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Review article

Epidemiologic characteristics and prevention strategies of neonatal birth defects in Equatorial Guinea

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ABSTRACT

Objective: Neonatal birth defects remain a significant public health concern globally, particularly in resource-limited regions like Equatorial Guinea. This article aims to determine the epidemiological characteristics of birth defects in newborns in Equatorial Guinea, including prevalence, geographic variations and trends, and to propose effective response strategies.

Design: A literature review using databases such as PubMed, Google Scholar and public database websites identified key types of birth defects, including congenital malformations, hereditary diseases and those influenced by environmental factors. Risk factors such as genetic, environmental and nutritional issues were analyzed. The impact of healthcare resources on diagnosis and treatment was evaluated.

Results: The estimated prevalence of birth defects in Equatorial Guinea is 6.59% (65.90 per 1,000 births), with approximately 1,300 annual cases. Urban areas like Malabo and Bata show lower rates due to better healthcare access, while rural areas have higher rates due to inadequate resources. Common birth defects include congenital malformations and hereditary conditions such as thalassemia and sickle cell anemia. According to the data from World Population Review, hemoglobin defects (10 per 1000) and heart defects (7.9 per 1000) are the most common birth defects in this area. Environmental factors, including pollution and malnutrition, are significant contributors. Healthcare challenges include limited diagnostic tools and insufficient training.

Conclusion: Birth defects in Equatorial Guinea are influenced by various genetic, environmental and socioeconomic factors. Strengthening preconception and pregnancy care, screening, early diagnosis and community education are vital. Enhancing healthcare infrastructure, professional training and supportive public health policies are essential to reducing birth defect rates and improving neonatal outcomes. Comprehensive data collection is needed for informed policy and resource allocation.

KEY WORDS: birth defects, Equatorial Guinea, perspective article, prevalence, public health

INTRODUCTION

Neonatal birth defects represent a major public health problem of global concern, which not only affects the survival and development of children but also imposes a heavy economic and emotional burden on families and society[1]. Birth defects are defined as abnormalities in body structure, function or metabolism that arise before birth and can be divided into two major categories: structural congenital anomalies, such as cleft lip, heart defects, atypical limbs and neural tube defects, and functional or developmental congenital anomalies, including nervous system problems, sensory problems, metabolic disorders and degenerative disorders[2,3]. They are the leading cause

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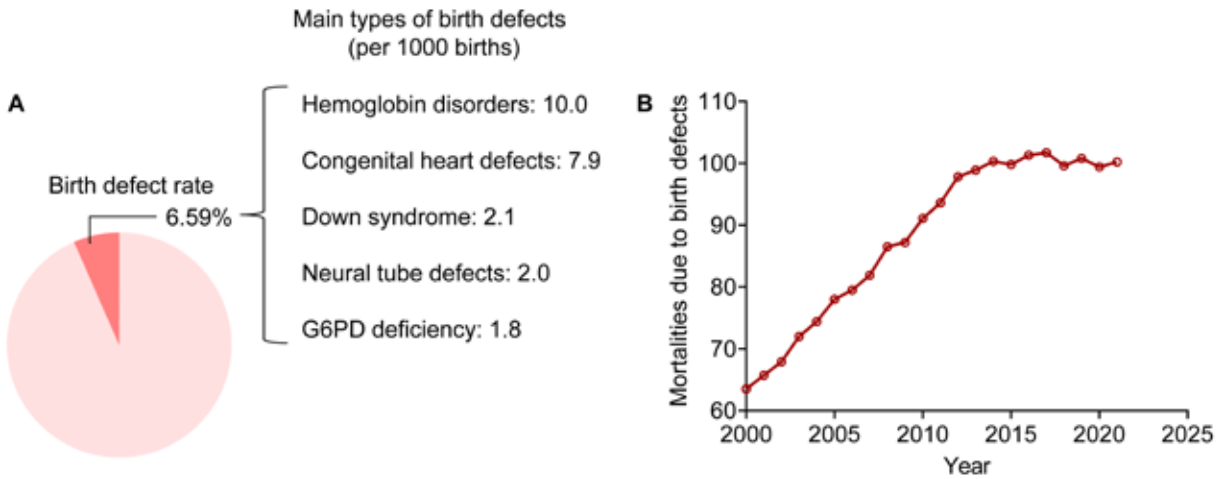

Figure 1: The birth defect rate and mortalities due to birth defects in Equatorial Guinea. (A) the pie chart shows the rates of birth defects in the newborns and their main types. The data were extracted from https://worldpopulationreview.com (accessed on 6/15/2024). **(B)** Mortalities of children under 5 years of age in Equatorial Guinea due to birth defects. The graph was plotted with data from the World Health Organization website.

of early miscarriage, stillbirth, infant mortality and congenital disability. According to recent reports, an estimated 8 million newborns worldwide are born with birth defects each year[4]. In particular, the prevalence of congenital heart defects is 5 to 8 per 1,000 newborns, making them the most common birth defect[5]. The types of birth defects are numerous, and their etiology is complex. Both genetic and environmental factors, such as mutations, can contribute to the development of birth defects[6].

Equatorial Guinea is one of the Central African countries where relatively little research has been done on birth defects in newborns. Still, this topic is very important for improving child health and optimizing the allocation of healthcare resources in the country. Equatorial Guinea is located in West Africa, and due to its special geographic location and historical background, there is a large gap between the country's healthcare conditions and those of developed countries[7]. The lack of healthcare resources and inequality in healthcare services make the diagnosis and treatment of neonatal birth defects challenging.

This perspective article aims to address the epidemiological characteristics of birth defects in Equatorial Guinea and assess the impact of influencing factors and healthcare resources on the management of these defects. Moreover, we hope this study could help provide a scientific basis and strategic recommendations for preventing and controlling birth defects in Equatorial Guinea and similar countries.

LITERATURE SEARCH

We conducted a literature review using various databases, including PubMed, Google Scholar and public database websites (e.g., https://worldpopulationreview.com), focusing on research on birth defects in newborns in Equatorial Guinea. The keywords used in the search were birth defects, newborn defects, congenital birth defects, congenital abnormalities and Equatorial Guinea.

Epidemiologic characteristics of birth defects in newborns in Equatorial Guinea

Prevalence statistics

To our knowledge, so far there are not many reliable publications reporting the prevalence of birth defects in newborns in Equatorial Guinea. We therefore extracted the data from several reliable online databases. Based on projections of the latest United Nations data, the current population of Equatorial Guinea is 1,752,553. According to the data on https://worldpopulationreview.com (accessed on 6/15/2024), the latest estimated birth defect rate in Equatorial Guinea is 6.59% (65.90 per 1000 births, Figure 1A).

The average annual births with defects are approximately 1,300 in total. According to data published by the World Health Organization in 2020, the number of deaths from congenital anomalies in Equatorial Guinea was 249, or 2.62% of the total number of deaths in the country. The age-adjusted mortality rate is 9.49 cases per 100,000 people, which is the 12th highest in the world (https://www.worldlifeexpectancy.com, accessed on 6/15/2024). The acquisition of these data relies mainly on hospital records and community surveys, but the actual prevalence may be underestimated due to limited medical resources. Further research and data collection are essential to accurately assess prevalence.

Geographical variation

Geographic variation in Equatorial Guinea is particularly evident in the prevalence of birth defects in newborns. The relatively low prevalence of birth defects in Malabo, the capital, and Bata, the main city, may be related to better healthcare facilities and higher socioeconomic levels in these areas. In contrast, the prevalence of birth defects is significantly higher in rural and remote areas, which is closely related to the lack of local medical resources, inadequate maternal health services and malnutrition[8]. In addition, cultural and living habits in different geographical areas may also influence the type and incidence of birth defects[9]. For example, traditional practices in some regions may lead to exposure of pregnant women to harmful substances, thereby increasing the risk of birth defects[10].

Annual trends

In recent years, annual trends in birth defects among newborns in Equatorial Guinea have shown some volatility. In general, the prevalence of birth defects has shown a decreasing trend in some regions with the gradual implementation of public health policies and improvement of medical conditions. However, the prevalence of birth defects is still increasing in certain regions due to uneven economic development and irrational distribution of medical resources. According to the World Health Organization, the number of deaths of children under 5 years of age in Equatorial Guinea due to birth defects increased between 2000 and 2015 but has remained stable since then (Figure 1B). This change in trend not only reflects the effectiveness of medical and public health interventions, but also reveals the need to further improve and strengthen the prevention and control of birth defects.

Types and classification of birth defects in newborns in Equatorial Guinea

Congenital malformations are one of the most common types of birth defects among newborns in Equatorial Guinea[2,3,11]. Such defects include but are not limited to, cardiac malformations, neural tube defects, limb malformations and facial malformations. Hereditary disorders also play an important role in birth defects in newborns in Equatorial Guinea. Thalassemia and sickle cell anemia are the most commonly inherited blood disorders in the region[12-14]. These diseases are mainly transmitted by autosomal recessive mode of inheritance and affected neonates require long-term medical management and support. Thalassemia mainly affects the production of red blood cells leading to anemia and related complications, while sickle cell anemia leads to circulatory disorders and pain crises due to abnormal red blood cell morphology. In addition, other genetic disorders such as cystic fibrosis and phenylketonuria have been reported in Equatorial Guinea, but their prevalence is relatively low. Managing these genetic disorders requires comprehensive medical resources including genetic testing, medication and regular monitoring. According to the data on https://worldpopulationreview.com, the rate of hemoglobin disorders was 10.0 per 1,000 births, congenital heart defects 7.9 per 1,000 births, Down syndrome 2.1 per 1,000 births, neural tube defects 2.0 per 1,000 births and G6PD deficiency 1.8 per 1,000 births (Figure 1A). More comprehensive studies on the classification of birth defects in Equatorial Guinea are warranted.

Environmental factors play an important role in the development of birth defects in newborns in Equatorial Guinea. Studies have shown that environmental pollution, exposure of mothers to harmful substances during pregnancy and malnutrition are important factors in the development of birth defects in newborns[15]. For example, there is a serious water pollution problem in some areas of Equatorial Guinea, and the consumption of contaminated water by pregnant women may lead to the development of various birth defects in newborns. In addition, exposure of mothers to pesticides, heavy metals and other harmful chemicals during pregnancy is also considered a risk factor for birth defects in newborns. Malnutrition, especially deficiencies in key micronutrients such as folic acid, iron and vitamin A, is also considered an important cause of birth defects in newborns. The combination of these environmental factors may have resulted in a significant geographical characterization of the type and incidence of neonatal birth defects in Equatorial Guinea[7].

Impact of medical resources on the management of birth defects in Equatorial Guinea

Medical facilities

The level of medical facilities and technology in Equatorial Guinea plays a crucial role in birth defects management. However, available studies have shown that the country's healthcare infrastructure is relatively underdeveloped, and the lack of healthcare resources is more pronounced especially in remote areas[16]. Many healthcare facilities lack advanced diagnostic equipment and technology, making early detection and intervention of birth defects difficult. For example, ultrasound equipment and genetic testing technology are still scarce resources in many places, which directly affects the diagnostic accuracy and timeliness of birth defects[17]. In addition, the uneven distribution of healthcare facilities, with

significant differences between urban and rural areas, and lower accessibility of healthcare services in rural areas further exacerbate the challenges in birth defect management.

Training of medical professionals

The training and professional competence of medical personnel are other key factors affecting the effectiveness of birth defect management. In some areas of Equatorial Guinea, the medical educational system is relatively weak, and many healthcare workers lack specialized training and continuing education opportunities. This not only limits their ability to diagnose and treat birth defects, but also affects their knowledge of the latest medical information and technology. In addition, the shortage of professionals is also a serious problem, especially in pediatrics and obstetrics, where the number of specialized doctors and nurses falls far short of the demand.

Public health policies and interventions

Public health policies and interventions play a crucial role in the management of birth defects[18]. The government of Equatorial Guinea still has many shortcomings in terms of investment and policy development in this area. Although the government has begun to focus on birth defects in recent years and has introduced a number of related policies, implementation has been limited. For example, nutritional supplementation programs and prenatal checkup programs for pregnant women have not yet been fully promoted in many areas, resulting in many pregnant women not receiving the necessary medical services and health education[19]. In addition, inadequate public health promotion and education and many families' lack of knowledge about the prevention and management of birth defects further exacerbate the problem. Therefore, strengthening the development and implementation of public health policies, especially interventions targeting birth defects, is key to improving the management of birth defects in Equatorial Guinea.

Prevention strategies for birth defects in newborns in Equatorial Guinea

Preconception and pregnancy interventions

In Equatorial Guinea, the primary strategy for preventing birth defects in newborns is to strengthen preconception and pregnancy interventions. Studies have shown that health management before and during pregnancy is essential to reduce the incidence of birth defects[1]. Preconception interventions include the provision of genetic counseling, comprehensive health assessment and micronutrient supplementation such as folic acid. Folic acid supplementation is widely recognized as an effective measure to prevent neural tube defects[20]. In addition, interventions during pregnancy focus on regular prenatal checkups, management of chronic diseases in pregnant women (e.g., diabetes and hypertension), and avoidance of exposure to harmful environmental factors, such as tobacco and alcohol. Scaling up these interventions in Equatorial Guinea will require strengthening public health education, raising women's awareness of preconception and pregnancy health management, and ensuring access to healthcare resources.

Screening and early diagnosis of birth defects

Early screening and diagnosis of birth defects is critical for timely intervention and treatment[21]. Equatorial Guinea's healthcare system should have robust newborn screening mechanisms in place, including ultrasound, blood screening and genetic testing. These screening methods can detect most of the common birth defects during pregnancy and early after birth, thus providing the possibility of early treatment and intervention. In addition, training medical personnel in advanced screening and diagnostic techniques to ensure the accuracy and reliability of screening results is an important part of improving the management of birth defects. Through early screening and diagnosis, not only can the long-term impact of birth defects on the health of newborns be reduced, but also the economic burden on families and society.

Community-based family education

Family and community education is one of the foundational strategies for preventing birth defects in newborns. Studies have shown that community education can significantly increase public awareness of birth defects and prevention[22]. In Equatorial Guinea, extensive community education activities to educate families about preconception and pregnancy health and to explain risk factors and preventive measures for birth defects are essential. Education should include rational nutritional intake, avoidance of exposure to harmful substances and the importance of regular prenatal checkups. In addition, the coverage and effectiveness of education can be improved by utilizing local cultural and linguistic advantages and disseminating health information through multiple channels such as community health workers, schools and the media. The active participation of families and communities will help to establish a supportive environment that will effectively prevent the occurrence of birth defects in newborns.

CONCLUSION

This perspective article shows that the prevalence of birth defects among newborns in Equatorial Guinea is high, with significant geographic variations and annual trends. Multiple risk factors, including genetic, environmental and nutritional, and socio-economic factors, all play an important role in the occurrence of birth defects. These findings align with patterns observed in other low- and middle-income countries (LMICs). For instance, Lo *et al* estimated the burden of neural tube defects in LMICs and highlighted the importance of folic acid supplementation and food fortification[23]. Similarly, Moges *et al* identified congenital anomalies, including hemoglobinopathies and cardiac defects, as major health concerns in Africa[24]. In addition, healthcare resources in Equatorial Guinea are significantly deficient in the diagnosis and treatment of birth defects, affecting the implementation of effective management and intervention. Based on these findings, this paper makes several policy recommendations with a view to improving the current situation of birth defects among newborns in Equatorial Guinea. First, preconception and pregnancy interventions should be strengthened, including the provision of comprehensive nutritional guidance during pregnancy and environmental risk assessment. Secondly, a system of screening and early diagnosis of birth defects needs to be promoted for timely detection and intervention. Thirdly, medical facilities and technology should be upgraded, especially to strengthen the training and professional capacity building of medical personnel. In addition, the government should formulate and implement effective public health policies, promote family and community education, and increase public awareness of and participation in birth defects prevention.

Although this paper provides an overview of neonatal birth defects in Equatorial Guinea, several limitations remain. First, the limited quality and coverage of data in the existing literature may affect the comprehensiveness and accuracy of the findings. Moreover, there is publication bias, partially due to the limited available data and publications addressing the birth defects in Equatorial Guinea. Future studies should focus on collecting and analyzing larger-scale and higher-quality data, especially long-term follow-up data.

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Conflict of Interest: None

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Original Article

Molecular distribution of high-level aminoglycoside resistance among vancomycin-resistant *Enterococci*

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ABSTRACT

Objectives: To determine high-level aminoglycosides resistance (HLAR) genes among vancomycin-resistant Enterococcus (VRE) species.
Design: Prospective experimental study
Setting: Tertiary University Hospital
Subjects: A total of 3595 rectal swab samples for VRE surveillance from intensive care units were investigated.
Interventions: Rectal swab samples were inoculated onto vancomycin resistance screening agar. Also, vancomycin resistance of the isolates was confirmed by performing a gradient test. HLAR among *Enterococcus* isolates was determined by the Kirby-Bauer method. HLAR genes were examined by PCR.
Main outcome measures: In this study with 5-year follow-up, we aimed to determine the HLAR frequency and related genes among VRE isolates.
Results: Vancomycin-resistant isolates were found in 8.6% of rectal swab samples. Of the isolates included in the study, 82 (82%) were identified as *E. feacium*, 11 (11%) as *E. faecalis* and 7 (7%) as *E. gallinarum*, while the detected genes were 67% *aph(3')-IIIa*, 2% *aph(2'')-Id*, 1% *aph(2'')-Ib*. In 30% of the isolates with HLAR, the modifying enzyme belonging to the investigated sites was not detected.
Conclusions: Our study is the first to report aminoglycoside resistance gene analysis among the VRE strains in Turkey. AME gene patterns of *Enterococcus* strains from clinical and various other sources in any given geographical region will contribute to the surveillance. Also, the similar findings between clinical studies and farm animals/products in aspect of AME genes create a major concern about farming techniques and its clinical consequences.

KEY WORDS: aminoglycoside, *Enterococcus*, gentamicin, vancomycin

INTRODUCTION

Enterococcus species are Gram-positive bacteria located in the gastrointestinal system flora of humans[1]. *Enterococcus* species are important nosocomial pathogens with the aid of their ability to live on environmental surfaces. As the second most common agent of nosocomial infections, they frequently colonize patients, and are mostly responsible for urinary tract infections and bacteremia, but also cause endocarditis, peritonitis, device-related infections and wound infections[2,3]. Usually, *Enterococcus* species are not expected to cause infections in immunocompetent people besides sporadic urinary tract infections; though *Enterococcus faecalis* and *Enterococcus faecium* are prevailing producers of nosocomial opportunistic infections in immunocompromised and critically ill patients[4].

Enterococci show intrinsic resistance to many antibiotics such as trimethoprim-sulfamethoxazole, lincosamide and clindamycin, and show low-level resistance to penicillin and aminoglycoside, depending on their structural features[5]. Moreover, *Enterococci* are capable of obtaining antibiotic resistance genes including vancomycin and high-level aminoglycosides resistance genes, via horizontal gene transfer[6,7]. The most important of the acquired resistance mechanisms is vancomycin resistance, which was first reported in England in 1988[8]. The point reached today for vancomycin-

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resistant *Enterococci* (VRE), which was regarded as a panic value in the years when it was first described, is alarming. Vancomycin resistance has caused restrictions on the use of antibiotics that can be used in enterococcal infections. Combining a beta-lactam antibiotic with an aminoglycoside to achieve a synergistic effect is one of the most commonly used treatment options[9]. Clinical studies support the use of aminoglycosides in combination with beta-lactams in severe *Enterococci* infections[10].

The low level of resistance that is structurally present in *Enterococci* against aminoglycosides is due to the decreased permeability of the cell walls. High level of aminoglycoside resistance (HLAR) occurs due to ribosomal target change or inactivating enzymes, and in its presence, the synergistic bactericidal activity achieved by the combination of aminoglycosides and beta-lactams that is crucial for treating serious enterococcal infections, such as endocarditis extinguishes[5,9]. It is essential to point out that the prevalence of HLAR among VRE is higher when compared to vancomycin-susceptible *Enterococci* (VSE)[11]. HLAR is most commonly caused by aminoglycoside-modifying enzymes (AMEs), involving nucleotidyltransferases, acetyltransferases and phosphotransferases or ribosomal target change[5]. The resistance created by ribosomal target change from these resistance mechanisms can not be transferred and spread between bacteria. HLAR, which is caused by the inactivation of aminoglycosides with AMEs, is of plasmidic or transposon origin and can be transferred and spread[9]. Therefore, the surveillance of AME is a major concern for HLAR monitorization.

The *aac(6')-Ie-aph(2'')-Ia* gene, encoding bifunctional AAC(6')-APH(2'') aminoglycoside modifying enzyme, is responsible for the high-level resistance to all aminoglycosides except for streptomycin. The expression of *aph(2'')-Ib*, *aph(2'')-Ic* and *aph(2'')-Id* genes, encoding monofunctional AMEs, cause high-level resistance to gentamicin (HLGR). The *ant(6')-Ia*, *ant(4')-Ia* and *aph(3')-IIIa* genes, encoding other monofunctional AMEs cause resistance to several aminoglycosides except for gentamicin[12-15]. Long-term antimicrobial treatment and hospitalization, poly-antimicrobial therapy, surgery, antimicrobial prophylaxis prior to surgery, urinary catheterization and renal failure are the defined risk factors for the development of HLAR *Enterococci* infections and these infections create a serious danger for patients with severe comorbidities and long hospital stays[16-18]. This study was conducted to ascertain the ratio and types of AMEs that are responsible for HLAR among the VRE isolates.

MATERIALS AND METHODS

Hospital settings and bacterial isolates

A total of 3595 rectal swab samples (duplications were excluded) for routine VRE surveillance from intensive care units (ICU; internal medicine ICU, surgical ICU, reanimation ICU, pediatric ICU and newborn ICU) of Gaziantep University Hospital, between January 2015 and January 2020 were investigated in our medical microbiology laboratory. Ethics approval to conduct research was obtained before the study from the Gaziantep University Faculty of Medicine Board of Review with decision number 2014/68.

VRE screening

Rectal swab samples were inoculated onto vancomycin resistance screening agar (Enterococcosel Agar, BD, USA) containing 6 μg / mL vancomycin. Conventional methods and Phoenix (BD, USA) automated bacterial identification system were used for identification of the growing colonies in screening agar. Afterward, vancomycin resistance of the isolates was confirmed by performing a gradient test (AB Biodisk, France). The bacterial inoculum prepared in the equivalent of 0.5 McFarland was spread over the entire surface of Mueller Hinton Agar (MHA) medium using a sterile swab and E-test strips were placed on it. Those with MIC values >4 μg/mL were considered resistant after 24 hours incubation at 35±2 °C[19].

Detection of HLAR

HLAR in *Enterococcus* isolates was determined by the Kirby-Bauer method. Adjusted to 0.5 McFarland turbidity, bacterial suspensions from an overnight bacterial culture were spread onto MHA. Gentamicin discs (30 μg; Oxoid, USA) were placed on the inoculated MHA plates. The plates were incubated at 35±2 °C for 24 hours. The evaluation was made in accordance with EUCAST standards[19] and strains with zone diameters ≤8 mm were considered HLAR (high level resistant to gentamicin and other aminoglycosides, except for streptomycin).

Amplification of the resistance genes

Template DNA was extracted using the High Pure PCR Template Preparation kit (Roche, Germany) according to the instruction manuals. Genes encoding AMEs were examined by PCR (primer sequences are given in Table 1)[20]. Amplification was carried out by Light Cycler (Roche, Germany) device.

