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Aims and Scope

Keimyung Medical Journal (KMJ) is the official publication of Keimyung University School of Medicine, a journal published in Korean or English with an abstract of English. The abbreviation Keimyung Med J.
KMJ publishes articles in all medical fields, including clinical research, basic medicine and nursing, with the goal of contributing to the treatment of diseases and promoting human health by sharing the latest information on medical and medical development.
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전국 의과대학 의료인문학 교육의 가치, 현황 및 교육 방향 고찰

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A Study on the Value, Current Status, and Education Direction of Medical Humanities Education in Korea

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The purpose of this study is to verify the pedagogical necessity of the medical humanities and to analyze the educational contents of medical humanities in medical schools of Korea. Medical humanities education should reflect the students' real life situations and attitudes because the educational goal of medical school students is to live as happy persons and good doctors. Understanding the medical humanities education that can achieve this goal will enable students to overcome various difficulties they will face in the future, and these contents should be included in graduation outcomes. The curriculum of medical humanities in Keimyung University School of Medicine was also analyzed, and based on this, we suggest the direction of education to be pursued. According to the analyzed data, medical humanities should be avoided from knowledge-oriented memorization education, and the curriculum should be supplemented by finding ways to integrate with basic and clinical medicine subjects. In addition, education that can increase resilience and form the identity of a doctor who can love and care for oneself is required even in difficult situations. Many attention and research will be needed in the future to achieve the original purpose of medical humanities education to understand others and society and to recognize the value of empathy and consideration.

Keywords: Humanism education, Medical education, Medical humanities, Professionalism

Introduction

우리나라 의과대학에 의료인문학이 도입된 지 약 20년이 지났다. 그러나 여전히 통합교육 과정 내에서 의료인문학의 정의, 개념, 범위, 교육주체, 수업방법 및 평가 등에 대해 정립하지 못하고 있다. 이러한 이유 중 하나로 의료인문학이 서구와 다르게 우리나라에 도입된 배경이 다른 것을 손꼽기도 한다. 서구에서는 현대 의학을 과학의 영역으로만 지나치게 접근시킴으로써 비인간화에서 시작된 비판적 반성에서 의료인문학이 태동했다면, 우리나라는 의사 파업이라는 초유의 사태 속에서 의료인문학이 긴급하게 소환되었다[1]. 즉, 한국의 의료인문학은 사회·정치적 요구와 얽혀서 시작

된 외형적 조건과 휴머니즘이라는 인문학 본연의 목적을 의료에 녹여내는 내재적 조건을 빠른 시간 안에 함께 충족시켜야 하는 과제를 안고 있다.

환자를 지지하는 관점에서 이 두 가지를 묶으면 의사의 사회적 책무성의 인지와 의료인문학은 깊게 연결된다. 사회적 책무성은 전문가로서 지녀야 할 책임행위 완결의 일종으로, 사회적 의무(social obligation)를 인식하는 사회적 책임감(social responsibility)과 사회적 요구에 대응하고 참여하는 사회적 대응성(social responsiveness)을 기반으로 한다[2]. 이러한 사회적 책무성의 관점에서 의과대학의 교육목적은 보건의료에서 핵심적인 역할을 하며 건강증진 및 건강평등이라는 사회적인 의료문제를 해결하고 사회적 요구를 충족하는 역량 있는 의사를 양성하는 것이다[3]. 이렇게 본다면 의료인문학의 주된 맥락은 생명윤리에 토대를 두고 있다고 볼 수 있겠다. 생명윤리는 크게 연구윤리와 임상윤리로 나누어지며, 연구윤리는 의학적 지식 생산의 정당성을 주제로 하는 것이고, 임상윤리는 환자-의사 관계 또는 죽음윤리 등 의료 활동과 관련된 것이다[4]. 이를 기반으로 1990년대 중반부터 세계적으로는 현재 및 예측 가능한 변화에 따른 미래의 건강, 의료자원 위기에 대응하는 사회적 요구를 탐색하게 되면서 의과대학의 사회적 책무에 대해 제안되기 시작하였고, 국내에서는 2019년부터 한국의학교육학회를 필두로 국내 의학교육계가 의료인의 책무에 대해 본격적으로 관심을 가지게 되었으나 현재는 개념 정립 단계에 있다[5]. 따라서 의학교육의 새로운 진보를 논하는 이 시점에서 의료인문학의 기본은 어떻게 구축되어야 하는지에 대한 고찰이 필요하다.

이에 의료인문학의 교육 필요성과 가치에 대한 재 고찰을 통해서, 국내 의과대학의 의료인문학 현황을 분석한 선행연구[6]를 바탕으로 계명대학교 의과대학의 의료인문학 교육 방향성도 모색하였다.

The need and value of medical humanities

교육은 지식 전달과 함께 '좋은 가치를 지향'하기 위해 '사유·실천하는 삶의 방식'을 스스로 구축할 수 있게 해주어야 한다. 매순간 합리적인 선택과 판단을 할 수 있는 능력을 길러 주는 것은 교육의 중요한 목적 중 하나이다. 이런 이성적 자율성을 삶에 잘 활용할 수 있는 역량은 건강한 사고 및 생활습관의 형성으로 드러나게 되는데, 결국 좋은 습관을 형성하는 것은 이성적 자율성을 달성하기 위한 주요 조건이라고 할 수 있겠다[7]. 스피노자는 '행복이란 올바른 삶을 살아서 얻어지는 보상이 아니라, 올바른 삶 그 자체가 축복'이라고 했다. 즉, 올바른 삶을 행복하게 여기는 것은 '욕망을 억제함'으로써 가능해지는 것이 아니라 '올바른 삶' 그 자체를 자율적으로 즐길 줄 알고 즐거워할 줄 알기 때문이다[8]. 환자지지와 국민건강증진을 토대로 하는 사회적 책무성 역시 의무의 일종으로만 인식된다면, 이것은 자율성에 입각해 의사 개인의 행복한 삶을 구축하는 교육 본래의 내재적 목적과는 결을 달리 할 수도 있다[7]. 의료인문교육은 사회적인 책임과 의사 개인의 행복을 함께 실현할 수 있는 행위 방식을 동시에 길러 줄 수 있어야 한다. 즉, 외적동기와 내적동기가 학생들의 성장에 함께 작용하도록 해야 하는데, 자신의 삶에 대한 자족과 의사로서의 충만한 삶의 의미를 드러내는 하나의 중요한 방식이 사회적 책무성 실천으로 이어지도록 해야 하기 때문이다.

그런데 이러한 교육 본질적 특성을 잘 담고 있어야 할 의료인문학 교육에서 이러한 면이 잘 작동하고 있지 못하다는 것을 다음과 같은 연구 결과들을 통해 성찰할 수 있다. 먼저, 2021학년도 계명대학교 의과대학의 학생생활실태조사에 따르면, 의과대학 만족도는 보통 이상이 86%이고, 의과대학 적성 만족도는 보통 이상이 91%였다[9]. 이에 더해 2019년 한국고용정보원 조사에 따르면, 만족도가 높은 직업 상위 10개에 의사 및 의료관련 직종들이 7개를 차지하고 있고, 2020년 현직 의사 1,000명을 대상으로 한 직업만족도 조사에서는 보통 이상으로 만족을 하는 경우가 83%였다[10,11]. 그러나 2019년 현직 의사 850명을 대상으로 실시한 다른 연구에서는 의사들의 직업 만족도에 대한 또 다른 면을 보여주었다. 조사자의 26%가 의사를 선택한 것에 대해 후회한다고 응답하였고, 자신의 아이를 의과대학에 보내고 싶지 않다고 20.6%가 응답하였으며, 특히 7.3%는 절대 보내지 않겠다고 답했다[12]. 일반적으로 다른 직업에 비해 의사의 직업 만족도가 높지만, 의학교육은 20% 이상에서 보이는 불만족과 후회하는 비율에도 관심을 가져야 할 필요성이 있다. 그 이유가 적성의 문제인지 적응의 문제인지를 정확히 파악하고, 적응의 문제라면 의료인문학 교육을 통해서 자신을 이해하고, 상호관계와 의료 환경 속에서 자신을 돌보는 방법을 배울 수 있도록 교육 설계가 되어야 할 것이다.

또한 2017년 현직 의사 8,564명을 대상으로 연령별 직업에 대한 불만족 비율을 조사한 설문 결과에 따르면, 30대에서 60대로 갈수록 15%에서 22%로 불만족 비율이 점차 증가 추세를 보였다. 60대 이상의 의사들이 예상하는 현직에서 은퇴하는 나이는 70세 초과 80대 이하로 가장 많이 대답하였다[13]. 이를 종합해볼 때, 의사의 나이가 많아질수록 직업에 대한 불만족의 비율이 더 증가하며, 향후 평균수명의 증가와 함께 의사로서 살아가는 시간도 더 길어짐에 따라 이런 불만족스러운 상황에 더 많이 노출될 것이 분명해 보인다. 이러한 불가피한 상황을 효율적으로 다룰 수 있고 주동적으로 대처하는 심적 기반을 확충하기 위해서 의료인문학 교육이 더욱 필요하다는 것을 시사하고 있다.

일상에서 지속되는 번아웃(burnout)은 일상에서 불만족을 표출하는 태도로 굳어지기도 한다. 실제로 2019년 미국의 10,000명의 의사를 대상으로 번아웃과 우울(depression)을 주제로 조사를 진행하였는데, 이를 살펴보면 교육의 방향성을 더 명확하게 인식할 수 있다[14]. 이 조사에서는 번아웃을 휴식 후에도 피곤이 계속되고 짜증이 나고 잦은 불만을 표출하는 심리상태로 정의하고 설문한 결

과, 42%의 의사가 번아웃을 경험하였다고 응답하였고, 15%는 우울감이 있다고 하였는데 특히 그중 3% 실제로 임상적 우울증 진단을 받았다고 하였다. 또한, 20대부터 번아웃 빈도는 지속적으로 증가해 45~54세에 약 50%로 가장 높은 수치를 기록했는데, 이런 결과를 대입해 보면 아직 한국에서의 연구는 없었지만 한국 의사에게서도 비슷한 경향일 것을 유추할 수 있었다[12,13]. 번아웃 유발 요인은 진료 이외의 사무적인 일이 가장 높았고, 이어서 과도한 업무시간과 동료관계였다. 우울감이 환자에게 끼치는 영향은 40%가 영향이 없다고 하였지만, 쉽게 화를 내게 되거나(33%), 환자의 말에 잘 경청하지 않게 되거나(32%), 불친절하게 된다(29%)고 응답했다. 여기서 더욱 중요하게 보아야 할 것은 차트 기록을 소홀히 하거나(24%), 평소에 안하던 실수를 저지르거나(14%), 환자의 건강에 피해가 될 수도 있는 실수를 한다(5%)고 응답한 것이다. 이런 영향을 끼치게 되는 우울감을 유발하는 이유는 업무적인 부분이 가장 컸고, 다음으로 경제적인 문제와 가족관계가 뒤를 이었다. 번아웃을 해소하는 방법에 대해서는 50%가 운동이라고 대답하였지만, 33%가 건강에 좋지 않은 음식섭취, 22%가 음주를 통해서 해결한다고 했다. 이처럼 자신이나 타인에 대한 이해 등을 통해 자신을 잘 관리하며 좋은 의사로서 살아가는 습관과 삶의 방식에 대한 교육이 의사 개인의 행복뿐만 아니라 사회 전체 의료시스템 발전을 위해서 반드시 필요하다.

2021학년도 계명대학교 의과대학의 학생생활실태조사에 따르면, 의예과 1학년에서 의학과 2학년까지 지각된 우울과 지각된 스트레스의 지수가 지속적으로 증가하였고, 2017년부터 5년 간의 평균에서도 지각된 우울이 59.2%, 지각된 스트레스가 70%에서 나타났다. 스트레스나 우울감을 느끼는 이유는 학업 및 성적(54%), 인간관계(29%), 경제적 문제(5.4%), 진로문제(4%), 가정문제(2%) 등으로 다양했지만, 이러한 스트레스나 우울감을 어떻게 다루어야 하는지 그 방법에 대해서는 잘 모르고 있었다. 앞선 조사[14]에서 미국의사들이 건강에 좋지 않은 음식을 먹거나(33%), 음주를 하거나(22%), 폭식을 하거나(20%), 흡연(3%) 등을 통해서 번아웃을 해소한다고 한 것과 같이 계명대학교 의과대학 학생들의 생활실태 조사[9]에서도 음주를 하는 학생들 중 73.4%는 술을 마시는 것으로 스트레스나 우울감이 해소된다고 대답하였고, 흡연을 하는 학생들 중 89.5%는 담배를 피는 것으로 스트레스나 우울감을 없앨 수 있다고 인식하고 있었다.

이러한 다양한 조사결과를 통해 의료인문학의 교육 필요성 및 교육 가치를 정리해보면, 의료인문학교육과정에서는 먼저, 환자지지 등 의사로서 갖추어야 할 태도 교육을 넘어서, 자신의 일상과 삶을 건강하게 구축할 수 있게 하는 사유 및 생활방식의 교육이 필요하다. 다음으로, 인성교육 및 사회적 책무성에 대한 교육도 규범적 행동양식의 지식 전달보다 자신의 몸과 마음을 이해하고 더불어 살아가는 이유를 자각하는 데 중점을 둠으로써 내적 동기 부여와 주체성을 함양하는데 초점이 맞추어져 있어야 학생들이 실제적 교육가치를 임상 현장에서 자율적으로 실현할 수 있게 된다. 마지막으로, 급변하는 교육환경에서 의료인문 교육은 프로페셔널리즘 역량을 갖출 수 있게 심적 토대를 구축해 주어야 한다. 이를 통해 의학교육에서 최종적으로 추구하고자 하는 목표인 의료전문가의 특징은 진료, 인성, 자기개발, 환자지지, 의사소통, 문제해결과 연구 모든 영역에서 탁월한 프로페셔널리즘 역량을 갖고 있는 것이다.

The curriculum of medical humanities and educational direction

2021학년도에 선행연구[6]로 국내 40개 의과대학에 개설된 총 802개의 의료인문학 교과목을 분석하였는데(Table 1, Fig. 1), 의예과 1학년에서 238개, 의예과 2학년에서 153개, 의학과 1학년에서 121개, 의학과 2학년에서 117개, 의학과 3학년에서 90개, 의학과 4학년에서 83개로 학년이 올라갈수록 교과목 수는 점차 감소하는 경향이 있었다.

그리고 각 교과목을 계명대학교 의과대학의 6가지 졸업성과(진료, 문제해결과 연구, 의사소통, 환자지지, 자기개발, 프로페셔널리

Table 1. Classification of medical humanities subjects by item according to graduation achievements and humanism education in Korea

Item	Education subjects
Clinical diagnosis	Artificial intelligence, Convergence treatment, Bioethics, Clinical ethics, Science/Reasoning/Critical thinking, Value judgment
Problem solving	Medical research, Research ethics, Research thesis, Statistics, Numeracy, Imagination, Creativity, Problem-solving ability
Communication	Communication basics, Communication skills, Discussion
Patient support	Behavioral science, Behavioral psychology, Medical interview, Respect for life, Hospice, Death studies, History of medicine, Patient support, Patient-Doctor-Society, Medical philosophy, Complementary and alternative medicine, Patient safety, Industrial environmental medicine
Self-development	Mentor, Coaching, Motivation, Career exploration, Self-development, Language, Religion, Teacher-student relationship
Professionalism	Social responsibility, Leadership, Professional ethics, Health policy, Preventive medicine, Medical laws, History of medicine, Hospital management, Hospital employment and Start-up, Politics, Economy, Society, Administration, Human rights, Professionalism
Humanism education	Humanities, Art, Physical education, Culture, Self-understanding, Anthropology, Humanism education, Reading, Camp, Classic reading, Writing, Volunteer work, Social practice, Experience activities

Data was quoted by modifying the results of Kim et al [6].

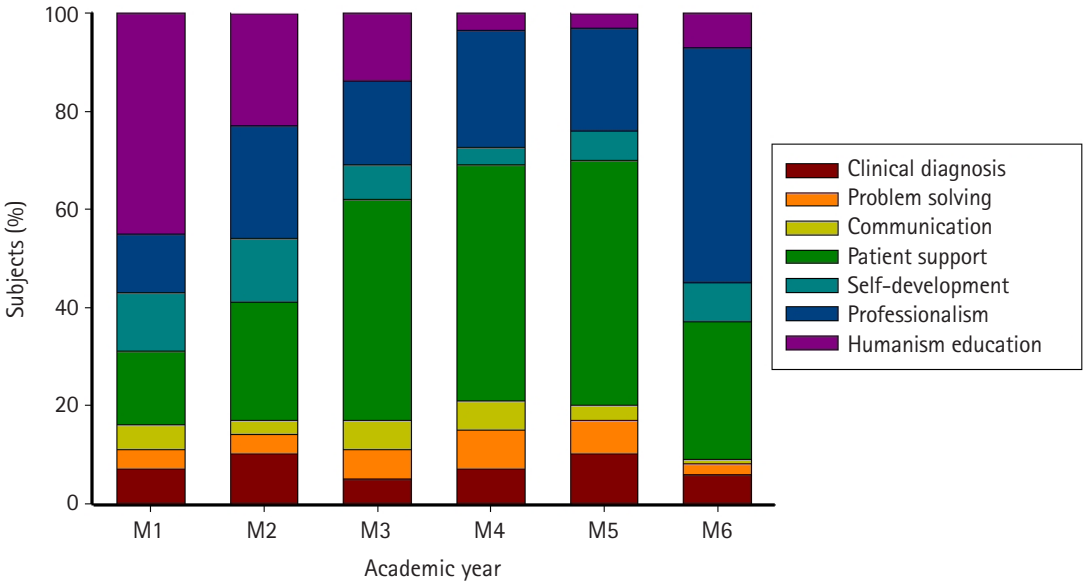

Fig. 1. Analysis of composition of medical humanities education by school grade in Korea. M1 to M6 represents the academic year of medical school. This data was quoted by modifying the results of Kim et al. [6].

즘)와 인성교육, 즉 7가지 갈래로 분류해 보았다(Table 1). 먼저, 환자지지에 관한 교육이 전 학년 평균 35%로 가장 높았고, 의학과 1~3학년의 3개 학년의 평균은 48%에 달했다(Fig. 1). 프로페셔널리즘 교육은 6개 학년 평균 24%로 의예과 2학년(23%), 의학과 2학년(24%), 의학과 4학년(48%)에서 많이 교육하고 있었다. 인성교육은 6개 학년 평균 16%로 의예과 1학년(45%), 2학년(24%)에 집중되어 있었고, 자기개발은 6개 학년 평균 8%로 주로 의예과 1학년(12%), 2학년(13%)에서 주로 교육되고 있었다. 진료는 6개 학년 평균 7%로 학년별로 거의 고른 분포를 보였고, 의예과 2학년(10%)과 의학과 3학년(10%)때 교육 비율이 가장 높았다. 문제해결과 연구는 6개 학년 평균 5%로 의예과 1학년(6%), 2학년(8%), 3학년(7%)에서 고르게 높은 비율을 보였다. 마지막으로 의사소통은 6개 학년 평균 4%로 의학과 1학년(6%)과 의학과 2학년(6%)의 수치가 약간 높았다. 의사소통은 환자지지 영역의 의료면담 과목과 교육내용이 중복되기는 하나, 의학적인 요소를 제외하고 커뮤니케이션의 기초 및 기본적인 의사소통 방법이나 토론 수업의 교과과정을 포함시켰다.

한편, 2021년 계명대학교 의과대학 재학생을 대상으로 한 포커스 그룹 인터뷰에서 학년별 인성덕목 요소의 중요성을 조사하였다. 그 결과, 의예과1~2학년에서는 자제력과 성실, 의학과1~2학년에서는 배려와 소통, 의학과3~4학년에서는 책임감이 중요하다고 나타났다[6]. 이는 국내 의과대학에서 시행하고 있는 의료인문 교육과정의 맥락과 비슷하며, 자신과 타인에 대한 순차적이고 충만한 이해는 궁극적으로 의료 전문가로서의 사회적 요구나 행위규범을 개인의 일상에 잘 이식시키는 것에 완충작용과 강화작용을 해 줄 것이라고 생각된다.

따라서 의료인문 교육은 먼저 자신에 대한 이해를 바탕으로 자제력과 성실의 자세를 함양하고(의예과 1~2학년), 이어서 타인에 대한 이해를 바탕으로 환자 및 의료 관계자들을 배려하고 소통할 줄 알며(의학과 1~2학년), 최종적으로 자신·가족·스승·학교·지역사회에 대한 사회적 책무성을 스스로 인식하고 그 가치를 주체적으로 자신의 일상에서 실현(의학과 3~4학년)시켜 낼 수 있도록 세 단계로 구성할 수 있다.

이러한 결과를 바탕으로 졸업성과 및 인성교육의 분류방식으로 현재 시행하고 있는 계명대학교 의과대학 의료인문학 교육과정을 분석해 보았다(Table 2). 학년별 교육과정으로 살펴보면 첫째, 생명과 인체의 구조와 기능을 이해하는 의예과 1~2학년에서 「인성교육실습(1)」, 「의학입문및체험실습」, 「행동과학」, 「더불어사는의사(1)」 등의 과목을 통해 존재의 소중함과 인간의 속성을 탐구하고, 정체성을 확립하는 경험을 하고, 둘째, 본격적인 임상통합교육을 학습하는 의학과 1~2학년에서는 질병 뿐 아니라 환자와 보호자의 고통까지 이해하고, 이를 치료하기 위해 동료 의료인들과 소통하며, 경청·소통·공감하는 역량을 강화하는데 필요한 「의료윤리(1,2)」, 「의료관리와지역사회(1,2)」, 「더불어사는의사(2)」, 「진로탐색」 등을 학습한다. 이를 통해 임상의학을 대함에 있어 윤리기준을 준수하고 의사로서 책임과 소명의식을 배양하고자 하며, 마지막으로 임상실습 과정에 중에 있는 의학과 3~4학년은 지역사회 속 전문 의료인으로서 프로페셔널 한 자세·태도를 배양하고, 사회적 책무성을 체득하기 위해 「환자안전」, 「의료법규」, 「인성교육실습(2)」, 「더불어사는의사(3)」을 학습하고 있다.

이에 더해, 졸업성과에 따라 의료인문학 교육과정을 분류해 보

Table 2. Reinforcement of learning outcomes for each phase through inter-connection between medical humanities subjects in Keimyung university school of medicine

Phase		Integrated medical humanities curriculum	Learning goal
Phase 1 (M1,M2)	Subject name	HUMANITY ENRICHMENT PROGRAM (1), SCIENTIFIC THINKING AND REASONING, BEHAVIORAL SCIENCE, INTRODUCTION TO MEDICINE AND INTER PROFESSIONAL PRACTICE, DOCTORS LIVING TOGETHER (1), INTRODUCTION TO MEDICAL RESEARCH (1)	Self-understanding
	Learning outcomes	Cultivation of medical students' attitudes - Volunteer work, Visiting various departments in the hospital	
		Self-understanding - Exploring human attributes, Establishing identity	
Phase 2 (M3,M4)	Subject name	MEDICAL ETHICS (1,2), HEALTH CARE MANAGEMENT AND COMMUNITY MEDICINE (1,2), DOCTORS LIVING TOGETHER (2), MEDICAL CAREER EXPLORATION, MEDICAL RESEARCH (2), , MEDICAL RESEARCH (1)	Patient understanding (understanding of others)
	Learning outcomes	Communicate with patients and colleagues, Recognizing the importance of existence and relationships, Improving empathy	
		Compliance with ethical standards after learning clinical medicine, Cultivation of responsibility as a doctor in the hospital	
Phase 3 (M5,M6)	Subject name	PATIENT SAFETY, MEDICAL INTERVIEW, MEDICAL LAWS, DOCTORS LIVING TOGETHER (3), HUMANITY ENRICHMENT PROGRAM (2), MEDICAL ETHICS (3), MEDICAL RESEARCH (2)	
	Learning outcomes	Cultivating doctors' attitudes in the community	Community understanding
		Formation of a doctor who practices service in the community	

면 환자지지(25%)와 문제해결능력(25%)에 집중적인 교육을 하고 있고, 프로페셔널리즘(20%) 역량강화에 중점을 두었다. 다음으로 자기개발(10%), 진료(10%), 인성교육(10%) 영역 순이었다. 사실, 한 과목 안에 다양한 인문학적 요소와 졸업성과가 융합되어 있고, 수업내용에 따라 여러 가지 덕목을 아우를 수도 있다는 것을 교과목 명이나 교과목 개요만으로는 모두 반영하지 못한 한계점을 가지지만, 이 연구를 통해 향후 교육과정 개선을 위해 거시적인 방향성을 제시하는데 이러한 연구결과가 도움이 될 것이라고 여겨진다.

