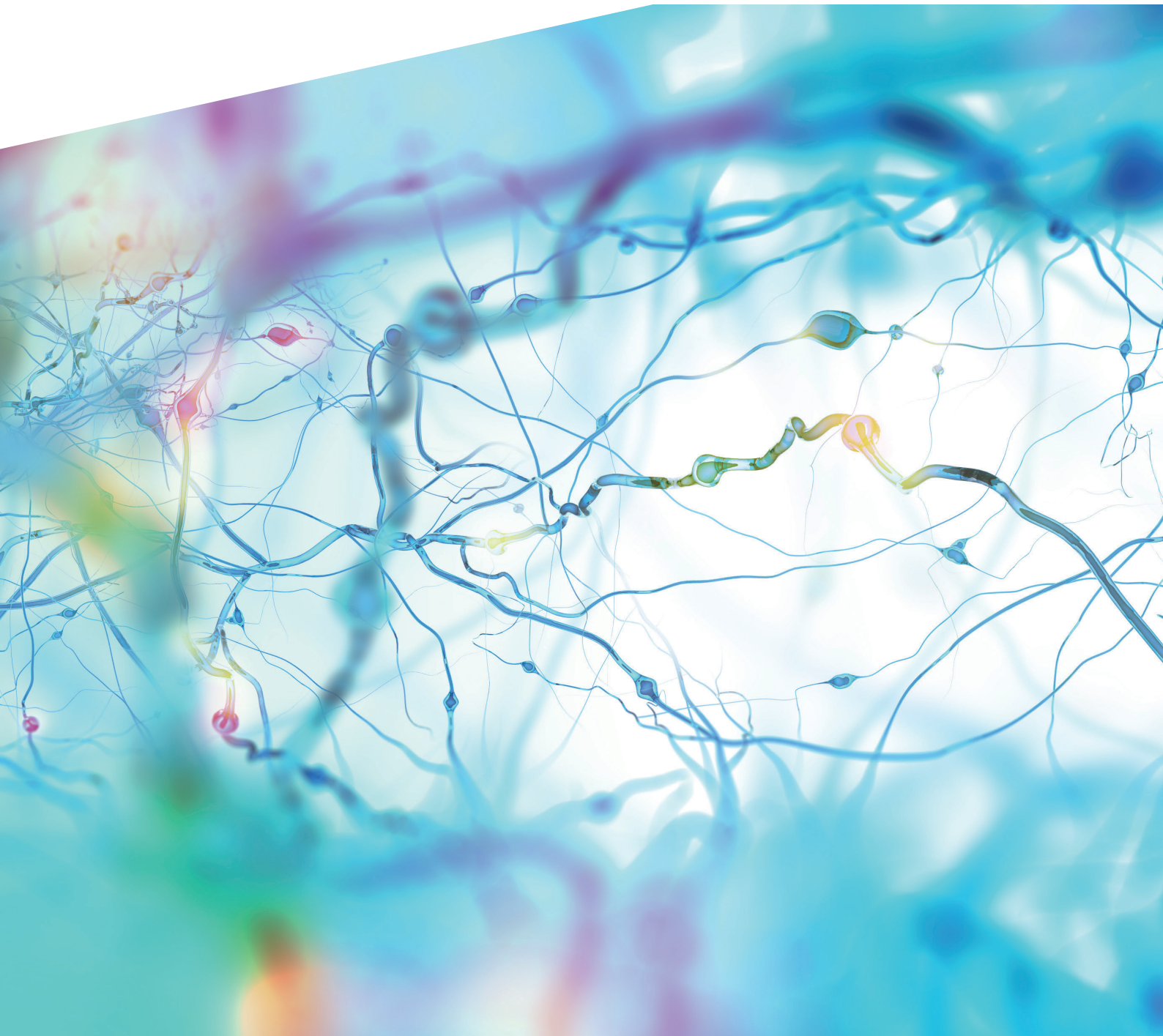

Ewha Medical Journal

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Aims & scope

Aims

Ewha Medical Journal aims to provide medical professionals with essential healthcare information and fundamental medical knowledge. The journal will contribute to improving and serving human society based on the Christian values of education, truth, goodness, and beauty. Additionally, the journal strives to nurture young editors, enabling them to demonstrate exceptional women's editorial leadership and provide innovative learning methods.

Scope

Its scope includes:

- Up-to-date medical knowledge and skills essential for patient care
- Preparing for the future of medicine
- Effective interprofessional communication
- Ensuring gender equity and diversity
- Medical education materials
- Sharing data and protocols

Regional scope

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Contents

Ewha Medical Journal

Vol. 49, No. 2, April 2026

Editorial

In this issue: April 2026
Ji Yeon Byun

Review articles

Jokbo-based learning among Korean medical students
Chul Han

Clinical guidance and practical recommendations for probiotic use in patients with irritable bowel syndrome, functional constipation, and *Clostridioides difficile* infection considering sex-based differences: a Korean translation
Yong Sung Kim, Seon-Young Park, Seung Joo Kang, Min Woo Lee, Yonghoon Choi, Byung Yong Kim, Miyoung Choi, Cheol Min Shin, Young Sun Kim, Nayoung Kim, Moo In Park, Gut Microbiota and Therapy Research Group of the Korean Society for Neurogastroenterology and Motility

Case reports

Compound heterozygosity with methylenetetrahydrofolate reductase (*MTHFR*) C677T and A1298C mutations likely causing recurrent thrombotic events in a middle-aged man: a case report
Yalini Suppu Saravanan, Viswanathan Pandurangan, Devasena Srinivasan

Atherosclerotic changes in an intrasellar persistent trigeminal artery in a patient presenting with dizziness: a case report from Korea
Jieun Byun, Boeun Lee

Elastofibroma dorsi: a rare case report emphasizing the clinical presentation, radiological diagnosis, and surgical treatment
Şükrü Kasap, Muhammed Said Aydin, Gokay Ozler, Onur Ozvurmaz, Celal Kahraman, Hasan Can Çoban, Mert Kahraman, Ozan Dağdelen

Nociceptive pain as a clinical presentation of chronic urticaria and disappearance with immunoglobulin/histamine complex therapy: a case report
Hyuk Soon Kim, Dae Hwan Kim, Yunyoung Nam, Jeong Eun Sohn, Geunwoong Noh

Images and solution

Skull base granulomatosis with polyangiitis presenting with multiple cranial neuropathies
Julia Mamprim de Arruda Monteiro, Gustavo Andreis, Marcelo de Queiroz Pereira da Silva, Renan de Almeida Agustinelli, Márcio Luís Duarte

Letter to the editor

Bridging theory and practice in generative artificial intelligence for medical education: insights from clinical teaching experience
Yoo Kyung Lee

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Editorial

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The Ewha Medical Journal

In this issue: April 2026

Ji Yeon Byun *

Department of Dermatology, Ewha Womans University College of Medicine, Seoul, Korea

The current issue of the *Ewha Medical Journal* presents a diverse and clinically relevant collection of articles that span medical education, emerging therapeutics, rare disease presentations, and diagnostic challenges.

The 2 review articles offer evolving perspectives spanning both medical education and clinical therapeutics. The first examines "jokbo-based learning" as a form of hidden curriculum in Korean medical education, exploring its dual role in fostering efficiency while raising concerns about depth of learning and academic integrity. The second provides an evidence-based synthesis of probiotic use in gastrointestinal disorders, with particular attention to strain-specific effects and sex-based differences—an important yet underexplored dimension of microbiome-targeted therapy.

Four case reports further illustrate the diagnostic and clinical breadth of this issue. These include recurrent thrombotic events associated with MTHFR (methylenetetrahydrofolate reductase) compound heterozygosity; a rare intrasellar persistent trigeminal artery with atherosclerotic changes causing symptomatic posterior circulation insufficiency; a symptomatic elastofibroma dorsi successfully managed with surgical excision; and an atypical presentation of chronic urticaria characterized by nociceptive pain responsive to immunoglobulin/histamine complex therapy. Together, these cases suggest the value of integrating genetic, anatomical, radiologic, and immunologic perspectives in clinical reasoning.

The "Image and Solution" article presents a diagnostically challenging case of skull base granulomatosis with polyangiitis manifesting as multiple cranial neuropathies. This report emphasizes the clinicoradiologic correlation—particularly in seronegative presentations—and the need for early recognition of potentially reversible inflammatory conditions.

Finally, a Letter to the Editor offers a practical perspective on incorporating generative artificial intelligence into medical education. The author addresses key considerations for responsible implementation, including domain-specific validation, mitigation of hallucination and bias, and the development of flexible, practice-oriented training strategies.

Taken together, this issue reflects the ongoing integration of emerging knowledge with real-world clinical application, reinforcing the enduring importance of critical appraisal, and adaptability in contemporary medical practice. We hope the articles here prove useful in both your studies and practice.

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Authors' contribution

All work was completed by Ji Yeon Byun.

Conflict of interest

Ji Yeon Byun has served as the editor of the *Ewha Medical Journal* since January 2026. However, she was not involved in the peer review process or decision-making for this article. No other potential conflicts of interest relevant to this article were reported.

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Data availability

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Supplementary materials

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Review article

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The Ewha Medical Journal

한국 의과대학생의 '족보 기반 학습(*Jokbo* based learning)'에 대한 고찰

Jokbo-based learning among Korean medical students

한철*

Chul Han*

Ewha Womans University College of Medicine, Seoul, Korea
이화여자대학교 의과대학

When the physician–government conflict was triggered by the Korean government's plan to increase medical school enrollment by 2,000 students, the government proposed the establishment of a "*Jokbo* Sharing Center." In Korean medical education, *jokbo* refers to collections of previous examination questions, summarized notes, and anticipated topics compiled by senior students and transmitted across cohorts. Their scope extends beyond preclinical education and written examinations to include practical tips and informal norms passed down during clinical clerkships and internship rotations. More than a mere compilation of study resources, *jokbo* functions as a form of hidden curriculum within medical education. As a learning culture that has emerged organically among students, it operates implicitly beneath the formal curriculum. The creation and sharing of *jokbo* can foster solidarity and a sense of belonging, and may serve as a process through which students begin to internalize the professional culture essential to their future roles as physicians. Nevertheless, reliance on *jokbo*-based learning may undermine the depth and quality of learning over time, impeding critical thinking, problem-solving skills, and the acquisition of integrated medical knowledge. Unregulated distribution of such materials also raises concerns about examination fairness, and their reproduction without faculty consent raises legitimate ethical concerns. At the same time, given their demonstrable educational benefits, some argue for institutionalizing *jokbo* through transparent procedures for constructive use in medical education. Despite its widespread presence, research on *jokbo* remains virtually nonexistent. This study aims to establish a scholarly and policy foundation for discussion of *jokbo* in Korean medical education by reviewing international cases of examination material sharing and providing a comprehensive analysis of *jokbo* in Korea.

Keywords: Examination questions; Medical education; Medical school; Test taking skills

서론

정부의 2천 명 증원이 촉발한 의정사태가 발생하였을 당시, 정부는 그 해결책 중 하나로 이른바 '족보공유센터'를 제시한 바 있다[1]. 우리나라에서 족보(族譜)는 동족이 그들의 시조로부터 현재 자손까지의 계보를 중심으로 기록한 것으로 가문의 내력과 씨성(氏姓)의 계보를 밝혀 놓은 일종의 씨족사 내지 가문의 역사를 의미한다[2]. 하지만 한국의 의과대학생에게 '족보'는 대학 강의나 시험에서 이전 선배들이 남긴 시험문제, 요약자료, 예상문제 등을 모아둔 문서 또는 파일을 의미하며, 학교에 따라 '야마,' 또는 '소스'라는 이름으로도 불린다. 그러나 정부와 언론이 이미 '족보'라는 명칭을 사용하였기 때문에 본 논문에서는 이 표현을 사용하도록 할 것이다.

족보는 종적(같은 학년 간), 횡적(선후배 간)으로 전수되며 사실 기본의학교육에 국한되지도 않는다. 심지어 전문의 자격시험 공부를 위해서도 족보는 활용된다. 족보는 시험에만 국한되지도 않으며 임상실습을 하거나, 인턴으로서 각 과를 순회할 때도 준수해야 할 여러 가지 소소한 사항들이 족보로서 전수되기도 한다. 이렇게 족보는 널리 활용되기 때문에 의과대학생들은 족보를 학습을 위한 실질적 도구로 인식하며, 이를 공부해야 시험에 실패하지 않는다고 인식하고 있다[3]. 의과대학생들은 학습해야 할 방대한 의학지식 앞에서 '선택'과 '집중'의 기로에 놓이는 경우가 대부분이고, 족보

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는 의과대학생들이 수업자료를 정리하고 요약하는 데 중요한 역할을 해왔다.

족보는 단순한 자료를 넘어 의학교육의 잠재적 교육과정으로서 그 역할을 해왔다. 잠재적 교육과정(hidden curriculum)은 학교의 물리적 조건, 제도 및 행정적 조직, 사회 및 심리적 상황을 통하여 학교에서는 의도하고 계획 세운 바 없으나 학교생활을 하는 동안에 은연중에 가지게 되는 경험을 의미한다[4]. 족보는 공식문서나 커리큘럼에 명시하거나 학교나 교수가 의도적으로 가르치지는 않지만, 학생들 사이에서 자생적으로 형성된 학습문화라는 측면에서 공식적인 교육과정 저변에 조용하고(the silent curriculum) 암시적(the implicit curriculum)으로 교육과정에 잠재되어 작동한다. 학생들은 '족보'를 통한 비공식적인 학습전략을 채택하고 교과서나 강의자료만 아니라 효율적인 학습을 위해서는 '족보가 더 중요하다'는 태도나 학습전략을 배우게 된다.

족보의 형성과정과 유형은 다음과 같다. 의과대학에서 족보는 학교마다 방식은 다르지만 크게 선배들의 필기내용을 모은 '선족,' 강의내용과 기출문제를 함께 정리한 '필족,' 시험 직후 문제를 기억해 재구성한 '문족'의 세 유형으로 나뉘며, 학생들이 자발적으로 역할을 나눠 제작하고 공유하는 것이 특징이다. 족보는 시험 대비에 핵심 자료로 활용되며, 시험문제의 반복 경향과 맞물려 그 영향력이 크고, 일정 수준 축적되면 '족장'이 이를 책자 형태로 배포하기도 한다[5]. 일부 의과대학의 경우, 학생들이 공부에 필요한 자료들을 자체적으로 족보로 편찬하는 학생자치활동을 대학 홈페이지에 공식적으로 소개하고 있기도 하다[6]. 족보와 관련된 형성과 공유의 모든 과정은 자기주도적이며, 공동의 작업이라는 점을 고려할 때 학습의 일종의 '집단 주도 학습(공동체 주도 학습)'의 특성을 가진다고도 볼 수 있다.

의과대학생들의 '족보의 제작과 공유'는 학생들 간의 유대감과 소속감을 경험하게 되는 하나의 학습과정으로, 그리고 앞으로 의사라는 전문직업성을 발휘하는 데 필수적인 문화를 학습할 수 있다는 측면에서 긍정적인 측면도 있다. 실제로 의과대학들은 지식을 평가하는 필기시험뿐만 아니라 임상실습에서도 족보를 통해 학습내용을 전수하는데, 그 내용은 과별 실습의 특성과 주요 술기 등이 포함된다. 뿐만 아니라 의과대학 졸업 이후의 수련과정에서도 족보는 중요한 역할을 한다. 진료 프로토콜, 환자관리 등 병원 내 업무 효율성과 직결된 다양한 요소들이 포함되어 있다. 족보는 시험 준비를 위한 도구일 뿐만 아니라 실습과 직무에 대한 가이드로서 그 역할을 하고 있는 것이다.

그럼에도 불구하고 족보를 기반으로 한 학습은 장기적으로는 학습의 깊이와 질을 저하시킬 수 있다. 기출 문제 암기에 집중한 지나친 족보 의존은 학생들의 비판적 사고력과 문제해결능력, 통합적 의학 지식의 습득을 방해하는 요인으로 작용할 수 있다. 또한 별다른 규제 없이 이루어지는 일반적인 족보 작성과 활용은 시험의 공정성을 해칠 가능성이 있으며, 시험 문항을 출제한 교수의 창작물로 간주할 경우, 당사자의 동의 없이 이를 보관하거나 복사, 배포하는 행위는 부적절하다는 비판도 제기된다. 하지만 시험문제 모음집이 교육적으로 일정 효과가 있는 현실을 인정한다면, 공정한 공개와 적절한 절차를 기반으로 이를 제도화해 교육적으로 활용하는 것이 타당하다는 의견도 있다[7]. 이를 위해서는 족보의 작성과 활용의 적절성에 대한 학계의 논의가 필수적이다.

이렇듯 한국의 의학교육에서 족보가 잠재적인 교육과정으로서 그 명맥을 이어오는 동안 의학교육계에서 족보에 대한 심도 있는 논의를 해오지 않은 것이 사실이다. 의학교육에서 족보의 생성과 역할, 교육적 적절성, 학습문화로서의 가치, 족보와 관련된 규제 등과 같은 족보를 중심으로 연구를 실시한 연구들이 거의 전무한 상황이다. 따라서 본 연구는 한국의 의과대학생들이 공동의 작업을 통해 학습의 내용 및 시험문제를 모아 전수하는 학습문화를 '족보 기반 교육'으로 정의하고, 한국 의학교육 맥락에서 족보에 대한 학문적 · 정책적 논의의 기초를 마련하고자 한다. 이를 위해 해외 의과대학생들의 시험문제 공유와 관련된 학습문화 사례를 살펴보고, 한국의 의학교육에서 '족보'가 어떻게 다뤄져 왔는지를 종합적인 고찰을 하고자 한다.

해외 의과대학 사례

과거 시험 공유

과거 시험지 공유(past papers)는 의과대학생들 간에 일어나는 가장 일반적인 시험 준비 형태이다. 영국 의과대학생들 사이에서 이루어지는 과거 시험지 공유에 대해 고찰한 Davies [8]의 연구에서 일반적으로 이루어지는 과거 시험지 공유가 윤리적 문제를 야기할 수 있다고 하였다. 의과대학생들 사이에서 지식을 공유하고 과거 시험지를 참고하는 것은 전통적인 학습방식의 일부로 여겨지지만, 해당 자료가 부정한 방법으로 획득되었거나 무단으로 배포된 경우 학문적 정직성을 침해할 수 있다는 우려가 있다고 하였다.

실제로 General Medical Council (GMC) [9]은 시험문제 공유가 미래 응시자에게 부당한 이득을 줄 수 있으므로 부정행위로 간주한다(GMC misconduct procedures)고 명시하고 있다. University College London 의과대학은 시험 공유를 "시스템적인 부정행위"로 규정하고 있다. 영국 의과대학협의회(Medical Schools Council)는 부정행위 대신 시험 준비를 돕는 자료를 공식적으로 제공하고 있다. 의사면허시험(Medical Licensing Assessment)을 대비할 수 있는 연습시험인 Applied Knowledge Test를 개발하여 [10], 학생들이 응시할 수 있도록 함으로써 윤리적이고 정당한 학습환경을 조성하고자 노력하고 있다.

시험 회상

또 다른 시험문제 공유의 명칭은 시험 회상(exam recall)이 있다. 시험 회상은 학생들이 시험장을 떠난 후 문제를 기억하고 기록하는 현상을 의미한다[11]. Tonkin [12]은 호주 애들레이드 의과대학의 시험 회상 사건을 주제로 말 그대로 "lifting the carpet," 의학교육의 감춰진 이면, 즉 의과대학 시험에서의 부정행위 실태를 조명하였다. 호주 애들레이드 의과대학 학생들은 시험을 마친 후 각자 기억한 문제들을 모아 문서로 정리하여 이후 시험을 준비하는 후배들에게 전달하였고, 시험문제 유출에서 일부 시험 규정에 위배되는

방식이 포함된 점이 문제가 되었다. 이 연구에서 시험문제 회상과 같은 행위는 단순한 개인적 일탈이 아니라 사회적 규범, 학업환경, 제도적 허점 등 복합적인 요인에서 비롯된 문제이며, 시험 회상은 '다음 세대에게 시험문제를 물려주는' 관행처럼 여겨지기도 한다고 하였다. 이러한 문제 유출의 대안으로 무작위 출제나 적응형 시험과 같은 정책 개혁, 부정행위에 대한 공개적 논의, 국제협력의 필요성을 제안하며, 의과대학은 신뢰받는 의료인을 양성하기 위해 이 문제를 근본적으로 해결해야 한다고 하였다.

시험 회상은 미국의 레지던트 시험에서도 나타나는데, Ruhnke와 Doukas [13]의 논문은 전문의 자격시험에서의 기출문제 공유행위가 의료전문직 윤리와 공정성, 그리고 대중의 신뢰에 미치는 영향을 분석하였다. 시험 회상이 단순한 학습이 아닌 시험문제의 재현이라는 점에서 명백한 부정행위이자 저작권 위반이라고 하였다. 시험 회상은 의사의 전문성과 의료계를 향한 신뢰가 훼손되는 결과를 초래하며, 높은 시험 난이도와 과도한 압박, 또래 문화 등이 이를 조장하는 요인으로 작용할 수 있다고 하였다. 시험 회상 금지를 명확하게 하는 윤리지침, 재사용되지 않는 시험문제 개발, 윤리교육 강화, 그리고 기관 차원의 문화적 변화가 필요하다고 강조하였으며, 단순한 징계보다 근본적 제도 개선이 중요하다고 결론짓는다. 논문의 제목("Trust in residents and board examinations: when sharing crosses the boundary")에서 명시하고 있는 대로 공유가 경계를 넘지 않도록 경계 설정을 촉구하였다.

뿐만 아니라, 미국 의사면허시험(United States Medical Licensing Examination, USMLE) [14]의 공식문서인 'USMLE Bulletin of Information'에서 시험문제 복원 및 공유행위를 명확히 부정행위로 규정하고 있다. 응시자들은 시험문제와 케이스 내용을 비밀로 유지해야 하며, 암기, 기록, 기타 어떤 방식으로든 시험내용을 재생산하거나 시도하는 행위, 시험문제와 관련된 정보를 제공하거나 인터넷에 게시하는 행위 모두를 금지하고 있다고 밝히고 있다.

한국 의과대학생의 '족보'

한국 의학교육 맥락에서 '족보'의 역할

'족보'가 그동안 우리의 의학교육의 맥락에서 어떠한 역할을 해왔는지를 살펴보면 다음과 같다.