RESULTS

A total of 309 (8.6%) vancomycin-resistant isolates were found among 3595 rectal swab samples during our study. HLAR was found in 100 (32.3%) VRE

Table 1: PCR primers used in amplification of AME genes[20]

Gene	Product size (bp)	Primers Sequences (5′-3′)
aac(6')-Ie-aph(2'')-Ia	369	CAGGAATTTATCGAAAATGGTAGAAAAG CACAATCGACTAAAGAGTACCAATC
aph(3')-IIIa	523	CAGAGCCTTGGGAAGATGAAG CCTCGTGTAATTCATGTTCTGGC
aph(2'')-Ib	867	CTTGGACGCTGAGATATATGAGCAC GTTTGTAGCAATTCAGAAACACCCTT
aph(2'')-Ic	444	CACAATGATAATGACTCAGTTCCC CCACAGCTTCCGATAGCAAGAG
aph(2'')-Id	641	GTGGTTTTTACAGGAATGCCATC CCCTCTTCATACCAATCCATATAACC

isolates. These 100 isolates that are both VRE and HLAR were included in our study. The average patient age was 7.6 in our study.

Of the 100 isolates that are both VRE and HLAR included in the study, 82 (82%) were identified as *E. feacium*, 11 (11%) as *E. faecalis* and 7 (7%) as *E. gallinarum*, while the detected genes were 67 (67%) *aph(3′)-IIIa*, 2 (2%) *aph(2′′)-Id*, 1 (1%) *aph(2′′)-Ib*. In 30 (30%) of the isolates with HLAR, the modifying enzyme belonging to the investigated sites was not detected.

Of the 70 isolates with detectable HLAR genes in our study, distribution of *aph(3′)-IIIa, aph(2′′)-Id, aph(2′′)-Ib* AME genes were 95.8%, 2.8% and 1.4%, respectively. AME genes *aac(6′′)-Ie-aph(2′′)-Ia* and *aph(2′′)-Ic* were not detected among our vancomycin-resistant HLAR *Enterococci* strains.

DISCUSSION

In this study, we have assessed the molecular epidemiology of HLAR among a large group of VRE strains isolated from patients in a university hospital in southern Turkey during a 5-year interval. *Enterococci* are currently ranked third worldwide among leading causes of nosocomial infections such as endocarditis, wound and urinary tract infections[21]. Also, one of the most serious clinical presentations of *Enterococci* infections is bacteremia that generally emerges in elderly patients with underlying comorbid disease, immunodeficiency or prolonged hospital stay. *Enterococci* are responsible for approximately 10% of the bacteremia episodes[22].

As members of the human and farm animals intestinal flora, *Enterococci* are subject to the selection of resistant strains fostered by antimicrobial usage. In the absence of selective pressure of antimicrobial administration, their ability to survive for prolonged periods on inanimate surfaces and endure heavy metal exposure and biocide tolerance may constitute potential traits for the selection of antimicrobial resistance[5]. *Enterococcus* species may emerge as significant stockpiles for the dispersal of antimicrobial resistance genes through the agency of the several genetic material transfer mechanisms they may induce and their capability to disseminate antibiotic resistance genes to other bacteria[5,23]. They are therefore used to effectively monitor the evolution and prevalence of antimicrobial resistance in different ecosystems[24]. Furthermore, opportunistic infections caused by antibiotic-resistant *Enterococci* strains give rise to a greater risk of mortality in immunocompromised patients[5]. The transposon responsible for vancomycin resistance, encoded on a target mobile genetic material in enterococci, can be transferred to other gram-positive cocci[25]. To add to the economic burden on health systems, the real significance of the VRE arising is that these strains could serve as a van genes reservoir for other organisms, especially *Staphylococcus aureus*, because vancomycin is the therapeutic agent of choice for methicillin-resistant *S. aureus*[26]. This is another extremely important and worrying dimension of this resistance pattern.

In our study, a total of 3595 rectal swab samples were examined and in 309 (8.6%) of the patients. VRE colonization is known to be related to the increase in the rate of invasive VRE infections. VRE infection can develop in 10% of cases with VRE colonization, this rate may increase up to 32-71% in cases with hematological malignancy[27]. Shadel *et al*[28] found 17% VRE colonization and 41% of the patients acquired VRE infections.

Aminoglycoside resistance appears via various mechanisms such as limited uptake of antibiotics or reduced permeability of cell membrane and ribosomal target changes or enzymatic inactivation of the antibiotics via AMEs[29]. Usually, *Enterococcus* species intrinsically display low-level aminoglycoside resistance due to their low cellular permeability[12]. Thus, determining the susceptibility of *Enterococcus* species to low levels of aminoglycosides may be insignificant.

The most common mechanism of HLAR in clinical bacteria is their enzymatic inactivation, and genes for AMEs are often plasmidic resulting in aminoglycoside resistance dissemination among different bacteria[30].

Aminoglycosides, preferably gentamicin, in combination with a cell-wall inhibitor, are the drugs of choice (to achieve a synergistic effect) for the treatment of enterococcal infection[31]. Therefore, the acquisition of HLAR is a major concern for the treatment outcome, especially in treatment of serious infections, because the bactericidal effect achieved by combination of aminoglycosides and a cell-wall-active agent, e.g. beta-lactams or vancomycin, synergy becomes ineffective[32].

Bifunctional AME gene *aac(6)-Ie-aph(2)-Ia* is responsible for the resistance to all aminoglycosides, except for streptomycin[33]. Among HLGR *Enterococcus* strains, monofunctional genes; chromosomal *aph(2)-Ib, aph(2)-Id* and plasmidic *aph(2)-Ic* encoding aminoglycoside-modifying enzymes have been also defined[29]. In our study, we used gentamicin for monitoring HLAR, as gentamicin can be used to screen for HLAR[19], among VRE isolates. While gentamicin resistance is a good marker for tobramycin, netilmicin, amikacin and kanamycin resistance, streptomycin resistance does not reflect resistance to other aminoglycosides[19]. Streptomycin is not a commonly used aminoglycoside due to its high side effects (ototoxic and nephrotoxic). Although streptomycin is used with combinations in specific treatments (such as tuberculosis, brucellosis), it is not a recommended treatment option in *Enterococci*[34].

In our study, our targeted population was VRE isolates from rectal swab samples from ICUs because in high-risk settings, such as ICUs and other units with high colonization pressure for VRE, clinical active surveillance seems the most efficient and cost-effective method for antimicrobial resistance surveillance[27]. Also, previous studies showed that HLAR tends to be higher among VRE compared to VSE. Mira *et al*[11] investigated the frequency of HLGR and found that HLGR rate was 87.6% in VRE strains and 9.9% in VSE strains. Also, Yazgi *et al*[33] found HLAR rate in VRE was two-fold higher than in VSE. In our study, HLAR was found in 100 (32.3%) VRE isolates. There are not enough studies to compare HLAR rates in VRE, but it is expected to see an increase trend. In a surveillance report from Canada, HLGR among VRE bloodstream infections increased from 10% to 42.5% in a 4-year period[35].

In our study, AMEs were not observed in 30% of the HLAR Enterococci strains, and it was thought that this may be due to other mechanisms responsible for aminoglycoside resistance (such as ribosomal target change, low cellular permeability and decrease in intracellular concentration of the antibiotic). In previous studies, Li *et al*[36] found 24.4% of the strains were not bearing any of the targeted aminoglycoside resistance genes, and Padmasini *et al*[10] found 31.57% of the HLGR isolates and 22.64% of the high-level streptomycin-resistant isolates were not bearing any of the resistance genes examined.

The available data shows a very broad range of distribution of AME genes among different studies. In a study in Iran as border neighbor to our country by Ramin *et al*[37], the detection of *aac (6′)-Ie –aph (2′′)-Ia, ant (4′)-Ia* and *aph (3′)- IIIa* genes were 59%, 30% and 49%, respectively. In previous studies, *aac(6′)-Ie-aph(2′′)-Ia* gene was the most prevalent cause of aminoglycoside resistance in HLAR Enterococci strains[12,20]. Padmasini *et al*[10] and Zarrilli *et al*[34] found *aac(6′)-Ie-aph(2′′)-Ia* in all of their strains, but we did not detect *aac(6′)-Ie-aph(2′′)-Ia* in any of the vancomycin-resistant HLAR strains. Similar to previous reports, Celik *et al*[38] in their 2014 study from Turkey, found that *aac(6′)-Ie-aph(2′′)-Ia* was the most preavalent AME gene, but followed by *aph (3′)- IIIa.* The most prevalent AME gene in our study was the *aph(3′)-IIIa* (95.8%). Haghi *et al*[39] in their study in Northwest Iran, found that the *aph(3′)-IIIa* (67%) was the second most common AME gene and the most frequent phosphotransferase gene, despite the fact that their VRE frequency (21%) was significantly lower. Li *et al*[36] also found *aph(3′)-IIIa* as the most prevalent AME gene in a study conducted in China. High-level streptomycin and kanamycin resistance in *Enterococci* are mediated by *aph(3′)-IIIa* gene encoding aminoglycoside phosphotransferase enzyme, APH(3′)-IIIa[40].

In our study, we detected *aph(3′)-IIIa* predominancy among AME genes. In a recent study, Özdemir *et al*[41] investigated AME genes in HLAR *Enterococci* isolated from raw milk and traditional cheeses in Turkey and the *aph(3′)-IIIa* gene was the most ubiquitous (94.92%) aminoglycoside resistance gene. It is well known for vancomycin-resistant *Enterococci*, the extensive use of the vancomycin analog avoparcin for growth promotion in animal farms has accelerated the emergence and distribution of VRE strains[42]. As a similar scenario, clinical isolates in our study and dairy products carrying the *aph(3′)-IIIa* gene at the highest rates may be related and create a major concern for public health.

CONCLUSION

In this study, the rate and importance of aminoglycoside resistance, and distribution of aminoglycoside resistance genes, which is the first treatment option in VRE isolates, was discussed. We believe that our study can be a source in terms of observing the change in resistance with similar studies to be conducted from now on and retrospective control of the applications. Our research is the first to report aminoglycoside resistance gene analysis among the VRE strains in Turkey. Studies conducted for AME gene patterns of *Enterococcus* strains from clinical and

other various sources in any given geographical region will contribute to the surveillance. Also, the similar findings between clinical studies and farm animals/ products in aspects of AME genes create a major concern about farming techniques and its clinical consequences.

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Original Article

Pterygium, pinguecula frequency and dry eye in patients with keloids

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ABSTRACT

Objective: In this study, our aim was to evaluate keloid patients for the presence of pterygium and pinguecula. We also investigated tear functions in keloid patients and compared the results with controls.
Design: A retrospective cohort study
Setting: Ophthalmology Department, Nigde Omer Halisdemir University, Faculty of Medicine, Nigde, Turkey
Subjects: Thirty-nine patients who developed keloids after surgery and 40 patients who had surgery and did not develop keloids were included in the study.
Intervention: Clinical and laboratory parameters
Main outcome measures: Ophthalmologic examinations were performed and the presence of pinguecula and pterygium were recorded.
Results: There were 17 (21.8%) pterygium in 78 eyes in keloid group and 10 (12.5%) pterygium in 80 eyes of control patients (P=0.142). There were 43 (55.1%) pinguecula in 78 eyes in keloid group and 29 (36.3%) pinguecula in 80 eyes in control group (P=0.025), the difference was statistically significant. Schirmer test results were significantly lower in keloid patients compared to control group (10.9±9.2 mm and 14.8±11.8 mm, respectively, P=0.03) and tear break-up time was also significantly lower in keloid patients (11.9±6.9 s and 15.3±6.9 s, P=0.005). Two patients had recurrent pterygia in the keloid group.
Conclusion: The frequency of pterygium was not different between keloid patients and control group, while pinguecula was more frequent in keloid patients. Keloid patients have lower tear production and lower tear film stability. These results suggest that keloid patients may have a predisposition to pinguecula formation and dry eye.

KEY WORDS: keloid, pterygium, pinguecula, Schirmer test, tear break-up time

INTRODUCTION

Pterygium is a common disease of the ocular surface, with a triangular conjunctival tissue covering a portion of the cornea mostly in the nasal interpalpebral area. The pathogenesis of pterygium is not completely understood but several risk factors were found to be associated with pterygium formation[1].

Ultraviolet (UV) light was reported as the most important factor in the studies[1-3]. The most frequent pathological changes reported in pterygium were squamous metaplasia and abnormal differentiation in the conjunctival epithelium with degeneration of elastic and collagen fibers and abnormality in their organization in the subepithelial connective tissue[4-6]. However, other authors suggested that these changes may be secondary and that the main pathological event in pterygium pathogenesis was the invasion of the cornea along natural tissue planes by the fibroblasts[7]. Also, reports indicate that pterygium fibroblasts show preneoplastic cell characteristics[8]. The recurrence of pterygium after surgery is still a frequent complication. It is proposed that recurrent pterygium is the result of abnormal wound healing and pterygium fibroblasts may have a major role in pterygium recurrence[9]. The exaggerated fibroblastic proliferation due to surgical trauma may cause the recurrence similar to keloid formation in the skin[7]. These studies emphasize the importance of fibroblasts and exaggerated wound healing in pterygium pathogenesis.

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Pinguecula is another conjunctival disease which is more prevalent than pterygium[10]. It is a yellow elevated mass often located on nasal conjunctiva[11]. It was proposed that pinguecula and pterygium share a common pathogenesis[12]. In fact, several authors think that pinguecula is the initial lesion in the pathogenesis of pterygium[13]. Similar pathological changes also support this hypothesis[4,5].

Keloids are fibroproliferative lesions of skin characterized by abnormal wound healing that occur in the wounds of predisposed patients after trauma or surgery[14]. Similar to pterygium, keloids are also unique to humans and a definitive animal model is lacking. There is excessive and uncontrolled synthesis of fibrous tissue in skin after injury. The similar process of increased fibroblastic proliferation in pterygium and keloid tissue was emphasized by studies on pterygium histology[7]. Cameron *et al* proposed that fibroblasts may be the main cells in pterygium formation and pterygium occurs due to invasion of cornea by subconjunctival fibroblasts. They also stated that similar to the formation of keloid in skin, recurrent pterygium may be due to accelerated fibroblastic proliferation caused by surgical trauma[7]. There are also similarities in histopathology of these diseases. Studies suggest that inflammation and angiogenesis are important in the pathogenesis, with similar molecules, including growth factors and cytokines, being involved in both diseases. These factors cause activation of fibroblasts and their conversion to myofibroblasts which lead to excessive fibrosis and scarring seen in both diseases[15,16]. Lastly, case studies reported concurrent dermal keloid formation and severe pterygium like conjunctivo-corneal dystrophy of the eye[17,18].

Based on these data, in this study, we evaluated a group of keloid patients for the presence of pterygium and pinguecula and compared the findings with a control group. We also performed dry eye tests to evaluate tear functions which were reported to be abnormal in pterygium and pinguecula patients and considered as a risk factor for pterygium formation and recurrence[19,20].

SUBJECTS AND METHODS

This study was performed in Nigde Omer Halisdemir University Training and Research Hospital, Departments of General Surgery and Ophthalmology. Seventy-eight eyes of 39 patients who were operated in the general surgery unit for various indications and who developed keloids after surgery were included in the study. Diagnoses of keloids were made by a surgeon based on the clinical and physical examinations. Patients with scar length greater than 2 cm and scar present for more than six months were included. A control group with similar age and gender characteristics were formed from patients who were operated for various indications in the general surgery department but did not develop keloids and show normal wound healing. Ophthalmological examination, Schirmer test (ST) and tear break-up time (TBUT) tests were performed in the ophthalmology department of the hospital. Both eyes of the participants were included for the study. All participants underwent an ophthalmologic examination including measurements of the best corrected visual acuity, anterior and posterior segment examination using slit-lamp and intraocular pressure measurement. The presence of corneal and conjunctival pathologies, especially pterygium and pinguecula, were recorded. For TBUT measurements, a drop of 2% fluorescein solution was applied to the lateral inferior fornix. The patient was asked to blink several times then instructed to look ahead without blinking. The time from the last blink to the appearance of first dry spot on the cornea was recorded. Three consecutive measurements were made and mean of three measurements was recorded. ST was performed using a standard Schirmer test filter strip (Bio Schirmer®, Bio-Tech Vision Care, Ahmedabad, Gujarat, India). The strip was inserted into the lateral inferior fornix at the junction of the middle and lateral thirds of the lower eyelid. The patient was asked to keep eyes open and blink as necessary. After five minutes, the filter strip was removed and wetting of the measurement strip was recorded. This study was performed according to the tenets of Declaration of Helsinki and the study received approval from Nigde Omer Halisdemir University Ethics Committee. The detailed information about the procedures was given to all patients and control group and written and verbal informed consent were received from them.

Statistical analysis

Statistical analysis was performed using SPSS version 20.0 (IBM Corporation, Armonk, NY). Quantitative data were expressed as the means ± standard deviations and and qualitative data were expressed as proportions (%). Chi-Square test was used to compare groups for gender, pinguecula and pterygium frequency. Independent-samples t-test was used to compare the groups for age, TBUT and ST results.

RESULTS

There we 39 patients in the keloid group and 40 patients in the control group. There was no significant difference in gender between groups (P=0.560; Table 1). Mean age and standard deviation was 52.0±12.1 for keloid group and 47.2±11.7 for control group (P=0.103; Table 1). There were 17 (21.8%) pterygium

Table 1: Demographic characteristics of the participants of the study

Demographic characteristics	Control Group (Participants without Keloid) n = 40	Keloid Group (Participants with Keloid) n = 39	*P*
Age (Years)			0.103
Mean±SD	47.2±11.7	52.0±12.1	
Range	21-69	31-77	
Gender			0.560
Female, n (%)	27 (67.5%)	28 (71.8%)	
Male, n (%)	13 (32.5%)	11 (28.2%)	

SD: standard deviation
Chi-square test was used to compare gender between groups. Independent samples t test was used to compare age between groups.

in 78 eyes in keloid group and 10 (12.5%) pterygium in 80 eyes in control group. This difference was not statistically significant (*P*=0.142). There were also two recurrent pterygium in the keloid group. There were 43 (55.1%) pinguecula in 78 eyes in keloid group and 29 (36.3%) pinguecula in 80 eyes in control group. The difference was statistically significant (*P*=0.025). The mean value and standard deviation of TBUT test results were 11.9±6.9s for keloid group and 6.9±15.3s for control group. Keloid group has significantly lower TBUT values compared to control group (*P*=0.005; Table 2). The mean value and standard deviation of ST results were 10.9±9.2 mm for keloid group and 14.8±11.8 mm for control group. Keloid group has significantly lower ST results compared to control group (*P*=0.03; Table 2).

We also compared the number of eyes with ST results lower than 10 mm and TBUT results lower than 10s in both groups. These are frequently used cut-off points for diagnosing dry eye. The number of eyes with ST results lower than 10 mm were significantly higher in keloid group compared to control group (65.4% vs 48.8% respectively, *P*=0.035). The number of eyes with TBUT results lower than 10s were also significantly higher in keloid group compared to control group (64.1% vs 22.5% respectively, *P*=0.035).

DISCUSSION

The importance of fibroblasts and abnormal fibrosis in pterygium pathogenesis and pterygium recurrence was stated in previous studies[7-9]. These studies emphasize the role of abnormal and exaggerated wound healing, especially in pterygium recurrence. Keloid is another disease which is caused by abnormal and exaggerated wound healing process. It primarily affects the skin and is characterized by excessive scarring[21]. This disease also has a tendency to recur, similar to pterygium.

Dysregulation of tissue repair has been reported to underlie keloid formation[22]. Excessive inflammation which causes release of profibrotic molecules and activation of fibroblasts leading to overproduction of collagen is important in keloid formation[22,16]. There is also augmented angiogenesis with endothelial dysfunction and altered expression of angiogenic genes in this process[16]. Various molecules including interleukins, interferon and growth factors are active in the formation of hypertrophic scars and keloids. Interleukin-6, transforming growth factor beta-1 and vascular endothelial growth factor are examples of these molecules.

Pterygium is also associated with enhanced inflammatory and angiogenic response mainly triggered by chronic injury due to UV radiation.

Table 2: Pinguecula and Pterygium frequency and Schirmer test TBUT results of the groups

Tear Function tests/ Ocular findings	Control Group (Participants without Keloid) n = 40 80 eyes	Keloid Group (Participants with Keloid) n = 39 78 eyes	*P*
TBUT(s)			0.005
Mean±SD	15.3±6.9	11.9±6.9	
Range	5-33	3-30	
ST (mm)			0.03
Mean±SD	14.8±11.8	10.9±9.2	
Range	1-35	1-¬34	
Pterygium, n (%)	10(12.5%)	17 (21.8%)	0.142
Pinguecula, n (%)	29 (36.3%)	43 (55.1%)	0.025

TBUT: tear break-up time; ST: Schirmer test; s: second; mm: millimeter; SD: standard deviation
Independent samples t test was used to compare TBUT and ST results. Chi-square test was used to compare pterygium and pinguecula frequency.

These factors cause release of various inflammatory mediators and growth factors that lead to activation of fibroblasts which play an important role in tissue repair and healing[15]. Activated fibroblasts cause increased synthesis and deposition of collagen fibers and thickening of the subepithelial connective tissue and severe fibrovascular growth[9]. Similar molecules that take part in the pathogenesis of keloids are also involved in pterygium formation, including IL-6, TGF-β1) and VEGF.

In terms of epidemiology, it was reported that a higher incidence of keloids and hypertrophic scars was seen in population groups with a high pigmentation of the skin[22,16]. The effect of race in pterygium is not clear but black race is considered as an important risk factor for pterygium recurrence after surgery[23,24].

In summary, both pterygium and keloids share some histopathological similarities, including activation of fibroblasts, excessive collagen deposition, increased vascularity, and the expression of various inflammatory and angiogenic mediators leading to severe fibrosis and scarring. The fibrous tissue formed has altered collagen content and includes significant amount of immature collagen type III in both diseases[15].

There are also case series which report concurrent dermal keloid formation and severe pterygium like conjunctivo-corneal dystrophy of the eye. The authors named this entity as "ocular pterygium-digital keloid dysplasia"[17,18]. The findings of these reports and similarities in the histopathology of both diseases suggest an association between pterygium and keloid. In this study, we investigated the frequency of pterygium and pinguecula in keloid patients. Although keloid patients had higher pterygium frequency than control group which consisted of patients with normal wound healing after surgery, the difference was not statistically significant. Pterygium prevalence were reported to be nearly 10-12% globally[25,26]. The frequency of pterygium in keloid group in our study is 21.8%, which is nearly twice the reported global prevalence. An important finding is the presence of two cases of recurrent pterygium in keloid group. On the contrary, all the pterygium patients were primary pterygium in the control group. Although this number of recurrent pterygium is low to make a definitive statistical analysis, it suggests that there may be a relation between keloid and pterygium pathogenesis and recurrence.

The prevalence of pinguecula is significantly higher in keloid group in our study. This result suggests that keloid patients may have a predisposition to pinguecula formation. It is proposed that exposure to chronic UV light affects the conjunctival stroma and in some patients pinguecula develops[13]. Patients with keloids may show an exaggerated healing response to UV light mediated stromal injury, which may lead to pinguecula formation.

Tear film abnormality and dry eye were reported to exist in pinguecula and pterygium patients[19,20,27]. So, during our evaluation of keloid patients for pterygium and pinguecula, we also evaluated tear functions in this study. We found significantly lower TBUT values and Schirmer scores in keloid patients. We also found that the keloid group had a significantly higher proportion of eyes with TBUT scores less than 10s and ST scores less than 10s. These results show tear film instability and dry eye in keloid patients. Tear function abnormalities, especially abnormal TBUT values, were reported in patients with pterygium and pinguecula[27-29]. The finding of decreased TBUT and ST results may be related to relatively high frequency of pterygium and pinguecula in keloid patients in our study. Dry eye is also associated with pterygium recurrence[30]. We did not find a study evaluating dry eye and tear functions in keloid patients in our literature search to compare our findings on the tear functions in keloid patients, but these results indicate that keloid patients have impaired tear functions.