Discussion

이번 연구에서 의료인문학의 교육 가치와 필요성에 대한 재 고찰을 통해서, 국내 의료인문학 현황 분석을 한 선행연구[6]를 바탕으로 계명대학교 의과대학의 교육과정을 검토해 본 결과, 다음과 같은 의료인문학의 교육방향성을 제언해 보고자 한다. 향후 의료인문학 교육에서 고려되어야 할 내용적인 측면에서는 첫째, 의사소통과 프로페셔널리즘 교육을 위해서 커뮤니케이션의 개념 및 기초 의사소통 방식에 대한 교육이 필요하다고 여겨진다. 아울러 정치·경제·사회·인권·의료정책 및 시스템 문제 등을 임상의학에 적용하기 위한 토론 수업이 함께 이루어져야 할 것이다. 둘째, 인성교육 영역으로 문학·역사·철학 등 인문학적 소양 함양을 비롯한 예술교육, 의학사, 고전 및 글쓰기 교육이 필요하겠다. 셋째, 자기개발 영역에서는 동기유발과 진로탐색을 위한 멘토·코칭·상담교육이 구성되어야 하겠다. 넷째, 진료 및 문제해결 능력 함양을 위해서는 인공지능, 빅데이터, 보건시스템과학(health system science) 등의 미래 의료환경 변화에 적응하는 교육이 통합과정 내에 적절히 융합된다면 자신·타인·세계로 점차 시야를 확장하면서 의사로서의 삶에 대한 정체성을 잘 형성하여, 건강한 일상 구축을 해내는 능력 향상에 도움을 줄 수 있을 것이다.

교육의 방법적인 측면으로는 의료인문학은 지식 위주의 암기식 교육을 줄이고, 학생들의 다양한 관심과 흥미를 유도해 현상에 대한 목적과 이유 등의 본질을 탐색할 수 있는 통찰력을 길러주는 교육방법을 개발해야 할 것이다. 한 예로, 한 가지 주제에 대해서 강의-토론-발표 3차시를 하나의 세트로 묶어 학생들의 사유와 담론이 수업의 중심이 되도록 구성할 수도 있겠다. 아울러 의료인문학이 기초의학 및 임상의학 과목들과 자연스럽게 융합해 갈 수 있는 방안을 모색하고 그 내용이 포함된 교육과정으로 개편해야 할 것이다. 주된 평가방법으로는 동료평가지를 통해 동료를 평가하지만, 지식·술기·태도에 관련된 항목에서 동료의 의견이나 자세 중 자신이 배울 점과 동료에게 조언해 주고 싶은 점을 중심으로 평가하도록 유도하고, 평가 내용이 동료의 성적이 아니라 자신의 성적에 반영될 수 있도록 구성하는 것도 제안한다. 이는 긍정적인 자세로 수업내용에 대한 관심 및 후속적인 탐구에 대한 호기심, 배려와 성장의 가치들을 학생들이 교육과정 중에 체득할 수 있게 해 줄 것이다. 이렇게 더불어 살아가는 의미의 체화에 대한 교육 성과는 타인과 세상을 이해하고, 공감과 성장이 주는 충만함을 스스로 인식하게 함으로써 사회적 책무성을 책임이나 의무가 아닌 기쁨으로 여길 수 있는 내적 자율성을 높이는 것으로 드러날 것이다.

향후, 학생들이 겪어야 할 의료환경은 현재보다 더 많은 딜레마가 존재할 것으로 예측할 수 있다. 이러한 힘든 상황 속에서도 번아

웃, 우울감, 스트레스, 좌절감에 대해서 적절하게 대하는 건실한 태도를 함양하고, 힘든 상황 속에서도 회복탄력성을 높여 더불어 살아가는 자세를 길러주는 것이 의료인문학의 교육철학이 되어야 할 것이다. 이를 위해 평정심을 삶의 기본적인 자세로 갖고 자신을 사랑하고 아껴줄 수 있는 의사로서, 긴 안목을 가진 삶의 목적 수립과 의사의 정체성을 형성할 수 있는 교육이 요구된다. 더 급변할 사회에서도 '좋은 의사는 좋은 사람'이라는 의술 본연의 목적을 지켜나가기 위해서, 향후 의료인문학의 교육학적 의미 고찰과 실제적 교육 방안에 대해서는 지속적인 후속연구가 필요할 것이다.

Conflict of interest

All authors declare no conflicts-of-interest related to this article.

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Comparison of COVID-19 between Korea and Japan

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The incidence of COVID-19 infection between Korea and Japan,was compared focusing on three periods covering 2020.1~2021.10, 2021.11~2021.12, and 2022.1~2022.4. Between 2020.1 and 2021.10, by population, the incidence of COVID-19 infection in Korea had always been lower than in Japan and was called "Korean protection", its contributing factors being as follows: 1. learning from the experience of Middle East Respiratory Syndrome, 2. thorough PCR examinations, 3. comprehensive triage policy, 4. efforts of medical staff, 5. cooperation between the citizens and government. In Korea between 2021.11 and 2021.12, the number of newly infected cases, hospitalized cases, and deaths per week increased 3.5-, 2.6-, and 4.8-fold, respectively, compared with October cases. The main reason for this increase was attributed to the so-called "with corona" policy adopted by the Korean government during the same period. In contrast, during the same period, the number of newly infected cases per day dropped dramatically to less than 1,000 in Japan, attributed to the high rate of vaccination implementation and adherence to social restrictions. Between 2022.1 and 2022.4, the Omicron variant (BA1 and BA2) of COVID-19 became prevalent in both countries. Especially, since March 12, an infection explosion occurred in Korea with over 300,000 people recorded consecutively every day. During the same period, in Japan, the number of newly infected cases remained at less than one hundred thousand. Intercommunication is needed between the two countries to attain COVID-19 containment.

Keywords: COVID-19, Korean protection, Restriction adherence to restrictions in Japanese society, Vaccination, With corona policy

Introduction

In China since the outbreak of COVID-19 in December 2019, the resulting pandemic has inflicted 6,251,567 deaths worldwide as of 10 May 2022.

In Northeast Asian areas including Korea and Japan, the situation of COVID-19 differs based on the governments' policies, people's attitudes, and the rate of vaccination implementation [1,2].

In this overview, the incidence of COVID-19 infection between Korea and Japan is compared, focusing on three periods: 2020.1~2021.10, 2021.11~2021.12, and 2022.1~2022.4.

COVID-19 infection in Korea and Japan between 2020.1–2021.10.

The first cluster in Korea occurred in Daegu City in February 2020.

The excellent and sophisticated and collaborative efforts by medical staff, civil servants, and the heroic stance of the citizens in Daegu City brought about the least number of victims. Vivid and impressive reports [3-7] were published which helped other Korean areas to prevent as much as possible the damage by COVID-19.

Thus, the Daegu protective measures became the prototype of Korean (K) pro-

tection.

Irrespective of the COVID-19 cluster (more than seven hundred infected persons) at a church in Daegu City in February 2020, the containment of COVID-19 in Korea has been relatively well implemented between March 2020 and October 2021.

The number of newly infected cases and deaths in Korea and Japan is shown in Fig. 1.

The number of newly infected cases was as follows.

As of April 2020, 101 in Korea, 268 in Japan.

As of October 2020, 77 in Korea, 633 in Japan.

As of April 2021, 551 in Korea, 2,605 in Japan.

The number of deaths in Korea and Japan, respectively, was as follows (Fig. 1).

As of April 2020, 3 and 3.

As of October 2020, 2 and 8.

As of April 2021, 4 and 18.

By population, the incidence of COVID-19 infection in Korea had always been lower than in Japan, and is attributed to the so-called K protection.

K protection was between March 2020 and October 2021 considered an excellent model against COVID-19 in the world. Its contributing factors being as follows:

First, learning from the experience with Middle East Respiratory Syndrome (MERS) contracted by 40 persons in 2015 [8].

Second, the precise assessment of infected persons by thorough PCR examination.

Third, the comprehensive triage policy, including intensive care, for severely affected persons and health-maintaining care for mildly affected persons.

Fourth, the dedicated efforts of medical staff.

Fifth, cooperation of the citizens in the mandated practices set by the government.

COVID-19 infection in Korea and Japan between 2021.11–2021.12

The situation had changed, however, since November 2021.

The weekly increase in the number of newly infected cases rose from 1,735 in October to 6,097 (3.5-fold) in December.

Hospitalized cases increased from 332 on 31 October to 875 (2.6-fold) on 13 December.

Deaths per week increased from 12 in October to 57 (4.8-fold) in December.

The main reason for this increase was attributed to the so-called "with corona" policy adopted by the government [9]. The government relaxed the restriction on gatherings, irrespective of opposition by medical experts. Another reason for the increase in the number of COVID-19 was attributed to overevaluation of the protection of vaccinations against COVID-19 [9]. According to the government report, the decrease in the titer of neutralizing antibodies, especially for elderly people, was very clear.

For example, the titer of neutralizing antibodies two weeks and three weeks after AstraZeneca's vaccine dropped to 392-fold and 146-fold, respectively, compared with 2,852-fold after Mod-

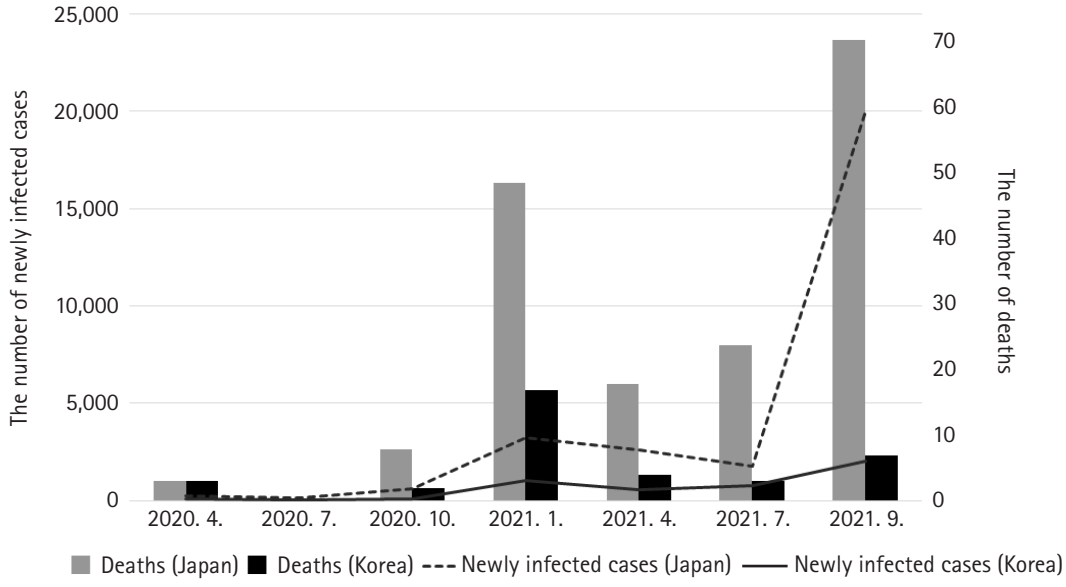

Fig. 1. Trends of daily number of newly infected cases and deaths in Korea and Japan (2020.4.~ 2021.10.). Based on NHK (Japan) and KBS (korea) news data.

erna's vaccine, and 2,119-fold after Pfizer's vaccine.

In cross-vaccination, AstraZeneca's vaccine (first shot) and Pfizer's vaccine (second shot), the titer of neutralizing antibodies dropped to 326-fold, whereas after Pfizer's vaccine (first shot) and AstraZeneca's vaccine (second shot) the titer dropped to 865-fold.

The data in terms of Moderna's vaccine were not reported [9].

That resulted in the remarkable increase in newly infected cases and deaths.

During the same period (2021.10~2021.12), the number of newly infected cases per day dropped dramatically to less than 1,000 in Japan, the so-called "golden period", explained by the high rate of the implementation of two-time vaccination and adherence to the restrictions set in Japanese society.

The number of newly confirmed infections and deaths in the two countries is shown in Fig. 2.

As of November 1 2021, newly confirmed infections stood at 1,684 in Korea and 84 in Japan, 9 deaths in Korea and 7 in Japan.

As of December 1 2021, newly confirmed infections stood at 5,122 in Korea and 119 in Japan, with 34 deaths in Korea, and none in Japan.

COVID-19 infection in Korea and Japan between 2022.1–2022.4

From January 2022, the Omicron variant (BA1 and BA2) of COVID-19 became prevalent in both countries (Fig. 3) [10,11].

The number of newly confirmed infections and deaths in the two countries is shown in Fig. 4.

Under the "with corona policy", an infection explosion occurred in Korea, irrespective of the implementation of a high rate of vaccination, which accounted for 80% of two-time vaccination in the general population and 80% of three-time vaccination in the elderly population. Especially, since 12 March, over 300,000 people were infected consecutively every day (Fig. 3A) [12].

Almost 620,000 people were infected on 17 March.

However, Korean people including medical professionals and the general population did not consider that the "with corona" was necessarily a failure, because the number of deaths was relatively low compared with the number of newly infected cases (Fig. 3B).

The paradoxical fact such as high infection rate and relatively low death rate was explained by the high rate of vaccinations in the general population, especially in the elderly population.

In contrast, about less than 100,000 infected people per day continued between 2022.1 and 2022.4 in Japan, a relatively low

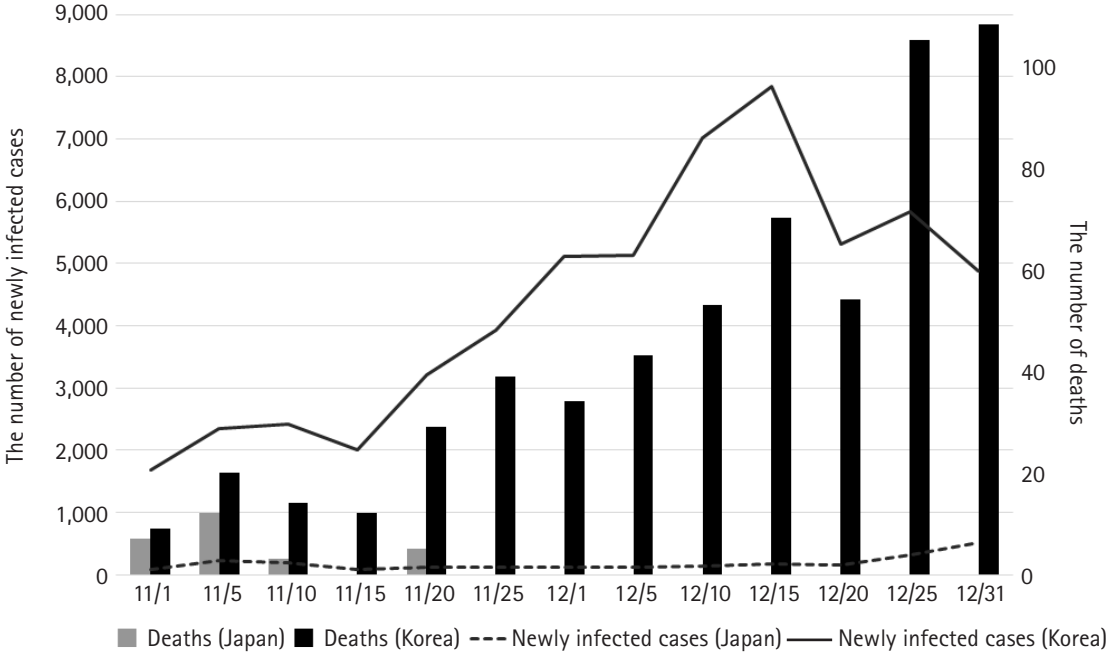

Fig. 2. Trends of daily number of newly infected cases and deaths in Korea and Japan (2021.11.~ 12.). Based on NHK (Japan) and KBS (korea) news data.

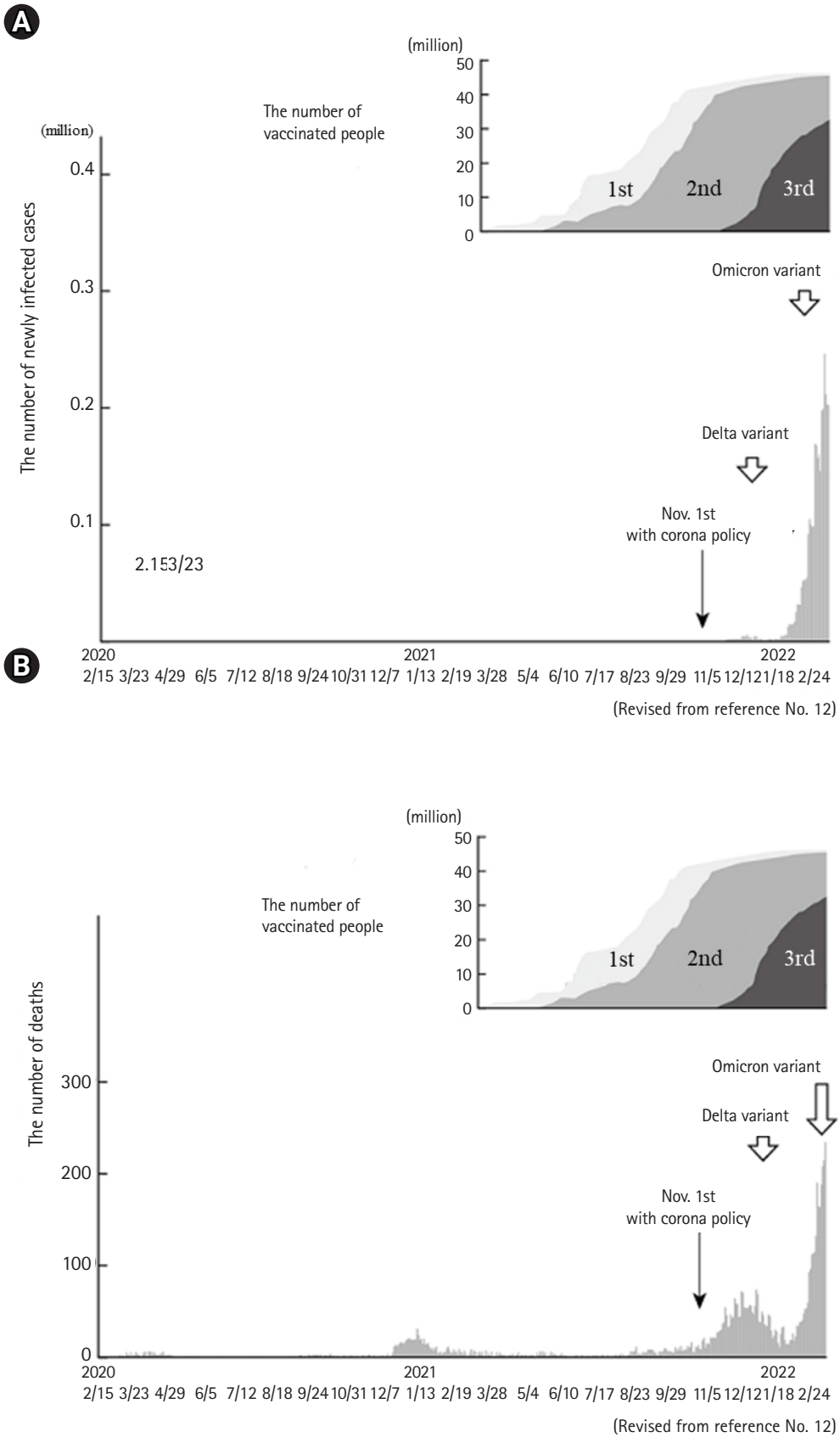

Fig. 3. COVID-19 in Korea. (A) The number of newly infected cases. (B) The number of deaths [12].

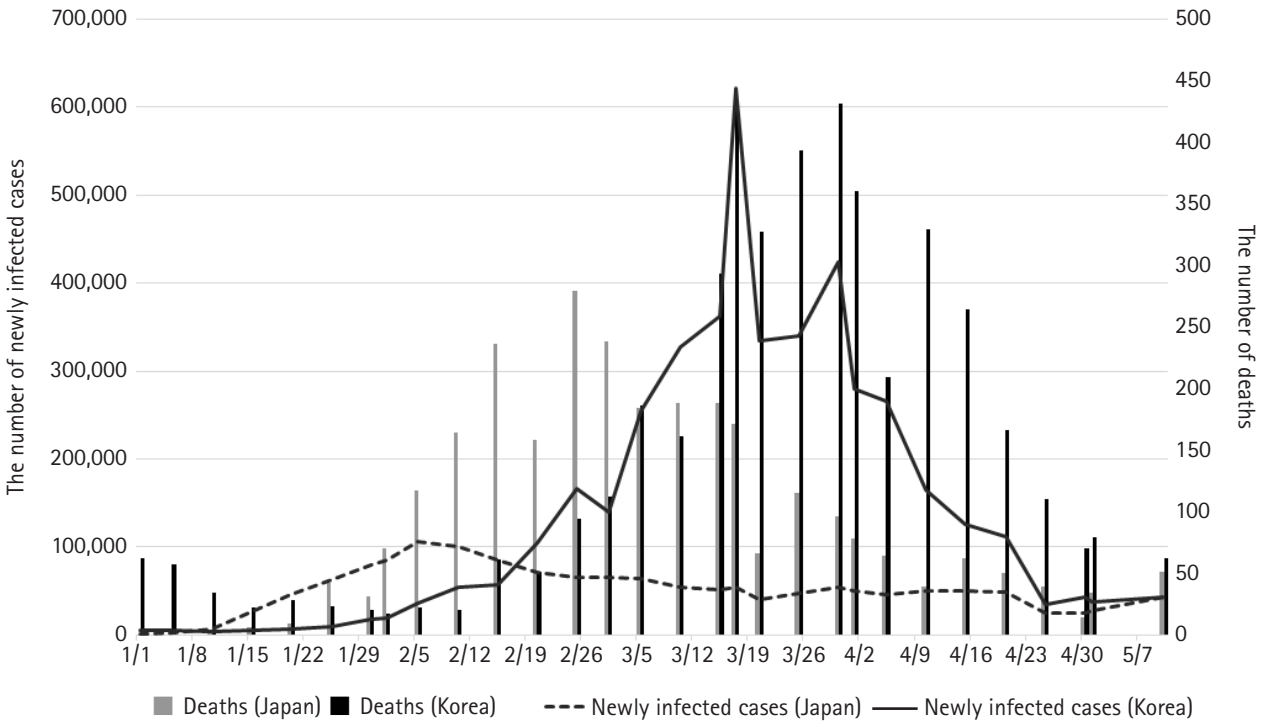

Fig. 4. Trends of daily number of newly infected cases and deaths in Korea and Japan (2022.1.~2022.5.). Based on NHK (Japan) and KBS (korea) news data.

level compared with the infected people in Korea. (Fig. 4)

That was explained by the high rate of vaccinations and adherence to restrictions such as prohibition of three Cs (closed spaces, crowded places, close-contact settings) in Japanese society. [12]

The number of newly infected cases was as follows: (Fig. 4)

As of 15 January 2022, 4,420 in Korea, 25,730 in Japan.

As of 15 February 2022, 57,147 in Korea, 84,195 in Japan.

As of 17 March 2022, 621,178 in Korea, 53,557 in Japan.

As of 15 April 2022, 125,800 in Korea, 49,738 in Japan

The number of deaths was as follows: (Fig. 4)

As of 15 January 2022, 22 in Korea, 6 in Japan.

As of 15 February 2022, 61 in Korea, 236 in Japan.

As of 17 March 2022, 429 in Korea, 171 in Japan.

As of 15 April 2022, 264 in Korea, 62 in Japan.

Regarding North Asian areas such as Korea and Japan, the incidence of COVID-19 and the rate of two-time vaccination implementation in England and Israel were also compared, where the Omicron variant became prevalent since November 2021.

The number of newly infected cases was as follows. (Cited from Johns Hopkins University's data)

As of 17 March 2022, 90,974 in England, 4,766 in Israel.

The number of deaths was as follows.

As of 17 March 2022, 153 in England, 6 in Israel.

The rate of two-time vaccination implementation in England and Israel were as follows.

As of 13 January 2022, 65% each of the general population in England and Israel [12].