첫째, 교수와 학생 모두 족보를 기반으로 한 학습 또한 학습의 한 형태로 인정하고 있을 가능성이 있다. 시험문제를 회상하고 이를 족보라는 형태로 조직화하여 공유하는 것이 일반적인 학습 관행으로 용인되고 있는 것으로도 이해할 수 있다. 따라서 족보가 단순한 암기수단이나 처벌의 대상이 아닌 교육적 도구로 활용될 수 있도록, 그 단점을 줄이고 장점을 극대화하려는 노력이 반드시 수반되어야 한다.

둘째, 방대한 의학 지식을 다루는 의학교육의 특성상, 모든 것을 학습하는 것은 불가능하며, 반드시 알아야 할 지식을 중심으로 학습하는 최적의 학습방법으로 족보가 기능하고 있을 가능성이 있다. 의사 국가시험은 면허 취득을 위한 최소 자격시험으로, 필기의 경우, 60점 이상, 과목별 과락 없이 40점 이상을 충족하면 합격할 수 있다[15]. 즉 의사 국가시험은 집단 내에서 우수자를 선발하는 상대평가가 아니므로, 전문가로서 반드시 알고 있어야 할 최소한의 내용을 정확하게 아는 것이 중요하다. 다시 말해 족보에 포함되어 있는 그 동안의 시험정보들이 의사 면허를 취득하는 데 필수적인 내용들로 잘 구성되어 있다는 가능성도 있다.

셋째, 한국의 의과대학들이 성과 기반 교육과정을 운영하며 졸업성과와 학습성과를 명시하고 있으나 학생들에게 와닿지 않았을 가능성이 있다. 성과와 실제 교육, 평가와의 관련성이 충분히 안내되지 않은 상태에서 학생들은 성과 보다 가시적이고 믿을만한 학습자료인 '족보'에 몰두하였을 가능성을 생각해볼 필요가 있다. 다르게 말하면 성과 기반 교육을 실시하고 있는 의과대학의 졸업성과를 달성하는 데 족보에 수록된 문제들로 충분하였다는 의미로 해석할 수도 있다. 한국의 의과대학생들의 높은 의사 국가고시 합격률로 미루어 짐작할 때, 족보를 기반으로 한 학습이 졸업성과를 달성하는 데 필요한, 그리고 의사면허 취득에 필요한 학습을 하는 데 충분했다는 것을 알 수 있다. 실제로 '나는 족보만 봤을 뿐'이라고 한 의사국시 수석합격자 인터뷰는 의과대학을 졸업하면서 갖추어야 할 역량과 족보가 맞닿아 있음을 시사한다[16].

넷째, 최근 의정사태로 인한 전공의 수의 감소로 인해[17], 기존에 암묵적이고 비공식적으로 이루어지던 학생 교육의 방식이 더 이상 효과적으로 작동하지 않게 될 가능성이 커지고 있다. 전공의는 수련을 받는 피교육자이면서 동시에 의과대학생을 교육하는 교육자 역할을 하며[18-20], 현재 벌어지고 있는 전공의들의 수련 공백은 의과대학생들의 교육 공백으로 이어질 수밖에 없다[21]. 병원 현장에서 전공의들이 담당하던 교육적 역할—예를 들어, 후배 학생들에게 실무적인 지식이나 술기 노하우를 자연스럽게 전수하던 구조—의 약화로 학생들은 대안적인 학습수단을 더욱 의존하게 될 것이다. 이로 인해 시험 기출자료나 선배들의 학습경험이 체계적으로 축적된 '족보'의 중요성은 오히려 더욱 강화될 가능성이 크며, 이는 족보가 단순한 편의적 학습도구를 넘어 구조적 공백을 메우는 핵심 자원으로 기능하게 될 수 있음을 시사한다.

한국의 의과대학생 학습문화 연구 속 '족보'

본 연구에서 살펴본 한국의 의학교육 논문들에서는 '족보'가 무엇을 의미하는지 조작적 정의가 부재할 뿐만 아니라 한국의 의학교육 영역에서 '족보'를 기반으로 한 의과대학생들의 학습문화를 직접 주제로 다룬 연구는 이루어지지 않았다. '족보'를 언급하고 있는 대부분의 논문에서 의과대학생들의 학습방식을 설명할 때, '족보'를 통해 이루어지고 있는 교육현상에 대해서 단편적으로 언급하고 있을 뿐이다.

의과대학/의학전문대학원 학생들의 학습에 대한 신념을 연구한 Park [3]의 연구는 의과대학생들이 가지고 있는 다양한 학습 신념의 내용과 그 형성 원인, 교육적 영향에 대해 분석하고, 이러한 신념들이 새로운 의학교육 방식에 어떤 저항 요인으로 작용하는지를 비판적으로 고찰하였다. 이때 족보는 학생들이 가지고 있는 다양한 신념 중 '교과서보다는 강의록, 기출문제집(족보) 위주로 공부해야 시험에 실패하지 않는다'는 학습 신념으로 다루어졌다. 시험 위주

의 평가와 과도한 학습량이 족보 중심의 암기식 학습을 강화하고, 협력보다는 경쟁을 유도하는 환경을 조성하여, 이러한 문제를 극복하기 위해 교육과정, 교수법, 평가방식의 구조적 변화와 함께 학생들의 학습 신념 자체를 바꾸는 노력이 필요하다고 하였다. 의과대학생들은 족보 외에 학습 분량 과다, 암기 중심, 경쟁적 분위기, 수동적 학습태도 등의 신념도 가지고 있으며, 이러한 신념들은 학습내용에 대한 깊이 있는 이해나 자기주도적 학습능력을 함양하는 데 부정적인 영향을 미친다고 주장하였다.

의과대학의 잠재적 교육과정과 학생문화를 연구한 Yoo [22]의 연구에서는 의과대학에서 공식 교육과정 외에 학생들이 일상적으로 경험하는 잠재적 교육과정의 개념과 그 영향력을 분석하며, 이 과정이 학생들의 정의적 역량과 문화 형성에 미치는 중요성을 강조하였다. 이 연구에서 족보는 학생들이 단기간의 최대한의 학습과 평가가 실시되는 교육체계 속에서 학생들이 행하고 있는 학습문화로 다루어졌다. 학생들은 의학교육을 받으며 의학을 아는 것보다 시험에 답을 쓸 수 있을 정도만 선별적으로 암기하기 위하여 '족보'를 활용하는 문화를 가지고 있다고 하였다. 이 연구에서 의과대학은 성적 중심의 경쟁적인 환경으로 인해 학생들이 동료를 협력보다는 경쟁의 대상으로 인식하게 만들고, 이는 심리적 스트레스와 팀워크 저해로 이어질 수 있다고 지적하고 있다. 잠재적 교육과정이 전문직업성, 윤리, 자기관리, 리더십 등의 형성에 중대한 영향을 미치므로, 공식 교육뿐 아니라 긍정적인 학생문화를 조성할 수 있는 교육 환경과 문화 풍토를 개선하는 것이 필요하다고 주장하였다.

Kim [23]은 2011년 임상실기시험에서 문항이 조직적으로 복원되어 족보로 구성되고, 족보가 금전 거래의 수단으로 활용된 윤리적 문제를 조명하며 "우리는 어떤 의사를 양성해야 하는가?"를 주제로 논문을 발표하였다. 의사국가시험에서의 족보의 구성과 판매는 시험 서약에 대한 파기일 뿐만 아니라 평가의 공정성을 훼손하고, 전문가로서의 책임감이 결여된 행동이라고 하였으며, 나아가 이는 의사 집단 전체의 신뢰와 사회적 위상을 약화시킬 수 있는 중대한 문제라고 지적하였다. 우리가 양성하는 의사는 학문적으로 뛰어난 과학자이면서 윤리적으로 도덕적으로 존경받을 수 있는 사회의 지도자이어야 하며, 이를 위해 교육자들 또한 스스로 존경받는 의사, 책임 있는 의사로서의 모습을 보이는 것이 필요하다고 하였다.

하지만 그 동안의 족보가 다뤄진 연구에서는 의과대학생의 학습문화 및 실제적인 학습을 경험한 연구가 이루어지지 않았다는 데 그 한계가 있다. '족보'가 교육 현상 그 자체를 넘어 어떠한 교육적 가치를 가지고 있는가에 대한 논의 역시 이루어지지 않았다. 다만, 그 동안의 연구를 통해 매우 경쟁적인 의학교육의 과정에서 학생들이 족보를 통해 상호협력적인 학습문화를 형성해왔을 가능성은 확인할 수 있었다.

결론

한국의 의학교육 연구에서 족보가 어떻게 다뤄져 왔는지를 살펴보고, 해외 의과대학생들의 학습문화 사례를 바탕으로 종합적인 고찰하는 것을 목적으로 하였다. 본 연구를 통한 논의는 다음과 같다.

해외 의과대학의 경우, 시험문제의 전수를 과거 시험문제(past papers)와 시험 회상(exam recall)으로 구분하여 개념화하고 탐색하고 있으며, 특히 '저작권'과 관련된 법적, 윤리적 문제에 대해서 깊이 다루고 있다. 시험문제 유출로 인해 논란이 된 사건을 시작점으로 하여, 해외에서는 의과대학협의회, 그리고 단과대학 단위에서 공론화된 논의를 바탕으로 시험문제 공유행위를 명백한 부정행위로 명시하고 있다. 뿐만 아니라 시험문제 전수와 관련된 문제를 대처하기 위하여 시험 회상 및 학생 간 시험문제 전달이 부정행위라는 정보를 공식적으로 창구를 통해 정보를 제공하고 연습시험을 실시하고 문제를 공유하는 대안을 제시하고 있다.

하지만 한국 의과대학협회나 한국의학교육학회 등 의학교육 관련 기관에서도 '족보' 또는 '시험 회상'과 관련된 행위를 다루고 있는 공식문서는 확인되지 않는다. 2011년 일어난 의사 국가시험 문제 유출에 대해서 한국보건의료인국가시험원이 면허 취소도 고려할 수 있다는 입장을 밝힌 것으로[24], 의사 국가시험 문제의 유출, 무단 복제, 공유, 재구성 등을 부정행위로 간주하고 있음을 추측할 수 있을 뿐이다. Kwon 등[7]의 '한국 의대생 자율규제 지침' 연구에서 시험문제의 보관, 복제, 배포 등이 학교의 정책이 위배되는 경우, 이러한 행위를 하지 않는다는 조항이 명시되어 있으나, 이는 어디까지나 '자율규제 지침'이며 각 의과대학의 행동강령, 학생, 시행세칙 등에 시험문제의 보관, 복제, 배포 등의 내용이 제대로 반영되어 있지 않다는 실제적인 한계를 가진다.

한 가지 분명한 것은 한국 의과대학의 족보를 해외 의과대학에서 시험문제 공유처럼 부정행위로 단순하게 정의하기에는 잠재적 교육과정으로서 그 역할이 크다는 점이다. 따라서 한국의 의학교육 맥락에서 족보가 가지는 교육적 가치와 학생들이 이러한 학습문화에서 얻게 되는 것과 잃게 되는 것에 대해서 명백하게 규명하고 '족보'를 한국의 의학교육 맥락에서 어떻게 다룰 것인가에 대한 공론화된 논의가 필요하다.

의학교육계 내부에서 학생들의 학습문화와 관련된 현상에 충분히 주의를 기울이지 못하는 동안, 정부 주도의 '족보 공유'가 현실로 다가오고 있다. 의과대학생들 사이에서 자생적으로 형성된 잠재적 학습문화를 위계적인(top-down) 방식으로 외부에서 통제할 경우, 그것이 의학교육 안에서 어떤 영향을 미칠지는 누구도 알 수 없다. 하지만 애석하게도 우리는 우리의 교육 맥락에서 족보를 어떻게 다뤄야 할지 논의한 바도, 합의를 진행한 바도 없다.

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Authors' contribution

All the work was done by Chul Han.

Conflict of interest

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과민성장증후군, 기능성 변비 및 클로스트리디오이데스 디피실리(*Clostridioides difficile*) 감염 환자에서 성별 차이를 고려한 프로바이오틱스(probiotics) 사용에 대한 임상지침 및 실용적 권고

Clinical guidance and practical recommendations for probiotic use in patients with irritable bowel syndrome, functional constipation, and *Clostridioides difficile* infection considering sex-based differences: a Korean translation

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Probiotics have gained increasing clinical attention as adjunctive treatment for lower gastrointestinal disorders. However, evidence supporting their therapeutic efficacy remains limited, particularly with regard to sex-related differences. This expert review provides evidence-based insights and practical recommendations for the use of probiotics in patients with irritable bowel syndrome (IBS), functional constipation (FC), and *Clostridioides difficile* infection (CDI), considering possible sex-related differences. Evidence from randomized controlled trials and meta-analyses indicates that probiotics can modestly improve global symptoms, abdominal pain, and bloating in IBS and enhance bowel movement frequency and stool consistency in FC. However, these effects are strain-specific and heterogeneous. Although clinical studies on probiotics in IBS have not confirmed significant sex-related differences, experimental animal studies using stress-induced IBS models have demonstrated sex-dependent responses to specific probiotic strains, supporting the biological plausibility of such differences. For CDI, the efficacy of probiotics in preventing primary or recurrent infections remains inconsistent across large trials, and current guidelines usually do not recommend their routine use. However, sex- and age-related immunologic differences support the clinical differences of CDI. Probiotics are generally considered safe for healthy individuals, although caution is advised in patients who are immunocompromised or critically ill. Clinicians should select probiotic products based on strain-specific clinical evidence, adequate viable doses, patient characteristics and sex. In conclusion, probiotics might play a role as adjunctive therapy for IBS and FC, with variability in responses influenced by microbial, host, and potential sex-related factors. Further research is needed to establish optimized personalized probiotic strategies.

Keywords: *Clostridioides difficile*; Constipation; Irritable bowel syndrome; Probiotics; Sex

프로바이오틱스(probiotics)는 하부 위장관질환의 보조 치료제로서 임상현장에서 점차 주목받고 있다. 그러나 특히 성별 차이에 따른 치료효과를 뒷받침하는 근거는 아직 충분하지 않다. 이 가이드라인은 과민성장증후군, 기능성 변비, 그리고 클로스트리디오이데스 디피실리(*Clostridioides difficile*) 감염 환자에서 프로바이오틱스 사용에 관한 근거 중심의 고찰과 함께, 성별 차이를 고려한 실용적 권고사항을 제시하고자 한다. 무작위 대조시험 및 메타분석의 근거에 따르면, 프로바이오틱스는 과민성장증후군에서 전반적인 증상, 복통 및 복부 팽만감을 일부 완화하는 효과가 있으며, 기능성 변비에서는 배변 빈도와 대변 굳기를 개선할 수 있다. 다만, 이러한 효과는 균주에 따라 차이가 있고 연구 간 이질성이 크다. 과민성장증후군 관련 임상연구에서는 프로바이오틱스 치료효과에 있어 뚜렷한 성별 차이가 확인되지 않았으나, 스트레스 유발 과민성장증후군 동물모델을 이용한 실험연구에서는 특정 프로바이오틱스 균주에 대한 성별 의존적 반응이 관찰되어, 성별에 따른 반응 차이의 생물학적 타당성을 뒷받침한다. *C. difficile* 감염의 경우, 1차 감염 및 재발 예방에 대한 프로바이오틱스의 효능은 대규모 연구에서 일관된 결과를 보이지 않으며, 현재 가이드라인에서는 일상적인 사용을 권고하지 않는다. 다만, 면역학적 성별 차이 및 연령에 따른 차이는 *C. difficile* 감염의 임상 양상 차이를 설명하는 근거가 될 수 있다. 프로바이오틱스는 일반적으로 건강한 성인에서 안전한 것으로 알려져 있으나, 면역 저하자나 중증 환자에게는 신중한 사용이 요구된다. 임상의는 프로바이오틱스 제품을 선택할 때 균주별 임상 근거, 적정 생균 수, 환자의 특성 및 성별 등을 종합적으로 고려하여야 한다. 결론으로, 프로바이오틱스는 과민성장증후군과 기능성 변비의 보조치료로 활용할 수 있으나, 미생물 · 숙주 · 성별 등 다양한 요인에 따라 치료반응이 달라질 수 있다. 최적화된 맞춤형 프로바이오틱스 치료전략을 확립하기 위해서는 향후 추가적인 연구가 필요하다.

Keywords: 클로스트리디오이데스 디피실리(*Clostridioides difficile*); 변비; 과민성장증후군; 프로바이오틱스; 성

서론

프로바이오틱스(probiotics)는 한 세기 이상 장 건강증진을 위해 발효음료 및 보충제로 널리 섭취되어 왔다. 지난 20년간 장내미생물군에 대한 연구가 급속히 확장되면서, 장내미생물이 인간 건강에 중요한 역할을 한다는 사실이 부각되었고, 이는 프로바이오틱스를 포함한 미생물 기반 치료제의 발전으로 이어졌다. 현재 프로바이오틱스는 과민성장증후군(irritable bowel syndrome, IBS)과 기능성 변비(functional constipation, FC) 같은 하부 위장관질환에 흔히 사용되지만, 클로스트리디오이데스 디피실리 감염(*Clostridioides difficile* infection, CDI)에서의 예방적 역할에 대해서 여전히 논란이 많은 측면이 있다[1-3]. 또한 기존의 여러 메타분석에도 불구하고, IBS, FC, 또는 CDI에서 증상을 의미 있게 개선하기 위해 필요한 프로바이오틱스 균주, 용량, 투여기간 등에 대해 상당한 불확실성이 남아있어 가장 신뢰할 수 있고 임상적으로 관련성 높은 근거를 바탕으로 심도 있는 고찰이 요구된다. 이러한 연구들 사이의 상당한 차이는 식이부터 생물학적 요인인 성별에 이르는 복잡한 환경요인의 영향에서 기인할 수 있다. IBS와 FC는 여성에게 더 흔하게 발생하며, 장내미생물의 성별 차이가 잘 알려진 점을 고려할 때, 프로바이오틱스는 성별 특이적 치료효과를 나타낼 가능성이 있다. 성호르몬이 특히 면역활동을 통해 장내미생물군에 영향을 미친다는 점은 잘 알려져 있다[4]. 또한 에스트로젠과 안드로젠 모두 장내미생물군에 의해 영향을 받는데, 특히 폐경기 여성과 노년 남성에서 β-glucuronidase 생성 미생물군에 의한 조절이 두드러진다[5]. 더 나아가 성별 차이와 장내미생물 구성, 면역 신호전달, 내장감각을 연결하는 생물학적으로 타당한 기전들이 제시되고 있다[4-6]. 그러나 프로바이오틱스의 효능이 성별에 따라 다른지에 대한 연구는 거의 없는 실정이다. 이 종설은 프로바이오틱스의 최신 개념을 요약하고, 하부 위장관질환 환자에서의 사용 근거를 성별 관련 차이에 초점을 맞추어 정리하고자 한다.

검색전략 및 문헌 선정

이 종설은 IBS, FC, CDI에 대한 프로바이오틱스의 최신 근거를 성차의 관점에서 요약하고 해석하고자 수행되었다. 문헌검색은 MEDLINE, EMBASE 및 Cochrane Central을 이용하였다. 프로바이오틱스 관련 검색어는 Probiotics, *Saccharomyces*, *Lactobacillus*, *Bifidobacterium*과 관련된 핵심 용어를 조합하여 구성하였다. IBS의 경우, 2023년에 발표된 해당 주제에 관한 최신 체계적 문헌고찰을 핵심 메타분석으로 선정하였다[7]. 해당 메타분석에 포함된 82건의 임상시험을 개별적으로 검토하였으며, 3개 데이터베이스에서 "irritable bowel syndrome" 또는 "IBS"를 검색어로 조합하여 2023년 1월부터 2025년 4월까지 새로 발표된 연구를 추가로 검색하였다. FC에 대한 프로바이오틱스 효과를 검토하기 위해 2000년 1월부터 2025년 4월까지 "functional constipation," "constipation," 및 "FC"를 조합해 상세 검색을 수행했다. CDI에 대한 프로바이오틱스의 효능을 분석하기 위해서는 유사한 검색전략을 사용하여 2000년 1월부터 2025년 8월 사이에 발표된 연구를 검색하였다. CDI 관련 검색어에는 "*Clostridium difficile* infection," "pseudomembranous colitis" 및 "CDI"를 포함하였다. 검색대상은 영어로 발간된 논문으로 제한하였다. 주제와 관련 있는 원저 논문(무작위 대조시험[randomized controlled trial, RCT] 및 관찰연구), 메타분석을 포함한 종설 논문 및 임상 진료지침을 포함하였다. 반면, 증례 보고 및 임상적 관련성이 낮은 연구는 제외하였다. 또한 주요 문헌의 참고문헌 목록을 수동으로 검색(manual screening)하여 추가적인 논문도 확보하였다. 이 논문은 체계적 문헌고찰이 아닌 서술적 종설이므로, 최종 문헌 선정은 임상현장과의 연관성, 연구방법론적 엄격성, 프로바이오틱스의 성별 차이 효과를 이해하는 데 기여하는 정도를 저자들이 질적으로 평가해 결정했다. 결과는 주로 서술적으로 통합했으며, 특정 질환에 미치는 영향, 견해가 일치하거나 논란이 있는 영역, 임상적 함의를 중점적으로 다루었다. 선정된 연구 중 남녀별 결과를 별도로 보고하거나 성별 특이적 하위분석을 제공한 연구를 별도로 분류·기술하고, 가능할 경우 정량적 통합도 시도하였다.

결과

과민성장증후군 환자에서의 장내미생물 불균형과 프로바이오틱스의 임상적 근거

IBS는 확인 가능한 기질적 위장관질환 없이 복통과 배변 이상을 호소하는 흔한 위장관-뇌 상호작용 장애이다(disorders of brain-gut interaction)[1]. IBS의 전 세계 유병률은 11.2%로 추정되며, 발생률은 1.35%에서 1.5% 사이이다[8]. IBS는 특히 성별에 따른 유병률 차이를 보이며, 남성보다 여성에서[9], 고령층보다 젊은 층에서 더 흔하게 나타난다[10].

IBS의 병태생리는 아직 부분적으로만 이해되고 있으며[11], 질환의 장기적인 자연 경과를 변화시키는 것으로 입증된 치료법은 아직 없다. 또한 상당수 환자가 기존 치료에 반응하지 않거나 치료결과에 만족하지 못한다[12,13]. 제시된 여러 가설 중에서도 장내미생물의 이상이 IBS의 발생 기전에 깊이 관여하는 것으로 알려지면서[14,15], 장내미생물군 조절이 잠재적 치료법으로 부상했다.