There are some limitations in this study. Firstly, our diagnosis of keloid was based on clinical and physical examination. We did not have pathological examination of keloid tissue. Secondly, we only included post-surgical keloid patients in our study. Patients with other causes of keloids were not included in our study. Thirdly, during our evaluation of tear functions, only tear break up time and ST were used. Other tests of tear functions could also be used.

CONCLUSION

In conclusion, this is the first study to evaluate pterygium and pinguecula frequency and tear functions in keloid patients. Keloid patients have impaired tear functions as shown by lower TBUT and Schirmer results. Keloid patients have significantly higher pinguecula prevalence. Future studies including patients with keloid due to other causes and using other tear function tests can be helpful in revealing the association between keloid, pterygium, pinguecula and tear functions.

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Original Article

Resilience of young Saudi females recently diagnosed with benign breast lesions- structural equation modeling

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ABSTRACT

Objective: Although an early diagnosis of breast lesions can improve the survival rate and the quality of life of the surviving patients, knowledge about patients' awareness of the investigations is still limited. This study examines the awareness of the diagnostic procedures, risk factors and sources of concern among young Saudi females (17-37 years old).
Design: We prepared a cross-sectional study using a self-administered multiple-choice questionnaire.
Setting: The survey was distributed to female Saudi patients recently diagnosed with a non-malignant breast lesion at our institution.
Subjects: We retrieved 181 responses from 215 patients.
Intervention*:* Structural equation modeling was used to assess 8 constructs and their 34 indicators.
Main outcome measures: The planned outcomes of the study was to test whether young Saudi females recently diagnosed with benign breast were aware of medical investigations and management needed for their medical conditions or not. Also, we intended to test how they behaved towards the obtained therapeutic modality.
Results: The survey results demonstrated that young female Saudi patients in Riyadh considered the demographic features a determinant of the sought treatment. They did not consider lesional parameters or pharmaceutical history sufficient for determining the therapeutic modality. Moreover, resilience and concern were reported to be influenced mostly by the medical investigations they ran and the treatment they required.
Conclusion: The young female Saudi patients in Riyadh showed good awareness of the variables that define the treatment modality and management of breast lesions. Multi-institutional large-scale populations should be investigated to generalize the suggested findings of this exploratory study.

KEY WORDS: breast lesions, patient perception, resilience, structural equation modeling

INTRODUCTION

Benign breast lesions affect a wide range of ages of females and rarely males. According to the histogenesis of the breast lesions and their histologic pictures, prognostic and diagnostic variables are determined. This involves major concerns for females, especially young and middle-aged females. Breast screening has evolved over the past decades. The information gleaned from regular check-up helps clinicians and patients, especially high-risk groups, fight their fears of developing cancers[1].

However, the cultural constraints, lack of motivation to comply with regular screening, and reluctance to start a diagnostic procedure when in doubt deters the time of starting therapeutic modalities, even when all are made available for free.

With advancements in diagnostic techniques and the worldwide application of screening programs, patients are encouraged to have regular check-ups at no cost. However, psychological and cultural barriers impede the reachability of oncologic screening programs to women, including young females and women at risk of developing breast neoplasms. Many Arab women avoid having breast examinations by surgeons, sonographers or mammographers. The majority of women reported being seen naked by

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a male, either a medic, paramedic or technician. Check-ups become more awkward when women are traveling abroad for studies, family unification or business concerns. What complicates matters is finding a suspicious lesion during the examination that necessitates surgical intervention. These barriers make the early diagnosis of breast neoplasms more difficult than if female patients could show more flexibility[2].

This study examines the influence of patients' demographics, their backgrounds in medical investigations, their health-related habits, past history of therapeutics and the parameters of the detected lesion on accepting a particular therapeutic modality, raising concerns and shaping resilience among young Saudi females.

SUBJECTS AND METHODS

Young females are usually diagnosed with benign breast neoplasms, of which some are reactive lesions or hamartomas. This does not exclude the possibility of developing breast malignancies at a young age. However, this study investigates the patient's knowledge about the nature of breast neoplasms in women who were diagnosed with benign or reactive breast disease at a Saudi teaching hospital. The majority of the diagnosed disease included tubular adenoma, lactating adenoma, fibroadenoma, sclerosing adenoma, apocrine adenoma, leiomyoma, and cysts or abscesses. Others included neurofibroma, hemangioma and pagetoid dyskeratosis.

Demographics

Women with a familial history of breast cancer are at greater risk than those with no oncologic history. Arab women develop breast lesions at a younger age than do Western women[3]. Out of 7251 histologically confirmed cancerous cases at the King Faisal Specialist Hospital and Research Centre in Riyadh, Saudi Arabia, breast cancer was the most commonly diagnosed tumor among Saudi females[4]. Risk factors include a familial history of developing breast lesions, smoking and taking medications with cancerous adverse effects.

Approximately 6,922 female breast cancer cases were recorded in the Saudi Cancer Registry from 2001 to 2008 in women who were 30-59 years of age. Circulating angiotensin II and triglycerides were reported to be associated with developing early breast cancer, which heightens the metabolic role of inducing the carcinogenesis of this disease[5]. The highest rate among Saudi women is observed in those who live in the eastern region, Riyadh and Makkah, more than in the Southern region[6]. Variations in the XRCC3 gene were alleged to be a key contributor to breast cancer susceptibility among female patients[7].

This study investigates the influence of age, genetic susceptibility, mammary density, pregnancy and lactation, sexual precocity and weight (body index) as determinants of the variable of demographics among young female Saudi patients recently diagnosed with benign or reactive breast lesions.

Health habits

Hazardous health habits can induce the development of benign or malignant breast lesions even in young females[2, 8]. In a study of ladies undergoing a routine check-up in Riyadh, 48% of breast cancer patients had a family history of developing breast cancer, while the majority of the diagnosed cases reported negative familial history[9]. We investigated the influence of lifestyle, athletic exercises, drugs, smoking and alcohol consumption as determinants of the variable of health habits on developing breast lesions among young female Saudi patients recently diagnosed with benign or reactive breast conditions.

Lesional parameters

Mammary hamartomas and hormone-induced breast lesions usually affect young females[10]. The age of onset is an important determinant of the coping mechanism of the affected young females, especially if the lesion is of large size or disfiguring the shape of the breast[8]. Although benign and low-grade lesions may affect only the nipple-areola complex, many underlying malignancies can arise at the bed of these lesions[1,11].

This study investigates the influence of clinical behavior, onset, site and size on developing breast lesions among young female Saudi patients recently diagnosed with benign or reactive breast conditions.

Medical investigations

Sonography and mammography (sonomammography) ensures early diagnosis in detecting all breast lesions, with good sensitivity and specificity[12], in national health programs worldwide[13], especially when it is combined with cytological examination and fine or core needle biopsies for women under 40 years of age[14]. MRI[15] and tomography[16] are also useful in detecting early lesions of the breast and distinguishing benign breast conditions from malignancies[17].

Immunohistochemistry panels of markers have both excellent diagnostic and prognostic values. Generally speaking, breast carcinomas are subcategorized into luminal A, luminal B, HER2-positive and triple negative subtypes. The most prevalent subtype in Saudi Arabia was luminal A, most commonly seen in lobular carcinoma. HER2-positive and triple-negative

were found least often among young women[18]. In the National Breast Screening Study, p53 protein accumulation, but not c-erbB-2 protein overexpression, was linked to the malignant transformation of benign breast lesions to breast carcinomas[19]. Expression for Annexin I[20], MED12[21], EZH2[22] and IL17[23] might correlate with malignant breast cancer progression, but they are most likely involved at an early stage of human breast cancer development. Napsin A, TTF-1, GATA3[24], SOX10[25] and p40[26] are also useful diagnostically and prognostically. Expression for glucose-regulated stress protein GRP78[27] might correlate with therapeutic resistance. Molecular findings suggest that the amplification of Her-2/neu in breast carcinoma is associated with poor prognosis, short disease-free interval and short survival rate in lymph node-negative and positive patients[28]. Serologically, semaphorin 4C[29], HE4[30], miRNA-27a[31], miRNA-34a in combination with cancer antigen 15-3[32] or CEA are of great diagnostic value in detecting early lesions of the breast and differentiating benign from malignant breast lesions.

This study investigates the effect of "medical investigation results" on young Saudi females with benign breast lesions. This effect could be either: a) influence on treatment sought; or b) impact on expressed concerns. These medical investigations include cytology, histology, immunohistochemistry, sonomammography and molecular investigation.

Pharmaceutical history

Prolonged use of oral contraceptive pill is associated with an increased risk of breast cancer in Saudi women[33]. Hormonal replacement therapy[34] and warfarin were associated with developing benign and malignant breast lesions. Among the drugs that might induce breast lesions are cyclosporin and insulin therapy. Nevertheless, reports are conflicting in this connection.

This study investigates the influence of cyclosporin, hormonal therapy, insulin therapy, warfarin and mixtures of many on developing breast lesions among young female Saudi patients recently diagnosed with benign or reactive breast conditions.

Solicited treatment

Breast cancer patients with the same stage of the disease can have markedly different treatment responses and overall outcome. Although chemotherapy or hormonal therapy are standard adjuvant therapeutic modalities, only a careful selection of patients who would benefit from adjuvant therapy reduces the risk of distant metastases remarkably[35]. Total mastectomy[36]and nipple-sparing mastectomy with immediate reconstruction are the standard surgical interventions[37-39]. This study investigates the influence of conservative excision, total mastectomy and plastic surgical reconstruction on improving resilience among young female Saudi patients recently diagnosed with benign or reactive breast conditions.

Patients concerns

The main concern of women with benign breast lesion is the susceptibility of malignant transformation. Notwithstanding, female populations are diverse regarding the potentiality of malignant transformation of benign breast lesions[39,40]. Multiple fibroadenomas were reported to develop phyllodes[41], and so were many benign conditions that affect young females[42].

This study investigates the influence of breastfeeding, disfigurement, malignant transformation and sexuality on developing breast lesions among young female Saudi patients recently diagnosed with benign or reactive breast conditions.

Study design

A cross-sectional study was performed using a structured, self-administered, multiple-choice questionnaire among patients who were recently diagnosed with non-malignant breast lesions at our institution. The questionnaire assessed young female patients' demographics, their backgrounds in medical investigations, their health-related habits, past history of therapeutics, and the parameters of the detected

Table 1: Participants' demographics (N=182)

Characteristic	Incidence	Percentage
Age, year		
17-23	64	35
24-30	104	57
31-37	13	7
Education		
High school	31	17
Bachelor degree	89	49
Master degree	42	23
Doctorate degree	19	10
Pathology		
Tubular adenoma	44	24
Lactating adenoma	29	16
Fibroadenoma	26	14
Sclerosing adenoma	14	8
Apocrine adenoma	18	10
Leiomyoma	13	7
Cyst/abscess	32	18
Others	5	3
Diagnosis		
Incidental	49	27
Self-examination	73	40
Regular check-up	59	33

lesion on accepting a particular therapeutic modality, raising their concerns and shaping resilience.

Study population

Using convenient sampling, 215 participants volunteered to contribute anonymously to this study. One hundred eighty-one patients returned the responses to the survey. The age of the participants ranged from 17 to 36 years old. Table 1 illustrates the participants' demographics.

Data collection

Informed consent was obtained from each respondent before they began the survey. All participants were anonymized; relevant information remained confidential and was distorted after the study was conducted. The collected data were analyzed using structural equation modeling. This technique is superior to other techniques as it can analyze the cause-effect relationship between several variables and their subvariables simultaneously. It also enables investigation of the moderation and mediation effect between the studied variables. SmarPLS software version 3.4 was used. Based on the measures of path analysis between the constructs and the corresponding *t*-values, the statistical significance was calculated. The reliability and discriminant validity for the studied constructs were also measured. The study was submitted to the ethics review committee. Because of data de-identification, the study was exempted.

The following hypotheses were formulated:

H1a. Demographics positively affects lesional parameters developed in the participants

H1b. Demographics positively influences treatment sought by the participants

H1c. Demographics positively shapes resilience demonstrated by the participants

H2. Habits positively influence concerns expressed by the participants

H3a. Lesional parameters positively affect medical investigations

H3b. Lesional parameters positively influence treatment sought by the participants

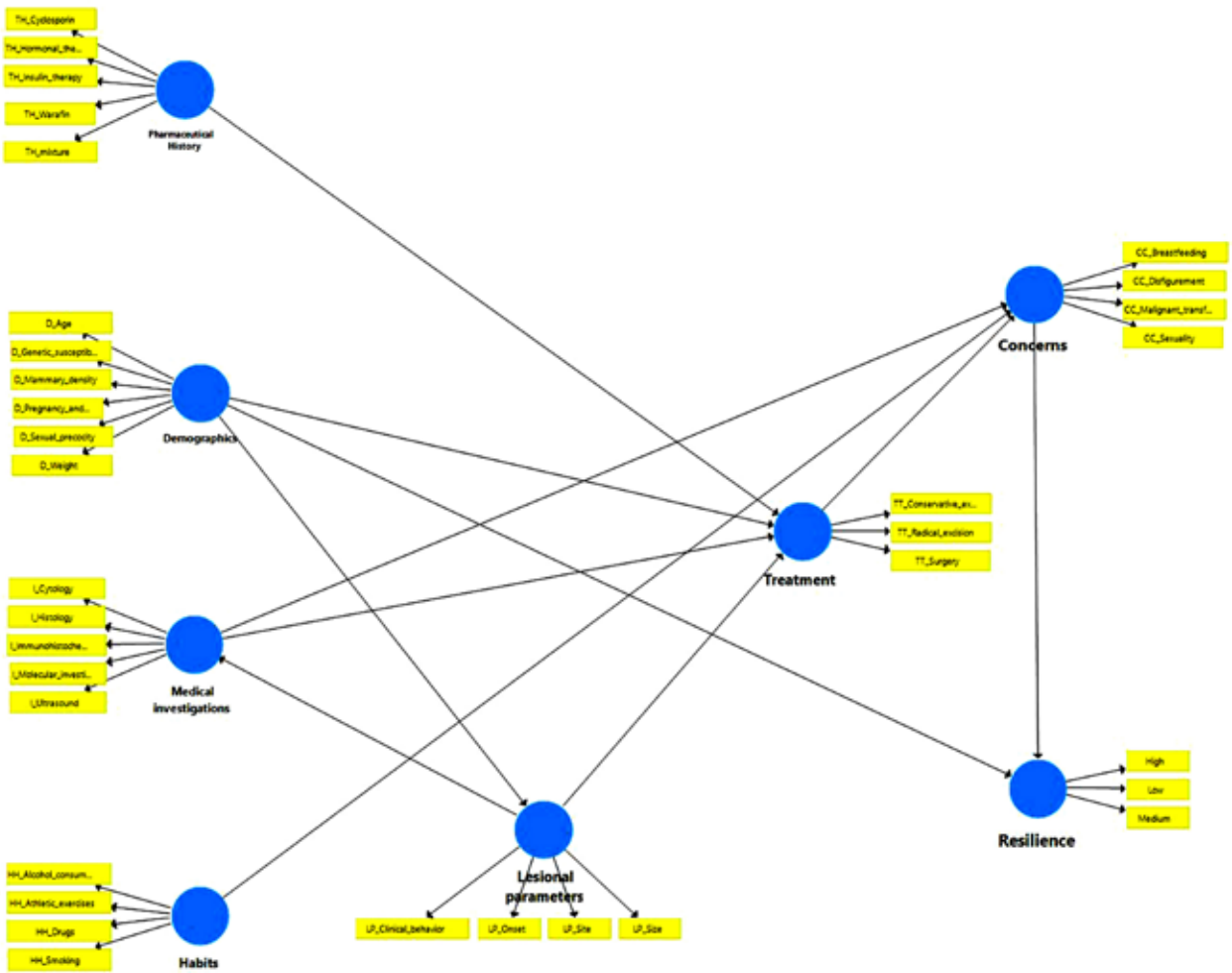

Figure 1: Conceptual model.

Table 2: Reliability measures

Construct	Cronbach's Alpha	Rho_A	Composite Reliability	Average Variance Extracted (AVE)
Concerns	0.863	0.868	0.907	0.708
Demographics	0.932	0.934	0.947	0.749
Habits	0.704	0.72	0.813	0.524
Lesional parameters	0.757	0.803	0.846	0.583
Medical investigations	0.816	0.859	0.87	0.578
Pharmaceutical history	0.888	0.898	0.918	0.692
Resilience	0.906	0.913	0.941	0.842
Treatment	0.691	0.776	0.746	0.697

H4a. Medical investigations positively influence treatment sought by the participants
H4b. Medical investigations positively impact concerns expressed by the participants
H5. Pharmaceutical history positively influences treatment sought by the participants
H6. Treatment positively induces concerns expressed by the participants
H7. Concerns positively affect resilience demonstrated by the participants

The conceptual model is displayed in Figure 1.

RESULTS

We distributed 215 questionnaires and obtained 181 responses. Approximately 15.8% either did not return their responses or provided incomplete responses.

Most patients were 24 to 30 years old (57%), followed by younger age (17-26), representing 35% of the 181 participants. The majority of participants were highly educated, obtaining a college degree or more (83%). We applied structural equation modeling to study the cause-effect relationships between the defined constructs. Therefore, it is imperative to measure the reliability and validity for each variable and subvariable. Tables 2 and 3 display the reliability and validity measures for latent variables (constructs), while Table 4 demonstrates the outer loadings and variance inflation factor values for the subvariables (indicators).

The first construct that was studied was the patient demographics, which included age, genetic susceptibility, mammary density, pregnancy and lactation, sexual precocity and body index. How positively these indicators influenced the lesional parameters (H1a), required treatment (H1b) and the resilience of the patients (H1c) were the subordinate hypotheses. Demographics positively affects lesional parameters developed in the participants (β=.0 845, P<0.001), treatment sought by the participants (β=0.62, P<0.001), and resilience demonstrated by the participants (β=0.659, P<0.001). Therefore, hypothesis 1a-c was supported. The population-based surveys demonstrate that the young female Saudi patients, who are recently diagnosed with benign or reactive breast conditions, find demographics a determinant variable that govern the choices of patients and the possibility of their developing malignant or non-malignant breast lesions.

The second examined hypothesis was health habits and how they positively affect patients' concerns. The studied indicators were lifestyle, doing sports, drugs, smoking and alcohol consumption. The exploratory factor analysis was not acceptable for lifestyle. Therefore, only athletic exercises, drugs, smoking and alcohol consumption were retained. It was found that health habits affected patients' concerns positively (β=0.638, P=0.021). Therefore, hypothesis 2 was supported. The enrolled young female Saudi patients considered health habits a determinant of patients' concerns.

The third hypothesis examined how young female Saudis find lesional parameters indicative of medical

Table 3: Fornell's matrix (validity)

Construct	1	2	3	4	5	6	7	8
Concerns	0.841							
Demographics	0.809	0.865						
Habits	0.224	0.161	0.824					
Lesional parameters	0.751	0.845	0.138	0.763				
Medical investigations	0.197	0.182	0.685	0.11	0.76			
Pharmaceutical history	0.725	0.839	0.132	0.739	0.138	0.832		
Resilience	0.74	0.723	0.106	0.704	0.116	0.744	0.918	
Treatment	0.549	0.588	0.652	0.474	0.615	0.517	0.477	0.755

investigation (H3a) and the overall concerns (H3b). The participants did lesional parameters influential when it comes to defining the medical investigation (β=0.11, *P*=0.247), or alleviating the overall concerns (β=0.007, *P*=0.915). Both H3a and H3b were not supported.

The fourth hypothesis examined how young female Saudi patients find medical investigations determinant of the required treatment (H4a) and the overall concerns (H4b). The participants found the different types of medical investigations influential when it comes to defining the therapeutic modality (β=0.734, *P*=0.247), or alleviating the overall concerns (β=0.417, *P*=0.915). Both H4a and H4b were supported.

Fifth, postulating that the pharmaceutical history of the patients might influence their required treatment was examined. Although most of the participants considered the intake of cyclosporine, hormonal therapy and insulin causative to developing breast diseases, they could not find it a sufficient determinant of seeking a particular treatment (β=0.115, *P*=0.089). Therefore, H5 was not supported.

Sixth, postulating that the treatment modality the patients seek influences their overall concerns was examined. Conservative excision, total mastectomy and plastic surgical reconstruction affected the overall concerns of young female Saudi patients (β=0.287, *P*=0.004). Therefore, H6 was supported. How patients' concerns affected their resilience was examined. It was also reported to be influential (β=0.33, *P*<0.001). Therefore, H7 was supported. The validation of the studied hypothesis is shown in Table 5. The SRMR value was 0.138 and RMS Theta was 0.191. Therefore, the measurement model is accepted. Figure 2 shows the measurement model.