Conclusion

Since the outbreak of COVID-19, the number of infections has been different between Korea and Japan in terms of the number of newly infected cases and the number of deaths. The situation seems to be associated with governments' policies, people's attitudes, and the rate of vaccination implementation.

The Japanese situation of COVID-19 is characterized as relatively stable over two years, explained especially by the adherence to the social restrictions set by the citizens, irrespective of inconsistent government policy.

The Korean situation of COVID-19 is, however, characterized by the remarkable contrast between 2020.2~2021.10 and 2021.11~2022.4, as explained especially by the change in government's "with corona policy".

Currently, it is difficult to conceive of absolute containment of COVID-19 in the near future. Nonetheless, a breakthrough including development of all-round vaccination and effective drugs against COVID-19 could be foreseen in the long run.

Probably, the process of containment of COVID-19, would

differ between the two countries. Mutual communication of containment processes, however, would be needed between the two countries to attain COVID-19 containment, which may lead to achieving COVID-19 containment not only in North Asian areas but also all over the world.

Conflict of interest

The authors declare no conflicts-of-interest related to this article.

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Clinical and Prognostic Values of DNMT3B Expression in Hepatocellular Carcinoma

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DNA methyltransferase 3B (DNMT3B), one of DNA methyltransferases has many roles in DNA methylation and cancer pathogenesis. However, its clinical and prognostic value was not studied in hepatocellular carcinoma (HCC). In this study, we analyzed DNMT3B expression in HCC by public big data, The Cancer Genome Atlas. Primary data about total 360 HCC were downloaded and its clinicopathological implication was analyzed. M stage ($p = 0.07$) and pathologic stage ($p = 0.04$) were associated with DNMT3B expression, though M stage did not get a statistical significance. And alpha fetoprotein level was positively correlated with DNMT3B expression ($p < 0.001$). Higher DNMT3B expression predicted shorter overall survival in HCC patients ($p < 0.05$). Disease-free survival was shorter in HCC with lower DNMT3B expression, within borderline statistical significance ($p = 0.081$). It suggested that DNMT3B expression may have an important role in HCC prognosis and its detail mechanism should be confirmed further.

Keywords: Carcinoma, hepatocellular; DNMT3B; Methylation; The Cancer Genome Atlas

Introduction

De novo methylation is occurred frequently during the early embryogenesis and is faithfully copied following DNA replication at each cell cycle [1]. DNA methylation is involved in many embryonic developments, biological processes, and cell differentiation [2]. The dysregulation of DNA methyltransferases (DNMTs) and subsequent aberrant DNA methylation is a key feature of human malignancies [3,4]. DNMT1, DNMT3A, and DNMT3B are the enzymatic players of DNA methylation [1,2]. DNMT3B overexpression is frequently found in tumors, especially in 30% of breast cancers [5,6]. And it result into variation in the targeting efficiency and abnormal catalytic activity contributing to cancer development and progression. Therefore, DNMT3B may act as an oncogene, and its overexpression induces an unfavorable prognosis [3-6].

Hepatocellular carcinoma (HCC) is a majority of human cancers in worldwide, and is a leading cause of death in Korea [7,8]. Recent studies about HCC showed an alteration of DNA methylation by dysregulation of DNMT3B [9,10]. Yu et al. described that telomerase reverse transcriptase (TERT) regulates DNMT3B expression in HCC and their co-operation may predict a poorer prognosis [11]. Recent advances in genomic profiling using next-generation sequencing have made it possible to identify the genetic characteristics of cancer. Large-scale cancer genome studies such as The Cancer Genome Atlas (TCGA) used to investigate genes in different cancer types [12]. However, clinicopatho-

logical characteristics have not been studied in HCC. Therefore, we aimed to examine the clinicopathologic and prognostic value of DNMT3B expression in HCC using gene expression RNA sequencing (RNAseq) data obtained from TCGA datasets.

Materials and Methods

Primary data were downloaded from TCGA data portal in March 2022. TCGA dataset consisted of 360 samples, including primary HCCs and adjacent tissues. The RNAseq data of HCC were sorted from TCGA with DNMT3B mRNA expression and clinical parameters. This study met the publication guidelines for using TCGA datasets (http://www.cancer.gov/about-nci/ organization/ccg/research/structrual-genomics/tcga/using-tcga/citing-tcga). Overall survival (OS) was defined as the days from the date of surgery to the date of the last follow-up visit or the date of death due to any cause. And disease-free survival (DFS) was defined as the days from surgery to any type of recurrence.

The Statistical Package for the Social Sciences (SPSS), version 24.0 for Windows (IBM, Armonk, NY, USA), was used for all statistical analysis. Chi-square and Mann-Whitney U-tests were used to analyze the relationship between variables. For survival analysis, the mean gene expression was used as a cutoff to divide the patients into high- and low-expression groups. Survival analysis was performed using the Kaplan-Meier method, and the log rank test was used to identify statistically significant differences between the two groups. A two-tailed P value < 0.05 was considered to signify statistical significance.

Results

Clinicopathological characteristics of DNMT3B mRNA expression were analyzed from TCGA data and presented in Table 1. Patients were divided into two groups according to the expression level of DNMT3B, and their clinical features were statistically analyzed. Age and sex were not different according to the DNMT3B expression level. Metastasis and Stage IV cancers were found in only lower expression of DNMT3B. Therefore, M stage ($p = 0.07$) and pathologic stage ($p = 0.04$) were associated with DNMT3B expression, though M stage did not get a statistical significance. And serum alpha fetoprotein (AFP) level was positively correlated with DNMT3B expression ($p < 0.001$).

The median follow-up period in the cohort examined in the survival analysis was 2032 ± 117 days (range: 9-3478 days). Univariate survival analysis revealed that shorter OS in HCC patients was associated with higher DNMT3B expression (1840.26 ± 164.36 vs. 2180.06 ± 150.16 days, $p = 0.003$, Fig. 1A). DFS was shorter in HCC patients with lower DNMT3B expression, it did not get a statistical significance (1474.18 ± 153.43 vs. 1625.30 ± 165.52 days, $p = 0.081$; Fig. 1B).

Discussion

Cancer is a kind of genetic disease, however, recent study introduced that epigenetic change are closely involved in this process. Therefore, to understand DNA methylation, one of the main events of epigenomic patterns, is extremely import-

Table 1. The Cancer Genome Atlas data of DNMT3B expressions in HCC

	DNMT3B expression (n, %)		P
	High (n = 180)	Low (n = 180)	
Age	55.88 ± 13.07	60.02 ± 13.51	0.42
Sex			0.31
Male	118 (48.2)	127 (51.8)	
Female	62 (53.9)	53 (46.1)	
T stage			0.20
T1	80 (44.9)	98 (55.1)	
T2	48 (53.9)	41 (46.1)	
T3	46 (58.2)	33 (41.8)	
T4	6 (46.2)	7 (53.8)	
N stage			0.93
N0	129 (52.2)	118 (47.8)	
N1	2 (50.0)	2 (50.0)	
M stage			0.07
M0	135 (51.7)	126 (48.3)	
M1	0 (0)	3 (100)	
Pathologic stage			0.04
I	76 (45.2)	92 (54.8)	
II	44 (53.0)	39 (47.0)	
III	49 (58.3)	35 (41.7)	
IV	0 (0)	4 (100)	
Serum AFP (μg/L)			< 0.001
< 20	52 (35.1)	96 (64.9)	
≥ 20	78 (61.4)	49 (38.6)	
Child-Pugh			0.56
A	105 (48.6)	111 (51.4)	
B	9 (45.0)	11 (55.0)	
C	1 (100)	0 (0)	

DNMT3B, DNA methyltransferase 3B; HCC, hepatocellular carcinoma; AFP, alpha fetoprotein.

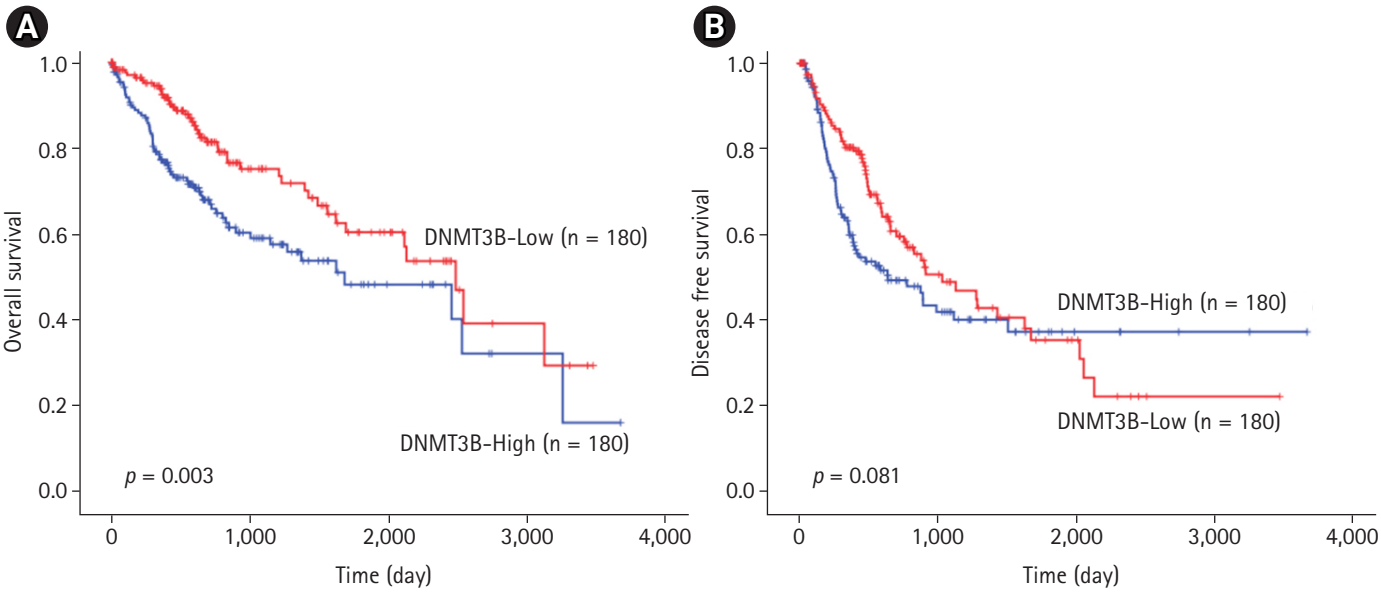

Fig. 1. Survival analysis of DNA methyltransferase 3B (DNMT3B) expression in hepatocellular carcinomas. (A) Overall survival. (B) Disease free survival.

ant in cancer. The DNA methylation is catalyzed by methyltransferases DNMT3A and DNMT3B, however, exact role of DNMT3B in cancer is not fully understood.

For a first time, we demonstrated clinical value of DNMT3B expression in HCC. Previous study demonstrated that DNMT3B expression level was remarkably higher in HCC than in non-tumorous tissue [13]. And this study showed DNMT3B deletion induced liver carcinogenesis suggesting its protective role against liver inflammation and HCC development. Many studies focused oncogenic role of DNMT3B in cancer [6,9,10] and our survival analysis also found that higher expression of DNMT3B predicts poorer prognosis. And its expression was positively correlated to AFP level.

However, its clinical implication was related to favoring prognosis. Our data showed that lower expression of DNMT3B was found only in metastasis and stage IV cancers. This clinical character of DNMT3B expression may be associated with its protective role in HCC, and it agreed with these result [14-16]. These data suggested that lack of DNMT3B facilitated cancer progression suggesting that its deficiency induced genetic instability. These completely opposite findings suggest that DNMT3B may have a paradoxical effect in cancer, as an oncogene and as a tumor suppressor gene. A recent study showed that higher TERT and DNMT3B expressions had statistically poorer survival in HCC patients by TCGA data [11]. And they suggested that TERT-DNMT3B-PTEN-AKT axis has multi-oncogenic activities in cancers. Therefore, the authors suggested that the role of DNMT3B in cancer should be confirmed in a larger scale study further. Then, its molecular mechanism should be identified, and prognostic value of DNMT3B in various cancers should be confirmed.

Here, we revealed clinical significance of DNMT3B mRNA expression in HCC by public data. DNMT3B expression may have various roles in hepatocellular carcinogenesis and future study about molecular mechanisms of DNMT3B will be required.

Conflict of interest

All authors declare no conflicts-of-interest related to this article.

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The Growth Inhibitory Effect on B16F10 Melanoma Cells by 4-BPCA, an Amide Derivative of Caffeic Acid

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Caffeic acid (CA) is a phenolic compound found naturally in plants and foods. CA and its natural derivatives are reported to have anti-cancer effects on many cancers, including melanoma. (E)-N-(4-Butylphenyl)-3-(3,4-dihydroxyphenyl)acrylamide (4-BPCA) is an amide derivative of CA. Thus far, the anti-cancer effect and mechanism of 4-BPCA in melanoma cells remain unknown. Here we investigated whether 4-BPCA inhibits the growth of B16F10 cells, a mouse melanoma cell line. Of note, treatment of 4-BPCA at 5 μM for 24 or 48 h significantly reduced the growth (survival) of B16F10 cells. On mechanistic levels, treatment with 4-BPCA for 24 h led to the activation of caspase-9/3, but not caspase-8, in B16F10 cells. 4-BPCA treatment for 2 or 4 h also decreased the expression levels of myeloid B-cell lymphoma 1 (Mcl-1) in B16F10 cells. However, 4-BPCA treatment for the times tested did not influence the expression levels of X-linked inhibitor of apoptosis protein (XIAP) in B16F10 cells. Of interest, treatment of 4-BPCA for 2 or 4 h greatly reduced the phosphorylation levels of JAK-2 and STAT-5 without altering their total protein expression levels. 4-BPCA also had abilities to increase the expression and phosphorylation levels of glucose-regulated protein-78 (GRP-78) and eukaryotic translation initiation factor-2α (eIF-2α) in B16F10 cells. In summary, these results demonstrate firstly that 4-BPCA has a strong growth-inhibitory effect on B16F10 melanoma cells, mediated via activation of the intrinsic caspase pathway, inhibition of JAK-2 and STAT-5, and triggering endoplasmic reticulum (ER) stress.

Keywords: 4-BPCA, B16F10, Caspase-9, Endoplasmic reticulum stress, JAK-2, STAT-5

Introduction

Melanoma is a malignant tumor deriving from melanocytes, and it is considered a rare disease that accounts for 4% of skin cancer cases [1]. In 2022, it is expected by the American Cancer Society that about 99,780 new melanomas will be diagnosed, and 7,650 are expected to die of melanoma in the United States. In the past 10 years, several treatment approaches for patients with localized and or metastatic melanoma have vastly improved. However, these therapies did not manifest a lasting response in most patients [1-3]. Therefore, there is an urgent need to identify or develop new therapeutic strategies for melanoma.

Currently, the cancer treatment strategy of eradicating cells through induction of apoptosis has obtained a lot of interest due to its minimal inflammation reaction [4]. Apoptosis (also called programmed cell death) is one of the cell death types needed to preserve the normal cell turnover with distinctive morphological events such as nuclear condensation and fragmentation, cell shrinkage, plasma membrane blebs, and adhesion loss of the cells [5,6]. It is well known that

there are two common types of apoptosis, including the intrinsic (or mitochondrial) and extrinsic (or death receptor) pathways. A wealth of information indicates that the main regulatory proteins in both apoptosis pathways are the caspases [5,7]. There is also accumulating evidence that multiple anti-apoptotic proteins, such as the family of myeloid B-cell lymphoma (Bcl-2) members and inhibitor of apoptosis proteins (IAPs), participate in the regulation of cancer cell survival and apoptosis [4]. Several studies have also illustrated that endoplasmic reticulum (ER) stress regulates cancer cell survival and apoptosis [8].

Caffeic acid (CA) is one of the major phenolic acids, which is usually found in numerous natural products, such as fruits, vegetables, olive oil, tea, and coffee [9,10]. Previous studies have reported that CA has a diversity of pharmacological effects, including anti-inflammation, antioxidant, and anti-cancer [11-13]. We have recently used diversity-oriented synthesis to prepare a series of CA derivatives, including (E)-N-(4-Butylphenyl)-3-(3,4-dihydroxyphenyl)acrylamide (4-BPCA), and demonstrated their anti-melanogenic effects [14]. 4-BPCA is an amide derivative of CA. However, up to now, the anti-cancer effect and mechanism of 4-BPCA in melanoma are unknown. In this study, we investigated whether 4-BPCA suppresses the growth of B16F10 cells, a mouse melanoma cell line. Here we demonstrated, for the first time, that 4-BPCA at 5 μM has a strong growth-suppressive effect on B16F10 melanoma cells, and the effect is mediated through regulation of the expression and phosphorylation levels of caspase-9/3, JAK-2, STAT-5, GRP-78, and eIF-2α.

Materials and methods

1. Materials

4-BPCA was developed as in our previously published papers [14,15]. All commercial antibodies and chemicals were purchased from the following resources: anti-procaspase-9, anti-procaspase-3, and anti-procaspase-8 were bought from Enzo (Farmingdale, NY, USA); anti-p-STAT-3, anti-STAT-3, anti-p-STAT-5, anti-STAT-5, anti-GRP-78, anti-p-JAK-2, anti-JAK-2, and anti-Mcl-1 antibodies were purchased from Santa Cruz Biotechnology (Delaware, CA, USA); the anti-XIAP antibody was obtained from R&D Systems (MN, USA); the anti-phospho (p)-eIF-2α was bought from Abcam (Cambridge, MA, USA); anti-p-JAK-1, anti-JAK-1, and anti-eIF-2α antibodies were bought from Cell Signaling (Danvers, MA, USA), and the anti-β-actin antibody was purchased from Sigma (St. Louis, MO, USA).

2. Cell culture

B16F10 melanoma cells (ATCC, Manassas, VA, USA) were grown in DMEM/RPMI-1640 media supplemented with 10% heat-inactivated fetal bovine serum (FBS) and 1% penicillin/streptomycin at 37°C in humidified air (95% air and 5% CO2).

3. Cell count assay and cell morphological analysis

B16F10 melanoma cells were seeded in a 24-well plate. After overnight incubation, cells were treated with vehicle control (DMSO; 0.1%), or 4-BPCA at the indicated concentrations (1, 5, and 10 μM) for different time points (2, 4, 8, and 24 h). The number of surviving cells was counted with the trypan blue exclusion method, which is based on the principle that live cells have intact cell membranes and cannot be stained. Approximately 100 cells were counted in each evaluation. For cell morphology analysis, phase-contrast images of the conditioned cells treated with or without 4-BPCA were taken with a phase-contrast microscope (Nikon Eclipse TS200, Nikon Corp., Tokyo, Japan).

4. Preparation of whole cell-lysates

B16F10 melanoma cells were grown in 6-well plates. After overnight incubation, cells were treated with 4-BPCA (1, 5, and 10 μM) or vehicle control (DMSO) for the designated times. At the designated time point, cells were washed twice with PBS and proteins were extracted using a modified RIPA buffer [50 mM Tris-Cl (pH 7.4), 150 mM NaCl, 0.1% sodium dodecyl sulfate, 0.25% sodium deoxycholate, 1% Triton X-100, 1% Nonidet P-40, 1 mM EDTA, 1 mM EGTA, proteinase inhibitor cocktail (1X)].

The cell lysates were collected and centrifuged at 12,074 × g for 20 min at 4°C. The supernatant was collected, and its protein concentration was determined by the bicinchoninic acid assay Protein Assay Kit (Thermo Scientific, Rockford, IL, USA).

5. Immunoblotting Analysis

Equal amounts of protein (50 μg) were separated via 10% SDS-PAGE and transferred onto polyvinylidene fluoride membranes (EMD Millipore) by electroplating. The membranes were washed with Tris-buffered saline (TBS; 10 mM Tris, 150 mM NaCl, pH 7.5) supplemented with 0.05% (v/v) Tween-20 (TBS-T), followed by blocking with TBS-T containing 5% (w/v) non-fat dried milk. The membranes were probed overnight using antibodies against procaspase-9 (1:2,000), procaspase-3 (1:2,000), procaspase-8 (1:2,000), Mcl-1 (1:2,000), XIAP (1:2,000), p-STAT-3 (1:2,000), T-STAT-3

(1:2,000), p-STAT-5 (1:2,000), T-STAT-5 (1:2,000), p-JAK-1 (1:2,000), T-JAK-1 (1:2,000), p-JAK-2 (1:2,000), T-JAK-2 (1:2,000), GRP78 (1:2,000), p-eIF-2α (1:2,000), T-eIF-2α (1:2,000) or β-actin (1:10,000) at 4°C, followed by incubation with secondary antibodies conjugated to at room temperature for 2 h. The membranes were washed, and immune reactivities were detected by Super Signal™ West Pico PLUS ECL (Thermo Fisher Scientific, Inc.) according to the manufacturer's instructions. Equal protein loading was assessed via β-actin expression levels.

6. Statistical analysis

Cell count analysis was done in triplicates and repeated three times. Data were expressed as mean ± SE. The significance of the difference was determined by One-Way ANOVA. All significance testing was based upon a p-value of < 0.05.

Results

1. 4-BPCA markedly inhibits the growth of B16F10 melanoma cells in a concentration-dependent manner

Initially, we examined the effect of 4-BPCA (Fig. 1A) at different concentrations (1, 5, and 10 μM) and times (24 and 48 h) on the growth (survival) of B16F10 melanoma cells by cell count analysis. As shown in Fig. 1B (left graph), compared with control (no 4-BPCA), treatment with 4-BPCA at 1 μM

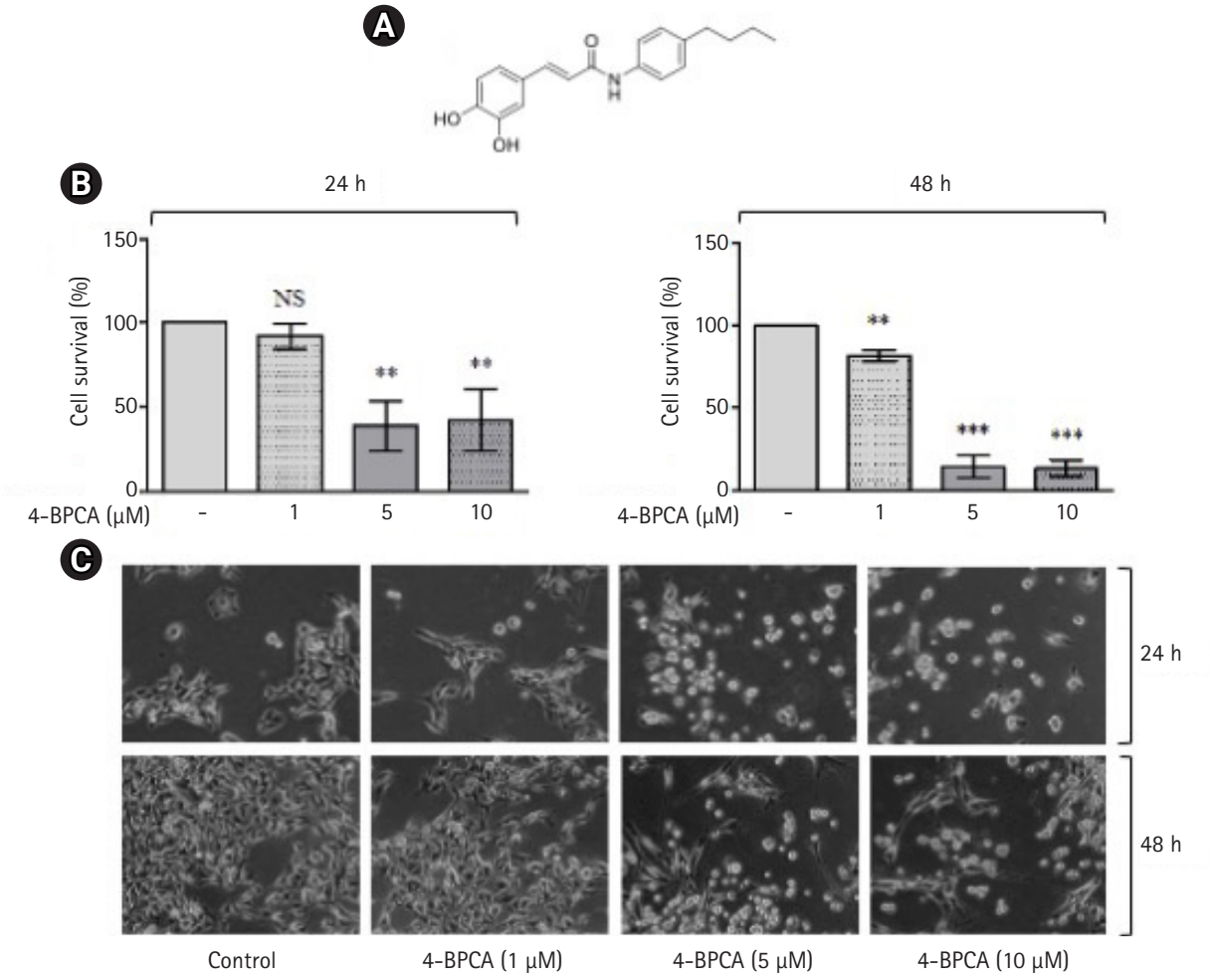

Fig. 1. Effect of 4-BPCA on the growth and morphology of B16F10 melanoma cells. (A) The chemical structure of 4-BPCA. (B,C) B16F10 melanoma cells were treated with 4-BPCA or vehicle control (DMSO; 0.1%) at the designated concentrations for 24 and 48 h, respectively. The numbers of surviving B16F10 melanoma cells were measured by cell count assay (B). Cell count assay was performed in triplicate. Data are means ± SE of three independent experiments. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ compared to the value of 4-BPCA free control at the times tested. Images of the conditioned cells were acquired by a phase-contrast microscope (C); the magnification rate, 200 ×. Each image is representative of three independent experiments. NS, non-significant.

for 24 h did not influence the survival of B16F10 melanoma cells. Of note, 4-BPCA treatment at 5 or 10 μM for 24 h led to a significant reduction of the survival of B16F10 melanoma cells. Moreover, treatment with 4-BPCA for 48 h further resulted in a concentration-dependent reduction of the survival of B16F10 melanoma cells (right graph). Apparently, the maximal growth inhibition of B16F10 melanoma cells was seen by treatment with 4-BPCA at 5 and 10 μM. Microscopic observation further revealed that 4-BPCA treatment caused a concentration-dependent decrease in the number of B16F10 melanoma cells in which the largest reduction of B16F10 melanoma cells was also seen at the 1 and 5 μM of 4-BPCA for 24 and 48 h (Fig. 1C). Due to most strong growth-inhibitory effects on B16F10 melanoma cells, we chose the 5 μM concentration of 4-BPCA for further studies.