프로바이오틱스는 IBS 환자에서 광범위하게 연구되었으며, 증상 완화효과는 수많은 임상시험과 메타분석을 통해 뒷받침되었다[7,16-19]. 비록 기전은 완전히 규명되지 않았고, 단쇄지방산(short chain fatty acid, SCFA) 증가, 염증성 사이토카인 감소, 장벽 기능 개선과 같은 임상 바이오마커는 간접적 표지자(surrogates)에 불과하지만, 프로바이오틱스는 IBS 증상 완화에 도움이 될 수 있다[20-22].

2023년 Goodoory 등[7]이 시행한 메타분석에서는 모든 IBS 아형 환자에서 프로바이오틱스의 효능을 평가했다. 이 분석에는 프로바이오틱스 투여군 1,733명과 대조군 1,636명을 포함한 31건의 RCT가 포함되었다. 메타분석 결과, 높은 이질성에도 불구하고 전반적인 증상(risk ratio [RR], 0.78; 95% confidence interval [CI], 0.71–0.87), 통증(RR, 0.72; 95% CI, 0.64–0.82), 복부 팽만감(RR, 0.75; 95% CI, 0.64–0.88)에서 이점이 있을 가능성을 시사했다.

그러나 균주별 효과는 크게 달랐고, 프로바이오틱스의 균종, 용량, 치료기간, 평가지표 등에서 연구 간 이질성이 컸다. *Escherichia* 속 균종들(spp.)은 전반적인 증상 개선에 있어 중등도의 신뢰수준 근거를 보였다. *Lactiplantibacillus plantarum* (*Lactobacillus plantarum*) 299v를 포함한 *Lactobacillus* 속 균종들은 *Bifidobacterium* 속 균종들과 마찬가지로 낮은 신뢰도를 보였으나[23-27], *B. infantis* 35624는 특정 용량에서 일부 효능을 나타냈다[28,29]. 혼합 균주 및 *Bacillus* 속 또한 낮은 신뢰도를 보였으나, 일부 조합은 제한된 수의 임상시험에서 가능성을 보였다. *Saccharomyces*, 특히 *S. cerevisiae* I-3856 역시 복통 감소에 있어 낮은 신뢰도의 근거와 연관이 있었다. 또한 IBS 아형에 따라 결과를 분석한 연구는 매우 제한적이며, 대부분의 메타분석은 아형에 따른 분석 없이 결과를 보고하였다[7,19]. 종합적으로, 이러한 결과들은 뚜렷한 이질성과 균주 특이적 효과로 인해 해석에 주의가 필요하며, 이는 현재의 임상 진료지침에서 균주나 아형에 따른 권고가 없는 원인이 되고 있다[1,17,18,30].

몇몇 IBS 연구에서 프로바이오틱스의 효능을 성별에 따른 치료반응의 차이의 관점으로 보고하였다(Table 1) [31-37]. 최종적으로 3개의 연구가 메타분석에 적합하였으며[32,34,35], 그 결과는 Fig. 1에 제시하였다. 분석결과, 여성 IBS 환자에서 프로바이오틱스의 치료효과가 더 뚜렷하게 나타났으며, 이는 최근 Mullish 등[38]의 또 다른 연구에 의해 뒷받침되었다. 이 연구에서는 여성 환자에서 IBS 증상 점수가 유의하게 감소하였고, 배변 습관 개선과 더불어 불안, 우울 및 IBS 관련 행동이 감소되었다. 그러나 성별 간의 통계적 유의성에는 도달하지 못하였다. 메타분석에서 개별 종(species) 또는 균주(strain)에 근거한 하위 그룹 분석 또한 불가능하였다. 이러한 결과들은 향후 IBS 치료에 있어 프로바이오틱스 효능의 성별 특이적 차이에 대한 연구의 필요성을 시사한다.

Table 1. Studies reporting sex differences in the efficacy of probiotics in irritable bowel syndrome

Study (year)	Country	Patients	Probiotics[a]	CFU	Total		Treatment group		Control group		Duration (wk)	Primary outcome	Results
					Male	Female	Male	Female	Male	Female			
Enck [31] (2008)	Germany	NA	*E. coli* DSM 17252, *E. faecalis* DSM 16440	1.35×10^8–4.05×10^8	150	147	77	72	73	75	8	Global symptoms and abdominal pain	NNT: males 2.49 (1.76–4.22), females 3.98 (2.55–9.13)
Enck [32] (2009)	Germany	NA	*E. coli* DSM 17252	6.8×10^7–2.0×10^8	151	147	76	72	75	75	8	Global symptoms and abdominal pain	Responder rate: males 22.6% vs. 7.2%, females 15.5% vs. 2.5%
Ludidi [33] (2014)	The Netherlands	Rome III	*L. casei* W56, *L. salivarius* W57, *L. lactis* W58, *L. acidophilus* NCFM, *L. rhamnosus* W71	5.0×10^9	13	27	6	15	7	12	6	Abdominal pain (visceral perception)	MSS: males −1.18 (−1.80 to −0.25) vs. 0.93 (−3.87 to 1.43), females −0.06 (−3.77 to 1.64) vs. −1.49 (−7.42 to −0.32)
Mack [34] (2022)	Germany	Rome III	*E. coli* DSM 17252, *E. faecalis* DSM 16440	1.3×10^8–3.9×10^8	187	197	56	131	63	134	26	Global symptoms and abdominal pain	IBS-GAI: males 16.1% vs. 17.2%, females 18.0% vs. 13.1%
Quigley [35] (2023)	USA, UK/Ireland	Rome IV	*B. hydrogenotrophica*	2.0×10^{10}–2.0×10^{11}	96	269	50	127	46	142	8	Bowel habit and abdominal pain	Overall response: males 19.1% vs. 20.0%, females 26.0% vs. 16.7%
Preston [36] (2018)	US, Canada	Rome III	*L. acidophilus* CL1285, *L. casei* LBC80R, *L. rhamnosus* CLR2	1.0×10^{11}	45	68	16	21	29	47	12	Global symptoms and abdominal pain	Improvement in QOL; IBS-D only in males
Chang [37] (2024)	South Korea	Rome III	*B. longum* IDCC 4101, *B. bifidum* IDCC 4201, *B. lactis* IDCC 4301, *B. breve* IDCC 4401, *E. faecium* IDCC 2102, *L. rhamnosus* IDCC 3201, *L. acidophilus* IDCC 3302, *L. casei* IDCC 3451, *L. plantarum* IDCC 3501, *L. helveticus* IDCC 3801	1.0×10^{10}	39	53	26	21	13	32	4	Global symptoms	Overall IBS symptom relief: males 3.54 ± 0.42 vs. 2.69 ± 0.44, females 3.48 ± 0.32 vs. 2.40 ± 0.28

CFU, colony-forming unit; NA, not applicable; *E. coli*, *Escherichia coli*; *E. faecalis*, *Enterococcus faecalis*; NNT, number needed to treat; *L. casei*, *Lactobacillus casei*; *L. acidophilus*, *Lactobacillus acidophilus*; MSS, mean symptom score; IBS-GA, irritable bowel syndrome-global assessment of improvement; *B. hydrogenotrophica*, *Blautia hydrogenotrophica*; QOL, quality of life; IBS-D, diarrhea-predominant irritable bowel syndrome.

[a]Studies listing multiple probiotic strains represent multi-strain probiotic formulations.

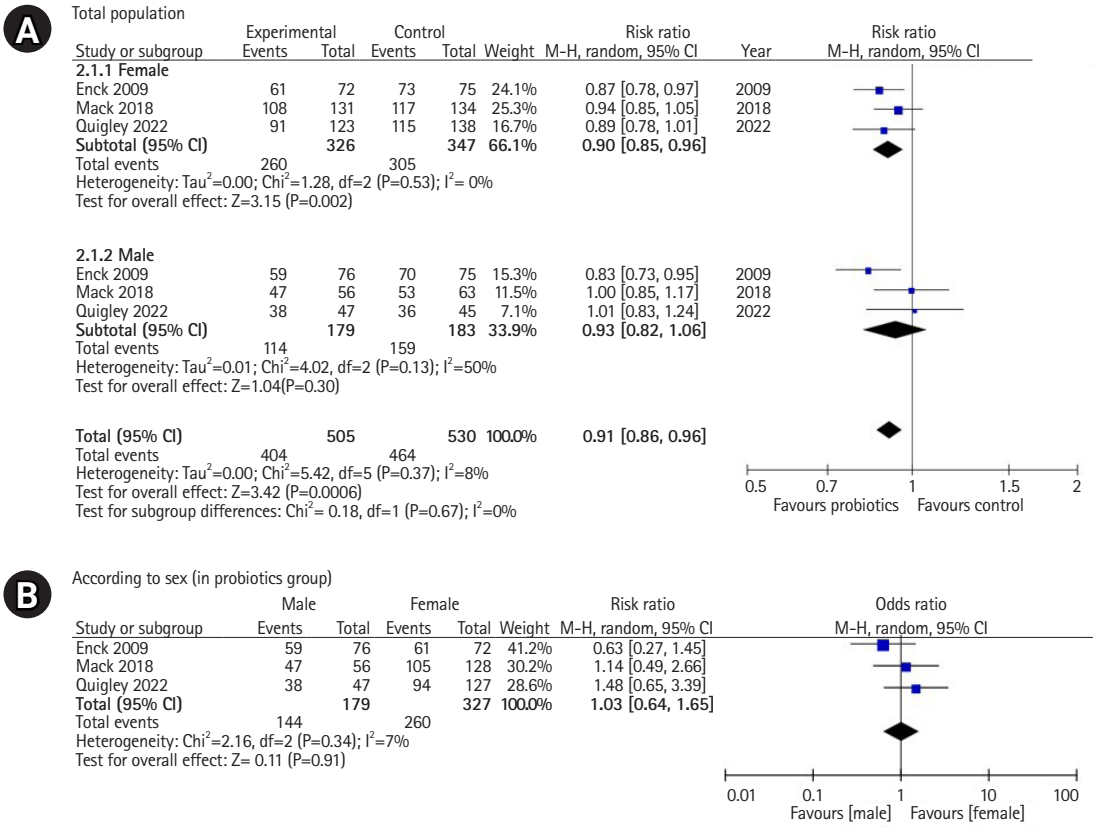

Fig. 1. Meta-analysis of studies reporting sex differences in the efficacy of probiotics in irritable bowel syndrome. (A) Total population. (B) According to sex (in probiotics group). CI, confidence interval; M-H, Mantel-Haenszel; df, degrees of freedom.

기능성 변비 환자에서의 장내미생물 불균형과 프로바이오틱스 사용을 뒷받침하는 임상적 근거

FC 환자에서는 장내미생물 불균형이 관찰되며, 이는 *Bifidobacterium* spp., *Lactobacillus* spp., *Prevotella* spp. 및 부티르산 생성속(genera)의 감소와 *Coprococcus*, *Ruminococcus* spp., *Akkermansia*, *Clostridium* spp.의 증가를 특징으로 한다[39,40]. 변비의 유형에 따라 장내환경과 미생물 구성이 다를 수 있으나, 일반적으로 FC 환자에서는 유익한 젖산 및 부티르산 생성균의 풍부도가 감소하는 반면, 메탄 생성 고균은 증가하는 양상을 보인다[41]. 반면, 전반적인 미생물 다양성은 연구마다 일치하지 않는데, 이는 IBS나 염증성장질환(inflammatory bowel diseases, IBD) 같은 다른 만성 위장관질환에서 전형적으로 다양성이 감소되는 것과는 대조적이다[42].

프로바이오틱스는 식이섬유 발효를 통해 SCFA를 생성하며, SCFA는 삼투압 효과로 대변량을 증가시키고 장신경계(enteric nervous system)를 자극해 연동운동을 촉진한다[43]. 특히 SCFA 중 부티르산은 장벽의 무결성(integrity)을 유지하고 세균성 내독소 및 염증반응을 방지하며, 장 운동성 저해를 감소시킨다[44]. 대장통과시간은 일반적으로 남성보다 여성에서 더 길고[45], 서행성 변비 또한 여성에게서 더 빈번하게 보고된다. 메탄 생성 미생물의 상대적 풍부도는 서행성 변비 환자에서 유의하게 더 높고, 메탄은 윤상근의 비추진성 수축을 강화하여 연동운동 속도를 지연시킨다[15,46]. 일부 프로바이오틱스는 장내미생물 항상성을 회복시키고 메탄 생성균 집단을 감소시킬 수 있다. 이러한 기전들은 프로바이오틱스가 여성 환자에서 더 큰 치료효과를 나타내는 근거가 되는 것으로 보인다.

프로바이오틱스 치료는 장내환경, 상피 면역반응, 장 운동 및 분비활동의 신경내분비적 제어를 조절해 변비증상을 완화하는 다중 기전을 가진다[47,48]. 흔히 사용되는 프로바이오틱스는 *Bifidobacterium*과 *Lactobacillus* 속의 균종들이지만, FC에 가장 효과적인 균주는 아직 논란이 있다[49]. Table 2에 FC 환자에서 프로바이오틱스 효과를 평가한 RCT 25편을 요약하였다[50-74]. 다양한 균주와 생균 수(colony forming unit, CFU)를 사용했으며, 각 연구에 포함된 환자 수는 비교적 적었다. 가장 많이 사용된 균주는 *Bifidobacterium*이며, 그 다음이 *Lactobacillus*였다. 전반적으로 프로바이오틱스 4주 복용 후 일주일 평균 자발 배변(spontaneous bowel movement, SBM) 횟수가 0.67회(95% CI, 0.22-1.12) 유의하게 증가하였다(Fig. 2). 그러나 연구 간 이질성은 매우 높았는데(I^2=96%), 이는 균주, 용량, 증상 중증도, 환자 특성 차이 때문으로 보인다. 균종별 하위 분석결과, 일주일 평균 SBM의 유의미한 증가는 관찰되지 않았으며, 균종 간의 효과 차이 또한 통계적으로 유의하지 않았다. 프로바이오틱스는 4주차에 브리스톨 대변 형태

Table 2. Characteristics of studies using probiotics in patients with constipation

Year	Country	Patients	Probiotics[a]	CFU	Treatment group: control group	Duration	Outcome
del Piano [50] (2008)	Italy	Evacuation disorder	*L. plantarum*, *B. animalis lactis*	5.0×10^9	80:110:110[b]	30 days	Increase in number of weekly evacuations in probiotics group
Fateh [51] (2011)	Iran	FC (Rome III)	*B. longum*, *B. breve*, *L. casei*, *L. rhamnosus*, *S. thermophilus*, FOS	1.0×10^8	31:29	4 wk	Increase in stool frequency in men receiving probiotics
Favretto [52] (2013)	Brazil	FC (Rome III)	*B. lactis* Bi-07	1.0×10^8	15:15	30 days	Increase in stool frequency in women receiving probiotics
Mazlyn [53] (2013)	Malaysia	FC (Rome III)	*L. casei* Shirota	3.0×10^{10}	50:50	4 wk	Probiotics did not alleviate constipation severity, stool frequency, and consistency.
Waitzberg [54] (2013)	Brazil	FC (Rome III)	*B. lactis*, *L. paracasei*, *L. rhamnosus*, *L. acidophilus*, and FOS	$< 10^9$	49:50	30 days	Synbiotics improved stool frequency and consistency in constipated women.
Ojetti [55] (2014)	Italy	FC (Rome III)	*L. reuteri* DSM17938	1.0×10^8	20:20	4 wk	Probiotics increased stool frequency. No difference in stool consistency.
Ding [56] (2016)	China	FC (Rome III)	*B. longum*, *L. acidophilus*, *E. faecalis*, soluble fiber (Pectin)	3.0×10^7	48:45	12 wk	Synbiotic exhibited increased stool; Frequency and improved stool consistency and constipation-related symptoms.
Cudmore [57] (2017)	Ireland	FC (Rome III)	*B. bifidum*, *L. rhamnosus*, *L. acidophilus*, psyllium/inulin	6.0×10^8	35:34	4 wk	Synbiotics did not significantly improve stool frequency.
Ibarra [58] (2018)	France	FC (Rome III)	*B. animalis* HN019	$1.0 \times 10^9/10^{10}$	76:76:76[c]	4 wk	No difference in stool frequency and consistency between the probiotics and placebo groups.
Lim [59] (2018)	Malaysia	FC (Rome III)	*B. lactis* BB12, *L. plantarum* LP01, inulin-oligofructose	1.0×10^{10}	43:42	12 wk	No difference in stool frequency and consistency between the probiotics and placebo groups.
Dimidi [60] (2019)	UK	FC (Rome III)	*B. lactis*	1.5×10^{10}	37:38	4 wk	There were also no improvements in stool output, symptoms, or quality of life between probiotics and placebo groups.
Martoni [61] (2019)	Canada	FC (Rome III)	*L. acidophilus*, *B. animalis lactis*, *B. longum*, *B. bifidum*	1.5×10^{10}	48:46	4 wk	No difference in stool frequency and consistency between the probiotics and placebo groups.
Botelho [62] (2020)	Brazil	FC (Rome IV)	*L. acidophilus*, *L. casei*, *L. lactis*, *B. bifidum*, *B. lactis*	5.0×10^9	21:14	30 days	Probiotics improved constipation-related symptoms.
Madempudi [63] (2020)	India	FC (Rome III)	*B. coagulans* Unique IS2	2.0×10^{10}	50:50	4 wk	Probiotics improved stool frequency and consistency.
Kang [64] (2021)	South Korea	FC (Rome III)	*B. coagulans* SNZ1969	1.0×10^9	40:40	8 wk	Probiotics improved stool frequency and colon transit time.
Wang [65] (2021)	China	FC (Rome III)	*S. thermophilus*, *L. bulgaricus*, *B. animalis*	1.0×10^{10}	23:21	4 wk	Probiotics improved constipation-related symptoms.
Mitelmao [66] (2022)	Brazil	FC (Rome IV)	Multiple combination of *Lactobacillus* and *Bifidobacterium*	8.0×10^9	51:51	30 days	Probiotics improved stool frequency and consistency.
Takeda [67] (2022)	Japan	FC (Rome IV) and elderly (>65)	*B. longum* BB536	5.0×10^{10}	39:41	4 wk	Probiotics improved stool frequency in elderly patients.
Wang [68] (2022)	China	FC (Rome IV)	*B. bifidum* CCFM16	2.0×10^9	53:50	4 wk	Probiotics improved stool consistency.
Lai [69] (2023)	China	FC (Rome IV)	*B. animalis* subsp. *lactis* HN019, *L. rhamnosus* HN0001		50:50	4 wk	Probiotics improved stool consistency and constipation-related symptoms, but did not increase stool frequency.

(Continued on the next page)

척도(Bristol stool form scale, BSFS) 점수를 0.31 (95% CI, 0.01–0.61)만큼 약간 개선시켰다(Fig. 3). SBM 변화와 마찬가지로 균종별 분석에서는 신바이오틱스만 대변의 굳기를 유의하게 개선했다. 일부 연구들이 증상 개선의 가능성을 시사하지만, 이질성과 전반적으로 낮은 근거 수준으로 인해 FC에서 프로바이오틱스의 치료적 가치를 확신하기에는 한계가 있다. 최근 발표된 네트워크 메타분석에서는 균주별로 분류했을 때 어떤 균주도 위약 대비 배변 횟수를 유의하게 증가시키지 못했다[75]. 이를 자세히 살펴보면, 3건의 연구가 여성 환자만을 대상으로 수행되었다[52,54,74]. Rome III 기준에 따라 진단된 변비 여성 100명을 대상으로 한 연구에서, 매일 6 g의 신바이오틱스(synbiotics, *Lactobacillus* 및 *Bifidobacterium* 종과 프락토올리고당의 혼합물)를 복용한 환자군은 위약군에 비해 더 높은 배변 횟수와 대변 굳기 점수를 기록하였다[54]. 40명의 여성 변비 환자를 모집한 또 다른 연구에서는 *L. gasseri* 투여군의 SBM이 5.0±0.9에서 9.4±1.6으로 증가했으나 위약군은 4.2±0.5에서 7.5±0.7회로 증가하는 데 그쳐 의미 있는 차이를 보였다[74]. 여성만을 대상으로 한 연구들을 분석한 결과, 남녀 모두를 포함한 연구들에 비해 SBM 변화량(주당 2.06회 증가[95% CI, 1.14–2.99])과 대변 굳기 변화량(BSFS 3.5점 증가[95% CI, 2.87–4.13])에서 유의미하게 더 큰 개선효과를 보였다.

Clostridioides difficile 감염에서 프로바이오틱스 사용: 현재 근거

CDI는 의료 관련 감염성 설사의 주요 원인으로, 특히 70세 이상에서 전 세계적으로 부담이 증가하고 있다[76]. CDI 예방에 있어 프로바이오틱스의 예방적 역할을 규명하기 위한 다수의 연구가 수행된 바 있으며(Supplement 1)[77-90], 이 중 대표적 임상시험으로는 1차 예방을 위한 PLACIDE 연구[79]와 2차 예방을 위한 PICO 연구가 있다[86]. 그러나 이들 연구는 주로 CDI의 낮은 발생률이나[79] 군 간 차이가 없어[86] 유의미한 효과를 입증하는 데 실패하였다. 또한 단일 및 다기관 연구를 포함한 후속 임상연구들에서 그 결과가 일관되게 재현되지 않고 있다[91,92].

2017년 코크란 리뷰[93]와 메타분석[94]은 프로바이오틱스가 CDI 예방에 유의한 효과가 있음을 보여주었으나, 몇 가지 제한점이 제기되었다. 2017년 코크란 분석에 따르면 *Clostridioides difficile* 연관 설사 발생률이 60% 감소하였으며, 면역저하자나 중증 쇠약 환자가 아닌 환자에게 항생제와 병용하는 단기 프로바이오틱스 투여는 안전하고 효과적인 것으로 결론지었다[93]. 그러나 포함된 연구 대부분이 높은 편향 위험을 가졌고, 사후 하위집단 분석결과, 기저 CDI 위험도가 5%를 초과하는 대상군에서만 그 이점이 관찰되었다. 또한 포함된 연구 중 일부에서만 예방효과가 입증되어 결과 해석에 주의를 요한다. 추가적으로 메타분석 과정에서 서로 다른 프로바이오틱스 속을 하나의 범주로 통합함으로써 독특한 생물학적 기전을 가리고 상당한 편향을 초래한다는 제한점도 있다.