Table 4: Outer loading and VIF

Indicator	Outer loading	VIF
CC_Breastfeeding	0.851	2.158
CC_Disfigurement	0.818	1.733
CC_Malignant_transformation	0.857	2.492
CC_Sexuality	0.84	2.44
D_Age	0.825	2.354
D_Genetic_susceptibility	0.901	4.395
D_Mammary_density	0.934	5.704
D_Pregnancy_and_lactation	0.854	2.905
D_Sexual_precocity	0.773	2.062
D_Weight	0.894	4.839
HH_Alcohol_consumption	0.606	1.303
HH_Athletic_exercises	0.804	1.684
HH_Drugs	0.755	1.328
HH_Smoking	0.715	1.253
I_Cytology	0.815	2.078
I_Histology	0.762	1.619
I_Immunohistochemistry	0.791	1.66
I_Molecular_investigation	0.86	2.146
I_Ultrasound	0.527	1.307
LP_Clinical_behavior	0.596	1.222
LP_Onset	0.719	1.402
LP_Site	0.868	2.03
LP_Size	0.841	1.955
TH_Cyclosporin	0.885	3.288
TH_Hormonal_therapy	0.859	3.037
TH_Insulin_therapy	0.82	2.482
TH_Warafin	0.767	1.883
TH_mixture	0.824	2.531
TT_Conservative_excision	0.695	1.455
TT_Radical_mastectomy	0.794	1.482
TT_Plastic_Surgery	0.615	1.023
R_Low	0.893	2.609
R_Medium	0.946	3.918
R_High	0.913	3.047

DISCUSSION

Benign breast lesions are too heterogeneous a group which encompasses developmental abnormalities, inflammatory lesions, epithelial and stromal proliferation, and neoplasms. This diversity poses diagnostic challenges, especially if the nature of the benign lesions (e.g. multiple fibroadenoma) have the potential to develop a malignancy or could be manifested in syndromes with a malignant tendency (Cowden's syndrome). New advances in managing breast lesions include round block technique[43,44], Proton MR spectroscopy[45,46]and optical coherence microelastography[47]. However, the validity of using these technologies to detect benign lesions and early malignant lesions are

Table 5: Hypothesis validation

Hypothesis	B-value	Mean	SD	T value	*P*	Validation
H1a. Demographics -> Lesional parameters	0.845	0.844	0.033	25.653	0.000	Supported
H1b. Demographics -> Treatment	0.353	0.332	0.159	2.218	0.027	Supported
H1c. Demographics -> Resilience	0.507	0.505	0.086	5.91	0.000	Supported
H2. Habits -> Concerns	0.638	0.581	0.276	2.311	0.021	Supported
H3a. Lesional parameters -> Medical investigations	0.11	0.116	0.095	1.159	0.247	Not Supported
H3b. Lesional parameters -> Treatment	0.007	0.009	0.062	0.106	0.915	Not Supported
H4a. Medical investigations -> Treatment	0.734	0.727	0.119	6.178	0.000	Supported
H4b. Medical investigations -> Concerns	0.417	0.297	0.562	2.523	0.012	Supported
H5. Pharmaceutical History -> Treatment	0.115	0.11	0.067	1.706	0.089	Not Supported
H6. Treatment -> Concerns	0.287	0.208	0.441	2.919	0.004	Supported
H7. Concerns -> Resilience	0.33	0.332	0.08	4.113	0.000	Supported

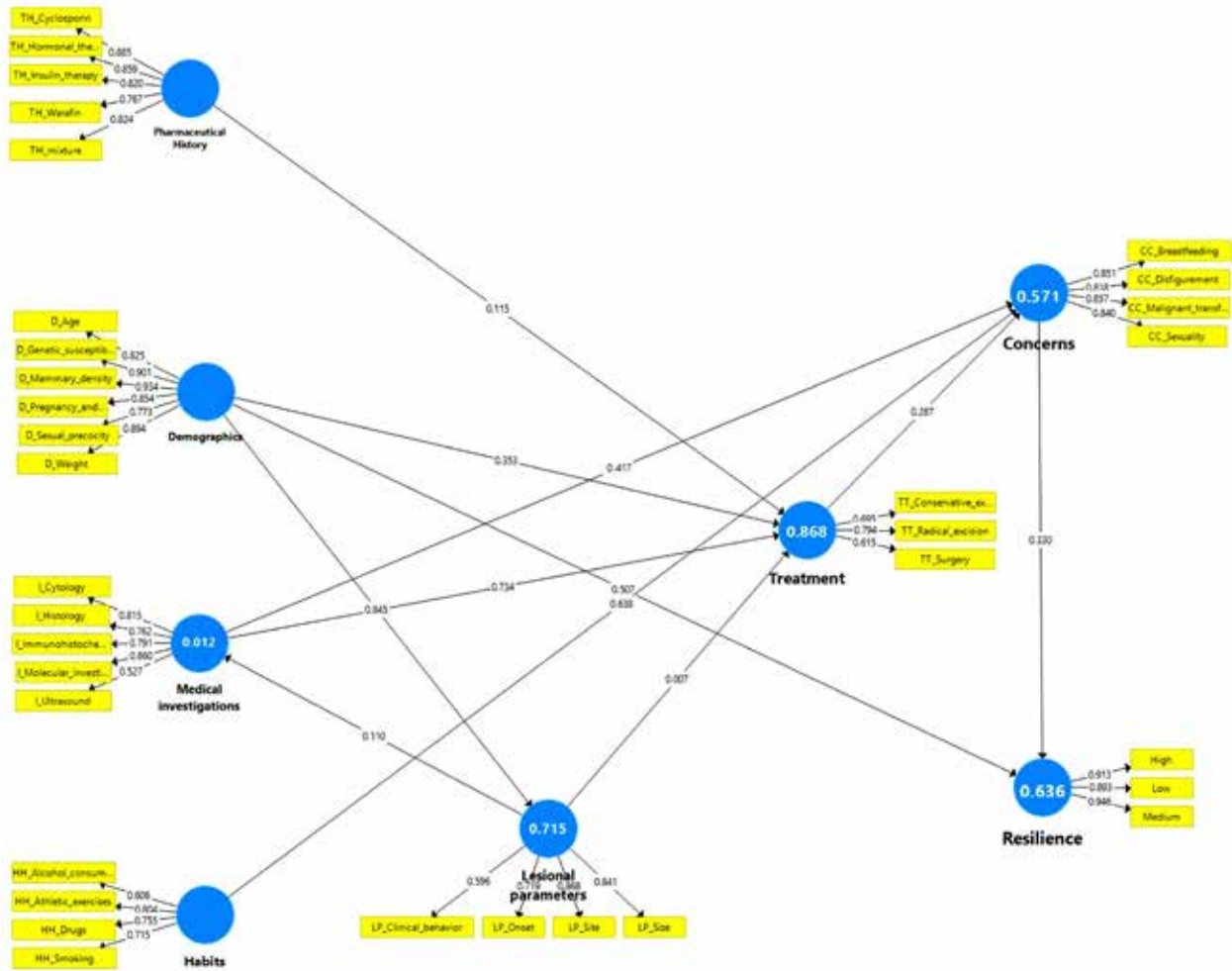

Figure 2: Measurement model.

viewed with extreme precautions in the Middle East given the lack of comprehensive medical insurance and the low acceptability rate of accepting new generations of high technologies, which could improve the accuracy at a very expensive cost.

The population-based survey demonstrated that the young female Saudi patients, who were recently diagnosed with benign or reactive breast conditions, found demographics a determinant variable that govern the patients' choices and the possibility of them developing malignant or non-malignant breast lesions. This reflects that the awareness of young Saudi females is excellent because they realize that they have to contribute to getting early diagnosis and even seeking some extra measures if they are not available for free (e.g. molecular amplification of HER2 in lesions suspicious for malignancy).

The enrolled young female Saudi patients considered health habits a determinant of patients' concerns. The only reason of understanding patients' concerns and individual resilience is by communicating with them. Family resilience facilitate survivors' individual resilience by protecting their psychosocial wellbeing[48]. Although patients with benign breast neoplasms do not experience severe fatigue, dyspnea, insomnia, appetite loss, weight loss or adverse effects of chemotherapy and radiotherapy, they face shocking psychological traumas owing to the possibility of sacrificing their breasts, partly or totally, and holding this trauma for longer lifetime in which sexuality and femineity is more active than that in geriatric population[49,50].

The clinical course of the benign tumor, date of onset, breast site and size of the lesion were not considered indicative of the indicated medical investigation and the overall concerns. This heightens the impression that all breast lesions, regardless of their neoplasticity, are nightmares for young Saudi females. This is consistent with the mainstream previously reported in the medical literature[51].

Until precision medicine is populated in the Middle East, patients and their caregivers are held responsible for self-pacing and committing themselves to do the periodic check-up regularly. Although Saudi citizens are not the wealthiest persons per capita in the Middle East, some of them can afford the cost of medical investigations in Europe. However, institutional programs should be initiated to guide self-financed patients to get the best medical care instead of being prey for commercially aiming predators.

CONCLUSIONS

The population-based perception of the management of breast lesions in the Middle East is very important because the medical literature reports higher incidences of breast cancers at a younger age than in the West. Saudi patients define their willingness to seek diagnosis and treatment or not based on the screening programs and the therapeutic protocols (invasive or non-invasive). The young female Saudi patients in Riyadh considered the demographic features a determinant of the sought treatment (family history, risk group, obesity, etc). They did not consider lesional parameters (not big lumps are lethal while small are not serious) or pharmaceutical history (e.g., history of hormone therapy) sufficient for determining the therapeutic modality. Moreover, resilience and concern were reported to be influenced most by the medical investigations they ran and the treatment they required. The more investigations and procedures are required, the more they are concerned.

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Original Article

Prognostic value of optical ultrasound in patients with altered consciousness

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ABSTRACT

Objective: We aimed to investigate the relationship between optical ultrasound and in-hospital mortality in patients with altered consciousness.
Design: Prospective cohort
Setting: Tertiary hospital in Konya, Turkey
Subjects: The demographic information, vital values, Glasgow coma score at presentation, laboratory values and ocular ultrasound findings of patients over 18 years of age with no trauma history were noted. The hospitalization diagnoses, death or discharge status were determined.
Intervention: None
Main outcome measure: In hospital mortality
Results: 107 patients were included in the study. The mean age of the patients was 64.7±19.4 years. 61 (57%) of the patients were women. The right optic nerve sheath diamater value was 5.0±1.7 mm in the deceased and 4.8±0.7 mm in the survivors. The left optic nerve sheath diamater value was found to be 4.8±0.8 mm in those who died and 4.7±0.5 mm in survivors (P>0.05). 68% of those with positive right optic disc elevation and 79.2% of those with positive left optic disk elevation died (P<0.05).
Conclusion: Optic disc elevation is associated with mortality in patients presenting to the emergency department with altered consciousness.

KEY WORDS: altered consciousness, optical ultrasound, point-of-care ultrasound (POCUS)

INTRODUCTION

Altered consciousness is among the most common reasons for admission to the emergency department. Many diseases can cause this condition. Common conditions are traumas, drug intoxications, infections, electrolyte and blood sugar disorders, central nervous system (CNS) infections, epilepsy, hypertension, stroke, brain tumor, uremia, hepatic encephalopathy and hypoxic-hypercarbic encephalopathy[1]. Although the mechanism that causes brain damage is different in each disease, the result is cellular swelling that develops after malnutrition, i.e. brain edema. Brain edema may be regional or widespread depending on the underlying disease, and if not treated, it may cause permanent damage by causing increased intracranial pressure (ICP) and may lead to a mortal course[2].

The optic nerve sheath (ONS) is an anatomical extension of the dura mater, and the subarachnoid space around the optic nerve is associated with the subarachnoid space in the head. In case of any pressure increase in the intracranial space, ONS dilatation and optic disc elevation (ODE), reflecting the increase in ICP occur in the early period[3,4]. Optic ultrasound (OU) is a non-invasive, easy, fast, reproducible and now accepted imaging technique used for ICP measurement. The diagnostic performance of OU has been demonstrated in many studies. However, its prognostic performance is uncertain.

In our study, we aimed to investigate the relationship between optical ultrasonography and mortality in nontraumatic altered consciousness.

SUBJECTS AND METHODS

This study was carried out in the emergency room of a 1096-bed academic regional hospital in Konya that provided tertiary level health services.

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This emergency department serves approximately 300,000 patients a year. Non-traumatic patients who had been admitted to the emergency department with impaired consciousness between 1 December 2018 and 1 September 2019 were included in the study. Consents were obtained from the guardians of the patients. Patients with no relatives from whom consent forms could be obtained were excluded from the study. Approval was obtained from the local ethics committee prior to the study, and it was in accordance with the Helsinki declaration (Necmettin Erbakan University Meram Faculty of Medicine Ethics Committee 2018/1612).

Study population

Patients over 18 years of age with a non-traumatic history and Glasgow coma score <15 were included in the study. Patients under 18 years of age, those with a history of trauma, those with anatomical eye defects that prevented examination or history of eye operations, and those with known eye disease (glaucoma), those who could not be evaluated due to Alzheimer's, dementia disease, those in whom the optic nerve diameter could not be evaluated without an increase in ICP (optic neuritis, optic patients with a history of arachnoid cyst of the nerve, optic nerve trauma, anterior orbital mass, cavernous sinus mass), patients with conversion disorder and those who did not give their consent were excluded from the study.

Study protocol

The demographic characteristics, vital values and the bilateral LR (light reflex) responses of the patients were recorded. The desired complete blood count, biochemistry and blood gases values of the patient were recorded.

The diagnoses of the patients were grouped under five main headings as drugs and intoxications, infections, metabolic disorders, brain diseases and systemic organ failure. The ward or intensive care admission and duration of hospitalization, death or discharge status of the patients were followed in the records in the hospital system.

Optic ultrasound

Optic nerve sheath diameter (ONSD) and ODE were investigated in OU. OU was performed upon admission to the emergency room with the linear probe of the Toshiba Color Ultrasound Xario (SSA-660A) device, which is available in the emergency department. Using the closed eye technique, a linear probe was placed directly into the gel applied eye, and the eyeball was viewed in the transverse plain. ONSD was measured transversely from 3 mm behind the papillae in the eyeball. For optic disc elevation, the distance between the anterior apex of the optic disc and its intersection with the posterior surface of the sphere was measured by USG. An increase of more than 0.6 mm of the optic disc towards the vitreous cavity was considered ODE[5].

Statistical method

Statistical analyses were performed using the SPSS version 15.0 software. The compliance of the variables to the normal distribution was examined by visual (histogram and probability graphics) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk tests). Descriptive analyses were expressed as mean ± SD for the normally distributed variables, median

Table 1: Demographic characteristics of patients.

Demographic characteristics	Patient group (n=107)
Age, years, mean ±SD	64.7±19.4
Sex, female gender, n(%)	61 (73)
Cerebrovascular disease, n(%)	11 (10.3)
Diabetes mellitus, n(%)	20 (18.7)
Chronic kidney failure, n(%)	5 (4.7)
Asthma, n(%)	14 (13.1)
Coronary artery disease, n(%)	31 (29)
Hypertension, n(%)	47 (43.9)
Systolic blood pressure, mm/Hg, median (IQR)	120 (63)
Diastolic blood pressure, mm/Hg, mean±SD	71.3±22.0
Oxygen saturation, %, median (IQR)	93 (9)
Heart rate, /min, mean±SD	99.2±19.8
White blood cell, *10^3/µL, median (IQR)	11.7 (7.2)
Hematocrit, %, mean±SD	39.6±7.9
Serum glucose, mg/dL, median (IQR)	133.0 (84)
Serum ürea, mg/dL, median (IQR)	54 (65)
Serum creatinine, mg/dL, median (IQR)	1.1 (0.8)
Serum sodium, mEq/L, mean±SD	139.4±6.3
Serum potassium, mEq/L, mean±SD	4.5±0.9
Serum calcium, mg/dl, mean±SD	8.9±1.1
Serum ALT, U/L, median (IQR)	19 (29)
Serum AST, U/L, median (IQR)	30.0 (43)
Venous COHB, %, median (IQR)	0.9 (1.0)
Venous OSM, mmol/kg, mean±SD	290.9±26.5
Venous Laktat, mmol/L, median (IQR)	2.3 (3.6)
Urinary multidrug test	24 (22.4)
Glasgow coma scale, total, median(IQR)	8 (9)
Glasgow coma scale 14, n(%)	11 (10.3)
Glasgow coma scale 9-13, n(%)	40 (37.4)
Glasgow coma scale 3-8, n(%)	56 (52.3)
Optic disk elevation right, n(%)	25 (23.4)
Optic disk elevation left, n(%)	24 (22.4)
Optic nerve sheath diameter right, mm, mean±SD	4.9±1.3
Optic nerve sheath diameter left, mm, mean±SD	4.8±0.7
Intensive care unit hospitalization, n(%)	90 (84.1)
Number of days in hospital, median(IQR)	9(18)
Exitus, n(%)	50 (46.7)

SD: Standard deviation; IQR: interquartile; CNS: central nervous system

Table 2: Comparison of patients who died and survived

Patient Characteristics	Exitus	Discharge	*P*-value
Age, years, mean ±SD	72.14±12.21	58.18±22.22	0.00
Female gender, n(%)	28 (45)	33 (54)	0.84
Glasgow coma scale 14, median (IQR)	6 (54.5)	5 (45.5)	0.17
Glasgow coma scale 9-13, median (IQR)	14 (35)	26 (65)	
Glasgow coma scale 3-8, median (IQR)	30 (53.6)	26 (46.4)	
Optic disc elevation right	17 (68)	8 (32)	0.02
Optic disc elevation left	19 (79.2)	5 (20.8)	0.000
Optic nerve sheath diameter right, mm, mean±SD	5.0±1.7	4.8±0.7	0.38
Optic nerve sheath diameter left, mm, mean±SD	4.8±0.8	4.7±0.5	0.69

SD: Standard deviation; IQR: interquartile; CNS: central nervous system

(Interquartile range IQR) for non-normally distributed variables and n (%) for the categorical variables. In the comparisons of two independent groups, the student-t test was used for the normally distributed variables, the Mann-Whitney U test for the non-normally distributed variables and the Fisher test for the categorical variables according to the chi-square location. A *P*-value of <0.05 was considered statistically significant.

RESULTS

126 patients were examined in the current period. The information and communication details of 9 patients were not found in the system, and hence the data could not be completed; 3 patients had been referred to an external center; 4 patients had a history of eye disease; and the records of 3 patients could not be reached. A total of 19 patients were excluded. Among the patients examined, 107 patients who fulfilled all criteria were included in the study. When the demographic characteristics of the study groups were examined, the mean age in the patients was 64.7±19.4 years. 61 (57%) of the patients were women (Table 1).

The reason for altered state of consciousness in 18% (n=20) of 107 patients included in the study group were drugs and toxins; in 7% (n=8) they were infections, in 6% (n=8) they were metabolic disorders, in 40% (n=42) they were CNS disease, and 27% (n=29) were altered state of consciousness due to systemic organ failure. The right ONSD values were 4.9±1.3 mm and the left ONSD values were 4.8±07 mm in the patients. Right ODE was detected in 25 patients (23.2%) and left ODE in 24 patients (22.4%) (Table 1). While CNS diseases were 40% (n=42) in total, changes in consciousness due to toxic-metabolic causes were 60% (n=65).

Considering the in-hospital mortality of the study group; the right ONSD value was 5.0±1.7 mm in the deceased and 4.8±0.7 mm in the survivors. The left ONSD value was found to be 4.8±0.8 mm in those who died and 4.7±0.5 mm in survivors (*P*>0.05). While 68% of those with right ODE died, 79.2% of those with left ODE died. Presence of both right and left ODE was associated with mortality (*P*<0.05; Table 2).

Two groups were formed as consciousness changes due to CNS and toxic-metabolic causes. The relationship between the presence of ODE and mortality in both groups was analyzed separately. In altered consciousness due to toxic metabolic causes, 9 of 65 patients had left ODE. Seven of these patients (77.8%) died (*P*=0.03). 15 of the patients with altered consciousness due to intracranial causes had left ODE and 12 (80%) of them died (*P*=0.009). In altered consciousness due to toxic metabolic causes, 16 of 65 patients had right ODE and 7 of them (58.3%) died (*P*=0.29). 13 of the patients with altered consciousness due to intracranial causes had right ODE and 10 (76.9%) of them died (*P*=0.009).

DISCUSSION

Our study is a prospective observational study investigating the prognostic significance of optical ultrasonography in patients brought to the emergency department with mental status change. According to the results of our study, the presence of ODE was associated with mortality. There is no difference in ONSD of deceased and surviving patients.

The reason for the alteration in consciousness in non-traumatic encephalopathies is brain edema secondary to malnutrition at cellular level. Since the cranium is a closed box, the ICP can be preserved up to certain stages as a result of increased brain edema, while ICP increases dramatically in the following process. Increased ICP impairs brain function, can cause permanent damage and may result in mortality. In acute liver failure guidelines, cerebral edema is defined as a complication of hepatic encephalopathy and the treatment of increased intracranial pressure is detailed. Invasive intracranial pressure monitoring is recommended in the follow-up of these patients[6]. For this reason, it is vital to quickly detect increased ICP, to be able to follow up and to start the appropriate treatment as early as possible. Although there are

many methods for detection of ICP, there is need for a non-invasive method that can be applied at the bedside, with low cost, and shorten the diagnosis and treatment process of the patient. OU measurement is a method, the technique of which can be easily learned, cheap, repeatable and can be used in the follow-up.

There are many studies examining diagnostic test features with methods such as extra ventricular drain, CT and MRI. In a meta-analysis conducted by Ohle *et al* in 2015, the sensitivity in detecting the increase in ICP with ONSD expansion was between 70% and 100%; the specificity ranged from 30% to 83%[7]. In a study conducted by Watanabe *et al* in 12 patients with chronic subdural hemorrhage and hygroma, ONSD measurements of the patients were made on MRI and the relationship of these measurements with ICP was examined[8]. As a result of the study, they found a significant relationship between ONSD and ICP. In this study, it was determined that with the decrease in ICP in the postoperative period, ONSD decreased simultaneously. Therefore, it was found that the ONSD demonstrated instant data of the patient simultaneously with the current state[8]. The number of studies based on ultrasonographic measurement of optic disc swelling is less. Teismann *et al* compared optic disc height with fundoscopic examination. Accordingly, they suggested that an optic disc height of more than 0.6 mm may be an appropriate threshold to be used by emergency physicians as an initial test for patients at risk for high ICP[5]. Tessaro *et al* investigated the diagnostic performance of ONSD and ODE in detecting ICP in their study on the pediatric patient population[4]. According to the results of the study, they found that the most successful parameter in predicting ICP was ODE with 96% sensitivity and 93% specificity. Agrawal *et al* reported that the measurement of optic disc height showed promise in detecting increased intracranial pressure, but ONSD did not reach a sufficient diagnostic accuracy level for routine use[9].

The number of studies investigating the relationship between OU and mortality is very few. In a study conducted by Ertl *et al* with the aim of early detection of hypoxic ischemic encephalopathy in post-cardiac arrest patients, they suggested that ONSD measurement had 100% specificity in testing mortality[10]. In our study, ONSD reflected they did not reach the same significance in predicting mortality. However, 68% of the patients with ODE in the right eye and 79.2% of the patients with ODE in the left eye died. Presence of ODE may predict mortality in all patients with encephalopathy. Point-of-care ultrasound (POCUS) applications such as optical USG are a virgin issue during the follow-up of these patients. We think that optical USG is promising in the initiation of emergency interventions such as antiedema and hyperventilation treatments, and in the monitoring of cerebral resuscitation in the emergency hospitalization and intensive care follow-up of patients with encephalopathy causing brain edema such as electrolyte disorders, hepatic encephalopathy in addition to CNS diseases. Detection of the presence of ODE by ultrasonography may guide emergency and intensive care physicians to initiate cerebral resuscitation. Thus, it allows rapid patient intervention at the bedside. Mortality and morbidity can be reduced with fast and accurate cerebral resuscitation. Whether these measurements made by USG are useful in evaluating and monitoring the effectiveness of treatments for lowering the ICP is a matter of curiosity. New studies are needed on this subject.

Studies emphasizing the easy and fast usability of ocular USG support that ocular USG findings can be used in daily practice and that the data are reliable[11-14]. Wang *et al* have demonstrated that ultrasonographic ONSD is a reproducible technique with a high interobserver reliability. They confirmed that this technique is easy to learn and has high inter- and intra-observer reliability. It is a reliable and reproducible technique with high diagnostic accuracy to detect high ICP[15]. Padayachy *et al* similarly stated that this technique has excellent reproducibility and inter-observer variability[16]. Ocular USG is superior to other invasive methods in emergency units and intensive care units with its ease of use, immediate applicability at the bedside and low cost. ICP projection will expand its usage area and allow the development of different application areas. New studies are needed in many topics such as evaluating the effectiveness of treatment, initiating cerebral resuscitation and predicting complications that may develop in metabolic encephalopathies.

Our study has some limitations. First of all, our number of patients was insufficient. We did not perform invasive ICP monitoring in our study because of ethical problems and resource constraints. Ocular ultrasonography may reflect high ICP, but it is important to keep in mind the potential clinical limitations and applicability of this measurement. In the emergency setting, continuous ICP monitoring has been established as a powerful non-invasive tool to assess ICP in unconscious patients. The effort to popularize and familiarize ONSD in the ER may find its place if done by well-trained personell.

CONCLUSION

Presence of ODE with ocular USG is associated with mortality and may be more valuable than ONSD.

We think that ocular USG can find a wider place in POCUS protocols in emergency clinics and intensive care units.

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Author contributions All authors contributed to writing the manuscript and revised and approved the final version for publication.

Muge Yenigun: methodology, investigation, formal analysis, writing of original draft

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Case Report

Liver transplantation in a patient with moderate hepatopulmonary syndrome due to hepatoblastoma: A case report

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ABSTRACT

Background: Hepatoblastoma (HB) is the most commonly diagnosed liver tumor in children younger than five. This embryonic tumor, which has a rapid growth rate, originates from the primitive epithelial cells of the fetal liver and is more common in boys. Between 60% and 80% of patients are defined as unresectable at diagnosis, but thanks to neoadjuvant chemotherapy, liver transplantation (LTx) remains the only option in only 20% of patients. Hepatopulmonary syndrome (HPS) manifests itself with abnormal arterial oxygenation due to intrapulmonary vascular dilatations and is caused by advanced liver disease, portosystemic shunt or portal hypertension.

Methods: This report is about the importance of the perioperative approach and multimodal treatment in a 6-year-old child with HB, distant organ metastasis and HPS.
Result: After successful perioperative management and LTx, the patient's liver functions were normal, HPS-related platypnea resolved, and significant improvement was achieved in the patient's oxygenation parameters.
Conclusion: Herein, we suggest that HPS should be kept in mind with a multidisciplinary and multimodal approach in the perioperative period while clinicians focus on the grade, metastases and treatment options of HB for a better prognosis and mortality rate.