2. 4-BPCA at 5 μM leads to the reduced expression levels of procaspase-9/3 and Mcl-1 in a time-differential manner in B16F10 melanoma cells

Next, to understand molecular mechanisms underlying the 4-BPCA (5 μM)'s growth-suppressive effect on B16F10 melanoma cells herein, we investigated the effect of 4-BPCA on the expression levels of survival and apoptosis-related factors, such as procaspase-9, procaspase-3, procaspase-8, Mcl-1, and XIAP, in B16F10 melanoma cells over time. As shown in Fig. 2, compared with control (no 4-BPCA), treatment with 4-BPCA for 24 h led to the reduced expression of procaspase-9 and its downstream effector procaspase-3 in B16F10 melanoma cells. In addition, 4-BPCA treatment for 2 or 4 h resulted in a decrease in the expression levels of Mcl-1 in B16F10 melanoma cells. However, 4-BPCA treatment for the times tested did not alter the expression levels of XIAP in B16F10 melanoma cells. The expression levels of control actin protein remained unchanged under these experimental conditions.

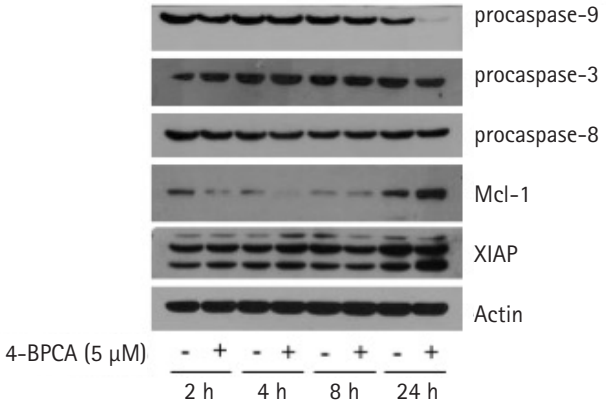

Fig. 2. Effect of 4-BPCA on the protein expression levels of procaspase-9/3, procaspase-8, Mcl-1, and XIAP in B16F10 melanoma cells. B16F10 melanoma cells were treated with 4-BPCA (5 μM) or vehicle control (DMSO; 0.1%) for the designated time periods. At each time point, whole-cell lysates were extracted and analyzed by Western blotting with corresponding antibodies.

3. 4-BPCA at 5 μM reduces the phosphorylation levels of JAK-2 and STAT-5 in B16F10 melanoma cells

Evidence indicates that the Janus-activated protein kinase-signal transducer and activator of transcription (JAK-STAT) pathway regulates cell survival and differentiation [16]. This promptly led us to investigate whether members of the JAK-STAT pathway including JAK-1, JAK-2, STAT-3, and STAT-5 are expressed and phosphorylated in B16F10 melanoma cells, and 4-BPCA (5 μM) regulates their expression and phosphorylation levels in these cells. Notably, as shown in Fig. 3, in the absence of 4-BPCA, high phosphorylation levels of JAK-2 and STAT-5 in a time-differential fashion were observed in B16F10 melanoma cells. However, there was no or little phosphoryla-

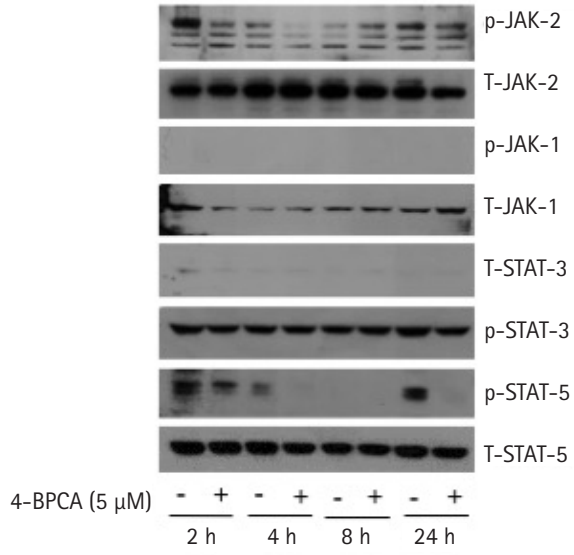

Fig. 3. Effect of 4-BPCA on the protein expression and phosphorylation levels of JAK-1/2 and STAT-3/5 in B16F10 melanoma cells. B16F10 melanoma cells were treated with 4-BPCA (5 μM) or vehicle control (DMSO; 0.1%) for the indicated times. Whole-cell lysates were prepared and analysed by Western blotting using respective antibody of JAK-1/2, STAT-3, and STAT-5. p-JAK-1/2, phosphorylated JAK-1/2; T-JAK-1/2, total JAK-1/2; p-STAT-3, phosphorylated STAT-3; T-STAT-3, total STAT-3; phosphorylated STAT-5; T-STAT-5, total STAT-5.

tion levels of JAK-1 and STAT-3 in B16F10 melanoma cells at the times tested. Strikingly, 4-BPCA treatment at 2 h resulted in a strong inhibition of JAK-2 phosphorylation in B16F10 melanoma cells. Moreover, 4-BPCA treatment at 2, 4, and 24 h led to a strong suppression of STAT-5 phosphorylation in B16F10 melanoma cells. Total protein expression levels of JAK-1, JAK-2, STAT-3, and STAT-5 remained unchanged under these experimental conditions.

4. 4-BPCA at 5 μM increases the expression and phosphorylation levels of GRP-78 and eIF-2α in B16F10 melanoma cells

We next sought to explore whether 4-BPCA (5 μM) regulates the expression and phosphorylation levels of ER stress-related proteins, such as glucose regulated protein (GRP-78) and eukaryotic initiation factor (eIF-2α), in B16F10 melanoma cells over time. As shown in Fig. 4, in the absence of 4-BPCA, there were substantial expression and phosphorylation levels of GRP-78 and eIF-2α proteins in B16F10 melanoma cells for the times analyzed. However, 4-BPCA treatment for 4, 8, and 24 h led to an increase in the protein expression levels of GRP-78 in B16F10 melanoma cells. Furthermore, treatment with 4-BPCA for 4, 8, and 24 h caused an increase in the phosphorylation levels of eIF-2α in B16F10 melanoma cells. Expression levels of total eIF-2α remained constant under these experimental conditions.

Discussion

Mounting evidence illustrates that CA and its natural derivatives including caffeic acid phenethyl ester and caffeic acid methyl and ethyl esters has anti-inflammatory, antioxidant, and anti-cancerous effects [11-13]. 4-BPCA is a new amide derivative of CA and its anti-melanogenic activity has been recently introduced [14]. However, up to now, 4-BPCA regulation of the growth of melanoma cells and its mode of action are not fully understood. In this study, we demonstrate firstly that 4-BPCA has a strong growth-inhibitory effect on B16F10 melanoma cells, and the effect is mediated through modulation of the expression and phosphorylation levels of procaspase-9/3, JAK-2, STAT-5, GRP-78, and eIF-2α.

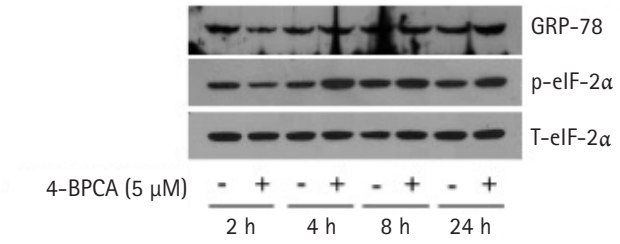

Fig. 4. Effect of 4-BPCA on the protein expression and phosphorylation levels of GRP-78 and eIF-2α in B16F10 melanoma cells. B16F10 melanoma cells were treated with 4-BPCA (5 μM) or vehicle control (DMSO; 0.1%) for different time points. At each time point, whole-cell lysates were prepared and analyzed by Western blotting using respective antibodies of GRP-78 and eIF-2α. p-eIF-2α, phosphorylated eIF-2α; T-eIF-2α, total eIF-2α.

Through initial experiments, we showed that treatment with 4-BPCA at 5 μM markedly inhibits the growth (survival) of B16F10 melanoma cells, pointing out its anti-survival effect. Aforementioned, cells undergoing apoptosis have distinctive morphological events including cell shrinkage, plasma membrane blebs, and adhesion loss of the cells [5,6]. Thus, considering the present finings with microscopic cell images that display cell shrinkage and adhesion loss of the cells, it is likely that 4-BPCA may also induce apoptosis in B16F10 melanoma cells. It is documented that apoptosis induction is conducted through two major pathways including the intrinsic (mitochondria-mediated) and extrinsic (receptor-mediated) pathways [17]. The mitochondria-mediated pathway is greatly regulated through cytochrome C release and the resultant Apaf-1-dependent proteolytic cleavage (activation) of caspase-9, followed by the subsequent proteolytic cleavage (activation) of downstream effector caspases such as caspase-3, whereas the receptor-mediated pathway such as death-receptor (DR) is initiated by its receptor superfamily stimulation that leads to the proteolytic cleavage (activation) of caspase-8 [18,19]. In this study, we demonstrated that 4-BPCA treatment at 5 μM resulted in the activation of caspase-9/3, as evidenced by a decrease in the expression levels of procaspase-9/3, but did not trigger the activation of caspase-8, as assessed by no altered expression levels of procaspase-8, in B16F10 melanoma cells. Given that the activation of caspase-9/3 is crucial for the induction of apoptosis, the present findings may further suggest that 4-BPCA treatment induces apoptosis in B16F10 melanoma cells not through the extrinsic pathway but via the intrinsic one associated with activation of caspase-9/3. Mcl-1 and XIAP are known anti-apoptotic proteins [4]. We herein observed that treatment with 4-BPCA lowered the expression levels of Mcl-1 without altering those of XIAP in B16F10 melanoma cells. It is thus conceivable that Mcl-1 down-regulation may also contribute to the growth-inhibitory and/or apoptosis-inducing effects of 4-BPCA on B16F10 melanoma cells.

A wealth of information exists that overexpression and hyperphosphorylation of the JAK-STAT components play im-

portant roles in tumorigenesis in solid tumors and blood cancers [16,20-23]. Notably, in the current study, we demonstrated the ability of 4-BPCA at 5 μM to reduce the phosphorylation levels of JAK-2 and STAT-5 in B16F10 melanoma cells. These results point out that 4-BPCA's anti-survival and pro-apoptotic effects on B16F10 melanoma cells are further attributable to inactivation of this JAK-2-STAT-5 axis in B16F10 melanoma cells.

The ER is the primary organelle in controlling protein folding, translocation and post-translation modification [24]. Multiple lines of evidence indicate that environmental stressors to cancer cells lead to induction of ER stress marked with high accumulation of unfolded or misfolded proteins in the ER [24,25]. It also has been shown that prolonged ER stress is closely linked to induction of apoptosis [26]. GRP-78, is a main chaperone protein in the ER, and is involved in protein folding and assembly of newly synthesized proteins in the ER [27]. Comparably, eIF-2α is another ER-stress marker and also regulates ER stress and/or protein synthesis [28]. It is worthy to note that the phosphorylated form of eIF-2α is an inactive protein that does not participate in the normal protein synthesis [29]. In the present study, we showed clearly that treatment with 4-BPCA at 5 bly of newly synthesized proteins in the ER [27]. Comparably, eIF-2 led to up-regulation of the protein expression and phosphorylation levels of GRP-78 and eIF-2α in B16F10 melanoma cells. These results indicate that 4-BPCA's anti-survival and pro-apoptotic effects on B16F10 melanoma cells are further likely to be attributed to induction of ER stress and global translation inhibition.

In summary, this the first study reporting that 4-BPCA, an amide derivative of CA, has strong anti-survival and pro-apoptotic effects on B16F10 melanoma cells, and these effects are mediated through activation of the caspase-9/3-mediated intrinsic pathway, inactivation of JAK-2 and STAT-5, induction of ER stress, and global translation inhibition. Despite the fact that there are still main issues that remain unresolved, such as 4-BPCA's anti-melanoma effects on animal models, this work suggests 4-BPCA as a lead or candidate small molecule for the treatment of melanoma.

Author Contributions

YuKyoung Park; Methodology, Data Curation, Visualization, Software, And Investigation. Shin-Ung Kang: Methodology, Data Curation, Visualization, Validation, Investigation. Jinho Lee; Resources. Byeong-Churl Jang; Conceptualization, Formal analysis, Funding acquisition, Project administration, Writing – original draft, Writing – review & editing, Validation, Supervision.

Conflict of interest

The authors declare no conflicts-of-interest related to this article.

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Clinical Implication of Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease

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Tolvaptan, a non-peptide arginine vasopressin V2 receptor antagonist, is a newly developed drug to reduce kidney volume and preserve kidney function in autosomal dominant polycystic kidney disease (ADPKD) patients. We aimed to evaluate the descriptive characteristics of patients according to the use of tolvaptan. Also, we tried to find the efficacy of tolvaptan on kidney volume and kidney function. We included patients with ADPKD who visited a tertiary hospital in South Korea during Sep. 2018 and Apr. 2022. The data was acquired from the Electric Medical Records system. A total of 64 patients were included in the study, and there were 33 (51.6%) patients taking tolvaptan during follow-up periods. During 17.8 ± 13.1 months of follow-up periods, estimated glomerular filtration rate (eGFR) changes were 89.4% compared to the baseline eGFR. Although the latest eGFR was lower in patients with tolvaptan (55.9 ± 24.7 mL/min/1.73 m^2) than without tolvaptan (68.4 ± 35.1 mL/min/1.73 m^2), there was no statistical significance (p = 0.108). We found that the mean change of height-adjusted total kidney volume (HtTKV) was –2.7% based on the baseline HtTKV in patients taking tolvaptan for more than 1-year. Although there was no statistical significance, the mean change of HtTKV was the highest in patients with 1E of Mayo classification (–4.3%). To anticipate the solid data on the efficacy of tolvaptan in the Asian population, more aggressive efforts are needed to search for suitable patients accompanied by appropriate monitoring over a more extended period.

Keywords: Chronic kidney disease; Polycystic kidney, autosomal dominant; Tolvaptan

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic kidney disease characterized by the growth of numerous fluid-filled cysts in the kidneys. It leads to progressive kidney enlargement and end-stage kidney disease (ESKD) [1,2]. ADPKD is a ciliopathy that involves abnormal cilia structure and function [3]. There are polycystin-1 and polycystin-2 in the kidney tubular cell protruding primary cilium. It has a role in detecting fluid flow and regulating calcium influx that activates an intracellular calcium signaling pathway [4]. In addition, increased levels of arginine vasopressin levels induced increased intracellular adenosine cyclic monophosphate (cAMP) levels in the distal tubule and collecting duct.

Tolvaptan is a vasopressin receptor antagonist; it selectively blocks the binding of V2 receptors in tubular cells and reduces fluid secretion, cell proliferation, and cyst development by reducing cAMP [5]. Tolvaptan in ADPKD pa-

tients was first approved in Japan in 2014 based on a phase 3 clinical trial (TEMPO 3:4) from 2007 to 2012 [6]. Additional trials showed positive results for reducing the rate of increased kidney volume with preserved kidney function; it was finally approved to use in Korea in 2019 [7-9]. However, there were rare data for Asian populations, with only 12.6% in the TEMPO 3:4 trial. Moreover, the used dosage of tolvaptan was lower in Japanese compared to the previously reported one [10]. In this regard, a phase 4 clinical trial has been performed in Korea.

Tolvaptan usually is prescribed in patients defined with the rapid progressor defined by rapidly decreased estimated glomerular filtration rate (eGFR) or Mayo classification 1C-1E. However, there are several hurdles to prescribing the tolvaptan, even in patients showing rapid progression. Aquaretic symptoms such as frequent urination and the requirement of a large amount of water intake were the most common cause of discontinuation of the drug [6]. In addition, the risk of hepatotoxicity required frequent monitoring by blood tests with monthly visits to the hospital. Therefore, before evaluating the hard outcome, we tried to search out the descriptive characteristics between patients with and without tolvaptan treatment in the real clinical field. In addition, this study aimed to evaluate the short-term changes in total kidney volume (TKV) and renal function in patients with tolvaptan.

Materials and Methods

Study populations

A subject who visited Keimyung University Dongsan Hospital during Mar. 2022 and May. 2022 with ADPKD was initially evaluated in this study. We included patients with age ≥ 18 years old with follow-up periods over 3 months. ADPKD was initially screened by the diagnostic code of Q612 based on the International Classification of Diseases 10th version. We confirmed the disease based on the computed tomography (CT) image with a family history. We defined patients with rapid progression as a Mayo Clinic image classification of 1C, 1D, or 1E. Among whole populations, patients with rapid progression, eGFR ≥ 30 mL/min/1.73 m^2, with informed consent were candidates for tolvaptan treatment.

Clinical data acquisition

We obtained anthropometric data, laboratory data, and image results using electric medical records. Kidney function was defined by serum creatinine-based eGFR calculated using the Chronic Kidney Disease-Epidemiology Collaboration equation [11]. We measured TKV based on the CT image finding using the ellipsoid equation [12]. TKV was adjusted by height (HtTKV), and it was divided into 5 classifications using Mayo classifications.

Statistical analysis

We compared the baseline characteristics of patients with and without tolvaptan treatment. We used the student t-test and Chi-square test for comparing the two groups with and without using tolvaptan. Also, in patients with tolvaptan treatment, we evaluated the change of TKV with 1-year follow-up CT findings. In comparing the groups according to the change of TKV, we used Mann-Whitney U-test. Continuous variables were represented as the mean and standard deviation in cases that followed a normal distribution and the median with an interquartile range in cases without normal distribution. The percent change of eGFR and TKV was calculated by dividing the latest result by the initial result. P-values less than 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics for Window, Version 23.0 (IBM Corp., Armonk, NY, USA).

Ethical consideration

The study was approved by the institutional review board of Keimyung University Dongsan Hospital (DSMC 2021-09-018). This study was performed based on the retrospectively reviewed database; thus informed consent for the study was waived.

Results

Study populations

A total of 64 patients were included in the study, and there were 33 (51.6%) patients taking tolvaptan during follow-up periods. The mean age was 44.6 years old, and 62.5% of patients were male. Total kidney volume was 2070.7 mL, and it was significantly higher in patients with tolvaptan (2,280.3 mL) than without tolvaptan (1,847.6 mL). Most patients were included in the rapid progressor with Mayo class 1C-E. Baseline kidney function was similar between the two groups, and the mean eGFR was 68.0 ± 28.8 mL/min/1.73 m^2. A comparison of laboratory results between patients with and without tolvaptan was demonstrated in Table 1.

Changes in kidney function according to the use of tolvaptan

During 17.8 ± 13.1 months of follow-up periods, the mean percent changes of eGFR were 89.4% compared to the base-

Table 1. Baseline characteristics between patients with and without tolvaptan treatment

Variables	Total (n = 64)	Tolvaptan (+) (n = 33)	Tolvaptan (-) (n = 31)	*P*-value
Age, year	44.6 ± 11.4	44.5 ± 9.1	44.6 ± 13.6	0.982
Male, n (%)	40 (62.5)	20 (60.6)	20 (64.5)	0.747
Body mass index, kg/m^2	24.7 ± 3.4	24.9 ± 3.3	24.6 ± 3.6	0.750
Total kidney volume, mL	2070.7 ± 865.2	2280.3 ± 726.1	1847.6 ± 953.8	0.045
Height adjusted total kidney volume, mL/m	1216.3 ± 499.4	1334.1 ± 414.2	1091.0 ± 556.2	0.051
Hemoglobin, mg/dL	13.6 ± 1.5	13.7 ± 1.5	13.5 ± 1.6	0.528
Calcium, mg/dL	9.4 ± 0.4	9.4 ± 0.4	9.4 ± 0.4	0.809
Phosphate, mg/dL	3.5 ± 0.6	3.5 ± 0.5	3.5 ± 0.7	0.960
Glucose, mg/dL	101.4 ± 16.0	102.1 ± 18.6	100.7 ± 12.9	0.721
Blood urea nitrogen, mg/dL	21.2 ± 8.1	20.2 ± 7.3	22.2 ± 8.8	0.347
Creatinine, mg/dL	1.3 ± 0.5	1.4 ± 0.5	1.3 ± 0.5	0.477
eGFR, mL/min/1.73 m^2	68.0 ± 28.8	62.9 ± 23.0	73.3 ± 33.5	0.156
Albumin, g/dL	4.6 ± 0.3	4.6 ± 0.3	4.5 ± 0.3	0.424
Uric acid, mg/dL	6.2 ± 1.7	6.2 ± 1.7	6.2 ± 1.7	0.946
ADPKD mayo class				
1B, n (%)	4 (6.3)	0 (0.0)	4 (12.9)	0.185
1C, n (%)	19 (29.7)	10 (30.3)	9 (29.0)	
1D, n (%)	28 (43.8)	15 (45.5)	13 (41.9)	
1E, n (%)	13 (20.3)	8 (24.2)	5 (16.1)	

All the continuous variables were demonstrated with mean and standard deviation. eGFR, estimated glomerular filtration; ADPKD, autosomal dominant polycystic kidney disease.

line eGFR. The mean decrease of eGFR was 6.1 mL/min/1.73 m^2. According to the use of tolvaptan, mean follow-up periods were 13.6 ± 8.3 months and 22.2 ± 15.7 months in subjects with and without tolvaptan, respectively (p = 0.007). Although the latest eGFR was lower in patients with tolvaptan (55.9 ± 24.7 mL/min/1.73 m^2, n = 33) than without tolvaptan (68.4 ± 35.1 mL/min/1.73 m^2, n = 31), there was no statistical significance (p = 0.108). The distribution of eGFR was wider in patients without tolvaptan, and each patient showed a different change in eGFR during follow-up periods (Fig. 1). Mean difference of eGFR during follow-up periods were 7.2 ± 6.7 mL/min/1.73 m^2 and 4.9 ± 9.9 mL/min/1.73 m^2 in patients with and without tolvaptan, respectively.

Among the subjects who were followed up over 1-year, changes in kidney function were comparable between the patients with tolvaptan (63.9 ± 32.7 mL/min/1.73 m^2, n = 15) and without tolvaptan (70.7 ± 38.1 mL/min/1.73 m^2, n = 21) (p = 0.580).

