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Original Article

Toxoplasmosis-related knowledge and preventive practices among undergraduate female students and pregnant women in Kuwait

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ABSTRACT

Objectives: To evaluate knowledge, attitude and preventive behavior towards toxoplasmosis among women in Kuwait
Design: This was a web-based cross-sectional study.
Setting: The study was conducted through an online self-administered questionnaire during 2019-2021.
Subjects: A total of 412 women of childbearing age participated in the survey, which included 114 pregnant and 298 non-pregnant women.
Intervention: Each of the 412 women participating in the study completed an online survey toxoplasma-related questionnaire.
Main outcome measures: The women in Kuwait had inadequate knowledge and preventive behavior towards toxoplasmosis.
Results: All participants belonged to medium-to-high social status and had high school or higher education. Overall, 45.9% of participants had no knowledge of toxoplasmosis, of which 79.9% were non-pregnant women (P<0.002). Only 13 (11.4%) of the pregnant women knew its modes of transmission compared to 55 (18.5%) of the non-pregnant women. A significantly higher number of pregnant women (54, 47.4%) knew it could be prevented (P<0.05). Overall, 59 (14.3%) women knew about toxoplasma screening tests, including only 6 (5.3%) of the pregnant women. Most women from both groups did not know that toxoplasma infection affects pregnant women (93.2%) or that the infection could be transmitted to the fetus (82.8%). However, a significantly higher number of pregnant women avoided high-risk activities to prevent infection than non-pregnant women (57, 50% *vs* 113, 37.9%; P<0.026) respectively. We documented that 39.5% of the pregnant women received toxoplasma-related information from family members/ friends and 25.4% from health care professionals.
Conclusion: This study highlights inadequate knowledge and preventive behavior towards toxoplasmosis among women of childbearing age in Kuwait. Strategies to improve toxoplasmosis-related knowledge and practices to reduce congenital toxoplasmosis are highly needed.

KEY WORDS: attitude, congenital toxoplasmosis, *T. gondii* prevalence, women of childbearing age

INTRODUCTION

Toxoplasmosis is caused by an obligate intracellular opportunistic protozoan parasite, *Toxoplasma gondii*, which has a worldwide distribution, affecting about one third of the human population[1]. Humans are infected by ingesting cysts from undercooked meat, or by consuming water or food contaminated with infectious oocysts. The consequences of *T. gondii* infection in humans depend on the genetic background and immunity of the host, and strain and inoculum size of the parasite[2]. Infection with *T. gondii* is usually asymptomatic or may cause a self-limiting flu-like illness, but it may lead to severe infection in individuals with supressed immune systems[1]. Seroprevalence of *T. gondii* infection in humans varies between 16%-80%, according to age, population group, geographical location and dietary habits[3]. In addition, *T. gondii* can be vertically transmitted during pregnancy from an immunologically naive mother to her fetus, with the prevalence of congenital toxoplasmosis reaching up to 10 per 10,000 live births in some countries/settings[4]. Epidemiological surveys among pregnant women and

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women of childbearing age have repeatedly shown a considerable variation in the seroprevalence of *Toxoplasma* infection ranging from 7.5% to 92.5% in different parts of the world, with the highest prevalence in South America and the lowest in the Western Pacific region[5-7].

However, there has been a decreasing trend of *T. gondii* prevalence in many countries, including the Middle East, during the last two decades due to lower exposure to the parasite because of better socio-economic conditions, changes in nutritional habits and improved hygiene practices and knowledge towards the disease[8-13].

The State of Kuwait is demographically comprised of a large expatriate population originating mainly from the Asian and Arab countries, comprising nearly 70% of the total 4.7 million inhabitants (The Public Authority for Civil Information, Kuwait, 2019)[14]. Previous studies in select populations had reported a prevalence of *T. gondii* infection (52%-95%) among women of childbearing age in Kuwait[15,16]. However, a more recent study reported a significant decline in prevalence of *T. gondii* infection among pregnant women in Kuwait (12.5%)[9].

Despite a significantly lower toxoplasma seroprevalence among pregnant women in Kuwait, there is no information on the knowledge (symptoms, transmission methods, treatment, prevention and control of the disease) and perception towards this disease among women of childbearing age and pregnant women in Kuwait.

The main objective of this study was to evaluate knowledge, attitude and preventive behavior towards toxoplasmosis among undergraduate female students and pregnant women and in Kuwait.

SUBJECTS AND METHODS

Study design and study population

This survey was conducted to evaluate socioeconomic status, knowledge, attitude and preventive practices towards toxoplasmosis among a total of 412 adult females through an online self-administered questionnaire between October 2019 and February 2021. The questionnaire was sent to women who could understand and complete the questionnaire without assistance. The target groups included pregnant women attending the antenatal clinics (n=86) at any gestational stage, graduating students at a public high school ≥18 years of age (n=57), and undergraduate students at the faculties of medicine: 1st year students (n=54), engineering & petroleum (n=76), business administration (n=75) and social sciences (n=64). However, for data analysis and discussion, the participants were divided into two main groups: non-pregnant women (298, 72.3%) and pregnant women (114, 27.7%), including 28 students with pregnancy.

Questionnaire

A structured questionnaire was constructed and used to collect sociodemographic characteristics of the participants, and knowledge, attitude and practice towards toxoplasma infection from the participants. The questionnaire was pre-tested on 25 randomly selected females to optimize the instrument for clarity and validity. The questionnaire was reviewed and edited to ensure that the participants clearly understood the questions. The questionnaire was self-administered and anonymous. Questionnaire items were designed to get the data on socioeconomic status and demographic characteristics of the participants, and to assess the basic knowledge, attitude and practice of the target groups towards the importance of the disease. All respondents were informed of their ethical and consensual rights and were assured of confidentiality of their identity and responses. The questionnaire consisted of 36 closed-ended questions and took approximately 15 minutes to be completed to obtain information on participant's demographic and background (6), basic knowledge (6), sources of information (6), preventive measures (5), risk behavior (5) and attitude (8) towards toxoplasmosis.

The survey was conducted online using WhatsApp and telephone. A copy of the questionnaire is added in the supplementary file. All respondents were informed about the objective of the study and informed consent was obtained from all respondents and confidentiality of their identity and responses was assured. The participation in this study/survey was voluntary, questionnaire was anonymous, and answer to the survey was in anonymous mode and did not contain any personal data of the participants. As such, no ethical approval was required.

Sample size

An online Epi Info™ 7, a public domain set of software tools by Centers for Disease Control and Prevention (CDC), was used to calculate the sample size[17]. For this purpose, we used: a) 20% as the expected frequency, though no data was available for such a study in Kuwait; b) 5% of confidence limits; and c) a 95% confidence level. The calculated sample size was 374 subjects.

Data management and statistical analysis

The survey data were coded and entered in Microsoft Excel spread sheets and statistics were computed using SPSS Version 20. Chi square test (X^2) and Fisher's Exact test were employed to see the

Table 1: General knowledge on *T. gondii* infection and its diagnostic screening tests among pregnant women and female undergraduate students in Kuwait, obtained through an online survey during 2019-2021.

Group	Total n	I know nothing n (%)	I know about the screening tests n (%)
First year medical students	54	12 (22.2)	17 (31.5)
Faculty of Engineering and Petroleum	67	36 (53.7)	14 (20.9)
Faculty of Business Administration	65	38 (58.5)	6 (9.2)
High school for girls	57	37 (64.9)	4 (7.0)
Faculty of Social Sciences	55	28 (50.9)	12 (21.8)
Pregnant	114	38 (33.3)	6 (5.2)
Total	412	189 (45.9)	59 (14.3)

association of demographic history with knowledge of the respondents. A *P*-value less than 0.05 was considered as statistically significant.

RESULTS

A total of 412 adult females participated in the online survey to evaluate their socioeconomic status and toxoplasma-related knowledge, attitude and preventive behavior between October 2019 and February 2021. The participants included pregnant women attending the antenatal clinics and female high school and university students in Kuwait. The age of the female high school students, university students and pregnant women ranged between 18-19 years, 19-25 years and 20-41 years respectively. The age ranges of the participants were 175 (42.5%) between 18-20 years, 126 (30.6%) between 21-25 years, 94 (22.8%) between 26-40 years, and only 17 (4.1%) participants were >40-years-old. At the time of the survey, most of the students 298 of 326 (91.4%) were unmarried. A total of 114 (27.7%) participants were currently pregnant, including 28 among the students. A total of 17 women (14.9%) also gave a history of abortion in the past. Almost all participants belonged to medium-to-high social status and lived in urban areas, and 44 of 86 (38.6%) pregnant women had a university degree.

Concerning 'what do you know about toxoplasmosis', 189 (45.9%) of all women who participated in the survey knew nothing about toxoplasmosis, which included 38 (33.3%) of the pregnant and 151 (79.9%) of the non-pregnant women (Chi-square *P*-value <0.002). Among the non-pregnant women, the high school girls were least informed (64.9%) about toxoplasmosis compared to other female undergraduate university students. The 1st year female medical students were the most informed student group (77.8%) compared to the students from the faculties of engineering & petroleum (46.3%), social sciences (49.1%) and business administration (41.5%). However, the differences were not statistically significant (Table 1).

Overall, 59 (14.3%) participants had knowledge about the screening tests for toxoplasma infection, which included only 6 (5.2%) of the pregnant women and 53 (17.8%) of the non-pregnant women (Chi-square *P*-value=0.001). Within the non-pregnant group,

Table 2: *Toxoplasma gondii* infection-related knowledge and preventive attitude of pregnant women and undergraduate students towards toxoplasmosis in Kuwait

Group	Pregnant (n=114) n(%)	Non-pregnant (n=298) n(%)	*P*-value
Knowledge			
I know it can be prevented	54 (47)	109 (37)	0.045*
I know how it is transmitted	13 (11)	55 (18)	0.084
Characteristics of Toxoplasmosis			
Nothing	44 (38.6)	165 (45.4)	0.002*
It is dangerous	54 (47.4)	119 (39.9)	0.171
Causes symptoms	15 (13.2)	79 (26.5)	0.003*
Affects pregnant women only	8 (7.0)	20 (6.7)	0.912
Can be transmitted by unwashed vegetables and under-cooked meat	20 (17.5)	56 (18.8)	0.770
Can be transmitted by blood transfusion	0 (0.0)	34 (11.4)	0.000*
Can cause miscarriage or stillbirth	44 (38.6)	110 (36.9)	0.752
Transmitted from pregnant woman to her fetus	15 (13.2)	56 (18.8)	0.175
Which of the following would prevent you from getting Toxoplasmosis?			
Not changing the cat's litter box	57 (50.0)	113 (37.9)	0.0258*
Cooking meat well	57 (50.0)	100 (33.6)	0.002*
Thoroughly washing fruits/vegetables	23 (20.2)	52 (17.4)	0.521
Gardening with gloves	11 (9.6)	44 (14.8)	0.172

Table 3: Knowledge, attitude and practices towards toxoplasmosis among pregnant women and women of childbearing age in countries of Eastern Mediterranean & African Region

Country	Sample size & target group	KAP	Predictors for KAP	References
Saudi Arabia				
Al Hassa	234 pregnant women	73.2% no knowledge	Old age	Amin *et al*[19]
Dharan	400 pregnant women	75.5% no knowledge	ND	Elsafi *et al*[20]
Jazan	400 female students	79% no knowledge	ND	Mahfouz *et al*[12]
Ahvaz, Iran	3,500 public	69% little knowledge		Baghlaninezhad *et al*[21]
Egypt, Beni-Suef University	1079 female students	97% little knowledge 63% negative attitude	ND	Senosy [22]
Jordon	280 women and 1390 female students	51% no knowledge 50% positive attitude	ND	Al-Sheyab *et al*[23]
Palestine, Al Najah	976 university female students	51% no knowledge 69% positive attitude		Sweileh *et al*[24]
Tikrit, Iraq	Pregnant women	75.2% no knowledge	ND	Mayada *et al*[25]

ND: not determined; KAP: knowledge, attitude and practices

1st year medical students were the most informed about the screening test (31.5%), followed by the students in social sciences (21.8%) and engineering faculty (20.9%) (Table 1).

Overall, 209 women (60.7%) had insufficient knowledge about important characteristics and symptoms of toxoplasmosis, including 44 (38.6%) of the pregnant women compared with 165 (55.4%) of the non-pregnant women (Chi-square=0.002, $P<0.005$). Table 2 shows data on responses to questions related to important characteristics of toxoplasmosis, including mode of transmission, symptoms and attitude towards

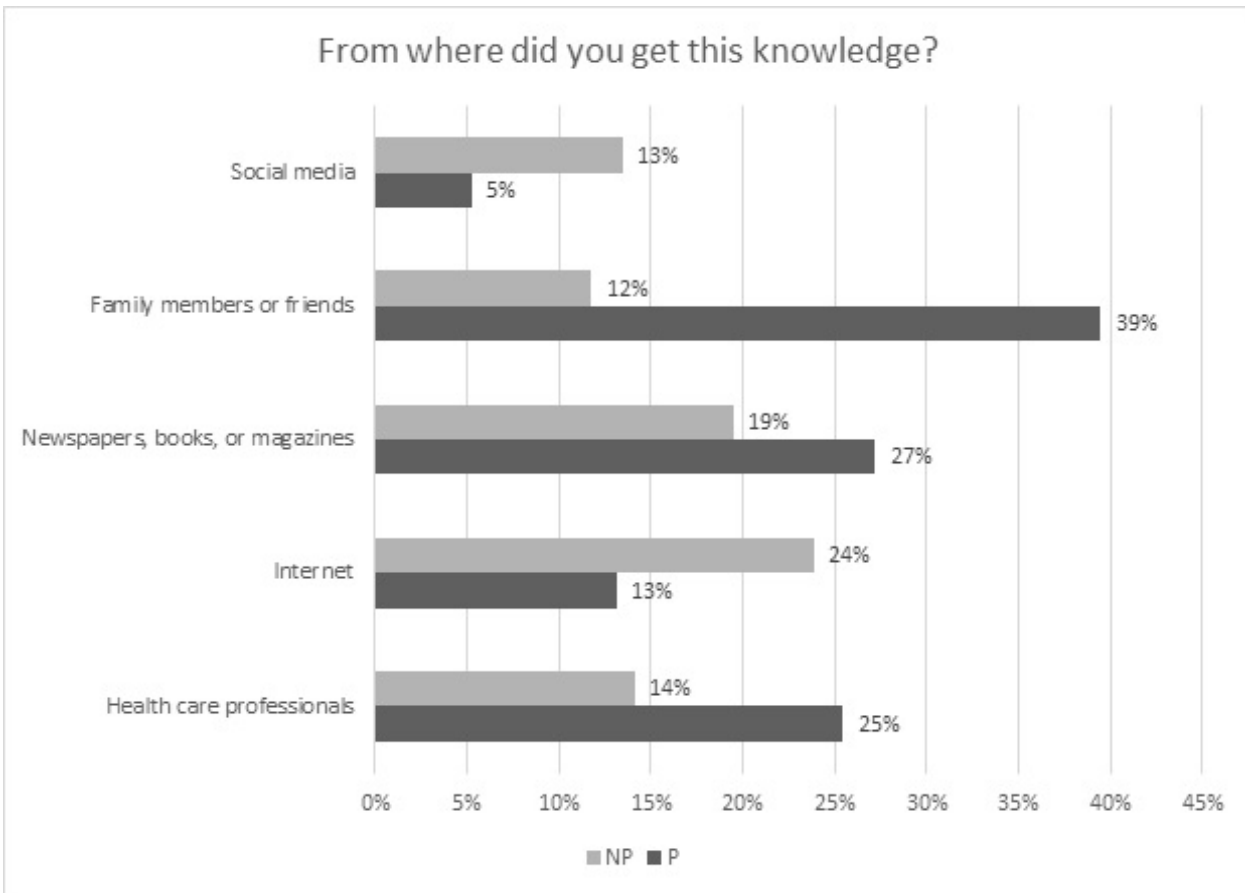

Figure 1: Sources of Toxoplasma-related knowledge and practices towards infection prevention among pregnant (P, n=114) and non-pregnant women (NP, n=298) in an online survey.
NP: non-pregnant; P: pregnant

infection prevention by avoiding high risk activities. Although only 13 (11.4%) of the pregnant women knew the modes of transmission of toxoplasmosis compared to 55 non-pregnant women (18.5%) (Chi-square *P*-value=0.084, >0.05), a significantly higher number of pregnant women (54, 47.4%) knew it could be prevented compared to 109 non-pregnant women (36.6%; Chi-square p-value=0.045, <0.05; Table 2).

Though 54 (47.4%) of the pregnant women and 119 (39.9%) of the non-pregnant reported that toxoplasmosis is a dangerous infection, a significantly lesser number (15, 13.2%) of the pregnant women knew that it may cause symptoms compared to the non-pregnant women (79, 26.5%; *P*=0.003). Similarly, most of the women from both groups did not know that toxoplasmosis could affect pregnant women (>93%) or that the infection could be transmitted to the fetus (>81%; Table 2). However, >37% of the women from both the groups knew that toxoplasmosis is dangerous for health and may cause miscarriage. With respect to the attitude towards toxoplasma infection transmission by not getting involved in high-risk activities, a significantly higher number of pregnant women compared with non-pregnant women reported that 'not changing the cat's litter box and cooking meat well' would prevent toxoplasma infection [57 (50%) *vs* 113 (37.9%); *P*<0.026 and 57 (50%) *vs* 100 (33.6%); *P*<0.002] respectively (Table 2).

A significantly higher number of pregnant women than the non-pregnant women received toxoplasma-related information from health care professionals (25.4% vs. 14.1%, Chi-square p-value=0.006, <0.05) and family members/friends (39.5% vs. 11.7%, Chi-square p-value=0.0014, <0.05) (Figure 1). Social media and internet were the least common source of information for all the groups. The data collection through online survey was quick and most of the participants felt comfortable in their spontaneous responses to the questionnaire.

DISCUSSION

Recently, we reported a significantly lower toxoplasma seroprevalence rate of 12.5% among pregnant women in Kuwait compared to 53.1% reported more than a decade ago[9,16]. Similar decreasing trends were also reported among pregnant women in Saudi Arabia (from 38.8% in 2014 to 21.2% in 2021)[10,11,18]. A detailed update on *T. gondii* seroprevalence in the Middle east is presented as a table in the supplementary file. To our knowledge, no previous study has investigated the knowledge and attitude of pregnant women and women of childbearing age towards toxoplasma infection and its associated risk factors in Kuwait. Though 45.9% of all women who participated in the survey knew nothing about toxoplasmosis, a significantly higher number of pregnant women (67.0%) had inadequate knowledge about toxoplasmosis compared with 21.1% of the non-pregnant women (p<0.002).

Several countries in the Eastern Mediterranean and African Region have reported a much higher number of pregnant women and women of childbearing age who had inadequate toxoplasmosis-related knowledge and preventive practices (Table 3)[12,19-25]. Recent studies from the neighboring country Saudi Arabia showed that 75.5% of the 400 pregnant women in Dharan[20] and 79.1% of the 440 female students at Jazan University[12] had insufficient knowledge about toxoplasmosis and its mode of transmission**.** A community-based cross-sectional study in Ahvaz County, Iran in 2017 showed that 31.3% of the 3,500 public had only basic knowledge on toxoplasma infection transmission[21] and 75.2% of the pregnant women in Tikrit city in north-central Iraq had no or inadequate knowledge on toxoplasma infection transmission and consequences of infection during pregnancy[25]. A multinational study conducted among 2598 pregnant women from Malaysia, Philippines and Thailand reported similar data[26].

In this study, 65% of the high school girls had no knowledge about toxoplasmosis compared to other undergraduate female students from various faculties (51%-58%). The majority of female students at Jazan University, Saudi Arabia (348; 79.1%) had low knowledge scores regarding toxoplasmosis[12]. A recent cross-sectional study showed that 96.8% of the 1079 female Beni-Suef University students in Egypt had no knowledge about toxoplasmosis and its mode of transmission[22].

In this study, only 13 (11.4%) of the pregnant women knew its mode of transmission compared to 18.5% among the non-pregnant women (*P*>0.05). However, a significantly higher number of pregnant women (97, 47.4%) knew it could be prevented and showed a positive attitude towards toxoplasma infection prevention by avoiding high risk activities of changing the cat litter box or eating under cooked meat. Recent cross-sectional studies showed that >70% of the Beni-Suef university students in Egypt and >90% of pregnant women in Tanzania's Temeke municipality unknowingly observed preventive practices towards toxoplasma infection transmission despite lack of knowledge about toxoplasmosis[22,27]. Several factors may be involved in the positive behavioral and lifestyle change towards toxoplasmosis by women during pregnancy and/or with a history of a previous pregnancy by avoiding high risk behavior, even without having an appropriate knowledge about it. A similar hypothesis was presented in an earlier study

from the USA, that preventive behavior during pregnancy was not necessarily associated with specific knowledge about toxoplasmosis[28].

In accordance with earlier studies, we documented that 39.5% of the pregnant women received toxoplasma-related information from family members/friends and 25.4% from health care professionals. Jones *et al* showed that 53% the pregnant women in the USA received toxoplasma-related information from health care workers and 45% from family/friends[28]. Socioeconomic status, demographic characteristics and higher education have been shown to influence the correct knowledge and attitude of a population or study group towards toxoplasmosis[29,30]. However, in this study, only 11% of the pregnant women had low level of knowledge about toxoplasma infection transmission, and only 5% of them knew about the screening tests to check for infection. Recently, we have reported significantly low levels of *T. gondii* infection among pregnant women in Kuwait (12.5%), one of the lowest in the Middle East, which was probably due to high education level and free access to high standard of health services[9].

In addition, this study was conducted through an online survey to collect information on sociodemographic status and toxoplasmosis related knowledge and preventive practices among pregnant women and women of childbearing age. The data collection through online survey was quick and the participants were more comfortable in their spontaneous responses to the questionnaire as compared to the traditional methods. Similar observations were reported in an earlier study conducted through an online survey[29]. The limitations of our study are relatively small sample size due to time constraint and the use of closed questions in the questionnaire for data collection.

CONCLUSIONS

This is the first study on toxoplasmosis-related knowledge and practices among pregnant women and undergraduate female students in Kuwait, highlighting the limited awareness of toxoplasma infection among the participants. The practical implication of our study is the necessity to improve the knowledge of toxoplasmosis and the prevention of the disease in pregnant women and undergraduate female students. The study also showed that online data collection was quick, and the participants were more comfortable in their spontaneous responses to the questionnaire.

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Institutional Review Board Statement: The study was approved by the Ethical Committee of the Health Sciences Center, Kuwait University, and the Ethical Committee for the Protection of Human Subjects in Research, Ministry of Health, Kuwait (Reference no. 187/2014).

Competing interest: None declared

Data Availability Statement: All data are available within the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

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Original Article

Comparison of video laryngoscopy and direct laryngoscopy for nasotracheal intubation during pediatric oral surgery: a randomized clinical trial

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ABSTRACT

Objectives: Airway control is a condition that should be evaluated primarily in anesthesia practice in the pediatric age group. Failed or prolonged intubation duration can cause atelectasis and hypoxia in children. The aim of this study was to examine the effects of Macintosh laryngoscopy and McGrath video laryngoscopy (VL) on hemodynamic parameters in pediatric patients who were scheduled to undergo elective oral surgery and required intubation for the application of general anesthesia.
Design: Prospective, randomized, single-blind study
Setting: Ordu University, Training and Research Hospital, Ordu, Turkey
Subjects: Sixty-six patients were divided into two groups.
Interventions: According to the procedure used during intubation, direct laryngoscopy (DL) or VL.
Main Outcome Measures: The Cormack-Lehane and Mallampati scores, intubation duration, heart rate and mean arterial pressure values were recorded for all the patients.
Results: We found that the intubation time in the VL group was shorter than that in the DL group (P=0.024). Magill forceps were significantly less frequently used in the VL group (P<0.001). When the VL and DL groups were compared, significant differences were observed in the heart rate at minute 3 (P=0.014) and minute 5 (P<0.001), systolic blood pressure at minute 3 (P=0.008), and mean arterial pressure at minute 3 and 5 (P=0.004, P=0.002, respectively).
Conclusion: Compared with the classic Macintosh laryngoscopy, McGrath video laryngoscope reduces the intubation time, facilitates intubation and reduces the stress response to intubation. We believe that video laryngoscopy devices should be extensively used in anesthesiology practice.
ClinicalTrials.gov Identifier: NCT04677894.

KEY WORDS: direct laryngoscopy, nasotracheal intubation, pediatric oral surgery, video laryngoscopy

INTRODUCTION

Providing and maintaining airway patency is one of the main responsibilities of an anesthesiologist. Hypoxia, which may occur as a result of delays in maintaining airway patency, and eventually anoxia can lead to irreversible brain damage or death. Continuity of vital functions depends on providing and maintaining airway patency[1].

A pediatric patient is different from an adult patient in many ways and is not simply proportionally smaller than an adult. Compared with adult patients, pediatric patients are characterized by more rapid metabolism, relatively higher oxygen demand and underdeveloped respiratory systems, and adaptation mechanisms to meet these demands constitute the baseline of this approach[2]. Although the approach varies among age groups in the pediatric population, the aim of this approach is to provide airway safety and respiratory support to tissues and to operate the basic "windbag" mechanism to provide the necessary oxygen and remove carbon dioxide within the shortest time possible. As a result, child airway management

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algorithms have been developed that include different parameters according to patient age, height and weight as well as drugs, materials, techniques and even maneuvers (such as positioning)[3].

Anesthesiologists, pediatricians, pediatric intensive care physicians and emergency physicians face various difficulties in pediatric airway management. Despite new tools and techniques in airway management, endotracheal intubation remains the gold standard in securing the airway[4].

In pediatric patients, awake fiberoptic intubation is difficult or even impossible[5,6]. The video laryngoscope is a new tool produced by combining video technology and laryngoscope. Published studies on the video laryngoscope were mostly performed in adults. Studies on this issue in pediatric patients are very few in the literature[7]. In this study, we used a Macintosh laryngoscope, which is a routinely used tool in anesthesiology, and a McGrath video laryngoscope, which is a type of a newly developed video laryngoscope that has not widely been used in the pediatric age group.

The aim of this study was to examine the effects of whether Macintosh laryngoscopy and McGrath video laryngoscopy (VL) on hemodynamic parameters in pediatric patients improved the stress response and whether these approaches facilitated the intubation procedure, who were scheduled to undergo elective oral surgery and required intubation for the application of general anesthesia.

SUBJECTS AND METHODS

This study was carried out after the approval of the Clinical Research Ethics Committee of Ordu University Medical Faculty (Date: 07.26.2018; Decision No: 2018/180). The parents of the patients were informed about the study, and their written informed consent was obtained. Our study was conducted between November 2020 and June 2021.

The age, sex, weight, height and American Society of Anaesthesiology (ASA) scores of the patients were recorded during the preoperative examination. The Mallampati (MP) score was determined at the preoperative visit. "Mallampati" scores, which are a valuable test in showing the ratio of tongue size to oral cavity, were examined and scores were given from 1 to 4. According to this scoring system,

Class 1: Anterior and posterior pleats, soft palate, tonsillar bed and the uvula is seen as relaxed.

Class 2: Uvula and soft palate are visible.

Class 3: The soft palate and base of the uvula are visible.

Class 4: The uvula is completely covered by the root of the tongue; the pharyngeal wall is not visible; accepted and recorded separately for each case.

Patients with a Cormack-Lehane (CL) score of 4 and MP score of 4 during intubation were also excluded from the study. The appearance of the larynx as a result of laryngoscopy is Grade 1 to 4 according to the ''Cormack and Lehane laryngoscopy classification'' rated. According to this classification,

Grade 1: The entire glottis is visible.

Grade 2: Glottis partially visible.

Grade 3: Only the epiglottis is visible.

Grade 4: The epiglottis is also absent; accepted and recorded separately for each case.

Children with neurological diseases, severe facial and jaw deformities and children with ASA risk class III to IV were excluded from the study. Preoperative standard monitoring was performed in all the patients after the patients entered the operating room. Monitoring included electrocardiography, heart rate (HR), noninvasive blood pressure, oxygen saturation (SpO_2) and end-tidal carbon dioxide ($EtCO_2$) monitoring (DatexOhmeda Monitor Device® 3030 OhmedaDrive, Madison Wİ 53707, USA).

The study design was a prospective, single-blind randomized clinical study. Participants did not know which method to intubate themselves. Researchers knew which method to intubate patients. The first patient was intubated by direct laryngoscopy (DL) and the second patient was intubated with VL. The patients were intubated by experienced anesthesiologists. The anesthetist who collected the data was different, she/he did not know by which method the patient was intubated, because she/he always came to the operating room to collect data after the patient was covered with sterile green covers. Patients scheduled for oral surgery were sequentially randomly divided into groups without any discrimination.

Group DL: Group of patients intubated using a Macintoch blade laryngoscope (SeaMed® Maxlite Macintosh Laringoskop, Istanbul, Turkey)

Group VL: Group of patients intubated using a McGrath video laryngoscope (McGrath® Series 5, Aircraft Medical Limited, Edinburgh, UK)

Patients were randomly divided into 2 groups: direct laryngoscope intubation and as video laryngoscope intubation. In Group DL, intubation was performed using a Macintosh blade. The blade was held in the left hand, the patient's mouth was slightly opened with the right hand and the blade was placed in the oropharynx and slid through the tongue. The glottic image was recorded using the CL score. A standard guide was used for the endotracheal tube. Nasotracheal intubation was used in all the patients.