이에 따라 여러 가이드라인은 CDI 예방을 위한 프로바이오틱스의 일상적 사용을 권고하지 않고 있다. 그 이유는 첫째, 프로바이오틱스 효능과 비용효과에 대한 명확하고 일관된 근거 부족이다. 앞서 언급한 1차 및 2차 예방 임상시험 모두 유의한 이점을 입증하지

Table 2. Continued

Year	Country	Patients	Probiotics[a]	CFU	Treatment group: control group	Duration	Outcome
Ma [70] (2023)	China	FC (Rome IV)	*L. plantarum* P9	1.0×10^{11}	78:85	4 wk, 6 wk	Probiotics significantly improved stool frequency and symptoms.
Cheng [71] (2024)	China	FC (Rome IV)	*B. animalis* subsp. *lactis* HN019	7.0×10^{9}	112:117	8 wk	No difference in stool frequency in probiotics and placebo groups.
Salo [72] (2024)	Spain	Constipation	*B. animalis* subsp. *lactis* BLa80	2.0×10^{9}	23:23	4 wk, 8 wk	Probiotics improved stool frequency.
Jin [73] (2025)	South Korea	Constipation	Multiple combination of *Lactobacillus* and *Bifidobacterium*	2.0×10^{9}	33:37	4 wk, 8 wk	Probiotics significantly improved stool frequency, consistency and symptoms.
Roos [74] (2025)	Sweden	Constipation	*L. gasseri*	1.0×10^{9}	20:20	4 wk	Probiotics improved constipation-related symptoms in women.

CFU, colony-forming unit; *L. plantarum*, *Lactobacillus plantarum*; *B. animalis*, *Bifidobacterium animalis*; FC, functional constipation; *B. longum*, *Bifidobacterium longum*; *L. casei*, *Lactobacillus casei*; *S. thermophilus*, *Streptococcus thermophilus*; FOS, fructo-oligosaccharide; *E. faecalis*, *Enterococcus faecalis*; *L. acidophilus*, *Lactobacillus acidophilus*.
[a]Studies listing multiple probiotic strains represent multi-strain probiotic formulations. [b]80 subjects with placebo, 110 subjects with mixed *L plantarum* LP01 and *B. breve* BR03, and 110 subjects with *B. animalis* subsp. *lactis* BS01. [c]76 subjects with placebo, 76 subjects with the low dose group, and 76 subjects with the high dose group.

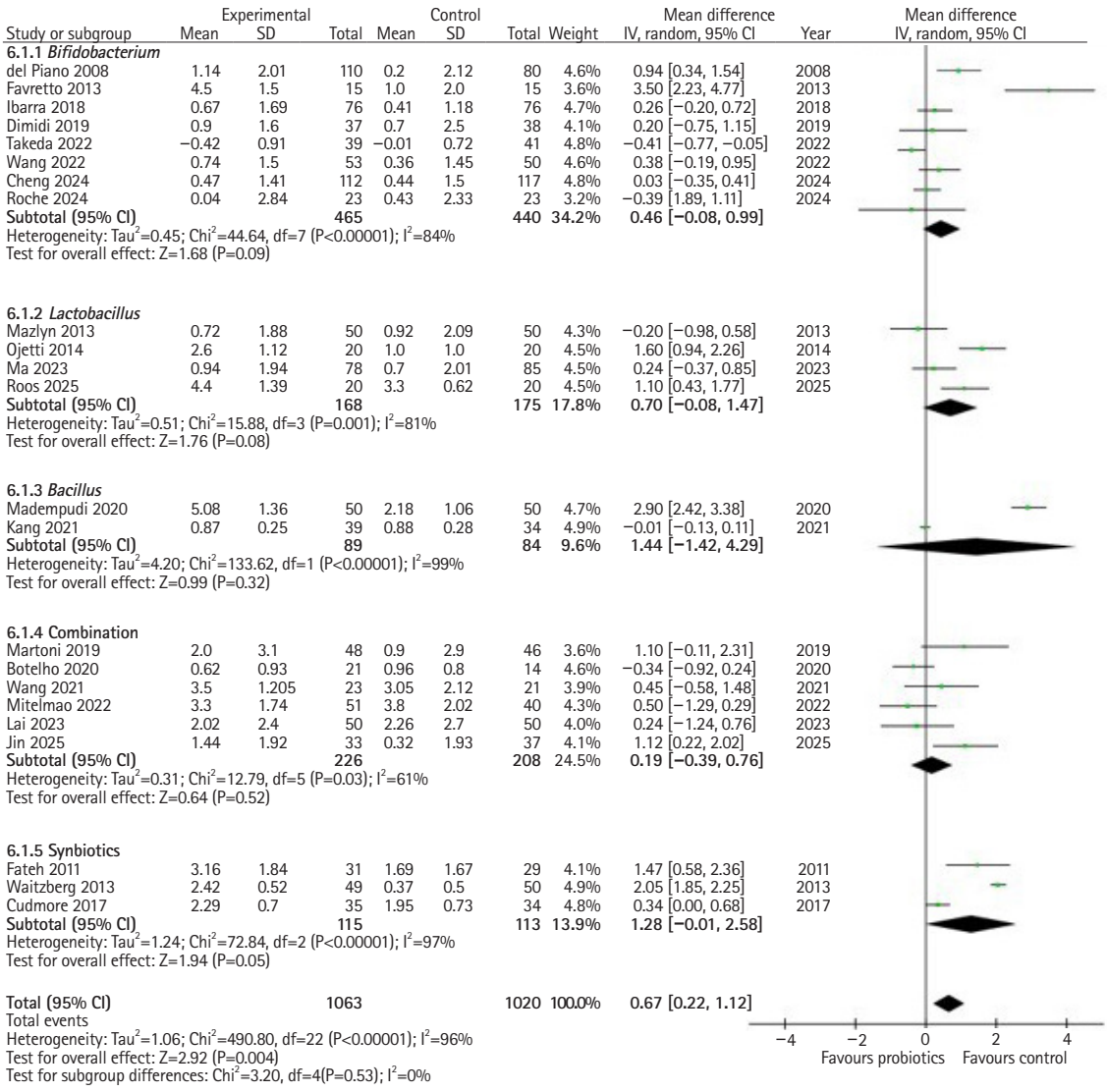

Fig. 2. Change of spontaneous bowel movement by species. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

못했다. 둘째, 프로바이오틱스 제품을 둘러싼 상당한 이질성과 불확실성이 주요 쟁점으로 대두되고 있다. 구체적으로는 제품 라벨 정보와의 불일치 및 편차, 균주의 빈번한 오식별 · 오분류 또는 생존력 상실, 오염, 그리고 기능적 특성 저하 등이 포함된다[95]. 이러한 불확실성으로 인해 현재 가이드라인들은 프로바이오틱스의 일상적 사용에 대해 신중하거나[96], 심지어 반대하는 입장을 취하고 있다[95,97]. 또한 안전성 문제도 제기되는데, CDI 위험군에 속하는 환자가 중증 상태이거나 면역이 저하되어 있어 프로바이오틱스 투여가 부적절할 수 있기 때문이다[95-97]. 이러한 우려는 항생제 노출 후 프로바이오틱스가 대장의 정상미생물 재정착을 오히려 저해할 수 있음을 시사하는 연구결과들에 의해 더욱 뒷받침된다[95].

성별 관점에서 여성은 CDI 발생 및 재발률이 높고, 남성은 사망률과 입원기간이 더 길다[98,99]. 이는 성별이 질병의 감수성과 예후에 영향을 미칠 수 있음을 시사한다. 최근 데이터는 장내미생물군 구성과 면역체계 등 성별 관련 요인이 역할을 할 수 있음을 보여준다[100]. 특히 여성은 일반적으로 남성보다 혈중 면역글로불린 M (immunoglobulin [Ig] M) 농도는 높지만 IgA 수치는 낮은 특성을 보이는데, 이는 *C. difficile*에 대한 점막 방어력을 저하시킬 수 있고 여성에서 관찰되는 높은 발생률이나 재발률의 원인이 될 수 있다[101,102]. 앞서 언급한 성별 차이를 고려할 때 프로바이오틱스 효능도 성별에 따라 다를 가능성이 있지만, 현재까지 성별 특이적 효능에 관한 근거는 불명확하다. 따라서 향후 프로바이오틱스 임상시험은 이러한 생물학적 차이를 반영해 세심하게 설계되어야 하며, 이는 궁극적으로 예방전략을 정교화하고 CDI 치료에 보다 개인 맞춤형 접근을 가능하게 할 것이다.

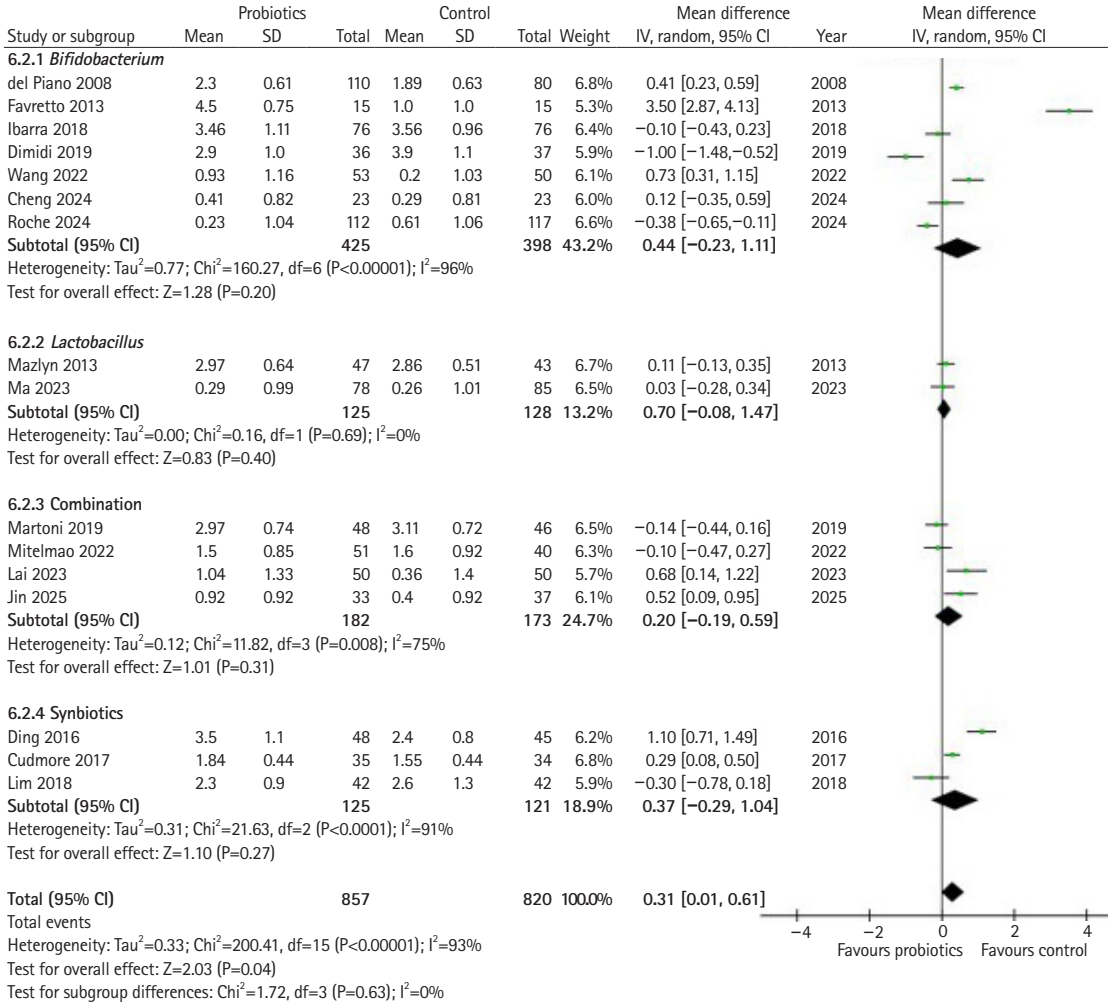

Fig. 3. Change of stool consistency (Bristol stool form scale) by species. SD, standard deviation; IV, inverse variance; CI, confidence interval; df, degrees of freedom.

고찰

호르몬 차이, 마이크로바이옴 변이 및 치료반응

장내미생물은 IBS, IBD, 대장암 등 다양한 위장관질환에 기여하는 것으로 알려져 있다. 정확한 병인은 아직 불분명하나, 장내미생물이 장 운동성, 염증 및 면역반응에 미치는 영향에 대한 증거가 점차 증가하고 있다[6,103]. 최근에는 위장관질환에서 성별 차이와 장내미생물과의 관련성이 제시되고 있다[5,6,103,104]. 또한 에스트로젠과 안드로젠의 대사가 장내미생물과 밀접한 관련이 있음이 보고되었다. 장내미생물이 성호르몬의 분비 및 순환과정에 관여함이 알려지면서, 성호르몬이 장내미생물에 미치는 역할을 나타내는 "마이크로젠더로옴(microgenderome)" 개념이 제안된 바 있다. 에스트로젠과 테스토스테론은 장내미생물과 면역세포에 직접적인 영향을 미치는 것으로 나타났다. β-estradiol(에스트라다이올)은 수지상 세포의 형질 전환을 유도하여 interleukin (IL)-12 및 interferon-γ 생성을 촉진하며[105], 이는 다시 염증성 사이토카인 경로를 활성화한다. 에스트라다이올은 B세포의 생존을 연장하고 다클론성 B세포를 활성화한다[105]. 이렇게 조성된 염증성 환경과 변화된 장 투과성은 장내미생물이 고유판(lamina propria)으로 이동하는 원인이 되며, 이는 다시 염증과정을 촉진한다[105]. 남성에서는 테스토스테론이 T 세포 증식을 억제하는 효과를 보이며 에스트라다이올과 달리 장벽기능을 변화시키지 않는다[105]. 장내미생물은 뇌-장 축과 장벽기능 조절에 핵심적인 역할을 한다[106-108]. 단쇄지방산은 풍부하고 가장 중요한 미생물 대사 산물로, 장 운동성과 상처 치유를 조절하는 염증 조절자이다[109]. 또한 미생물-장-뇌축 사이를 잇는 매개체로 밝혀졌다[110-112]. 흥미롭게도 부티르산 생성 장내미생물의 성별 차이가 보고된 바 있다[100]. 추가적으로, 최근 연구에 따르면 oligofructose가 포함된 식단을 투여했을 때 암컷과 수컷 쥐의 장내미생물에서 서로 다른 단쇄지방산 프로파일이 나타났다. 암컷의 경우 oligofructose 보충이 Bacteroidetes의 풍부도를 증가시켰으나, 수컷에서는 차이가 없었다. 나아가 분변 내 낙산, 간 IgA, IL-6 및 맹장 IL-6 수치는 수컷에서 증가한 반면, IL-10 수치는 암컷에서 더 높았다[113]. 흥미롭게도 토착 아프리카인들은 *Faecalibacterium prausnitzii*, *Clostridium* cluster IV,

Clostridium cluster XIVa와 같은 부티르산 생성 박테리아가 현저히 풍부했으나, 아프리카계 미국인에서는 *Bacteroides*가 우세했다[114]. 또한 성별 차이를 분석해보면 *Bacteroides-Prevotella* 그룹은 남성에서 여성보다 더 높게 나타났다[115]. 성별에 따른 프로바이오틱스 치료반응의 측면에서는, 루푸스 모델 쥐에 5종 *Lactobacillus* 균주 혼합물을 투여했을 때 여성과 거세된 수컷에서는 신장 기능이 개선되고 항염증 효과가 나타났으나, 생식기가 온전한 수컷에서는 효과가 없었다[116]. 이는 프로바이오틱스 투여에 있어 성별 차이를 시사하지만, 대부분의 연구는 동물에서 수행되었다.

프로바이오틱스 효과는 성별에 따라 다른가? 전임상 모델에서의 증거

프로바이오틱스의 생물학적 효과는 균주의 특성과 숙주요인에 의해 영향을 받는데, 여기에는 생리, 면역 및 미생물 구성의 성별 차이 등이 포함된다. IBS와 같이 명확한 성차가 있는 질환에서는 치료반응도 성별에 따라 다를 가능성이 있다[117]. 그러나 임상적 증거는 연구설계의 이질성과 성별 분석 부족으로 인해 아직 결론적이지 않다. 반면, 통제된 동물모델에서는 프로바이오틱스에 대한 성별 의존적 반응이 뚜렷하게 나타났으나, 이를 평가하기 위해 특별히 설계된 전임상 연구의 수는 여전히 부족한 실정이다(Table 3).

반복적 물회피 스트레스(repeated water avoidance stress, rWAS) 모델과 같은 스트레스 유발 위장관질환 모델에서, 암컷 설치류는 수컷에 비해 전형적으로 심한 내장과민성, 비만세포 침윤, 과도한 점막 사이토카인 발현을 특징으로 하는 높은 취약성을 나타낸다. rWAS 모델연구에서 *Companilactobacillus farciminis*(구 *Lactobacillus farciminis*) 또는 *Bifidobacterium longum* BBH016을 10일간 경구 투여하면 암컷 쥐에서만 내장과민성과 대장 미세염증이 유의하게 감소했다[118,119]. 반면, *Roseburia faecis* BBH024와 R22-12-24는 수컷 쥐에서 더 뚜렷한 항염증 효과를 나타내며 배변량을 줄이고 기능적 미생물 경로를 개선했다[120]. 이와 유사한 성별 의존적 반응이 IBS 모델을 넘어 대사 및 면역 맥락에서도 관찰된다. 고지방 식이를 한 쥐에서 *Clostridium butyricum* IDCC 1301 투여에 의한 장 염증 완화 및 장벽 기능 개선효과는 성별에 따라 다르게 나타났다. 항염증 및 장벽 보호효과는 수컷에서 더 뚜렷한 반면, 암컷은 담즙산 프로필과 염증지표에서 독특한 변화를 보였다[121]. 또한 *C. butyricum* IDCC 1301은 성별에 따라 장내미생물군을 다르게 재구성하여, 수컷에서 주로 부티르산 생성 균주를 증가시키고 암컷에서는 *Akkermansia muciniphila*를 더 현저히 감소시켰다[122]. 이러한 결과는 스트레스로 유발된 장 기능장애가 성별 특이적 염증 및 미생물 반응을 유발하며, 이러한 반응들이 프로바이오틱스 균주뿐만 아니라 숙주의 성별에 따라서 다르게 조절된다는 점을 시사한다.

면역 및 신경행동 동물모델을 이용한 다른 연구들에서도 이와 유사한 성별 의존적 차이가 보고되었다. *Limosilactobacillus reuteri*(구 *Lactobacillus reuteri*) DSMZ 8533 투여는 수컷과 암컷 사이에 뚜렷하게 다른 미생물 구성과 사이토카인의 변화를 일으켰다[123]. 또한 태아기에 아편에 노출된 쥐에서 VSL#3 치료는 성별에 따라 장내미생물 불균형과 통각 변화가 다르게 개선되었는데, 수컷에서는 통증 민감도가 완화되었고 암컷에서는 미생물 프로필이 정상화되었다[124]. 종합하면, 이러한 결과들은 성별 특이적인 프로바이오틱스 효과가 스트레스, 대사 및 통증을 조절하는 미생물 및 신경 면역축에 영향을 미친다는 점을 부각한다. 축적된 전임상 증거들은 프로바이오틱스의 효과가 성별에 따라 다르다는 점을 시사하며, 이는 호르몬 환경, 면역 활성화, 그리고 기초 장내미생물 무리의 차이에서 기인할 가능성이 높다. 이러한 실험적 결과들은 맞춤형 미생물 기반 치료로 발전시키기 위해 성별을 핵심적인 생물학적 변수로 고려해야 할 필요성을 강조한다.

연구와 현실의 간극 메우기: 임상 현실과 성별 특이적 프로바이오틱스 치료 가능성

검토한 임상 증거에 따르면, 프로바이오틱스는 하부 위장관질환 관리에 있어 미미하지만 유의한 잠재력을 보인다. IBS 환자에서는 특정 균주가 전반적인 증상, 특히 복통과 복부 팽만감을 완화할 수 있음을 시사하고 있다. FC에서는 일부 프로바이오틱스 및 신바이오틱스가 배변 횟수와 굳기를 개선한다. CDI에서는 1차 예방을 위한 일상적 사용은 여전히 논란의 여지가 있으나, 특정 고위험군에서 이점이 있을 수 있다. 그러나 연구 설계, 균주, 용량, 치료기간의 현저한 이질성으로 인해 이러한 결과를 임상에 적용하는 것은 여전히 어려움이 있다. 또한 대부분의 임상시험에서 서로 다른 제형을 사용하고 있어 균주 특이적 효과를 명확히 파악하기 어렵게 만들며, 표준화된 가이드라인의 수립을 복잡하게 한다. 특히 성별 차이에 관련하여 전임상 결과와 임상시험 사이의 불일치가 두드러진다. 통제된 실험환경의 동물모델에서는 특정 프로바이오틱스에 대해 뚜렷하고 강력한 성별 의존적 반응이 확인된 반면, 인간을 대상으로 한 임상시험에서는 아직 이러한 명확한 차이가 확인되지 않았다. 임상현장에서 유의미한 성별 특이적 근거가 부족한 이유는 대개 통계적 검정력의 부족한 연구 규모, 사후 분석, 또는 남성이나 여성 집단의 과소 대표성에서 기인한다. 따라서 현재로서는 환자의 성별에 근거하여 특정 프로바이오틱스 균주를 선택하도록 결정적인 임상 권고안을 제시하기는 어렵다. 그 대신, 향후 연구와 RCT에서는 이러한 성별 요소를 핵심적인 생물학적 변수로 우선적으로 고려해야 한다. 이처럼 명확한 근거가 부족한 현재 상황에서 임상의는 주요 증상과 근본적인 병태생리에 기반하여 균주를 선택하는 개인별 맞춤형 접근방식을 취해야 한다. 결과적으로, 임상의는 개별 환자의 다양성에도 불구하고 표준화되고 안전한 중재를 보장하기 위해 품질, 안정성, 환자별 위험요인을 포함한 프로바이오틱스의 실제적 이용과 안전성 측면에 대해 기본적인 이해를 갖추어야 한다.

임상의가 프로바이오틱스를 사용할 때 고려해야 할 사항은 무엇인가?