Effect of tolvaptan for changing in TKV

Among 33 patients taking tolvaptan, 15 patients were follow-up over 1 year. There were 10 patients with decreased TKV at 1-year follow-up CT compared to the baseline image. The mean percent change of TKV was 97.8%, and the minimum and maximum were 88.9% and 108.5%, respectively. The distribution of changes in TKV and HtTKV was different in each patient (Fig. 2).

In comparing the characteristics between patients with increased TKV and decreased TKV, there were more patients with larger baseline TKV with lower baseline eGFR, but there was no statistical significance (Table 2).

Cases with discontinuation of tolvaptan

A total of 4 patients discontinued tolvaptan in this study. Three of four patients took tolvaptan for 2 years, and they decided to stop to take because of the fatigue and uncomfortable lifestyle. All three patients were female, and they have willing to restart taking medicine within a few months. One of four patients showed severe hepatotoxicity with increasing aspartate aminotransferase (AST) and alanine aminotransferase (ALT) up to 240 mg/dL and 550 mg/dL, respectively. After 2 month-later of discontinuation of tolvaptan, liver function was finally normalized.

Discussion

We found that patients with tolvaptan treatment showed larger TKV than patients without tolvaptan. During 17.8

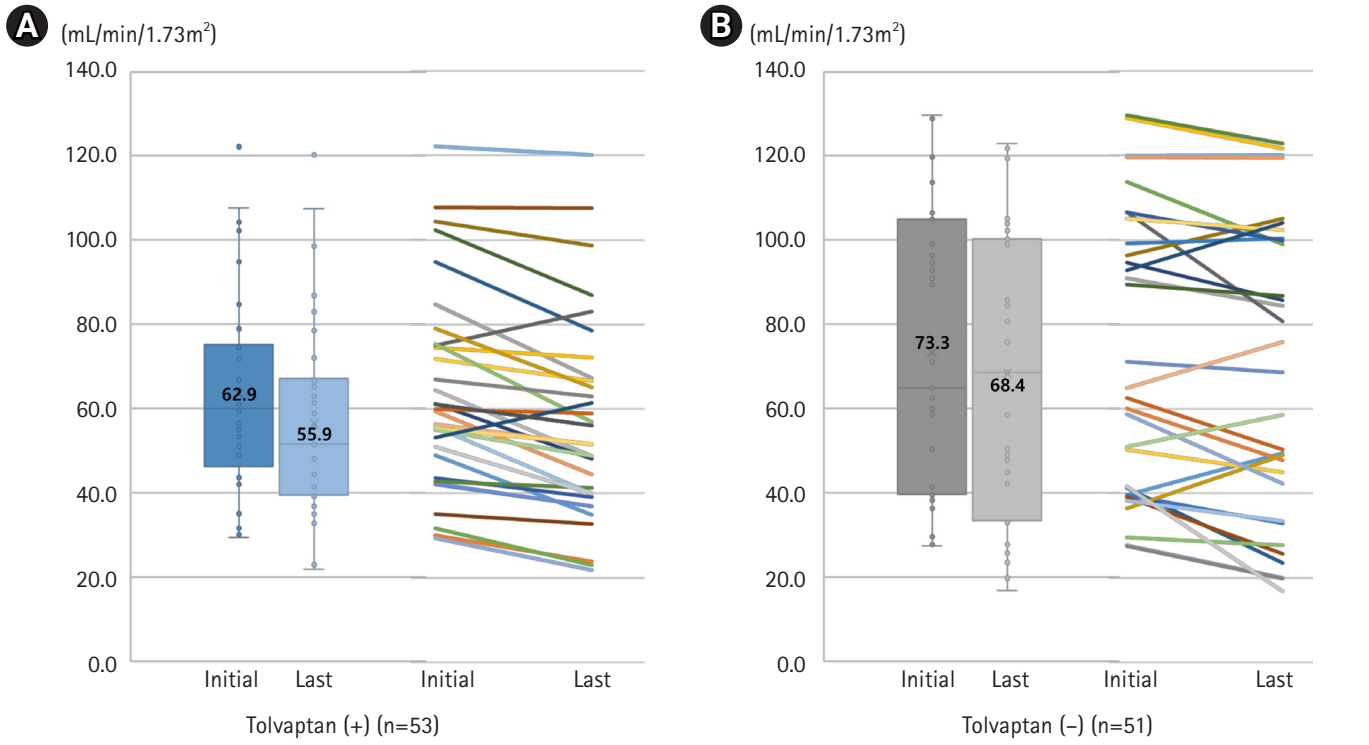

Fig. 1. Changing in eGFR between initial and latest visit in patients (A) with and (B) without tolvaptan. Mean follow-up periods were 13.6 ± 8.3 months and 22.2 ± 15.7 months in subjects with and without tolvaptan, respectively. The number in box plot was mean value of eGFR. Each line located in right side of box plot demonstrated eGFR changing in each patient. eGFR, estimated glomerular filtration rate.

months, patients experienced 6.1 mL/min/1.73 m^2 of decreased eGFR, and there was no statistical difference according to the treatment with tolvaptan. Tolvaptan has the effect of decreasing the TKV in 60% of patients taking tolvaptan over 1 year. Although there was 1 patient suffered from severe hepatotoxicity after taking tolvaptan, it was finally recovered, and he has maintained a stable kidney and liver function. The aquaretic symptom is usually regarded as a critical hurdle for starting tolvaptan, but there was no report of discontinuing the drug in this study.

Kidney volume, especially HtTKV, is regarded as a critical indicator for differentiating the prognosis of ADPKD. The Mayo classification for ADPKD was based on the HtTKV; it was divided into five classes, 1A to 1E. Patients included in classes 1C to 1E are usually expected to progress rapidly to ESKD [12]. The frequency of ESKD at 10-year was significantly increased from class 1A (2.4%) to 1E (66.9%). Based on the result of the renal survival based on the Mayo classification, patients with class 1C-1E were sub-classified as those who have rapidly progressive disease. Moreover, the efficacy of tolvaptan was also different according to the Mayo classification [13]. As a result, tolvaptan was only approved to use in patients categorized into the rapid progression in Korea. In this study, all patients with tolvaptan showed Mayo classification 1C-1E.

The rate of increase of TKV is closely associated with the Mayo classification. Patients with Mayo class 1C, 1D, and 1E were expected to increase in HtTKV by around 3, 5, and > 6% annually [14]. However, tolvaptan significantly influenced the rate of increase in HtTKV; it decreases the size by 0.1 to 0.2% according to Mayo classification 1C to 1E [15]. In this study, we found that the mean change of HtTKV was -2.7% based on the baseline HtTKV. Although there was no statistical significance, the mean change of HtTKV was the highest in patients with class 1E (-4.3%). A more extensive dataset with ADPKD patients is needed to improve the quality of statistical significance.

Baseline kidney function is another critical factor in predicting kidney outcome. The earlier start of tolvaptan in patients with preserved kidney function has been expected to delay the time of renal replacement therapy more. On the contrary, the efficacy of tolvaptan was prominent in patients with chronic kidney disease (CKD) stage 2, 3 [16]. In this regard, we usually prescribe tolvaptan to patients with eGFR ≥

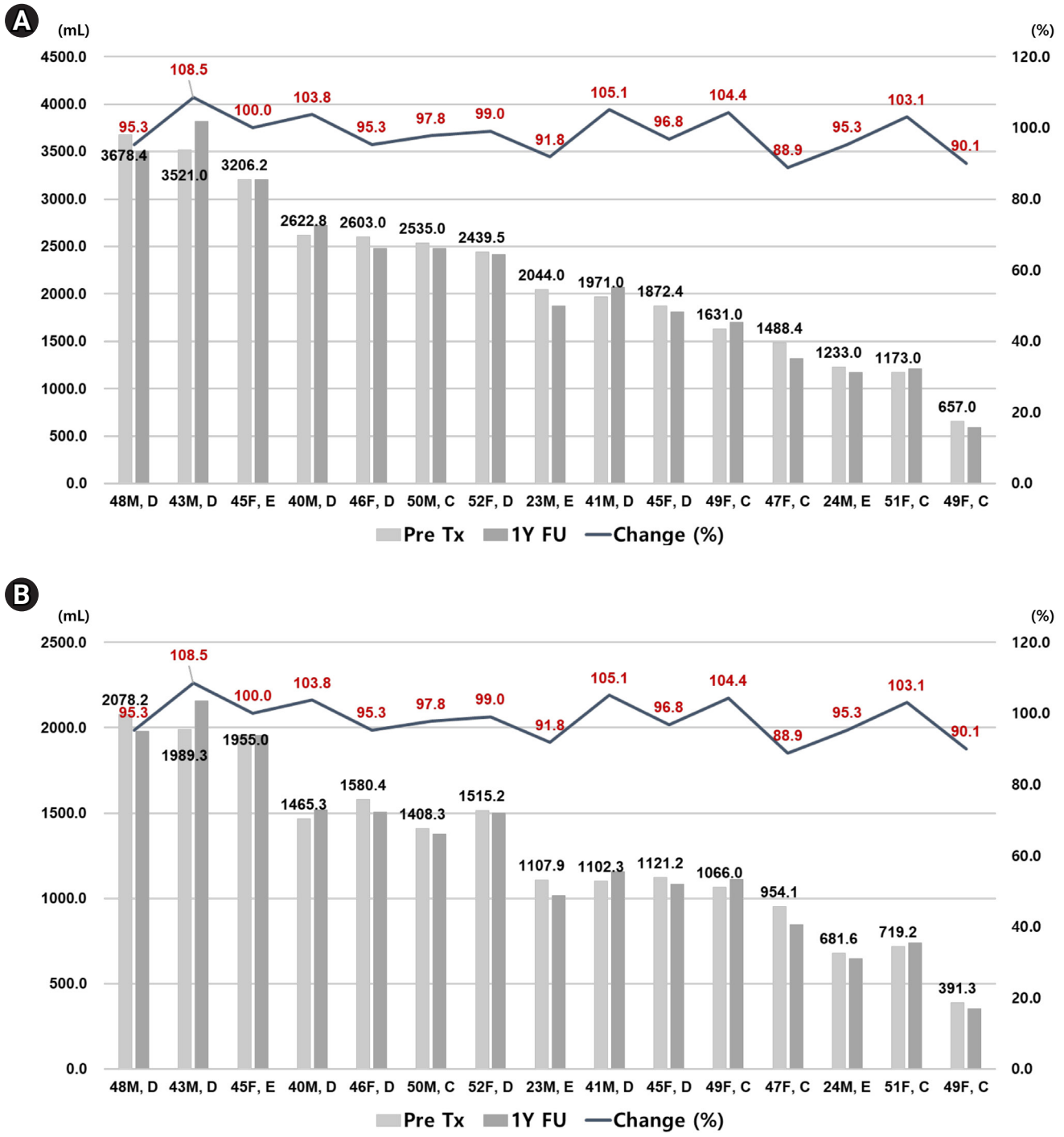

Fig. 2. Chainging in (A) total kidney volume (TKV) and (B) height adjusted total kidney volume (HtTKV) in each patient with tolvaptan treatment over 1 year. Left-sided axis and right-sided axis showed kidney volume and percent change of kidney volume, respectively. Light grey and dark grey bar represents initial and 1-year kidney volume in each patient. The number located on the top of light grey bar shows the kidney volume measured at first visit. Line above the bar graph showed percent change of kidney volume. The light grey colored bar represents the TKV (A) and HtTKV (B) at the time before initiation of tolvaptan. The dark grey colored bar represents the TKV (A) and HtTKV (B) at the time of 1-year follow-up state.

Table 2. Comparison of characteristics between two groups according to the change of total kidney volume.

Variables	Decreased TKV (n = 10)	Increased TKV (n = 5)	*P*-value
Age, year	46.5 (39.8, 49.3)	43.0 (40.5, 50.0)	0.768
Male, n (%)	4 (40.0)	3 (60.0)	0.800
Body mass index, kg/m^2	23.7 (20.2, 28.3)	26.0 (22.7, 28.8)	0.679
Total kidney volume, mL	2,242.0 (1424.3, 2753.8)	1,971.0 (1402.0, 2982.5)	0.859
Height adjusted total kidney volume, mL/m	1,264.5 (886.0, 1673.8)	1,102.0 (892.5, 1681.0)	0.768
Hemoglobin, mg/dL	13.9 (12.6, 14.9)	13.8 (12.5, 14.9)	1.000
Calcium, mg/dL	9.4 (9.0, 9.8)	9.6 (9.2, 9.7)	0.768
Phosphate, mg/dL	3.5 (3.3, 3.9)	3.4 (3.2, 4.0)	0.953
Glucose, mg/dL	95.5 (90.8, 100.8)	105.0 (98.5, 122.0)	0.040
Blood urea nitrogen, mg/dL	19.0 (14.5, 24.0)	16.0 (11.5, 20.5)	0.310
Creatinine, mg/dL	1.1 (0.9, 1.8)	1.0 (0.7, 1.6)	0.440
eGFR, mL/min/1.73 m^2	65.6 (39.5, 83.2)	94.9 (53.7, 103.3)	0.594
Albumin, g/dL	4.5 (4.3, 4.7)	4.5 (4.5, 4.9)	0.371
Uric acid, mg/dL	5.9 (4.4, 7.3)	4.6 (3.8, 6.9)	0.440
ADPKD mayo class			
1C, n (%)	3 (30)	2 (40)	0.185
1D, n (%)	4 (30)	3 (60)	
1E, n (%)	3 (30)	0 (0)	
Final creatinine, mg/dL	1.2 (0.9, 2.4)	1.2 (0.7, 2.0)	0.594
Final eGFR, mL/min/1.73 m^2	55.4 (31.0, 86.8)	73.4 (42.1, 94.7)	0.679
1-year total kidney volume, mL	2,146.6 (1285.6, 2661.9)	2,072.0 (1455.5, 3270.8)	0.768
1-year height adjusted total kidney volume, mL/m	1,231.4 (798.2, 1618.3)	1,158.8 (926.9, 1839.3)	0.594
Tolvaptan dose, mg/day	90 (90, 120)	90 (90, 112.5)	0.679
Follow-up periods, months	23.0 (15.8, 24.3)	24.0 (17.5, 27.0)	0.513

All the continuous variables were demonstrated with median and interquartile range. TKV, total kidney volume; eGFR, estimated glomerular filtration rate; ADPKD, autosomal dominant kidney disease.

30 and < 90 mL/min/1.73 m^2. In this study, most patients with tolvaptan showed stage 3 CKD. The mean percent change of eGFR incrementally increased from 5.0%, 9.7%, to 13.3% in CKD stages 1, 2, to 3, respectively. Decreases in eGFR was more prominent in subjects with tolvaptan (7.9%, 11.3%, 13.5% in CKD stages 1, 2, and 3) than without tolvaptan (3.9%, 15.2%, 30.2% in CKD stages 1, 2, and 3) irrespective of stage CKD. However, after adjusting the time-interval, annual decreases in eGFR were smaller in subjects with tolvaptan (7.9%, 13.6%, 15.4% in CKD stages 1, 2, and 3) than without tolvaptan (8.2%, 11.6%, 29.2% in CKD stages 1, 2, and 3). Because of the small number of patients included in the study and short-term follow-up duration, it was hard to evaluate the significance of tolvaptan on kidney function. In addition, the absolute latest eGFR was lower in subjects with tolvaptan even though there was no statistical significance. Considering the pharmacological effect of tolvaptan, it could be due to the effect of tolvaptan on suppressing glomerular hyperfiltration. Therefore, to compare the exact effect of tolvaptan on kidney function, it needs to have a wash-out period before the evaluation.

Aquaretic symptom such as polyuria, nocturia, thirst, and polydipsia is a representative side effects of tolvaptan. These symptoms were a significant reason to discontinue the drug in the TEMPO 3:4 clinical study. However, with repetitive education and periods of adjustment, the adherence to the medication was improved with a decreased rate of discontinuation in the TEMPO 4:4 clinical study. Most patients included in this study suffered from aquaretic symptoms, but no one discontinued the drug due to these symptoms. Therefore, we also suggest that assertive education and counseling about these symptoms need to be performed before starting the medication.

Tolvaptan has been associated with idiosyncratic and reversible elevations of blood AST and ALT with infrequent cases of concomitant elevations in total bilirubin [17]. The incidence was low, and most patients completely recovered from hepatotoxicity in previously reported clinical trials [6,8,9]. Nevertheless, one case showed severe injury requiring liver transplantation in Japan [18]. Among 33 patients with

tolvaptan, one patient permanently discontinued the medication due to hepatotoxicity in this study. Considering the patient's clinical characteristics without any risk factors for hepatotoxicity such as hepatitis B, hepatitis C, and fatty liver disease, it was hard to expect this event. Therefore, regular follow-up of liver function test is strongly recommended in patients taking the drug.

In this study, there were 27 patients with ADPKD mayo class 1C-1E among the group without tolvaptan. Following the clinical management flow, for all subjects who are eligible to start tolvaptan, we assertive recommend taking tolvaptan. Nevertheless, there were several concerns not to start tolvaptan. First, the use of tolvaptan has been permitted for only subjects with eGFR $\geq$ 30 and $<$ 90 mL/min/1.73 m^2. Therefore, more than half of the subjects included in the group without tolvaptan could not take tolvaptan irrespective of TKV. Second, aquaretic symptoms make one hesitate to take tolvaptan, especially for subjects who have hurdles to drinking enough water and going to the bathroom frequently. In this regard, the effort to educate with practical application and extend the criteria based on the political policy would be warranted.

Unfortunately, there is still no suitable way to cure ADPKD. The chance to use tolvaptan is a meaningful challenge in patients with ADPKD, even with lots of hurdles to experience during the treatment periods. This study could represent descriptive characteristics of patients with and without tolvaptan. Also, we provided the result of the effect of tolvaptan on change of TKV and kidney function with additive information on side effects. However, there were several limitations to be discussed in this study. It was a retrospective single-center study. The number of included patients was too small to evaluate the statistical significance. In addition, we could not figure out the clinical outcome with a relatively short-term follow-up period. It requires a prospective study with a large number of participants with more extended follow-up periods.

Tolvaptan could be the only option to reduce the rate of increase of TKV and preserve kidney function in ADPKD. However, to expect better outcomes, more attention and effort to excavate suitable patients based on a proper monitoring process.

Conflict of interest

All authors declare no conflicts-of-interest related to this article.

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Predictive Factors for Sexual Behaviors among High School Students in South Korea: a Nationwide Analysis

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We aimed to investigate the associated factors for sexual intercourse among high school students using data from the Korea Youth Risk Behavior Web-based Survey (KYRBWS) conducted between August and October 2020. This study was based on the 16th KYRBWS, conducted by the Korea Centers for Disease Control and Prevention. A total of 25,592 high school students were included. The questionnaire included topics such as sexual behavior, alcohol consumption, smoking, drug use, mental health, physical activity, weight management, and health equity, to determine the factors influencing sexual behavior. In male students, the associated factors for sexual behavior included smoking, alcohol consumption, history of drug use, short sleep time, high physical activity, feelings of sadness, and good economic status. In female students, the associated factors for sexual behavior included smoking, alcohol consumption, low body mass index, high physical activity, feelings of sadness, suicidal thoughts, and poor economic status. In both male and female high school students, smoking and alcohol consumption were strong associated factors for sexual behavior. Good economic status was associated with sexual behavior in males, while a poor economic condition was associated with sexual behavior in females. These factors should be considered in the sexual education of high school students.

Keywords: Associated factors, Coitus, High school students, Sexual behavior, Teenagers

Introduction

Teenage pregnancies are on the rise worldwide and result in several medical problems [1,2]. Teenage pregnancy is highly risky and likely to be accompanied by anemia, premature birth, low birth weight, and gestational hypertension. Teenage pregnancies increase medical and social costs, and they are a huge social problem.

Recently, the coitus experience of high school students in South Korea is increasing. According to the Korea Youth Risk Behavior Web-based Survey (KYRBWS), 6.2% of high school students has coitus experience in 2014. This percentage increased to 7.3% in 2020. Consequently, sexual disease transmission rates among high school students have also increased.

In a survey of single mothers, the percentage of single teenage mothers increased from 49.9% in 1999 to 53.3% in 2001 in South Korea. Among single teenage mothers, those aged 15 years or younger accounted for 6% in 1999, 8.7% in 2000, and 8.3% in 2001. In 2005, the sexually transmitted infection rate among runaway teenagers was 22.3% [3]. Teenage pregnancy is an important public health issue as it increases the economic burden and lowers educational attainment [4].

It is crucial to study the association of sexual behaviors in high school students to prevent teenage pregnancies and associated disease - anemia, prema-

ture birth, low birth weight, and gestational hypertension, etc.

So, we investigate the associated factors for sexual behaviors in high school students using data from the 16th KYRBWS, which is conducted annually to assess the prevalence of risky health behaviors among middle and high school students in South Korea.

Materials and Methods

This study was performed according to the ethical standards of the Declaration of Helsinki and was approved by the Keimyung University Dongsan Hospital Institutional Review Board (IRB No. 2021-07-005).

Data collection was based on the 16th KYRBWS, which was developed and conducted by the Korea Centers for Disease Control and Prevention. It was conducted nationwide between August and October 2020. The 16th KYRBWS is a web-based survey using a complex sampling design [5]. It consisted of 15 areas, including smoking, alcohol consumption, physical activity, diet, weight management, mental health, safety cognition, oral health, self-hygiene, sexual behavior, atopy and asthma, drug, internet addiction, health equity, and violence. There were 103 survey questions, and the participants entered data anonymously online using a computer. All surveys were conducted through questionnaires, and questions about academic and economic status were also asked about the degree to which they thought. The 16th KYRBWS included 400 schools, and there were 57,925 students in total, among whom 54,948 middle school and high school students completed the survey. The participation rate was 94.9%. The 16th KYRBWS was stratified into 44 regions. There were 117 strata in the survey. This study focused specifically on high school students. The total number of high school students was 25,592, with 13,325 male and 12,267 female students. The questionnaire was about sexual behavior, alcohol consumption, smoking, drug intake, mental health, physical activity, weight management, health equity, and other topics.

All statistical analyses were performed using a complex sampling design. The base characteristics of the participants were evaluated using the t-test or chi-square test. Logistic regression analysis was used to confirm the relationship between sexual experience and other factors. Statistical analyses were performed using SPSS (version 21.0; SPSS Inc., Chicago, IL, USA).

Results

Among the 25,592 students included in this survey. The number of students who had sexual intercourse was 1,904, and the weighted percentage was 7.3% (males: 9.2%, females: 5.1%). The students with no sexual experience group had a lower body mass index (BMI) and lower physical activity. Sleep time was longer in the sexual experience group. Students with poor health and happiness perceptions were associated with sexual experience. Feelings of sadness, suicidal thoughts, alcohol consumption, smoking, and drug use were associated with experience. Sex education was not associated with sexual experience (Table 1).

The association between academic performance and sexual experience exhibited a J-curve. Low economic conditions were associated with sexual experience among female students. A J-curve association was determined between economic conditions and sexual experience in male students (Fig. 1).

In our study, the factors in the logistic model were selected using the backward method. Other factors were insignificant in the logistic regression model. Smoking was the most common associated factor for sexual experience among male students (odds ratio [OR]: 4.041, 95% confidence interval [CI]: 3.438–4.751). Short sleep times, high physical activity, feelings of sadness, alcohol consumption, drug use, and good economic status were other identified associated factors in male students (Table 2).

The most common associated factor for increased sexual experience among female students was smoking (OR: 6.525, 95% CI: 5.102-8.345). Low BMI, high physical activity, feelings of sadness, suicidal thoughts, alcohol consumption, and low economic status were other identified associated factors in female students (Table 3).

Discussion

This is a study to determine associated factors for sexual intercourse in high school students in South Korea. In our study, BMI was associated with sexual experience. Males with a normal weight were most likely to engage in coitus. Meanwhile, females with a lower BMI were more likely to engage in coitus. BMI was also a significant associated factor for female students based on the logistic regression model. This tendency was also observed in another study [6]. This was attributed to the sensitivity of women to weight and courtship behavior [7]. In addition, female students with boyfriends were more likely to engage in coitus [8,9].