In Group VL, intubation was performed using a McGrath (McGrath® Series 5, Aircraft Medical Limited, Edinburgh, UK) video laryngoscope. All the parts of the video laryngoscope were assembled before the procedure, and the operability of the light was checked. The McGrath video laryngoscope was held

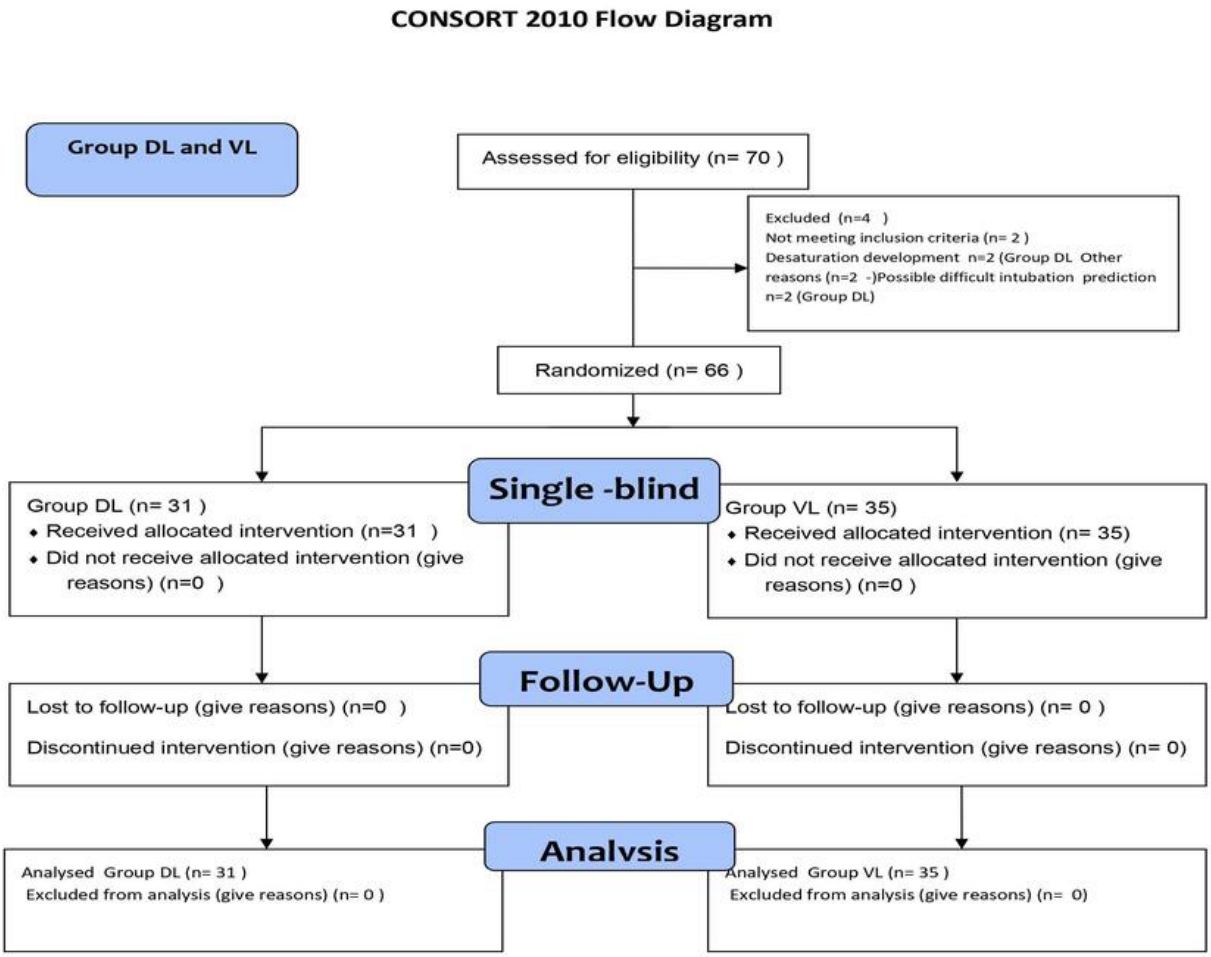

Figure 1: Flow diagram of the patients who participated in the study.

in the left hand while the patient's mouth was slightly opened with the right hand. The blade was inserted through the midline to the oropharynx and slid over the tongue. The blade was advanced until the Rima glottis was observed. The glottic image was recorded using the CL score. A standard guide was used during endotracheal intubation. The patients were intubated nasotracheally.

Considering the SpO_2 parameter, 95% confidence (1-α), 95% test power (1-β), d=1,111 effect size, the minimum number of samples to be taken in each group according to the result of two-way independent samples t test power analysis was determined as 23[8]. Since there may be cases that could be excluded from the study, more than 23 patients for each group were included in the study.

The study included 66 ASA I-II patients with an age range of 4-13 years and who were scheduled for elective oral surgery under general anesthesia with intubation. The patients were not premedicated, and the same brand of endotracheal tube was used in all the patients. During the intubation, the head of the patient was kept in a neutral position and a guide was used. Patients with preoperative oxygen saturation below 94% in room air or patients with an anticipated difficult airway were excluded from the study. Attempts with a prolonged intubation time (longer than 10 minutes) and intubations that failed after three attempts were considered failures and were excluded from the study; alternative methods were used in those patients. A failure was determined when peripheral SpO_2 dropped below 94% during the intubation procedure. In this case, the patient was mask ventilated with 100% oxygen, and alternative methods were used for anesthesia. In both groups, induction of anesthesia was started using 6% sevoflurane (Sevorane®, 250 ml Liquid, AbbVie, Illinois, USA) inhalation anesthesia and 100% oxygen. A vascular access was created using a suitable gauge cannula in patients who had no vascular access present, and infusion of 1/3 physiologic serum was started. In addition to anesthesia, intravenous infusion of remifentanil (Ultiva®, GlaxoSmithKline, Brentford, London, UK) at a dose of 0.15 μg/kg/hour was applied. After observing that the mask ventilation was

Table 1: Comparison of demographic characteristics by groups with Mann Whitney U test

Demographic variables	Statistical method	DL (n=31)	VL (n=35)	Total (n=66)	*P**
Age (year)	mean±std	7.2±3.2	6.9 ± 2.9	7(2.9)	0.769
	Median (min-max)	6 (3-13)	6 (3-13)	6 (3-13)	
Weight (kg)	mean±std	28.8±12.3	28.2±11.6	28.5±11.8	0.913
	Median (min-max)	26 (14-68)	25 (16-68)	26 (14-68)	
Length (cm)	mean±std	118.3±26.3	118±24.7	118.1±25.3	0.990
	Median (min-max)	118 (15-165)	115 (15-165)	116 (15-165)	
Duration of intubation (sec)	mean±std	58.8±24.4	47.6±12	52.8±19.5	0.024*
	Median (min-max)	58 (7-137)	45 (20-71)	51 (7-137)	

*Mann-Whitney U test; DL: direct laryngoscopy; VL: video laryngoscopy

comfortable and the lungs were ventilated, 0.6 mg/kg rocuronium bromide (Curone® 50 mg/5 ml, Istanbul, Turkey) was administered intravenously for muscle relaxation. After three minutes of ventilation with a mask, the patient was intubated with a nasotracheal tube (Portex® Ivory PVC, North Facing, Nasal, Profile Soft Seal Cuff, Polar Preformed Endotracheal Tube) of appropriate size for the age of the patient.

Patients parameters related to endotracheal intubation were evaluated. MP scores were recorded. The need for airway during mask ventilation and the need for laryngeal compression during intubation were recorded. The cause of difficult intubation (difficulty seeing the larynx, difficulty seeing the tube, difficulty in both) was recorded. Notations were also made if Magill forceps were used, laryngeal compression was performed or complications (bleeding, laceration, tooth damage, etc.) developed during intubation. In both laryngoscopy methods, the glottic image was recorded using the CL scoring system. The scores were recorded as 1, 2, 3, 4 degrees. Patients with a CL score and MP score of IV were excluded from the study. The hemodynamic parameters of the patients, such as the HR, systolic artery pressure, diastolic artery pressure, mean arterial pressure, and SpO_2 values were recorded at 0 (after intubation), 1, 3 and 5 minutes. The minute immediately after intubation was considered to be minute 0. The time between the first minute and third minute after intubation was accepted as the third minute. The 5^{th} minute after intubation was accepted as the 5th minute when the recordings were made. Additionally, the $EtCO_2$ values at minutes 1, 3 and 5 after intubation were recorded. Type (tooth extraction, cleft lip-cleft palate, etc.) and duration of surgery were recorded in both groups. The patients included in the study were intubated by anesthesiologists who were experienced and trained in video laryngoscope. The anesthesiologist performing the intubation and the anesthesiologist who followed up in the recovery room in the early postoperative period were different anesthesiologists. The authors of our study, that is, the anesthesiologists, were changed according to daily rotation. All the parameters were recorded from the beginning to the end of the operation period. Decurarization was achieved with 2 mg/kg sugammadex (Bridion ®200 mg/2 mL flakon, MSD, USA). The patients were extubated at the end of the surgical procedure and observed during the early postoperative period (first postoperative six hours) and complications (hoarseness, laryngeal edema, stridor, cough, laryngospasm) were recorded.

Statistical methods

The data were analyzed using IBM SPSS program version 23 (IBM Corp., Amrock, New York, United States). Normal distribution was analyzed using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare quantitative data with nonnormal distribution. Inter-group time changes were analyzed using the Friedman test. Categorical data were evaluated by the chi-square test. The level of significance was accepted as $P<0.05$.

RESULTS

The patients included in the study are shown in the consort flow diagram (Figure 1). Four patients in the DL group were excluded from the study. Two patients were excluded from the study due to desaturation while ventilating. Two patients were excluded due to a prediction of possible difficulty in intubation. There was no difference between the groups in terms of the age, weight and height of the patients ($P>0.05$). A difference was found in the median duration of intubation between the two groups ($P=0.024$). The median duration of intubation in the DL group was 58 seconds while it was 45 seconds in the VL group. The demographic and clinical data of the patients are presented in Table 1.

No difference was found in sex, ASA score, surgery type, MP grade, CL grade and presence of laryngeal compression between the groups ($P<0.05$).

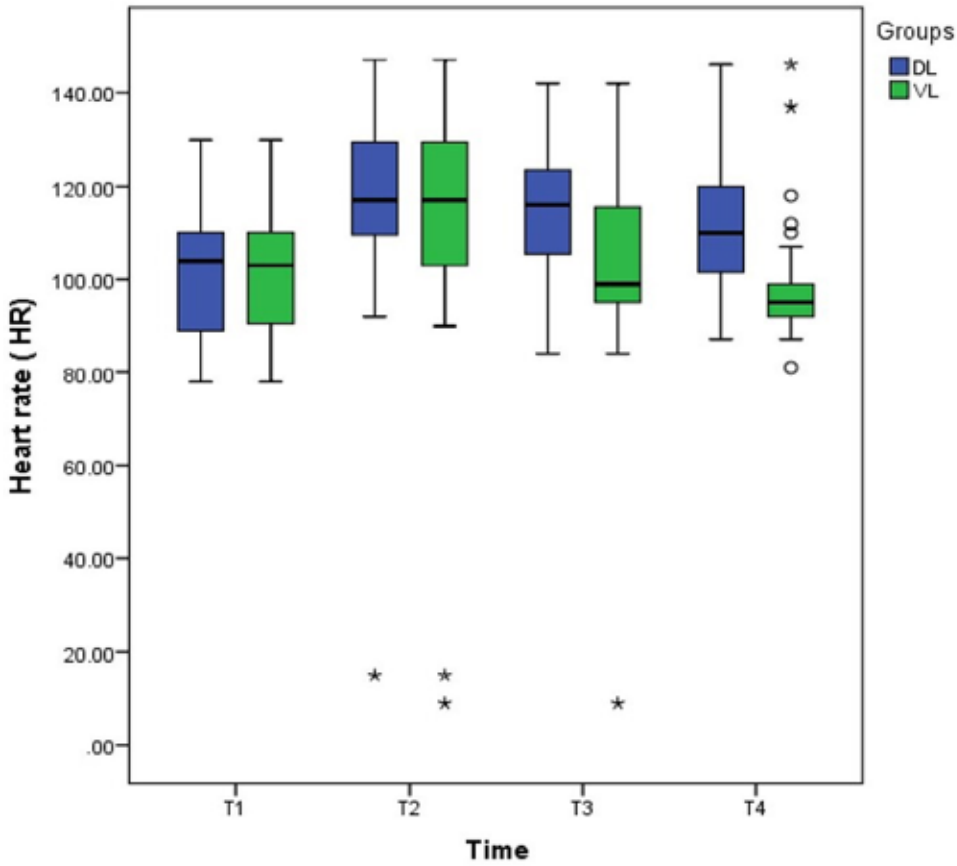

Figure 2: Graphical representation of the heart rate (HR) values of direct laryngoscopy (DL) and video laryngoscopy (VL) groups.

The use of Magill forceps varied according to the groups (P<0.001). Magill forceps were found to be used in 80.6% of the patients in the DL group and 20% of the patients in the VL group. A comparison of the categorical data is presented in Table 2.

Comparison of the median HR between the two groups revealed a difference in the median HR at minute 3 and minute 5 (P=0.014 and P=0.001, respectively). The HR was higher in the DL group. No difference was found between the groups at the other time points. Within group comparison of the DL group revealed no difference among the median values obtained at minute 3, minute 1 and minute 5. The lowest value was obtained at minute 0 (P<0.001). In the VL group, the median value was the lowest at minute 0, and there was no difference among the remaining time points (P<0.001; Table 3 and Figure 2).

The mean systolic blood pressure varied between the groups only at minute 3 (P=0.008). The value obtained in the DL group was higher than that obtained in the VL group. Within group evaluation of the DL group revealed that the minute 1 value was higher than the values at all the other time points, but there was no difference among the rest of the time points (P<0.001). Similar results were observed in the VL group (P<0.001; Table 3).

No difference was found in the diastolic blood pressure between the groups at any time point (P>0.05). Within the DL group, no difference was found among minute 0, 1 and 3, while a difference was found among the other time points (P<0.001). In the VL group, no difference was found between minute 0 and minute 1 and 3 or between minute 3 and minute 5; the values of all the remaining time points were different (P<0.001; Table 3).

The median mean arterial pressure was different in the two groups at minutes 3 and 5 (P=0.004 and P=0.002, respectively). The values were higher in the DL group. The differences at the various time points in the DL group were statistically significant (P<0.001). There was no difference between min 0 and min 1, min 1 and min 3, and min 3 and min 5. However, the groups differed at all the other time points. Similarly, the changes at the time points were found to be significant in the VL group (P<0.001). No difference was found among the values at min 0, min 1 and min 3, while differences were observed at all the other time points (Table 3 and Figure 3). No in-group or intergroup differences was found in the median SpO_2 values (P>0.05; Table 3).

The median $EtCO_2$ values were similar between the two groups (P>0.05). No difference was found between min 0 and min 3 in the DL group, while differences

Table 2: Comparison of categorical data with the chi-square test

Categorical variables	DL (%) (n=31)	VL (%) (n=35)	Total (%) (n=66)	P*
Gender				0.794
Girl	14 (45.2)	18 (51.4)	32(48.5)	
Boy	17 (54.8)	17 (48.6)	34 (51.5)	
ASA				1.000
ASA I	21 (67.7%)	23 (65.7%)	44(66.7)	
ASA II	10 (32.3)	12 (34.3)	22 (33.3)	
Type of operation				0.559
Tooth Extraction	25 (80.6)	25 (71.4)	50 (75.8)	
Cleft lip- cleft palate	6 (19.4)	10 (28.6)	16 (24.2)	
Grade of MP				0.883
Grade 1	15 (48.4)	16 (45.7)	31 (47]	
Grade 2	15 (48.4)	17 (48.6)	32(48.5)	
Grade 3	1 (3.2)	2 (5.7)	3 (4.5)	
Grade of CL				0.890
Grade 1	11 (35.5)	12 (34.3)	23 (34.8)	
Grade 2	16 (51.6)	17 (48.6)	33 (50)	
Grade 3	4 (12.9)	6 (17.1)	(15.2)	
Were Magill forceps used?				<0.001
Yes	25 (80.6)	7 (20)	32(48.5)	
No	6 (19.4)	28 (80)	34 (51.5)	
Was laryngeal compression performed?				0.067
Yes	9(29)	3 (8.6)	12 (18.2)	
No	22 (71)	32 (91.4)	54 (81.8)	

*Chi-square test, n(%); DL: direct laryngoscopy; VL: video laryngoscopy; ASA: American Society of Anesthesiology; MP: Mallampati; CL: Cormack-Lehane

were observed at all the other time points (P<0.001). Similar results were observed in the VL group, and no difference was found between min 0 and min 3, but differences were found at all the other time points (Table 3).

Patients extubated at the end of the surgical procedure were observed during the early postoperative period for complications such as hoarseness, laryngeal edema, stridor, cough and laryngospasm; none of these complications were found in any patient.

DISCUSSION

As a result of our study, we found that the duration of intubation in the VL group was shorter than that in the classic Macintosh laryngoscopy group. The use of Magill forceps was found to be significantly decreased in the VL group. Significant differences were found between the two groups in the minute 3 and 5 HR, minute 3 systolic pressure, and minute 3 and 5 mean arterial pressure. It can be concluded that VL reduces the stress response to intubation and facilitates intubation.

Currently, failure or difficulty in providing an airway in anesthesia practice is an important cause of anesthesia-related morbidity and mortality. The ASA reports difficult intubation as the third most common cause of respiratory-related death and permanent brain damage[9]. Compared to intubation in adults, intubation is more difficult in children due to the pediatric airway anatomy and the significant differences in the respiratory system. Additionally, difficult airway is encountered more frequently in the pediatric age group[10]. Since pediatric patients have decreased oxygen reserve, hypoxia and cardiac arrest can rapidly develop when difficult airways are encountered. Therefore, it is very important to control the airway in a short time in children. From the beginning of the use of the laryngoscope in anesthesia practice, alternative laryngoscope blades and instruments for intubation have been developed in order to increase the comfort of the intubation intervention and reduce the complications that may develop. With the development of laryngoscopy blades, the laryngeal structures have been better visualized, and the success rate of the intubation process has been increased[11].

To observe the glottic space with a direct laryngoscope, a line of sight is needed throughout the blade. The field of vision is limited due to oropharyngeal structures and is measured as 15°. With the video camera system placed on the tip of the blade, it is possible to better view the glottis by increasing the field of vision[12]. Video laryngoscopes are considered a different approach in intubation and laryngoscopy, as they allow an indirect view through an optical system located at the tip of the blade. The primary role of the video laryngoscope is to achieve a better performance

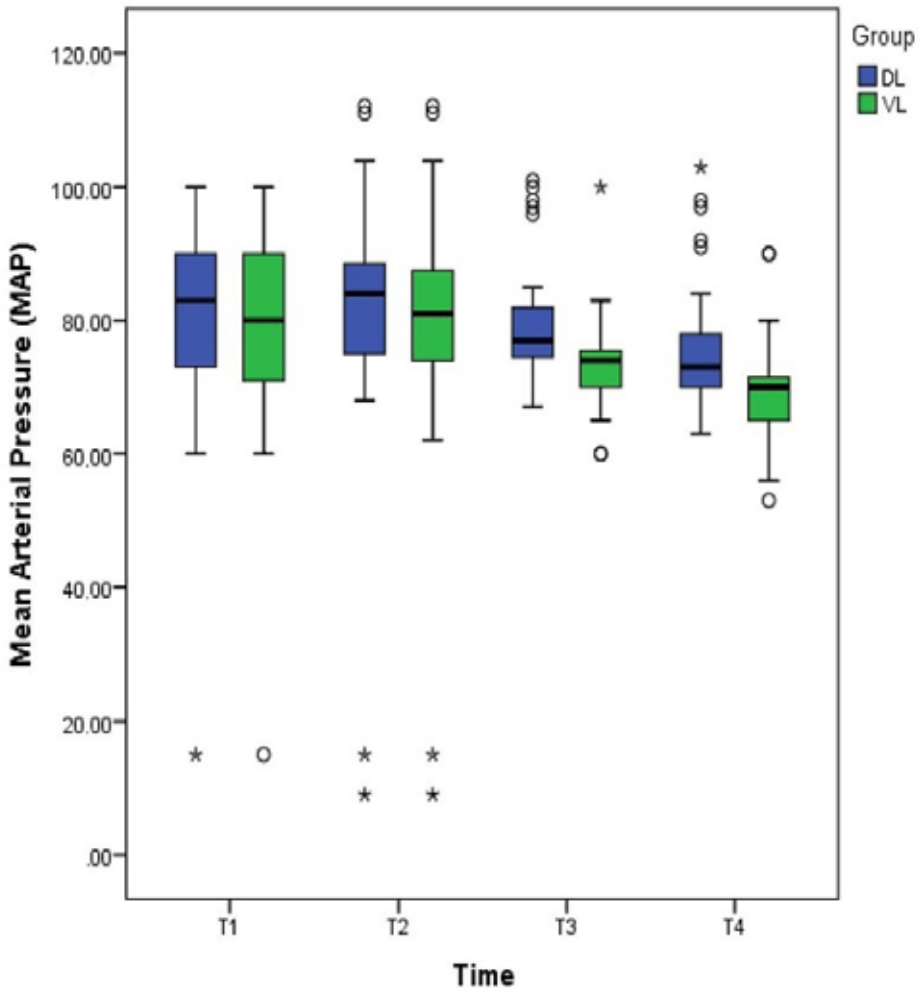

Figure 3: Graphical representation of the mean arterial pressure values in direct laryngoscopy (DL) and video laryngoscopy (VL) groups.

in intubation for patients in whom intubation is difficult or even impossible with standard methods[10]. For this purpose, studies on video laryngoscopes have been frequently conducted in recent years. There is an increase in studies on video laryngoscopes in the pediatric age group[11].

In their randomized prospective study, Vlatten *et al* compared the Storz video laryngoscope used in 56 children (aged 4 years and under) who required endotracheal intubation with the Miller 1 or Macintosh 2 laryngoscopes. The best duration of intubation was recorded as the time period between the passage of the blade through the lips and the appearance of the $EtCO_2$ curve. This time was recorded as 21 (17-29) seconds for the DL and 27 (22-37) seconds for the Storz video laryngoscope. The intubation time was found to be significantly elevated with the video laryngoscope. The CL score was recorded as a percentage of glottic patency and was found to be 97.5% for direct laryngoscope and 100% for Storz video laryngoscope. The percentage of glottic patency was significantly elevated by the use of Storz video laryngoscope. In that study, the authors concluded that use of the Storz video laryngoscope in children with normal airway anatomy improved the glottic patency percentage score by requiring a longer time for intubation[12]. In this present study, the duration of intubation was found to be shortened in the VL group. We conclude that video laryngoscope shortens the intubation time and facilitates intubation.

In our study, the CL scores of the laryngoscopic images were similar in both groups. Video laryngoscopes have been suggested to provide better quality views during intubation due to the wide angle of the blade and better visualization of the laryngeal structures on the screen. However, in our study, no statistically significant difference between the CL scores was found, similar to the study conducted by Vlatten *et al*[4]. This may be due to the exclusion of patients for whom airway difficulties were expected based on the preoperative evaluation in our study.

Table 3: Friedman test for time dependent variables between groups and Mann Whitney U test for comparisons between groups

Value	DL (n=31)		VL (n=35)		P**
	$x \pm \sigma$	Median (min-max)	$x \pm \sigma$	Median (min-max)	
Heart rate					
min 0	102.6 ± 14.1	104 (78-130) [a]	102.4 ± 14.2	103 (78-130) [a]	0.913
min 1	116.6 ± 24	117 (15-147) [b]	113.2 ± 29.8	117 (9-147) [b]	0.728
min 3	115.4 ± 14.9	116 (84-142) [b,c]	104.5 ± 23.5	99 (9-142) [b]	0.014**
min 5	111.8 ± 14.6	110 (87-146) [c]	98.9 ± 12.8	95 (81-146) [b]	0.000**
P*		<0.001*		<0.001*	
Mean arterial pressure					
min 0	80.5 ± 16.7	83 (15-100) [c]	78.8 ± 16.5	80 (15-100) [a,b]	0.571
min 1	81.2 ± 21.7	84 (9-112) [b,c]	79.9 ± 20.8	81 (9-112) [a]	0.589
min 3	79.4 ± 9.5	77 (67-101) [a,b]	73.4 ± 6.9	74 (60-100) [b]	0.004**
min 5	76 ± 10.4	73 (63-103) [a]	69.1 ± 7.9	70 (53-90) [c]	0.002**
P*		<0.001*		<0.001*	
SpO_2					
min 0	90.9 ± 26.9	100 (10-100)	91.9 ± 25.4	100 (10-100)	0.844
min 1	99.7 ± 0.7	100 (97-100)	99.7 ± 0.6	100 (97-100)	0.987
min 3	96.8 ± 16.1	100 (10-100)	97.1 ± 15.2	100 (10-100)	0.980
min 5	99.7 ± 0.6	100 (97-100)	99.7 ± 0.6	100 (97-100)	0.986
P*		0.053		0.127	
$EtCO_2$					
min 0	42.2 ± 2.4	41 (39-49) [a]	41.7 ± 2.8	41 (36-49) [a]	0.479
min 1	46.4 ± 3.8	47 (37-56) [b]	45 ± 4.7	46 (34-56) [b]	0.209
min 3	41.1 ± 3.3	42 (34-47) [a]	39.4 ± 7.3	41 (4-47) [a]	0.493
min 5	37.1 ± 3.1	37 (30-43) [c]	36.8 ± 2.9	37 (30-43) [c]	0.766
P*		<0.001*		<0.001*	

[a,b,c:] There is no difference between the time points with the same letter in the group for each parameter; *Friedman test; **Mann-Whitney U test; SpO_2: oxygen saturation (%); $EtCO_2$: end tidal carbon dioxide values; DL: direct laryngoscopy; VL: videolaryngoscopy; min-max: minimum-maximum; min: minutes

In another simulation study by Vlatten A *et* al[12], use of the Macintosh laryngoscope and GlideScope video laryngoscope was compared in pediatric models with an immobile cervical spine and with predicted difficult airways. The authors found that the video laryngoscope significantly reduced the glottic vision and prolonged the intubation time[12]. In our study, the intubation time was found to be shortened by McGrath video laryngoscope. These results were incompatible with the results of Vlatten *et al*[12], perhaps because their study was a simulation study.

Kim *et al*[13] compared the CL scores of 203 pediatric patients using the Macintosh laryngoscope and GlideScope video laryngoscope. That study intubated 100 patients with a DL and 103 patients with a GlideScope. The authors recorded the time required for intubation and the CL scores in each group. The authors recorded the tracheal intubation time as 36.0 (17.9) sec and 23.8 (13.9) sec in the groups intubated using the GlideScope and direct laryngoscope, respectively. In the same patient, the authors evaluated the CL scores using both methods and recorded an improvement in the CL score with the GlideScope. As a result, use of the GlideScope in children provided an image equal to or better than that provided by the direct laryngoscope; however, the authors concluded that this approach required longer time for intubation[13]. Unlike Kim *et al*, we used McGrath video laryngoscope in this present study. We found no difference between the CL scores. Kim *et* al[13] reported a prolonged duration of intubation with GlideScope video laryngoscope. We, on the other hand, found a significantly shorter duration of intubation in the VL group. The results of our study are contradictory to the study by Kim et *al*[13], and this might be due to the different brand of video laryngoscopes used in the two studies.

Enomoto *et al*[14] compared the ease of intubation in their study using a Pentax-AWS (Tokyo, Japan) video laryngoscope and a standard Macintosh laryngoscope in 203 patients who had limited neck movement and were scheduled to receive general anesthesia. While the authors considered all the 99 intubations performed with the video laryngoscope to be successful, they considered 93 of the 104 intubations performed with the direct laryngoscope to be successful. The authors concluded that the video laryngoscope provided favorable conditions and proper glottic imaging for intubation; however,

they stated that this observation could not guarantee an easy and successful tracheal tube placement[15]. No failure of intubation was encountered in this present study. In our study, we concluded that the McGrath video laryngoscope facilitates intubation since it decreases the need for Magill forceps and laryngeal compression maneuver. This might be because Enomoto *et al* used a different brand of video laryngoscope. In addition, the study by Enomoto *et al*[14] was performed in adult patients and not in a pediatric age group as in our study.

Tseng *et al*[15] compared intubation in 105 adult patients undergoing maxillofacial surgery using the Macintosh laryngoscope and 2 different video laryngoscopes. Among the three groups in which the Pentax video laryngoscope, Glide Scope video laryngoscope and standard Macintosh laryngoscope were used, the authors found that the nasotracheal intubation time was shortened and the rate of complications was reduced in the two groups in which a video laryngoscope was used[15]. Although the study by Tseng *et al* was focused on nasotracheal intubation in adult patients, the results were similar to ours.

Ruetzler *et al*[16] compared the use of McGrath video laryngoscope and Macintosh direct laryngoscope in adult morbidly obese patients scheduled for surgery; 130 patients were included in the study. At a confidence interval of 95%, odds logistic regression analysis revealed that the McGrath video laryngoscope provided much better glottic visualization and reduced the possibility of unsuccessful intubation compared to the Macintosh laryngoscope[16]. Our study results coincide exactly with those of Ruetzler *et al*.