KEY WORDS: hepatoblastoma, hepatopulmonary syndrome, orthodeoxia, orthotopic liver transplantation, metastasis

INTRODUCTION

Hepatoblastoma (HB) is the most commonly diagnosed liver tumor in children younger than five[1]. This embryonic tumor with a rapid growth rate originates from the primitive epithelial cells of the fetal liver. It usually presents with abdominal distention, pain and growth retardation[2]. Serum alpha-fetoprotein (AFP) level is elevated in 70% of patients, and this tumor marker is reliable in diagnosing, monitoring response to treatment and detecting recurrence[3]. Between 60% and 80% of patients are defined as unresectable at diagnosis. However, thanks to neoadjuvant chemotherapy (NACT), up to 85% of patients initially considered unresectable become resectable, and liver transplantation (LTx) remains the only option in up to 20% of patients[4,5]. Ultrasonography (USG) is preferred as an imaging method in diagnosis, as it helps in the surgical staging by showing intrahepatic spread and major vessel involvement in the first stage. In addition, hepatocellular carcinoma can be ruled out by performing histopathological examination with surgical or USG-guided percutaneous biopsy. Most cases benefit from partial hepatectomy, but especially in patients with four sector involvement in the liver and major vessel involvement such as hepatic vein and portal vein, cure can be achieved with total hepatectomy and LTx.

Hepatopulmonary syndrome (HPS) manifests itself with abnormal arterial oxygenation due to intrapulmonary vascular dilatations and is caused by advanced liver disease, portosystemic shunt or portal

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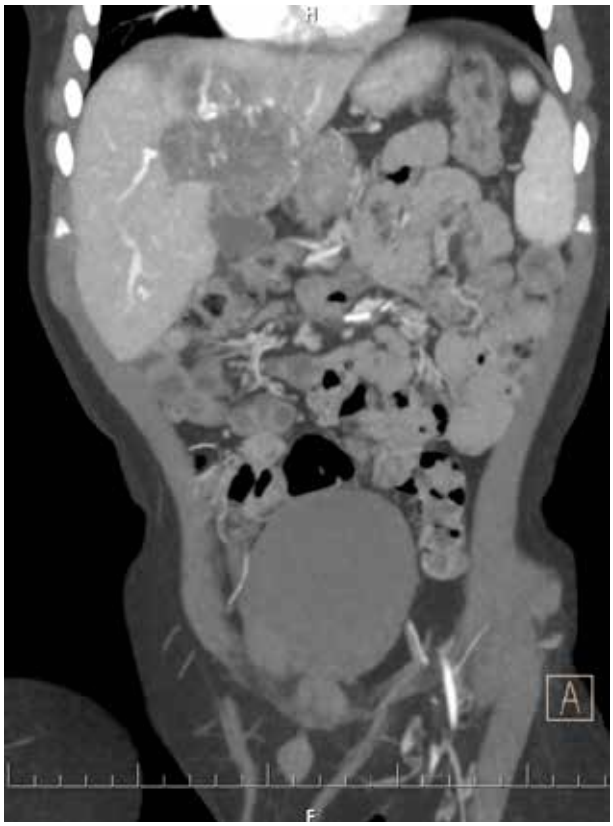

Figure 1: Contrast-enhanced tomography of the liver. Multiple mass lesions in both lobes.

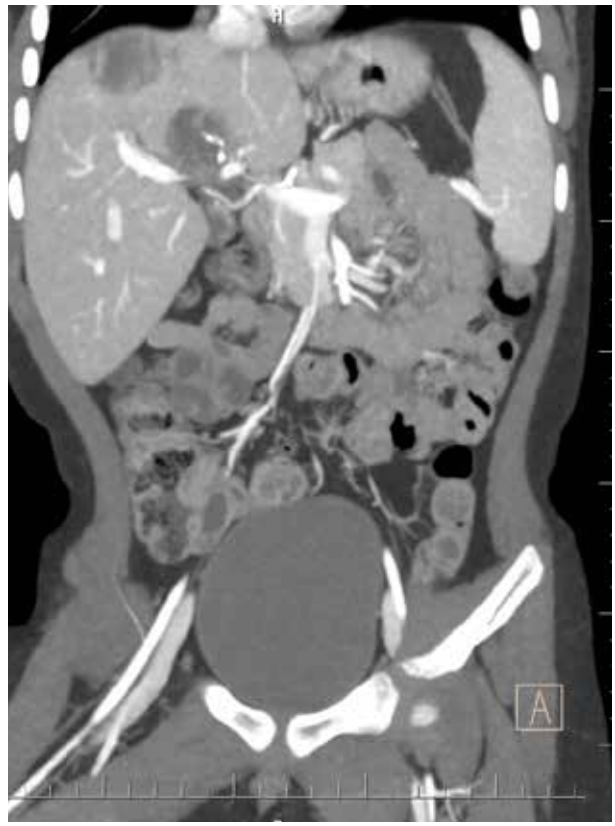

Figure 2: Contrast-enhanced tomography of the liver. Invasion of the right portal vein by the mass.

hypertension[6]. Abnormal arterial oxygenation in HPS can be defined as an alveolar-arterial gradient ≥15 mmHg in sitting while breathing room air[7]. Typical findings of advanced HPS are digital clubbing and cyanosis. Platypnea and orthodeoxia can be seen in up to 25% of HPS patients[8].

Herein, we present a patient diagnosed with HB stage 4, developed HPS, had distant organ metastasis (DOM) and underwent LTx.

CASE REPORT

Ethics committee approval and written consent from the patient's relatives were obtained. A 6-year-old boy, who applied to an external center with hip and abdominal pain 10 months ago, was hospitalized for further diagnosis and examination after his hemoglobin level was detected as 7 g/dL. Hepatomegaly was detected in the abdominal USG, and HB was diagnosed as a result of liver biopsy. Genetic analysis was not performed on the patient who did not have a current diagnosis of the syndrome. As a result of radiological imaging, it was graded as stage 4, and it was stated that the mass invaded the portal vein (Figures 1 and 2). In addition, sacroiliac metastases were detected in the examinations. The patient, who was scheduled for NACT, received 5 cycles of cisplatin and 5 cycles of carboplatin-doxorubicin. After 1 month of this treatment, the family voluntarily applied to our hospital. No sacroiliac lesion was detected in the follow-up after chemotherapy. In laboratory tests, the liver function values of the patient were within normal limits, and the AFP level was measured as 1261.65 ng/ml. The platelet value was 58.000/µl. Viral markers were normal. In the arterial blood gas analysis in room air, the PaO_2 value was 72 mmHg, the SaO_2 value was >90%, and the patient had platypnea. A diagnosis of moderate HPS was made in the patient with dilatation in the pulmonary vascular structures on chest computed tomography angiography, together with the present findings (Figure 3). The visual field of the patient, in whom bilateral papilledema was detected in the preoperative eye examination, was evaluated as normal, and the neurological examination of the patient was normal at the neurology consultation. The cerebrospinal fluid pressure and cytology at the lumbar puncture were also normal. In addition, no pathology was detected in the brain MRI. The evaluation determined CHILD class A and PELD scores as 0. The decision of LTx was made for the patient presented at the council because of the stage of HB and the development of HPS.

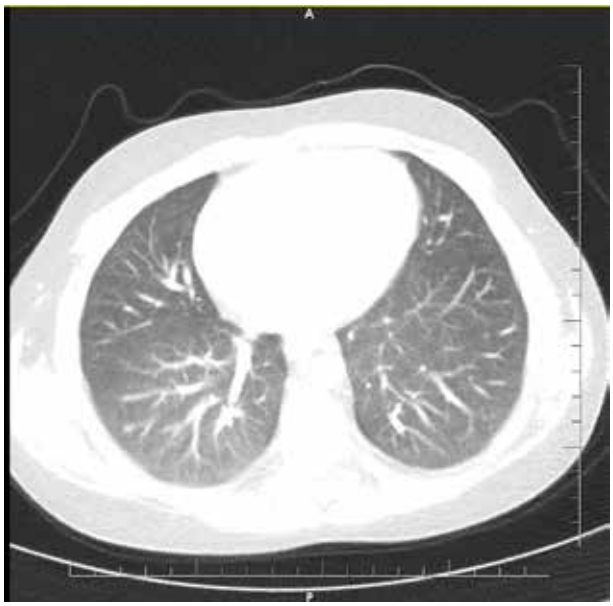

Figure 3: Chest computed tomography angiography. Peripheral branching and vasodilation in pulmonary vascular structures.

Figure 4: Liver removed from the patient (815 grams).

The patient was taken to the operating room on the day of surgery, and standard monitoring (electrocardiography, non-invasive blood pressure and pulse oximetry) was performed. Fluid therapy was started from the central venous catheter. Anesthesia induction was achieved with 2 mg/kg of propofol, and 0.6 mg/kg of rocuronium was used as a muscle relaxant. He was intubated with direct laryngoscopy without complication. Bilateral lung sounds were evaluated as equal. Remifentanil 0.05 μg/kg/min and rocuronium 0.3 mg/kg/h were used as IV agents for anesthesia maintenance. Sevoflurane was used as an inhaler. Tidal volume was set to 6 mL/kg, PEEP: 4, respiratory rate was set to 14 in mechanical ventilator, and end-tidal CO_2 was monitored. Left radial artery catheterization was provided with USG. Arterial blood pressure, central venous pressure and body temperature were monitored. Catheterization was provided with Pulse Contour Cardiac Output (PiCCO) and monitored. The removed liver was 815 grams (Figures 4 and 5). A 260 g graft was taken from his father (Figures 6 and 7). The patient's vital signs, arterial blood gas parameters, urinary output and PiCCO values remained stable throughout the operation. 1500 mL of crystalloid liquid, 1600 mL of liquid containing 5% albumin and 290 mL of

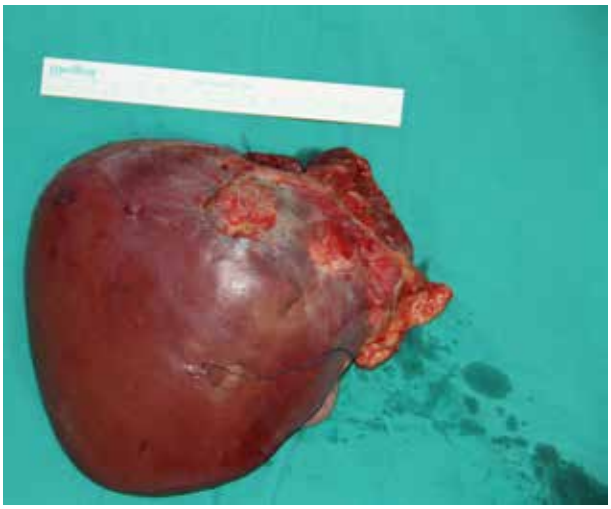

Figure 5: The size of the removed liver.

Figure 6: The weight of the liver from the donor was 260 grams.

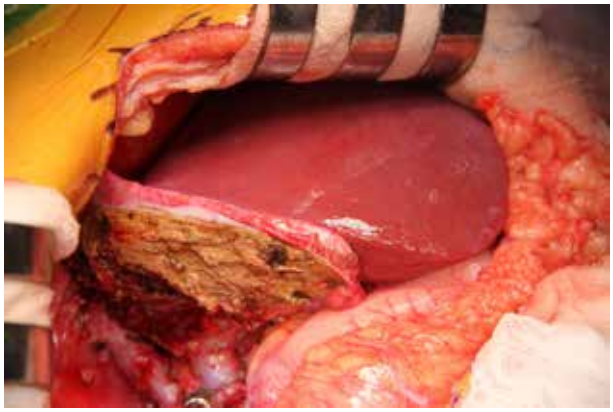

Figure 7: After the anastomoses are completed, the liver in the recipient patient.

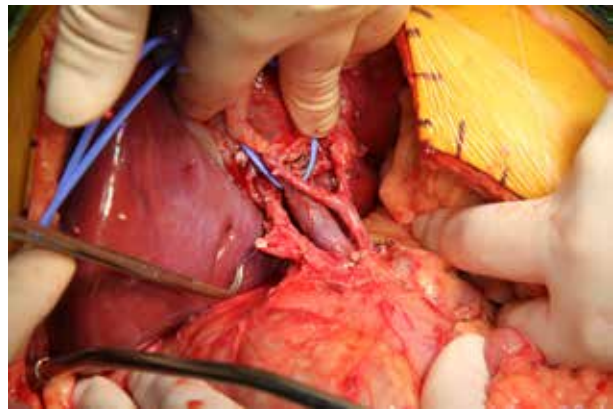

Figure 8: In preparation for the anhepatic phase.

erythrocyte suspension were administered. The anhepatic phase lasted 61 minutes (Figure 8). He was extubated in the operating room and uneventfully transferred to the ICU. Appropriate analgesia and immunosuppressive treatment were started for the patient. The patient was transferred from the ICU to the ward on the second postoperative day. The patient's platypnea and orthodeoxy regressed significantly in the follow-up, and he was discharged on the 21st day without any complications.

DISCUSSION

HB is a rare but most common hepatic tumor in childhood, which is usually diagnosed at an advanced stage when diagnosed and frequently involves major vascular structures. HPS is a pathology that requires immediate resolution of the underlying cause, such as HB stage 4, which causes intrapulmonary vascular vasodilation[1,6].

We reviewed the studies in the literature on HPS and LTx and studies with HB and distant organ metastasis. In the studies we could reach, we could not find any patient who developed HPS due to HB and underwent LTx.

SIOPEL-1 and World Experience Review reported the rate of positive AFP as 82.4% in 511 patients aged 0 to 17 years diagnosed with HB between 2004 and 2016, and LTx was applied to 82 patients in this study. This study shows the 10-year survival after LTx as 82%[9,10]. However, we did not find a case of HPS associated with HB in the literature.

Zsiros *et al* collected 151 patients in their SIOPEL-3 and-4 study, 20.6% of the patients were treated with LTx, and the 3-year survival rate was reported at 75% in these patients[11].

Krowka M *et al* reviewed more than 1000 articles on HPS and portopulmonary hypertension. They stated that the incidence of HPS in children with advanced liver disease ranges from 3% to 20%. They also stated that LTx should be considered in severe hypoxemia (PaO_2 <60 mmHg) due to HPS[6]. Goldberg D *et al* associated pre-LTx PaO_2 <45 mmHg with increased post-LTx mortality in patients[12]. Our patient's HPS stage was moderate, and the pre-LTx PaO_2 was >72 mmHg.

Emre *et al* reported that HPS symptoms regressed 2 months after LTx in a 9-year-old female patient with Abernethy malformation and HPS[13]. Our patient has no diagnosed syndrome, and liver transplantation was indicated because of moderate HPS and HB stage 4. However, we would like to point out that no genetic testing has been performed.

Herein, we wanted to point out that it should be kept in mind that HPS may develop in HB patients and that HPS findings can rapidly regress after LTx. Distant organ metastasis is rarely seen in the literature, and we would like to state that distant organ metastasis should be controlled before LTx with NACT without wasting time, and the development of severe HPS should be prevented in the HB stage 4 patients who are unresectable.

CONCLUSION

We think that the degree of HPS should be kept in mind while determining the NACT plan and duration in HB patients with DOM. It is very important to make an LTx decision based on the severity of HPS. A multidisciplinary and multimodal approach should be kept in mind for HPS patients caused by HB in the perioperative period.

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Author contribution: Nedim Cekmen and Ahmed Uslu designed and performed the interventional therapy. Nedim Cekmen drafted the manuscript. Nedim Cekmen, Zeynep Ersoy and Ahmed Uslu critically reviewed the manuscript and provided constructive suggestions. All authors read and approved the final manuscript.

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Case Report

From anticoagulation to atrial appendage closure in atrial fibrillation

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ABSTRACT

Introduction: Most embolic strokes in patients with nonvalvular atrial fibrillation (NVAF) are caused by a left atrial auricle thrombus, followed by high risk of recurrence and serious neurological deficits. New oral anticoagulation is the mainstay of the treatment. Percutaneous left atrial auricle occlusion is one of the unique strategies for overcoming the shortcomings of direct anticoagulant therapy such as the risk of bleeding and patients' noncompliance.
Case presentation: We present a case of a 64-year-old male patient with a history of long-term NVAF, treated with direct oral anticoagulant therapy (Rivaroxaban at full dose), but who nevertheless suffered an ischemic stroke of embolic origin. After successful mechanical thrombectomy, additional evaluation revealed a thrombus of the left atrial auricle. After conversion to other anticoagulant medication (Dabigatran followed by Edoxaban), percutaneous closure of the left atrial auricle with Watchman FLX LAAC device preceded. At the time of writing this report, the patient had not consulted for recurrence of neurological symptoms.
Conclusion: If the patient experiences a stroke at the full dose of anticoagulant therapy, it is necessary to expand the treatment as well as diagnostic approach and to suspect another source of embolization.

KEY WORDS: anticoagulants, appendage closure, prevention, stroke

INTRODUCTION

Stroke is the second most common cause of death in the world[1]. Cardioembolic stroke accounts for 14% - 30% of all cerebral infarctions and atrial fibrillation (AF) increases the risk of ischemic stroke by up to 4-5 times[2]. The left atrial appendage (LAA) is responsible for >90% of embolic strokes, and in the literature, it is also called "the most lethal human attachment"[3].

The mechanisms of cardio embolization that are responsible for the occurrence of stroke include: 1) blood path and thrombus formation; 2) aneurysm of the left heart; and 3) paradoxical embolization[4].

Emboli caused by blood clots within the left ventricle are usually large and can cause occlusions of large blood vessels such as the middle cerebral artery[5]. In most cases, recurrent cardio embolization can be prevented with oral anticoagulants. Therefore, early confirmation of a diagnosis of cardioembolic infarction is extremely important. New oral anticoagulants (NOAC-s) that are not vitamin K antagonists have been shown to be safer and equally effective in preventing stroke in patients with non-valvular atrial fibrillation (NVAF) compared to warfarin, taking into account a 15% and 58% relative reduction in thromboembolism and intracranial bleeding, respectively, compared to dose-adjusted warfarin[6].

Ongoing studies aim to further address the usefulness of left atrial appendage occlusion (LAAO) in primary and secondary prevention of stroke for patients with AF, including those at high risk of bleeding, contraindications to the introduction of oral anticoagulant therapy[7]. Current investigations suggest lower risk of the composite outcome of stroke, major bleeding and all-cause mortality with LAAO therapy compared to direct oral anticoagulants (DOAC) in the prevention of stroke for patients with

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AF, but the incidence of embolic stroke recurrence in LAAO patients still remains uncertainly reported[8]. The periprocedural complications of LAAO include death, ischemic or hemorrhagic stroke, tamponade and device embolization, and they still remain a challenge[9].

The following is a case report that has shown how expanded treatment and diagnostic approach is of utmost importance for patients who had experienced embolic stroke.

CASE REPORT

A 64-year-old male Croatian patient with a history of long existing NVAF, arterial hypertension and insulin-dependent diabetes mellitus presented to the emergency department due to difficulty in speech and weakness of the left extremities. The symptoms started approximately two hours before arrival in the emergency department, and before their onset the patient had properly used his anticoagulant therapy (Rivaroxaban) in a dose of 20 mg per day, as well as antihypertensive, antiplatelet (acetylsalicylic acid), gastroprotective and hypolipidemic medication. On physical examination, he presented with left-sided central hemiparesis of moderate severity with dysarthria. His laboratory tests were normal. Echocardiographic findings from before showed known AF. Urgent neuroradiological imaging was performed and occlusion of the dominant M2 branch of the right middle cerebral artery was established. Due to the antiplatelet and anticoagulant therapy that he had primarily been taking, the patient did not get systemic thrombolysis. Therefore, the team decided to intervene with mechanical thrombectomy. Upon successful mechanical thrombectomy, neurological status was monitored until complete regression. The patient was discharged cardiocirculatory-stable with prescribed oral anticoagulant therapy (Apixaban), in addition to his chronic therapy.

Further echocardiographic assessment (transthoracic and transesophageal ultrasound) verified thrombus in the left atrium (Fig 1), followed by dilated atrial cardiopathy- New York Heart Association of Heart failure (NYHA II). After six months of follow-up (magnetic resonance imaging of the endocranium, Doppler ultrasound of carotid and vertebral arteries, regular blood pressure control, electrocardiography and echocardiography), the patient was without any neurological problems, but with permanent AF.

Therefore, the patient was recommended to replace Apixaban with Dabigatran in the dose of 150 mg/12 hours. Because of persistent AF and stable state, the application of an LAA occluder was indicated. Watchman FLX LAAC device (27 mm length) was implanted in the left auricle without complication.

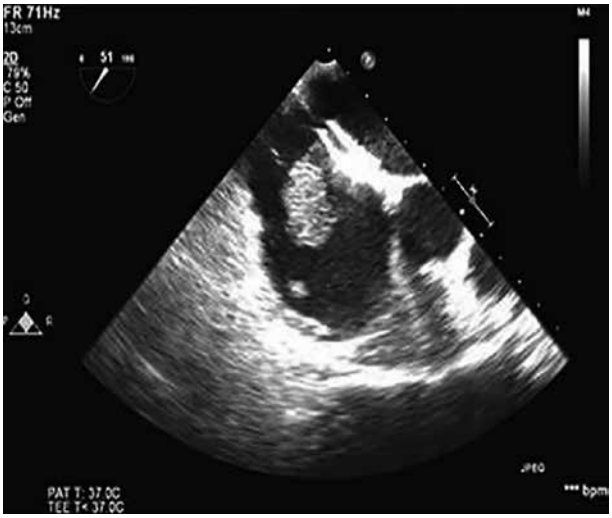

Figure 1: Initial transesophageal ultrasound

Meeting all criteria for the introduction of Edoxaban (NVAF with one or more risk factors, such as congestive heart failure, hypertension, diabetes and stroke) due to the convenience of taking, the same drug was introduced at a dose of 60 mg per day. No adverse events were recorded.

In conclusion, after ischemic stroke of embolic origin, followed by mechanical thrombectomy as well as the careful use and adjustment of DOAC therapy in combination with percutaneous closure of the left atrial auricle, the patient was followed up for two years without recurrence of cerebrovascular incident.

DISCUSSION

This case proves that although significant progress has been made in the diagnosis and treatment of stroke patients with pre-existing NVAF, the long-term risk of recurrence of stroke and bleeding complications are still the subject of research[5]. In this patient, usage and replacement of the anticoagulant drugs showed lack of efficacy as the strategy per se, and LAAO differentiated it from other cases reported in the literature. All the same, evidence supporting the use of LAAO is limited, while research results are consistent that NOAC are the standard therapy for preventing stroke in NVAF[10].