Lower sleep time was another associated factor with increased sexual experience seen in male students. Many studies have shown that a lower sleep time negatively impacts teenagers' health. Short sleep duration influences depression, aca-

Table 1. Participants' characteristics

	Non-experience for coitus (n = 23,688)	Experience for coitus (n = 1,904)	*p*-value
Sex			0.000
Male	12,078 (50.9%)	1,252 (65.7%)	
Female	11,610 (49.1%)	652 (34.3%)	
BMI (kg/m^2)	22.02 (0.047)	22.28 (0.103)	0.008
Sleep time (hours)	5.47 (0.018)	5.35 (0.037)	0.001
Physical activity for more than 60 min in the last week (daily frequency)	1.62 (0.030)	2.36 (0.071)	0.000
Subjective health perception			0.000
Very healthy	6,263 (26.5%)	632 (32.9%)	
Healthy	9,842 (41.5%)	673 (35.6%)	
Ordinary	5,431 (22.9%)	382 (20.0%)	
Unhealthy	2,035 (8.6%)	186 (9.8%)	
Very unhealthy	117 (0.5%)	31 (1.7%)	
Subjective body perception			0.001
Very skinny	979 (4.2%)	90 (4.7%)	
Skinny	4,675 (19.7%)	412 (21.6%)	
Ordinary	8,367 (35.4%)	708 (37.1%)	
Fat	7,894 (33.3%)	563 (29.7%)	
Very fat	1,773 (7.4%)	131 (6.9%)	
Subjective happiness perception			0.000
Very happy	5,640 (23.8%)	459 (24.0%)	
Little happy	8,901 (37.6%)	601 (31.3%)	
Ordinary	6,951 (29.4%)	533 (28.2%)	
Little unhappy	1,858 (7.8%)	230 (12.3%)	
Very unhappy	338 (1.4%)	81 (4.2%)	
Feelings of sadness and hopelessness in the last 12 months			0.000
None	17,514 (74.0%)	1,075 (56.1%)	
Yes	6,174 (26.0%)	829 (43.9%)	
Suicidal thoughts in the last 12 months			0.000
None	21,176 (89.4%)	1,488 (78.0%)	
Yes	2,512 (10.6%)	416 (22.0%)	
Experience of alcohol drinking			0.000
None	13,635 (57.6%)	317 (16.7%)	
Yes	10,053 (42.4%)	1,587 (83.3%)	
Experience of smoking			0.000
None	20,752 (87.6%)	828 (43.5%)	
Yes	2,936 (12.4%)	1,076 (56.5%)	
Experience of habitual drug abuse except for therapeutic purposes			0.000
None	23,516 (99.3%)	1,843 (96.8%)	
Yes	172 (0.7%)	61 (3.2%)	
Experience of education for sexual behavior in the last 12 months			0.867
None	7,979 (33.8%)	615 (32.3%)	
Yes	15,709 (66.2%)	1,289 (67.7%)	
Academic performance			0.000
High	2,001 (8.5%)	200 (10.5%)	
Medium-high	5,117 (21.6%)	294 (15.4%)	
Medium	7,525 (31.8%)	500 (26.1%)	
Medium-low	6,329 (26.7%)	490 (25.7%)	
Low	2,716 (11.5%)	420 (22.3%)	
Economic condition			0.000
High	1,827 (7.8%)	251 (13.2%)	
Medium-high	5,999 (25.4%)	469 (24.5%)	
Medium	12,144 (51.2%)	767 (40.4%)	
Medium-low	3,045 (12.8%)	299 (15.8%)	
Low	673 (2.8%)	118 (6.1%)	

Data are mean ± standard error or an unweighted number and weighted participants (%), *p*-values are calculated by t-test or chi-square test using a complex sampling design. SD, standard deviation; BMI, body mass index.

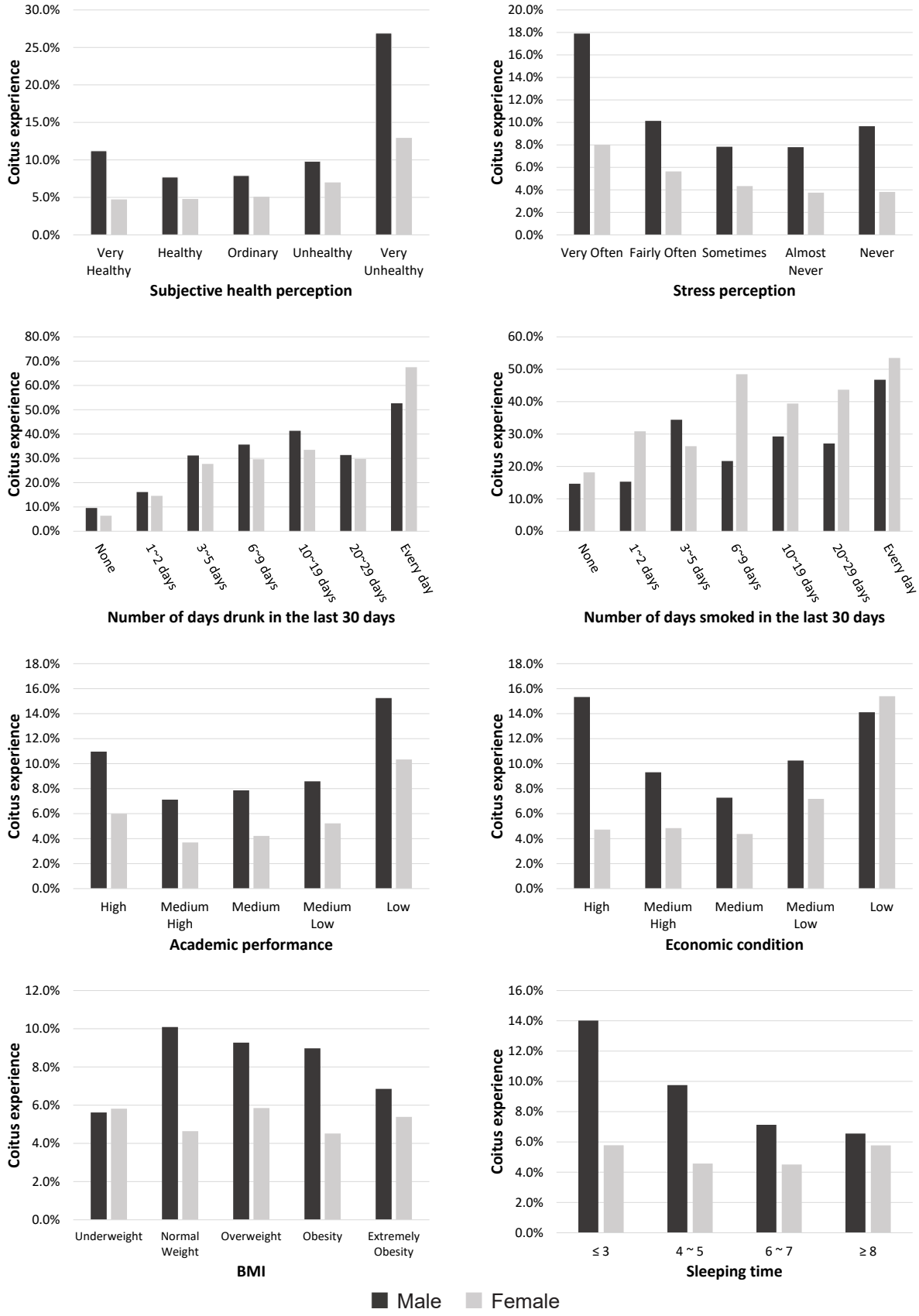

Fig. 1. This figure shows the difference in the percentages between men and women for each variable. BMI, body mass index.

Table 2. Final model of the logistic regression analysis of coitus experience in male students

	OR	95% Confidence interval	*p*-value
Sleep time (hr)	0.903	0.853–0.956	0.001
Physical activity for more than 60 min in the last week (daily frequency)	1.108	1.070–1.148	0.000
Feelings of sadness and hopelessness in the last 12 months	1.658	1.401–1.961	0.000
Experience of alcohol drinking	2.613	2.134–3.200	0.000
Experience of smoking	4.041	3.438–4.751	0.000
Experience of habitual drug abuse except for therapeutic purposes	2.318	1.275–4.213	0.006
Economic condition	1.147	1.037–1.269	0.008

Data are analysed by logistic regression model by backward method. OR, odds ratio.

Table 3. Final model of the logistic regression analysis of coitus experience in female students

	OR	95% Confidence interval	*p*-value
BMI (kg/m^2)	0.961	0.930–0.993	0.019
Physical activity for more than 60 min in the last week (daily frequency)	1.086	1.031–1.145	0.002
Feelings of sadness and hopelessness in the last 12 months	1.457	1.178–1.802	0.001
Suicidal thoughts in the last 12 months	1.562	1.239–1.969	0.000
Experience of alcohol drinking	5.044	3.666–6.939	0.000
Experience of smoking	6.525	5.102–8.345	0.000
Economic condition	0.836	0.745–0.937	0.002

Data are analysed by logistic regression model by backward method. OR, odds ratio; BMI, body mass index.

demic failure, behavioral issues, and aggressive behavior [10-13]. And low academic status and aggressive behavior are associated with coitus experience [6]. So it is possible that this association may have reduced sleep time.

Physical activity was a significant associated factor for sexual experience based on the logistic regression model (OR: 1.108 in males, 1.086 in females). Several studies have shown that exercise increases sexual desire [14,15]. However, only a few studies focused on adolescents. The relevant mechanisms behind this observation are likely to be similar between adolescents and adults. However, further studies are needed to confirm this hypothesis.

Sadness was an associated factor influencing sexual experience in both male and female students. Other studies have reported that depression is associated with sexual experience [16,17]. But suicidal thoughts were not associated factor with sexual experience for male students, unlike for female students. Vasilenko [17] reported that depression affected the sexual experience of females more than that of males. This difference could influence the results of our study.

In our study, alcohol, smoking, and drugs were found to increase the association of sexual intercourse. Abuse of these substances is known to be associated with antisocial tendencies in adolescents [18,19]. Antisocial tendencies are known to be associated with an increase in teenage sexual experiences [20]. These relationships could influence our result. Therefore, adolescents with these associated factors are predicted to have a high association of teenage pregnancy and sexually transmitted diseases.

In our study, sex education does not appear to have any effect on the sexual experience of high school students. But, previous studies have found that sex education suppresses sexual experience [21]. These differences may be due to cultural differences or differences in sex education. According to our study, the current sex education in South Korea is presumed to be ineffective in suppressing the sexual experience of high school students, and a deep consideration is required for the current direction of sex education.

Interestingly, high economic status in boys and low economic status in girls were found to have association with sexual experience. In the case of female students, there is a previous study stating that a low socioeconomic status increases the association of teenage pregnancy [22]. However, according to the results of our study, in the case of male students, the association of sexual experience was high not only in those with low economic status but also in those with high economic status (Fig. 1). Therefore, it should be recognized that, unlike female students, the association of sexual experience may be high for male students with high economic status.

A poor health status was associated with sexual experience.

Teenage sexual intercourse can cause several medical diseases - anemia, premature birth, low birth weight, and gestational hypertension, etc [1,2]. But depression, tobacco, and alcohol also associated with health status and sexual experience. Therefore, these confounding factors should be considered to interpret this result.

This study has some limitations. As our study had a cross-sectional design, causality was not established. Therefore, only associations were confirmed by this study. And the information of this study was collected through self-reporting. This can lead to reporting errors and biases. However, the KYRBWS contained numerous samples and was representative of South Korean high school students. The results of our study can be used as a primer to understand the sexual behaviors of adolescents. Moreover, this will help address problems in adolescent sexual behavior.

Conflict of interest

The authors declare no conflicts-of-interest related to this article.

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COVID-19 초기 유행 환자에서 회복후 스트레스, 우울, 불안, 낙인 정도

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Post-recovery Stress, Anxiety, Depression and Stigma in Early COVID-19 Pandemic Patients

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COVID-19, the first pandemic experienced in the current generation, results various physical and mental stress and stigma. Stress (Korean version of the stress perception scale), anxiety and depression (hospital anxiety depression scale) and stigma was evaluated from the 20 patients recovered from the initial pandemic period, during February to March 2020. The average age was 51.3 (± 8.26) years old. The average hospital and therapeutic living center admission period was 26.8 (± 5.24) days, and the average period after discharge was 19.4 (± 4.33) days. The severity of the symptoms was 3 (15%) asymptomatic, 13 (65%) mild, and 4 (20%) severe (pneumonia). The average score on the perceive stress scale was 19.6 (± 6.52) and 65% (13/20) perceived moderate or severe stress status. The average score for hospital anxiety depression was 15.0 (± 5.45) points, the average score for anxiety was 6.6 ± 3.25 points, and the average score for depression was 8.4 (± 3.86). The average stigma score was 79.6 (± 16.16) points. Post-recovery patients from COVID-19 was perceived significant stress, experiencing anxiety, depression, and stigma in early pandemic period.

Keywords: Anxiety, COVID-19, Depression, Stigma, Stress

Introduction

코로나바이러스감염증-19(2019 Novel Coronavirus Diseases, COVID-19) 유행은 2020년 2월에 시작되어 우리나라에서는 2022년 현재 1,800만/24,000명의 확진자/사망자가 발생하고 있다[1]. COVID-19는 현 세대가 처음 겪는 특이하고 드문 상황으로 감염에서 회복된 사람들에게서도 피로, 무력감과 같은 신체적 증상과 스트레스, 불안 및 우울과 같은 심리 증상을 호소하고 있다.

다른 사람에게 전파시킬 수 있다는 감염병의 특성 때문에 환자들은 다양한 심리적 스트레스와 낙인 현상을 겪게 된다. 특히 2020년 감염 유행의 초기에는 방역수칙을 어기고 대량 환자를 발생하게 한 어느 종교단체가 여론의 비난을 받고 낙인 현상이 발생하였다. 환자가 발생한 지역을 봉쇄하자는 일부 정치인의 지역차별성 발언으로 지역주민들이 이동의 제한을 받게 되고, 감염환자들은 질병으로 인한 신체적인 증상과 격리 스트레스뿐만 아니라 질병을 전파하는 숙주가 되었다는 집단적인 스트레스를 받게 되었다[2].

감염병유행이 어느 정도 진행되면 공동체 구성원들 간에 적응하고 협조하는 현상이 나타나지만, 유행의 초기에는 방역에 대한 무력감과 감염에 대한 집단적 공포로

감염자를 낙인 찍고 비난하는 현상이 나타나고 감염자들이 심리적 스트레스와 우울, 불안, 죄책감을 가질 수 있다. 이에 초기 COVID-19 유행 시기인 2020년 2~3월에 COVID-19에서 회복된 사람들에게서 우울, 불안, 낙인 스트레스 정도를 평가해 보고자 하였다.

Materials and methods

COVID-19 초기 유행 시기에 입원 치료하고 퇴원한 환자들의 심리적 스트레스를 평가하기 위하여, 기관윤리심의위원회의 승인을 받았다(승인번호: 2020-03-114). 2020년 2~3월 대구 1개 병원에서 입원치료 후 퇴원한 환자들 중 외래를 추적 방문한 20명을 대상으로 연구의 취지를 설명한 후 스트레스 자각, 불안, 우울, 낙인 정도를 평가하였다.

연구 참가자의 기초적인 정보를 수집하기 위하여 성별, 연령, 증상의 중증도(무증상, 경증, 폐렴), 병원이나 생활치료센터 입원기간, 퇴원 후 경과일자 등 총 6개 항목에 대해 자료를 수집하였다.

스트레스 평가는 주관적으로 지각하는 스트레스 정도를 평가하는 한글판 스트레스 자각척도(perceived stress scale)[3]를 사용하였다. 이 검사표는 10개 항목으로 구성되며, 각문항에 대한 측정은 리커트식 5점 척도로 피검자가 전혀 없음(0점), 거의 없음(1점), 때때로 있음(2점), 자주 있음(3점), 매우 자주 있음(4점)에 표시하도록 하였다.

불안과 우울은 병원 불안우울척도(hospital anxiety depression scale)[4]를 사용하여 평가하였다. 이 검사는 14개 항목으로 구성되며, 측정은 리커트식 4점 척도로 전혀 아니다(1점), 아니다(2점), 그렇다(3점), 매우 그렇다(4점)에 표시하도록 하였다.

낙인 정도는 Bunn 등[5]의 AIDS 환자 낙인 척도(stigma scale)를 COVID-19에 맞추어 수정하여 사용하였다. 이 검사법은 총 32개 항목으로 구성되며 128점 만점으로 평가한다. 하부요인으로는 낙인 정도(enacted stigma), 노출 부담(disclosure concerns), 부정적 자기 이미지(negative self-image), 타인의 태도에 대한 관심(concern with public attitudes)를 평가하는 4개 영역으로 평가한다. 각 항목은 리커트식 4점 척도로 매우 아니다(1점), 아니다(2점), 그렇다(3점), 매우 그렇다(4점)에 표시하도록 하였다.

Results

1) 인구사회학적 특성

조사 대상자의 연령은 34세에서 66세까지의 남녀 각각 7명과 13명이었으며, 평균 연령은 51.3(± 8.26)세였다. 평균 병원 입원과 생활치료센터 입소 기간은 26.8 ± 5.24일이였으며, 퇴원 후 경과 기간은 19.4 ± 4.33일이었다. 증상의 중증도는 무증상이 3명(15%), 경증이 13명(65%), 폐렴(중증)이 4명(20%)이었다(Table 1).

2) 스트레스 지각 척도 점수[3]

스트레스 지각 척도 평균점수는 19.6 ± 6.52점으로 심한 스트레스 정도였다. 스트레스 지각 정도가 정상(0~13점)이 4명(20%), 약한 정도의 스트레스 지각 정도(14~16점)가 3명(15%), 중등도의 스트레스 지각 정도(17~19점)가 5명(25%), 심각한 정도의 스트레스 지각 정도(19점 이상)가 8명(40%)로, 13/20명(65%)에서 중등도 이상의 스트레스 지각 상태였다(Table 2).

3) 우울 불안 점수[4]

병원 불안 우울 평균점수는 15.0 ± 5.45점이었다. 불안 하위 영역 평균점수가 6.6 ± 3.25점이었고, 불안장애를 의심할 수 있는 경계 점수(8점)이상이 45%였다. 우울 하위 영역 평균점수가 8.4 ± 3.86점이었으며, 우울 장애를 의심할 수 있는 경계 점수(8점)이상이 70%였다(Table 3).

Table 1. Demographic data (n = 20)

Age (mean ± SD), yrs	51.3 ± 8.26
Sex (M/F)	20 (7/13)
Hospital admission (mean ± SD), days	26.8 ± 5.24
After discharge (mean ± SD), days	19.4 ± 4.33
Symptom severity, n (%)	
No symptomatic	3 (15%)
Mild symptomatic	13 (65%)
Severe (pneumonia)	4 (20%)

Table 2. Perceived stress scale (n = 20) [3]

Total (mean ± SD)	19.6 ± 6.52
Normal (0-13)	4 (20%)
Mild (14-16)	3 (15%)
Moderate (17-18)	5 (25%)
Severe (19-40)	8 (40%)

Table 3. Hospital anxiety-depression scale (n = 20) [4]

Total (mean ± SD)	15.4 ± 5.45
Anxiety(mean ± SD)	6.6 ± 3.25
Normal	11 (55%)
Borderline	5 (25%)
Abnormal	4 (20%)
Depression(mean ± SD)	8.4 ± 3.86
Normal	6 (30%)
Borderline	7 (35%)
Abnormal	7 (35%)

Table 4. Stigma scale [5]

Total (mean ± SD)	79.6 ± 16.16
Enacted stigma	20.5 ± 4.21
Disclosure concerns	20.2 ± 3.82
Negative self-image	17.9 ± 3.53
Concern with public attitudes	20.9 ± 4.38

4) 낙인 척도[5]

낙인 평균점수는 79.6±16.16점이었다. 4개의 하위 척도 평균점수는 낙인 정도(enacted stigma) 20.5 ± 4.21점, 노출 부담(disclosure concerns) 20.2±3.82점, 부정적 자기 이미지(negative self-image) 17.9 ± 3.53점, 타인의 태도에 대한 관심(concern with public attitudes) 20.9 ± 4.38점이었다(Table 4).

Discussion

COVID-19 유행 초기에 치료 후 회복한 사람들을 대상으로 우울, 불안, 낙인 스트레스 정도를 평가한 결과 상당한 스트레스 자각과 불안, 우울, 낙인 상태를 보였다.

스트레스 지각 척도 평균점수 19.6±6.52점으로 심한 스트레스 정도였으며, 65%에서 중등도 이상의 스트레스 지각상태임을 보였다. 스트레스는 비정상적인 상황에 대한 정상적인 생리적 반응이며 우리 삶의 일부분이지만 지나친 스트레스는 심혈관 질환, 정신질환의 위험요인이 될 수 있다. 미지의 질병의 경과를 말수 없다는 점, 타인에게 감염의 우려, 감염자에 대한 비판여론이 완치판정 이후에도 환자에게 스트레스로 작용하고 있음을 알 수 있었다.

병원 불안 우울 평균 점수는 15.4 ± 5.45점이었으며, 45%에서 불안장애, 70%에서 우울장애를 의심할 수 있다. 불안은 실제적인 위협에 대한 반응인 정상적인 두려움과 달리, 불확실한 미지의 위협에 대한 반응이다. 불안은 위험하거나 불행한 사건이 일어날 가능성이 있다고 믿고 기대할 때 나타나며 스트레스상황에서 무력감, 낙담, 슬픔의 상태로 다양한 신체적, 심리적 증상으로 나타날 수 있다. COVID-19 감염 초기에는 급성외상으로 작용하여 급성스트레스장애 현상을 의심할 필요가 있을 것이다.

스트레스, 불안, 우울 반응은 개인에 따라 다양한 신체적, 심리적, 정서적 및 행동적 방식으로 나타날 수 있다. COVID19에 감염된 사람들은 죽음의 위협을 느끼고 정신적으로도 큰 충격을 받을 수 있다. 회복한 후에도 재발을 의심할 수 있는 신체적 증상을 확인하여 빠르게 진단하고, 정신과적인 후유증을 확인하여 정신건강 악화로 인한 피해를 줄일 수 있다. 본 연구의 결과로 감염병 유행의 초기 급성 스트레스기에는 감염에 대한 집단적 공포와 무기력감으로 감염자에게 낙인을 찍고 비난하는 현상이 나타나서 감염에서 회복된 후에도 상당한 스트레스와 불안, 우울을 경험함을 알 수 있었고, 반복되는 유행으로 많은 감염자가 발생하고 적응하는 말기단계에서는 심리적 스트레스가 줄어드는 것을 확인할 수 있었다.

낙인 평균 점수는 79.6 ± 16.16점이었으며, 4개의 하위 척도는 타인의 태도에 대한 우려, 낙인 정도, 노출 부담, 부정적 자기 이미지 순서로 높았다. 낙인(stigma, labeling)은 '마음속에 완전히 정상적인 인간에서 보잘것없는 인간으로 평가절하하여 끌어내리는 것'으로 유행 초기에 환자들이 감염질환에 대한 스트레스로 우울과 불안뿐만 아니라 낙인으로 인한 죄책감을 느끼게 된다는 것을 보여준다. 갑자기 COVID-19 대량환자가 발생한 대유행(outbreak)시기에 환자들은 자신이 감염되어 주위사람들에게 부담이 된다는 부정적인 자기개념을 형성하게 된다. 낙인은 주위와의 교류를 어렵게 하고, 불안과 우울같은 부정적 정서와 질병치료를 악화시킬 수 있다[6].

현재 세대가 처음 경험하는 2020년의 감염병 대유행(pandemic)은 많은 인적, 경제적 피해를 주고 있으며 다양한 변이를 거쳐 2년만에 유행의 규모는 줄어들고 있다. 유행의 초기에는 미지의 질병에 대한 공포와 낙인(labeling)으로 환자들에 대한 심리적 스트레스가 크고 우울, 불안, 죄책감을 느낄 수 있다는 것을 알 수 있다.

본 연구의 제한점으로는, 첫째, 초기에 환자들의 연구 설문에 대한 거부감으로 많은 수의 환자를 조사하지 못하였다는 점을 들 수 있다. 초기에는 낙인현상으로 COVID-19 환자임을 밝히기를 두려워하는 분위기가 있었다. 둘째, 질병의 중증도나 치료기관(병원, 생활치료센터, 재택치료)별로 구분하여 환자 사례를 조사하지 못하였다. 셋째, COVID-19의 유행이 반복되면서 스트레스가 줄어들 때 심리적 평가를 추적하지 못한 것이다.