임상현장에서 프로바이오틱스의 사용이 크게 증가했음에도 불구하고, 제품의 다양성, 불명확한 라벨 표기, 표준화된 처방 가이드라인의 부재로 인해 임상의들은 여전히 어려움에 직면해 있다. 아래에서는 용량, 안정성, 제형 및 환자별 요인을 포함하여 임상의가

Table 3. Summary of preclinical studies investigating sex-dependent effects of probiotics

Study (year)	Animal, model	Probiotics	CFU/day/rat	Experimental design	Sex-dependent results
Lee [118] (2017)	Wistar rats; rWAS (1 hr/day for 10 days)	*C. farciminis*	1.0×10^{11}; 10 days during rWAS	3 groups (no-stress, rWAS, rWAS + *C. farciminis*)	• Female : rWAS → ↑FPO, visceral analgesia, ↑mast cells & proinflammatory cytokines; Probiotics → ↓mast cells, ↓IFN-γ, ↓TNF-α, ↓IL-6, ↓PRSS1-3 • Male : rWAS → mild ↑FPO, no analgesia; Probiotics → no reduction in inflammation, ↑IL-1β, ↑IL-17
Choi [119] (2024)	Wistar rats; rWAS (1 hr/day for 10 days)	*B. longum* BBH016	1.0×10^{9}; 10 days during rWAS	3 groups (control, rWAS, rWAS + *B. longum*)	• Females : rWAS → ↑FPO, ↑mast cells, dysbiosis; Probiotics → ↓FPO, ↓mast cells, mitigated dysbiosis • Males : rWAS → ↑FPO; Probiotics → no significant effect
Choi [120] (2023)	Wistar rats; rWAS (1 hr/day × 10 days)	*R. faecis* BBH024 and R22-12-24	1.0×10^{9}; 10 days during rWAS	3 groups (control, rWAS, WAS + *R. faecis*)	• Female : rWAS → ↑FPO, ↑mast cells; probiotics → ↓FPO, ↑IL-6 • Male : rWAS → ↑FPO, ↑mast cells, ↑IL-6; Probiotics → ↓FPO, ↓mast cells, ↓IL-6
Choi [121] (2023)	Fischer-344 rats, HFD (8 wk)	*C. butyricum* IDCC 1301, Biovita	Low 1×10^{7}; Medium 1×10^{8}; High 1×10^{9}; 8 weeks during HFD	5 groups (control, Biovita, *C. butyricum* at low/medium/high concentrations)	• Female : HFD → ↓TJPs, ↑MPO, ↓butyrate, ↓IL-6; Probiotics → ↑TJPs, ↑IL-6 • Male : HFD → ↑TJPs, ↑TNF-α, ↑MPO, ↓butyrate; Probiotics → ↓TNF-α, ↓ MPO, ↑IL-10, ↑butyrate
Choi [122] (2024)	Fischer-344 rats, HFD (8 wk)	*C. butyricum* IDCC 1301, Biovita	Low 1×10^{7}; Medium 1×10^{8}; High 1×10^{9}; 8 weeks during HFD	5 groups (control, Biovita, *C. butyricum* at low/medium/high dose)	• Female : HFD → ↓α-diversity, ↓Ruminococcaceae, ↑Lachnospiraceae, ↑*A. muciniphila*, altered carbohydrate/energy metabolism; Probiotics → ↑Ruminococcaceae, ↓*A. muciniphila* • Male : HFD → ↓Ruminococcaceae, ↑*A. muciniphila*, ↓energy metabolism, altered carbohydrate/energy metabolism; Probiotics → ↑Lachnospiraceae, ↓*A. muciniphila*, recovered carbohydrate/energy metabolism
He [123] (2019)	BALB/c mice, healthy	*L. reuteri* DSMZ 8533	Low 1.0×10^{8}; High 1.0×10^{10}; 28 days	3 groups (control, *L. reuteri* at low/high dose)	• Females : ↑ *Helicobacter* ↓Actinobacteria • Males : ↓ *Bacteroides*, ↓*Prevotella*, ↑ *Clostridium* IV
Singh [124] (2025)	C57BL/6 mice, POE	VSL#3	4.5×10^{11}; Late gestation–postnatal day 21	2 groups (POE only, POE + VSL#3)	• Females : POE → ↓α-diversity, analgesia; Maternal probiotics → partial, transient normalization of analgesia • Males : POE → ↑α-diversity, hyperalgesia; Maternal probiotics → robust normalization of hyperalgesia

Biovita contains *C. butyricum* 1301, *L. sporogenes* IDCC 1201, and *Bacillus subtilis* IDCC 1101.
CFU, colony-forming unit; rWAS, repeated water avoidance stress; *C. farciminis*, *Companilactobacillus farciminis*; FPO, fecal pellet output; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha; IL, interleukin; PRSS, mucosal serine protease gene; *B. longum*, *Bifidobacterium longum*; *R. faecis*, *Roseburia faecis*; HFD, high fat diet; *C. butyricum*, *Clostridium butyricum*; TJP, tight junction protein; MPO, myeloperoxidase; POE, prenatal opioid exposure; *L. reuteri*, *Limosilactobacillus reuteri*; *A. muciniphila*, *Akkermansia muciniphila*.

프로바이오틱스를 처방할 때 고려해야 할 요소들을 논의하고자 한다.

용량 및 제형에 따른 적응증

의사는 제조사의 문서를 통해 프로바이오틱스의 유통기간 동안 안정성과 생균 수(CFU) 유지 여부를 확인해야 한다. 임상적 이익을 얻기 위해서는 일반적으로 최소 1.0×10^9 CFU/일 투여량이 요구되나[125-127], 규제기준은 국가별로 다르다(한국: 1.0×10^8 CFU; EU/캐나다: 1.0×10^9 CFU 이상; 미국: 1.0×10^8–10^{11} CFU/일)[128,129]. 고용량이 반드시 효능 향상으로 이어지는 것은 아니므로, 복용량은 임상시험을 통해 입증된 균주별 근거 용량을 따라야 한다[130]. 제조사는 유통기한까지 생존 균수를 보장하기 위해, 제품에 표시된 용량보다 더 많은 양을 투여하여 제조(overage)하는 경우가 많다[131]. 제형 측면에서는 일반적으로 액상 현탁액보다 캡슐이나 분말과 같은 고형 제제가 더 높은 안정성을 보인다[132]. 최근에는 마이크로캡슐화 및 나노기술과 같은 진보된 기술이 도입되어 특정 부위로의 전달 효율을 최적화하고 있다[133].

프로바이오틱스 복용 시점

프로바이오틱스의 생존과 정착은 식사시간, 생체리듬, 그리고 병용 약물의 영향을 받는다. 공복상태의 위내 강산성 환경은 세균의 생존율을 저하시키므로, 프로바이오틱스는 식사 중 또는 식사 직후에 복용하는 것이 통과 생존율을 높이며, 특히 지방이 포함된 식단과 함께 섭취할 때 더욱 효과적이다[134]. 동물실험에서는 숙주-미생물 상호작용에 일주기(diurnal) 변동이 관찰되지만, 인간에서는 특정 시간대에 복용을 권고할 충분한 증거는 없다[135]. IBS, 감염성 설사, IBD 등에 관한 메타분석에서는 정확한 복용시간보다 매일 꾸준한 복용이 더 중요하다고 제시하고 있다[2,136]. 아침이나 저녁 등 복용 시간대와 상관없이, 복약순응도가 프로바이오틱스 효능의 강력한 예측인자로 작용한다. 항생제와 병용할 경우 직접적 비활성화를 방지하기 위해 2-3시간 간격을 두는 것이 권장된다.

프로바이오틱스 효능에 영향을 미치는 숙주 요인

프로바이오틱스 효과는 여러 주요 요인의 개인 간 변이성에 결정적인 영향을 받는다. 각 개인의 장내미생물은 기저 다양성과 정착 저항성이 프로바이오틱스의 성공적인 정착을 결정하는 일차적 요인이므로 핵심적인 역할을 한다[137]. 선천면역 수용체(예: Toll-like receptors 또는 nucleotide-binding oligomerization-containing domain 2)의 유전자 다형성은 숙주와 미생물 간 상호작용에 영향을 미쳐 점막 면역을 조절하는 프로바이오틱스의 효능을 변화시킬 수 있다[138]. 연령도 효능에 영향을 미치며, 영유아의 미성숙 면역계와 노인의 노화된 면역계는 정착 잠재력을 다르게 나타낸다[139,140]. 또한 식습관은 생존 및 지속성에 영향을 미치는데, 지방은 위 통과 시 프로바이오틱스 생존력을 높이고 섬유질은 프리바이오틱 기질로 작용한다[141]. 마지막으로, 환자의 면역상태나 양성자펌프억제제(proton pump inhibitor), 면역억제제 등의 현재 복용 중인 약물도 투여된 프로바이오틱스의 생존 및 기능적 반응을 변화시킬 수 있다[142,143].

프로바이오틱스 안전성

프로바이오틱스는 일반적으로 안전성이 우수하며, 가장 흔한 부작용은 경미한 위장관 증상(복부팽만, 가스)이다[144,145]. 그러나 안전성 데이터는 사용된 균주와 제형에 따라 크게 다르며, 대부분의 임상시험은 부작용 보고의 미비나 장기적 위험평가를 위한 추적관찰 부족 등 방법론적 한계를 지니고 있다[146]. 실제 임상 데이터(Food and Drug Administration Adverse Event Reporting System 2005–2023)에서는 심각한 부작용 발생률이 매우 낮게 보고된다[147]. 그러나 성별에 따른 차이, 불명확한 제품 표기, 그리고 보고된 부작용 사례 자체가 적다는 점 때문에 이러한 결과가 실제 생물학적 차이를 온전히 반영하지 못할 가능성이 있다. 따라서 결과 해석에 주의가 필요하며, 향후 연구에서는 성별 층화 분석, 충분한 표본 크기 및 장기적인 모니터링을 반드시 갖추어야 한다. 중환자실 환자, 중심정맥관 보유자, 심한 면역억제 환자 등 고위험군에서는 미생물 전이(translocation)로 인한 균혈증이나 진균혈증 등의 드문 위험성이 보고되고 있다[148-150]. PROPATRIA 연구에서 사망률 증가 원인은 프로바이오틱스 병원성보다는 특정 대사인자로 밝혀졌다[148]. 또한 제조 및 유통과정에서 오염 또는 라벨링 오류로 인해 의도하지 않은 병원성 미생물에 노출될 수 있다[144,146,151,152]. 따라서 프로바이오틱스 사용 시 안전성과 연관된 다양한 측면을 고려해야 하고, 임상에서는 프로바이오틱스 사용 후 부작용 신호를 인지하는 것이 필수적이다[144,146,151,152]. 다만, 위에서 언급한 위험들은 매우 드물며, 특정 조건 아래에서만 발생함을 강조할 필요가 있다[153].

기존 연구의 한계 및 향후 연구방향

균주 특이적이며 충분한 검정력을 갖춘 RCT의 필요성

프로바이오틱스가 마치 하나의 균질한 치료군인 것처럼 논의되기도 하지만, 축적된 증거들은 이들의 임상적 효과가 매우 균주 특이적(strain-specific)임을 명확히 보여준다. IBS와 FC에서 대부분의 RCT는 작용기전, 용량, 생존력 특성이 서로 다른 여러 균주를 이용해 만들어진 다양한 제형의 프로바이오틱스 제품을 평가해왔다. 이러한 이질성은 결과를 해석하거나 재현하기 매우 어려우며, 성별에 따른 효능 평가와 같은 정밀한 하위 그룹 분석을 어렵게 만든다. 또한 많은 연구가 임상적으로 의미 있는 효과를 감지하기에 통계적 검정력이 부족하며, 특히 성별로 층화할 경우 더욱 그렇다. 프로바이오틱스에 대한 반응이 질환의 표현형뿐 아니라 복용자의 성별에 따라 다를 수 있으므로, 향후 RCT는 균주 특이적 분석과 성별 기반 분석이 가능하도록 충분한 표본 크기를 확보하여 설계되어야 한다.

표준화되고 임상적으로 유의미한 평가지표의 필요성

현재까지 축적된 근거들이 가진 또 다른 주요 한계는 표준화된 임상 평가지표의 부재이다. IBS, FC, CDI에서 프로바이오틱스를

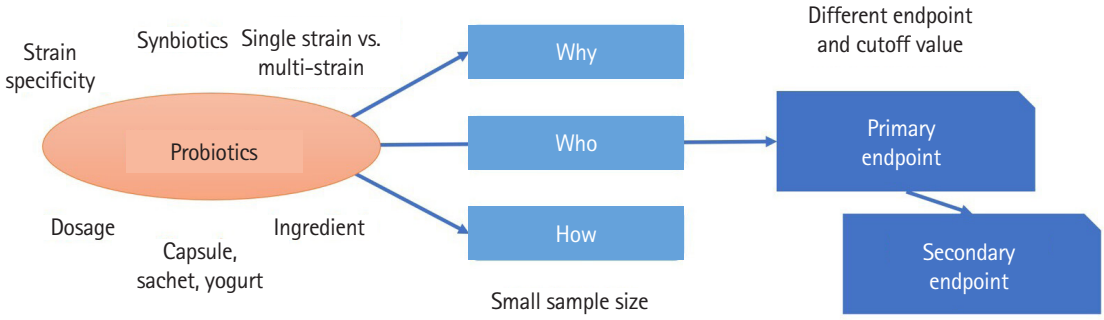

Fig. 4. Factors contributing to heterogeneity in probiotic clinical trials.

평가한 연구들은 전반적 증상 개선, 개별 증상 점수, 배변 빈도, 대변 굳기, 삶의 질, 다양한 복합 평가지표 등 매우 광범위한 결과지표를 사용했다. 이러한 지표의 다양성은 메타분석 시 결과의 불균질성을 높이는 원인이 되며, 연구 간 비교를 어렵게 만든다. 향후 연구에서는 서로 조율되고 검증된 결과지표를 도입해야 한다.

임상연구 내 남녀 참여 불균형 및 대표성 부족

IBS, FC, CDI의 유병률과 병태생리, 그리고 임상적 양상에서 성별 차이가 이미 잘 알려졌음에도 불구하고, 대부분의 프로바이오틱스 연구는 성별을 생물학적 변수로 고려하지 않고 설계되었다. 많은 연구가 정당한 근거 없이 남성이나 여성 중 어느 한쪽 성별에 치우친 집단을 대상으로 진행되었다. 또한 일부 임상시험에서는 성별 분석이 탐색적이거나 사후 분석에 그쳐 그 결과를 타당하게 해석하는 데 한계가 있다. 이러한 불균형은 통계적 검정력을 저하시킬 뿐 아니라 효능 및 안전성 측면에서 임상적으로 유의미한 차이를 가릴 위험이 있다. 개인 맞춤형 프로바이오틱스 치료로 나아가기 위해서는, 향후 임상시험에서 남녀 피험자를 균형 있게 모집하고, 성별 기반 하위 그룹 분석을 사전에 계획하며, 성별로 세분화된 결과를 투명하게 보고해야 한다.

성별 기반 가설의 기전적 검증 필요성

전임상 연구는 프로바이오틱스가 장 염증, 내장감각, 면역반응, 미생물 구성에 대해 남녀 간 현저히 다른 영향을 미칠 수 있다는 강력한 증거를 제시해왔다. 이는 성별에 따라 프로바이오틱스의 효능이 달라질 수 있다는 생물학적 타당성을 뒷받침한다. 그러나 인간 연구에서의 기전적 검증은 여전히 제한적이다. 대부분의 임상시험은 미생물의 기능적 프로파일, 면역지표, 상피 장벽 마커, 또는 호르몬과 장내미생물 무리의 상호작용과 같은 기전적 바이오마커를 통합하지 않은 채, 증상 기반의 결과에만 의존하고 있다. 향후 연구는 잘 설계된 임상시험에 이러한 기전적 평가지표를 포함함으로써, 기초연구와 임상시험 사이의 연구 간 간극을 메워야 한다.

결론

프로바이오틱스를 이용한 IBS, FC, CDI 치료에 있어 현재 이용 가능한 데이터들은 균주, 용량, 그리고 연구설계의 다양성으로 인해 여전히 일관성이 부족하다(Fig. 4). 그러나 일부 환자에서 배변 습관과 증상 정도가 개선되었고, 동물실험에서는 성별 차이가 있다는 명확한 증거가 제시되었다. 특히 IBS와 FC가 여성에게서 뚜렷하게 많이 나타난다는 점을 고려할 때, 성별과 관련된 생물학적 기전에 대한 심도 있는 고려가 필요하다. 성별에 따른 프로바이오틱스의 기전적 · 임상적 효과를 규명하기 위해 대대적인 체계적 노력이 요구되며, 이러한 노력은 결국 환자 개개인에게 최적화된 맞춤형 프로바이오틱스 전략을 수립하는 데 크게 기여할 것이다.

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Conceptualization: YSK, NK, MIP. Project administration: NK, MIP. Methodology: NK. Investigation (literature review): YSK, SYP, SJK, MWL, YC, BYK, CMS, YSnK (Young Sun Kim). Data curation: SYP, SJK. Visualization (tables): SYP, SJK. Supervision: NK, MIP. Funding acquisition: NK. Writing–original draft: YSK (lead), SYP, SJK, MWL, YC, BYK, CMS, YSnK, NK. Writing–review and editing: YSK, SYP, SJK, MWL, YC, BYK, CMS, YSnK, MC, NK, MIP.

Conflict of interest

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

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Data availability

Not applicable.

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Supplementary materials

Supplementary files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/4GYO5K.

Supplement 1. Major studies on the preventive effects of probiotics against CDI.

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Case Report

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Compound heterozygosity with methylenetetrahydrofolate reductase (*MTHFR*) C677T and A1298C mutations likely causing recurrent thrombotic events in a middle-aged man: a case report

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Methylenetetrahydrofolate reductase (*MTHFR*) gene mutations, particularly homozygous mutations, have been associated with a higher incidence of venous thrombosis, coronary heart disease, and obstetric complications. We report the case of a 41-year-old man who presented with multiple vascular thrombotic events over a period of 4–5 years, including deep vein thrombosis with pulmonary thromboembolism, cerebral venous thrombosis and posterior circulation stroke. The patient was found to have elevated serum homocysteine levels and subsequently underwent genetic testing for *MTHFR* mutations after other potential prothrombotic conditions were excluded. This case is notable because compound heterozygous mutations of the *MTHFR* gene (C677T and A1298C) were identified in association with recurrent vascular thrombotic events. Management focused on long-term anticoagulation and supplementation with vitamin B6, vitamin B12, and folic acid.

Keywords: Compound heterozygosity; Hyperhomocysteinemia; MTHFR gene; Thrombosis; Case reports

Introduction

Homocysteine is produced during the metabolism of methionine to cysteine. Vitamins B6, B12, and folate play essential roles in homocysteine metabolism through the transsulfuration and remethylation pathways. Transsulfuration requires vitamin B6 as a cofactor, whereas the remethylation of homocysteine—catalyzed by methionine synthase—requires vitamin B12 as a cofactor [1,2]. Methylenetetrahydrofolate reductase (*MTHFR*) is an enzyme that plays a critical role in folate metabolism and the regulation of homocysteine levels. Reduced *MTHFR* enzymatic activity, often secondary to gene mutations, may result in hyperhomocysteinemia and associated vascular thrombotic events [2,3]. This case report describes recurrent thrombosis in a patient likely attributable to compound heterozygosity of the *MTHFR* gene.

Case presentation

Ethics statement

Written informed consent for publication was obtained, and the patient's identifying details were anonymized in the manuscript.

Case report

A 41-year-old man with type 2 diabetes mellitus treated with oral hypoglycemic agents presented with right lower limb swelling associated with pain. He had quit smoking 6 months before symptom onset and abstained from alcohol. The patient had no history of recent surgery, trauma, fever, or immobilization. On examination, the right lower limb was edematous and tender, with no skin blisters. Venous Doppler ultrasonography of the right lower limb showed deep venous thrombosis (DVT) involving the right common iliac vein, extending into the right external iliac vein and the

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deep veins of the entire right lower limb, as well as the great saphenous vein. Computed tomography (CT) venography showed inferior vena cava thrombosis and thrombosis of the right common iliac vein extending to the popliteal, anterior peroneal, and posterior tibial veins, along with the great saphenous vein. The patient was admitted under the vascular

surgery service and started on subcutaneous low-molecular-weight heparin (LMWH) 60 mg twice daily. CT of the thorax showed thrombi in the segmental and subsegmental branches of both lower lobes. The patient subsequently underwent right lower limb catheter-directed thrombolysis with alteplase injection. His serum homocysteine level was elevated at 58.69 μmol/L, representing intermediate hyperhomocysteinemia. Because the patient had been taking an over-the-counter multivitamin supplement containing vitamin B12 and folate, serum vitamin B12 and folate levels were not measured at that time. However, his vitamin B12 level measured at an outside hospital before admission to our center was reportedly > 2,000 pg/mL. Bridging to oral anticoagulation was performed, and the international normalized ratio (INR) was monitored with dose adjustments made accordingly. The INR at discharge was 2.64. The patient remained on regular follow-up with the vascular surgery team, and oral anticoagulation with nicoumalone 2 mg once daily was discontinued 1 year after the first event.

Three years later, the patient was again admitted under the general medicine service for evaluation of severe headache. He reported a 3-day history of throbbing holocranial headache with a pain score of 8/10 on the visual analog scale. There were no associated symptoms of fever, nausea, vomiting, blurred vision, loss of consciousness, seizures, or limb weakness. He had no family history of unprovoked thrombosis. On examination, the blood pressure was 130/80 mm Hg, the patient's pulse rate was 82/min, and he was afebrile. There was no neck stiffness. His Glasgow coma scale score was 15/15, extraocular movements were full, visual acuity was 6/6, and no focal motor deficit or facial asymmetry was noted. Hemogram results showed polycythemia, with a hemoglobin level of 18.4 g/dL and a hematocrit of 52.8%, and the workup performed for cerebral venous thrombosis (CVT) is summarized in Table 1. Renal and liver function test results were within normal limits.

Arterial blood gas analysis performed on room air showed no hypoxemia, with a partial pressure of oxygen of 86 mm Hg. Brain magnetic resonance imaging (MRI) with venography revealed cerebral venous sinus thrombosis involving the superior sagittal sinus, right transverse sinus, and sigmoid sinus (Fig. 1).