Clinical studies (RE-LY, ROCKET AF, ARISTOTLE) showed that all drugs in the NOAC group are more effective in preventing stroke than warfarin, that differences in efficacy among NOAC drugs exist, and that they should be adapted to the specific profiles of patients with AF[11]. The choice between different NOAC-s is based on the choice of physician, due to the small number of randomized trials that directly compare NOAC drugs to each other[12]. The NOAC

medication that was used for the treatment of our patient and the prevention of recurrence of stroke, belong to the group of factor Xa inhibitors. Apixaban, which was introduced to the patient after his initial therapy with Rivaroxaban, has, according to the study conducted in 2016, the lowest risk of major bleeding compared to the other anticoagulant drugs[13]. Prior to the implantation of the left atrial occluder, the patient was converted from Apixaban to Dabigatran therapy, which according to the combined results of the research, proved to be the best in the prevention of ischemic and hemorrhagic stroke[14]. LAAO has been proposed as a nonpharmacological method to prevent stroke in patients with AF[7]. The majority of reference centers (94%) estimate that indications for the installation of occluders exist in patients with high thromboembolic risk (CHA2DS2-VASc ≥ 2)- Congestive heart failure (hypertension, age, diabetes, previous stroke / transient ischemic attack) [15], if there is preexisting history of bleeding as well as thromboembolic events despite adequate NOAC[9]. If there is a failure of NOAC, it is important to conduct detailed etiologic evaluation in order to exclude cardiac source of embolus, artery to artery embolization as well as causes of embolic stroke of undetermined source (subclinical AF, atrial cardiomyopathy, patent foramen ovale, etc)[16]. After the conducted and repeated neuro-cardiological evaluation, our patient was a candidate for percutaneous closure of the left atrium due to: high risk of recurrent stroke (CHADS2 score 5)[15], thrombus determined by transesophageal ultrasound and persistent electrocardiographic signs of AF despite attempts at cardioversion on several occasions. In our case, Watchman FLX LAAC device (27mm length) was used. The Amplatzer and Watchman LAAC devices are the two most frequently used devices for LAAC worldwide[17]. According to meta-analysis conducted by Qiao J, Amplatzer LAAC device was associated with higher rates of major procedure-related complications, especially in device embolization. Watchman LAAC device was associated with higher rates of device leak and device related thrombosis[17]. This result suggests that the choice of the device could influence the reduction of the risk of peridevice leaks and embolization[17]. There were no significant differences between the two in ischemic stroke/TIA, embolization, hemorrhagic stroke, all-cause death, cardiovascular death and bleeding. CLOSURE-AF is a continuous randomized trial that aims to evaluate the usefulness of percutaneous LAAO compared to anticoagulant therapy (Warfarin or NOAC-s) in patients with nonvalvular AF[9]. LAAO has shown equivalent efficacy compared to oral anticoagulants in the prevention of cardiovascular and neurological complications, however, the CLOSURE-AF study indicated caution regarding the safety of the LAAO procedure itself due to complications including death caused by the procedure, pericardial effusion, tamponade and occluder thrombosis[18]. 50% of referral centers do not prescribe oral anticoagulant therapy after the procedure[9]. Nevertheless, anticoagulation was started after the intervention in our case, and the patient was converted from Apixaban to Edoxaban due to the suitability of taking it in the form of a one-day dosage. One of the largest comparative studies of the efficacy of DOAC drugs was a retrospective analysis of 434,046 patients in the USA (ARISTOPHANES), according to which high-dose Edoxaban is generally comparable to Apixaban for endpoints in terms of prevention of stroke[12]. The conflicting results of studies in secondary prevention of stroke emphasize the limitations of the research that has been performed. Seiffge D concluded that a change in the type of anticoagulant after a history of cerebrovascular events was not associated with a reduced risk of further ischemic stroke[19]. One of the strengths of this case were the early notification as well as permanent monitoring of AF, careful adjustment of anticoagulant therapy regarding patients' needs and indications, as well as the comprehensive assessment done on the patient. At the time of initial assessment of our patient, as well as during the evaluation and the treatment, the broad spectrum of etiology of the cardioembolic stroke was continuously taken into consideration (left atrial appendage malformations, heart emboli and rare causes of embolic stroke) - the etiological background is presented in Table 1[16,20]. The results of the study by Korsholm K, proved that there was a significant lower risk of the composite outcome of ischemic stroke, systemic embolism, major bleeding and all-cause mortality in the LAAO cohort in comparison to the DOAC cohort[8]. Cardiovascular mortality and the rate of ischemic stroke did not differ statistically between the LAAO and DOAC group. According to the literature, the benefit of LAAO over DOAC, in the terms of composite outcome, requires confirmation in the ongoing randomized OCCLUSION-AF trial[8]. This study aims to assess the effect of LAAO to reduce the incidence of stroke, systemic embolism, bleeding and mortality in patients with AF and a prior ischemic stroke. The randomized PROTECT-AF trial has demonstrated the superiority of LAAO to warfarin for prevention of the combined endpoint of stroke, major bleeding and cardiovascular mortality. However, studies comparing LAAO to NOAC still have to be carried out[21].

Table 1: Etiology of cardioembolization[16,20]

Atrial disease		Valvular heart disease	Structural and functional ventricular diseases	Myocardial infarction	Embolic Stroke of undetermined source
Arrhythmias	Structural disease	Rheumatic valvular disease	Ventricular aneurysm	Mural tromb	Subclinical atrial fibrillation
Non-valvular atrial fibrillation	Patent foramen ovale	Infective endocarditis	Septal aneurysm	Left ventricular dysfunction	Patent foramen ovale
Sick sinus syndrome		Non-infective endocarditis (maranticendocarditis)	General ventricular hypokinesia (heart failure with reduced ejection fraction)		Non-stenotic arterial plaque
		Valvular calcifications			cardiopathies
		Mechanical prosthetic heart valves			vasculopathy
		Mitral valve prolapse			

CONCLUSION

One of the biggest questions clinicians face in patients with AF at risk of stroke is which oral anticoagulant to start. A number of factors need to be considered, including efficiency, convenience and cost. The left atrial appendage source should be considered in the recurrent embolic stroke with AF. LAAO is performed prophylactically in patients who are stable and "asymptomatic". Further data analysis may help guide selection criteria for patients who would benefit from therapeutic strategies such as combining oral anticoagulant therapy with left atrial auricle closure intervention, as was the case with our patient.

Patient's perspective

The patient understood the importance of the follow-ups, treatment and conducted procedure. He did not record any adverse effects of the applied medications. Despite the fact that left atrial appendage closure is not being conducted frequently in our region, the patient accepted the procedure, previously being introduced to possible risks.

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Author's contribution: Isidora Semnic primarily wrote the manuscript, David Bonifacic provided the data, gave critical feedback and revised the work.

The institution where the work was done: Department of Neurology, Medical faculty of Rijeka, University Hospital Rijeka, Kresimirova 42, 51000, Rijeka, Croatia.

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Case Report

COVID-19 patients with infective endocarditis and septic embolism to the brain

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ABSTRACT

Infective endocarditis (IE), an infection of the endocardium, is an infection with serious complications such as heart failure, valvular diseases and systemic embolism. It has risk factors such as intravenous drug use, poor oral hygiene and dental intervention, and infectious symptoms such as fever, tremble, loss of appetite and weight loss. It is an infection with high morbidity and mortality that affects various organs and systems such as heart, skin and retina.
Coronavirus disease (COVID-19), which can have a similar clinic with both IE and various infections, can also be seen at the same time with other infections, which causes a delay in its diagnosis and treatment. There can be similar clinical symptoms between COVID and IE during their cardiac involvement. This is another factor that creates difficulties in diagnosis. It should always be considered that COVID-19 may coexist with IE and/or other infections.
Our case presented here is a patient with diabetes mellitus for 20 years and using oral antidiabetic drugs. Progressive speech disorder has occurred for two days and the patient has no history of any surgical or dental intervention, intravenous drug or drug use. IE was not considered in the initial diagnosis, and the patient was admitted to the emergency department with a prediagnosis of cerebrovascular disease and diabetes mellitus. After hospitalization in the intensive care unit, IE and septic embolism were detected with the presence of COVID-19 infection.

KEY WORDS: COVID-19, infective endocarditis, septic embolism

INTRODUCTION

Infective endocarditis (IE), an infection of the endocardium, is an infection with serious complications such as heart failure, valvular diseases and systemic embolism[1-2].

Intravenous drug use, prosthetic valve, poor oral hygiene and dental intervention are important risk factors[3-4]. IE is characterized by symptoms such as fever, tremble, anorexia and weight loss and cardiac involvement, skin involvement, splenomegaly, retinal involvement, and primarily central nervous system embolism. Despite the advances in diagnosis and treatment, it is a severe infection with a poor prognosis due to its high morbidity and mortality[5-7].

Both IE and coronavirus disease (COVID-19), which may have similar clinical features such as fever, chills, shortness of breath, fatigue, cough with other infectious diseases, may occur simultaneously with other infections. Therefore, the diagnosis of other infectious diseases accompanying COVID-19 can be difficult and sometimes delayed. In such cases, the co-existence of COVID-19 and other infections should always be considered[8]. Cardiovascular diseases are common in COVID-19 patients. Cardiac symptoms and signs of IE and COVID-19 may be similar, which is another factor that complicates the diagnosis[9].

Our case presented here is a patient with diabetes mellitus for 20 years and using oral antidiabetic drugs. Progressive speech disorder has occurred for two days and the patient has no history of any surgical or dental intervention, intravenous drug or drug use. IE was not considered in the initial diagnosis, and the patient was admitted to the emergency department with a pre-diagnosis of cerebrovascular disease and diabetes mellitus. Chest x-ray was compatible with COVID. After hospitalization in the intensive care unit, PCR test was positive and IE and septic embolism were detected with the presence of COVID-19 infection.

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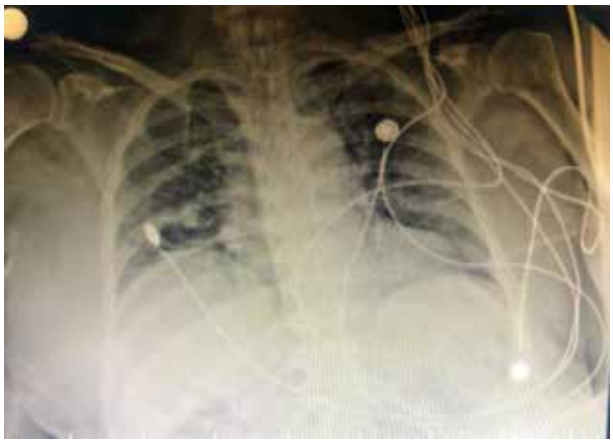

Figure 1: Postero-anterior chest radiograph taken in the emergency room is compatible with COVID-19.

CASE REPORT

The patient, a 66-year-old female, was admitted to the emergency department with complaints of dyspnea, fatigue and high fever. The patient was conscious. The patient, who had a speech disorder that had been increasing for two days, had a fever of 38.3 degrees, a blood pressure of 130/70 mm/Hg, and a pulse rate of 120/minute in the examination performed. Her saturation was 86% with oxygen. On physical examination, the patient was conscious and had somnolence and speech disorder. Abdominal examination and cardiovascular examination were normal. In laboratory examinations; leukocyte 14000/mm^3, lymphocyte 27.6%, monocytes 11.5%, hemoglobin 11.6 g/dl, hematocrit 32.1%, platelet 143000/mm^3, urea 22 mg/dl, creatinine 0.8 mg/dl, aspartate aminotransferase 27 IU/l, alanine aminotransferase 20 IU/l, total bilirubin 0.5 mg/dl, direct bilirubin 0.28 mg/dl, C-reactive protein 95.5 mg/dl, procalcitonin 0.14ng/ml. Posteroanterior chest X-ray of the patient taken in the emergency room was compatible with COVID (Figure 1). Magnetic resonance imaging (MRI) of the brain taken to exclude cerebrovascular disease was found to be compatible with ischemia (Figure 2). Piperacillin-tazobactam treatment was started for the patient who was admitted to the intensive care unit. The result of the PCR taken for the COVID-19 infection of the patient was positive. Diffusion MRI was performed in the patient who had a tendency to sleep in the intensive care unit. Septic embolism was considered in the patient whose neurology consultation was requested. The treatment of the patient with *Staphylococcal aureus* growth in the blood culture was changed to cefazolin and vancomycin. No vegetation was detected in the echo of the patient who underwent bedside echocardiography by the cardiology department.

The symptoms and signs of the patient, who was followed up and treated in the intensive care unit for five days, started to improve after the third day. The patient whose clinic improved was transferred to the infectious disease service. After two days of hospitalization, the patient was discharged with the recommendation of cardiology and infectious diseases polyclinic control.

DISCUSSION

IE, which is characterized as a focus of infection in the heart, is an infection of the endocardium[1]. Despite advances in diagnosis and treatment, IE has a poor prognosis, and valvular vegetations that can cause heart and valvular insufficiency and embolisms may occur[2]. *Staphylococcus aureus* is the most common cause of acute IE in patients with normal valves. *Streptococcus viridians* is the most common causative agent in patients with prosthetic valves using intravenous drugs, elderly patients and dialysis

Figure 2: Compatible with MRI ischemia in the emergency department.

patients, and causes subacute infective endocarditis[3-4]. Male gender, history of prosthetic valves, history of IE, intravenous drug use, history of chronic hemodialysis, poor oral hygiene and dental intervention can be counted among the risk factors[5].

COVID-19 can have cardiovascular complications similar to IE such as arrhythmia, acute coronary syndrome and venous thromboembolism. There is no clear information about the association between IE and COVID-19, where common symptoms such as fever, tremble, fatigue and weakness can be seen and their differential diagnosis might be difficult in their co-existence[6]. Physical examination in IE may reveal murmur due to cardiac involvement, skin involvement such as petechiae, splinter hemorrhage, Janeway lesions and Osler nodules, splenomegaly, and Roth spots characterized by exudative hemorrhagic lesions on the retina.

Diagnosis is primarily made according to clinical findings. Duke criteria are used to aid in diagnosis. These criteria are divided into major and minor criteria.

Major criteria

a) Presence of positive blood cultures characterized by growth in at least two cultures in IE or positive results of IE agents such as *Staphylococcus aureus*, *Streptococcus viridians*, *Streptococcus bovis* in three of the four (4) blood cultures taken within one hour.
b) Presence of findings on echocardiography such as vegetation on valve, abscess, perforation and mobile intracardiac mass.

Minor criteria

a) Presence of fever over 38 °C
b) Presence of facilitating factors such as intravenous drug use
c) Embolism in large arteries, conjunctival hemorrhage and skin lesions (Janeway lesions
d) Presence of immunological symptoms (Osler nodules, Roth spots, glomerulonephritis)
e) Presence of microbiological factors characterized by the presence of a positive blood culture that does not meet the major criteria.

Definitive diagnosis

Demonstration of the microorganism in culture or histological examinations in the sample taken from the lesion or abscess

Clinical presence of

- Two major criteria
- 1 major + 3 minor criteria
- Five minor criteria

Possible diagnosis:

Presence of

- 1 major + 1 minor
- Three minor criteria

Echocardiography is particularly important in diagnosis and treatment. Transesophageal echocardiography, which is more sensitive than transthoracic echocardiography (TTE), and TTE is performed in patients with suspected IE. Other imaging methods such as ultrasonography and computed tomography are also helpful in diagnosis. Definitive diagnosis is made by culture of the sample taken from the lesion or by showing the microorganism in histological examinations[6-13].

The primary aim of treatment is to eradicate the infection and treat the vegetation. Therefore, the treatment, which usually takes 2-6 weeks, may be prolonged[14-15].

Surgical treatment may be needed in the development of complications such as heart failure, valve dysfunction, endocarditis unresponsive to antibiotics and systemic embolism, especially cerebral embolism, in patients with endocarditis despite antibiotic therapy[16-18].

There is an increased risk of thromboembolism both in COVID-19 and IE. Various tissue and organ embolisms, especially kidney, spleen, coronary arteries and central nervous system, have been reported in both infections. However, the use of anticoagulants in patients with coexistence of IE and COVID-19 is controversial. The use of anticoagulants in patients with IE may increase the morbidity and mortality. On the other hand, in some studies, it has been found that there is an increased risk of cerebral hemorrhage due to IE[19-20]. For this reason, anticoagulant treatment should be evaluated in terms of benefit and harm in IE and COVID-19 patients and the treatment should be planned accordingly.

CONCLUSION

Other infectious diseases should be considered in the differential diagnosis. A complete physical examination should be performed in patients diagnosed with IE and COVID-19. It should be kept in mind that these diseases may be presented with complications, and in such a case, the diagnosis should be made as soon as possible, and the treatment should be done without delay.

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Conflicts of interest: None

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Case Report

Neuroendocrine tumor as an incidental finding in bariatric surgery: A case report and review of the literature

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ABSTRACT

Neuroendocrine tumors (NETs) are frequently found in the gastrointestinal tract. Gastric NETs are uncommon, accounting for less than 1% of all gastric neoplasms, but show increasing incidence in obese patients as compared to the general population. Although most cases reported in the literature were detected preoperatively by upper endoscopy, in this case report, I describe an incidental discovery of a gastric NET after a sleeve gastrectomy. Our case highlights the importance of preoperative endoscopic examination and biopsy of suspicious areas in the gastric mucosa of obese patients who wish to undergo bariatric procedures. Postoperative pathological examination should be mandatory and precise, as incidental findings can be expected.

KEY WORDS: bariatric, gastric, incidental, neuroendocrine tumor

INTRODUCTION

Neuroendocrine tumors (NETs) are frequently found in the gastrointestinal tract[1]. Gastric NETs are uncommon, accounting for less than 1% of all gastric neoplasms[2]. Their incidence is increasing in obese patients as compared to the general population. There are controversial studies as to whether routine histopathological examination of sleeve gastrectomy specimens should be performed[3,4]. Most cases reported in the literature were detected preoperatively by upper endoscopy[5]. However, in this unique case report, I present an incidental finding of a NET that was only discovered postoperatively. This finding urges medical practitioners not to underestimate the possible pathologies that could be hidden in asymptomatic patients.

CASE REPORT

A 36-year-old male patient with type II diabetes mellitus, bronchial asthma and morbid obesity (body mass index: 49.6 kg/m^2) with unremarkable surgical history failed to lose weight despite several diet regimens and underwent a laparoscopic sleeve gastrectomy. Routine preoperative blood investigations like complete blood count, liver function test, renal function test, coagulation profile, chest x-ray and ultrasound to rule out gallbladder stones were done and all were unremarkable. Upper endoscopy was not indicated preoperatively because the patient was asymptomatic. Under general anesthesia, the patient underwent a sleeve gastrectomy that proceeded smoothly without complication. No abnormality was observed on the serosal surface. The sleeve gastrectomy specimen was sent for histopathological analysis. Examination of the specimen revealed a single nodule of 0.7 cm on the mucosal surface, which was well clear from surgical margins. Microscopic examination revealed a nest of monotonous, small, round cells with abundant granular cytoplasm in the background of moderately inactive chronic gastritis, and intestinal metaplasia was identified (Fig 1). Immunohistochemical examination was positive for synaptophysin and chromogranin, with a Ki-67 proliferative index of <1% (Fig 2). A diagnosis of a

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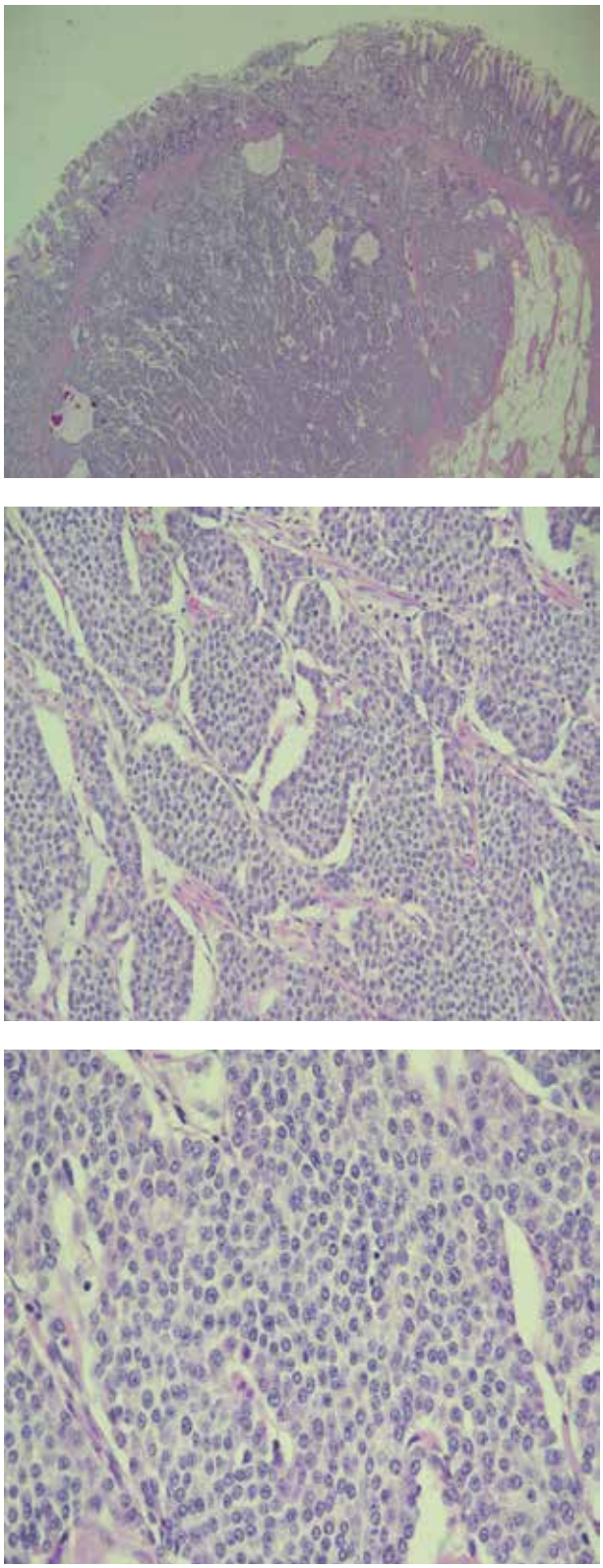

Figure 1: A, B, & C. Light microscopy photographs of the tumor show solid nests and trabecula of small round monotonous cells with coarse salt and pepper nuclear chromatin and small nucleoli. (Hematoxylin and eosin stain; A, B, & C, ×20, ×200, and ×400, respectively.)

well-differentiated NET (grade I) was established. The pathological stage classification using pTNM (AJCC 8th edition) was pT1 pNx. The patient was followed up at the clinic and had no further complications; the whole-body ^{99m}Tc-octreotide scan result was negative.

The patient provided informed written consent for the publication of this report.

DISCUSSION

I present an incidental finding of a NET after sleeve gastrectomy. Obese patients have an increased incidence rate of NETs compared to non-obese patients[1]. Şen *et al* reported the incidence of gastric NETs in the obese and general population to be 0.6-0.8% and 0.0006-0.0015%, respectively[2]. This increase in incidence could be related to the fact that obese patients seek medical help for bariatric procedures[5]. Other pathological findings in routine histological examination of sleeve gastrectomy specimens include chronic gastritis and fundic gland polyps[3]. Examination of resected tissues from patients provides opportunities to discover any hidden pathology. Some studies underestimate the value of routine histopathologic examination for sleeve gastrectomy[3]. However, other studies find it important and useful[4]. Our case confirms the benefit of pathological examination for elective sleeve gastrectomies as incidental findings cannot be excluded.

Gastric NETs can be classified based on cell hormone production. The most common type is enterochromaffin-like (ECL) cell (histamine-producing) tumors. Other pathologies, such as enterochromaffin cell (serotonin-producing), D-Cell (somatostatin-producing) and G-cell (gastrin-producing) tumors are very rare. ECL cell NETs are further subcategorized into three subtypes based on the histology of the adjacent mucosa: antral G-cell hyperplasia, hypergastrinemia and coexisting clinical conditions. The most common subtype is type I ECL cell NET, which is associated with autoimmune chronic atrophic gastritis. It usually manifests as multiple small-sized tumors with hypergastrinemia and antral G-cell hyperplasia, with a good prognosis. Type II ECL cell NETs are gastrin-producing tumors that occur in patients with multiple endocrine neoplasia type 1 or Zollinger-Ellison syndrome. They are characterized by multiple tumors measuring less than 2 cm and hypertrophy of the surrounding mucosa. Their metastatic potential is low but higher than that of type I tumors. Type III ECL cell NETs are sporadic and usually present as single masses. They are characterized by the absence of ECL cell hyperplasia or dysplasia and are not associated with multiple endocrine neoplasia type 1 or Zollinger-Ellison syndrome[6]. Type III carries a high risk of metastatic disease.