갑자기 발생한 COVID-19 유행 초기에 치료 후 회복한 사람들에게서 상당한 스트레스 자각과 불안, 우울감, 낙인 상태를 확인할 수 있었다. 질병에 대한 스트레스가 줄어든 유행의 말기에 감염된 환자를 대상으로 동일한 스트레스, 불안, 우울, 낙인 정도를 조사하여 비교하는 추가 연구가 필요할 것이다.

Conflict of interest

The author declares no conflicts-of-interest related to this article.

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Ultrasound Guided Infraorbital Nerve Radiofrequency Thermocoagulation in Patients with Trigeminal Neuralgia

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Trigeminal neuralgia (TN) is a sudden intensive orofacial pain disorder characterized by a unilateral recurrent paroxysmal lancinating pain occurring in the area of trigeminal nerve distribution. Diagnosis is made with characteristic clinical presentations and requires brain magnetic resonance imaging to rule out intracranial tumor or multiple sclerosis which potentially causes secondary TN. Among the various interventional managements, the conventional radiofrequency thermocoagulation (RFT) of Gasserian ganglion results in the highest rate of complete pain relief. We report two cases who presented severe facial pain due to intractable TN of V2 division. For pain relief, Gasserian ganglion RFT was planned. However, both patients could not tolerate the neck extension and chin-up position. Therefore, ultrasound guided infraorbital nerve RFT which does not require such position was performed successfully. When the patients came to the pain clinic 2 weeks later, the numerical rating scale for TN was 2/10 with mild hypoesthesia of V2 division. Infraorbital nerve RFT is an alternative option in patients who is unable to tolerate the ganglion RFT.

Keywords: Radio waves, Trigeminal nerve, Trigeminal neuralgia, Ultrasonography

Introduction

Trigeminal neuralgia (TN) is the most commonly diagnosed form of orofacial pain which usually occurs in 50 to 70 years of age and more frequent in females than in males [1]. TN is characterized by brief episodes of intensive pain, lancinating in nature, occurring recurrently in the area of trigeminal nerve distribution. Pain is triggered by innocuous cutaneous sensations such as chewing, face washing, teeth brushing and talking. Diagnosis is made with characteristic clinical presentations described above and requires brain MRI to rule out intracranial tumor or multiple sclerosis which potentially causes secondary TN [2]. Neurovascular conflict is the leading cause of TN, accounting for 80-90% of cases, although some patients of TN do not present any neurovascular conflict. An aberrant loop of artery or vein close to the trigeminal nerve root can result in such neurovascular conflict [3,4]. Carbamazepine or oxcarbazepine with gradually increasing doses are usually used to treat TN initially [5]. About 25-30% of patients either become resistant to the medications or develop unacceptable side effects which eventually requires further interventional management [6]. Among the various interventional managements, the conventional radiofrequency thermocoagulation (RFT) of Gasserian ganglion results in the highest rate of complete pain relief. Over 90% of patients shows significant pain relief with that treatment [7]. However, various complications have been reported including weakness of masticatory muscles, meningitis, keratitis, anesthesia dolorosa, and intolerable dysesthesia [8,9]. Also, it shows sudden in-

crease of blood pressure or heart rate during the puncture of foramen ovale [10]. Conventional RFT on the Gasserian ganglion requires the position of neck extension to facilitate visualization of foramen ovale. The infraorbital nerve, which is the terminal branch of trigeminal nerve, exits the maxilla via the infraorbital foramen and provides sensory innervation to the lower eyelid, upper lip, and one side of the nose. Recent studies showed that conventional RFT on this peripheral nerve, not the Gasserian ganglion, was effective in relieving the facial pain of TN [11,12]. Here, we report two cases of successful infraorbital nerve RFT which were impossible to receive the ganglion RFT due to limited neck extension and severe underlying illness.

Case 1

A 77-year old man came to the pain clinic complaining of severe recurrent lancinating pain involving right sided upper teeth and gum pain which developed 5 months ago. His pain showed abrupt onset and termination with an electric shock like sensation. The duration of the pain was within 2 minutes. The pain tended to be suddenly triggered by chewing, washing face, and brushing teeth. We assessed that patient as TN based on the characteristic clinical presentation. Brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) findings showed no vascular anomaly, intracranial tumor or any other lesion. He was first treated with 200 mg of carbamazepine twice a day, but it showed minimal efficacy. The numerical rating scale (NRS, 0 being no pain and 10 being the worst pain imaginable) for TN was 9/10. The patient had underlying hypertension, diabetes mellitus, Parkinson's disease, and unilateral leg weakness due to previous cerebral infarction and was taking 50 mg of cilostazol twice a day. He was also previously diagnosed with TN involving right maxillary division 8 years ago.

Ultrasound guided infraorbital nerve blockade was performed twice with one week interval with 0.2% ropivacaine 0.5 mL using a hockey stick probe (GE Healthcare, Logiq S8, USA) (Fig. 1). The patient was followed up after 10 days and the NRS score for TN was 6/10 but maintaining normal daily activities was still impossible due to residual pain attacks. The patient was educated to stop cilostazol for 2 days before treatment and was scheduled for the next appointment 10 days later. Since his underlying illness was complicated and severe, we thought that the infraorbital nerve RFT rather than the Gasserian ganglion would be more safe.

The patient lay in the supine position and sterile draping with povidone was done at right midface area. A radiofrequency cannula of 22-gauge, 5 cm, and 5 mm active tip was used. After confirming the clear visualization of infraorbital foramen, the cannula was inserted toward the infraorbital foramen using an in-plane approach. The cannula was advanced under continuous ultrasound guidance until reaching proximity to the infraorbital nerve and the location of cannula tip was confirmed. Then, the electrical stimulation of 0.3 V at 50 Hz frequency were in concordance with the location of the pain. The final position of the cannula tip was modified minutely according to the effect of the stimulation. After successful concordant electrical stimulation in maxillary area, radiofrequency was performed at 70°C for 60 seconds for one time. Just after finishing RFT, the patient's vital signs were stable. The patient came to the pain clinic 2 weeks later and the NRS score for TN was 2/10 with mild hypoesthesia involving right maxillary division of trigeminal nerve. After 5 months, the NRS score for TN was still 2/10 with mild hypoesthesia.

Case 2

An 84-year old man came to the pain clinic complaining of severe recurrent lancinating pain involving right upper gum and cheek which developed one month ago. That patient was medicated with 200 mg of carbamazepine twice a day at our hospital's neurology department and showed alleviation of symptoms for 2 weeks. However, medication showed only minimal efficacy as time goes on. The NRS score for TN was 9/10. We assessed the patient as TN based on the characteristic clinical presentation. Brain MRI and MRA findings showed no vascular anomaly, intracranial tumor or any other lesion. Ultrasound guided infraorbital nerve blockade was performed twice with one week interval using 0.2% ropivacaine 0.5 mL (GE Healthcare, Logiq S8, USA) (Fig. 1). The patient was followed up after 7 days and the NRS score for TN was 1/10.

He came to the pain clinic one month later presenting with recurrence of previous symptoms with NRS score 9/10 and was treated again with infraorbital nerve blockade. After this blockade, the NRS decreased to 7, but maintaining normal daily activities was still impossible due to residual pain attacks. RFT of Gasserian ganglion with intravenous anesthesia was planned to relieve his intractable pain. He was monitored with electrocardiography, blood pressure and pulse oximetry.

Facial mask was applied to supply oxygen (3 L/min). Patient lay in the supine position with neck extended and chin-up. However, with the position of neck extension and chin-up,

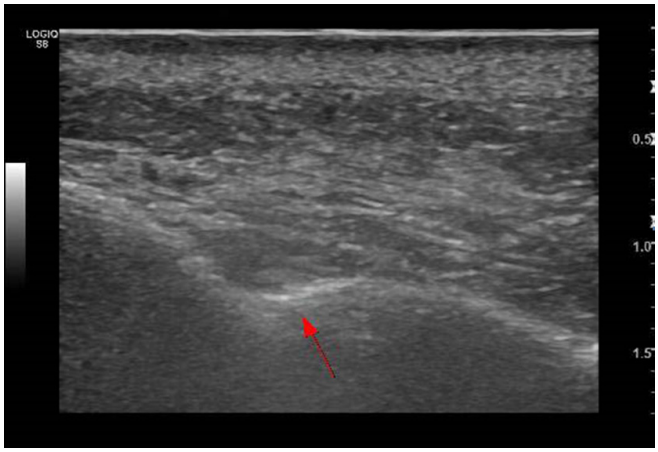

Fig. 1. Ultrasound guided infraorbital nerve blockade. Arrow indicates the infraobital foramen.

the patient felt severe preexisting shoulder pain. This shoulder pain was thought to come from his cervical foraminal stenosis. Since the patient could not bear the position required to the Gasserian ganglion RFT, we could not perform the RFT moreover. Although the ganglion RFT was abandoned due to the occurrence of severe shoulder pain, peripheral nerve RFT was planned to relieve facial pain.

The patient lay in the supine position with sterile draping. A radiofrequency cannula of 22-gauge, 5 cm, and 5 mm active tip was used. After confirming the clear visualization of infraorbital foramen, the cannula was inserted toward the infraorbital foramen using an in-plane approach. The cannula was advanced under continuous ultrasound guidance until reaching proximity to the infraorbital nerve and the location of cannula tip was confirmed. Then, the electrical stimulation of 0.3 V at 50 Hz frequency were in concordance with the location of the pain. The final position of the cannula tip was modified minutely according to the effect of the stimulation. After successful concordant electrical stimulation in maxillary area, radiofrequency was performed at 70°C for 60 seconds for one time. Just after finishing RFT, the patient's vital signs were stable. The patient came to the pain clinic 10 days later and the NRS score for TN was 1/10 with mild hypoesthesia around cheek. After 6 months, the NRS score for TN was maintained to 2-3/10.

Discussion

Two patients of this case report demonstrated significant pain relief after infraorbital nerve RFT. When we tried to perform the ganglion RFT, the first patient had severe underlying illness. The second patient could not bear the neck extension with chin-up position due to the occurrence of shoulder pain. Conventional RFT of Gasserian ganglion under fluoroscopy guidance has been proven to be effective in treating TN and has been widely used in the treatment of TN in the past decade [9]. The position with neck extension and chin-up is essential for the visualization of foramen ovale. However, such position can be uncomfortable and intolerable in some patients. Neck extension and chin-up can be difficult if the patient has a stiff neck due to ankylosing spondylitis or they can cause unexpected provocation of shoulder pain by aggravating foraminal narrowing just like a patient in this case report. Compared with the ganglion RFT, infraorbital nerve RFT does not require such difficult position. For the confirmation of infraorbital foramen with ultrasound, just lying in bed with neutral position is enough.

Among the procedure steps of ganglion RFT, the puncture of foramen ovale led to significant increase in heart rate (42/48, 88%) and mean arterial pressure (48/48, 100%). Also, the heating stimulation of RFT obviously increased mean arterial pressure and heart rate [10]. Intravenous sedation anesthesia should always be performed during the ganglion RFT since this procedure is very painful and challenging. Considering such unwanted hemodynamic responses and additional intravenous anesthesia during Gasserian ganglion RFT, we thought that first patient who had severe underlying illness would be proper for the infraorbital nerve RFT rather than the ganglion RFT.

The infraorbital RFT has many technical advantages over the ganglion RFT. Moreover, the procedure itself is less challenging and it does not require the intravenous sedation anesthesia. The treatment outcome of the infraorbital nerve RFT showed nearly equivalent efficacy compared with that of the ganglion RFT. Recent study showing the effectiveness of supraorbital nerve RFT has shown 93% immediate pain relief [12]. Bharti et al. [11] reported that 90% of patients who received peripheral trigeminal nerve RFT showed successful pain reduction up to 3 months. However, the number of patients who required supplementary medications was more in patients who received peripheral trigeminal nerve RFT than those who received ganglion RFT.

RFT of the peripheral division of trigeminal nerve is considered to produce a conduction block of the irritated nerve axon which results in ultimate pain reduction. RFT of the peripheral division of the trigeminal nerve have been applied for the alleviation of various facial pain [13-15]. RFT of the mental nerve demonstrated significant pain reduction in both pa-

tients who showed painful neuropathy after tooth extraction [15]. Also, pulsed RFT of the infraorbital nerve in patients of postherpetic neuralgia showed significant pain reduction [13]. RFT of the supraorbital nerve was very effective in relieving the headache of medically intractable hemicranias continua [14].

For the performance of peripheral trigeminal nerve RFT, identification of supraorbital, infraorbital or mental foramen is most important. For such identification, previous studies used fluoroscopy or computed tomogragphy (CT) [11,12]. Foramen ovale is deeply located within the skull base of posterior cranial fossa. Therefore, the identification of foramen ovale has been performed under guidance of fluoroscopy or CT [9]. In contrast to the foramen ovale of skull base, the supraorbital, infraorbital or mental foramen is a superficially located skull foramens [13]. Ultrasound provides good views when we try to identify superficial foramens [13]. In this case report, we used the ultrasound for the confirmation of infraorbital foramen. The possibility of ultrasound guidance during the RFT of infraorbital nerve is another advantage of this procedure with technical easiness compared to the ganglion RFT. However, clinical studies showing good treatment outcome after infraorbital nerve RFT is still lacking compared to Gasserian ganglion RFT.

In conclusion, we could perform the infraorbital nerve RFT successfully in both patients who showed unexpected shoulder pain provocation and with severe underlying illness.

Conflict of interest

All authors declare no conflicts-of-interest related to this article.

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COVID-19 백신 접종 후 발생한 백혈구파쇄혈관염 1례

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A Case of Leukocytoclastic Vasculitis Following COVID-19 Vaccination

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As the coronavirus disease 2019 (COVID-19) vaccination rate has recently risen, various cutaneous adverse events have been reported. We report on a 75-year-old woman who developed leukocytoclastic vasculitis after the first dose of BNT162b2 (Pfizer, United States of America) vaccine. The cause of leukocytoclastic vasculitis can be idiopathic or secondary to medications, infections, connective tissue disorders, and malignancy. Developing and exacerbation of leukocytoclastic vasculitis has been reported following vaccinations such as influenza, hepatitis B virus, and bacillus Calmette-Guerin vaccine. The pathogenesis might involve hyperactivation of the immune system secondary to cross-reactivity and molecular mimicry between the virus and self-antigens. As it is important to consider COVID-19 vaccine as a cause of leukocytoclastic vasculitis, we report a case of leukocytoclastic vasculitis following COVID-19 vaccination.

Keywords: BNT162b2, COVID-19 vaccine, Leukocytoclastic vasculitis

Introduction

최근 coronavirus disease 2019(COVID-19) 백신 접종률이 증가함에 따라 다양한 피부 부작용(Cutaneous adverse events)이 보고되고 있으며, 지연형 국소반응(delayed large local reaction), 국소주사부위반응(local injection site reaction), 두드러기, 수포성 유천포창양(Bullous pemphigoid-like), 홍역모양 반응(morbilliform reactions), 홍색사지통증(erythromelalgia), 대상포진 (herpes zoster lesion), 혈관염(vasculitis), 동창(chilblains) 등의 피부 반응이 흔히 보고되었다[1,2]. 저자는 COVID-19 백신 접종 후 피부 반응이 동반되어 발생한 백혈구파쇄혈관염(Leukocytoclastic vasculitis) 1례를 경험하여 문헌고찰과 함께 보고하는 바이다.

Case

75세 여성이 양측 하지 및 체간에서 통증과 소양감을 동반한 적자색의 자반성 반점 및 반을 주소로 내원하였다(Fig. 1). 내원 7일전 BNT162b2 COVID-19 백신(Pfizer, United States of America) 접종하였고, 하루 뒤인 내원 6일전 양측 하지에 자반이 발생하였으며 설사와 복통이 2일간 지속된 뒤 내원 4일전 자반이 체간으로 넓어지며 악화되어 내원하였다. 내원 당시 설사와 복통은 없었으며 우측 고관절통을 호소하였다.

과거력상 고혈압으로 약물 복용 중이었으며 기존 고혈압 약제 외 약물 복용력은 없

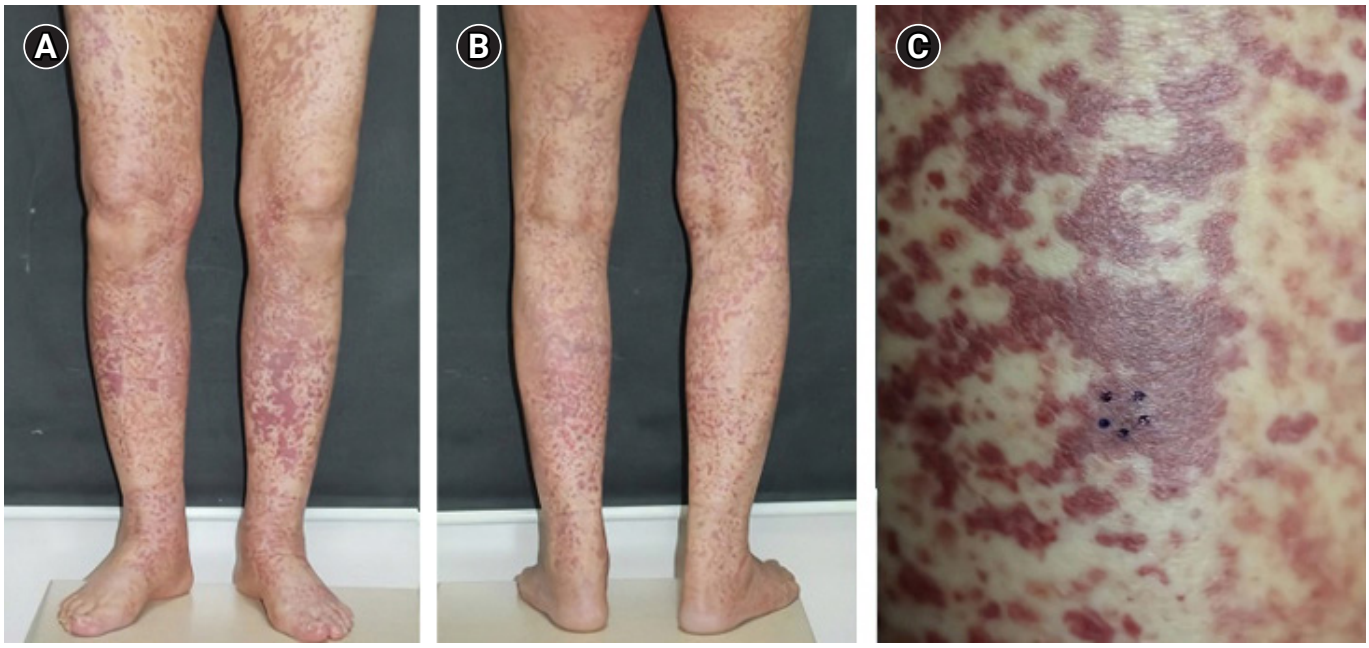

Fig. 1. Multiple reddish to violaceous confluent patches and macules on both lower legs. (A) Anterior view. (B) Posterior view. (C) Closed-up view.

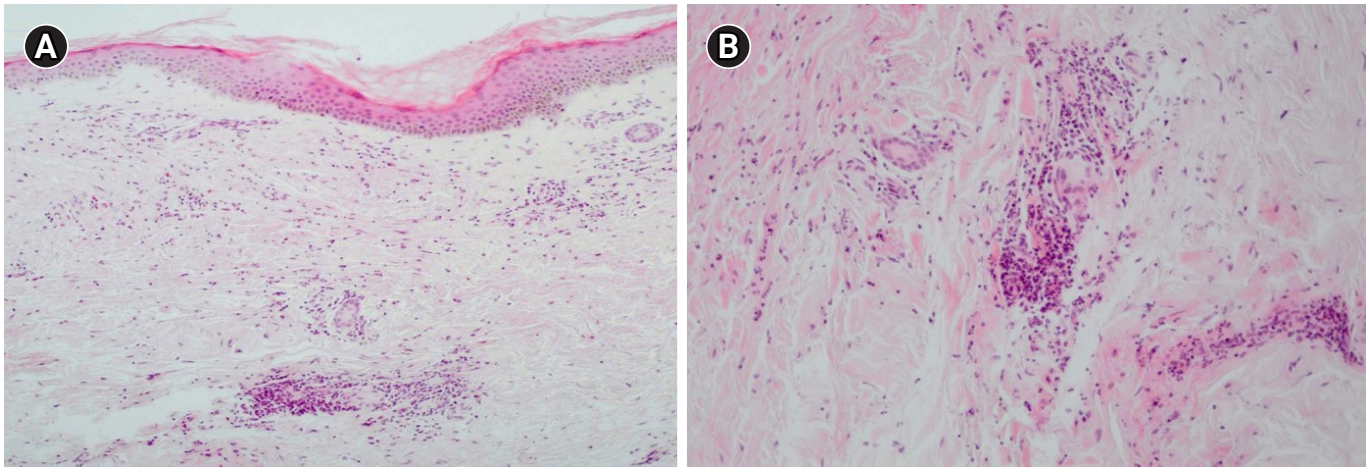

Fig. 2. (A) Histopathologic finding perivascular inflammatory infiltration (H&E, x100). (B) Perivascular mixed inflammatory infiltrate with numerous neutrophils, lymphocytes and occasional eosinophils, vascular necrosis and fibrin, erythrocyte extravasation and nuclear dust in the dermis (H&E, x200).

었다. 신체검사에서 피부소견 외 특이소견은 없었다. 일반혈액검사에서 적혈구침강속도 42 mm/hr, C-반응성단백 0.6 mg/dL로 증가되어있었고 혈액응고검사에서 섬유소원분해산물 14.5 μg/mL, D-이합체 3.77 μg/mL로 증가되어있었다. 자가면역 관련 항체검사에서 항핵항체 1:160으로 양성 외 특이소견은 없었고 면역글로불린 및 보체검사에서도 특이소견은 없었다. 그 외 신장, 간 기능검사 및 소변검사에서도 특이소견은 없었다. D-이합체 상승에 대한 검사를 시행하려 하였으나 환자가 동의하지 않아 시행하지 못하였다. 우측 하지에서 시행한 병리조직검사상 저배율에서 진피의 혈관주위로 염증세포의 침윤이 관찰되었으며, 고배율에서 주로 호중구와 때때로 림프구 및 호산구로 구성된 염증세포의 침윤, 혈관벽의 괴사와 섬유소 침착, 적혈구혈관외유출과 핵먼지가 관찰되었다(Fig. 2). 면역형광염색에서 IgG, IgA, IgM, C3, 섬유소원 침착은 관찰되지 않았다. 이상의 임상 및 병리조직학적 소견을 바탕으로 COVID-19 백신에 의한 백혈구파쇄혈관염으로 진단 후 전신스테로이드, 항히스타민제 및 국소스테로이드제재를 사용하였고 입원 6일째 병변부가 어두워지며 호전을 보여 퇴원하였다. 이후 외래에서 치료를 지속하여 3주에 걸쳐 대부분 피부병변이 호전되었고, 2

Table 1. Summary of published cases of leukocytoclastic vasculitis following COVID-19 vaccination

Case	Age/Sex	vaccine	Comorbidities	Time to onset	DIF
Fritzen et al. [5]	60/F	ChAdOx1 (AstraZeneca): 2nd dose	Chronic liver disease, Portal hypertension, Polycythemia vera, Hypothyroidism, Diabetes mellitus	11 dyas	Granular deposit of IgA and IgM
Larson et al. [6]	83/F	BNT162b2 (Pfizer-BioNTech): 2nd dose	No	5 days	Fibrinogen
Kar et al. [7]	46/F	BBV152 (Bharat Biotech): 1st dose	No	5 days	Not available
Sandhu et al. [8]	55/F	ChAdOx1 (AstraZeneca): 1st dose	No	5 days	Negative
	48/M	ChAdOx1 (AstraZeneca): 2nd dose	Hypertension	2 days	Negative
Cohen et al. [9]	46/F	BNT162b2 (Pfizer-BioNTech): 1st and 2nd dose	Psoriasis, psoriatic arthritis, irritable bowel syndrome	2 days	Not available
Bencharattanaphakhi et al. [10]	23/F	CoronaVac(Sinovac): 1st dose	No	36 hr	C3 and fibrinogen
	26/F	CoronaVac(Sinovac): 1st dose	No	4 hr	IgA, IgM and C3
Fiorillo et al. [11]	71/F	ChAdOx1 (AstraZeneca): 2nd dose	Fibrocystic mastopathy, arterial hypertension	5 days	Linear and granular deposition of IgM
Bostan et al. [12]	33/M	Inactivated COVID-19 vaccine: 1st dose	No	3 days	IgA
Dicks et al. [13]	65/F	BNT162b2 (Pfizer-BioNTech): 3rd dose	Diabetes mellitus, hypertension	2 days	Not available
Jin et al. [14]	68/F	ChAdOx1 (AstraZeneca): 1st dose	No	7 days	Not available
Erler et al. [15]	42/F	BNT162b2 (Pfizer-BioNTech)	Hypertension, severe obesity	4 days	Not evaluable

M, Male; F, Female; DIF, Direct immunofluorescence.