In a study conducted by Javaherforooshzadeh *et al*[8], they used VL and DL while intubating cases in pediatric congenital heart surgery. They emphasized that VL prolongs the duration of intubation in this group of pediatric patients, and anesthetists should be trained to shorten this period[8]. The authors emphasized that VL significantly improves visualization. However, in our study, we found a shortened intubation time in the VL group. The study of Javaherforooshzadeh *et al* is very similar to our study in terms of the patient population age group and the number of patients enrolled in the study. In our study, in addition to the study of Javaherforooshzadeh *et al*[8], we found that VL shortened the intubation time at a statistically significant level. In other words, we can say that VL made our work much easier and provided much more patient safety, which may be related to our use of VL in our clinical practice much more.

In a study by Risse *et al*[17], the adult age group compared DL with double lumen tubes and VL in thoracic surgery. Risse *et al*[17] found results that completely corresponded with our study. The authors emphasized that VL shortened the intubation time and improved visualization, as in our study.

Our study has some limitations. The age groups could be more homogenized. The fact that the age groups were not analyzed by dividing them into subgroups is the limiting factor.

CONCLUSION

Compared to classic Macintosh laryngoscopy and Mc Grath VL shortens the time of intubation, facilitates intubation and decreases the stress response to intubation. These effects are much more important in the pediatric age group where airway control is much more important and hypoxia can develop in even seconds. Video laryngoscope will minimize the risk of infection transmission as it will reduce the exposure to patients. We believe that video laryngoscope devices should be extensively used in anesthesiology practice.

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Original Article

Comparative analysis of surgical outcomes and quality of life after cardia-preserving proximal gastrectomy and conventional proximal gastrectomy for early gastric cancer of upper third of the stomach

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ABSTRACT

Objective: Proximal gastrectomy has become an optional surgical procedure for early cancer in upper third of the stomach, but gastroesophageal reflux (GER) is a main issue of this operation. We previously reported a kind of new function preserving gastrectomy for early gastric cancer (EGC) of upper stomach, cardia-preserving proximal gastrectomy (CPPG), in which the new technique could prevent reflux esophagitis and anastomotic stricture. This study aimed to compare the surgical outcomes and quality of life (QOL) of CPPG and conventional proximal gastrectomy (CPG).

Design: A retrospective comparative analysis of 21 patients who had undergone CPPG and 14 patients who had undergone CPG from October 2006 to July 2019 was performed.

Setting: Chosun University Hospital, Gwangju, South Korea

Subjects: Surgical outcomes such as operative time, bleeding, complications and modified Postgastrectomy Syndrome Assessment Scale-45 (mPGSAS-45) questionnaires of the two procedures were compared.

Intervention: Preserving cardia for CPPG

Main outcome measures: Operative times of CPPG and CPG were 189 and 177 minutes respectively (P<0.05). There were no differences in terms of blood loss, hospital stay, complication rate and 5-year survival rate. CPPG has similar QOL and lower incidence of GER compared to CPG.

Results: CPPG is a feasible and safe surgical procedure for EGC of upper stomach.

Conclusion: CPPG has favorable surgical outcomes and superior to CPG in terms of GER.

KEY WORDS: cardia preserving proximal gastrectomy, early gastric cancer, quality of life, surgical outcomes

INTRODUCTION

With the increase in the incidence and mortality of gastric cancer worldwide, countries have launched health checkup programs and the proportion of early gastric cancer (EGC) has been increasing. EGC accounts for more than 70% of all gastric cancers and has an increased five-year survival rate higher than 90%. Therefore, the treatment of EGC, including eradicating the tumor, providing minimal invasiveness and improving patients' quality of life (QOL), has become a focus of study. Originally, total gastrectomy (TG) was performed for the EGC of upper third of stomach. Poor QOL of patients after TG make surgeons carry out function preserving gastrectomy such as conventional proximal gastrectomy (CPG) or jejunal interposition (JI). However, CPG is not commonly performed for severe gastroesophageal reflux (GER) and JI is a complicated surgical procedure making several additional bowel anastomoses. Cardia-preserving proximal gastrectomy (CPPG) can complement the TG or JI. CPPG preserve cardia and reduce GER and avoid additional jejunal resection and anastomosis.

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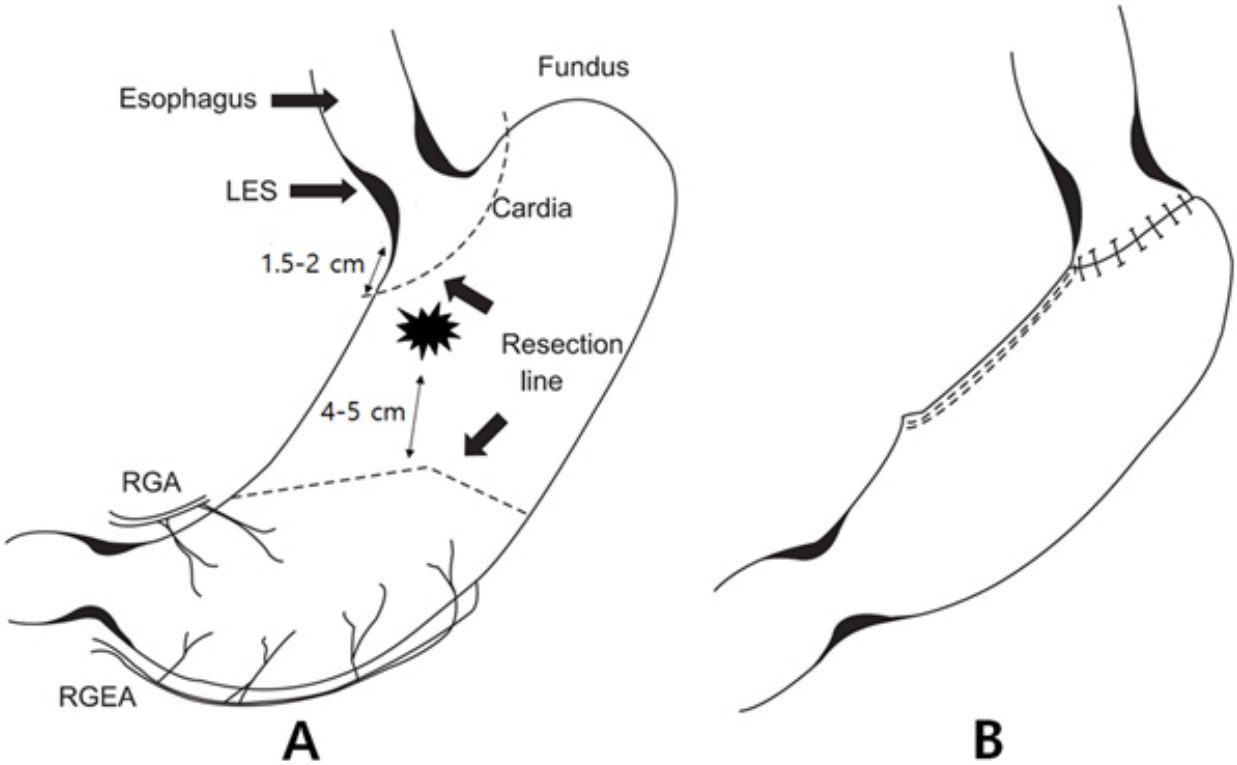

Figure 1: Illustration of CPPG. (A) The tumor located in the proximal stomach between 4 cm below EGJ and upper body. Resection was carried out 1.5 to 2 cm below the EGJ and 4 to 5 cm below the lower margin of tumor. (B) The anastomosis was performed by conventional methods or linear stapler.
CPPG: cardia-preserving proximal gastrectomy; EGJ: esophago-gastric junction; RGA: right gastric artery; RGEA: right gastroepiploic artery; LES: lower esophageal sphincter

It is performed not only with the goal of curing the tumor, but also with consideration of the patient's postoperative QOL. We reported a new method of CPPG in EGC of upper stomach in a series of 10 cases in 2012[1].

However, its clinical feasibility such as short-term surgical results, long-term oncologic results and QOL of patients are not investigated yet. This study aimed to compare the surgical outcomes and QOL of CPPG as a modified treatment for EGC in the upper third of the stomach with the CPG.

MATERIALS AND METHODS

A retrospective comparative analysis of 21 patients who had undergone CPPG and 14 patients who had undergone CPG from October 2006 to July 2019 in Chosun University Hospital was performed.

Inclusion and exclusion criteria

All patients were clinically diagnosed as EGC (T1N0) by esophagogastroduodenoscopy (EGD), computed tomography (CT). The location of tumor was a major criteria in patient selction. To save cardia with favorable proximal resection margin, the tumor should be located below the line, 4 cm from esophagogastric junction (EGJ). If the tumor was located above the line, CPG or TG was carried out. The patients were informed about this new technique and gave their consents. Open surgery was selected only when troublesome bleeding was encountered during laparoscopic surgery or the patients have considerable cardiopulmonary problem or previous abdominal surgery hindering pneumoperitoneum.

Surgical procedure of CPPG and CPG

In all patients, CPPG or CPG with D1+ dissection was performed according to the Japanese gastric cancer treatment guidelines[2]. The tumor should be located in the proximal stomach between 4 cm below EGJ and upper body. Resection was carried out 1.5 to 2 cm below the EGJ and 4 to 5 cm below the lower margin of tumor. The anastomosis was performed by conventional methods or linear stapler (Figure 1). The range of lymph node (LN) dissection in CPPG was similar to that used in CPG and the hepatic branch of the vagus nerve was preserved in all cases. Frozen biopses were performed on selectively dissected LN No. 1, 2 (Figure 2). Then, if positive, the conventional

method of TG and Roux-en-Y reconstruction were performed. During partial omentectomy, to preserve the right gastroepiploic artery, LN No. 6 was checked with fingers without enbloc dissection. The greater omentum was dissected toward the spleen to remove all LN No. 4 and the gastroepiploic vessels were dissected on 2/3 from the top to the bottom of the greater curvature and divided the short gastric vessels to separate the fundus from the spleen. The lesser curvature including LN No. 3 and 5 was dissected toward from the origin of the right gastric artery to the esophagus. The branches of perigastric vessels in the 2/3 of the lesser curvature were divided from the top and removed with the lesser omentum. The abdominal esophagus was not widely dissected to avoid damage of phrenoesophageal ligament on the diaphragm and the LN No. 1 and 2 were excised. In case of CPPG, a negative metastasis to these LNs was confirmed on the frozen biopsy, an excision was performed about 1.5-2 cm below EGJ and securing the proximal free resection margin was confirmed through a frozen biopsy. The anastomosis of remaining stomach with layers, mucosa-submucosa and sero-muscular suture, was performed by hand-sewn for laparotomy, and the gastro-gastrostomy was performed by linear stapler in case of the laparoscopic surgery. The pyloroplasty was not performed and the nasogastric tube was not inserted. The oral intake started from the 4th day after the surgery. All surgeries were done by a single surgeon in the institute.

Postoperative assessment and follow up

Patients' demographic characteristics and short-term postoperative outcome data were surveyed. Postoperative follow up was done every 6 months for two years. Two years after surgery, follow up was done annually for three years. Follow up was finished five years after surgery. Follow up survey included tumor marker of CEA, CA19-9, abdominopelvic computed tomography and esophagogastroduodenoscopy.

Reflux symptoms and oral intake were determined in an interview 1 year postoperatively because several studies had revealed that the patients were generally stable 1 year after gastrectomy. Endoscopy was performed every-year postoperatively. The Post-gastrectomy Syndrome Assessment Scale (PGSAS)-45 was used for QOL assessment in this study, multidimensional quality of life questionnaire based on the 8-Item Short-Form Health Survey (SF-8) and the Gastrointestinal Symptom Rating Scale (GSRS). The PGSAS-45 questionnaire consisted of a total of 45 questions, with 8 items from the SF-8, 15 items from the GSRS, and 22 clinically important items selected by the Japan Post-gastrectomy Syndrome Working Party[3]. Among 45 questions of PGSAS-45, 27 questions were selected and QOL survey was carried out at 1 year after surgery. Originally, PGSAS-45 was invented for patients to select five to seven-point Likert scale according to the items. However, many patients could not select the point because there was no clear definition of the point in some items. The scale was modified in this study using clear definition as follows: 0 = none; 1 = mild, medication not required; 2 = moderate, relieved by medication; 3 = severe, not relieved by medication. For the subdomain of satisfaction and dissatisfaction, we used a 5-point scale; 1 = strongly disagree; 2 = disagree; 3 = do not know; 4 = agree; 5 = strongly agree. This study was approved by the Institutional Review Board of Chosun University Hospital (No. 2020-11-005).

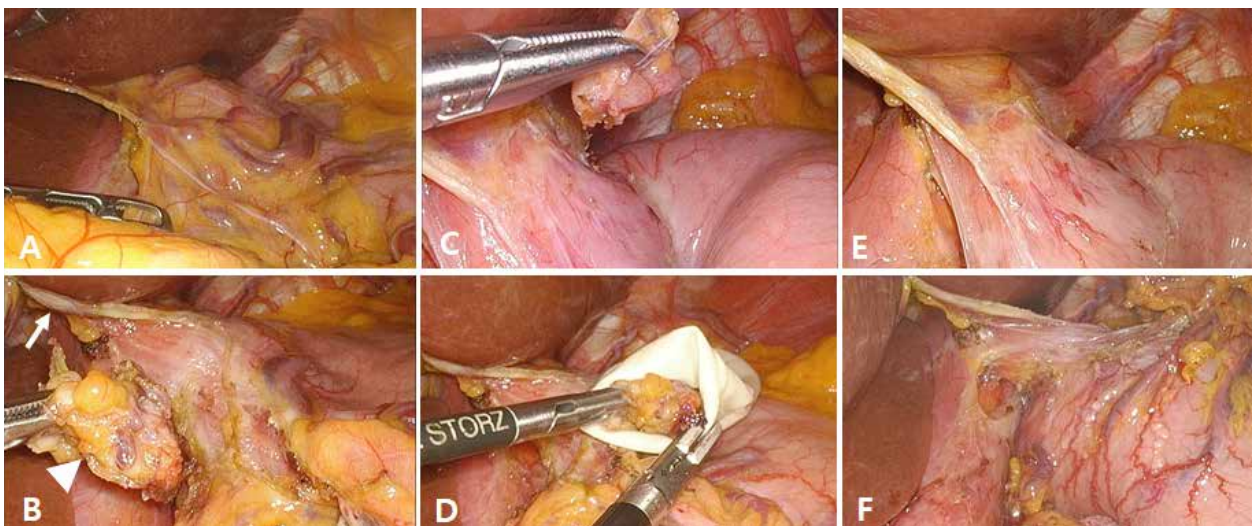

Figure 2. Laparoscopic findings of No. 1 and 2 lymph nodes extraction. (A) Multiple enlarged lymph nodes of No 1 and 2 are observed; (B) No 1 nodes are dissected (arrow head) and hepatic branch of left vagus nerve is preserved (arrow); (C) No 2 nodes are dissected; (D) No 1 and 2 nodes are entrapped in latex glove and extracted; (E-F) laparoscopic view after the extraction of No 1 and 2 nodes.

Statistical analysis

SPSS 25.0 (SPSS Inc., Chicago, IL, USA) statistical software was used for statistical analysis. Categorical data were evaluated by the chi-square test, and continuous data were evaluated by the Student's t-test. Statistical significance was defined as $P<0.05$.

RESULTS

General characteristics of the patients

Table 1 shows the demographic characteristics of the patients in this study. A total of 35 patients were enrolled. CPPG was carried out for 21 patients and CPG for 14 patients. Among 21 patients of CPPG, eleven patients chose open surgery the first time. Three patients were converted to open surgery during laparoscopic surgery. Among 14 patients of CPG, nine patients chose open surgery the first time and two patients were converted to open surgery. They were all treated for the first time. EGD and pathological confirm was performed before the surgery. The sex ratios were 1:1.3 and 1:2.5 in the CPPG and CPG groups, and the mean ages were 64.3 and 65.7 years without any significant differences. The mean body mass index and pathologic stage were not significantly different. There was no significant difference between the two groups (Table 1).

Surgical outcomes

For short-term surgical outcomes, operative time in CPPG group was longer than in CPG group, 136.4±17.0 and 127.5±20.0 minutes respectively ($P<0.05$). Total amount of blood loss during surgery in CPPG group was more than in CPG group, 115.0±20.0 and 100.0±18.0 ml respectively ($P<0.05$). However, total length of hospitalization in CPPG group was shorter than in CPG group, 7.1±2.5 and 7.9±1.8 days ($P<0.05$). The incidence of GER in CPPG group was lower than in CPG group, 28.5% and 35.7% respectively ($P<0.01$). There were two cases of postoperative bleeding, one case of intra-abdominal abscess and one case of gastric stasis in CPPG group, and one case of postoperative bleeding, one case of anastomotic leakage, one case of gastric stasis and one case of intestinal obstruction in CPG group, but all cases were managed conservatively. There was no mortality between the two groups and five-year survival rate was not different (Table 2).

Table 1: General characteristics of patients

Characteristics	CPPG (n=21)	CPG (n=14)	*P*-value
Age (years)	64.3	65.7	NS
Sex ratio (male:female)	9:12	4:10	NS
Body mass index (kg/m²)	24.6	24.3	NS
cT category (%)			
1a	21 (100)	14(100)	
cN category (%)			NS
N0	21 (100)	14 (100)	
pT category (%)			
1a	16 (76.2)	8 (57.1)	
1b	5 (23.8)	6 (42.9)	
pN category (%)			NS
N0 N1	21 (100)	14 (100)	
Surgical approach			NS
Open	14 (66.7)	11 (78.6)	
Laparoscopic	7 (33.3)	3 (21.4)	

CPPG: cardia-preserving proximal gastrectomy; CPG: conventional proximal gastrectomy; NS: not significant (P>0.05)

Table 2: Surgical outcomes

Surgical results	CPPG (n=21)	CPG (n=14)	*P*-value
Operative time (minutes)	136.4 ± 17.0	127.5 ± 20.0	<0.05
Blood loss during surgery (ml)	115.0 ± 20.0	100.0 ± 18.0	<0.05
Length of hospitalization (day)	7.1 ± 2.5	7.9 ± 1.8	<0.05
Complications (Number of case)			
Postoperative bleeding	2	1	
Anastomotic leakage	0	1	
Intra-abdominal abscess	1	0	
GER (%)	6 (28.5)	5 (35.7)	<0.01
Gastric stasis (%)	1 (4.7)	1 (7.1)	
Intestinal obstruction	0	1	
Recurrence (%)	0	0	
5-year survival rate	21 (100)	14 (100)	

CPPG: cardia-preserving proximal gastrectomy; CPG: conventional proximal gastrectomy; GER: gastroesophageal reflux
*Only *P*-values of statistical significance are shown

Assessments of QOL

Calculated QOL measurements of patients in CPPG and CPG groups were compared according to the modified items (Table 3). Among the major outcome measures, CPPG group showed significantly lower score of acid reflux, bloating symptom and bile reflux than CPG group. There were no other significant differences in QOL between CPPG and CPG groups. Also, there was no significant difference in QOL measurements between the two groups of patients for other symptoms, meals, work, dissatisfaction or satisfaction in daily life (Table 4).

DISCUSSION

Classically, TG was performed for EGC of upper third stomach. However, TG lost all the function of stomach and resulted in poor QOL and nutritional status. CPG was developed to preserve the gastric function and overcome the disadvantage of TG. In spite of the issue of limited lymph node dissection, CPG with regional lymph node dissection had positive effects on maintaining body weight and preventing post-gastrectomy anemia[4]. Korean practice guideline for gastric cancer 2018 introduced CPG with D1 lymph

Table 3: QOL of cardia-preserving proximal gastrectomy and conventional proximal gastrectomy

Subdomains	CPPG (n=21)	CPG (n=14)	*P*-value
SF-8			
Physical functioning impairment*	1.36	1.63	
Bodily pain*	1.33	1.67	
General health impairment*	2.17	2.43	
Vitality impairment*	2.45	2.22	
Social functioning restriction*	2.22	2.46	
Mental health impairment*	1.34	1.27	
GSRS			
Abdominal pain	0.57	0.65	
Stomach heat	1.23	1.20	
Acid reflux	0.57	1.23	<0.05
Nausea and vomiting	0.76	0.81	
Constipation	0.12	0.23	
Bloating	1.61	2.69	<0.05
Loose stools	0.67	0.38	
Abnormal bowel movements	0.23	0.41	
Increased stool frequency	1.45	1.72	
PGSAS			
Bile reflux	1.14	1.98	<0.05
Early satiety	1.08	0.78	
Lower abdominal pain	0.43	0.32	
Early dumping syndrome	1.76	1.53	
Late dumping syndrome	0.45	0.38	
Meals			
Decreased food intake per meal	2.71	2.54	
Decreased food intake per day	2.65	2.53	
Decreased complementary food	2.56	2.34	
Decreased Appetite	1.34	1.46	
Decreased Hunger	0.45	0.65	
Abnormal satiety feeling	1.11	1.45	
Social activity			
Impairment of ability to work	2.45	2.65	

*Higher scores indicate better conditions; in other items, higher scores indicate worse conditions.
Only *P*-values of statistical significance are shown.
QOL: Quality of life; SF-8: Short-Form Health Survey; GSRS: Gastrointestinal Symptom Rating Scale; PGSAS: Postgastrectomy Syndrome Assessment Scale; CPPG: cardia-preserving proximal gastrectomy; CPG: conventional proximal gastrectomy.

node dissection for cT1A of upper third of stomach[5]. Japanese guideline also gave similar practice guideline of CPG if more than half of the distal stomach can be preserved. In spite of original intention of preserving function, CPG showed high incidence of GER and poor QOL[6]. Several surgical techniques, such as double flap technique or jejunal interposition, were developed to reduce reflux[7,8]. However, these techniques need additional surgery and bowel anastomosis. CPPG is a relatively new surgical modification of CPG which preserve cardia and phrenoesophageal ligament which are most important anatomic structures to prevent GER. This technique does not make additional bowel resection, contrary to previous surgical techniques.

CPPG showed a longer operative time compared to CPG. This is because we separated LN No. 1, 2, 5 and 6 lymph nodes and performed frozen biopsy before excision of stomach. Preserving function should not be placed above surgical radicality. Frozen biopsy of regional LN is troublesome and time-consuming but by now, there is no reliable indicator of LN metastasis but frozen biopsy. Two-dimensional values measured using preoperative multidetector CT or peak-standardized uptake value by preoperative positron emission tomography-computed tomography (PET-CT) can help to reduce the operative time for detecting LN metastasis[9-11]. Recently, sentinel node navigation surgery is intensively investigated and show promising results to decrease the time for LN dissection[12].

Hospital stay is influenced by many factors, but anastomotic leak is most important[13]. There was one case of anastomotic leak in CPG and this patient stayed in hospital more than 90 days. Excluding this patient, there was no difference of hospital stay between CPPG and CPG groups. The rate of anastomotic leak of CPPG seems to be similar with CPG. CPPG has no advantage in terms of hospital stay. CPPG showed more blood loss during surgery than CPG. It was guessed that this was due to selective lymph node dissection for frozen section. Compared to en-bloc resection, separate lymph node dissection was a delicate procedure and bled more. In many cases, electrocautery was used for lymph node dissection. Sometimes, ultrasonically activated shears had merits of decreasing bleeding and help to reduce blood loss during CPPG[14].

CPPG helped to reduce acid or bile reflux. However, this advantage failed to promote patients' overall QOL. QOL is decided by multiple factors. It is suggested that mild to moderate GER symptoms can be controlled by medication and does not impact overall QOL. Robertson *et al* showed similar results. They assessed the GER symptoms and QOL following laparoscopic sleeve gastrectomy. In their study, a small portion of patients had troublesome GER, but overall satisfaction was high[15]. Nutritional status, strength of skeletal muscle, weight gaining or symptoms

Table 4: Main outcomes of overall quality of life following cardia-preserving proximal gastrectomy and conventional proximal gastrectomy

Subdomains	CPPG (n=21)	CPG (n=14)	*P*-value
Dissatisfaction			
Dissatisfaction with symptoms	3.45	3.67	NS
Dissatisfaction at the meals	3.34	3.65	NS
Dissatisfaction at working	3.12	3.21	NS
Satisfaction			
Satisfaction with the body	2.34	2.10	NS
Psychological satisfaction	3.21	3.54	NS

CPPG: cardia-preserving proximal gastrectomy; CPG: conventional proximal gastrectomy; NS: not significant (*P*>0.05)

after chemotherapy that were not well controlled by medication seemed to have stronger impact on QOL than reflux[16]. The rate of reflux in CPPG is higher than total gastrectomy. Because of this, some authors advocate TG for EGC of upper third of stomach. However, TG has poor surgical outcomes in terms of nutrition, surgical time and anastomotic problems. CPG and CPPG seem to be acceptable as long as the oncologic outcomes are not different.

CPG has an issue of surgical radicality. Contrary to TG, CPG has a limitation to carry out standard D2 lymph node dissection. However, if we select patients cautiously, surgical radicality does not matter. Nai *et al* investigated the survival rate of CPG and TG for EGJ adenocarcinoma (Siewert II types) and reported the overall 3-year survival rate in CPG and TG group was 65.6% and 62.6% respectively and the overall 5-year survival rate was 53.8% and 44.5% respectively. No significant difference was found between the two groups[17]. Pu *et al* made meta-analysis comparing CPG and TG about long-term survival and complications. They showed that 5-year survival rate was similar, but CPG had higher recurrence rate and anastomotic stenosis rate[18]. By now, CPG is not inferior to TG for 5-year survival rate. Since CPPG needs to retain the nerve and blood supply of the cardia, the dissection of corresponding regional lymph nodes is greatly affected. This is the main debate about the radicality of CPPG. At first, we selected 21 patients with cT1a for CPPG. There were six pT1b. Recently, we have used endoscopic ultrasound to evaluate the cT and cN stage and the discrepancy will be decreased and give better oncologic outcomes. In this study, the 5-year survival rate of CPPG was not different from CPG. CPPG has similar surgical radicality but superior in some aspect compared to CPG. So, it is suggested that CPPG was a modified surgical procedure for upper third EGC rather than TG.

There are some limitations in this study. Since this study was retrospective in design and the degree of gastrectomy was not controlled, there was a significant difference in the size of the residual stomach. To evaluate the GER or other postoperative complication, this study needed to measure residual volume of stomach after CPPG. Namikawa reported that a larger proximal residual stomach resulted in less weight loss and dissatisfaction with meals and daily life. To evaluate the true impact of CPPG on QOL, it needs to measure the metric of remnant stomach[19]. CPG is being tried for advanced gastric cancer of upper stomach. It needs to evaluate the clinical feasibility of CPPG for advanced gastric cancer[20,21]. Reflux and other anastomotic problems take place several years after surgery. One meta-analysis demonstrated that weight loss and QOL decreased throughout the post-operative 5 years[22]. We investigated QOL one year after surgery. Exact QOL investigation needs longer follow up. QOL about reflux needs more objective tests such as endoscopy or acidity test. Since symptoms of reflux do not always accompany endoscopic findings, exact diagnosis of reflux needs endoscopic evaluation[23]. We could not clarify why decrease in GER failed to improve QOL. If the QOL evaluation was designed sophisticatedly, we could have found the relation between GER and QOL.

CONCLUSION

CPG was carried out for the EGC of upper third of stomach. Compared to CPG, CPPG has similar short-term and long-term surgical outcomes and better QOL reducing GER and hospital stay. We recommend that if the tumor is located below the line of upper body 4 cm from esophagogastric junction, CPPG seems to substitute CPG in EGC of upper third gastric cancer. Surgeons need to consider CPPG as the useful option for the treatment of early upper third gastric cancer.

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Conflict of interest: None

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Original Article

Effect of intelligent walker on walking function in children with spastic diplegia

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ABSTRACT

Objective: This study aims to explore the effect of intelligent walker on walking function in children with spastic diplegia.
Design: Prospective
Setting: Study was carried out at the Third Affiliated Hospital of Jiamusi University, Heilongjiang, China from September 2018 to November 2019.
Subjects: Forty-six patients with spastic diplegia were selected for the study.
Intervention: Patients were divided in two groups randomly. The patients in the control group were subjected to conventional intervention, and those in the observation group were treated with intelligent walker based on the conventional intervention.
Main outcome measures: The Gross Motor Function Measure-88D (GMFM-88D) and E scores, modified Ashworth scale scores and ankle motion range was observed between the groups before and after the intervention.
Results: The scores of dimension D, dimension E and dimensions DE were significantly increased after the intervention in the observation group compared with those before intervention in the control group ($P<0.05$). The modified Ashworth scale scores were significantly lower in the observation group after intervention than those before intervention in the control group ($P<0.05$). The active and passive range of motion were significantly higher in the observation group after intervention than in the control group ($P<0.05$). In the observation group, three cases presented skin discomfort, but it was tolerable and did not affect the subsequent treatment.
Conclusion: The intelligent walker can improve the functional recovery of patients with spastic diplegia after treatment, it can improve the walking function of children, reduce the spasm of lower extremity muscles, increase the ankle range of motion, and is worthy of clinical application.