The patient was started on subcutaneous enoxaparin 60 mg twice daily and antiepileptic therapy and was later switched to oral anticoagulation with nicoumalone after a 5-day bridging period with LMWH. Fundus examination showed bilateral papilledema. Given the presence of polycythemia, JAK2 V617F mutation analysis was performed and was negative, and the patient's erythropoietin level was normal at 7.99 mIU/mL

(reference range, 4.3–29 mIU/mL). Due to the recurrent vascular events, vasculitis and thrombophilia workups were performed and were negative for antinuclear antibodies, antiphospholipid antibody profile, and antineutrophil cytoplasmic antibodies (Table 1). The patient also had an elevated glycated hemoglobin (HbA1c) level of 11% and dyslipidemia. He was discharged on nicoumalone 2 mg and 3 mg on alternate days, atorvastatin 20 mg, and glipizide 5 mg twice daily. On follow-up, the nicoumalone dose was adjusted to maintain a target INR of 2–3.

Approximately 2 months after the second hospitalization, the patient again presented with giddiness, vomiting, and swaying while walking. MRI of the brain showed a right cerebellar infarct. In addition to oral anticoagulation, single-antiplatelet therapy with aspirin 75 mg and atorvastatin 20 mg was started. The patient reported adherence to oral anticoagulation and had no bleeding symptoms. Echocardiography showed no regional wall motion abnormalities, an ejection fraction of 62%, and normal pulmonary artery pressure. During this hospitalization, HbA1c had decreased from 11% to 9.9%, total cholesterol was 124 mg/dL, high-density lipoprotein cholesterol was 35 mg/dL, and low-density lipoprotein cholesterol was 65 mg/dL. Hemogram results showed a hemoglobin level of 14.3 g/dL and a packed cell volume of 41.6%, suggesting that the previously observed polycythemia was transient. Qualitative polymerase chain reaction (PCR) testing of the *MTHFR* gene detected heterozygous mutations at both C677T and A1298C. Although diabetes and dyslipidemia may have increased the risk of atherosclerosis and arterial ischemic events, the recurrent venous and arterial thrombotic events in this patient were considered likely attributable to compound heterozygosity (C677T/A1298C genotype) of *MTHFR*. The patient was switched to a newer oral anticoagulant, dabigatran 150 mg twice daily, and continued on single-antiplatelet and antiepileptic therapy. The switch to the newer oral anticoagulant was made to improve treatment adherence and avoid frequent INR monitoring. On follow-up, the patient reported blurred vision associated with postural variation, especially while walking, that resolved within 2–3 minutes of onset. Ophthalmologic evaluation revealed established papilledema secondary to cortical venous thrombosis. Optical coherence tomography showed thickening of the retinal nerve fiber layer with hemorrhages. The patient was advised to continue lifelong oral anticoagulation and to monitor for bleeding symptoms. He has improved symptomati-

Table 1. Laboratory investigation results

Investigations	Patient value	Reference value
Hemogram results		
Hemoglobin	18.1 g/dL	13–17 g/dL
Hematocrit	50.7%	40%–50%
White blood cell count	8,650 cells/mm^3	4,000–11,000 cells/mm^3
Platelet count	255,000/μL	150,000–450,000/μL
Renal profile		
Blood urea nitrogen	10 mg/dL	8–23 mg/dL
Serum creatinine	0.9 mg/dL	0.7–1.2 mg/dL
Liver function tests		
Aspartate aminotransferase	18 IU/L	< 32 IU/L
Alanine aminotransferase	17 IU/L	< 33 IU/L
Alkaline phosphatase	113 IU/L	25–104 IU/L
Total protein	7.1 g/dL	6.6–8.7 g/dL
Fasting lipid profile		
Total cholesterol	212 mg/dL	< 200 mg/dL
Triglycerides	361 mg/dL	< 150 mg/dL
Low-density lipoprotein cholesterol	126 mg/dL	< 100 mg/dL
Autoimmune workup		
ANA by immunofluorescence assay	Negative	
c-ANCA and p-ANCA	Negative	
Anticardiolipin antibodies (IgG and IgM)	Negative	
Anti-beta-2 glycoprotein antibodies (IgG and IgM)	Negative	-
Lupus anticoagulant	Not detected	
Viral markers		
HIV-1/2 with p24 antigen	Negative	-
HBsAg	Negative	
Anti-HCV	Negative	

ANA, antinuclear antibodies; c-ANCA, cytoplasmic antineutrophil cytoplasmic antibody; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; IgG, immunoglobulin G; IgM, immunoglobulin M; HIV, human immunodeficiency virus; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus.

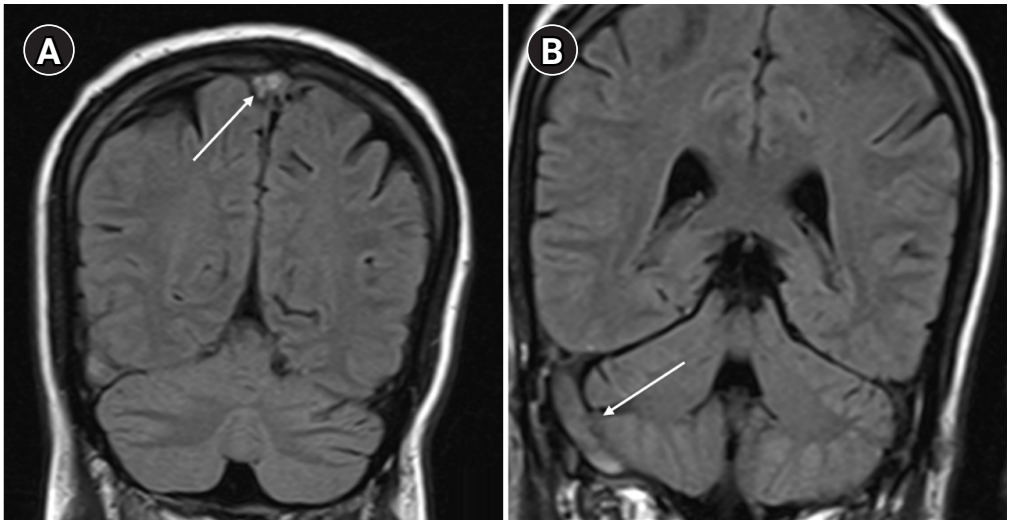

Fig. 1. (A) Coronal and sagittal magnetic resonance imaging (MRI) brain images showing thrombosis of the superior sagittal sinus (arrow). (B) MRI brain image showing thrombosis of the right transverse sinus and sigmoid sinus (arrow).

cally, with no active bleeding, and his last recorded INR was 2.21.

Discussion

Homocysteine in blood is predominantly protein-bound (80%), and normal levels range from 5 to 15 μmol/L. Hyperhomocysteinemia can be classified as moderate (15–30 μmol/L), intermediate (30–100 μmol/L), or severe (> 100 μmol/L) [1]. Markedly elevated blood homocysteine levels have atherogenic and prothrombotic properties. Most cases of hyperhomocysteinemia are attributable to vitamin B12 or folate deficiency. Other causes include genetic factors, chronic kidney disease, and smoking. Conditions associated with hyperhomocysteinemia include ischemic heart disease, cerebrovascular disease, venous thromboembolism, obstetric complications, osteoporosis, dementia, and cognitive impairment [1,3].

Reduced *MTHFR* enzymatic activity can result from polymorphisms in the *MTHFR* gene at either the C677T or A1298C locus. Individuals with homozygous mutations carry 2 copies of the same mutant allele, whereas heterozygous individuals carry 1 copy of either C677T or A1298C. Compound heterozygous (double heterozygous) carriers harbor 1 copy each of the C677T and A1298C alleles. In the general population, 60%–70% of individuals may carry 1 of these variants; among them, approximately 2.25% may have compound heterozygous mutations involving both C677T and A1298C, whereas 8.5% may have a homozygous mutation [4]. Homozygous mutation is more clearly associated with thrombotic events than *MTHFR* heterozygosity, for which the association remains a topic of debate. Heterozygous carriers may be at increased risk of recurrent thrombosis in the presence of coexisting risk factors, such as oral contraceptive use or pregnancy. Proposed mechanisms in heterozygous carriers include impaired vascular nitric oxide generation, which may promote oxidative stress and contribute to a prothrombotic milieu [4].

Naushad et al. [5] investigated *MTHFR* gene polymorphisms using PCR-based restriction fragment length polymorphism analysis in 163 patients with DVT in South India. They reported a 3.5-fold higher risk of DVT among patients with compound heterozygosity (C677T/A1298C genotype) [5]. This finding is consistent with the recurrent thrombotic events observed in our patient, who was of similar South Indian ethnicity. Ghaznavi et al. [6] studied *MTHFR* gene polymorphisms in 50 Iranian patients with CVT and 50 healthy controls and reported an odds ratio (OR) of 1.35 for patients with the heterozygous C677T genotype and a higher OR of 1.73 in the homozygous 677TT group. However, neither association was

statistically significant, and the study identified *MTHFR* gene polymorphism as a significant determinant of homocysteine levels. In a Spanish study of patients with rheumatoid arthritis, the association between *MTHFR* gene polymorphism and endothelial dysfunction was evaluated using brachial ultrasonography to assess flow-mediated vasodilatation, with values < 7% suggesting endothelial dysfunction. In that study, patients with the heterozygous *MTHFR* C677T genotype also demonstrated endothelial dysfunction, with a mean value of 5.9% [7]. Published data on heterozygous *MTHFR* mutations and the risk of vascular thrombosis are summarized in Table 2 [5,6,8,9].

The heterozygous A1298C mutation mildly reduces *MTHFR* enzymatic activity; however, in the presence of additional risk factors, such as pregnancy or the postpartum state, recurrent thrombosis may occur [8]. Compound heterozygosity (C677T/A1298C genotype) of the *MTHFR* gene may increase the risk of

Table 2. Published studies on heterozygous *MTHFR* gene mutations and vascular events

Study no.	Article title	Reported findings
1.	Hyperhomocysteinemia and the compound heterozygous state for methylene tetrahydrofolate reductase are independent risk factors for deep vein thrombosis among South Indians [5]	*MTHFR* genotyping was performed in 163 South Indian patients with DVT. The compound heterozygous C677T/A1298C genotype was identified as an independent risk factor associated with a 3.5-fold higher risk of thrombosis.
2.	Association study of methylenetetrahydrofolate reductase C677T mutation with cerebral venous thrombosis in an Iranian population [6]	In this study of 50 Iranian patients with CVT, higher plasma homocysteine levels were observed among patients with *MTHFR* polymorphisms, and the heterozygous C677T *MTHFR* genotype was associated with an OR of 1.35 for CVT. However, this association was not statistically significant (95% CI, 0.64–2.84; P = 0.56).
3.	Cerebral vein thrombosis associated with *MTHFR* A1298C mutation in a young postpartum woman [8]	A postpartum woman who developed CVT despite anticoagulation was found to have a heterozygous A1298C mutation without a C677T polymorphism.
4.	Compound heterozygosity for the C677T and A1298C mutations of the *MTHFR* gene in a case of hyperhomocysteinemia with recurrent deep thrombosis at young age [9]	A 21-year-old woman with recurrent DVT and cryptogenic cirrhosis was found on evaluation to have compound *MTHFR* heterozygosity (C677T and A1298C).

MTHFR, methylenetetrahydrofolate reductase; DVT, deep venous thrombosis; CVT, cerebral venous thrombosis; OR, odds ratio; CI, confidence interval.

recurrent thrombosis, particularly when additional risk factors are present. It should be noted, however, that compound heterozygosity alone, especially in the absence of other concomitant thrombophilic conditions, has not been conclusively associated with a high thrombotic risk.

In conclusion, this case report highlights a rare presentation of multiple unprovoked thrombotic events despite anticoagulation, likely attributable to compound heterozygosity of the *MTHFR* gene. However, a multifactorial contribution cannot be excluded in this patient, given the transient nature of the polycythemia, suboptimal glycemic control, and dyslipidemia, all of which may have contributed to large-vessel atherosclerosis. Testing for genetic thrombophilia, including *MTHFR* polymorphisms, may be worth considering in patients with unexplained recurrent unprovoked thrombotic events.

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Authors' contribution

Conceptualization: YSS, VP, DS. Data curation: YSS, VP. Investigation: VP, DS. Methodology: VP, DS. Writing–original draft: YSS, VP. Writing–review & editing: YSS, VP, DS.

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Atherosclerotic changes in an intrasellar persistent trigeminal artery in a patient presenting with dizziness: a case report from Korea

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We present a rare case of a 68-year-old woman who experienced dizziness, nausea, vomiting, and imbalance for 2 months. Imaging studies, including magnetic resonance imaging, magnetic resonance angiography, and digital subtraction angiography, revealed an intrasellar course of the persistent trigeminal artery (PTA) with atherosclerotic changes. Additionally, hypoplasia of the basilar artery and left vertebral artery was observed. The anatomically rare intrasellar PTA, combined with atherosclerosis and vertebrobasilar hypoplasia, likely contributed to compromised posterior circulation and the patient's symptoms. This case highlights the importance of considering vascular anomalies and the associated pathological changes in patients with otherwise unexplained posterior circulation symptoms.

Keywords: Intrasellar persistent trigeminal artery; Persistent trigeminal artery; Atherosclerosis; Vertebrobasilar insufficiency; Vertebrobasilar hypoplasia; Case reports

Introduction

Persistent trigeminal artery (PTA) is the most common carotid–vertebrobasilar anastomosis, with a reported incidence of 0.1%–0.6% [1-3]. It typically arises from the posterolateral aspect of the cavernous internal carotid artery (ICA), traverses Meckel's cave, and joins the basilar artery, providing a direct connection between the anterior and posterior circulations. Although PTA is usually asymptomatic, it may be associated with vascular anomalies such as hypoplasia, aneurysms, or atherosclerotic changes, which can alter hemodynamics and produce posterior circulation symptoms [4-7]. An intrasellar course of the PTA is a very rare anatomical variant that can pose diagnostic challenges and may have clinical significance when coexisting vascular pathology is present. This case report describes an unusual presentation of symptomatic intrasellar PTA with atherosclerotic narrowing associated with dizziness.

Case presentation

This retrospective study was approved by the institutional review board of Ewha Womans University Seoul Hospital, Korea (2025-06-090-001), and the requirement for informed consent was waived.

A 68-year-old woman with hypertension and dyslipidemia visited the outpatient clinic of our hospital, reporting dizziness, nausea, vomiting, and imbalance that had persisted for 2 months. The dizziness was non-rotatory and was intermittently accompanied by a subjective sense of gait instability.

Neurological examination was largely unremarkable except for mild gait instability. Contrast-enhanced brain magnetic resonance imaging revealed no definite acute infarction or space-occupying lesion. Magnetic resonance angiography and digital subtraction angiography (DSA) showed a right intrasellar PTA arising from the cavernous segment of the right ICA and passing through the sellar fossa to join a hypoplastic basilar artery (Fig. 1). DSA also

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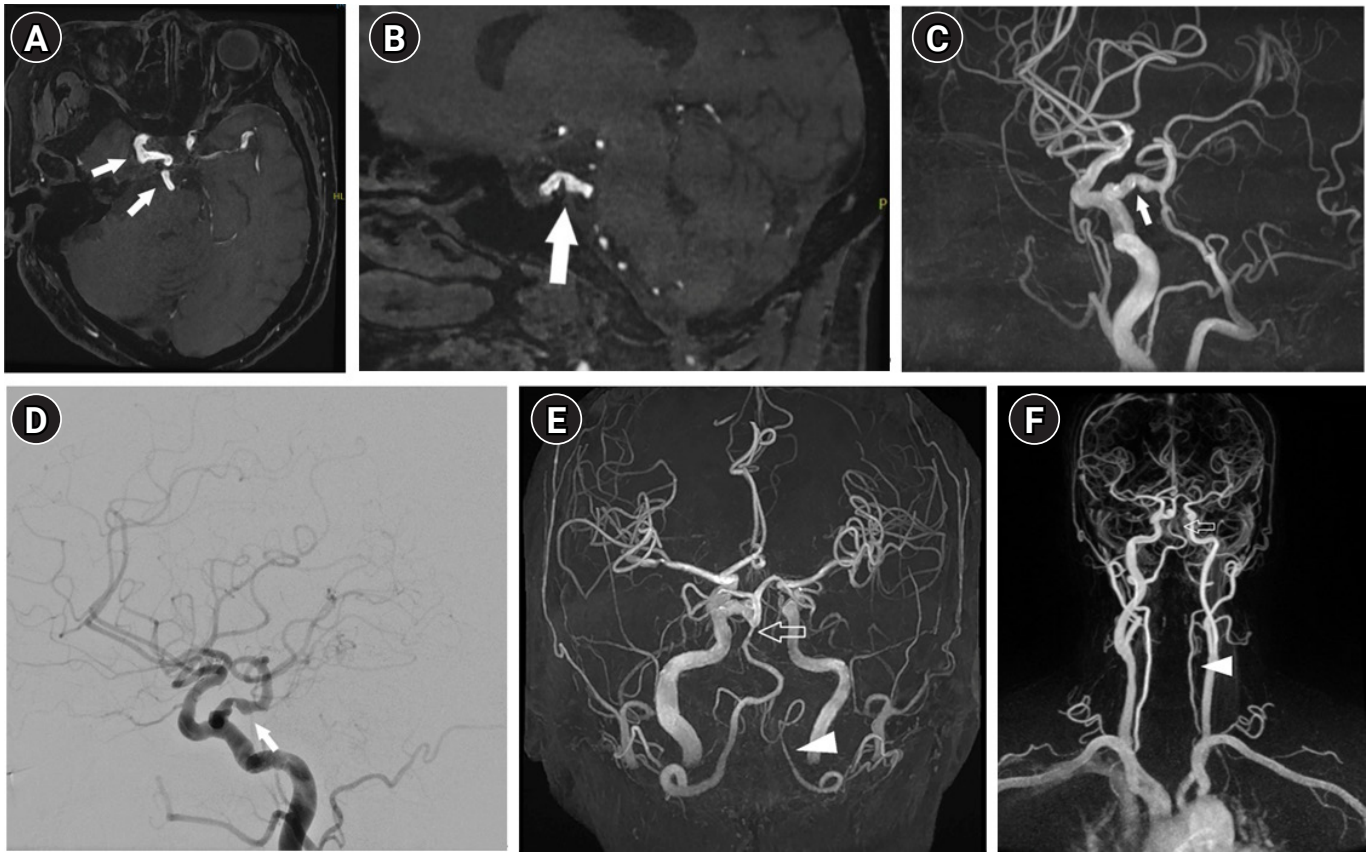

Fig. 1. (A, B) Axial and sagittal magnetic resonance angiography (MRA) time-of-flight (TOF) source images show the intrasellar persistent trigeminal artery (PTA) (arrow) arising from the right cavernous internal carotid artery (ICA) and passing through the sellar fossa. (C, D) Brain MRA maximum intensity projection (MIP) and digital subtraction angiography show arterial irregularity with luminal narrowing of the PTA. (E) Brain MRA MIP and (F) neck MRA show hypoplasia of the basilar artery (empty arrow) and vertebral artery (arrowhead), without severe steno-occlusion or dissection of the proximal ICA.

revealed luminal narrowing and irregularity of the right PTA, findings consistent with atherosclerosis (Fig. 1). Additionally, hypoplasia of the basilar artery and left vertebral artery was identified (Fig. 1). This case corresponds to Saltzman type I PTA, which typically connects the ICA to the basilar artery and compensates for vertebral artery hypoplasia. The anatomical and hemodynamic features of this rare PTA variant likely contributed to compromised posterior circulation and the patient's symptoms. Aside from ongoing medication for hypertension and dyslipidemia, no additional specific treatment was administered. Follow-up magnetic resonance imaging demonstrated no significant interval change.

This case highlights the potential clinical significance of an intrasellar PTA in posterior circulation insufficiency, particularly when accompanied by vascular anomalies and atherosclerotic changes.

Discussion

An intrasellar course of the PTA is a very rare anatomical variant, and symptomatic presentation with superimposed atherosclerosis is even rarer. Previous reports of vertebrobasilar insufficiency associated with PTA have predominantly implicated stenosis of the ICA as the underlying cause [8-10]. Some reports have described PTA involvement in the setting of ICA stenosis [8,10]. In contrast, our case demonstrated isolated atherosclerotic narrowing of the PTA without concurrent ICA stenosis. PTA is often considered an incidental finding; however, in this patient, it served as the dominant supply to the posterior circulation. Therefore, atherosclerotic compromise of the PTA appeared to have direct symptomatic consequences. To our knowledge, this is the first reported case of intrasellar PTA stenosis resulting in vertebrobasilar insufficiency in the absence of ICA stenosis.

To date, no established theory or direct evidence has clearly explained the mechanism by which an intrasellar PTA develops ath-

erosclerosis. However, its unique anatomical location and hemodynamic characteristics suggest several plausible contributing factors. The intrasellar course carries the artery through the sellar fossa, an anatomically constrained space that may subject the vessel to abnormal mechanical forces [11,12]. Mechanical compression within the narrow confines of the sellar fossa could disrupt normal flow patterns in the PTA. Such altered hemodynamics, characterized by low wall shear stress and increased turbulence, are well-recognized contributors to endothelial dysfunction and subsequent atherogenesis [13-16]. In addition, the PTA's acute angulation at its origin and termination may further increase localized stress on the vessel wall. Repeated pulsatile contact with surrounding bony structures could cause microvascular trauma and provoke chronic inflammatory responses, thereby accelerating atherosclerotic plaque formation. In our case, vertebrobasilar hypoplasia was also present. Saltzman type I PTA typically connects the ICA to the basilar artery to compensate for vertebral artery hypoplasia, as observed in this case. The coexisting left vertebral artery hypoplasia reduced posterior circulation reserve, rendering the PTA a critical conduit for posterior cerebral perfusion. Any stenosis or other flow-limiting pathology in this vessel could therefore lead to posterior circulation insufficiency, manifesting as dizziness or even transient ischemic symptoms. Nevertheless, these proposed mechanisms remain speculative because direct histopathological evidence or large-scale imaging studies confirming atherosclerosis specifically within an intrasellar PTA are lacking. Further research is needed to clarify the vascular pathology associated with this rare anatomical variant.