차 백신접종 후 증상 재발 없이 현재까지 경과 관찰 중이다.

Discussion

백혈구파쇄혈관염의 원인은 대부분 미상이며 50%정도는 약물과 감염에 의한 것이나 결체조직질환이나 악성종양과 관련하여 발생하기도 한다[3]. 인플루엔자바이러스, B형간염바이러스, bacillus Calmette-Guerin 등의 백신 접종 후 혈관염이 발생한 사례들이 보고된 바 있으며 백신항원과 자가항원의 교차반응에 의한 면역활성이 그 기전으로 추정된다[4]. COVID-19 백신 접종에 의한 백혈구파쇄혈관염의 원인은 아직까지 명확히 밝혀진 바 없다. 그러나 COVID-19의 원인 바이러스인 severe acute respiratory syndrome coronavirus 2(SARS-CoV-2)가 교차반응과 분자모방를 통해 과도한 면역반응을 일으킬 수 있다고 알려져 있으며, SARS-CoV-2 spike 당단백질을 암호화하는 백신의 성분이 이와 유사한 면역반응을 통해 면역복합체를 형성해 혈관염을 일으키는 것으로 추정된다[5].

COVID-19 백신 접종 후 발생한 백혈구파쇄혈관염의 경우 국외에서 12례, 국내에서는 1례만 보고되었다(Table 1). 미국피부과학회(American Academy of Dermatology)의 registry를 기반으로 한 임상양상만으로 COVID-19 백신 접종 후 피부 부작용을 분류한 연구에서는 총 3례의 혈관염이 보고되었다[1]. 2례는 mRNA-1273 COVID-19 백신(Moderna, United States of America) 접종 후 발생하였고 이는 첫번째 mRNA-1273 백신 접종 후 보고된 피부반응의 0.7%에 해당하였다[1]. 나머지 1예는 BNT162b2 백신 접종 후 발생하였고, 첫번째 BNT162b2 백신 접종 후 보고된 피부반응의 2.9%에 해당하였다[1]. 이후 registry에 등록된 사례 중 조직 생검을 시행한 경우만 모아서 연구해 보았더니 총 58건 중 2건에서 백혈구파쇄혈관염의 소견이 관찰되었다[2].

본 증례는 피부병변 외 설사를 동반한 복통과 우측 고관절통을 호소하여 IgA혈관염과의 감별이 필요하였으나 면역형광염색검사에서 IgA 침착이 관찰되지 않아 배제할 수 있었다. 현재까지 보고된 COVID-19 백신 접종 후 발생한 백혈구파쇄혈관염 증례들의 경우 백신 접종 후 4시간에서 11일 사이에 발생하였는데(Table 1), 본 증례에서도 COVID-19 백신 접종 하루 뒤 피부 병변 발생하였으며 최근 변경된 약제 및 감염의 증거가 없고 고혈압 외 기저질환이 없으므로 COVID-19 백신 접종에 의한 백혈구파쇄혈관염으로 진단을 내렸다.

이에 저자들은 COVID-19 백신 접종 후 발생한 백혈구파쇄혈관염 1례를 경험하고 COVID-19 백신 접종 후 유사한 임상양상을 보이는 경우 고려해보아야 할 원인이라 생각되어 보고하는 바이다.

Conflict of interest

The authors declare no conflicts-of-interest related to this article.

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계명의대학술지

Keimyung Medical Journal

Instructions to authors

Enacted: June 15, 2020

계명의대학술지(KMJ)는 계명대학교 의과대학의 공식 간행물로 영어 초록과 함께 한글 혹은 영어로 발행되는 학술지이며 약칭은 Keimyung Med J 입니다. KMJ는 의료정보학과 의과학에 관한 최신의 정보를 공유함으로써 질병의 치료에 기여하고 인류 건강을 증진시키는 것을 목표로 하고 있으며, 임상연구, 기초의학 및 간호학을 포함한 모든 보건의료 분야의 발전을 촉진할 논문을 게재하고 있다. KMJ는 1982년 창간호가 발간되었으며, 매년 6월 15일, 12월 15일 2회에 걸쳐 발행되고 있으며, 창간호부터 최신호까지 http://www.e-kmj.org에서 무료로 이용할 수 있다.

KMJ에 제출 된 모든 원고는 아래의 지침을 준수하여야 하며, 아래에 명시되지 않은 경우, 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (http://www.icmje.org)'을 따라야 한다. 학술지에 게재 된 논문에 대한 저작권은 KMJ 측에 있으며, 저작권의 양도에 모든 저자가 승인해야 한다.

원고 종류와 언어

KMJ에 투고하는 원고는 창의적이어야 하며, 질병의 치료와 예방을 포함한 보건의료, 의료서비스 및 의용기술, 의학교육의 발전에 기여할 수 있어야 한다. 원고의 형태는 원저, 증례보고, 종설(최근 이슈, 새로운 정보, 심층검토, 임상실험), 독자의견 등이 포함된다. 투고 중인 원고는 다른 출판물에 게재되지 않은 것이어야 하며, 심사가 끝나는 시점까지 다른 학술지에 중복하여 투고되지 않아야 한다. 심사 과정에 있는 원고에 대하여 저자(들)는 계명의대학술지 편집위원회의 요청에 따라야 한다. 원고에 기술되는 언어는 특별한 경우를 제외하고는 한글 또는 영문으로 혼용 없이 작성하여야 한다. 그러나 모든 원고의 초록은 영문으로 작성하여야 한다. 원고에 기술되는 학술용어는 대한의사협회에서 최근에 발행한 의학용어집 또는 해당 전문분야의 최신 용어를 사용하여야 한다.

연구출판윤리

1. 저자 자격

저자는 다음의 4가지 조건을 만족시켜야 한다. 즉, 1) 원고를 구성하는 개념과 설계, 자료의 수집, 분석과 해석 과정에서 상당한 기여를 했는지, 2) 원고를 직접 작성하였거나 또는 학문적으로 중요한 내용의 수정에 대해 결정적 역할을 했는지, 3) 원본의 게재에 관한 최종 승인권을 가졌는지, 4) 원고의 모든 측면에 대해 책임을 지고 정확성이나 완전성에 문제가 있을 경우 이를 해결하겠다고 동의했는지 여부에 따라 인정된다. 교신저자는 원고를 최초로 투고한 후 저자 자격에 대한 모든 변경사항(저자의 추가나 삭제, 순서 변경 등)은 반드시 공문으로 편집위원회에 통보하여야 하며, 모든 저자의 서명을 첨부하여야 한다.

- 교신저자 및 제1저자: 한 원고에 대해 한명의 교신저자만 두는 것을 원칙으로 한다. KMJ는 제1저자가 공동연구를 수행함에 있어 교신저자와 동등한 기여를 한 것이 명백한 경우에 승인한다.
- 게재 후 저자 수정: KMJ는 편집 상의 명백한 실수가 아닌 이상 게재 후에는 저자를 수정하지 않는다.

2. 중복게재 및 표절

중복 출판물은 원본 출처의 귀속 없이 실질적으로 동일한 저작물이 2회 이상 발행(발행 또는 출판 시도)하는 것으로 정의한다. 이전에 다른 출판물로 출간된 원고는 본 학술지에 게재할 수 없다. 또한 다른 학술지에서 게재 심사가 진행 중인 원고는 본 학술지에 중복하여 투고할 수 없으며, 다른 학술지의 심사가 종료된 후에 본 학술지에 투고하여야 한다. 원고가 일단 채택된 후에는 편집위원회의 허가 없이 원고의 어떠한 부분도 다른 학술지에 중복하여 게재 할 수 없다. 만약 KMJ에 게재된 원고가 다른 학술지에 중복으로 게재된 것이 밝혀질 경우 해당 원고는 게재를 철회함과 동시에 KMJ는 해당 저자가 중복 게재한 사실을 공개한다. 이러한 사실은 저자가 소속된 기관에 통지하여야 하며, 저자에게는 추가적인 징계를 내릴 수 있다.

원고의 표절에 대한 점검은 심사 전에 Ithenticate (https://app.ithenticate.com/)를 활용하여 시행한다.

3. 이차출판

다른 학술지에 출판된 원고를 KMJ에서 이차로 출판하고자 하는 경우에 본 학술지 편집위원회가 원전을 출판한 학술지 편집위원회의 동의를 획득한 경우에 한하여 이차 출판을 허용하며, 이 경우에는 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org)'의 일반적인 사항에 따른다.

4. 이해관계 명시

교신저자는 잠재적으로 저자의 자료 해석에 영향을 줄 수 있는 이해상충 또는 갈등을 유발할 수 있는 모든 관계를 편집위원회에 알려야 한다. 예로는 특정 기업에서 받은 금전적 지원이나 그 기업과의 관계, 이익 집단으로부터 받은 정치적 압력, 학문적으로 관련한 문제 등을 들 수 있다. 특히 연구비 수혜 내용은 표지

에 명기하고, 연구와 관련된 투자, 자문료, 주식 등 이해관계가 있는 모든 사항은 본문 말미의 하단에 명시하여야 한다.

5. 인간 및 동물 연구에 대한 규칙 및 규정

인간과 관련이 있는 연구에서는 1964년 채택된 헬싱키선언의 윤리적 기준을 준수해야 하고 'Institutional Review Board (IRB)'의 승인을 받아야 한다. 사진을 포함한 설명 자료에는 환자의 이름, 의 이니셜, 및 병원 식별번호를 등이 공개 되어서는 안된다.

동물을 대상으로 한 연구일 경우 실험동물의 사육과 사용에 관련된 규정 또는 'NIH Guide for the Care and Use of Laboratory Animals'를 준수하여야 한다.

6. 연구 및 게재 부정행위 해결을 위한 절차

중복게재, 표절, 허위 자료, 수치 조작, 저자 변경, 이해상충 미공개, 투고된 원고에 대한 윤리적 문제, 심사위원이에 의한 저자의 아이디어나 자료 차용, 편집위원에 대한 항의 등 연구나 게재의 부정행위로 의심되는 사례가 발견되는 경우 이를 해결하기 위한 절차는 'Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts)'가 제공하는 업무절차 단계를 따른다. 의심되는 사례에 대해서는 편집위원회에서 논의 한다.

7. 편집위원회 및 편집위원의 책임

KMJ 편집위원회는 출판윤리를 준수하기 위해 지속적으로 노력하며, 논문 철회에 관한 지침 준수, 학술 자료의 완전성 유지, 학문이나 윤리적 기준에 위배되는 모든 이해상충방지, 필요한 경우 수정이나 해명, 철회, 사과문 게재 조치, 그리고 모든 표절이나 허위 자료를 제거하고 규탄하는 책임을 다하기 위해 노력한다.

편집위원은 투고된 원고를 채택하거나 거부할 권한을 가지며, 이 때 원고에 대하여 이해상충이 없어야 한다. 편집위원은 원고가 합리적으로 확실한 경우 채택할 수 있으며, 원고에 오류가 발견되면 수정이나 철회를 공시 하며, 심사위원의 익명성을 보장하는 등 사항에 대해 책임을 진다.

투고 및 검증 절차

1. 투고

모든 원고는 온라인 논문 투고 시스템(http://e-kmj.org/)을 통해 투고되어야 한다. 원고를 투고한다는 것은 해당 원고가 이전에 게재된 적이 없으며 다른 학술지에서 게재를 위한 심사가 진행되고 있지 않다는 것을 의미한다. 또한 원고가 일단 채택되면 저자는 해당 원고를 편집위원회의 동의 없이 다른 언어로 변환하여 다른 출판물에 게재하지 않을 것에 동의해야 한다.

2 검증 절차

KMJ 편집위원회는 접수된 모든 원고를 심사함을 원칙으로 한다. 먼저 원고가 양식을 갖추었는지, 본 학술지의 목적과 범위에 부합하는지를 심사하며, 다음 단계로 유사도 검사를 통해 표절이나 중복게재 여부를 확인한다. 이후 편집위원회에 의해 선정된 익명의 심사위원 2명이 원고를 교차검증 한다. 교차검증에서는 저자의 이름과 소속기관을 제거하고 심사하는 더블 블라인드(이중맹검) 방식을 사용한다. 편집위원회는 심사위원들이 보낸 심사결과를 심의하여 원고의 일차 채택 여부를 결정한다. 통상적으로 편집위원회는 원고의 게재 여부를 접수 후 3주 내에 일차적으로 결정하며, 이후 즉시 교신저자에게 원고의 심의 결과와 심사 의견서를 전자메일로 전달해야 한다. 교신저자는 심사 의견서에 따라 수정이 이루어진 모든 부분을 항목별로 표시하여 편집위원회에서 정한 기한 내에 수정된 원고를 다시 제출하여야 한다. 특별한 사유가 없는 한 원고가 수정되지 않은 채 다시 제출되거나 또는 수정된 원고가 기한 내에 편집위원회에 도착하지 않으면 저자가 자의로 투고를 철회한 것으로 간주한다. 만약, 수정기간을 연장하고자 할 경우 교신저자는 편집위원회에 연락해야 한다.

편집위원회는 원고의 심의 결과는 '원고대로 게재, 수정 후 게재, 수정 후 재심사, 게재 불가' 중에 한 유형으로 통지한다.

저작권, 라이선스, 데이터 공유

1. 저작권

모든 출판물에 대한 저작권은 KMJ가 소유한다. 교신저자는 원고를 투고할 때 모든 저자가 서명한 '저작권이양동의서'를 전자투고시스템을 통해 제출해야 한다.

저작권 양도에는 재출판, 번역, 사진 복제, 마이크로 폼, 전자형식(오프라인, 온라인) 또는 기타 유사한 성격의 복제물을 포함하여 원고를 재생성 및 배포할 수 있는 독점적 권리가 포함된다.

2. 라이선스

KMJ는 적절히 인용되는 전제 하에 모든 매체를 통해 원래 저작물을 비상업적 목적으로 활용하거나 배포, 재생산하는 것을 무제한적으로 허용하는 "Creative Commons Attribution Non Commercial License (https://creativecommons.org/licenses/by-nc/4.0/)"의 조건에 따라 배포되는 오픈액세스 학술지이다. KMJ에 게재된 모든 표나 그림을 학문적, 교육적 목적으로 다른 학술지, 책, 매체에 사용하는 경우 "Budapest Open Access Initiative (BOAI)"의 오픈 액세스에 대한 정의에 따라 따로 허가를 받지 않아도 된다.

3. 데이터 공유

KMJ는 윤리, 개인정보 보호, 비밀유지와 관련된 문제로 제한되는 경우가 아닌 이상 ICMJE Recommendations for data sharing statement policy에 따른 데이터 공유를 권장한다.

원고작성의 세부사항

1. 원고 작성

1) 원고는 한글 또는 영문으로 작성하여야 하며, 특별한 경우를 제외하고는 한글과 영문을 혼용하지 않는다. 초록은 한글이나 영문 원고 모두 영문초록을 첨부한다.
2) 원고는 A4용지에 상하좌우 2.5cm 여백을 두고 MS Word로 작성하고, 본문은 글자크기 10포인트, 줄 간격 200으로 기술한다.
3) 원고는 표지, 영문초록, 본문(서론, 방법, 결과, 고찰, 요약), 참고문헌, 표 및 그림 설명, 표, 그림 등의 순서로 작성하며, 각 부분은 새 쪽으로 시작한다.
4) 학술용어는 대한의사협회에서 최근에 발행한 의학용어집을 기준으로 사용함을 원칙으로 한다. 번역어가 있으나 의미 전달이 어려운 경우에는 번역어를 처음 사용할 때 번역어 다음에 괄호 안에 원어를 표기한 다음 이 후 사용 시에는 번역어만 기술한다. 적절한 번역어가 없는 학술용어, 고유명사, 지명, 인명, 약품명, 단위 등은 원어로 직접 표기할 수도 있다.
5) 약자를 사용해야 할 경우에는 용어를 처음 사용할 때 전체 용어를 표기한 다음에 괄호 안에 약자를 기입한다. 이후에는 약자만 사용한다.
6) 숫자는 아라비아 숫자, 도량형은 미터법을 사용하고 모든 단위는 국제표준(SI) 단위를 사용하는 것을 원칙으로 한다.

2. 표지

1) 표지에는 원고의 종류, 제목, 저자명, 소속 등을 명시한다(한글논문인 경우 영문도 표기). 소속이 각기 다른 저자가 포함된 경우에는 주 연구기관을 먼저 기록한 다음, 나머지 기관은 해당하는 저자명과 일치시켜 저자명과 소속기관에 각각 같은 어깨번호를 표기하되 저자명의 순으로 번호를 붙인다.
2) 제목은 원고의 취지와 내용을 적절히 반영하여야 하고 한글 제목은 40자, 영문 제목은 20단어를 넘지 않도록 한다. 영문 단어의 첫 문자는 대문자로 한다.
3) 표지 하단에는 교신저자의 성명, 소속, 주소, 연락처 등을 명시하고, 연구비 수혜나 학술대회 발표 등 관련사항을 기재한다.

3. 영문초록

1) 영문초록은 문단의 구분이 없이 기술하며 250 단어를 넘지 않아야 한다.
2) 중심단어(Key Words)는 초록 하단에 최대 5개까지 영문으로 제시한다. 중심단어는 미국국립의학도서관이 제공하는 Medical Subject Headings (MeSH) 를 참조한다.

4. 본문

1) 원저는 서론, 재료 및 방법(대상 및 방법), 결과, 고찰, 감사의 글, 이해관계의 순으로 기술한다.
2) 증례보고는 서론, 증례, 고찰, 감사의 글, 이해관계의 순으로 기술하고, 본문의 용량은 5쪽 내외로 한다.

5. 참고문헌

1) 참고문헌은 본문에서 인용된 것이어야 하며 본문에 인용된 순으로 영문으로 기술한다.
2) 저자명의 기술방법은 먼저 성을 기술한 뒤에 이름은 약어로만 표기한다.
3) 저자의 수가 6명 이하일 경우 모든 저자명을 기재한다. 저자가 6명을 넘으면 6명까지는 저자명을 기술한 다음 'et al.'로 나머지 저자명을 대체한다.
4) 학술지명의 표기는 Index Medicus의 공인된 약어를 사용한다.
5) 본문에서 참고문헌은의 표기는 인용된 순서대로 번호를 대괄호 속에 붙이며, 번호는 저자 의 성 뒤에 기재하여야 하고 저자의 성이 없는 경우는 문장의 마침표나 쉼표 앞에 기재한다.
   저자가 2명 이하일 때는 모든 저자의 성을 다 쓰며, 3명 이상일 때에는 첫 저자의 성 다음에 'et al.'을 붙인다.
6) 기타 명시되지 않은 참고문헌 기술방법은 Uniform Requirement for Manuscripts

참고문헌 기술방법은 다음의 예시에 준한다.

Journal Article

1. Skinnider BF, Amin MB. An immunohistochemical approach to the differential diagnosis of renal tumors. Semin Diagn Pathol 2005;22:51-68.
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3. Xin H, Liu D, Songyang Z. The telosome/shelterin complex and its functions. Genome Biol. 2008;9. DOI: 10.1186/gb-2008-9-9-232.

Book

4. Rosai J, Ackerman LV. Rosai and Ackerman's Surgical Pathology. 9th ed. Edinburgh, New York: Mosby; 2004.

Book Section

5. Zipfel GJ, Day AL. Surgical treatment of intracavernous and paraclinoid internal carotid artery aneurysm. In: Winn HR, editor. Youmans Neurological Surgery. 5th ed. Philadelphia: W.B.Saunders; 2004. p.1895-913.

Web Page:

6. National Cancer Institute. The Cancer Genome Atlas Program. [cited 2020 Mar 16]. Available from: https://www.cancer.gov/about-nci/organization/ccg.

7. 표(Tables)

1) 표는 본문에서 기술되는 것만 순서대로 배열하고 아라비아 숫자를 매긴다.
2) 표는 영문으로 작성하며 제목과 가로축 및 세로축의 범례에서 첫 글자만 대문자를 사용한다.
3) 표의 제목은 표의 왼쪽 상단에 절이나 구의 형태로 표기한다.
4) 표는 구획은 세로 줄의 가로 실선만 사용하여 나타내며 수직선은 긋지 않는다.
5) 본문에서 특정 표를 지칭할 때 'Table 1'과 같이 표기한다.
6) 표에 약자를 사용할 때는 표의 하단에 약자를 풀어서 설명한다.

8. 그림 및 사진(Figures)

1) 그림은 본문에서 언급되는 순서대로 나열하고 아라비아 숫자를 매긴다.
2) 그림은 선명해야 하며, 크기는 15 x 20cm 이하, 용량 크기는 5MB 이하, 해상도는 300 dpi이상을 권장하며, ppt, jpg, tif 파일로 접수한다.
3) 동일 번호에서 2개 이상의 그림인 경우 아라비아 숫자 이후에 A, B, C 글자를 기입하여 표시한다.
4) 본문에서 특정 그림을 지칭하는 경우에는 'Fig. 1'과 같이 표기한다.
5) 도화(line drawing)는 원칙적으로 원본이어야 한다. 다른 논문의 그림을 인용할 때는 원칙적으로 원저자의 동의를 얻어야 한다.

9. 기타

본 투고규정에 언급되지 않은 사항은 일반적인 관례에 준한다.

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Author's checklist

☐ 원고는 다른 학술지에 중복해서 제출(투고)되지 않았다.

☐ 원고와 동일한 내용이 다른 학술지에 게재되지 않았다.

☐ 원고는 의학논문 출판윤리 가이드라인을 모두 준수하고 있다.

☐ 원고의 규격은 A4 용지에 위아래 및 좌우 각각 2.5cm 여백을 두었고, 텍스트는 10포인트, 줄 간격 200으로 작성하였다.

☐ 원고는 표지, 제목, 영문초록, 본문, 참고문헌, 그림설명, 표, 그림의 순서로 작성하였으며, 각 부분은 새로운 쪽으로 시작하였다.

☐ 제목은 간결하면서도 본문의 내용을 함축적이고 명료하게 표현하고 있다.

☐ 영문초록은 문단 구분 없이 작성하였고, 250단어를 초과하지 않았다.

☐ 중심단어는 최대 5개를 초과하지 않았으며, 영문초록 하단에 제시하였다.

☐ 본문은 서론, 재료 및 방법, 결과, 고찰, 요약의 순으로 제시하였다.

☐ 참고문헌은 모두 본문에 인용되어 있고, 본문에 인용된 순서대로 나열되어 있다.

☐ 참고문헌 표기방법이 투고규정과 일치한다.

☐ 표와 그림에서 제목과 내용은 영문으로 작성하고 일관되게 표시하였다.

☐ 표와 그림의 영문 제목에는 첫 단어와 고유명사만 대문자로 시작하였다.

☐ 표 혹은 그림은 그 자체만으로 독자가 충분히 이해할 수 있을 정도로 작성하였고, 본문에서 동일한 내용을 표와 그림으로 중복해서 제시하지 않았다.

☐ 그림과 사진은 축소 인쇄되더라도 영향을 받지 않을 정도로 명료하다.

☐ 모든 저자가 원고 제출에 동의하였다.

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논문제목: _____

라는 제목의 논문이 "계명의대학술지"에 출간될 경우 그 저작권을 계명대학교 의과대학에 양도한다.
저자는 저작권 이외의 모든 권한 즉, 특허 신청이나 향후 논문을 작성하는 데 있어서 본 논문 일부 혹은 전부를 사용하는 등의 권한을 소유한다. 저자는 계명의대학술지 편집위원회로부터 서면으로 승인을 받으면 타 논문에 본 논문의 자료를 사용할 수 있으며, 이 경우 자료가 발표된 원 논문을 밝힌다. 논문의 모든 저자는 본 논문에 실제적이고 지적인 공헌을 하였으며 논문의 내용에 대해서 책임을 공유한다.

본 논문은 과거에 출판된 적이 없으며 현재 타 학술지에 제출되었거나 제출할 계획이 없음을보장하고 아래에 서명하는 바이다.
(6명 이상의 저자가 있는 경우에는 이면에 서명해도 가함)

저자명	년/ 월/ 일	(서명)