KEY WORDS: intelligent walker, spastic diplegia, walking function

INTRODUCTION

Spastic diplegia is a symptom of cerebral palsy mainly with mental damage, which is characterized by increased muscle tone of the lower limbs[1]. Children often show hypotonia of the lower limbs within 1-3 months, followed by the so-called hypotonia period. When the child is in a standing position and the soles of the feet touch the examination table, the lower limbs will be induced to straighten and cross scissors. Finally, it enters the spastic phase, with flexion of the hip and knee joints, internal rotation of the lower limbs, and scissors gait[2]. In severe cases, they cannot walk independently. The upper limbs are slightly involved, and they often show abnormal posture of the upper limbs when walking, but the function of the hands is not obvious. Currently, effective conventional methods for the treatment of cerebral palsy contain neurodevelopmental therapy, botulinum toxin A, traditional Chinese medicine, massage and physical agent therapy. Nevertheless, previous rehabilitation training paid more attention to the coordination of functions and the musculoskeletal system, and lacked the training for innervation, thereby resulting in unsatisfactory results[3]. Through the information input of low-frequency pulse current stimulation, the

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intelligent walker forms excitement trace in the cerebral cortex, improves muscle tension, induces effective local muscle movement, gradually improves lower limb movement and helps the recovery of nerve stimulation[4]. This study was designed to explore the effect of intelligent walker on the walking function of children with spastic diplegia.

SUBJECTS AND METHODS

General information

Children with spastic diplegia treated in our hospital from September 2018 to November 2019 were enrolled as the research subjects. Inclusion criteria: (1) definite diagnosis with clinical symptoms, signs, electroencephalograph, in accordance with the Diagnostic Criteria of Spastic Diplegia in the Diagnosis and Classification Criteria of Cerebral Palsy formulated by Chinese Guidelines for Rehabilitation of Cerebral Palsy in 2015[5]; (2) age range from 3 to 12 years old, irrespective of sex; (3) gross motor function measure (GMFM) levels I–III[6]; (4) Spastic diplegia is mainly based on the whole body flexion mode, the major joints are flexed, adducted and internally rotated, the range of motion (ROM) becomes smaller, the anti-gravity extension is insufficient, the lower limbs are limited in separation movement, and the lower limbs support body weight when the soles of the feet touch the ground followed by difficult and small movement range, fixed direction, slow movement rate. The visual problem of spastic diplegia leads to slow visual development, insufficient visual experience effects and insufficient visual function development, which affects the speed and quality of gross and fine motor development. The guardian of the child was informed about the study and signed informed consent was taken for the study.

Exclusion criteria: those who had undergone orthopedic surgery; those who had taken inotropic drugs within the past 2 weeks or received botulinum toxin treatment within 6 months; history of epilepsy; inherited metabolic diseases, severe dysfunction of the heart, liver and kidney hematopoietic system; dysfunction of vision, hearing, touch and cognition, or mental illness; combined with hip dislocation, hip dysplasia, polio sequelae, congenital spinal deformity, neuromuscular junction transmission disorder or a history of trauma to the brain, spine, or lower limbs; drug dependence; those who have been included in other clinical studies and may affect the determination of the results of this study. Using the random number table method, 46 children were assigned to the control and the observation groups (n=23 per group). The baseline data were not significantly different between the two groups (P>0.05), and they were comparable (Table 1).

Table 1: Comparison of baseline data of children from the two groups

Clinical features	Control group (n=23)	Observation group (n=23)	t/χ2	P
Sex [male/female n(%)]	15/8	13/10	0.365	0.546
Age (X̄±S, year)	7.53±1.49	7.62±1.57	-0.363	0.718
Muscle tension score (X̄±S, point)	3.02±0.61	3.11±0.59	-0.278	0.782
GMFM classification [I/II/III, n(%)]	5/10/8	4/12/7	0.437	0.861

GMFM: Gross motor function measure

Research methods

Children in the control group underwent neurotrophic treatment and conventional rehabilitation training, including exercise therapy, occupational therapy, speech therapy, sensory integration therapy and massage therapy. Neurotrophic treatment includes: (i) Monosialyltetrahexose ganglioside, once a day, 20 mg intravenously each time, 10 times a month, continuous use for three months; (ii) Rat Nerve Growth Factor for injection, 30μg intramuscular injection each time, once every other day, for three months. On the basis of the treatment in the control group, subjects in the observation group were treated with the intelligent walker. The DC-L-500 intelligent walker was utilized in the functional electrical stimulation mode (Figure 1). Electrode sheets were placed on the common peroneal nerve and anterior tibial muscle. Gait sensors were fixed on the calf. Static mode was set at a pulse width of 100 μs and pulse frequency of 20 Hz. The current intensity gradually increased from 10 mA until the patient's foot presented ideal movement and discomfort. Each stimulation lasted for 5 seconds, for 20 minutes. The dynamic mode started after the static mode, and the corresponding angle parameters were set at a pulse width of 200 μs and frequency of 40 Hz; the current intensity was the same as that in the static mode. The stimulation lasted for 15 minutes. Patients were treated once in the static mode and once in dynamic mode per day. The treatment was performed from Monday to Friday for 8 consecutive weeks.

Observation indicators

Before and after the intervention, GMFM-88 items were used to assess the improvement of children's walking function. GMFM-88 items include lying and rolling (dimension A, including 17 items), sitting (dimension B, including 20 items), crawling and kneeling (dimension C, including 14 items), standing (dimension D, including 13 items), walking, running and jumping (dimension E, including 24 items), a total of 88 items. Each item score ranges from 0 (nothing) to 3 (severe) points. Walking-related dimension D and

Table 2: Comparison of motor function between the two groups before and after intervention (ẋ ± S, point)

Group	n	Time	Dimension D	Dimension E	Dimension D + Dimension E
Control	23	Before Intervention	19.57±4.86	30.05±4.62	49.62±6.03
		After Intervention	26.45±3.92*	38.59±5.02*	65.04±6.19*
Observation	23	Before Intervention	19.89±4.07	30.88±4.27	50.77±5.82
		After Intervention	31.16±5.02*#	45.62±5.03*#	76.78±7.68*#

Note: *P<0.05, vs. before intervention; #P<0.05, vs. control group in the same period.

dimension E were selected in this study. A higher score indicates better motor function of the child. Before and after the intervention, the modified Ashworth scale was applied to evaluate the muscle tension and the ROM of the ankle joint.

Statistical analysis

Data were analyzed using SPSS 23.0 software. Measurement data were expressed as the mean ± standard deviation (±S) and analyzed using a *t*-test. Count data were expressed as rate or percentage and analyzed using the χ^2 test. A value of P<0.05 was considered statistically significant.

Ethical clearance

Ethical clearance was obtained from the institutional committee of Third Affiliated Hospital of Jiamusi University and informed written consent was obtained from the parents or guardian of the participants.

RESULTS

Comparison of walking function in children of the two groups before and after intervention

There were no significant differences in the scores between dimension D, dimension E and the dimensions DE (GMFM-88) in the two groups before the intervention (P>0.05). The scores in dimension D, dimension E and dimensions DE were significantly higher after the intervention than those before the intervention in the two groups (P<0.05). The scores were significantly higher in the observation group than those of the control group in the same period (P<0.05; Table 2).

Comparison of muscle tension between the two groups before and after intervention

The modified Ashworth scale scores were not significantly different between the two groups before intervention (P>0.05), but found to be significantly lower after intervention than those before intervention in the two groups. The above scores were significantly lower in the observation group than those in the control group in the same period (P<0.05; Table 3).

Comparison of the active and passive ROMs of the ankle joint between the two groups before and after intervention

The active and passive ROMs were not significantly different between the two groups before intervention (P>0.05). The ROMs were significantly higher in the observation group than those in the control group in the same period after intervention (P<0.05; Table 4).

Adverse reactions

During the application of the intelligent walker, three children presented skin discomfort in the observation group, but it was tolerable and did not affect the subsequent treatment.

DISCUSSION

Cerebral palsy, defined as a disorder of movement and postural development caused by central nervous system injury, is a common cause of dyskinesia in children. In Europe, there are approximately 2.11 children with cerebral palsy per 1000 children. Statistical data in China showed that approximately 6 million children suffered from cerebral palsy in 2018. The number may increase at a rate of 46000 per year in the future. Cerebral palsy has become an important factor affecting the quality of life of children in China[7,8]. Approximately 60% of cerebral palsy belongs to spastic cerebral palsy, and spastic diplegia accounts for 32% of cerebral palsy. Spasticity refers to the speed-dependent increase in the tension-stretch response when the tendon hyperreflexia occurs, mainly due to the reduction of inhibitory lower motor neuron

Table 3: Comparison of modified Ashworth scale scores before and after intervention in the two groups (ẋ ± S, point)

Group	n	Before Intervention	After Intervention	t	P
Control	23	3.02±0.61	2.12±0.57	3.702	0.001
Observation	23	3.11±0.59	1.59±0.61	5.427	< 0.001
t		-0.474	2.577		
P		0.638	0.013		

Table 4: Comparison of active and passive ROMs of the ankle joint before and after intervention in the two groups (X ± S, °)

Group	n	Time	Active ROM	Passive ROM
Control	23	Before Intervention	5.03±2.86	15.32±5.43
		After Intervention	6.72±1.87*	17.44±4.20*
Observation	23	Before Intervention	5.16±1.99	15.08±4.96
		After Intervention	9.14±3.05*#	19.83±4.22*#

Note: *P<0.05, vs. before intervention; #P<0.05, vs. control group in the same period.
ROM: range of motion

impulse[9]. Ankle plantar flexor spasm, ankle dorsiflexor weakness, and poor selective control can lead to foot drop or clubfoot, resulting in a decreased walking distance and an increased incidence of trips and falls, which seriously impacts mobility, especially walking ability[10]. Improving children's motor function and quality of life and helping children return to family and society as soon as possible is the focus of intervention for spastic diplegia. Unlike many other diseases, there is no cure for spastic diplegia. Suppressing abnormal postures, promoting the establishment of normal exercise patterns, and reducing the occurrence of musculoskeletal deformities are the main points of the intervention[11].

The current treatment methods focus on rehabilitation, such as Bobath for inhibiting abnormal postures and movement patterns, and promoting normal postures and movement patterns, but the lack of training for innervation has led to poor results[12]. Some scholars also choose ankle-foot orthosis for children with insufficient dorsiflexion during the swing phase; however, the ankle-foot orthosis restricts active movement and easily aggravates muscle weakness; moreover, the compliance of children wearing ankle-foot orthosis is low[13]. A recent study has confirmed that in the treatment of spastic diplegia, the rehabilitation and reconstruction of the children's nerves should be emphasized to promote significant improvement and recovery of the motor function of the lower limbs[14]. The intelligent walker belongs to the category of functional electrical stimulation, which directly stimulates the anterior tibial muscle or peroneal nerve (that is, indirectly stimulates the anterior tibial muscle, other extensor muscles and peroneal muscle group). Electrically stimulating the muscles with impaired motion control can result in muscle contraction so as to obtain useful movement function. The intelligent walker can be employed as a dynamic functional orthosis.

The results from this study demonstrated that the GMFM-88 dimension D and dimension E scores were remarkably improved, and the modified Ashworth score was dramatically reduced in the observation group after intervention. These results suggest that the intelligent walker improves walking function and lower extremity muscle spasm, which may be

Fig 1: DC-L-500 Intelligent walker with electrical stimulation and sensors

associated with the following factors: (1) The intelligent walker generates a bidirectional action potential through an electric field to induce direct depolarization of muscle fibers. (2) The intelligent walker directly stimulates the common peroneal nerve when landing and activates the dorsiflexor muscle in the swing phase of gait so as to improve muscle strength of the lower limbs, which can improve the coordination of antagonistic muscles and agonistic muscles, and improve joint stability. (3) The functional electrical stimulation of the intelligent walker can improve the excitability of the cerebral cortex and the control function of the central nervous system over the limbs. The results from the present study showed that the active and passive ROMs of the ankle joint were higher in the observation group than those in the control group after intervention. These results suggest that the intelligent walker can increase the strength of ankle dorsiflexion, and it is also an important way for the intelligent walker to exert its therapeutic effect, which is consistent with a previous study[15]. Skin irritation is a common adverse reaction of the intelligent walker[16]. Although three children in this study experienced skin discomfort, it did not affect the subsequent treatment. Theoretically, the current of the intelligent walker may be conducted throughout the body, which may induce epilepsy and/or heart attacks. Thus, the present study excluded the above risky diseases. The findings from this study suggest that the intelligent walker is safe to treat spastic diplegia after strictly grasping the indications.

Limitation

This study may have some bias, as children with spastic diplegia were all from our hospital who came for the treatment. Therefore, the selection of inclusion and exclusion is subjective, and the results of the study may not be completely relevant as sample size is small and a higher number of patients should be included in this type of treatment to access the effectiveness of treatment. Also, representativeness may be biased in this study.

CONCLUSION

The study revealed that the intelligent walker can improve the functional recovery of patients with spastic diplegia, it can improve the walking function of children, reduce the spasm of lower extremity muscles, increase the ankle ROM, and is worthy of clinical application. This treatment strategy has provided an insight for the better treatment of children with spastic diplegia and needs to be reciprocated for developing a promising treatment regime for this disease.

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Conflict of interest: Authors declare no conflict of interest

Ethical approval: Research was approved by institutional board. The guardian of the children were informed about the study and signed an informed consent.

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Authors contribution: Zhao Yanbo, Li Jiaxia, Fan Yanping, Guo Jin: methodology, investigation, data curation; Zhang Shuai, Kang Beibei: data analysis review & editing; Zhao Yanbo, Li Jiaxia, Fan Yanping, Zhang Shuai, Kang Beibei, Guo Jin: review, editing and original draft writing. All authors reviewed the results and approved the final version of the manuscript.

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Original Article

Evaluation of the effect of the position on intraoperative cerebral oxygenation and postoperative cognitive functions in patients with the beach-chair position: a pilot study

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ABSTRACT

Objective: This study aimed to evaluate the effect of the beach-chair position on intraoperative cerebral oxygenation and postoperative cognitive functions in different age groups by comparing the data of patients who were under 65 years of age with those ≥65 years of age.
Design: Prospective cross-sectional study
Setting: Department of Anesthesiology and Reanimation, Hacettepe University Medical School, Ankara, Turkey.
Subjects: Fifty patients who underwent shoulder surgery were included in the study. Intraoperative hemodynamic and brain oxygenation were measured with invasive arterial blood pressure monitoring and Near-Infrared Spectroscopy (NIRS). Neurocognitive functions were evaluated using the Mini-Mental Test (MMT).
Intervention: The first test (MMT1) was performed during the preoperative evaluation and the second test (MMT2) was performed within the first 24 hours after the operation.
Main outcome measure: Preoperative (MMT1) and postoperative (MMT2) MMT results were similar when evaluated between groups (*P*=0.377).
Results: There was no statistically significant difference between the groups in terms of NIRS, blood pressure, heart rate or end-tidal carbon dioxide values at any time. Preoperative (MMT1) and postoperative (MMT2) MMT results were similar when evaluated between groups (*P*=0.377).
Conclusions: The beach chair position during shoulder surgery was found to result in hemodynamic fluctuations regardless of the patients' age, and a change in brain tissue oxygenation which parallels the fluctuations in hemodynamic parameters was observed. The MMT test results were similar in both age groups.

KEY WORDS: geriatric assessment, near-infrared, postoperative cognitive complications, sitting position, spectroscopy

INTRODUCTION

The beach-chair position has been a preferred position in shoulder operations since the early 1980s. It is preferred over the lateral decubitus position due to the surgical advantages such as better visualization of the joint, ease of transition to open surgery when necessary, and a lower incidence of neurovascular complications[1,2]. Approximately two-thirds of shoulder procedures in the USA are performed in this position[3]. As a result of changing positions under general anesthesia from the supine to the sitting position, undesirable effects such as decreased blood pressure, decreased cardiac output and cerebral perfusion occurs. Alongside the surgical advantages, severe complications due to the beach-chair position such as stroke, coma, spinal cord ischemia and temporary vision loss have been reported in the literature[4].

Postoperative cognitive dysfunction (POCD) can be observed as a common complication in elderly patients after cardiac and non-cardiac major surgery[5]. POCD refers to patients who do not have mental impairment before anesthesia but who have permanent or temporary impairments in memory and abstract

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thinking and a marked decrease in social activities after anesthesia. The postoperative POCD rate is as high as 10-62%, especially in elderly patients, and it seriously affects the social life skills and quality of life of the patients[6]. The etiology of POCD may be due to many factors such as the duration and extent of the surgery, the position of the patient during surgery and associated blood pressure-brain perfusion changes, general anesthetics, postoperative analgesia, increased hospital stay as well as metabolic and endocrinal causes[7]. Although it is predicted that the possibility of cerebral desaturation due to position changes in elderly patients is high, there are also studies in the literature showing no difference between the age group in terms of cerebral desaturation after position change[8].

Today, there are many tests to evaluate cognitive functions. One of these, the Mini-Mental Test (MMT), was first published in 1975 by Folstein *et al*[9]. It is a practical tool to evaluate cognitive performance. It is frequently preferred by researchers in studies evaluating cognitive functions, as it is easy to apply, valid and reliable, and can be applied to patients with low education levels as well. Güngen *et al*[10] conducted a study on the validity and reliability of MMT in Turkish society in 2002. The validity and reliability of the revised form of the test was studied by Keskinoğlu *et al*[11].

Near-Infrared Spectroscopy (NIRS) is a specialized non-invasive monitoring method used to evaluate tissue oxygenation, especially cerebral regional oxygen saturation in adult patients. Regional measurement is taken from the right and left frontal lobes, 1.5-2 cm below the skin, with two separate sensors attached to the forehead area, 2 cm above the eyebrows. Infrared light at 730 and 810 nm wavelengths is used to measure hemoglobin oxygen saturation changes in the region below the sensor. It measures the change in concentration by using the difference in the absorption of oxygen and deoxygenated hemoglobin[12,13].

In this study, we aim to compare the data of patients under 65 years of age with patients aged 65 years and over and evaluate the effect of the beach-chair position, which is thought to cause intraoperative hypotension and a decrease in cerebral oxygen perfusion, on intraoperative cerebral oxygenation and postoperative cognitive functions.

MATERIALS AND METHODS

Ethics committee approval for this study was obtained from the Non-Interventional Clinical Research Ethics Committee (Date: May 16th, 2017, No.: 16969557-760, Project No.: GO 17/353) of Hacettepe University. All patients were given information about the trial, and all provided written informed consent. The research was performed following the ethical principles for medical research involving human subjects of the 1964 Declaration of Helsinki and all of its subsequent revisions (revised 2013).

Fifty adult patients with American Society of Anesthesiologists (ASA) scores ranging from I to III, aged 21-78, who underwent shoulder surgery between June 1, 2017 and December 31, 2018 were included in the study. The patients were divided into two groups: under 65 years old (Group I) and 65 years and above (Group II). Patients with dementia and previous neurological diseases, patients who received anesthesia in the last month, and patients who did not sign consent forms for the study were excluded from the study. The pre-operative evaluation was done at least one day before surgery, all information about the study was provided, informed consent was obtained from all of the patients and the first Mini-Mental Tests (MMT1) were applied.

Patients were not premedicated before being taken to the operating room where vascular access was established on the dorsum of the hand of the non-operated side with a 20G Intra Cath. Invasive arterial blood pressure monitoring was achieved by applying electrocardiography, pulse oximetry and radial artery cannulation from the contralateral upper extremity. Near-Infrared Spectroscopy (NIRS, Invos 5100 Somentics/Covidien, Inc., Mansfield, MA) was used to monitor cerebral oxygenation. After being pre-oxygenated with 100% oxygen for five minutes, induction was performed with 2.5 mg/kg propofol, 0.6 mg/kg rocuronium and 0.5 mcg/kg fentanyl. Endotracheal intubation was performed and the tube's location was confirmed; after the endotracheal tube was fixed, all patients were placed in the beach-chair position for surgery. In order to prevent venous pooling in the lower extremity, all patients were dressed in compression stockings before the operation. Information such as patient file number, age, height, weight, ASA score, education status, comorbidities, the surgical method used, duration of operation, duration of anesthesia, amount of bleeding and MMT results were recorded in the patient follow-up and evaluation form. In addition, NIRS (right and left separately), arterial blood pressure, heart rate, oxygen saturation (SpO_2), and end-tidal carbon dioxide ($EtCO_2$) values were recorded starting from preinduction to after extubation as follows: pre-induction (T1), after induction (T2), before (T3) and after taking the position (T4), at 15-minute intervals during the perioperative period (T5, T6, T7, T8, T9, T10), at the end of surgery (T11), after returning to supine position (T12) and after extubation (T13). The measurements T5-T10 were recorded as needed depending on the operation time. There were fewer recordings for shorter operations and a higher number of recordings for longer operations.

During the maintenance period, 2% sevoflurane, 50% N_2O + 50% O_2 were administered to all patients

Table 1: Demographic data of the patients, operation times and anesthesia durations

Parameter	Group ı Age <65 (n=33)	Group ıı Age ≥65 (n=17)	All patients (n=50)	*P*
Height (cm)	166.79±9.7	160.65±9.3	164.7±9.91	0.037
Weight (kg)	77.24±13.16	75.18±12.8	76.54±12.95	0.598
Gender (F/M)	17/16	13/4	30/20	0.088
Operation time (min)	74.73±20.11	86.29±17.54	78.66±19.88	0.051
Anesthesia period (min)	101.94±22.5	115.94±20.43	106.7±22.62	0.037
ASA score				<0.001
I (n (%))	17 (51.5)	0 (0)	17 (34)	
II (n (%))	15 (45.5)	12 (70.6)	27 (54)	
III (n (%))	1 (3)	5 (29.4)	6 (12)	
Educational status (n (%))				0.610
Primary school	10 (30.3)	8 (47.1)	18 (36)	
Secondary school	3 (9.1)	2 (11.8)	5 (10)	
High school	7 (21.2)	3 (17.6)	10 (20)	
University	9 (27.3)	4 (23.5)	13 (26)	
Master degree	4 (12.1)	0 (0)	4 (8)	

ASA: American Society of Anesthesiologists
cm: centimeter; kg: kilogram; F: Female; M: Male; min: minute; n: number of patients

with a fresh gas flow of 4 L/min. Severe bradycardia (peak heart rate <45) in the perioperative period was treated with 0.5 mg atropine IV. If patients had hypotension (mean arterial pressure <60 mmHg), ephedrine 5 mg IV was administered. Patients with adequate spontaneous breathing who opened their eyes with verbal stimulation were extubated and sent to the recovery unit.

Cognitive functions were evaluated with the MMT. The MMT consists of 19 questions grouped into 5 sections: orientation, recording memory, attention and calculation, recall and language; it is scored with a potential total of 30 points. The "standardized practice guide" developed by Molloy *et al* has increased the test's reliability and compatibility by minimizing the differences that occur during the application between

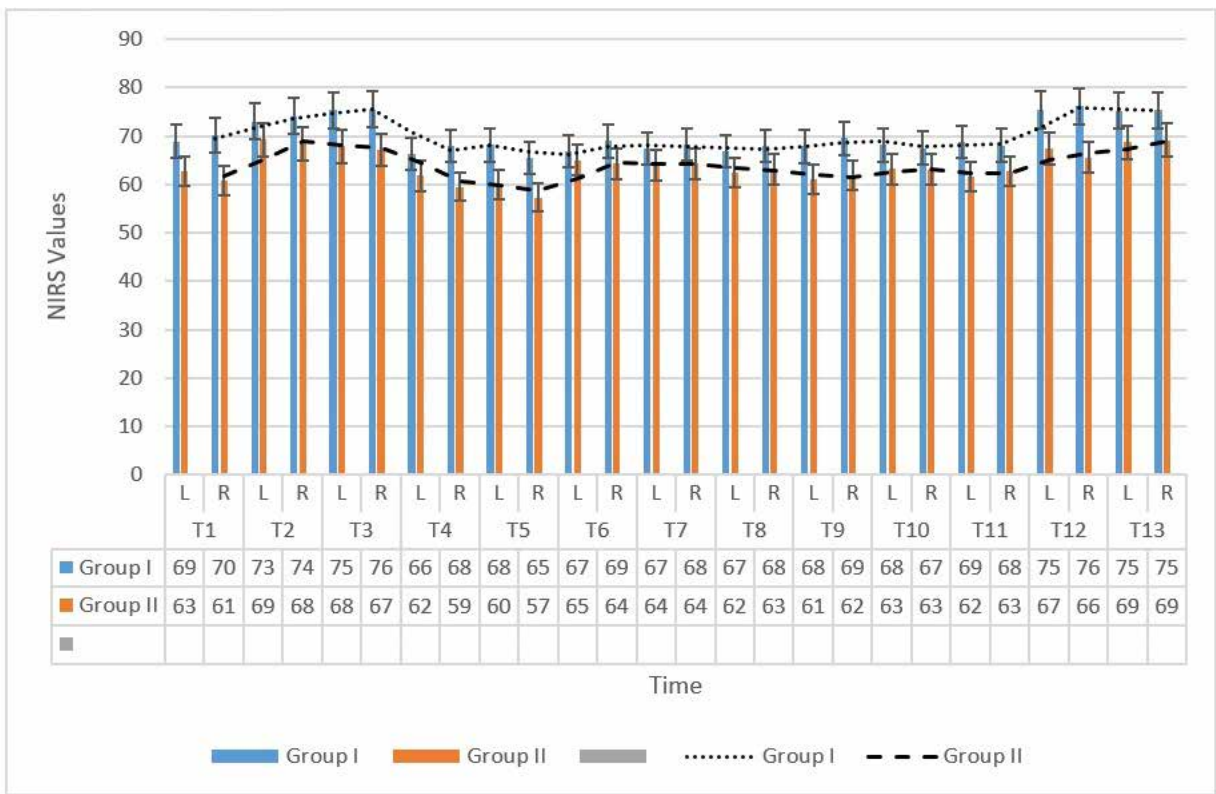

Figure 1: NIRS values
L: left, R: right

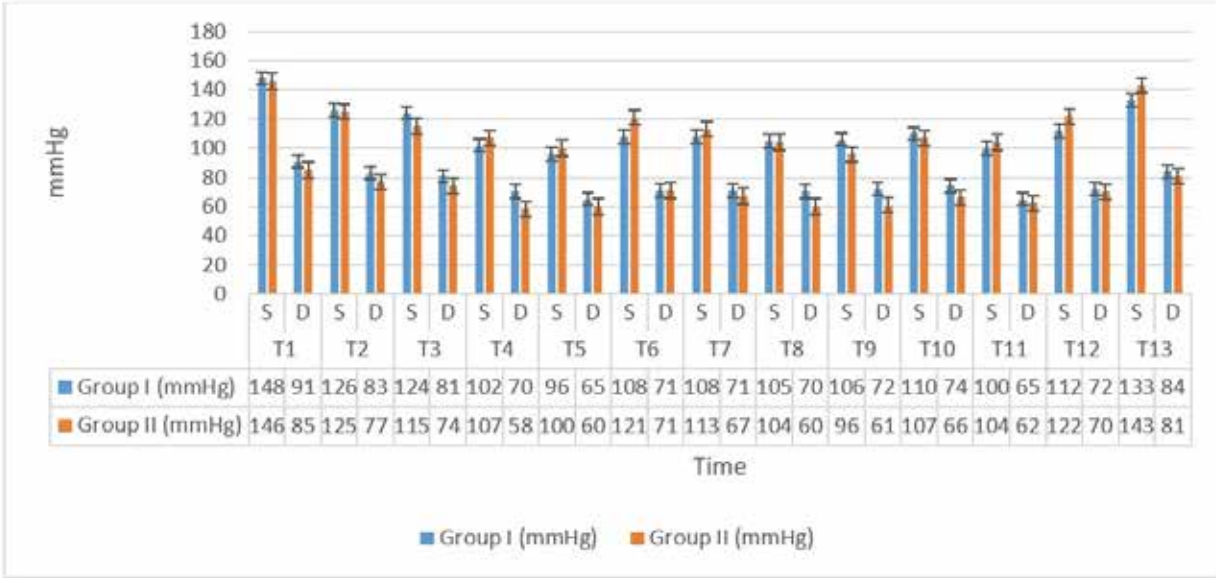

Figure 2: Arterial blood pressure values
S: systolic blood pressure, D: diastolic blood pressure

different practitioners[14]. The first test (MMT1) was performed during the preoperative evaluation, and the second test (MMT2) was performed within the first 24 hours after the operation. Both MMTs were applied to all patients by the same anesthesiologist who did not take part in their perioperative care and was not aware of the patients' follow-up. Patients who had a formal education of 5 years or less were given a revised form of the test devised for uneducated patients.

Statistical analysis of the data was calculated with the SPSS 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) statistical package program. Normal distribution was assessed by the Shapiro-Wilk test. The T-test was used for comparisons of two groups of data with a normal distribution. In comparing repeated measures within and between groups, analysis of variance was used for repeated measures. If significance was found, the Bonferroni test, one of the multiple comparison tests, was used. Relationships between variables were analyzed using Pearson correlation and Spearman correlation coefficients. The Pearson Chi-square test, Fisher's Exact Chi-square test and Fisher-Freeman-Halton test were used to examine categorical data. The level of significance was determined as P=0.05.

RESULTS

A total of 50 patients with ASA scores I-III who underwent shoulder surgery in the beach-chair position were included in the study. For evaluation, they were divided into two groups: under 65 (Group I) and 65 and over (Group II). The demographic data, operation times and anesthesia durations of the patients are given in Table 1. While the difference between the two groups in terms of height (P=0.037), ASA score (P<0.001), and comorbid diseases (P<0.001) was statistically significant, there was no statistically significant difference for other characteristics. While 17 of the 33 patients in the first group did not have any comorbidities, it was observed that all 17 patients in the second group had at least one comorbidity. While the procedure applied most often in Group I was "shoulder arthroscopy" (57.6%), "rotator cuff repair" was most frequent in Group II (41.2%).