Saltzman first described the classification of PTA, dividing it into 3 types on the basis of angiographic features [17]. In Saltzman type I, the PTA joins the basilar artery between the origins of the superior cerebellar artery (SCA) and the anterior inferior cerebellar artery (AICA). In this variant, the proximal basilar artery and posterior communicating artery (PComA) are typically hypoplastic, and the PTA supplies both posterior cerebral arteries (PCAs) and SCAs. In Saltzman type II, the PTA connects with the basilar artery at a level superior to the origin of the SCAs, whereas the PComAs remain intact and supply the PCAs. Type III has traditionally been regarded as a combination of types I and II. Subsequently, Ali et al. [18] refined the Saltzman classification by incorporating additional PTA variants into type III, characterized by the absence of a basilar artery connection. In these variants, the PTA arises from the ICA and terminates directly as the SCA (type IIIa), AICA (type IIIb), or posterior inferior cerebellar artery (type IIIc), without interposition of the basilar artery. Our case corresponds to Saltzman type I PTA, which typically connects the ICA to the basilar artery and compensates for hypoplastic basilar and vertebral arteries. Several reports have described PTA associated with posterior circulation symptoms [4-6,9,19]. Ferreira et al. [19] documented a case of Saltzman type I PTA that resulted in an acute ischemic event because of decreased vascular supply to the posterior fossa. Other studies have reported posterior territory infarction due to embolism from ICA stenosis or dissection via the PTA [20,21]. Battista et al. [9] described extensive thrombosis of the cavernous ICA and PTA secondary to proximal ICA dissection, in which the PTA, normally serving as a collateral route, became the primary pathway for the posterior circulation. In these cases, ICA occlusion compromised this essential collateral channel, leading to ischemic events in both circulatory territories. However, these previously reported cases were largely attributable to secondary vascular conditions such as ICA stenosis or vertebral artery hypoplasia, in which the PTA functioned as a compensatory route [4,7,22]. Lee and Kelly [12] described an intrasellar PTA associated with a pituitary adenoma, but no evidence of atherosclerosis was identified. To date, no previous case has clearly documented atherosclerotic changes within an intrasellar PTA as the direct cause of symptoms. Our case is the first to describe symptomatic intrasellar PTA with angiographically confirmed atherosclerotic narrowing, providing novel insight into the potential for primary vascular pathology within this embryonic remnant to produce clinically significant posterior circulation insufficiency.

In summary, this case highlights a potential association between the intrasellar course of the PTA and the development of atherosclerotic changes, likely driven by altered hemodynamics. The anatomical constraints and resultant turbulent flow in this rare variant may predispose the vessel wall to early pathological changes. In patients presenting with posterior circulation symptoms such as dizziness, an intrasellar PTA should be considered in the differential diagnosis. Moreover, PTA-associated atherosclerosis in the setting of vertebrobasilar hypoplasia may further exacerbate hemodynamic compromise and contribute to symptomatic posterior circulation insufficiency. Comprehensive vascular imaging is therefore essential for accurate diagnosis and appropriate management planning.

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Conflict of interest

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Elastofibroma dorsi: a rare case report emphasizing the clinical presentation, radiological diagnosis, and surgical treatment

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Elastofibroma dorsi is a rare, benign soft tissue tumor that typically arises in the infrascapular region. Although it is often asymptomatic, some patients experience pain or a snapping sensation during shoulder movement, which warrants surgical excision. We report a symptomatic case in a middle-aged male patient, highlighting the diagnostic imaging features and surgical management of this condition.

Keywords: Elastofibroma dorsi; Infrascapular soft tissue tumor; Shoulder pain; Case reports

Introduction

Background

Elastofibroma dorsi is an uncommon, slow-growing benign soft tissue neoplasm that is predominantly located in the infrascapular region and is histologically characterized by the proliferation of collagenous and elastic fibers interspersed with adipose tissue. It primarily affects older adults and demonstrates a marked female predominance [1]. Although elastofibroma dorsi is frequently asymptomatic, some patients experience pain or discomfort, particularly during shoulder movement, which represents a characteristic clinical manifestation of the lesion [2].

The diagnosis of elastofibroma dorsi is primarily based on clinical findings and characteristic imaging features. Ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) are commonly used. Ultrasonography typically demonstrates a pattern of alternating hyperechoic and hypoechoic linear areas beneath the scapula. CT reveals a well-demarcated lesion containing areas of fat attenuation that are usually less dense than adjacent muscle. MRI provides superior diagnostic accuracy, demonstrating a heterogeneous soft tissue mass with interspersed fatty streaks. Biopsy is rarely required unless imaging findings are atypical or there is evidence of rapid lesion growth [3].

Although elastofibroma dorsi typically presents with characteristic clinical and imaging findings, its underlying pathogenesis remains incompletely understood. Several hypotheses have been proposed, with one widely accepted theory suggesting that repetitive mechanical stress between the scapula and the thoracic wall contributes to lesion development. In addition, a possible hereditary predisposition and abnormalities in elastic fiber formation have been proposed as contributing factors [4].

The management of elastofibroma dorsi is guided by the presence and severity of clinical symptoms. In asymptomatic cases, which are often detected incidentally, active treatment is not required, and periodic observation is sufficient. When the lesion causes discomfort or restricts shoulder movement, surgical excision is generally recommended. Complete excision typically results in symptom resolution, with a low risk of recurrence and minimal postoperative complications, such as seroma formation [5]. Given the benign nature of elastofibroma dorsi, marginal excision with minimal removal of surrounding healthy tissue is considered adequate and is associated with low recurrence and complication rates [6].

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Objectives

This case report describes a symptomatic case of elastofibroma dorsi in a middle-aged male patient, with emphasis on clinical presentation, radiological diagnosis, and surgical management.

Case presentation

Ethics statement

Written informed consent was obtained from the patient for publication of this case report and the accompanying images.

Patient information

A 51-year-old male patient presented with a 2-month history of right shoulder discomfort accompanied by a clicking sensation during arm abduction. The patient had no significant past medical history. He reported frequent occupational and recreational use of the right shoulder, which may have contributed to repetitive mechanical stress, a factor often implicated in the development of elastofibroma dorsi.

Clinical findings

Physical examination revealed a non-tender, mobile, firm mass in the right infrascapular region (Fig. 1). A distinct clicking sound was elicited during active shoulder movement.

Diagnostic assessment

Ultrasonography demonstrated a heterogeneous, hypoechoic lesion with poorly defined margins located beneath the latissimus dorsi muscle, without evidence of internal vascularity. MRI revealed a well-circumscribed soft tissue mass measuring 7×2×7 cm, located between the inferior border of the scapula and the chest wall, deep to the latissimus dorsi muscle. The lesion exhibited a characteristic combination of fibrous and fatty components, producing a layered or striated appearance on both T1- and T2-weighted images, without evidence of invasion into adjacent structures. Based on the clinical presentation and characteristic radiological features, elastofibroma dorsi was considered the most likely diagnosis. Given the symptomatic nature of the lesion, surgical excision was recommended.

Therapeutic intervention

The patient subsequently underwent surgical excision under general anesthesia. A posterior approach was used, and the patient was placed in the prone position to optimize access to the infrascapular region. Careful dissection was performed through the fibers of the latissimus dorsi muscle to expose the lesion (Fig. 2). During dissection, elevating the arm to approximately 90°–120° with slight anterior angulation helped shift the scapula laterally and loosen the underlying tissue. This maneuver brought the lesion into a more superficial plane, thereby improving visibility and facilitating surgical access. As a result, exposure was enhanced,

Fig. 1. Mobile soft tissue mass in the right infrascapular region. The lesion becomes more prominent with shoulder abduction. Written informed consent for the publication of this image was obtained from the patient.

Fig. 2. Intraoperative image after dissection of the latissimus dorsi muscle, exposing the elastofibroma dorsi lesion. Written informed consent for the publication of this image was obtained from the patient.

the need for extensive deep dissection was reduced, and lesion handling became easier and safer. Although the tumor lacked a distinct capsule, it was well demarcated from the surrounding tissues and was removed en bloc (Fig. 3). Intraoperatively, the lesion had a firm, rubbery consistency, consistent with previous descriptions of elastofibroma dorsi. Hemostasis was achieved meticulously, and the surgical site was closed in layers. A suction drain was placed to minimize postoperative seroma or hematoma formation, which are common complications related to the lesion's deep location and size.

Histopathological findings

Histopathological examination of the excised lesion revealed dense collagenous stroma interspersed with abnormal elastic fibers and mature adipose tissue, consistent with elastofibroma dorsi. No cellular atypia or features suggestive of malignancy were identified. These findings confirmed the presumptive diagnosis based on the clinical and radiological assessment (Fig. 4).

Follow-up and outcomes

The postoperative course was uneventful, and the patient was discharged on postoperative day 3. At the 2-week follow-up visit, the incision had healed satisfactorily (Fig. 5), and the patient reported marked symptomatic improvement, including resolution of the clicking sensation and improvement in shoulder range of motion.

Discussion

Elastofibroma dorsi is an uncommon benign soft tissue tumor that predominantly affects older adults, and several studies have reported a higher prevalence in females than in males [5-7]. Although most cases are unilateral, bilateral involvement has also been described, albeit less frequently. However, because comprehensive meta-analyses directly comparing these patterns are lack-

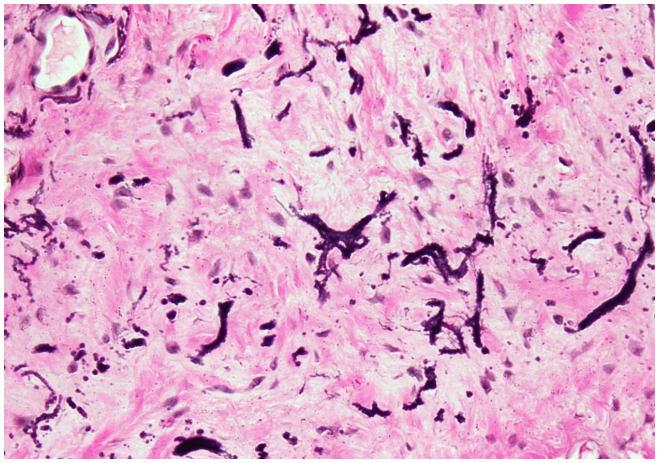

Fig. 4. Histopathological section of the excised lesion demonstrating dense collagenous stroma with interspersed, coarse, wavy elastic fibers. The general tissue architecture is shown with hematoxylin and eosin (H&E) stain, while elastic fibers are highlighted using Verhoeff–Van Gieson (VVG) stain, consistent with elastofibroma dorsi (original magnification ×10).

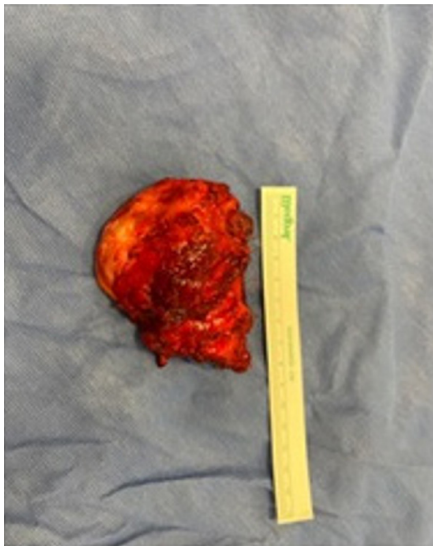

Fig. 3. Macroscopic view of the resected elastofibroma dorsi. The lesion appears as a well-defined, firm, gray-white mass with characteristic fibrous and elastic tissue components.

Fig. 5. Postoperative wound at 2 weeks, demonstrating satisfactory healing with no signs of infection, dehiscence, or hypertrophic scarring. Written informed consent for the publication of this image was obtained from the patient.

ing, definitive conclusions regarding their relative prevalence remain limited [8,9]. Elastofibroma dorsi is often asymptomatic and is discovered incidentally, but it may become clinically apparent when symptoms such as scapular snapping, localized swelling, or discomfort during shoulder movement develop. Although the pathogenesis of elastofibroma dorsi remains incompletely understood, repetitive mechanical friction between the scapula and thoracic wall has been widely proposed as a factor that contributes to lesion development via degenerative changes in the connective tissues [10]. Histologically, the tumor is composed of dense collagenous stroma interspersed with abnormal elastic fibers and variable amounts of mature adipose tissue. This histological architecture closely corresponds to its characteristic radiological appearance and helps distinguish it from malignant soft tissue neoplasms [11]. Radiological evaluation plays a central role in the diagnosis of elastofibroma dorsi. Ultrasonography often demonstrates a poorly defined, heterogeneous, hypoechoic lesion with minimal or absent internal vascularity. However, because ultrasonography is operator-dependent and may be less accurate in differentiating deep infrascapular soft tissue tumors, MRI is generally preferred for precise characterization. MRI remains the imaging modality of choice and typically reveals a well-circumscribed mass with alternating fibrous and fatty layers. This appearance produces the characteristic striped or speckled pattern on T1- and T2-weighted images, which supports the diagnosis. Although MRI findings are highly suggestive, they are not entirely pathognomonic. Lesions such as desmoid-type fibromatosis, fibroma, or low-grade soft tissue sarcoma may show partially overlapping imaging features. Furthermore, as in our case, the lesion's location beneath the latissimus dorsi and adjacent to the inferior scapular margin supports the diagnosis and may reduce the need for invasive diagnostic procedures.

In our patient, right shoulder discomfort and a characteristic clicking sound prompted further imaging evaluation. Ultrasonography demonstrated a heterogeneous hypoechoic lesion; however, because of the lesion's depth and the operator-dependent nature of ultrasonography, MRI was performed for more precise assessment.

Although elastofibroma dorsi is benign and slow growing, surgical resection is often indicated in symptomatic patients, particularly when pain, mechanical irritation, or shoulder dysfunction interferes with daily activities. Surgery may also be considered when imaging findings are inconclusive or when there is concern for malignancy. Complete surgical excision is typically curative, and reported recurrence rates are low. The literature supports operative treatment in appropriately selected patients and indicates excellent postoperative outcomes. Postoperative recovery is generally uneventful. Nevertheless, because of the lesion's deep anatomical location and relatively large size, complications such as seroma or hematoma formation may occur. These complications are usually minor and can be effectively managed with meticulous intraoperative hemostasis and placement of suction drains to reduce fluid accumulation.

Although elastofibroma dorsi is generally more prevalent in females, our case involved a male patient. Consistent with previous reports, the patient presented with pain and a characteristic clicking sensation. Following surgical treatment, his symptoms resolved completely. This outcome further supports the effectiveness of surgery in symptomatic patients.

This case illustrates the clinical, radiological, and surgical management of elastofibroma dorsi in a symptomatic male patient. It also highlights practical considerations in operative planning and provides useful insights for clinicians managing similar lesions.

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Conflict of interest

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Case Report

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Nociceptive pain as a clinical presentation of chronic urticaria and disappearance with immunoglobulin/histamine complex therapy: a case report

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Itching is a representative manifestation of urticaria. However, under certain conditions, urticaria may be characterized by nociceptive sensations, such as stinging or tingling, either instead of or in addition to itching. Three patients with chronic urticaria (CU) who experienced nociceptive pain accompanied by itching were identified and treated with immunoglobulin/histamine complex (IHC) therapy. Nociceptive pain resolved along with improvement in CU symptoms after 8 injections of IHC in the first patient and after 4 injections in the second and third patients. Nociceptive pain may present as a symptom of CU. The clinical characteristics of the transition from itching to nociceptive pain, together with the observed outcomes of IHC therapy, appear to support the intensity theory explaining this shift, which may be mediated by histamine. Further clinical and basic immunological studies are warranted to clarify the underlying mechanisms.

Keywords: Chronic urticaria; Histamine; Immunoglobulin; Nociceptive pain; Case reports

Introduction

Itching is a characteristic and typical manifestation of urticaria, including chronic urticaria (CU) [1]. However, under certain conditions, urticaria may present with nociceptive pain, such as stinging or tingling, either instead of or in addition to itching [2].

Histamine plays a central role in the pathogenesis of CU [3]. In addition, histamine is a known mediator of pain sensation [4]. Both itching and nociceptive signals are typically transmitted through C-fibers [5].

Histobulin (Green Cross PD) is an immunoglobulin/histamine complex (IHC) preparation comprising 0.15 μg of histamine dihydrochloride and 12 mg of immunoglobulin G [6]. It was developed to regulate serum histamine levels through histaminopexy [7]. IHC is effective in the treatment of allergic rhinitis, bronchial asthma, CU, and atopic dermatitis [8].

IHC therapy has been reported to be effective for the treatment of CU [9,10]. Its therapeutic effects are progressive and gradual, in contrast to those of other treatments, including omalizumab and antihistamines, which typically produce more rapid symptom relief [11,12]. Recent studies have suggested that IHC may induce remission and have proposed IHC therapy as a potentially effective therapeutic modality for CU [8].

The primary mechanism of action of IHC is histaminopexy, which involves regulation of circulating histamine levels through inhibition of histamine release from mast cells and induction of antibodies against histamine [13-15].

Given current understanding of the pathophysiology of histamine-mediated nociceptive signaling [4,5], the clinical presentations of CU—itching and nociceptive pain—may represent closely related manifestations rather than entirely distinct symptoms.

This report describes 3 patients with CU who presented with

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nociceptive pain. The clinical characteristics of itching and nociceptive pain in these patients, as well as their changes during IHC therapy, are detailed.

Case presentation

Ethics statement

Informed consent was obtained from all patients.

Case 1

The first patient was a 39-year-old Korean woman who presented to the Department of Allergy and Clinical Immunology at Cheju Halla General Hospital with urticaria and itching accompanied by a tingling sensation described as nociceptive pain for 1 month (Fig. 1). She reported recurrent episodes of nociceptive pain associated with itching. There was no personal or family history of CU.

Because the patient's symptoms persisted for more than 6 weeks during evaluation, a diagnosis of CU was established according to accepted diagnostic criteria [1]. Following this diagnosis, laboratory evaluations were performed, including a complete blood count with differential and measurements of serum eosinophil cationic protein, total serum immunoglobulin E (IgE), and allergen-specific IgE using a multiple allergosorbent test (MAST; Green Cross PD). Serum immunoglobulin A levels were also measured prior to initiation of IHC therapy (Table 1). In the MAST, specific IgE levels for 41 allergens were assessed, and values < 0.35 IU/mL were considered negative. A skin prick test was also performed for 53 allergens. Histamine hydrochloride (10 mg/mL) served as the positive control, and normal saline served as the negative control. Wheal diameters were measured, and re-

Fig. 1. Urticaria in a patient with chronic urticaria (case 1).

Table 1. Results of basic allergy laboratory tests

	Case 1	Case 2	Case 3
Laboratory tests (normal range, unit)			
Blood eosinophil fraction (0%–5%)	1.7	0.2	3
Blood basophil fraction (0.0%–1.0%)	0.9	0.1	0.5
Serum eosinophil cationic protein (0–24 ng/mL)	48.9	16	104
Serum total IgE (≤ 350 IU/mL)	52	179	726
Serum IgA (70–400 mg/dL)	271	232	240
MAST allergens (IU/mL)			
Alternaria alternata	< 0.35	< 0.35	< 0.35
Aspergillus fumigatus	< 0.35	< 0.35	< 0.35
Penicillium notatum	< 0.35	< 0.35	< 0.35
Cladosporium herbarum	< 0.35	< 0.35	< 0.35
Cockroach	< 0.35	< 0.35	< 0.35
House dust mites	< 0.35	< 0.35	< 0.35
Dermatophagoides pteronyssinus	< 0.35	1.54	19.79
D. farinae	< 0.35	0.65	5.37
Dog	< 0.35	< 0.35	< 0.35
Cat	< 0.35	< 0.35	< 0.35
Birch-Alder mix	< 0.35	< 0.35	9.05
Mugwort	< 0.35	< 0.35	0.97
Short Ragweed	< 0.35	< 0.35	0.98
Sallow willow	< 0.35	< 0.35	< 0.35
Orchard grass	< 0.35	< 0.35	46.56
Bermuda grass	< 0.35	< 0.35	0.47
Timothy grass	< 0.35	< 0.35	97.76
Sweet vernal grass	< 0.35	< 0.35	19.71
Rye pollen	< 0.35	< 0.35	29.37
White oak	< 0.35	< 0.35	< 0.35
Japanese cedar	< 0.35	< 0.35	0.38
Reed	< 0.35	< 0.35	< 0.35
Japanese hop	< 0.35	< 0.35	< 0.35
Acacia	< 0.35	< 0.35	< 0.35
Pine	< 0.35	< 0.35	< 0.35
Poplar mix	< 0.35	< 0.35	< 0.35
Sycamore	< 0.35	< 0.35	< 0.35
Ash mix	< 0.35	< 0.35	0.35
Oxeye daisy	< 0.35	< 0.35	< 0.35
Dandelion	< 0.35	< 0.35	< 0.35
Russian thistle	< 0.35	< 0.35	< 0.35
Goldenrod	< 0.35	< 0.35	0.95
Pigweed	< 0.35	< 0.35	0.38
Crab	< 0.35	< 0.35	< 0.35
Shrimp	< 0.35	< 0.35	< 0.35
Mackerel	< 0.35	< 0.35	< 0.35
Soybean	< 0.35	< 0.35	< 0.35
Hazelnut	< 0.35	< 0.35	0.98
Peach	< 0.35	< 0.35	< 0.35
Milk	< 0.35	< 0.35	< 0.35

(Continued on the next page)

Table 1. Continued

	Case 1	Case 2	Case 3
Egg white	< 0.35	< 0.35	< 0.35
Skin prick test (grade) allergens			
Alternaria alternata	-	-	-
Aspergillus fumigatus	-	-	-
Aspergillus niger	-	-	-
Candida albicans	-	-	-
Cladosporium	-	-	2
Penicillium chrysogenum	-	-	-
German cockroach	-	2	-
D. pteronyssinus	-	3	3
D. farinae	-	3	3
Dog	-	-	-
Cat	-	-	-
Grey alder, silver birch	-	-	2
Grass mix	-	-	4
Mugwort	-	-	4
Short ragweed	-	-	-
Black willow pollen	-	-	-
Orchard	-	-	4
Bermuda grass	-	-	-
Timothy	-	-	-
English plantain	-	-	-
English ryegrass	-	-	4
Holm oak	-	-	-
Japanese cedar	-	-	2
Latex	-	-	-
Milk	-	-	-
Egg	-	-	-
Chicken	-	-	-
Beef	-	-	-
Pork	-	-	-
Cod	-	-	-
Oyster	-	-	-
Salmon	-	-	-
Prawn	-	-	-
Mackerel	-	-	-
Tuna	-	-	-
Almond	-	-	-
Peanut	-	-	-
Bean	-	-	-
Carrot	-	-	-
Cabbage	-	-	-
Walnut	-	-	-
Maize	-	-	-
Peach	-	-	-
Tomato	-	-	-
Black pepper	-	-	-
Spinach	-	-	-
Wheat	-	-	-
Rabbit	-	-	-
Kapok	-	-	-
Hop	-	-	-
F acacia	-	-	-
Pine	-	-	-
Poplar	-	-	-

(Continued on the next column)

Table 1. Continued

IgE, immunoglobulin E; IgA, immunoglobulin A; MAST, multiple allergosorbent test.

actions were read after 15 minutes. Responses were graded as follows: negative (0, no reaction); 1+ (reaction greater than the control but less than half the size of the histamine reaction); 2+ (equal to or more than half the size of the histamine reaction); 3+ (equal to or more than the size of the histamine reaction); or 4+ (equal to or more than twice the size of the histamine reaction). A wheal size of ≥ 3 mm was considered positive. The patient was instructed to discontinue antihistamines for at least 5 days before testing.