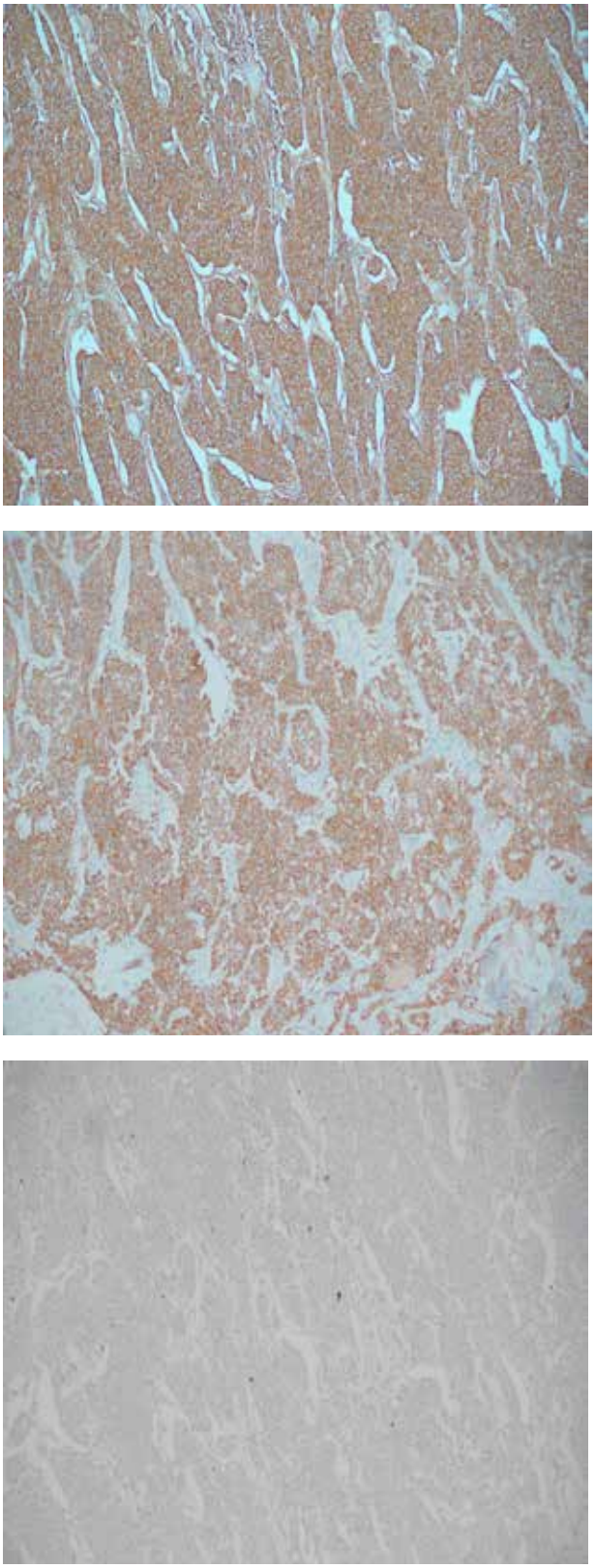

Figure 2: A, B, & C. Light microscopy photographs of the immunohistochemistry staining study of the tumor cells show (A) cytoplasmic positivity to chromogranin, (B) cytoplasmic positivity to synaptophysin, and (C) low index of nuclear positivity for Ki-67. (All magnifications are ×100.)

Immunohistochemistry results show that gastric NETs are positive for general neuroendocrine markers, such as synaptophysin and chromogranin A. Additionally, all ECL cell NETs are positive for vesicular monoamine transporter 2, histidine decarboxylase and somatostatin receptor 2A (SSTR2A)[7,8]. Gastric EC cell NETs are positive for serotonin, SSTR2A and CDX2. Gastrin-producing G-cell NETs are positive for gastrin and SSTR2A. Somatostatin-producing D-cell NETs are positive for somatostatin, chromogranin A, synaptophysin and SSTR2A.

The World Health Organization uses Ki-67 and mitotic rate as criteria for grading NETs to evaluate the aggressiveness of neoplasms. The grading system is summarized in Table 1[9]. It is recommended to review 50 high-power fields for the mitotic count and at least 500 cells for the Ki-67 labeling index from hot spots for more accurate grading[7]. The World Health Organization classification system continues to be the most important prognostic tool.

Table 1: World Health Organization grading of well-differentiated NETs.

Grade	Mitotic count (per 10 HPFs)	Ki-67
Grade 1	Less than 2	Less than 3%
Grade 2	2-20	3-20%
Grade 3	More than 20	More than 20%

HPFs: High-power fields; NET: neuroendocrine tumor

CONCLUSION

NETs are rare, particularly in the stomach. The present case highlights the importance of preoperative endoscopic examination and biopsy of any suspicious areas in the gastric mucosa, especially in obese patients who wish to undergo bariatric procedures. Postoperative pathological examination should be mandatory and precise for all sleeve gastrectomy specimens, as incidental findings can be expected.

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Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

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Management of hyperkalemia: Expert consensus from Kuwait - a Modified Delphi Approach

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INTRODUCTION

Hyperkalemia is common in heart failure (HF) patients on renin angiotensin aldosterone inhibitors (RAASi), in chronic kidney disease (CKD), and in hemodialysis, and it negatively impacts their management. New potassium binders, such as sodium zirconium cyclosilicate (SZC), are effective in management of acute and chronic hyperkalemia. However, guidelines inconsistencies and lack of standardized treatment protocols are hindering proper and wider use of such agents. Therefore, an expert panel from Kuwait developed a consensus statement to address hyperkalemia management in acute settings, in HF, in CKD, and in hemodialysis.

METHODS

A three-step modified Delphi method was adopted to develop the present consensus, which consisted of two rounds of voting and in-between a virtual meeting. Twelve experts from Kuwait participated in this consensus. Statements were developed and shared with experts for voting. A meeting was held to discuss statements that did not reach consensus at the first round and then the remaining statements were shared for final voting.

RESULTS

The consensus consists of 44 statements involving an introduction to and the management of hyperkalemia in acute settings, HF, CKD, and hemodialysis. Thirty-six statements approved unanimously in the first vote. In the second vote, four statements were removed and four were approved after editing.

CONCLUSION

Hyperkalemia management lacks standardized definitions, treatment thresholds and consistent guidelines and laboratory practices. This consensus is in response to lack of standardized treatment in the Arabian Gulf, and it aims to establish guidance on hyperkalemia management for healthcare practitioners in Kuwait and highlight future needs.

ADAM9 Genetic Variants and Their Role in Modulating Enzyme Activity in Diabetes and Metabolic Traits

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A disintegrin and metalloproteinase Domain 9 (ADAM9) is a zinc-dependent proteinase involved in various biological processes. However, its role in the pathophysiology of metabolic syndrome remains unclear, and studies exploring the association between ADAM9 polymorphisms and metabolic traits are limited. In this study, we investigated the potential link between ADAM9 variants and metabolic syndrome traits in a cohort of adult participants from Kuwait. Using a genome-wide association study (GWAS), followed by a replication study, we identified two ADAM9 variants-ADAM9-E76K (rs61753672) and ADAM9-P750L (rs144750648)-that were associated with various metabolic traits. The replication phase confirmed the association of ADAM9-P750L with HbA1c levels and revealed new associations with systolic blood pressure, waist-to-hip ratio, fasting blood glucose, triglycerides, and cholesterol. Functional analysis showed that both variants exhibited reduced proteolytic activity, potentially contributing to the pathogenesis of Type 2 diabetes. These findings suggest that ADAM9 variants may play a significant role in metabolic health and diabetes risk.

Ropivacaine Local Infiltration for Pain Control After Thyroidectomy: A Systematic Review and Meta-Analysis

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OBJECTIVE
To evaluate the analgesic role of ropivacaine local infiltration in patients undergoing thyroidectomy.

DATA SOURCES
PubMed, Google Scholar, CENTRAL, Scopus, and Web of Science.

REVIEW METHODS
A systematic review and meta-analysis synthesizing evidence from randomized controlled trials (RCTs). Our specific endpoints include pain severity, total opioid analgesia consumption, patient satisfaction, length of hospital stay, postanesthesia care unit (PACU) length of stay, surgery duration, and the incidence of postoperative nausea and vomiting (PONV). Using Stata, we pooled dichotomous outcomes and continuous outcomes using risk ratio (RR) and standardized mean difference (SMD) or mean difference (MD), respectively, with a 95% confidence interval (CI).

RESULTS
Eight RCTs and 633 patients were included. Ropivacaine significantly decreased pain after 1 to 2 hours postoperatively (SMD: -1.40, 95% CI [-2.30, -0.51]). However, there was no difference between both groups after 4 hours (*P* = .11), 6 to 8 hours (*P* = .05), 16 to 18 hours (*P* = .10), and 24 hours (*P* = .37). Also, ropivacaine significantly decreased analgesia consumption (SMD: -0.75, 95% CI [-1.30, -0.20]), with no effect on surgery duration (*P* = .59), length of hospital stays (*P* = .32), patient satisfaction score (*P* = .25), and PACU length of stay (*P* = .25). Finally, there was no difference between both groups regarding the incidence of PONV (RR: 1.01, 95% CI [0.70, 1.45]).

CONCLUSION
Ropivacaine local infiltration after thyroidectomy significantly decreased pain for up to 1 to 2 hours and analgesia consumption compared to control, but with uncertain evidence. However, ropivacaine had no effect on pain from 4 to 24 hours, surgery duration, length of PACU stay, length of hospital stay, and patient satisfaction.

Haploidentical stem cell transplantation in DOCK8 deficiency: a case report of successful outcomes

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[3]Pediatric Department, College of Medicine, Kuwait University, Kuwait City, Kuwait.

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DOCK8 deficiency syndrome, formerly known as autosomal recessive hyper-IgE syndrome (AR-HIES), is a rare combined immunodeficiency disorder characterized by recurrent infections, eczema, eosinophilia, and elevated immunoglobulin E (IgE) levels. We present a case of a 6-year-old girl with DOCK8 deficiency syndrome, who experienced recurrent skin infections and molluscum contagiosum since infancy. Genetic testing confirmed the diagnosis. Due to the high morbidity and mortality associated with DOCK8 deficiency syndrome, she underwent hematopoietic stem cell transplantation (HSCT) from her father. Posttransplant, the patient's skin condition significantly improved, and she achieved full donor chimerism. This case highlights the importance of considering DOCK8 deficiency in patients with recurrent infections, eczema, eosinophilia, and high IgE levels, and the potential curative effect of HSCT for these patients.

Forthcoming Conferences and Meetings

Compiled and edited by
Vineetha Elizabeth Mammen

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International Conference on **Nano science and Nanotechnology**
Jun 01, 2025
Italy, Genoa
Organized by: Conference Fora
Conference inquiry email: info@conferencefora.org

International Conference on **Infectious Diseases and Cancer Research Treatments**
Jun 01, 2025
United States, New York
Organized by: Society for Engineering and Research
Conference inquiry email: sfer.conference@gmail.com

Annual Meeting on **Dentistry, Endodontics and Hypnodontics**
Jun 01, 2025
Indonesia, Bali
Organized by: Biofora
Conference inquiry email: papers.biofora@gmail.com

International Conference on **Virology, Influenza and Infectious Diseases**
Jun 01, 2025
Greece, Athens
Organized by: Global Science Society
Conference inquiry email: info.globalsciencesociety@gmail.com

International Conference on **Cardiology and Diabetes**
Jun 02, 2025
United States, Seattle, Washington
Organized by: IARED
Conference inquiry email: info.iared.org@gmail.com

International Conference on **Neurological Disorders and Stroke Treatment**
Jun 02, 2025
Germany, Hamburg
Organized by: Conference Research Network
Conference inquiry email: info.conferenceresearchnetwork@gmail.com

International Conference on **Veterinary Oncology and Animal Cancer**
Jun 02, 2025
Spain, Barcelona
Organized by: United Research
Conference inquiry email: info.unitedresearch@gmail.com

International Conference on **Virology and Immunology**
Jun 03, 2025
Germany, Berlin
Organized by: Academics conference
Conference inquiry email: papers.academicsconference@gmail.com

International Virtual Conference on **COVID-19** and its Effect
Jun 03, 2025
United States, Philadelphia
Organized by: Conference Online
Conference inquiry email: info.conferenceonline@gmail.com

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Jun 04, 2025
Italy, Florence
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Conference inquiry email: sfer.conference@gmail.com

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Jun 04, 2025
Germany, Cologne
Organized by: Conference Research Network
Conference inquiry email: info.conferenceresearchnetwork@gmail.com

International Conference on **Radiology and Diagnostic Imaging**
Jun 04, 2025
Canada, Halifax
Organized by: Global Conference
Conference inquiry email: summit.globalconference@gmail.com

2nd Edition of International Summit on **Hematology and Blood Disorders**
Jun 05, 2025
Italy, Rome
Organized by: Conference coordinator
Conference inquiry email: hematology@magnusconference.com

International Conference on **Biodiversity, Ecology and Climate Change**
Jun 05, 2025
United States, Memphis, Tennessee
Organized by: InterGlobe Research Network
Conference inquiry email: igrnetconference@gmail.com

International Conference on **Cardiology and Cardiovascular Research**
Jun 05, 2025
India, Pune, Maharashtra
Organized by: United Research
Conference inquiry email: info.unitedresearch@gmail.com

International Conference on **Cancer Biology and Therapeutics**
Jun 05, 2025
Thailand, Phuket
Organized by: United Science Research Society
Conference inquiry email: info.usrsociety@gmail.com

International Conference on **Virology and Immunology**
Jun 07, 2025
Czech Republic, Prague
Organized by: Academics conference
Conference inquiry email: papers.academicsconference@gmail.com

International Conference on **Applied Sport Science and Physiology**
Jun 07, 2025
Brazil, Natal
Organized by: Global Science Networks
Conference inquiry email: info.globalsciencenetworks@gmail.com

International Conference on **ENT Surgery and Otorhinolaryngology**
Jun 07, 2025
Canada, Burlington
Organized by: Japanese Society for Academic Research and Publication
Conference inquiry email: info.jsarap@gmail.com

International Conference on **Psychology and Behavioral Sciences**
Jun 08, 2025
United States, Dallas, Texas
Organized by: United Science Research Society
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International Conference on **Obesity and Weight Management**
Jun 08, 2025
United Arab Emirates, Dubai
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Saudi Arabia, Khamis Mushait
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International Virtual Conference on **Vaccines and Virology**
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Spain, Palma
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International Conference on Latest Research on **Corona Virus and its Vaccine**
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India, Goa
Organized by: Research Conferences
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Saudi Arabia, Dammam
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Conference inquiry email: info.conferenceresearchnetwork@gmail.com

International Conference on **Medical, Pharmaceutical and Health Sciences**
Jun 09, 2025
Qatar, Doha
Organized by: GSRD
Conference inquiry email: info.gsrd@gmail.com

International Conference on **Vaccines and Immunization**
Jun 09, 2025
Canada, Gatineau
Organized by: Science Guru
Conference inquiry email: info.scienceguru@gmail.com

International Conference on **Urology and Nephrology**
Jun 11, 2025
Sri Lanka, Colombo
Organized by: Research Era
Conference inquiry email: info.researcheraconference@gmail.com

World Congress on **Human Genetics and Genetic Diseases**
Jun 11, 2025
Canada, Barrie
Organized by: Academic Research Network
Conference inquiry email: info.academicresearchnetwork@gmail.com

International Conference on **Psychology and Allied Sciences**
Jun 11, 2025
Australia, Melbourne
Organized by: Universal Research Cluster
Conference inquiry email: info.universalconference@gmail.com

International Conference on **Cardiology and Diabetes**
Jun 12, 2025
India, Hyderabad, Telangana
Organized by: Science Guru
Conference inquiry email: info.scienceguru@gmail.com

Global Conference on **Rheumatology and Orthopedics**
Jun 12, 2025
Romania, Constanta
Organized by: aserd.org
Conference inquiry email: info.aserd@gmail.com

International Conference on **Orthopedics, Arthroplasty and Rheumatology**
Jun 12, 2025
Qatar, Al Wakrah
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Conference inquiry email: info.unitedresearch@gmail.com

International Conference on **Medical, Healthcare and Pharmaceutical Science**
Jun 13, 2025
United Arab Emirates, Abu Dhabi
Organized by: Conference Online
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International Conference on **Behavioral and Educational Psychology**
Jun 14, 2025
Spain, Valencia
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Conference inquiry email: info.academicresearchnetwork@gmail.com

International Conference on **Behavioral and Educational Psychology**
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Qatar, Al Rayyan
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International Research Conference on **COVID-19 and its Impact on Mental Health**
Jun 15, 2025
Australia, Sydney
Organized by: Research Conferences
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International Conference on **Stem Cells and Cancer**
Jun 15, 2025
Canada, Alberta
Organized by: Research Era
Conference inquiry email: info.researcheraconference@gmail.com

International Conference on **Medical and Health Sciences**
Jun 16, 2025
Australia, Sydney
Organized by: Academics conference
Conference inquiry email: papers.academicsconference@gmail.com

International Conference on **Cardiology and Diabetes**
Jun 16, 2025
United States, Washington DC
Organized by: IARED
Conference inquiry email: info.iared.org@gmail.com

2nd International Conference on **Clinical and Medical Case Reports**
Jun 16, 2025
Italy, Rome
Organized by: Case reports
Conference inquiry email: casereports@crgconferences.org

International Conference on **Diabetes and Endocrinology**
Jun 17, 2025
South Korea, Seoul
Organized by: Diabetes world
Conference inquiry email: info.diabetesworld@gmail.com

International Conference on **Cancer Biology and Oncogenesis**
Jun 17, 2025
Maldives, Utheemu
Organized by: aserd.org
Conference inquiry email: info.aserd@gmail.com

International Conferences on Advances in **Nursing Science, Medical and Health Care**
Jun 18, 2025
United States, New Orleans, Louisiana
Organized by: Theires
Conference inquiry email: info@theires.org

International Congress on **Cell Science and Molecular Biology**
Jun 18, 2025
Georgia, Atlanta
Organized by: World Research Society
Conference inquiry email: contact@worldresearchsociety.com

International Conference on **Paediatrics and Child Health**
Jun 19, 2025
United Kingdom, Liverpool
Organized by: Global Conference
Conference inquiry email: summit.globalconference@gmail.com

International Conference on **Gastroenterology and Hepatology**
Jun 19, 2025
Germany, Wurzburg
Organized by: Society for Engineering and Research
Conference inquiry email: sfer.conference@gmail.com

International Conference on **Paediatrics and Child Health**
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South Korea, Incheon
Organized by: Society for Engineering and Research
Conference inquiry email: sfer.conference@gmail.com

International Conference on **Geriatrics and Gerontology**
Jun 20, 2025
Spain, Madrid
Organized by: Conference Research Network
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International Conference on **Forensic Dentistry and Odontology**
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United States, Guam
Organized by: Society for Engineering and Research
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International Conference on **Public Health and Healthcare Research**
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International Conference on **Women's Health and Breast Cancer**
Jun 21, 2025
Canada, British Columbia
Organized by: Science Guru
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International Conference on **Infectious Diseases and Cancer Research Treatments**
Jun 21, 2025
Russia, Novosibirsk
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Conference inquiry email: info.globalsciencesociety@gmail.com

International Virtual Conference on **Vaccines and Virology**
Jun 21, 2025
United States, Oklahoma City
Organized by: United Research
Conference inquiry email: info.unitedresearch@gmail.com

International Conference on **Central Nervous System and Neurology**
Jun 22, 2025
Belgium, Antwerp
Organized by: Conference Research Network
Conference inquiry email: info.conferenceresearchnetwork@gmail.com

International Congress on **Cell Science and Molecular Biology**
Jun 22, 2025
France, Strasbourg
Organized by: World Research Society
Conference inquiry email: contact@worldresearchsociety.com

International Conference on **Chronic Diseases and Obesity**
Jun 22, 2025
Singapore, Singapore
Organized by: Biofora
Conference inquiry email: papers.biofora@gmail.com

International Conference on **Obesity and Exercise**
Jun 22, 2025
Switzerland, Geneva
Organized by: Global Conference
Conference inquiry email: summit.globalconference@gmail.com

International Conference on Recent Trends in **General Surgery and Oncology**
Jun 23, 2025
Barbados, Oistins
Organized by: Conference Research Network
Conference inquiry email: info.conferenceresearchnetwork@gmail.com

International Conference on **Obesity, Diabetes, Metabolic Syndrome and Alternative Medicines**
Jun 23, 2025
Germany, Frankfurt
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International Conference on **Gynecologic Oncology and Critical Care**
Jun 23, 2025
Germany, Nuremberg
Organized by: Global Science Society
Conference inquiry email: info.globalsciencesociety@gmail.com

Global Conference on **Surgery and Anaesthesia**
Jun 23, 2025
France, Paris
Organized by: Surgery conference
Conference inquiry email: support@scientificiq.org

International Conference on **Nanomaterials and Biomaterials**
Jun 23, 2025
Kuwait, Al Jahra
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International Conference on **Oncology and Orthopaedic Surgery**
Jun 25, 2025
Egypt, Luxor
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International Conference on **Surgery and Surgical Nursing**
Jul 01, 2025
Jordan, Amman
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World Congress on **Women's Health Reproduction and Fertility**
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Conference inquiry email: info.aserd@gmail.com

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United Arab Emirates, Abu Dhabi
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Jul 05, 2025
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Conference inquiry email: info.unitedresearch@gmail.com

International Conference on **Allergy, Asthma, Immunology and Rheumatology**
Jul 05, 2025
Fiji, Suva
Organized by: Society for Engineering and Research
Conference inquiry email: sfer.conference@gmail.com

International Conference on **Cardiology and Cardiovascular Medicine**
Jul 05, 2025
Singapore, Singapore
Organized by: Global Conference
Conference inquiry email: summit.globalconference@gmail.com

International Conference on **Neuroscience and Psychiatry**
Jul 05, 2025
Malaysia, Sungai Petani
Organized by: Academic Research Network
Conference inquiry email: info.academicresearchnetwork@gmail.com

International Conference on **Diabetes and Cardiovascular Diseases**
Jul 06, 2025
Romania, Brasov
Organized by: Global Science Society
Conference inquiry email: info.globalsciencesociety@gmail.com

International Conference on **Cancer Biology and Therapeutics**
Jul 06, 2025
Greece, Crete
Organized by: Science Guru
Conference inquiry email: info.scienceguru@gmail.com

International Conference on **Women's Health and Breast Cancer**
Jul 07, 2025
Qatar, Doha
Organized by: United Science Research Society
Conference inquiry email: info.usrsociety@gmail.com

International Conference on **Nephrology, Urology and Therapeutics**
Jul 08, 2025
Japan, Nara
Organized by: Conference Research Network
Conference inquiry email: info.conferenceresearchnetwork@gmail.com

Annual Congress on **Clinic Thyroid and Parathyroid Disorders**
Jul 08, 2025
Netherlands, Amsterdam
Organized by: Society for Engineering and Research
Conference inquiry email: sfer.conference@gmail.com

International Conference on **Public Health and Healthcare Research**
Jul 09, 2025
United Arab Emirates, Dubai
Organized by: Universal Research Cluster
Conference inquiry email: info.universalconference@gmail.com

Global Conference on **Rheumatology and Orthopedics**
Jul 09, 2025
Qatar, Al Wakrah
Organized by: Science and research
Conference inquiry email: summit.scienceandresearch@gmail.com

International Conference on **Oncology and Orthopaedic Surgery**
Jul 09, 2025
United States, Oklahoma City, Oklahoma
Organized by: Japanese Society for Academic Research and Publication
Conference inquiry email: info.jsarap@gmail.com

International Conference on **Virology and Immunology**
Jul 10, 2025
Egypt, Cairo
Organized by: Academics conference
Conference inquiry email: papers.academicsconference@gmail.com