During the perioperative follow-up, there was no statistically significant difference between the groups in terms of NIRS, arterial blood pressure, heart rate and $EtCO_2$ values at any time. However, when evaluated within the group, the difference between the measurement times was statistically significant. Severe bradycardia was not observed in any patient and atropine was not administered. Changes in NIRS and arterial blood pressure values are given in Figure 1 and Figure 2. The difference between the arterial blood pressure and NIRS values recorded just before the beach-chair position was taken (T3), and the values recorded immediately after (T4) were statistically significant in both groups (P<0.05). When the arterial blood pressure and NIRS values were evaluated within the group, the lowest values were observed at T5 (the second time point recorded after the patient was given the beach-chair position, before the surgery began). In a 56-year-old female patient scheduled for shoulder arthroscopy in the first group, the mean arterial blood pressure value decreased to 60mmHg in the period between T4 and T5, and 10 mg of ephedrine was administered to increase the arterial blood pressure. When the SpO_2 values were evaluated, there was no

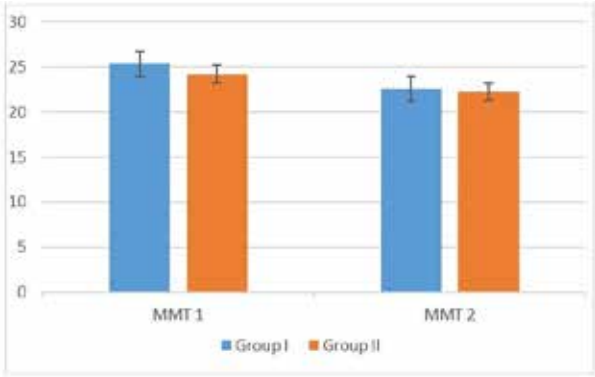

Figure 3: MMT values in groups
MMT: Mini Mental Test

significant difference between the groups. In the in-group evaluation, there was no statistically significant difference between the values at any measurement time in Group I, while the difference between the measurement at T1 (before induction, with the baseline SpO_2 value measured while the patient is on room air) and the measurements at all other times was statistically significant in Group II (P<0.05).

Preoperative (MMT1) and postoperative (MMT2) MMT results were similar between groups (P=0.377). However, the in-group difference between MMT1 and MMT2 was found to be significant. MMT1 scores were significantly higher in both groups with P<0.001 for Group I and P=0.027 for Group II (Table 2, Figure 3).

When the relationship between education level and MMT results was evaluated, a significant positive relationship was found between MMT2 (r=0.350; P=0.046) and education level in Group I. On the other hand, a statistically significant relationship was not found in Group II.

DISCUSSION

In previous studies, it has been shown that the incidence of POCD is high, especially in the elderly patient group who undergo major surgery[5]. In this study, we examined the effect of hemodynamic changes during shoulder surgery performed in the beach-chair position on POCD; we evaluated the patients by dividing them into two groups according to their age. In the literature, studies are evaluating the effects of different anesthesia methods on POCD in patients undergoing different surgeries, but there is a need for studies evaluating the effect of hemodynamic changes on intraoperative brain tissue oxygenation according to age groups and on POCD in the beach-chair position with the patient's head above the heart level. In this study, we aim to evaluate the effect of the beach-chair position on intraoperative cerebral oxygenation and postoperative cognitive functions and compare patients under 65 years of age with patients over 65 years of age and reveal whether there is a significant difference between them.

When the patients undergoing shoulder surgery in the beach-chair position with regional anesthesia were evaluated previously, it was reported that there was a decrease in mean arterial pressure and brain tissue oxygenation 5 minutes after positioning, but no significant difference in heart peak beat[15]. In a case report concerning cerebral desaturation cases, it was reported that there was a significant decrease in mean arterial blood pressure and a parallel decrease in cerebral tissue oxygenation in two patients who were scheduled for shoulder arthroscopy in the beach-chair position[12]. In another study, it was reported that NIRS values also decreased along with a decrease in systolic and diastolic blood pressures after the beach-chair position[8]. A review evaluating the safety of the beach-chair position in shoulder surgery reported that post-position hypotension might occur, and a decrease in cerebral blood flow and perfusion could be observed[4]. In a study evaluating the beach-chair position and the lateral decubitus position in shoulder surgery, the mean arterial blood pressures were found to be higher in the beach-chair position than in the lateral decubitus position. However, it was reported that the measurements at the tragus level were lower, and the NIRS values were also lower in the beach-chair position than in the lateral decubitus position[1]. In our study, within both groups, we saw that systolic and diastolic blood pressure values decreased significantly compared to the previous measurement, especially in the first measurement after position. We saw that the NIRS values were also parallel to this, and the lowest values recorded were (T5) values obtained 15 minutes after positioning, before the surgical procedure began. There was no significant difference in the comparison between the groups. We found that there was no significant difference in peak heart rate, SPO_2 and $EtCO_2$ values when compared within and between groups. Our findings were consistent with the literature. When the patient was moved from a supine position where the head and heart are at the same level to a sitting beach-chair position where the head was raised above the heart level, even young and hemodynamically stable patients without additional problems showed a drop in blood pressure and a decrease in brain tissue perfusion was observed.

Table 2: Distribution of MMT values in groups

Group	MMT 1	MMT 2	*P*
Group I (n=33)	25.36±2.78	22.60±2.81	<0.001
Group II (n=17)	24.23±4.14	22.23±3.25	0.027

MMT: Mini Mental Test

In a study, Laflam *et al*[1] used psychometric tests and evaluated serum S100β, neuron-specific enolase and glial fibrillary acidic protein, and stated that the position did not have a significant effect on these parameters. In our study, when the MMT values of both patient groups were examined, we found that there was no significant difference between the groups. However, when the evaluation was made within the groups, the difference was found to be statistically significant. The values obtained from MMT tests in the postoperative period were lower in both groups than those obtained in the preoperative period, but we thought that this situation was caused by the patients not answering all questions in the postoperative MMT tests as compared to the preoperative period, due to the fact that some patients were not able to use their hands because they were operated on the side of their dominant hand and could not answer the questions that needed to be drawn.

In their study evaluating the effect of patient age on brain oxygen regulation in position changes, Gatto *et al*[16] reported that the change in O_2 levels due to the change in position was not significantly different in the group with a higher mean age. In our study, we found that there was a statistically significant decrease in blood pressure values and NIRS values in both groups after the change in position, but there was no significant difference between the groups.

Studies comparing the effects of patients' age on MMT results are also available in the literature. In the study published by Onat[17], it was reported that MMT scores decreased with advancing age in the elderly population. In addition, in a thesis study[18], it was found that older patients' MMT scores were lower when considering age as a variable. The same study stated that education level also affected MMT scores, and low education level was a risk factor for impairment in cognitive functions. In our study, when we examined the relationship between education level and MMT scores, it was found that education level was effective on the scores of the tests applied in the postoperative period in Group I, but not Group II.

Our study has some limitations. The fact that the surgery involves the upper limb, hence affecting patients' ability to draw, caused some problems in the postoperative period, affecting MMT2 scores. This test was used nonetheless, because it is a very easy test, applicable in a short time and validated for our country. Also, there were no differences between groups in the proportions of patients operated on the dominant side, so it would not be a major concern about our primary aim of the study. Nonetheless, interpreting the in-group differences was not easy. Hence, we think any further studies directed at evaluating in-group differences such as we found should be carried out using different tests that do not require the use of a pen and paper.

The average age of our "elderly" group was 71 and we were not able to show any difference to the "young" age group. It is a possibility that the "super elderly" group over the age of 85 would have shown a significant difference. Any further studies could address this, focusing on the very old.

CONCLUSION

Considering the data of this study, we can conclude that there are fluctuations in hemodynamic parameters and parallel to this in brain tissue perfusion, regardless of the patients' age, in shoulder surgeries performed in the beach-chair position. With the effect of these fluctuations, the MMT test results showed a similar decrease in both elderly patients and young patients between the groups. This decrease should be evaluated with caution and additional studies using different tests should be carried out.

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Case Report

Wegener's granulomatosis: challenges in making the diagnosis - a case report

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ABSTRACT

Wegener's granulomatosis is a rare multi systemic illness with unclear aetiology. It can present with various signs and symptoms with involvement of multiple organ systems. Here, we present a case of a 45-year-old male who presented with multiple episodes of epistaxis. Upon subsequent follow up, he also developed right facial nerve palsy and bilateral mixed hearing loss. Subsequently, there was incidental findings of opacities on chest radiograph, which did not resolve with antibiotics treatment. Computed tomography thorax was performed, which revealed features suggestive of lung malignancy. Lung biopsy finally revealed a diagnosis of Wegener's granulomatosis (WG). This case is particularly interesting due to the diverse presenting symptoms, radiological findings mimicking other pathology and lastly the diagnosis of WG upon histopathology result.

KEY WORDS: granulomatosis with polyangiitis, lung lesion, Wegener's granulomatosis

INTRODUCTION

Wegener's granulomatosis (WG) is a rare multi-systemic autoimmune inflammatory condition of unknown aetiology[1].

Its clinical signs vary. Several case reports have been written about atypical presentations and related difficulties of diagnosing the disease at an early stage[1-3]. Due to it being a rare illness with high variety of presenting symptoms, this case is believed to remain highly educational.

CASE REPORT

This is a case of a 45-year-old male, a chronic smoker with history of Bell's palsy, who claimed was treated by a general practitioner two months prior. He had a history of alleged motor vehicle accident and sustained right radial fracture one month prior to initial presentation. He presented to the casualty department with a one-month history of intermittent epistaxis associated with nasal blockage. International normalised ratio (INR) was raised at 1.6, thus the epistaxis was attributed to the deranged INR. Nasoendoscope examination showed bulky right Fossa of Rosenmuller, bilateral inferior turbinate hypertrophy and congested left nasopharynx. Holoprosencephaly was taken for right Fossa of Rosenmuller. Otoscope showed clear right external auditory canal, bulging left tympanic membrane with left mucoid discharge.

Upon review after one month, patient had developed right facial nerve palsy, bilateral moderate to profound mixed hearing loss, worsening nasal congestion, rhinorrhea and few episodes of epistaxis. With a history of past motor vehicle accident, he was planned for high resolution computed tomography (HRCT) temporal bone for suspicion of temporal bone fracture causing the hearing loss. He was started on budesonide nasal spray and oral cetirizine to relieve his symptoms. HRCT temporal bone was performed, which showed fluid / soft tissue densities occupying both middle ear cavities and both mastoid air cells with no evidence of bony erosion. Features

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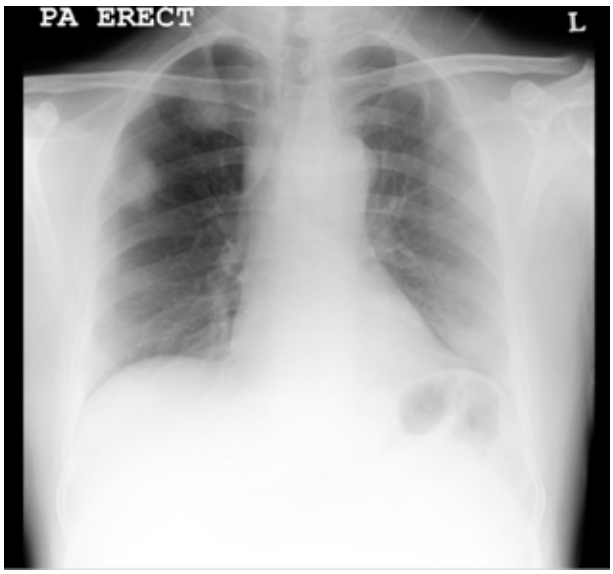

Figure 1: Initial chest radiograph showed subtle ill-defined opacities in the right upper zone.

are suggestive of bilateral otitis media with chronic mastoiditis and pansinusitis.

During his hospital admission for iron deficiency anemia, routine chest radiograph (Figure 1 and Figure 2) showed two well defined rounded opacities in right upper zone. On further history, patient claimed he had loss of appetite and significant weight loss (>10 kg) over the past three months. He denied family history of malignancy. In view of recent radiological findings, the main suspicion was infective in nature rather than malignancy. Therefore, antibiotic treatment was started. Sputum AFB x 3 were negative. Repeated chest radiograph showed persistent and larger size of the right lung lesions. Thus, patient was planned for CT thorax. Sputum cultures yielded mixed growth. Mycobacterium sputum culture and fungal sputum culture were negative.

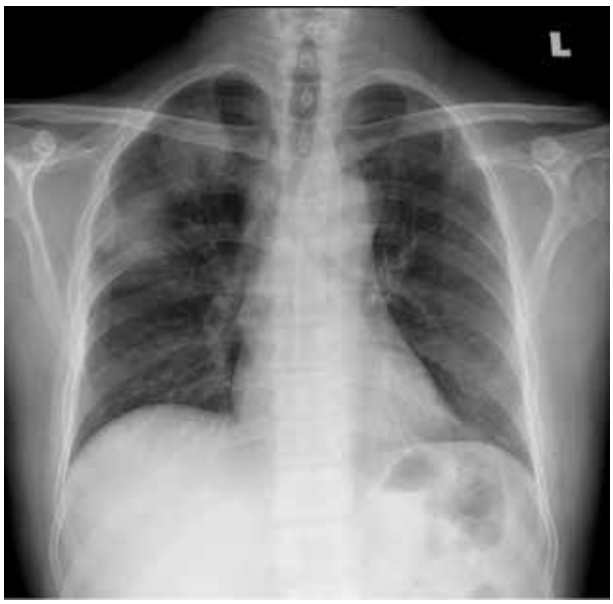

Figure 2: Subsequent chest radiograph (3 months after initial chest radiograph) showed increase in size of the right upper zone opacities.

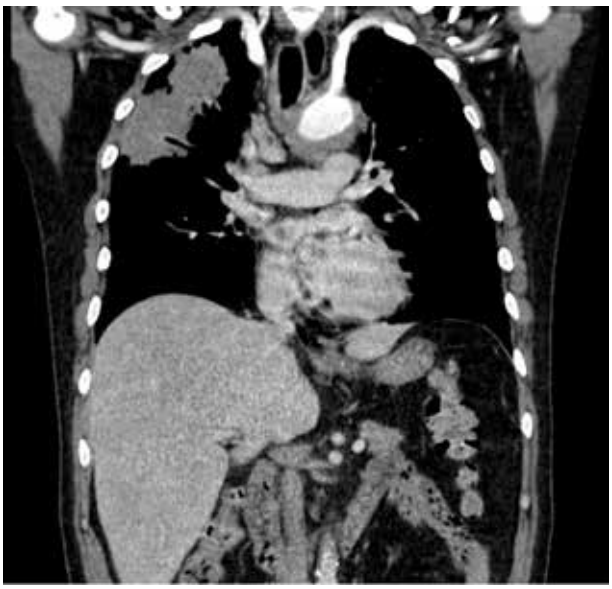

Figure 3: Contrasted CT thorax (coronal view in soft tissue window) showed two spiculated right upper lobe lesions which confluence into a bigger mass (CT: computed tomography)

CT thorax (Figure 3) performed 4 months after his initial presentation showed two right upper lobe lung masses with mediastinal nodal metastases, features in favour with lung malignancy. Considering the CT findings, CT guided lung biopsy was performed. Lung core biopsy resulted as WG. Blood sent for c-ANCA was positive with raised C-reactive protein and erythrocyte sedimentation rate. Results for p-ANCA and ANA were negative. Patient was taken over by rheumatology team as soon as the diagnosis of WG was confirmed. He was planned for IV cyclophosphamide regime. As for his bilateral chronic otitis media, he was planned for bilateral myringotomy, but did not proceed as patient was unable to tolerate the procedure. He was put on oral medications to relieve his symptoms.

DISCUSSION

WG is a chronic granulomatous necrotizing vasculitis involving small- to medium-sized vessels. It is a rare systemic disorder with unclear aetiology which can affect any organ systems, predominantly upper respiratory tract, lungs and kidneys[4]. Gastrointestinal involvement is rare, with less than a handful of case reports being documented in the literature[2]. WG has posed many challenges in making the diagnosis as it often presents with various clinical symptoms and clinical presentations involving multiple organ

systems. It is often rapidly progressive in nature and can be fatal if left untreated[1]. A number of case reports have demonstrated that WG often presents with non-specific symptoms which include otalgia, rhinorrhea, nasal congestion, bloody nasal discharge, polyarthralgia, skin rashes, pulmonary infiltrates and renal function deterioration[1]. Vague symptoms such as fever and weight loss may be reported at the onset of the disease and during the course of the illness.

In this case, the patient initially presented with symptoms involving the upper respiratory tract with epistaxis and nasal congestion. Thus, patient was managed under the primary care of the otorhinolaryngology team. There were subsequent findings of right facial nerve palsy and bilateral mixed hearing loss. In view of recent history of trauma, temporal bone fracture was suspected, however excluded based upon HRCT temporal bone findings. The patient was managed according to his presenting symptoms, thus directing the attention away from other possible diagnosis including a systemic illness. However, his recurrent presentations to the hospital with anemia and unresolved epistaxis lead to other numerous investigations, which finally revealed a diagnosis of WG.

In the beginning, due to the acute onset of the lung opacities found on chest radiographs, infective causes were highly considered. The patient was treated with antibiotics hoping for resolution of the lung changes. Further assessment with CT thorax then revealed right upper lobe masses with nodal metastases. The patient was a chronic smoker of 20 years; therefore, lung malignancy is one diagnosis that needs to be considered.

Additionally, the pulmonary imaging findings in this case are not typical of WG. The most common lung manifestation of WG are multiple and bilateral lung nodules with no zonal predilection[5]. It can also present with nodular cavitation and can easily mimic tuberculosis, metastases, lung abscesses or septic infarcts[5]. A retrospective study in 2012 involving 37 patients with WG found that the pulmonary opacities were bilateral in 62.1% and unilateral in 37.9% of the patients[4]. WG mimicking other illnesses also posed a challenge in making the correct diagnosis.

The gold standard in making the diagnosis remains in tissue biopsy, thus a positive c-ANCA alone is not sufficient in diagnosing WG[3]. This could also contribute to the delay in diagnosing WG, as tissue biopsy may not be feasible in all situations. It took 4 months from the patient's initial presentation to arrive at the final diagnosis and it took almost 5 months before patient was started on proper treatment for WG. One study has shown that the mean period from the onset of the first symptoms to diagnosis of WG was 4.59±6.15 months[4].

CONCLUSION

WG is a systemic illness which can present with various non-specific symptoms. Despite being a rare illness, it should be considered whenever there is multi organ systems involvement. Radiological findings of WG can mimic other pathologies such as infection, metastases or septic emboli. Clinical, laboratory and histological correlation are undeniably crucial in interpreting the radiological investigations. Multidisciplinary approach is critical in diagnosing and managing this illness. Early diagnosis is crucial to enable early treatment initiation to halt progression of disease.

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Case Report

Atypical location of transient hepatic attenuation differences secondary to acute pancreatitis with splenic vein thrombosis: A case report

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ABSTRACT

Transient hepatic attenuation differences (THAD) lesion is a cardinal but uncommon finding to detect hypervascular hepatic lesion. The most common causes of THAD are associated with arterioportal shunts in hepatocellular carcinoma and portal vein compression by mass lesions. We reported a 34-year-old man presenting to emergency department with acute onset of severe epigastric pain. The computed tomography showed severe form of pancreatitis, splenic vein thrombosis and an atypical location of sectorial wedge-shaped THAD in S8 of the liver. Here, we discussed the mechanisms for this rare finding.

KEY WORDS: pancreatitis, transient hepatic attenuation differences, venous thrombosis

INTRODUCTION

The liver receives dual blood supply: approximately 70% from the portal vein and 30% from the hepatic artery[1]. Transient hepatic attenuation differences (THAD) refer to enhancement of liver parenchyma during hepatic arterial phase imaging on computed tomography (CT)[2-4]. Generally, etiologies of THAD can be classified into 2 categories: arterioportal shunts and vascular invasions[2-4]. The arterioportal shunts are caused by fistulas between interlobular artery and venules and mostly seen in hepatocellular carcinoma[4]. The vascular invasion of portal vein causes a secondary increase of hepatic arterial inflow[2-4]. Localization of THAD is related to the anatomy of blood supply. Here, we report a rare case of acute pancreatitis with the complication of splenic vein thrombosis and intra-abdominal abscess. Additionally, an incidental finding of THADs was noted on CT with atypical localization.

CASE REPORT

A 34-year-old man presented to our emergency department because of sudden onset of epigastric pain. Acute pancreatitis was diagnosed according to the elevated serum lipase level and clinical presentation. Ultrasound was performed in the first admission. It showed heterogeneous parenchymal swelling of the pancreas with ascites and dilated bowel loops around the peripancreatic area. His physical condition resolved after standard treatment and hospitalization. Three months later, he returned to our ED due to recurrence of epigastric pain. The physical examination showed abdominal distension with signs of peritoneal inflammation. Auxiliary examinations revealed leukocytosis (17,880 cells/μL) and elevated serum C-reactive protein concentration (13.91 mg/dL). The serum lipase levels were within the normal range. His CT revealed an abscess (2.2

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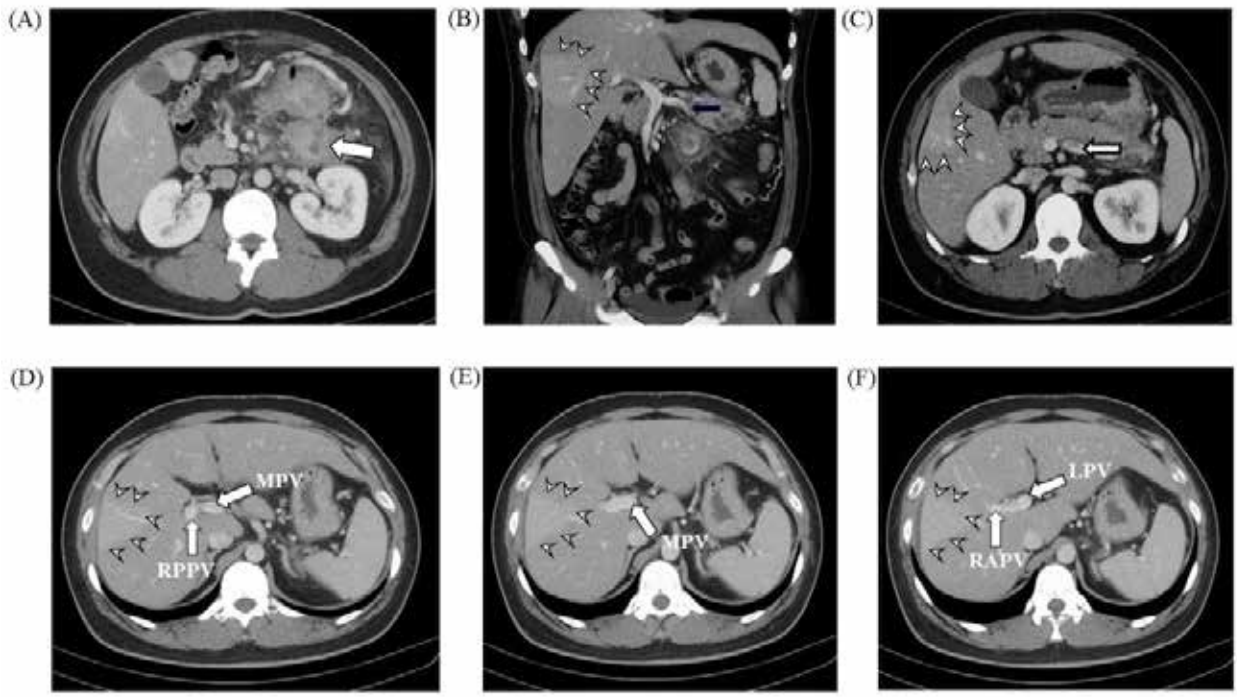

Figure 1: Contrast-enhanced CT shows: (A) A small abscess in the left mesenteric root region with an extensive adjacent proximal jejunum and distal transverse colon swelling (arrow). (B) Coronal view and (C) axial view of partial thrombosis in the splenic vein (arrow) and transient hepatic attenuation differences (THAD) lesion (arrowheads). (D), (E), (F) Arrowhead indicates transient hepatic attenuation differences (THAD) lesion in S8 of the liver and type II anatomic variation is demonstrated.
MPV: main portal vein; LPV: left portal vein; RPPV: right posterior portal vein; RAPV: right anterior portal vein

× 3.6 cm) in the left mesenteric root region (Figure 1a) complicated with partial thrombosis in the splenic vein (Figures 1b and 1c) and a pseudocyst in pancreatic tail. Besides, an arterial phase wedge-shaped hyperintensity was noted in segment 8 of the liver with an impression of THADs (Figure 1d and 1e). Besides, a type II portal vein variation was noted on CT in this patient (Figure 1d, 1e, and 1f). Thereafter, the patient was treated with flomoxef 1 gram every 8 hours for infection control and asked to maintain fasting with intravenous fluid therapy for three days. Oral intake resumed on day 4 when his abdominal pain resolved. He exhibited clinical improvement and was discharged after hospitalization for 7 days. The Joint Institutional Review Board of Taipei Medical University approved this study.

DISCUSSION

Splanchnic vein thrombosis is an uncommon but critical complication in acute pancreatitis due to its anatomical proximity to the inflamed pancreas[5,6]. During the inflammation process, the swelling of the pancreas can cause a compression of the splenic vessels in the splenorenal ligament. The consequent hypoperfusion in the splanchnic veins may lead to an increased risk of thrombosis and subsequent emboli formation[6,7].

Inamoto *et al*[8] first described the CT finding of segmental low attenuation areas within the liver that did not correspond to mass lesions. Itai *et al*[9] first mentioned the term THADs in 1982, and they explained the pathophysiology and etiology of this phenomenon. Formation of THAD is based on the altered dual blood supply of the liver. When the proportion of hepatic arterial to the portal venous inflow is abnormally increased, the arterial phase on CT presents a uniform high attenuation in the affected location of liver parenchyma[2-4]. Early studies had indicated THAD lesions are associated with malignant hepatic tumors. However, many benign focal hepatic lesions such as hemangioma, focal nodular hyperplasia and pyogenic abscess also presented THADs changes on imaging[10]. A sectional wedge-shape of THAD is usually caused by portal hypoperfusion with portal venous compression or infiltration by thrombosis, resulting in portal branch blockade[11]. In our case, the splenic vein thrombosis caused the portal hypoperfusion and the hepatic arterial inflow was relatively increased.

The blood perfusion of the liver from the portal vein is streamlined: the right hepatic lobe receives large amounts of blood from the superior mesenteric vein (SMV), and the left hepatic lobe receives large amounts of blood from the splenic vein[12]. Given this

inference, THADs in the left hepatic lobe could be induced from splenic vein thrombosis theoretically. However, in our case, the THAD was found in S8 of the liver (right hepatic lobe), which was not intuitively compatible with the CT finding of splenic vein thrombosis. We speculated two possible mechanisms. First, the intra-abdominal abscess in this patient could have induced portal branch compression or infiltration and resulted in hypoperfusion. A type II anatomic variation of portal venous system causes the turbulence of venous return. The SMV might have been compressed in the setting of the abscess. Second, small venous embolism from splenic vein obstructs the SMV.

Chronic pancreatitis was considered the continuum of previous acute pancreatitis, and it could exhibit mildly elevated or even normal value of lipase[13]. In our patient, his addiction to alcohol consumption and uncontrolled hypertriglyceridemia remained as strong risk factors for chronic pancreatitis. A new pseudocyst of pancreas on CT supported his recent inflammation process in the last 3 months. Accordingly, we considered that the formation of an abscess, venous thrombosis and THADs occurring in the second admission were strongly associated with recent pancreatitis.

CONCLUSION

In conclusion, THAD lesions should become more ubiquitous in imaging findings with the recent development of multidetector CT and rapid bolus injection rate protocols. Some THADs can be associated with clinically important findings, such as malignancy, acute hepatic injury and cholangitis; however, in many cases, THADs are only accidentally discovered. To clarify the reasons behind the occurrence of THADs, future research should include more cases to study the underlying mechanisms of THAD formation.

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Case Report

Nephrotic syndrome and corneal opacities due to lecithin–cholesterol acyltransferase (LCAT) deficiency

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ABSTRACT

Lecithin-cholesterol acyltransferase (LCAT) deficiency is a very rare autosomal recessive disease caused by mutation in the LCAT gene, located on chromosome 16q22. Clinical and biochemical manifestations of LCAT deficiency vary considerably from one patient to another, even in the same affected family, and include an abnormal lipid profile with hypercholesterolemia, markedly decreased high-density lipoprotein cholesterol and hypertriglyceridemia; corneal opacities; hematologic abnormalities and nephropathy followed by progressive deterioration of renal function. Herein, we present a 37-year-old male patient with steroid-resistant nephrotic syndrome of 3 years duration. His renal biopsy's ultrastructural examination revealed classic features of LCAT deficiency. He had corneal opacities and abnormal lipid profile.

KEY WORDS: high-density lipoprotein cholesterol, lecithin cholesterol acyltransferase deficiency, lipoprotein function, low-density lipoprotein cholesterol, nephrotic syndrome

INTRODUCTION

This case describes a spectrum of biochemical and renal manifestations of lecithin-cholesterol acyltransferase (LCAT) deficiency. LCAT deficiency is a very rare condition with an incidence rate of less than 1 in 1 million individuals[1]. LCAT gene, located on chromosome 16, encodes the enzyme LCAT, which binds blood and tissue cholesterol to lipoproteins in order to transport it to the liver[2].