All allergy laboratory tests yielded results within normal ranges, including the eosinophil fraction on complete blood count, serum eosinophil cationic protein, and total serum IgE levels (Table 1). No allergen-specific IgE levels were elevated on MAST, and no positive reactions were observed on skin prick testing.

The clinical severity of CU was assessed using the Urticaria Severity Scale described by Jariwala et al. [16], which has a maximum possible score of 93 points. Pain severity was evaluated using a numerical rating scale with a maximum score of 10 [2].

Histobulin (Green Cross) was used as the IHC preparation. Each 2-mL ampule contains 12 mg of human immunoglobulin and 0.15 μg of histamine [6]. IHC was administered by weekly subcutaneous injection into the deltoid region of the upper arm until remission was achieved. During therapy, the patient was instructed to take levocetirizine 5 mg once daily as needed if symptoms interfered with activities of daily living, work, or sleep. Nociceptive pain resolved as CU symptoms improved following 8 IHC injections (Fig. 2A).

During symptomatic episodes, itching developed first and was followed shortly thereafter by nociceptive pain (Fig. 3). In all 3 patients, administration of levocetirizine led to resolution of nociceptive pain; itching subsequently reappeared briefly before gradually subsiding during each episode.

Case 2

The second patient was a 42-year-old Korean woman who presented to the Department of Allergy and Clinical Immunology at

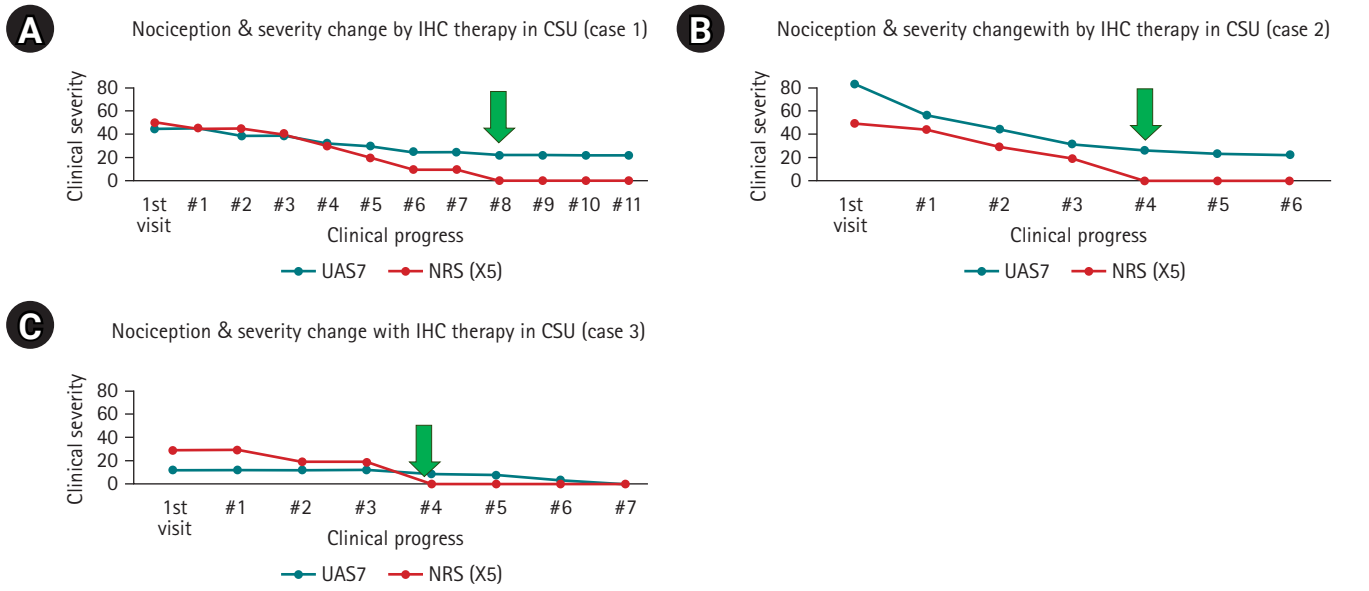

Fig. 2. Changes in nociceptive pain and clinical severity during immunoglobulin/histamine complex (IHC) therapy. (A) Case 1. (B) Case 2. (C) Case 3. Nociceptive pain resolved with decreasing clinical severity of chronic urticaria during IHC therapy. The green arrows in (A), (B), and (C) indicate the points at which nociceptive pain resolved. CSU, chronic spontaneous urticaria; UAS7, urticaria activity score for 7 days; NRS, numeric rating scale.

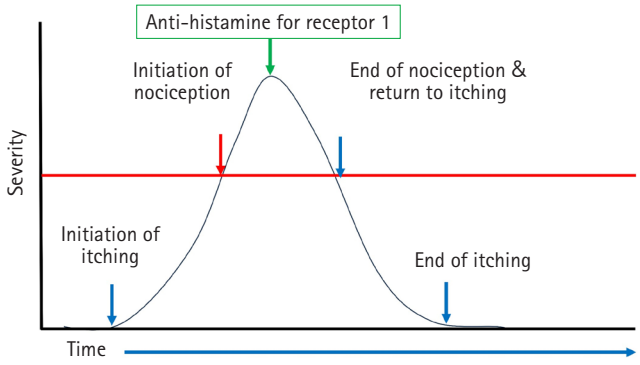

Fig. 3. Schematic of changes during an episode of itching and nociceptive pain symptoms in a representative case (case 1). Severity on the y-axis is shown schematically based on patient descriptions. Nociceptive pain and itching resolved after administration of an antihistamine (histamine receptor 1 blocker).

Cheju Halla General Hospital with urticaria, combined itching and stinging described as a nociceptive sensation, and frequent angioedema of the lips for 4 months. She had no personal history of CU; however, her brother had previously experienced urticaria and itching. She underwent the same basic allergy evaluation as described in case 1, including MAST and skin prick testing.

No abnormal laboratory findings were identified except for elevated allergen-specific IgE levels to *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, and cockroach on MAST and positive skin reactivity on skin prick testing (Table 1). IHC therapy was initiated, and nociceptive pain resolved as CU symptoms improved after 4 IHC injections (Fig. 2B).

Case 3

The third patient was a 57-year-old Japanese woman who presented to the Department of Allergy and Clinical Immunology at Cheju Halla General Hospital with urticaria and combined itching and a tingling sensation described as a nociceptive symptom. Her history included several prior episodes of urticaria. She also reported a family history of urticaria in both parents, and her grandmother had atopic dermatitis. Basic allergy testing with MAST and skin prick tests was performed as described in case 1.

Laboratory testing showed allergen-specific IgE to multiple allergens, including *D. pteronyssinus*, *D. farinae*, and pollens, on MAST, along with positive skin reactivity on skin prick testing (Table 1). IHC therapy was administered, and CU symptoms improved. After 4 IHC injections, the patient's nociceptive pain resolved as her CU presentation improved (Fig. 2C).

Discussion

As shown in this report, some patients with CU may experience nociceptive pain in addition to itching. In all 3 patients, nociceptive pain resolved as CU symptoms improved following IHC therapy (Fig. 2).

The primary mechanism of action of IHC is thought to involve

histaminopexy, including histamine-fixing effects that promote the production of antihistamine antibodies [13]. Nociceptive pain has been reported as a symptom of cholinergic urticaria [2]. Histamine plays a central role in the pathogenesis of CU [3] and is also a known mediator of pain sensation [4]. Accordingly, some patients with CU may experience nociceptive symptoms, including pain, either instead of or in addition to itching. In these cases, the resolution of nociceptive pain following IHC therapy suggests that histamine may contribute to nociceptive pain in CU (Fig. 2). Levocetirizine also improved both itching and nociceptive pain (Fig. 3), suggesting involvement of histamine receptor 1. Histamine receptor 1 activation increases intracellular Ca2+, which activates protein kinase C–dependent phosphorylation and promotes formation of calmodulin complexes; these processes suppress potassium voltage-gated type 7 (Kv7) channels, leading to depolarization and increased nociceptive pain [17]. In animal models, venom-induced hyperalgesia in rats was reduced by histamine receptor 1 and 2 antagonists [18,19]. Collectively, these observations suggest that nociceptive symptoms, as well as itching, should be considered in CU.

Itching and nociceptive signals are typically transmitted through C-fibers [5]. Several theories have been proposed to explain the relationship between itching and nociceptive pain; one is the intensity theory, which posits that the transition from itch to pain occurs because of increased nociceptor discharge frequency [4,20]. In the 3 cases described here, itching consistently preceded nociceptive pain. After nociceptive pain resolved, itching was alleviated but then returned (Fig. 3) before ultimately resolving. These clinical observations appear consistent with the intensity theory. In addition, the disappearance of nociceptive pain alongside decreasing CU severity during IHC therapy also seems to support this explanation (Fig. 2).

In a previous report, CU symptoms were schematically classified according to disease severity [8]. After IHC therapy, symptoms reportedly resolved in parallel with decreasing clinical severity, beginning with angioedema, followed by urticaria, and ultimately itching as severity continued to decline. This pattern of resolution may be related to the intensity of allergic effects. Systemic manifestations, including angioedema, respiratory difficulty, and nociceptive pain, may represent the most severe symptoms, followed by urticaria and then itching as the least severe symptom.

In these patients, nociceptive pain was the first symptom to resolve as CU improved. More broadly, symptom severity may be related to the emergence of nociceptive pain during episodes and as the disease progresses. Thus, these findings suggest that nociceptive pain may reflect a more severe manifestation of CU than urticaria and itching.

To our knowledge, formal reports emphasizing the transition and coexistence of itching and pain in CU have been limited. In addition, the clinical transition between itching and nociceptive pain has not been described in detail. Although this report includes only 3 cases, it describes clinical characteristics of itching and nociceptive pain during symptomatic episodes and the resolution of nociceptive pain as CU severity decreased during IHC therapy. The clinical changes observed during IHC therapy also appear to support the intensity theory regarding the transition from itching to nociceptive pain. Histamine may mediate the resolution of nociceptive pain, based on the effects of histamine receptor 1 blockade and IHC therapy, which has histaminopexy effects.

The primary limitation of this analysis is that, as a descriptive case series involving only 3 patients, the findings cannot be conclusive. In addition, the absence of a control group represents a clear methodological limitation.

In conclusion, nociceptive pain occurred in association with typical urticaria manifestations in 3 patients with CU. Based on the clinical findings reported in this case series, nociceptive pain may represent a more severe manifestation than urticaria and itching. The observed clinical characteristics and response to IHC therapy appear to support the intensity theory regarding the transition from itching to nociceptive pain, which may be mediated by histamine. Pain may represent a type of histamine-mediated syndrome. Further clinical and basic immunological studies are needed.

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Images and solution

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The Ewha Medical Journal

Skull base granulomatosis with polyangiitis presenting with multiple cranial neuropathies

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A 30-year-old woman presented with a progressive, stabbing left-sided hemicranial headache, dysphagia, bilateral hearing loss, and facial paralysis. Her recent medical history was notable for left-sided otomastoiditis, for which she had undergone tympanomastoidectomy and facial nerve decompression. Neurological examination revealed left-sided lower motor neuron facial paralysis, anisocoria, and mild dysarthria. Electroneuromyography demonstrated bilateral facial nerve axonal injury, along with severe axonal injury of the left accessory nerve.

Brain magnetic resonance imaging (MRI) demonstrated homogeneous, enhancing soft-tissue thickening at the skull base, extending into the nasopharynx and involving the courses of cranial nerves IX–XII, with more prominent involvement on the right side (Fig. 1). Additional MRI findings included enhancing soft tissue within the tympanic cavities, involving the tympanic segments of the facial nerves bilaterally. These findings provide an anatomical explanation for the facial paralysis, even in the absence of intracanalicular nerve enhancement. Although the skull base lesion was more pronounced on the right, bilateral involvement of the tympanic segments accounts for the clinical presentation. Serologic testing, including cytoplasmic antineutrophil cytoplasmic antibody (ANCA), perinuclear ANCA, anti-proteinase 3, and anti-myeloperoxidase antibodies, was negative. Histopathology reportedly demonstrated granulomatous inflammation with multinucleated giant cells. As histologic slides were not available for review in this teleradiology case, the diagnosis of granulomatosis with polyangiitis (GPA) was established based on clinicoradiologic correlation and a compatible biopsy report. Treatment with corticosteroids and rituximab was initiated. According to follow-up information from the treating team, the patient demonstrated marked clinical improvement, particularly in headache, dysphagia, and facial nerve function.

GPA is a necrotizing vasculitis that only rarely involves the central nervous system; however, cranial neuropathies related to skull base or otologic involvement may occur in fewer than 10% of patients [1]. ANCA-negative disease is more commonly observed in cases with localized head and neck involvement and may present a diagnostic challenge. In such cases, diagnosis typically relies on tissue biopsy in conjunction with clinical and radiologic correlation, rather than serologic findings alone. Otologic manifestations are relatively common, but the association with peripheral facial paralysis remains uncommon, reported in only 8%–10% of cases [2,3]. The relatively young age of this patient further underscores the diagnostic complexity.

The differential diagnosis of inflammatory skull base lesions includes skull base osteomyelitis, tuberculosis, sarcoidosis, immunoglobulin G4 (IgG4)-related disease, inflammatory pseudotumor, and lymphoma. Skull base osteomyelitis was initially considered given the history of otomastoiditis; however, the presence of extensive infiltrative soft tissue, skull base foraminal involvement, and multiple cranial neuropathies was more suggestive of an inflammatory granulomatous process. Tuberculosis and sarcoidosis

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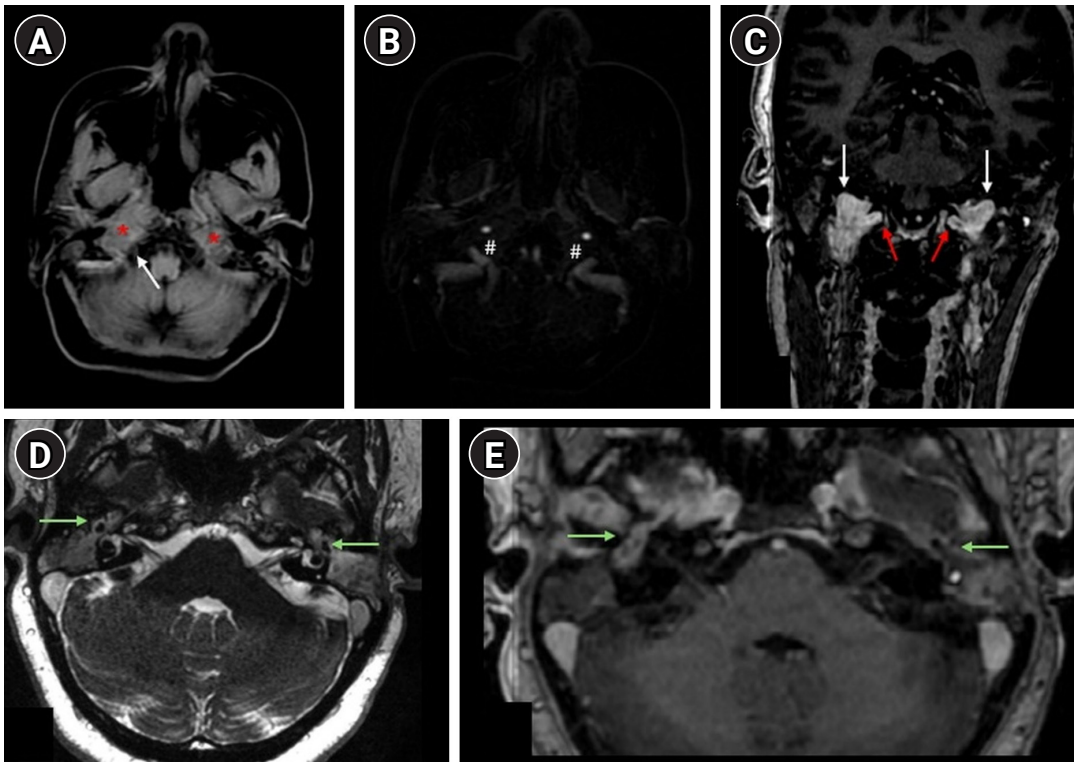

Fig. 1. Magnetic resonance imaging. (A) Axial post-contrast T1-weighted images with fat suppression; (B) axial magnetic resonance venography; (C) coronal post-contrast T1-weighted images; (D) axial FIESTA sequence; (E) axial post-contrast T1-weighted image. Amorphous enhancing soft-tissue formations are observed following intravenous contrast administration, centered in the superior portion of the carotid spaces and the prevertebral component of the paravertebral spaces (*), with extension into the jugular foramina (white arrow) and hypoglossal canals (red arrows). A mass effect with obliteration of the jugular bulbs (#) is also noted. Heterogeneously enhancing tissue is present within the tympanic cavities and adjacent mastoid air cells, infiltrating the tympanic segments of the facial nerves (green arrows). Panel (E) highlights enhancing soft tissue within the tympanic cavity involving the tympanic segment of the facial nerve.

were not supported by the biopsy findings. IgG4-related disease and inflammatory pseudotumor were considered less likely based on the pattern of cranial nerve involvement and the clinical course. Lymphoma was also included in the differential diagnosis but was not supported by histopathologic findings. Ultimately, the diagnosis was established based on clinicoradiologic correlation and compatible biopsy findings. A limitation of this report is the unavailability of histopathologic slides for review, as this was a teleradiology case; however, the diagnosis was supported by the pathology report, clinical presentation, imaging findings, exclusion of alternative diagnoses, and response to treatment.

This case highlights the importance of considering GPA in the differential diagnosis of skull base lesions that may mimic neoplastic or infectious processes. Early diagnosis and prompt initiation of immunosuppressive therapy are essential to prevent irreversible neurological sequelae [4].

Informed consent was obtained from the patient for publication of this case and the accompanying images.

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Letter to the editor

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Bridging theory and practice in generative artificial intelligence for medical education: insights from clinical teaching experience

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The narrative review by Kang and Ahn [1] on integrating generative artificial intelligence (GenAI) into medical education provides a timely framework for educators navigating this rapidly evolving field. As a practicing obstetrician–gynecologist who has taught artificial intelligence (AI) applications to medical professionals over the past 2 years, I wish to share practical observations that complement their theoretical analysis.

Kang and Ahn [1] correctly note that most medical schools lack formal GenAI policies and structured training programs. In my experience conducting AI education workshops for practicing physicians, this gap extends beyond institutional policy to fundamental questions regarding how clinicians should interact with these tools. Although the review emphasizes AI literacy—including prompt engineering and critical appraisal skills—the practical challenge lies in teaching these competencies to clinicians who are already managing demanding patient care responsibilities. In my experience, short, case-based training sessions focused on immediate clinical applications have proven more effective than comprehensive theoretical courses.

Although the review discusses GenAI applications broadly, domain-specific considerations warrant further attention. Previous work on AI in obstetrics has demonstrated that several machine learning methods can be used for the early diagnosis of maternal–fetal conditions, including preterm birth and abnormal fetal growth [2]. These findings illustrate that AI tools are both task- and domain-dependent; accordingly, GenAI tools should undergo specialty- and task-specific validation before adoption for educational use.

Kang and Ahn [1] appropriately highlight the risk of hallucinations in AI-generated content, a concern that is particularly relevant for medical education, where inaccurate information could affect patient care. Studies have reported substantial hallucination rates in systematic review contexts [3], underscoring the need for rigorous verification protocols. In my teaching practice, I emphasize the principle of "verify before trust" and require learners to cross-reference AI outputs with established medical references. This approach aligns with the DEFT (diagnosis, evidence, feedback, and teaching)-AI framework described in the review, which promotes critical evaluation of AI-generated content.

Algorithmic bias represents another key concern raised by the authors, and emerging evidence supports this caution. Recent research has demonstrated sociodemographic biases in large language models during medical decision-making scenarios [4]. For medical educators, this finding has important implications: AI-generated case scenarios, assessment materials, and learning content may inadvertently perpetuate healthcare disparities. Integrating bias awareness into AI education curricula should therefore be prioritized, as recommended in current frameworks for responsible AI integration [5,6].

One practical avenue that is not extensively discussed in the review is the development of custom GPT applications for specific educational purposes. Guidelines for creating custom GPTs in health professions education provide a framework for developing tailored AI tools that address specific learning objectives while maintaining appropriate guardrails [7]. In my work, I have developed custom GPTs for obstetric ultrasound education and pregnancy counseling, enabling more controlled and contextually appropriate AI interactions than those provided by general-purpose models.

Kang and Ahn [1] propose reimagining assessment in the AI

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era, emphasizing higher-order cognitive skills and AI-resilient assessment formats. ChatGPT has demonstrated passing-level performance on licensing examinations [8], which has implications for medical education that extend beyond examination security. The fundamental question is whether current assessment paradigms adequately capture competencies that will remain distinctly human in an AI-augmented healthcare environment. Comprehensive reviews of AI in medical education suggest that innovations in the domain of assessment should focus on clinical reasoning processes, ethical judgment, and interpersonal communication skills that AI cannot reliably replicate [9].

The review advocates for structured AI literacy programs integrated into medical curricula. Scoping reviews of curriculum frameworks for AI education provide useful models for such integration [10]. However, the rapid pace of AI advancement presents a unique challenge: curricula developed today may become outdated before they are fully implemented. A modular, continuously updated approach to AI education may therefore be more sustainable than static curriculum reform.

In conclusion, Kang and Ahn [1] provide a strong foundation for understanding GenAI integration in medical education. From a practitioner-educator perspective, particular emphasis should be placed on domain-specific validation, practical skill-focused training, and flexible curriculum structures capable of adapting to rapid technological change. As the review concludes, AI should function as a collaborator rather than a replacement, helping cultivate physicians with strong clinical judgment, ethical reasoning, and empathy. Achieving this goal will require ongoing dialogue among AI researchers, medical educators, and practicing clinicians to ensure that theoretical frameworks translate into effective educational practice.

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