LCAT deficiency may present with a broad spectrum of manifestations, including renal disease with proteinuria progressing to end-stage renal disease (ESRD), corneal opacification, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol levels and anemia[3].

Although originally described as an autosomal recessive inherited disorder, recent reports revealed a few acquired cases of LCAT deficiency, possibly secondary to liver disorder or immune mediated disorders[3].

The most significant sequel of LCAT deficiency is probably renal disease, followed by potential cardiac disease, mainly due to abnormalities in lipid metabolism, oxidation and removal from tissues.

Abnormal deposition of lipids in kidney may occur in a number of disorders either due to an inborn error of metabolism or as a consequence of metabolic alteration such as the ones seen in nephrotic syndrome[4].

Distinction of the underlying disease depends on the variance in clinical manifestations, detailed biochemical tests, distinct histopathological findings including ultrastructural examination, and if available specific gene analysis[2].

CASE REPORT

A 37-year-old male patient with history of nephrotic range proteinuria for 3 years was admitted for evaluation and renal biopsy. He had no history for systematic diseases including diabetes mellitus, hypertension or connective tissue diseases. He had

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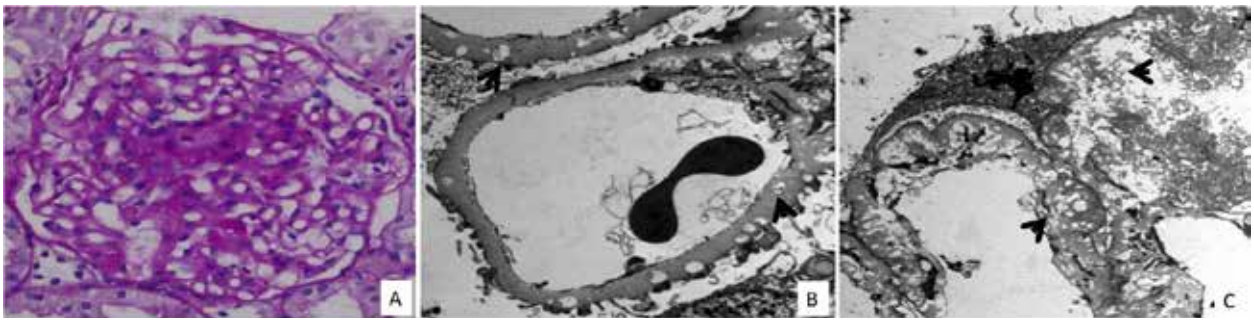

Fig 1: Histopathology of the renal biopsy in LCAT case. (A) Light microscopy shows mesangial expansion, vaculation and thickening of capillary walls and some foam cells in capillary lumina (100x Periodic Acid Schiff stain). Electron microscopy shows intra-membranous lucencies (B) and mesangial widening (C) by electron-dense, rounded lamellar deposits (arrow heads 25000x, TEM).

negative family history for renal diseases and he was not using any medications prior to his complaints.

Physical examination was unremarkable, with normal blood pressure and absence of peripheral edema. There were bilateral corneal opacities and no xanthelasmas.

He had been investigated thoroughly for possible secondary causes of his nephrotic proteinuria, but all were negative; including workup for lupus nephritis, hepatitis profile, antineutrophilic cytoplasmic antibody, and his serum complements titers were within normal. The patient was then started on angiotensin-converting enzyme inhibitors with some improvement of his proteinuria. His laboratory data were as follows: serum total protein 5.3 g/dl; serum albumin 2.6 g/dl; serum creatinine 75.0 umol/l; blood urea nitrogen 6.2 mmol/l; serum uric acid 7.0 mg/dl; white blood cell count 8600/mm^3 and hemoglobin 13.4 g/dl. Blood film showed normochromic normocytic anemia with target cells. Urinalysis was positive for protein but negative for blood and sediment. The urinary spot protein was elevated to 506.6 mg/dl. Urine protein electrophoresis revealed albumin fraction to be 49%, followed by alpha-1 12.8%; alpha-2 10.3%; gamma 21.5% and beta 6.4%. No Bence-Jones protein or free light chains were detected. The serum lipid profile showed the following: normal total cholesterol 4.8 mmol/l; low-density lipoprotein (LDL) unmeasurable due to high triglycerides; low HDL 0.69 mmol/l and high triglycerides 4.52 mmol/l.

Computed tomography for abdomen and pelvis showed unremarkable normal-sized bilateral kidneys without hydronephrosis or stones.

Percutaneous kidney biopsy was then performed. The specimen for light microscopy contained 34 glomeruli, none of which was globally sclerosed. The glomeruli exhibited mesangial widening and glomerular basement membrane thickening and vacuolization. Focal mesangiolysis and foamy macrophages in the glomeruli without marked mesangial hyper cellularity were also evident (Fig 1A). There was no evidence of endocapillary proliferation, hyaline thrombi, fibrinoid necrosis or crescents. Minimal interstitial fibrosis and tubular atrophy was present. There was no hyaline arteriolosclerosis or arterial atherosclerosis seen.

Electron microscopy using transmission electron microscope revealed that the glomerular capillaries were distended by large subendothelial and intramembranous vacuoles. These electron lucent vacuoles contained small, solid, thread like or lamellar dense structures. There were also nodular expansions within the mesangial areas by similar material along with mesangiolysis. The overlying podocytes were prominent with cytoplasmic vacuolization and effacement of foot processes. The average glomerular basement membrane thickness is 790 nm (Fig 1B and 1C).

DISCUSSION

LCAT deficiency is a very rare autosomal recessive disease caused by mutation in the LCAT gene, located on chromosome 16q22, and with an incidence rate of ≤1 in 1 million individuals[2]. LCAT enzyme is involved in transport of lipoproteins from plasma and tissues to the liver. Lipoproteins are vital transporters of lipids and fat-soluble vitamins through the plasma from their site of production (intestine or liver) to their site of uptake[2]. Abnormal levels of plasma lipids and lipoproteins is known to increase the risk of cardiovascular disease, such as myocardial infarction and stroke[4].

Genetic and environmental factors collaborate to determine the individual's plasma levels of lipids and lipoproteins. For instance, at the molecular genetic level, severe monogenic dyslipidemias typically present earlier in life, while dyslipidemias presenting later in life prove that expression further depends on interactions with non-genetic environmental or lifestyle factors[2].

Molecular background

LCAT deficiency disorder (OMIM 606967) is a very rare condition with an incidence rate of less than 1 in 1 million individuals. Inheritance is autosomal recessive, through more than 40 designated mutations[1].

Two general categories of mutations in the LCAT gene are identified. They result in either milder phenotype known as fish-eye disease or familial LCAT deficiency[5].

Patients with familial LCAT deficiency have complete loss of LCAT activity leading to increased un-esterified cholesterol in plasma and markedly reduced HDL. Clinical features include renal disease with proteinuria, and progression to ESRD, corneal opacification and anemia[6].

In fish-eye disease, there is a partial selective loss of LCAT enzyme activity for HDL whereas preserved activity toward Apo lipoprotein B-containing lipoprotein. It causes normal to slightly elevated free cholesterol, marked reduction in HDL and corneal opacification without renal disease[5].

Historical background

Familial LCAT deficiency was initially described in the last century in people of northern European origin and afterward in different geographic areas, including Japan and North America[7,8]. LCAT deficiency can be either acquired, usually secondary to liver disorder, or congenital with an autosomal recessive mode of inheritance[3].

Clinical and biochemical manifestations of LCAT deficiency vary considerably, even among same family members[9]. Initially, patients may only show mild abnormal laboratory tests in early childhood, including a decreased HDL level and increases in no esterified cholesterol and triglyceride levels[10]. As the patient grows older, the spectrum of reported manifestations include an abnormal lipid profile (characterized by hypercholesterolemia with markedly decreased HDL and hypertriglyceridemia), corneal opacities, hematologic abnormalities (normochromic anemia of varying intensity), splenomegaly, variable early coronary artery disease and nephropathy (initially proteinuria, followed by progressive deterioration of renal function)[11].

The most significant sequel of LCAT deficiency is renal disease, which is the most frequent cause of morbidity and mortality in LCAT deficiency[11]. LCAT deficiency produces steroid-resistant focal segmental glomerulosclerosis and ESRD by the fourth decade of life[12].

Dyslipidemia has been claimed as a contributory factor for the progression of renal insufficiency by development of glomerulosclerosis and tubulointerstitial lesions together with accelerated atherosclerosis[13].

Eye abnormalities in LCAT d are variable, and may include corneal opacities as well as retinal macular degeneration and hemorrhage[14]. Cardiac disease is also a significant sequel of LCAT d, mainly due to abnormalities in lipid metabolism, oxidation and removal from tissues[2,15].

Mild anemia with target cells was seen in our patient. Anemia is probably due to mild hemolysis, insufficient erythropoiesis and decreased osmotic fragility due to altered phospholipid composition of red blood cells[16].

Diagnosis

Early diagnosis of LCAT deficiency is essential to precise dietary, lifestyle and pharmacologic interferences to delay morbidities and mortalities[2].

LCAT deficiency is diagnosed when LCAT levels are negligible, un-esterified cholesterol and cholesterol ester levels are low, and LDL and triglyceride levels are increased. The diagnosis is also made with genetic testing[11].

LCAT deficient patients may present with renal disease even with normal HDL levels[17]. Thus, it needs high index of suspicion for LCAT deficiency when renal biopsy is suggestive of lamellar foamy deposits in mesangium and capillary walls even if serum HDL levels are normal[17].

Role of histopathology

The characteristic light microscopic findings (i.e., mesangial expansion, capillary wall thickening and vaculation) and the ultrastructural appearance (lipid deposits in many areas including sub endothelium and mesangium and lamellar structures) of the kidney specimen from our patient are typical findings described in LCAT deficiency[9].

Immunofluorescence is negative or nonspecific in such cases. Electron microscopy is the mainstay in diagnosis and characteristically shows intra-membranous lucencies and vacuoles containing electron-dense rounded lamellar deposits in addition to mesangial widening by similar deposits[18].

Differential diagnoses for renal lipidosis

Abnormal lipid deposits in the glomeruli may occur in several inborn errors of metabolism, in addition to the classic dyslipidemia that is seen in nephrotic syndrome patients[2]. Such disorders should be kept in mind when dealing with a case of proteinuria associated with dyslipidemia that appears unlike that classic for nephrotic syndrome patients.

Distinction of the underlying disease depends on the variance in clinical manifestations, detailed biochemical tests, distinct histopathological findings, and if available specific gene analysis. Such distinction is vital for appropriate management and screening of affected families.

The hereditary disorders associated with renal abnormalities include in addition to LCAT d; Fabry disease[19], Gaucher disease[20], Niemann-Pick disease, type III hyperlipoproteinemia[21] and lipoprotein glomerulopathy[22].

Lipoprotein glomerulopathy is a major differential diagnosis in our case[22]; an autosomal recessive rare disorder which results from several gene mutations affecting ApoE. This entity shares in common with LCAT the presence of dyslipidemia, hyperlipoproteinemia and proteinuria leading to progressive renal impairment. It can be differentiated, however, from LCAT deficiency by careful ultrastructural histopathological renal examination. Lipoprotein glomerulopathy is characterized by lipid special stains-positive lipoprotein thrombi in dilated ectatic capillaries. Besides, no macrophages or foam cells are identified in glomeruli. The lipoprotein thrombi on electron microscopy reveal laminated appearance of lipoprotein droplets[22].

There is no specific treatment yet for familial LCAT deficiency. Kidney transplantation was performed; however, disease may recur in the allograft[11]. However, studies advocated that management of dyslipidemia, normalization of blood pressure and reduction of proteinuria could offer revenues to hinder progression to chronic renal failure[13].

Recently, the infusion of recombinant human LCAT[23] has been tried with promising outcomes that includes improvement of anemia, normalization of HDL and slowing progression to chronic kidney disease[24].

CONCLUSION

LCAT deficiency is a very rare disorder of lipoproteins that is mainly an inborn error of metabolism. It has a broad spectrum of manifestations, including renal disease with proteinuria progressing to ESRD, corneal opacification, dyslipidemia and potential cardiac disease. LCAT deficiency diagnosis depends on a constellation of abnormal cholesterol and lipoprotein plasma levels, the described clinical findings and is supported by genetic testing and ultrastructural renal features.

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Authors' contribution: Nisreen Abu Shahin: histopathological examination, interpretation, writing of manuscript; Mohammad Rabab'a: revising manuscript for intellectual content.

Conflicts of interests: None

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Case Report

Retinal capillary ischemia and fern-like of paracentral acute middle maculopathy: Three case reports

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ABSTRACT

Paracentral acute middle maculopathy (PAMM) is defined by the spectral domain optical coherence tomography demonstrating a characteristic hyper-reflective band-like lesion within the inner nuclear layer, which is caused by ischemia of the intermediate and deep retinal capillary plexus. En face optical coherence tomography (OCT) has classified these lesions into 3 principal patterns: arteriolar (along the major retinal artery), globular (around distal capillaries) and fern-like (along the retinal veins). Fern-like pattern of PAMM mainly involves capillary ischemia distributed in central retinal vein or branch retinal vein. Here, we report three cases diagnosed as having PAMM in a fern-like pattern. En face OCT is a key method to locate and identify PAMM damage patterns. Multi-mode imaging will be helpful to further explore the etiology of PAMM.

KEY WORDS: central retinal vein occlusion, en face optical coherence tomography, paracentral acute middle maculopathy, retinal ischemia, spectral domain optical coherence tomography

INTRODUCTION

Paracentral acute middle maculopathy (PAMM) refers to characteristic hyper-reflective band-like spectral-domain optical coherence tomography (SD-OCT) lesions involving the middle layers of the retina at the level of the inner nuclear layer (INL) , which is developed in response to ischemia of the intermediate (ICP) and deep capillary plexuses (DCP)[1,2]. PAMM can be an idiopathic retinal ischemic disease, or can also occur in various retinal vascular disorders, such as central retinal vein occlusion (CRVO), branch and central retinal arterial occlusion, diabetic retinopathy, hypertensive retinopathy, and Purtscher retinopathy, and may even develop in young and healthy individuals with an otherwise normal ocular exam and systemic history[2-8]. It is currently recognized that SD-OCT imaging and near infrared reflectance remain the most sensitive modalities for imaging this type of retinal ischemic lesion. Until recently, en face OCT orientation more clearly delineates and localizes PAMM than current imaging methods and may emerge as the preferred method to image and follow the clinical course of these patients[9]. Sridhar *et al*[10] used en face OCT to classify PAMM in eyes with retinal vascular occlusion into three principal patterns: arteriolar (along the major retinal artery), globular (around distal capillaries), and fern-like (along the retinal veins). Fern-like PAMM mainly involves capillary ischemia distributed in the central retinal vein or branch retinal vein and has not been described with arterial occlusion[10,11]. Here, we present three cases of fern-shaped PAMM occurring in association with retinal capillary ischemia.

CASE REPORT

Case 1

A 35-year-old previously healthy man reported with a 5-day history of acute decreased vision in his right eye. He had a history of intermittent vision loss for 30 minutes at a time. Visual acuity was 0.01 in the right eye and 0.4 in the follow left eye. There

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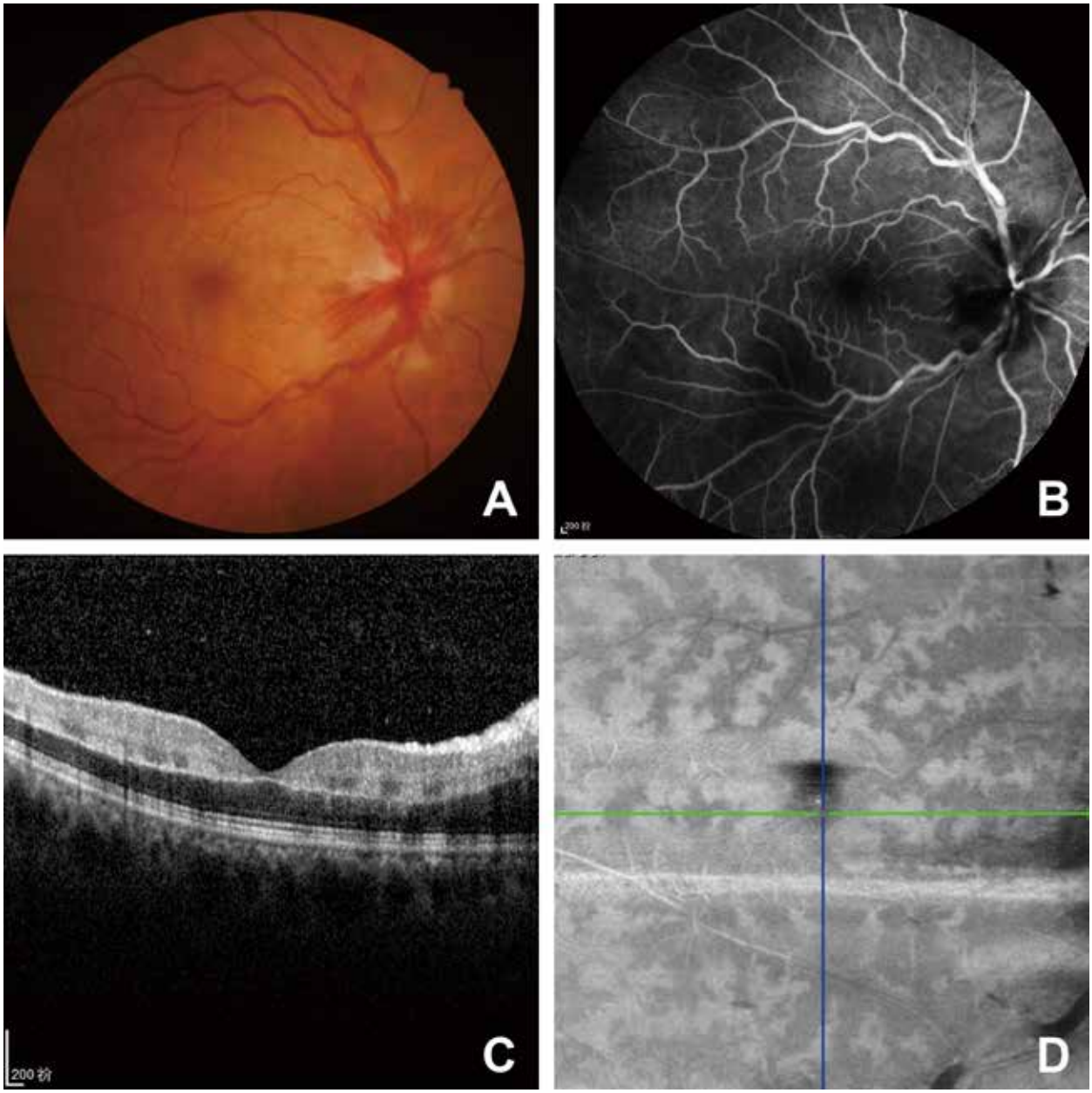

Figure 1: Multimodal retinal imaging of the right eye at presentation of 35-year-old man (case 1). **A:** Fundus examination of the affected right eye shows edema of the optic papilla, tortuous and dilated venous blood vessels, and a little bleeding. **B:** Fluorescein angiography of the affected right eye demonstrated delayed retinal arterial filling, prolonged venous return time, and tortuous veins. **C:** SD-OCT showed intermittent hyper-reflective bands at the level of the INL. **D:** En face OCT segmented at the level of the INL with vascular mapping showed areas of characteristic perivenular fern-like lesions.

was a relative afferent pupillary defect in the right eye. Dilated fundus examination showed edema of the optic disc, tortuous and dilated venous blood vessels and peripapillary hemorrhage. SD-OCT showed intermittent hyper-reflective bands at the level of the INL. En face OCT segmented at the level of the INL with vascular mapping showed areas of characteristic perivenular fern-like lesions. This case was diagnosed as having PAMM (Figure 1).

Case 2

A 29-year-old previously healthy man presented with sudden transient loss onset in his left eye one day before and lasting 30 minutes. He noticed for the second time that the decline in vision was continuous the next morning. He had no other visual complaints. Visual acuities were 0.5 in the right eye and hand motion in the left eye. Anterior segment examination was unremarkable. Fundus examination of the

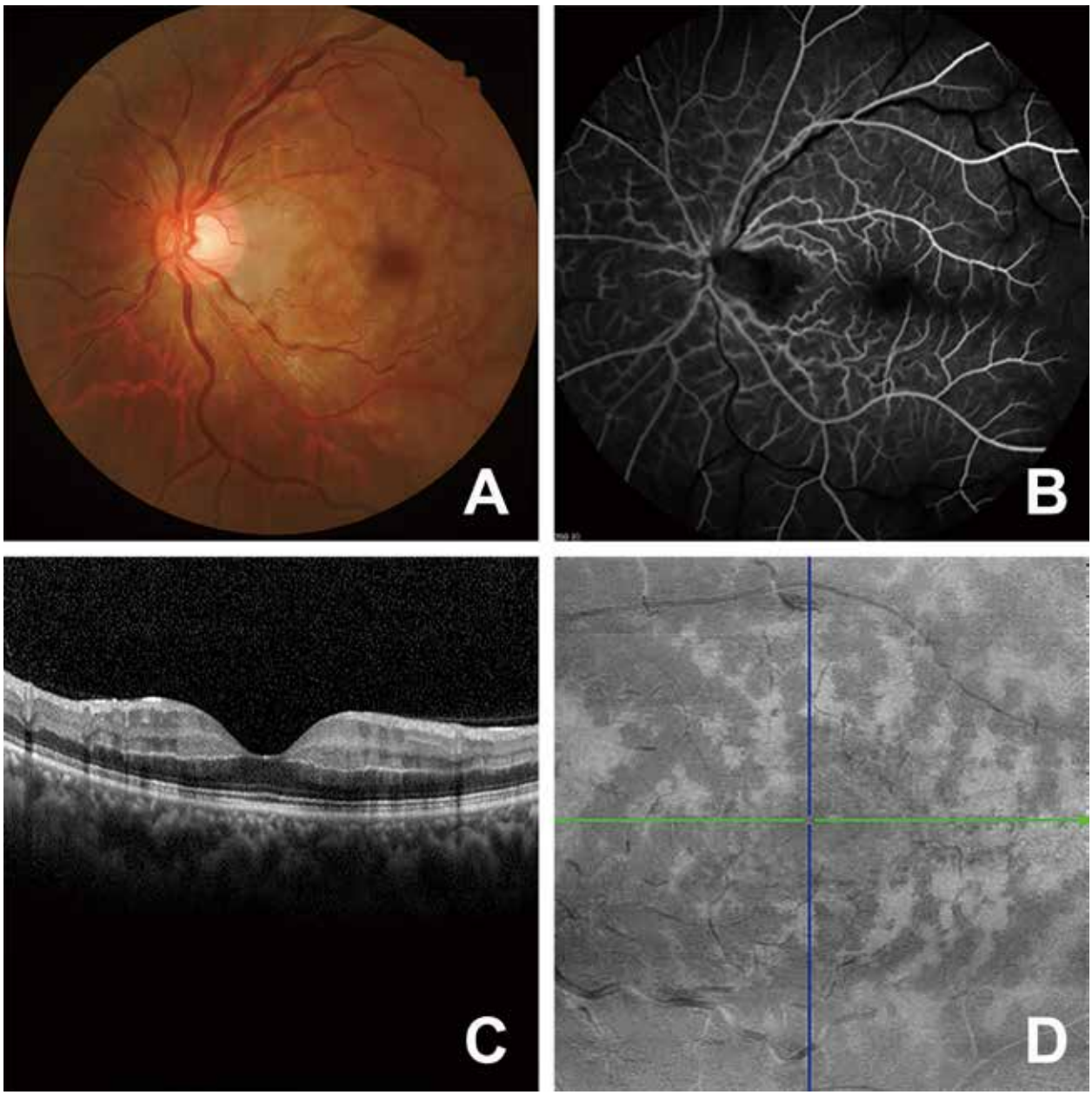

Figure 2: Paracentral acute middle maculopathy in the left eye of 29-year-old man (case 2). **A:** Fundus examination showed retinal edema, partial arterial flow interruption. **B:** Fluorescein angiography of the left eye demonstrated delayed retinal arterial filling indicating obvious occlusion of central retinal artery. **C:** SD-OCT was discontinuous hyperreflection bands at the level of the INL. **D:** en face OCT showed areas of decreased perfusion in the DCP showing areas of perivenular fern-like lesion.

affected left eye showed retinal edema, partial arterial flow interruption. However, the external and internal carotids were normal on each side. Fluorescein angiography of the left eye demonstrated delayed retinal arterial filling indicating obvious occlusion of central retinal artery. SD-OCT illustrated retinal edema in the left eye. Half a month later, in the left eye, fundus examination showed venous tortuosity and dilation, retinal edema and hemorrhage. SD-OCT showed discontinuous hyper-reflective bands at the level of the INL. En face OCT showed areas of decreased perfusion in the DCP showing areas of perivenular fern-like lesion. He was diagnosed as having PAMM (Figure 2).

Case 3

A 53-year-old man presented with a 3-day history of decreased vision in the right eye. Visual acuities were 0.1 in the affected right eye and 1.2 in the left eye. Anterior segment examination was within

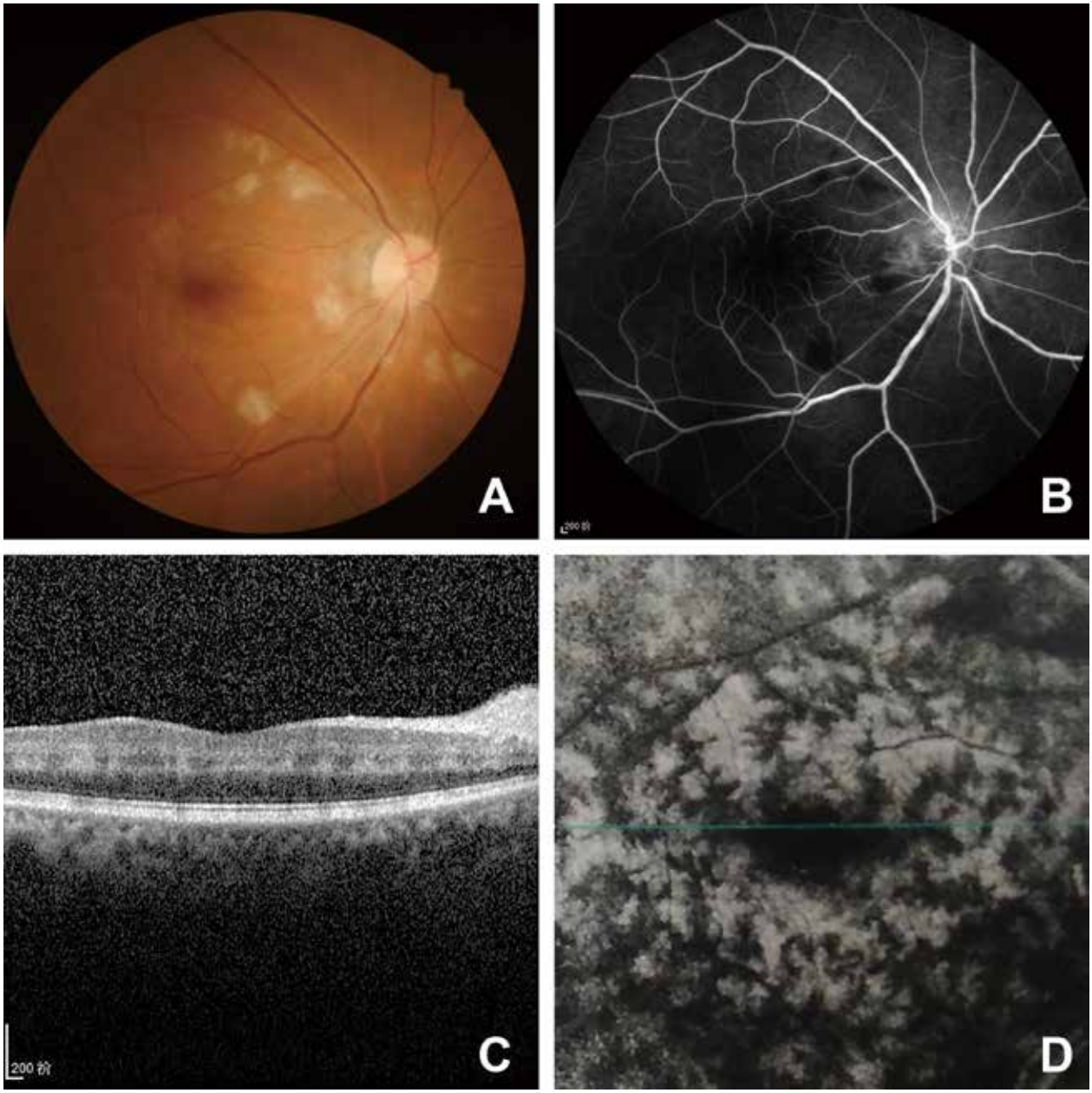

Figure 3. Multimodal retinal imaging of the right eye at presentation of 53-year-old man (case 3). **A:** Fundus examination showed scattered retinal whitening along the retinal blood vessel. **B:** Fluorescein angiography demonstrated delayed retinal arterial filling, scattered sheet masking fluorescence seen early and optic disc staining later period. **C:** SD-OCT illustrated intermittent hyper-reflective bands at the level of the INL. **D:** En face OCT segmented at the level of the INL with vascular mapping showed a characteristic perivenular fern-like pattern of PAMM.

normal limits. Medical history was notable for type 2 diabetes, hyperlipidemia and gout. He had bilateral cataract surgery by phacoemulsification. Fundus examination of the affected right eye showed scattered retinal whitening along the retinal blood vessel and a normal retinal examination of the left eye. Fluorescein angiography demonstrated delayed retinal arterial filling, scattered sheet masking fluorescence seen early and optic disc staining later period. SD-OCT illustrated intermittent hyper-reflective bands at the level of the INL and macular edema in the right eye. En face OCT segmented at the level of the INL with vascular mapping showed a characteristic perivenular fern-like pattern of PAMM (Figure 3).

DISCUSSION

PAMM is recently defined as a characteristic hyperreflective lesion on SD-OCT which affects the middle layers of the retina at the level of the INL and the outer plexiform layer, which leads to INL thinning,

suggesting a potential ischemic etiology[1]. Anatomical theory of retinal circulation seems to support this ischemic pathogenesis. These lesions are precisely aligned with the ICP and DCP of the macula[2]. The middle retinal is a watershed-like region and is more susceptible to ischemia caused by a high perfusion demand[6]. Although near infrared reflectance and SD-OCT imaging are still the most sensitive modalities for imaging of PAMM so far, it is increasingly important to use more advanced retinal imaging systems to elucidate this ischemic pathogenesis. Recent optical coherence tomography angiography (OCT-A) studies identified severe attenuation of the DCP in the zones of PAMM lesions, supporting a vaso-occlusive origin for these hyperreflective lesions[12,13]. En face OCT can segment the retina and delineates and localizes PAMM. Sridhar *et al*[10] have classified PAMM lesions into the three different subtypes according to morphologic appearance: arteriolar, globular and fern-like. The arteriolar pattern of perivenular hyperreflectivity can be seen in band-like areas where distribution of major arteriole may be related to transient or true arterial occlusion. The smaller, oval patches of hyperreflectivity seen in the focal and multifocal globular patterns likely represent distal ischemic events in smaller terminal retinal arterioles, precapillaries and capillaries. Fern-like distribution of PAMM analysis of eyes with CRVO and presumably due to perivenular capillary ischemia[10].

Since the initial report, Sarraf *et al* assessed the spectrum of fern-like perivenular PAMM of 7 of 11 eyes and demonstrated clear evidence of a CRVO or hemiretinal vein occlusion[1]. They also reported a case of a CRVO with a remarkable fern-like PAMM. Follow-up OCT-A demonstrated significant flow reduction of the deep capillary plexus in a perivenular pattern[8]. Fern-like PAMM mainly involves capillary ischemia distributed in CRVO or branch retinal vein occlusion and has not been described in the context of arterial occlusion. Capillaries are considered the most dense in the venous portion of the capillary network[3]. The DCP is the primary site of venous drainage for the retinal microvasculature[14,15]. The oxygen saturation of blood diminishes during transit to the venous system, so that the tissue adjacent to veins becomes exposed to the lowest oxygen levels[16]. This may explain the trend of PAMM lesions in vein occlusion areas and the results of characteristic perivenular fern-like PAMM lesions with periarterial sparing illustrated. Of note, the symptoms of two patients in our case partially experienced a partial resolution of symptoms within 30 minutes of onset. This is presumably due to transient hypoperfusion of DCP that may occur in advance before vascular occlusion and the retina may also have the ability to autoregulate flow to the deeper plexi[10]. Forty percent of CRVO and PAMM patients were found to have retinal artery occlusion[3], which is due to high pressure caused by sudden occlusion of the central retinal vein and is transmitted to the arterial system through the entire retinal capillary bed, resulting in relative hemodynamic occlusion[3,11]. Although secondary arterial insufficiency caused by CRVO is considered to be the most common cause of this characteristic perivenular fern-like lesion, primary arterial hypoperfusion may also cause a delay in blood flow of the deep capillary plexus, resulting in fernlike PAMM[8,17].

PAMM can be an idiopathic retinal ischemic disease and can also be found in healthy and young individuals who have normal ocular exam and systemic medical history, although most commonly seen in elderly patients with vascular high-risk factors[1,2,4,7,18]. However, targeted medical history and assessment of potential vascular risk factors are necessary, such as drugs (amphetamines, caffeine, vasopressors and oral contraceptives), migraine, severe hypovolemia, orbital compression injury or viral diseases (previous upper respiratory tract infection or H1N1 influenza vaccination) have been reported before[1,4,9].

CONCLUSION

These three cases prove the importance of en face OCT as a key method to locate and identify PAMM damage patterns. We propose that retinal multi-mode imaging will be helpful to further explore the etiology of PAMM.

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Author contribution: Wenqiao Huang, Yuqing Yan, Yi Du: contributed to diagnosis and management of the case; Wenqiao Huang: drafted initial manuscript; Yuqing Yan and Yi Du: reviewed and revised the manuscript.

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Brief Communication

Age-related macular degeneration pharmacotherapy: What have we learned?

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ABSTRACT

Age-related macular degeneration (AMD) is the third leading cause of irreversible blindness worldwide and a leading cause of severe vision impairment in older people, representing a healthcare challenge taking into account increased life expectancy in many parts of the world.
A new era in eye diseases treatment, particularly in AMD, starts from the development of therapy with antiangiogenics or vascular endothelial growth factor inhibitors (anti-VEGF).
Real-world evidence reveals significant rate of suboptimal therapeutic effect and lack of efficacy in more than half of the patients. On the other hand, long-term therapy with endless intravitreal injections of anti-VEGF in aging population causes an economic and cost-effectiveness concerns. The development of impactful, accessible, affordable, provider- and user-friendly (noninvasive), cost-effective agents is critical for successful management of retinal diseases, specifically AMD.

KEY WORDS: aflibercept, age-related macular degeneration, bevacizumab, brolucizumab, faricimab, ranibizumab, vascular endothelial growth factor inhibitors

INTRODUCTION

Age-related macular degeneration (AMD) is the third leading cause of irreversible blindness worldwide[1] and "a leading cause of severe vision impairment in older people"[2].

The incidence and prevalence of AMD are exponentially growing due to increased life expectancy in many parts of the world. It has been estimated that the number of persons with AMD will reach 288 million by 2040[3]. Both types of AMD: exudative neovascular (nAMD) and nonexudative (dry) cause visual impairment among elderly population, representing a healthcare challenge[4].

A new era in eye diseases treatment, particularly in AMD, starts from the development of therapy with antiangiogenics or vascular endothelial growth factor inhibitors (anti-VEGF)[5]. The term antiangiogenic therapy was introduced by J. Folkman more than 50 years ago[6]. Bevacizumab became the first therapy approved by the US - FDA designed to inhibit angiogenesis in tumors[7], and since 2004 widely used off-label in ophthalmology[8].

Currently, FDA-approved ranibizumab[9] and aflibercept[10] are being successfully used for the treatment of eye diseases like nAMD.

VEGF as a key regulator of angiogenesis and vascular permeability is involved also in the pathogenesis of retinal diseases associated with neovascularization and edema, such as nAMD[11].

Starting from 2006 intravitreal anti-VEGF injections, the gold standard therapy for nAMD[2], have transformed outcomes evidenced in multiple clinical trials[12], but not reconfirmed in real-world experience. Treatment regimens by bevacizumab, ranibizumab and aflibercept without universal approach have evolved through experience gained in clinical trials and clinical practice[13]. Real-world evidence reveals significant rate of suboptimal therapeutic effect[11], lack of efficacy in more than half of the patients[14] and underscores the need for new anti-VEGF agents with better durability[15].

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Newer antiangiogenics brolucizumab and faricimab were FDA-approved in October 2019 and January 2022 respectively. Brolucizumab is the first anti-VEGF with longer duration impact. Since its commercial availability, many papers have reported the therapeutic efficacy of this drug[16], however cases of intraocular inflammation, retinal occlusive vasculitis leading to severe vision loss are documented[16]. Currently brolucizumab represents a second-line treatment for poor responders due to accompanying risks. The newest anti-VEGF faricimab is a bispecific monoclonal antibody with dual mechanisms of action, that inhibits VEGF-A and angiopoietin-2[12]. A recent multicenter study[17] based on retrospective chart review evaluating 6-month efficacy of faricimab in patients with nAMD evidenced visual acuity amelioration or maintenance. Incidence of reported intraocular inflammation was low. Another retrospective, noncomparative cohort study of nAMD patients previously treated with anti-VEGF investigating short-term outcomes after switching to faricimab was conducted by Szigiato *et al*[18]. Researchers reported reduction of central subfield thickness and pigment epithelial detachment height with stable visual acuity. Ongoing research is required to validate real-world data on faricimab.

Despite significant advancements in the therapy of nAMD by anti-VEGF, accumulating evidence has suggested the undesirable effect manifesting by macular geographic atrophy[14,16]. Real-world experience underscores the need for comprehensive evaluation of the adverse effects in antiangiogenic intraocular pharmacotherapy, including ocular local injection-related and ocular chemical compound-related[19], and also systemic[20]. Local injection-related undesirable rarely occurring effects include acute-onset endophthalmitis, pseudo-endophthalmitis, cataract development/ progression, retinal detachment, hemorrhage, hypotony and angle closure. The preferred prophylactic method to minimize the risk of endophthalmitis is the preparation of the intravitreal injection site with topical povidone-iodine. Ocular chemical compound-related side effects include aforementioned macular geographic atrophy and intraocular inflammation, retinal occlusive vasculitis; retinal pigment epithelial tear, ocular hemorrhage (subretinal hemorrhage, macular hematoma), ocular blood flow disturbances leading to retinal venous and retinal arterial occlusions, anterior ischemic optic neuropathy, ocular ischemic syndrome, macular ischaemia. Special attention should be paid on the problem of tolerance/tachyphylaxy, taking into account that regular intraocular injections over long periods of time are required to maintain vision. In order to avoid this issue, it is recommended to switch to another anti-VEGF. The undesirable evidenced systemic side effects of antiangiogenics are cardiovascular and cerebrovascular events including myocardial infarction, heart failure, arrhythmias, transient ischemic attacks, deep vein thrombosis, pulmonary embolism and thrombophlebitis[20]

From the other hand, long-term therapy with endless intravitreal injections of anti-VEGF in aging population causes an economic and cost-effectiveness concerns. Ongoing efforts must address these challenges.

What may future look like for nAMD?

The development of impactful, accessible, affordable, provider- and user-friendly (noninvasive), cost-effective agents is critical for successful management of retinal diseases, specifically AMD. This will improve patient outcomes worldwide. Overlapping the risk factors for AMD and cardiovascular disease (hypertension, cholesterol and smoking) indicate a feasibility of versatile multitarget therapy. It is well-known that AMD is a disease with bilateral involvement. With this in mind, it should be considered that oral systemic therapy targeting both eyes simultaneously could result in clinically meaningful change in the manageability of AMD.

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The author had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2024; 56 (3): 264 - 265

Sex differences in the association between vitamin D and prediabetes in adults: A cross-sectional study

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BACKGROUND/OBJECTIVES
Vitamin D status has been shown to be associated with prediabetes risk. However, epidemiologic evidence on whether sex modulates the association between vitamin D and prediabetes is limited. The present study investigated sex-specific associations between vitamin D and prediabetes.

SUBJECTS/METHODS
The Kuwait Wellbeing Study, a population-based cross-sectional study, enrolled nondiabetic adults. Prediabetes was defined as 5.7 ≤ HbA1c% ≤6.4; 25-hydroxyvitamin D (25(OH)D) was measured in venous blood and analyzed as a continuous, dichotomous (deficiency: <50 nmol/L vs. insufficiency/sufficiency ≥50 nmol/L), and categorical (tertiles) variable. Associations were evaluated by estimating adjusted prevalence ratios (aPRs) and 95% confidence intervals (CIs), while stratifying by sex.

RESULTS
A total of 384 participants (214 males and 170 females) were included in the current analysis, with a median age of 40.5 (interquartile range: 33.0-48.0) years. The prevalence of prediabetes was 35.2%, and 63.0% of participants had vitamin D deficiency. Assessments of statistical interaction between sex and 25(OH)D status were statistically significant ($P_{Sex \times 25(OH)D\ Interaction} < 0.05$). In the sex-stratified analysis, after adjustment for confounding factors, decreased 25(OH)D levels were associated with increased prevalence of prediabetes in males ($aPR_{Deficiency\ vs.\ In\text{-}/Sufficiency}$: 2.35, 95% CI: 1.36-4.07), but not in females ($aPR_{Deficiency\ vs.\ In\text{-}/Sufficiency}$: 1.03, 95% CI: 0.60-1.77). Moreover, the prevalence of prediabetes differed between males and females at 25(OH)D levels of ≤35 nmol/L, with a higher prevalence of prediabetes in males compared to females. Such a sex-specific difference was not observed at 25(OH)D levels of >35 nmol/L.

CONCLUSIONS
Sex modified the association between vitamin D levels and prediabetes, with an inverse association observed among males, but not among females. Moreover, the observed sex-disparity in the prevalence of prediabetes was only pronounced at 25(OH)D levels of ≤35 nmol/L.

miR-24-3p and miR-484 are potential biomarkers for neurodegeneration in multiple sclerosis

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Multiple sclerosis (MS) is a complex, neurodegenerative chronic disorder. Circulating diagnostic biomarkers for MS have remained elusive, and those proposed so far have limited sensitivity and specificity to MS. Plasma-circulating microRNAs (miRNAs) have advantageous biochemical and physiological attributes that can be utilized in clinical testing and disease monitoring. MS miRNA expression microarray datasets analysis resulted in four candidate miRNAs that were assessed for their expression in a separate MS case-control study. Only miR-24-3p was downregulated in all MS patients compared to healthy controls. MiR-484 was significantly upregulated in relapsing-remitting MS (RRMS) patients compared to healthy controls. Mir-146-5p and miR-484 were significantly downregulated in secondary-progressive MS (SPMS) compared to RRMS. MiR-484 downregulation was associated with worsening disability and increased lipocalin-2 levels. Mir-342-3p and miR-24-3p downregulation were associated with increased semaphorin-3A levels in MS and RRMS patients. In conclusion, mir-24-3p downregulation is diagnostic of MS, and mir-484 upregulation and downregulation are potential biomarkers for RRMS and SPMS conversion, respectively. The differential expression of miR-146a-3p in MS subtypes suggests its potential as an SPMS transition biomarker. The association of downregulated mir-24-3p and mir-484 with increased neurodegeneration biomarkers suggests they play a role in MS pathogenesis and neurodegeneration.

Congenital optic disc pits and optic disc pit maculopathy: a review

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Optic disc pits are a rare but significant anomaly of the optic nerve head that can lead to visual impairment and associated complications. These pits are characterized by a small, oval-shaped depression in the disc, which can cause fluid accumulation and subsequent damage to the adjacent retina. Although the etiology and pathogenesis of optic disc pits are not fully understood, several theories have been proposed, including abnormal embryonic development and degenerative changes. Diagnosis is typically made through a comprehensive eye examination, including a dilated fundus exam and optical coherence tomography. Management options vary depending on the severity of the condition and associated complications, ranging from observation to surgical intervention.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

Kuwait Medical Journal 2024; 56 (3): 266 - 274

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India, Chennai
Organized by: National conference
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Organized by: AFTER
Conference inquiry email: event@after.org.in

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International Conference on **Healthcare and Clinical Gerontology**
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Global **Cardiology and Healthcare** Summit
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Sep 27, 2024
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United States, San Antonio, Texas
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International Conference on **Cardiology and Cardiovascular Medicine**
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Sep 28, 2024
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International Conference on **Cardiology and Cardiovascular Medicine**
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Conference inquiry email: papers.asar@gmail.com

International Conference on Advances in **Health and Medical Science**
Oct 04, 2024
Scotland, Glasgow
Organized by: SAARD
Conference inquiry email: info.saard.org@gmail.com

International Conference on **Medical & Health Science**
Oct 04, 2024
Germany, Frankfurt
Organized by: Research fora
Conference inquiry email: info@researchfora.com

International Conference on **Nano Chemistry & Nano Medicine**
Oct 04, 2024
Czech Republic, Liberec
Organized by: Japanese Society for Academic Research and Publication
Conference inquiry email: info.jsarap@gmail.com

International Research Conference on **COVID-19** and its Impact on **Mental Health**
Oct 04, 2024
United States, Mohall, North Dakota
Organized by: Research Conferences
Conference inquiry email: info.researchconferences@gmail.com

International Conference on **Epidemiology & Public Health**
Oct 06, 2024
Japan, Tokyo
Organized by: Meeting fora
Conference inquiry email: info@meetingfora.com

International Conference on **Healthcare and Clinical Gerontology**
Oct 06, 2024
Germany, Berlin
Organized by: Science fora
Conference inquiry email: info.sciencefora@gmail.com

International Conference on **Medical, Medicine and Health Sciences**
Oct 06, 2024
Egypt, Cairo
Organized by: International Institute of Engineers Researchers and Doctors
Conference inquiry email: contact.iierd@gmail.com

Digital Health & AI Innovation Summit
Oct 07, 2024
United States, Masachusetts, Masachusetts
Organized by: Worldbigroup
Conference inquiry email: info@worldbigroup.com

International Conference on **Bioinformatics, Biomedicine, Biotechnology and Computational Biology**
Oct 08, 2024
United States, Detroit, Michigan
Organized by: Eurasia Web
Conference inquiry email: info@eurasiaweb.com

International Conference on **Medical, Pharmaceutical and Health Sciences**
Oct 09, 2024
Qatar, Doha
Organized by: GSRD
Conference inquiry email: info.gsrd@gmail.com

International Conference on **Medical & Health Science**
Oct 09, 2024
Greece, Athens
Organized by: Researchfora
Conference inquiry email: info@researchfora.com

International Conference on Recent Advances in **Medical and Health Sciences**
Oct 10, 2024
Russia, Moscow
Organized by: Academicsworld
Conference inquiry email: info@academicsworld.org

Dermatology Council Conference in **Immunodermatology, Dermatosurgery & Laser Therapeutics**
Oct 10-12, 2024
Kuwait, Kuwait city
Grand Hyatt Hotel
Conference inquiry email:
www.dermacouncilconferencekw.com

International Conference on **Medical and Health Sciences**
Oct 11, 2024
Spain, Barcelona
Organized by: ISERD
Conference inquiry email: info@iserd.co

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Oct 12, 2024
Qatar, Doha
Organized by: WRFER
Conference inquiry email: contact.wrfer@gmail.com

Research International Conference on **Medical, Medicine and Health Science**
Oct 12, 2024
United Arab Emirates, Dubai
Organized by: Research Conferences
Conference inquiry email: info.researchconferences@gmail.com

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Oct 13, 2024
India, Ooty, Tamil Nadu
Organized by: ISSRD
Conference inquiry email: papers.issrd@gmail.com

International Conference on **Medical, Pharmaceutical and Health Sciences**
Oct 16, 2024
Denmark, Copenhagen
Organized by: GSRD
Conference inquiry email: info.gsrd@gmail.com

International Video Conference on **Healthcare**
Oct 16, 2024
United Arab Emirates, Abu Dhabi
Organized by: Conference Online
Conference inquiry email: info.conferenceonline@gmail.com

4th International Meet on **Public Health and Healthcare Management** Public Health Meet 2024
Oct 17, 2024
Switzerland, Bern
Organized by: Public health meet 2024
Conference inquiry email:
publichealthmeet2024@albedomeetings.com

International Conference on **Medical, Medicine and Health Sciences**
Oct 18, 2024
Australia, Sydney
Organized by: International Institute of Engineers Researchers and Doctors
Conference inquiry email: contact.iierd@gmail.com

International Conference on **Bioinformatics, Biomedicine, Biotechnology and Computational Biology**
Oct 19, 2024
United States, Louisville
Organized by: Eurasia Web
Conference inquiry email: info@eurasiaweb.com

International Conference on **Veterinary Forensic Medicine**
Oct 19, 2024
Germany, Berlin
Organized by: United Research
Conference inquiry email:
info.unitedresearch@gmail.com

International Conference on **Healthcare Innovation and Medical Sciences**
Oct 19, 2024
United States, New York
Organized by: Biofora
Conference inquiry email: info@biofora.org

International Conference on Recent Advancement in **Medical Education, Nursing and Health Sciences**
Oct 20, 2024
Turkey, Istanbul
Organized by: IRF conference
Conference inquiry email:
info.irfconference@gmail.com

Research International Conference on **Medical, Medicine and Health Science**
Oct 20, 2024
Taiwan, Taipei
Organized by: Research Conferences
Conference inquiry email:
info.researchconferences@gmail.com

5th Edition of Global Conference on **Addiction Medicine, Behavioral Health and Psychiatry**
Oct 21, 2024
United States, Baltimore, Maryland
Organized by: Magnus Group
Conference inquiry email: addiction@magnusconference.com

The **Digital Health** Forum
Oct 21, 2024
Saudi Arabia, Malham, Riyadh
Organized by: Global Health Saud
Conference inquiry email: sales@globalhealthsaudi.com

International Congress on **Physical Activity and Public Health**
Oct 22, 2024
Egypt, Alexandria
Organized by: Academic Research Network
Conference inquiry email: info.academicresearchnetwork@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Oct 23, 2024
United States, Houston
Organized by: Academics world
Conference inquiry email: info@academicsworld.org

International Conference on **Science, Health and Medicine**
Oct 25, 2024
Italy, Rome
Organized by: ISER
Conference inquiry email: info@iser.co

International Conference on **Epidemiology & Public Health**
Oct 27, 2024
United Arab Emirates, Dubai
Organized by: Meeting fora
Conference inquiry email: info@meetingfora.com

International Conference on **Healthcare and Clinical Gerontology**
Oct 28, 2024
Japan, Saitama
Organized by: Science fora
Conference inquiry email: info.sciencefora@gmail.com

III CME **Heartcare and Cardiovascular Medicin**e Conference
Oct 28, 2024
United Kingdom, London
Organized by: PLENARENO
Conference inquiry email: eaccm@plenareno.net

2nd Kuwait **Public Health** Conference
Oct 28-29, 2024
Kuwait, Kuwait city

International Conference on Recent Advancement in **Medical Education, Nursing and Health Sciences**,
Oct 30, 2024
China, Shanghai
Organized by: IRF conference
Conference inquiry email: info.irfconference@gmail.com

International Conference on **Medical, Medicine and Health Sciences**
Oct 30, 2024
United States, Washington
Organized by: International Institute of Engineers Researchers and Doctors
Conference inquiry email: contact.iierd@gmail.com

Global **Cardiology and Healthcare** Summit
Oct 30, 2024
Indonesia, Bali
Organized by: Bio fora
Conference inquiry email: info@biofora.org

International Conference on **Laboratory Medicine & Pathology**
Oct 31, 2024
Japan, Fukuoka
Organized by: aserd.org
Conference inquiry email: info.aserd@gmail.com

2nd **Kuwait Pediatric Association Conference** and Workshop
Oct 31 - Nov 2, 2024
Kuwait, Kuwait city
Conference inquiry email: www.kpacw2024.com

International Conference on **Medical and Health Sciences**
Nov 01, 2024
United Kingdom, Edinburgh
Organized by: Science plus
Conference inquiry email: papers.scienceplus@gmail.com

International Conference on **Nutrition & Health**
Nov 02, 2024
China, Beijing
Organized by: ASAR
Conference inquiry email: papers.asar@gmail.com

International Conference on **Epidemiology & Public Health**
Nov 03, 2024
Malaysia, Kuala Lumpur
Organized by: Meeting fora
Conference inquiry email: info@meetingfora.com

International Conference on **Medical and Health Sciences**
Nov 03, 2024
Germany, Munich
Organized by: ISERD
Conference inquiry email: info@iserd.co

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Nov 04, 2024
Switzerland, Geneva
Organized by: WRFER
Conference inquiry email: contact.wrfer@gmail.com

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Nov 06, 2024
Turkey, Antalya
Organized by: WRFER
Conference inquiry email: contact.wrfer@gmail.com

International Conference on **COPD and Lung Health**
Nov 07, 2024
Italy, Rome
Organized by: Conference coordinator
Conference inquiry email: copd@sciconxevents.com

International Conference on **Medical, Pharmaceutical and Health Sciences**
Nov 08, 2024
Japan, Kyoto
Organized by: GSRD
Conference inquiry email: info.gsrd@gmail.com

International Conference on **Medical and Health Sciences**
Nov 09, 2024
Russia, Saint Petersburg
Organized by: ISERD
Conference inquiry email: info@iserd.co

International Conference on **Food, Nutrition, Health & Lifestyle**
Nov 10, 2024
Canada, Toronto
Organized by: Bio fora
Conference inquiry email: info@biofora.org

Global **Cardiology and Healthcare** Summit
Nov 10, 2024
Canada, Toronto
Organized by: Bio fora
Conference inquiry email: info@biofora.org

International Webinar on **Sports Medicine**
Nov 11, 2024
United Kingdom, London
Organized by: Sciconx
Conference inquiry email: sportsmedicine@sciconxevents.com

International Conference on **Medical & Health Science**
Nov 12, 2024
Oman, Muscat
Organized by: Research fora
Conference inquiry email: info@researchfora.com

International Conference on **Healthcare and Clinical Gerontology**
Nov 12, 2024
Switzerland, Bern
Organized by: Science fora
Conference inquiry email: info.sciencefora@gmail.com

International Conference on Recent Advancement in **Medical Education, Nursing, and Health Sciences**
Nov 16, 2024
Australia, Melbourne
Organized by: IRF
Conference inquiry email: info.irfconference@gmail.com

International Conference on **Nutrition & Health**
Nov 16, 2024
United States, Boston, Massachusetts
Organized by: ASAR
Conference inquiry email: papers.asar@gmail.com

International Conferences on Advances in **Nursing Science, Medical and Health Care**
Nov 18, 2024
United Kingdom, London
Organized by: Theires
Conference inquiry email: info@theires.org

International Conference on **Women's Health and Breast Cancer**
Nov 18, 2024
United Arab Emirates, Dubai
Organized by: Womens health
Conference inquiry email: womenshealth@presentresearch.org

International Conference on **Mental Health and Psychiatry**
Nov 19, 2024
France, Strasbourg
Organized by: The International Society for Researchers and Doctors
Conference inquiry email: info.theisrd@gmail.com

World Congress on **Animal Science & Veterinary Medicine**
Nov 20, 2024
Italy, Rome
Organized by: Inovine Scientific Meetings
Conference inquiry email: animalscience@inovineconferences.com

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Nov 20, 2024
India, Nashik, Maharashtra
Organized by: ISSRD
Conference inquiry email: papers.issrd@gmail.com

International Conference on **Advanced Medical and Healthcare**
Nov 21, 2024
Germany, Cologne
Organized by: The International Society for Researchers and Doctors
Conference inquiry email: info.theisrd@gmail.com

2nd **Kuwait Pediatric Conference**
Nov 22-24, 2024
Kuwait, Kuwait city
Conference inquiry email: www.kpc2024.com

International Conference on **Science, Health and Medicine**
Nov 23, 2024
United States, Houston
Organized by: ISER
Conference inquiry email: info@iser.co

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Nov 24, 2024
Italy, Rome
Organized by: ISSRD
Conference inquiry email: papers.issrd@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Nov 27, 2024
United Arab Emirates, Abu Dhabi
Organized by: Academics world
Conference inquiry email: info@academicsworld.org

International Conference on Recent Advancement in **Medical Education, Nursing, and Health Sciences**
Nov 28, 2024
Canada, Toronto
Organized by: IRF conference
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International Conferences on Advances in **Nursing Science, Medical and Health Care**
Nov 29, 2024
Italy, Milan
Organized by: Theires
Conference inquiry email: info@theires.org

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Nov 30, 2024
India, Navi Mumbai, Maharashtra
Organized by: ISSRD
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International Conference on **Cardiology and Cardiovascular Medicine**
Dec 03, 2024
Australia, Ballarat
Organized by: The International Society for Researchers and Doctors
Conference inquiry email: info.theisrd@gmail.com

Global **Cardiology and Healthcare** Summit
Dec 05, 2024
Singapore, Singapore
Organized by: Biofora
Conference inquiry email: info@biofora.org

The 17th Annual **Kuwait Urology Association Conference**
Dec 5-7, 2024
Kuwait, Kuwait city

International Conference on **Bioinformatics, Biomedicine, Biotechnology and Computational Biology**
Dec 06, 2024
Scotland, Glasgow
Organized by: Eurasia Web

International Conference on **Medical, Pharmaceutical and Health Sciences**
Dec 07, 2024
Japan, Osaka
Organized by: GSRD
Conference inquiry email: info.gsrd@gmail.com

International Congress on **Mental Health Psychiatry**
Dec 09, 2024
United Kingdom, Paris, England
Organized by: Sciconx Conferences
Conference inquiry email: mentalhealth@sciconxevents.com

International Conference on **Epidemiology & Public Health**
Dec 10, 2024
Thailand, Bangkok
Organized by: Meeting fora
Conference inquiry email: info@meetingfora.com

International Conference on Recent Trends in **Herbal & Traditional Medicine** Summit
Dec 12, 2024
United Arab Emirates, Dubai
Organized by: Biofora
Conference inquiry email: info@biofora.org

7th KNC and 14th GCC **Neurology** Conference
Dec 12-14, 2024
Kuwait, Kuwait city
Grand Hyatt Hotel
Conference inquiry email: www.kuwaitneurology.com

International Conference on **Science, Health and Medicine**
Dec 13, 2024
France, Cannes
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Conference inquiry email: info@iser.co

International Conference on **Nutrition & Health**
Dec 15, 2024
China, Shanghai
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International Conference on **Healthcare and Clinical Gerontology**
Dec 16, 2024
Switzerland, Geneva
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Conference inquiry email: info.sciencefora@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Dec 17, 2024
Ukraine, Kiev
Conference inquiry email: info@academicsworld.org

International World Research Congress on **Dentistry and Oral Health**
Dec 19, 2024
Philippines, Manila
Organized by: Biofora
Conference inquiry email: info@biofora.org

International Conference on **Medical Health Science, Pharmacology & Bio Technology**
Dec 20, 2024
South Korea, Seoul
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International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Dec 20, 2024
United States, Las Vegas
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International Conference on **Medical and Health Sciences**
Dec 21, 2024
United States, Washington
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International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
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Dec 23, 2024
United States, Houston
Organized by: Research fora
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International Conference on **Medical, Pharmaceutical and Health Sciences**
Dec 25, 2024
Australia, Sydney
Organized by: GSRD
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International Conference on **Medical, Pharmaceutical and Health Sciences**
Dec 25, 2024
France, Paris
Organized by: GSRD
Conference inquiry email: info.gsrd@gmail.com

International Conference on Recent Advances in **Medical and Health Sciences**
Dec 28, 2024
Kuwait, Kuwait City
Organized by: Academics world
Conference inquiry email: info@academicsworld.org

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Dec 29, 2024
Turkey, Istanbul
Organized by: WRFER
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WHO-Facts Sheet

1. Diphtheria
2. Multiple sclerosis
3. Refugee and migrant health
4. Typhoid
5. Yellow fever

Compiled and edited by
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1. Diphtheria

KEY FACTS

- Diphtheria is a disease caused by a bacterium that affects the upper respiratory tract and less often the skin. It also produces a toxin that damages the heart and the nerves.
- Diphtheria is a vaccine preventable disease, but multiple doses and booster doses are needed to produce and sustain immunity.
- Those who are not immunized or under immunized are at risk of the disease.
- For unvaccinated individuals, without proper treatment, diphtheria can be fatal in around 30% of cases, with young children at higher risk of dying (1).
- Recent diphtheria outbreaks stress the importance of sustaining high levels of vaccination coverage in communities across the life course.
- In 2023, an estimated 84% of children worldwide received the recommended 3 doses of diphtheria-containing vaccine during infancy, leaving 16% with no or incomplete coverage. There is wide coverage variation between and within countries.

Overview

Diphtheria is a contagious disease that is caused by toxin producing bacteria. It can spread from person to person when an infected person coughs or sneezes. Some people may not develop disease manifestations but can still transmit the bacteria to others. Others will develop mild disease, although severe disease, complications and death can also occur.

Diphtheria can affect anyone but was most common in unvaccinated children. The diphtheria toxin causes damage to the respiratory tract and can spread throughout the body. Common symptoms include fever, sore throat and swelling of the neck glands.

Being vaccinated is the best way to prevent getting sick with diphtheria or spreading it to other people. The vaccine is safe and helps your body fight off the infection. Before the introduction of diphtheria vaccine and widespread vaccination in the 1930s, cases occurred throughout the world.

Recently, as a result of under vaccination, outbreaks have been occurring with increasing frequency despite the availability of a safe and effective vaccine.

Effects of the COVID-19 pandemic

The COVID-19 pandemic impacted delivery of routine immunization services and surveillance activities. These setbacks have left many children susceptible to vaccine preventable diseases such as diphtheria.

No WHO region is completely free from diphtheria, and areas with low immunization coverage with the diphtheria toxoid-containing vaccine allow the bacteria to circulate, increasing the likelihood of outbreaks and putting all unvaccinated and under vaccinated individuals at risk.

Immunization and surveillance programs should be strengthened within primary healthcare, and efforts should be made to reach all children with 3 diphtheria toxoid-containing vaccine doses during infancy, childhood and adolescence. Countries should also implement robust surveillance systems to identify and confirm cases and close immunity gaps rapidly.

Signs and symptoms

Symptoms of diphtheria usually begin 2–5 days after exposure to the bacteria. Typical symptoms of the infection include a sore throat, fever, swollen neck glands and weakness. Within 2–3 from infection, the dead tissue in the respiratory tract forms a thick, grey

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coating that can cover tissues in the nose, tonsils and throat, making it hard to breathe and swallow.

Most severe disease and deaths from diphtheria occur as a result of the diphtheria toxin and its effects. Complications can include inflammation of the heart and nerves. For unvaccinated individuals without adequate treatment, diphtheria can be fatal in around 30% of cases, which children younger than 5 years of age at greater risk of dying.

Who is at risk?

Any non-immune person (not vaccinated or under vaccinated) can become infected. Diphtheria has seen resurgences any time immunization coverage becomes low. Damaged health infrastructure and health services in countries experiencing or recovering from a natural disaster or conflict interrupt routine immunization. Overcrowding in residential camps increases the risk of infection.

Treatment

The risk of complications or death decrease considerably if appropriate treatment is provided early in the course of illness. For this reason, if diphtheria is suspected, testing to confirm the disease should be done promptly and treatment should be started as soon as possible.

Cases of diphtheria are usually treated with diphtheria antitoxin as well as antibiotics. Diphtheria specific antitoxin neutralizes circulation toxin in the blood. Detailed instructions for giving antitoxin can be found in the WHO treatment guidelines. Antibiotics stop bacterial replication and thereby toxin production, speed up getting rid of the bacteria and prevents transmission to others. However, many current strains of diphtheria have exhibited resistance to some commonly used antimicrobial drugs. Anyone that has had diphtheria should also receive vaccine after the acute phase of the illness is over.

Individuals who have been in contact with cases of diphtheria should be treated with antibiotics prophylactically to prevent illness. Their immunization status of all contacts should also be checked. If they are not fully vaccinated, they should also be offered vaccine.

Prevention

Diphtheria can be prevented by vaccines that are often given in combination with tetanus and pertussis and other diseases. WHO recommends a total of 6 diphtheria-containing vaccine doses be given starting at 6 weeks of age through adolescence to provide long term protection.

Community-wide vaccination with high coverage as a part of routine immunization services embedded in primary health care is the most effective way to prevent diphtheria. All children should be vaccinated against diphtheria with a full primary series and 3 additional booster doses for long term protection. The vaccine is safe and effective.

The diphtheria vaccine is given most often combined with vaccines for diseases such as tetanus, pertussis, Hemophilus influenzae, hepatitis B and inactivated polio.

Combining vaccines slightly increases the cost but allows for shared delivery and administration costs, and importantly adds the benefit of protection against other childhood illness that can cause tetanus, pertussis, meningitis and polio.

In 2023, 84% of children received all 3 doses of the primary series of diphtheria vaccine. However, there are substantial variations in coverage levels between and within countries. Under vaccination in successive cohorts of children can lead to cases and outbreaks of diphtheria.

WHO response

The essential programme on immunization began in 1974. Combination diphtheria vaccines were introduced as part of this programme since its inception and have prevented >90% cases of disease between 1980–2000. WHO continues to work with member states to promote vaccination to sustain vaccine coverage and prevent disease in communities.

In recent years, there have been outbreaks of diphtheria due to inadequate vaccine coverage. To control these outbreaks, WHO has worked with member states in outbreak response and in strengthening routine immunization programmes to improve and sustain immunization coverage to prevent diphtheria infections and deaths.

REFERENCES

1. Truelove SA, Keegan LT, Moss WJ, Chaisson LH, Macher E, Azman AS, Lessler J. Clinical and Epidemiological Aspects of Diphtheria: A Systematic Review and Pooled Analysis. Clin Infect Dis. 2020 Jun 24;71(1):89-97. doi: 10.1093/cid/ciz808. PMID: 31425581; PMCID: PMC7312233. https://pubmed.ncbi.nlm.nih.gov/31425581/

2.Multiple sclerosis

KEY FACTS

- Multiple sclerosis (MS) affects function in cognitive, emotional, motor, sensory, or visual areas and occurs as a result of a person's immune system attacking their brain and spinal cord.

- It is estimated that over 1.8 million people have MS worldwide.
- People of all ages can be affected, but it is more common in young adults and in females.
- MS can improve or stabilize by being treated with medicines early in the course of the disease and treatments will be different for each person depending on the severity of the disease and symptoms.

Overview

Multiple sclerosis (MS) is a condition that happens when the immune system attacks the brain and spinal cord.

Symptoms of MS vary from person to person and depend on the location and severity of nerve fibre damage. These often include vision problems, tiredness, trouble walking and keeping balance, and numbness or weakness in the arms and legs. Symptoms can come and go or last for a long time.

The causes of MS are not known but a family history of the disease may increase the risk. While there is no cure for MS, treatment can reduce symptoms, prevent further relapses and improve quality of life.

MS can present in a variety of ways including:

- clinically isolated syndrome (CIS): describes an episode of neurologic symptoms that are the first clinical sign of possible MS;
- relapsing remitting (RRMS): the most common form of MS characterized by intermittent attacks of symptoms (relapses), followed by a short or long period of no clinical attacks (remissions);
- secondary progressive (SPMS): after living with RRMS for a long period of time, relapses decrease and symptoms continue progressively without relapses or remissions; and
- primary progressive (PPMS): starting from the initial symptoms, the disease gradually progresses and gets worse without any clear relapses or remissions.

MS is not always easy to diagnose in its early stages. Typically, people who have been diagnosed with MS will have been through several diagnostic stages, which can be an unsettling and frightening experience.

Symptoms

Symptoms of multiple sclerosis can be different from person to person. They can come and go or get worse over time. MS can affect any part of the central nervous system.

MS symptoms can worsen with heat or during other infections such as urinary tract or respiratory infections. Symptoms can include:

- vision problems
- difficulty walking or keeping balance
- difficulty thinking clearly
- numbness or weakness especially in the arms and legs
- muscle stiffness
- depression
- problems with sexual function or urination
- feeling very tired.

Causes

MS is an inflammatory demyelinating condition that results from an autoimmune attack on myelin, the fatty insulation that surrounds the nerves in the brain and spinal cord. This disrupts the electrical impulses that are sent through the nerves to the rest of the body and results in scars (plaques or sclerosis).

It is not known what triggers the immune system to attack myelin, but genetic and environmental factors are thought to play a role. MS happens most commonly in young to middle-aged adults, more in females than males, and is more common in higher latitudes, possibly due to sun exposure and vitamin D.

Diagnosis

MS is a diagnosis of exclusion and there are no definitive diagnostic tests. Magnetic resonance imaging (MRI) can help with diagnosis by showing plaques or sclerosis on the brain and spinal cord. Other tests such as lumbar puncture, optical coherence tomography (OCT) and visual evoked potentials can also help support the diagnosis.

Treatment and care

Treatments for MS will be different for each person. They depend on the stage of the disease and symptoms. The goals of MS treatment are to reduce the frequency and severity of relapses, slow disease progression, manage symptoms, and improve quality of life.

Specific MS disease modifying therapies (DMTs) are started as early as possible to slow disease progression and prevent relapses. Steroids are sometimes used in the short term to treat relapses. Other medicines can be used to reduce the symptoms of MS such as fatigue, muscle tightening, depression and urinary or sexual problems. These medicines do not change the course of the disease but help manage the symptoms.

Rehabilitation specialists can help improve functioning, quality of life and reduce muscle stiffness and spasms. Many people feel fatigue with multiple sclerosis. Ways to manage fatigue include:

- regular exercise
- healthy sleep patterns
- avoiding medicines that make fatigue worse.

In the past twenty years treatment options for MS have improved dramatically. In high income countries many oral, intravenous and injectable options exist to treat MS. However, most of these medications are not available in low- and middle-income countries and there is still a lack of treatment options for progressive types of MS.

People with MS and their families should be encouraged to seek services and guidance from local and national Organizations of Disabled People (ODPs) and other disability focused organizations, which can provide vital advice about legal rights, economic opportunities and social engagement to ensure that people disabled by MS or other neurological disorders are able to live full and rewarding lives.

WHO Response

In May 2022, the World Health Assembly endorsed the Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031. The action plan addresses the challenges and gaps in providing care and services for people with epilepsy and other neurological disorders such as MS that exist worldwide and ensure a comprehensive, coordinated response across sectors. This includes raising policy prioritization and strengthening governance, providing effective, timely and responsive diagnosis, treatment and care, implementing strategies for promotion and prevention, fostering research and innovation and strengthening information systems.

WHO also supports countries to manage MS by:

- working to include MS medications in WHO Essential Medicines Lists (EML);
- collaboration with civil society such as Multiple Sclerosis International Federation (MSIF) on broad issues and advocacy including through World MS Day (May 30);
- creation of the Atlas of Multiple Sclerosis for use by people with MS, health professionals and MS groups and organizations to stimulate and inform campaigns for improvements in the services and support provided to people with MS and those with an interest in their well-being and quality of life; and
- supporting countries to implement guidelines and strengthen health systems to improve the rehabilitation services for people with neurological disorders.

3.Refugee and migrant health

KEY FACTS

- More than 1 billion people are on the move globally, about 1 in 8 of the global population.
- Of this total, 281 million people are international migrants (1) and 84 million are forcibly displaced (48 million are internally displaced, 26.6 million are refugees, 4.4 million are asylum seekers). Among the forcibly displaced, 35 million are children and 1 million were born into refugee life (2).
- The number of people on the move is expected to grow due to poverty, lack of security, lack of access to basic services, conflict, environmental degradation and disasters.
- Migration could both improve or diminish an individual's health status. Refugees and migrants often face worse health outcomes in countries of transit and destination due to barriers including language and cultural differences, institutional discrimination and restricted use of health services.
- Social, political and economic exclusion can result in poverty, homelessness and exploitation, which can create a higher risk for noncommunicable diseases.
- The COVID-19 pandemic has exacerbated existing inequalities in certain populations, which may include refugees and migrants, particularly those in irregular situations.

Overview

Refugees and migrants have a variety of different physical and mental health needs, shaped by experiences in their country of origin, their migration journey, their host country's entry and integration policies, and living and working conditions. These experiences can increase the vulnerability of refugees and migrants to chronic and infectious diseases.

The COVID-19 pandemic has disrupted health services, putting people already in vulnerable situations at heightened risk and hampering the ability of health systems to respond to their needs.

Key data and information on refugees and migrants

The term refugee is defined in Article 1 of the 1951 Convention Relating to the Status of Refugees (3). There is no universally accepted definition of the term migrant (4). However, the United Nations Department of Economic and Social Affairs defines an international migrant as "any person who changes his or her country of usual residence", and this definition includes people who are moving or have moved across an international border, regardless of legal status, duration of the stay abroad and causes for migration (5).

Migrants may be given a migration status that limits their entitlement and access to health care. However, international law guarantees universal access in line with the 2030 Agenda for Sustainable Development, in particular with Sustainable Development Goal 3 (ensure healthy lives and promote well-being for all at all ages) (6).

Although governed by separate legal frameworks, refugees and migrants are entitled to the same universal human rights and fundamental freedoms as other people (7).

In 2021, countries with the highest number of refugees fleeing were 1. Syrian Arab Republic, 2. Venezuela, 3. Afghanistan, 4. South Sudan and 5. Myanmar while countries hosting the highest number of refugees were 1. Turkey, 2. Colombia, 3. Uganda, 4. Pakistan, 5. Germany (8).

In the first 5 weeks since the escalation of conflict in Ukraine on 24 February 2022, more than 4 million refugees from Ukraine crossed borders into neighbouring countries, and many more have been forced to move inside the country (9).

In 2020, the top countries of origin for international migrants were 1. India, 2. Mexico, 3. Russian Federation, 4. Syrian Arab Republic, 5. China. The United States of America has been the main country of destination for international migrants since 1970, and Germany is the second top destination (10).

Common health needs and vulnerabilities of refugees and migrants

Refugees and migrants are a diverse group and have a variety of health needs, which may differ from those of the host populations.

Refugees and migrants often come from communities affected by war, conflict, natural disasters, environmental degradation or economic crisis. They undertake long, exhausting journeys with inadequate access to food and water, sanitation and other basic services, which increases their risk of communicable diseases, particularly measles, and food- and waterborne diseases. They may also be at risk of accidental injuries, hypothermia, burns, unwanted pregnancy and delivery-related complications, and various noncommunicable diseases due to the migration experience, restrictive entry and integration policies and exclusion.

Refugees and migrants may arrive in the country of destination with poorly controlled non-communicable diseases, as they did not have care on the journey. Maternity care is usually a first point of contact with health systems for female refugees and migrants.

Refugees and migrants may also be at risk of poor mental health because of traumatic or stressful experiences Many of them experience feelings of anxiety and sadness, hopelessness, difficulty sleeping, fatigue, irritability, anger or aches and pains but for most people these symptoms of distress improve over time They may be at more risk of such as depression, anxiety and post-traumatic stress disorder (PTSD) than the host populations.

Refugee and migrant health is also strongly related to the social determinants of health, such as employment, income, education and housing

Barriers to access to health services

Refugees and migrants remain among the most vulnerable members of society and are often faced with xenophobia; discrimination; substandard living, housing and working conditions; and inadequate or restricted access to mainstream health services.

Migrants, particularly in an irregular situation, are often excluded from national programmes for health promotion, disease prevention, treatment and care, as well as from financial protection in health. They can also face high user fees, low levels of health literacy, poor cultural competency among health providers, stigma and inadequate interpreting services.

Barriers are even greater for people with disabilities. Women and girls may find difficulty in accessing sexual and gender-based violence protection and response services. Refugee and migrant children, especially unaccompanied minors, are more likely to experience traumatic events and stressful situations, such as exploitation and abuse, and may struggle to access health care.

The ability to access health services in humanitarian settings is usually compromised and complicated by shortages of medicines and lack of healthcare facilities.

COVID-19

The COVID-19 pandemic has brought an increased risk of infection and death for refugees and migrants. People on the move may have limited tools to protect themselves such as social distancing, hand hygiene and self-isolation are often not possible.

The pandemic has highlighted existing inequities in access to and utilization of health services. Refugees and migrants have also suffered the negative economic impact of lockdown and travel restrictions. Income loss and health care insecurity may have particularly affected labour migrants. They may have also experienced legal and social insecurity caused by the postponement of decisions on migration status or a reduction of employment, legal and administrative services.

WHO response

WHO believes that everyone, including refugees and migrants, should be able to enjoy the right to health and access to people-centred, high-quality health services without financial impediment, as expressed by our commitment to universal health coverage. Health systems should incorporate the needs of refugees and migrants in national and local health policies, financing, planning, implementation,

monitoring and evaluation. In rapid and effective emergency responses, health care may sometimes need to be delivered in a parallel structure to the national health system, but in the long term, refugee and migrant health should be mainstreamed into existing services.

WHO works around the world to secure the health rights of refugees and migrants and achieve universal health coverage. Through the Health and Migration Programme, and in collaboration with regional and country offices, WHO provides global leadership, advocacy, coordination and policy on health and migration; sets norms and standards to support decision-making; monitors trends, strengthens health information systems and promotes tools and strategies; provides technical assistance, response and capacity-building support to address public health challenges; and promotes global multilateral action and collaboration by working with UN agencies and other international stakeholders, as well as by being part of the United Nations Network on Migration.

WHO works with countries to build strong health systems that are supported by a well trained, culturally sensitive and competent workforce, and are sensitive to the needs of refugees and migrants, their languages and their unique health problems.

Notes

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4.Typhoid

KEY FACTS

- As of 2019, an estimated 9 million people get sick from typhoid and 110 000 people die from it every year.
- Symptoms include prolonged fever, fatigue, headache, nausea, abdominal pain, and constipation or diarrhoea. Some patients may have a rash. Severe cases may lead to serious complications or even death.
- Typhoid fever can be treated with antibiotics although increasing resistance to different types of antibiotics is making treatment more complicated.
- The typhoid conjugate vaccine is recommended for use in children from 6 months of age and in adults up to 45 years or 65 years (depending on the vaccine).
- Two typhoid conjugate vaccines have been prequalified by WHO since December 2017 and are being introduced into childhood immunization programmes in typhoid endemic countries.

Overview

Typhoid fever is a life-threatening infection caused by the bacterium Salmonella Typhi. It is usually spread through contaminated food or water. Once Salmonella Typhi bacteria are ingested, they multiply and spread into the bloodstream.

Urbanization and climate change have the potential to increase the global burden of typhoid. In addition, increasing resistance to antibiotic treatment is making it easier for typhoid to spread in communities that lack access to safe drinking water or adequate sanitation.

Symptoms

Salmonella Typhi lives only in humans. Persons with typhoid fever carry the bacteria in their bloodstream and intestinal tract. Symptoms include prolonged high fever, fatigue, headache, nausea, abdominal pain, and constipation or diarrhoea. Some patients may have a rash. Severe cases may lead to serious complications or even death. Typhoid fever can be confirmed through blood testing.

Epidemiology, risk factors and disease burden

Improved living conditions and the introduction of antibiotics resulted in a drastic reduction of typhoid fever morbidity and mortality in industrialized countries. However, the disease continues to be a public health problem in many developing areas of the WHO African, Eastern Mediterranean, South-East Asia and Western Pacific Regions.

As of 2019 estimates, there are 9 million cases of typhoid fever annually, resulting in about 110 000 deaths per year.

Typhoid risk is higher in populations that lack access to safe water and adequate sanitation, and children are at highest risk.

Treatment

Typhoid fever can be treated with antibiotics. Antimicrobial resistance is common with likelihood of more complicated and expensive treatment options required in the most affected regions.

Even when the symptoms go away, people may still be carrying typhoid bacteria, meaning they can spread it to others, through shedding of bacteria in their faeces.

It is important for people being treated for typhoid fever to do the following:

- Take prescribed antibiotics for as long as the doctor has prescribed.
- Wash their hands with soap and water after using the bathroom and avoid preparing or serving food for other people. This will lower the chance of passing the infection on to someone else.
- Have their doctor test to ensure that no Salmonella Typhi bacteria remain in their body.

Prevention

Typhoid fever is common in places with poor sanitation and a lack of safe drinking water. Access to safe water and adequate sanitation, hygiene among food handlers and typhoid vaccination are all effective in preventing typhoid fever.

Typhoid conjugate vaccine, consisting of the purified Vi antigen linked to a carrier protein, is given as a single injectable dose in children from 6 months of age and in adults up to 45 years or 65 years (depending on the vaccine).

Two additional vaccines have been used for many years in older children and adults at risk of typhoid, including travellers. These vaccines do not provide long-lasting immunity (requiring repeat or booster doses) and are not approved for children younger than 2 years old:

- an injectable vaccine based on the purified antigen for people aged 2 years and above; and
- a live attenuated oral vaccine in capsule formulation for people aged over 6 years.

Two typhoid conjugate vaccines have been prequalified by WHO since December 2017 and are being introduced into childhood immunization programmes in typhoid endemic countries.

All travellers to endemic areas are at potential risk of typhoid fever, although the risk is generally low in tourist and business centres where standards of accommodation, sanitation and food hygiene are high. Typhoid fever vaccination should be offered to travellers to destinations where the risk of typhoid fever is high.

The following recommendations will help ensure safety while travelling:

- Ensure food is properly cooked and still hot when served.
- Avoid raw milk and products made from raw milk. Drink only pasteurized or boiled milk.
- Avoid ice unless it is made from safe water.
- When the safety of drinking water is questionable, boil it, or if this is not possible, disinfect it with a reliable, slow-release disinfectant agent (usually available at pharmacies).
- Wash hands thoroughly and frequently using soap, in particular after contact with pets or farm animals, or after having been to the toilet.
- Wash fruits and vegetables carefully, particularly if they are eaten raw. If possible, vegetables and fruits should be peeled.

WHO response

In October 2017, the Strategic Advisory Group of Experts on Immunization (SAGE), which advises WHO on vaccine use, issued a recommendation for the typhoid conjugate vaccine to be added to routine childhood immunization programmes in typhoid endemic countries. SAGE also called for the introduction of typhoid conjugate vaccine to be prioritized for countries with the highest burden of typhoid disease or high levels of antibiotic resistance to Salmonella Typhi.

Starting in 2019, Gavi, the Vaccine Alliance has provided funding to support typhoid conjugate vaccine use in eligible countries.

As at March 2023, WHO has prequalified two conjugate vaccines for the prevention of typhoid. Typhoid conjugate vaccine has longer-lasting immunity than the older typhoid vaccines and can be given as a single dose to children from the age of 6 months.

In addition to decreasing the disease burden in endemic countries and saving lives, widespread use of the typhoid conjugate vaccine in affected countries is expected to reduce the need for antibiotics for typhoid treatment and slow the increase in antibiotic resistance in Salmonella Typhi.

5.Yellow fever

KEY FACTS

- Yellow fever is an infectious disease transmitted by mosquitoes that bite mostly during the day.
- As of 2023, 34 countries in Africa and 13 countries in Central and South America are either endemic for, or have regions that are endemic for, yellow fever.
- Yellow fever is prevented by a vaccine, which is safe and affordable. A single dose of yellow fever vaccine is sufficient to grant life-long protection.

- A modelling study based on African data sources estimated the burden of yellow fever during 2013 was 84 000–170 000 severe cases and 29 000–60 000 deaths (1).

Overview

Yellow fever is an epidemic-prone mosquito-borne vaccine preventable disease that is transmitted to humans by the bites of infected mosquitoes. Yellow fever is caused by an arbovirus (a virus transmitted by vectors such mosquitoes, ticks or other arthropods) transmitted to humans by the bites of infected Aedes and Haemagogus mosquitoes.

These day-biting mosquitoes breed around houses (domestic), in forests or jungles (sylvatic), or in both habitats (semi-domestic). Yellow fever is a high-impact high-threat disease, with risk of international spread, which represents a potential threat to global health security.

Symptoms

The incubation period for yellow fever is 3 to 6 days. Many people do not experience symptoms. Common symptoms include fever, muscle pain, headache, loss of appetite, nausea or vomiting. In most cases, symptoms disappear after 3 to 4 days.

A small percentage of patients enter a second, more toxic phase within 24 hours of recovering from initial symptoms. High fever returns and several body systems are affected, usually the liver and the kidneys. In this phase, people are likely to develop jaundice (yellowing of the skin and eyes, hence the name yellow fever), dark urine, and abdominal pain with vomiting. Bleeding can occur from the mouth, nose, eyes, or stomach. Half of the patients who enter the toxic phase die within 7–10 days.

Treatment

There is no specific anti-viral drug for yellow fever. Patients should rest, stay hydrated and seek medical advice. Depending on the clinical manifestations and other circumstances, patients may be sent home, be referred for in-hospital management, or require emergency treatment and urgent referral. Treatment for dehydration, liver and kidney failure, and fever improves outcomes. Associated bacterial infections can be treated with antibiotics.

Diagnosis

Yellow fever is difficult to diagnose, especially during the early stages. A more severe case can be confused with malaria, leptospirosis, viral hepatitis, other haemorrhagic fevers, infection with other flaviviruses (such as dengue), and poisoning.

Polymerase chain reaction (PCR) testing in blood can sometimes detect the virus in early stages of the disease. In later stages, testing to identify antibodies is needed (ELISA and PRNT).

Prevention

1. Vaccination

Vaccination is the most important means of preventing yellow fever. The yellow fever vaccine is safe, affordable and a single dose provides life-long protection against yellow fever disease. A booster dose of yellow fever vaccine is not needed.

The vaccine provides effective immunity within 10 days for 80–100% of people vaccinated, and within 30 days for more than 99% of people vaccinated.

Side-effects from the yellow fever vaccine are rare. People who are usually excluded from vaccination include:

- infants aged less than 9 months;
- pregnant women – except during a yellow fever outbreak when the risk of infection is high;
- people with severe allergies to egg protein; and
- people with severe immunodeficiency due to symptomatic HIV/AIDS or other causes, or who have a thymus disorder.

In accordance with the International Health Regulations (IHR), countries have the right to require travellers to provide a certificate of yellow fever vaccination. If there are medical grounds for not getting vaccinated, this must be certified by the appropriate authorities.

2. Vector control

The risk of yellow fever transmission in urban areas can be reduced by eliminating potential mosquito breeding sites, including by applying larvicides to water storage containers and other places where standing water collects.

Preventive measures, such as wearing clothing to minimize skin exposure and repellents are recommended to avoid mosquito bites. The use of insecticide-treated bed nets is limited by the fact that Aedes mosquitos bite during the daytime.

Both vector surveillance and control are components of the prevention and control of vector-borne diseases, especially for transmission control in epidemic situations. For yellow fever, vector surveillance targeting Aedes aegypti and other Aedes species will help inform where there is a risk of an urban outbreak.

3. Epidemic preparedness and response

Prompt detection of yellow fever and rapid response through emergency vaccination campaigns are essential for controlling outbreaks. However, underreporting is a concern; WHO estimates the true number of cases to be 10 to 250 times what is now being reported.

WHO recommends that every at-risk country has at least one national laboratory where basic yellow fever blood tests can be performed. A confirmed case of yellow fever in an unvaccinated population is considered an outbreak. A confirmed case in any context must be fully investigated. Investigation teams must assess and respond to the outbreak with both emergency measures and longer-term immunization plans.

WHO response

The Eliminate Yellow Fever Epidemics (EYE) Strategy was developed in response to two urban yellow fever outbreaks – in Luanda (Angola) and Kinshasa (Democratic Republic of the Congo), with international exportation to other countries, including China, showing that yellow fever poses a serious global threat requiring new strategic thinking.

The EYE strategy is comprehensive, multi-component and multi-partner. In addition to recommending vaccination activities, it calls for building resilient urban centres, planning for urban readiness, and strengthening the application of the International Health Regulations (2005).

It is expected that by the end of 2026, almost 1 billion people will be protected against yellow fever through vaccination.

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