International Conference on **Orthopedics, Sports Medicine and Arthroscopic Surgery**
Jul 11, 2025
Germany, Cologne
Organized by: Global Science Society
Conference inquiry email: info.globalsciencesociety@gmail.com

International Conference on **Diabetes and Endocrinology**
Jul 12, 2025
Singapore, Singapore
Organized by: Diabetes world
Conference inquiry email: info.diabetesworld@gmail.com

International Conference on **Stem Cells and Cancer**
Jul 12, 2025
Hungary, Budapest
Organized by: Research Era
Conference inquiry email: info.researcheraconference@gmail.com

Global **Cardiology and Healthcare** Summit
Jul 13, 2025
Netherlands, Amsterdam
Organized by: Biofora
Conference inquiry email: papers.biofora@gmail.com

International Conference on **ENT Surgery and Otorhinolaryngology**
Jul 14, 2025
United States, Dallas, Texas
Organized by: United Science Research Society
Conference inquiry email: info.usrsociety@gmail.com

International Conference on **Health Care Reform Health Economics and Health Policy**
Jul 14, 2025
United States, Charlotte, North Carolina
Organized by: Global Science Society
Conference inquiry email: info.globalsciencesociety@gmail.com

3rd World Conference on **Pediatrics, Neonatology and Infectious Diseases**
Jul 14, 2025
United Kingdom, London, Hounslow
Organized by: CLS Events and Publications
Conference inquiry email: pediaconf@clsconf.com

International Conference on **Obesity and Weight Management**
Jul 15, 2025
United States, Oakland, California
Organized by: Global Science Networks
Conference inquiry email: info.globalsciencenetworks@gmail.com

International Conference on **Psychology and Behavioral Sciences**
Jul 15, 2025
Russia, Volgograd
Organized by: aserd.org
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International Conference on **Pediatrics, Perinatology and Child Health**
Jul 15, 2025
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Organized by: Academic Research Network
Conference inquiry email: info.academicresearchnetwork@gmail.com

Global Conference on **Orthopedic Surgery and Trauma Care**
Jul 18, 2025
Egypt, Giza
Organized by: All Conference Series
Conference inquiry email: info.allconferenceseries@gmail.com

International Conference on **Cardiology and Cardiovascular Research**
Jul 19, 2025
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Organized by: Science and research
Conference inquiry email: summit.scienceandresearch@gmail.com

International Conference on **Virology and Immunology**
Jul 19, 2025
Malaysia, Kuala Lumpur
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Conference inquiry email: papers.academicsconference@gmail.com

International Conference on **Paediatrics and Child Health**
Jul 20, 2025
Germany, Frankfurt
Organized by: Conference Research Network
Conference inquiry email: info.conferenceresearchnetwork@gmail.com

International Conference on **Cancer Research and Anticancer Therapies**
Jul 20, 2025
China, Yantai
Organized by: Conference Research Network
Conference inquiry email: info.conferenceresearchnetwork@gmail.com

International Symposium on **Triglycerides and HDL**
Jul 20, 2025
Uruguay, Montevideo
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International Conference on **ENT Surgery and Otorhinolaryngology**
Jul 21, 2025
Poland, Lublin
Organized by: Conference Research Network
Conference inquiry email: info.conferenceresearchnetwork@gmail.com

International Conference on **Medical Ethics and Professionalism**
Jul 21, 2025
Singapore, Singapore
Organized by: Science fora
Conference inquiry email: info.sciencefora@gmail.com

33rd International Congress on **Cardiology and Medical Interventions**
Jul 21, 2025
Canada, Toronto
Organized by: Annual Cardiology 2025
Conference inquiry email: annualcardiology@conferencesemail.com

International Conference on **Gastroenterology and Gastrointestinal Illness**
Jul 22, 2025
Ireland, Cork
Organized by: Conference Research Network
Conference inquiry email: info.conferenceresearchnetwork@gmail.com

International Conference on **Women Gynecology, Childbirth and Reproductive Medicine**
Jul 22, 2025
France, Toulouse
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Global Conference on **Orthopedic Surgery and Trauma Care**
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Japan, Chiba
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International Conference on **Virology and Infectious Diseases**
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Czech Republic, Olomouc
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Conference inquiry email: info.researcheraconference@gmail.com

International Conference on **Vaccines and Immunization**
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Organized by: Science Guru
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International Research Conference on **COVID-19 and its Impact on Mental Health**
Jul 26, 2025
Germany, Berlin
Organized by: Research Conferences
Conference inquiry email: info.researchconferences@gmail.com

International Video Conference on **Healthcare**
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United Arab Emirates, Dubai
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Conference inquiry email: info.conferenceonline@gmail.com

International Conference on **Urology and Renal Health**
Jul 27, 2025
South Korea, Seoul
Organized by: Science and research
Conference inquiry email: summit.scienceandresearch@gmail.com

International Conference on **Neuroscience and Psychiatry**
Jul 28, 2025
Jordan, Amman
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International Conference on **Cancer Biology and Oncogenesis**
Jul 29, 2025
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International Conference on **Virology and Immunology**
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International Conference on **Cancer Biology and Oncogenesis**
Jul 30, 2025
United Kingdom, London
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Conference inquiry email: info.aserd@gmail.com

International Conference on Recent Advances in **Physical Education, Fitness and Sports Science**
Jul 31, 2025
Saudi Arabia, Al Khobar
Organized by: Japanese Society for Academic Research and Publication
Conference inquiry email: info.jsarap@gmail.com

International Conference on **Obesity and Weight Management**
Aug 01, 2025
Italy, Genoa
Organized by: United Research
Conference inquiry email: info.unitedresearch@gmail.com

Global Conference on **Rheumatology and Orthopedics**
Aug 01, 2025
Poland, Warsaw
Organized by: United Science Research Society
Conference inquiry email: info.usrsociety@gmail.com

International Conference on **Cardiology and Diabetes**
Aug 03, 2025
France, Paris
Organized by: IARED
Conference inquiry email: info.iared.org@gmail.com

2nd International Conference on **Ophthalmology and Vision Science**
Aug 04, 2025
United States, Boston
Organized by: Scitech series
Conference inquiry email: ophthalmology@scitechconference.com

World Congress on **Mental Health**
Aug 05, 2025
Kuwait, Kuwait City
Organized by: Universal Research Cluster
Conference inquiry email: info.universalconference@gmail.com

International Conference on **Cancer Biology and Oncogenesis**
Aug 07, 2025
United Arab Emirates, Abu Dhabi
Organized by: United Science Research Society
Conference inquiry email: info.usrsociety@gmail.com

International Conference on **Epidemiology and Public Health**
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Netherlands, The Hague
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Conference inquiry email: info.scienceguru@gmail.com

International Conference on **Pediatrics, Perinatology and Child Health**
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Canada, Ottawa
Organized by: All Conference Series
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International Conference on **Gynecology, Obstetrics and Infertility**
Aug 10, 2025
South Africa, Soweto
Organized by: Research Era
Conference inquiry email: info.researcheraconference@gmail.com

International Conference on **Mental Health and Psychiatry**
Aug 11, 2025
United States, Tucson, Arizona
Organized by: aserd.org
Conference inquiry email: info.aserd@gmail.com

International Conference on **Veterinary and Clinical Pathology**
Aug 13, 2025
United Arab Emirates, Abu Dhabi
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International Conference on **Psychology and Allied Sciences**
Aug 14, 2025
Bahrain, Hamad Town
Organized by: Universal Research Cluster
Conference inquiry email: info.universalconference@gmail.com

World Conference on **Pharma Industry and Medical Devices**
Aug 15, 2025
United Arab Emirates, Sharjah
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Conference inquiry email: info.ifearpworld@gmail.com

International Conference on **Oncology and Orthopaedic Surgery**
Aug 18, 2025
Bahamas, Nassau
Organized by: Japanese Society for Academic Research and Publication
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International Conference on **Virology and Immunology**
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International Conference on **Neurology and Neuro Disorders**
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United Kingdom, Bristol
Organized by: Japanese Society for Academic Research and Publication
Conference inquiry email: info.jsarap@gmail.com

International Conference on Latest Research on **Corona Virus and its Vaccine**
Aug 20, 2025
Japan, Tokyo
Organized by: Research Conferences
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International Conference on **Psychology and the Behavioral Sciences**
Aug 20, 2025
Singapore, Singapore
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Conference inquiry email: info.universalconference@gmail.com

International Congress on **Physical Activity and Public Health**
Aug 21, 2025
South Korea, Incheon
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International Conference on **Cancer Biology and Therapeutics**
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Hungary, Nyiregyhaza
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International Conference on Latest Research on **Corona Virus and its Vaccine**
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Australia, Melbourne
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International Conference on **Cancer Biology and Therapeutics**
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Argentina, La Plata
Organized by: aserd.org
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International Conference on **Cancer Biology and Oncogenesis**
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United Kingdom, Liverpool
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International Conference on **Sport Science and Disability**
Aug 22, 2025
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International Conference on **Pediatrics and Healthcare**
Aug 23, 2025
United Arab Emirates, Dubai
Organized by: United Research
Conference inquiry email: info.unitedresearch@gmail.com

International Conference on **Disability and Diversity**
Aug 24, 2025
Denmark, Copenhagen
Organized by: United Research
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International Conference on Latest Research on **Corona Virus and its Vaccine**
Aug 25, 2025
Italy, Rome
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International Conference on **Cardiology and Diabetes**
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International Conference on **Urology and Nephrology**
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Canada, Alberta
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International Conference on **Neurology and Brain Disorders**
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Japan, Kagoshima
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International Conference on **Diabetes and Nutrition**
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Organized by: Diabetes world
Conference inquiry email: info.diabetesworld@gmail.com

International Conference on **Medical and Health Sciences**
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International Conference on **Veterinary Pathology and Management**
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Australia, Sydney
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International Conference on **Cardiology and Diabetes**
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Hungary, Budapest
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International Conference on **Healthcare and Clinical Gerontology**
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International Conference on **Diabetes and Endocrinology**
Sep 20, 2025
Japan, Tokyo
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Qatar, Doha
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Organized by: Universal Research Cluster
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United Arab Emirates, Dubai
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Sep 28, 2025
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International Conference on **Urology and Nephrology**
Sep 28, 2025
Italy, Bologna
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Sep 29, 2025
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Sep 29, 2025
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Organized by: Research Conferences
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International Conference on **Medical, Healthcare and Pharmaceutical Science**
Oct 03, 2025
United States, Philadelphia, Pennsylvania
Organized by: Conference Online
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2nd World Congress on **COPD and Pulmonary Diseases**
Oct 09, 2025
United States, Philadelphia
Organized by: Conference coordinator
Conference inquiry email: Pulmonology@scitechconference.com

Dermatology and Plastic Surgery World Conference 2025
Oct 19, 2025
France, Paris
Organized by: Conference coordinator
Conference inquiry email: info@precisionglobalconferences.com

Hematology and Blood Disorders
Oct 20, 2025
United Arab Emirates, Dubai
Organized by: Sci synopsis conferences
Conference inquiry email: hematology@speakersmeetings.com

International Conference on **Chronic Diseases and Obesity**
Oct 22, 2025
Hong Kong, Hong Kong
Organized by: Biofora
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WHO-Facts Sheet

1. Burns
2. Endometriosis
3. Leishmaniasis
4. Pneumonia in children
5. Tetanus

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1. Burns

KEY FACTS

- An estimated 180 000 deaths every year are caused by burns. The vast majority occur in low- and middle-income countries.
- Non-fatal burn injuries are a leading cause of morbidity.
- Burns occur mainly in the home and workplace.
- Burns are preventable.

Overview

A burn is an injury to the skin or other organic tissue primarily caused by heat or due to radiation, radioactivity, electricity, friction or contact with chemicals.

Thermal (heat) burns occur when some or all the cells in the skin or other tissues are destroyed by:

- hot liquids (scalds)
- hot solids (contact burns)
- flames (flame burns).

The problem

Burns are a global public health problem, accounting for an estimated 180 000 deaths annually. The majority of these occur in low- and middle-income countries and almost two thirds occur in the WHO African and South-East Asia Regions.

In many high-income countries, burn death rates have been decreasing, and the rate of child deaths from burns is currently over 7 times higher in low- and middle-income countries than in high-income countries.

Non-fatal burns are a leading cause of morbidity, including prolonged hospitalization, disfigurement and disability, often with resulting stigma and rejection.

- Burns are among the leading causes of disability-adjusted life-years (DALYs) lost in low- and middle-income countries.
- Hospitalization for burns varies by country and is influenced by health service payment programmes, but among countries studied hospitalization trends are going towards shorter stays and an increased proportion of burns being treated in specialized burn centres *(1).*

Some country data

- In India, over 1 million people are moderately or severely burnt every year.
- Nearly 173 000 Bangladeshi children are moderately or severely burnt every year.
- In Bangladesh, Colombia, Egypt and Pakistan, 17% of children with burns have a temporary disability and 18% have a permanent disability.
- Burns are the second most common injury in rural Nepal, accounting for 5% of disabilities.
- In 2008, over 410 000 burn injuries occurred in the United States of America, with approximately 40 000 requiring hospitalization.

Economic impact

Direct care costs for burns vary widely but tend towards being generally expensive with a 2014 systematic review finding a mean total healthcare cost per burn patient of US$ 88 218 (range US$ 704–717 306).

In South Africa an estimated US$ 26 million is spent annually for care of burns from kerosene (paraffin) cookstove incidents. Indirect costs such as lost wages, prolonged care for deformities and emotional trauma, and commitment of family resources, also contribute to the socioeconomic impact.

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Who is at risk?

Gender

Females have slightly higher rates of death from burns compared to males according to the most recent data. This contrasts with the usual injury pattern, where rates of injury for the various injury mechanisms tend to be higher in males than females.

The higher risk for females is associated with open fire cooking, or inherently unsafe cookstoves, which can ignite loose clothing. Open flames used for heating and lighting also pose risks, and self-directed or interpersonal violence are also factors (although understudied).

Age

Along with adult women, children are particularly vulnerable to burns. Burns are the fifth most common cause of non-fatal childhood injuries. While a major risk is improper adult supervision, a considerable number of burn injuries in children result from child maltreatment.

Regional factors

There are important regional differences in burn rates.

- Children under 5 years of age in the WHO African Region have over 2 times the incidence of burn deaths than children under 5 years of age worldwide.
- Boys under 5 years of age living in low- and middle-income countries of the WHO Eastern Mediterranean Region are almost 2 times as likely to die from burns as boys living in the WHO European Region.
- The incidence of burn injuries requiring medical care is nearly 20 times higher in the WHO Western Pacific Region than in the WHO Region of the Americas.

Socioeconomic factors

People living in low- and middle-income countries are at higher risk for burns than people living in high-income countries. Within all countries however, burn risk correlates with socioeconomic status.

Other risk factors

There are a number of other risk factors for burns, including:

- occupations that increase exposure to fire;
- poverty, overcrowding and lack of proper safety measures;
- placement of young girls in household roles such as cooking and care of small children;
- underlying medical conditions, including epilepsy, peripheral neuropathy, and physical and cognitive disabilities;
- alcohol abuse and smoking;
- easy access to chemicals used for assault (such as in acid violence attacks);
- use of kerosene (paraffin) as a fuel source for non-electric domestic appliances; and
- inadequate safety measures for liquefied petroleum gas and electricity.

In which settings do burns occur?

Burns occur mainly in the home and workplace. Community surveys in Bangladesh and Ethiopia show that 80–90% of burns occur at home. Children and women are usually burned in domestic kitchens, from upset receptacles containing hot liquids or flames, or from cookstove explosions. Men are most likely to be burned in the workplace due to fire, scalds, chemical and electrical burns.

Prevention

Burns are preventable. High-income countries have made considerable progress in lowering rates of burn deaths, through a combination of prevention strategies and improvements in the care of people affected by burns. Most of these advances in prevention and care have been incompletely applied in low- and middle-income countries. Increased efforts to do so would likely lead to significant reductions in rates of burn-related death and disability.

Prevention strategies should address the hazards for specific burn injuries, education for vulnerable populations and training of communities in first aid. An effective burn prevention plan should be multisectoral and include broad efforts to:

- improve awareness
- develop and enforce effective policy
- describe burden and identify risk factors
- set research priorities with promotion of promising interventions
- provide burn prevention programmes
- strengthen burn care
- strengthen capacities to carry out all the above.

The document A WHO plan for burn prevention and care discusses these 7 components in detail.

In addition, there are several specific recommendations for individuals, communities and public health officials to reduce burn risk.

- Enclose fires and limit the height of open flames in domestic environments.
- Promote safer cookstoves and less hazardous fuels and educate regarding loose clothing.
- Apply safety regulations to housing designs and materials and encourage home inspections.
- Improve the design of cookstoves, particularly

with regard to stability and prevention of access by children.
- Lower the temperature in hot water taps.
- Promote fire safety education and the use of smoke detectors, fire sprinklers and fire-escape systems in homes.
- Promote the introduction of and compliance with industrial safety regulations, and the use of fire-retardant fabrics for children's sleepwear.
- Avoid smoking in bed and encourage the use of child-resistant lighters.
- Promote legislation mandating the production of fire-safe cigarettes.
- Improve treatment of epilepsy, particularly in developing countries.
- Encourage further development of burn-care systems, including the training of health-care providers in the appropriate triage and management of people with burns.
- Support the development and distribution of fire-retardant aprons to be used while cooking around an open flame or kerosene stove.

First aid

Basic guidance on first aid for burns is provided below.

What to do
- Stop the burning process by removing clothing and irrigating the burns.
- Extinguish flames by allowing the patient to roll on the ground, or by applying a blanket, or by using water or other fire-extinguishing liquids.
- Use cool running water to reduce the temperature of the burn.
- In chemical burns, remove or dilute the chemical agent by irrigating with large volumes of water.
- Wrap the patient in a clean cloth or sheet and transport to the nearest appropriate facility for medical care.

What not to do
- Do not start first aid before ensuring your own safety (switch off electrical current, wear gloves for chemicals etc.)
- Do not apply paste, oil, haldi (turmeric) or raw cotton to the burn.
- Do not apply ice because it deepens the injury.
- Avoid prolonged cooling with water because it will lead to hypothermia.
- Do not open blisters until topical antimicrobials can be applied, such as by a health-care provider.
- Do not apply any material directly to the wound as it might become infected.
- Avoid application of topical medication until the patient has been placed under appropriate medical care.

WHO response

WHO is promoting interventions that have been shown to be successful in reducing the incidence of burns.

The Organization is also supporting the development and use of a global burn registry for globally harmonized data collection on burns and increased collaboration between global and national networks to increase the number of effective programmes for burn prevention.

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2. Endometriosis

KEY FACTS
- Endometriosis affects roughly 10% (190 million) of reproductive age women and girls globally.
- It is a chronic disease associated with severe, life-impacting pain during periods, sexual intercourse, bowel movements and/or urination, chronic pelvic pain, abdominal bloating, nausea, fatigue, and sometimes depression, anxiety, and infertility.
- There is currently no known cure for endometriosis and treatment is usually aimed at controlling symptoms.
- Access to early diagnosis and effective treatment of endometriosis is important, but is limited in many settings, including in low- and middle-income countries.

Overview

Endometriosis is a disease in which tissue similar to the lining of the uterus grows outside the uterus. It can cause severe pain in the pelvis and make it harder to get pregnant.

Endometriosis can start at a person's first menstrual period and last until menopause. With endometriosis, tissue similar to the lining of the uterus grows outside the uterus. This leads to inflammation and scar tissue forming in the pelvic region and (rarely) elsewhere in the body. The cause of endometriosis is unknown. There is no known way to prevent endometriosis. There is no cure, but its symptoms can be treated with medicines or, in some cases, surgery.

It causes a chronic inflammatory reaction that may result in the formation of scar tissue (adhesions, fibrosis) within the pelvis and other parts of the body. Several lesion types have been described:

- superficial endometriosis found mainly on the pelvic peritoneum
- cystic ovarian endometriosis (endometrioma) found in the ovaries
- deep endometriosis found in the recto-vaginal septum, bladder, and bowel
- in rare cases, endometriosis has also been found outside the pelvis.

Symptoms

Endometriosis often causes severe pain in the pelvis, especially during menstrual periods. Some people also have pain during sex or when using the bathroom. Some people have trouble getting pregnant.

Some people with endometriosis don't have any symptoms. For those who do, a common symptom is pain in the lower part of the belly (pelvis). Pain may be most noticeable:

- during a period
- during or after sex
- when urinating or defecating.

Some people also experience:

- chronic pelvic pain
- heavy bleeding during periods or between periods
- trouble getting pregnant
- bloating or nausea
- fatigue
- depression or anxiety.

Symptoms often improve after menopause, but not always.

Endometriosis symptoms are variable and broad, meaning that healthcare workers may not easily diagnose it. Individuals with symptoms may not be aware of the condition.

Causes

Endometriosis is a complex disease that affects many women globally from the onset of their first period (menarche) through menopause, regardless of ethnic origin or social status. Many different factors are thought to contribute to its development. At present endometriosis is thought to arise due to:

- Retrograde menstruation is when menstrual blood containing endometrial cells flows back through the fallopian tubes and into the pelvic cavity at the time that blood is flowing out of the body through the cervix and vagina during periods. Retrograde menstruation can result in endometrial-like cells being deposited outside the uterus where they can implant and grow.
- Cellular metaplasia is when cells change from one form to another. Cells outside the uterus change into endometrial-like cells and start to grow.
- Stem cells can give rise to the disease, which then spreads through the body via blood and lymphatic vessels.

Other factors may also contribute to the growth or persistence of ectopic endometrial tissue. For example, endometriosis is known to be dependent on estrogen, which increases the inflammation, growth and pain associated with the disease. However, the relationship between estrogen and endometriosis is complex since the absence of estrogen does not always mean the absence of endometriosis.

Impact

Endometriosis has significant social, public health and economic implications. It can decrease quality of life due to severe pain, fatigue, depression, anxiety and infertility. Some individuals with endometriosis experience debilitating pain that prevents them from going to work or school. Painful sex due to endometriosis can lead to interruption or avoidance of intercourse and affect the sexual health of affected individuals and their partners. Addressing endometriosis will empower those affected by it by supporting their human right to the highest standard of sexual and reproductive health, quality of life and overall well-being.

Prevention

At present, there is no known way to prevent endometriosis. Enhanced awareness, followed by early diagnosis and management may slow or halt the natural progression of the disease and reduce the long-term burden of its symptoms, including possibly the risk of central nervous system pain sensitization. Currently there is no cure.

Diagnosis

A careful history of menstrual symptoms and chronic pelvic pain provides the basis for suspecting endometriosis. Although several screening tools and tests have been proposed and tested, none are currently validated to accurately identify or predict individuals or populations that are most likely to have the disease. Endometriosis can often present symptoms that mimic other conditions and contribute to a diagnostic delay. Ovarian endometrioma, adhesions and deep nodular forms of disease often require ultrasonography or magnetic resonance imaging (MRI) to detect. Histologic verification, usually following surgical/laparoscopic visualization, can be useful in confirming diagnosis, particularly for the most common superficial lesions. The need for histologic/laparoscopic confirmation should not prevent the commencement of empirical medical treatment.

Treatment

Treatments to manage endometriosis can vary based on the severity of symptoms and whether pregnancy is desired. No treatments cure the disease. A range of medications can help manage endometriosis and its symptoms.

Non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics (painkillers) like ibuprofen and naproxen are often used to treat pain.

Hormonal medicines like GnRH-analogues and contraceptive (birth control) methods can also help control pain. These methods include:

- pills
- hormonal intrauterine devices (IUDs)
- vaginal rings
- implants
- injections
- patches.

These methods may not be suitable for those wanting to get pregnant. Fertility medicines and procedures are sometimes used for those having difficulty getting pregnant because of endometriosis. Surgery is sometimes used to remove endometriosis lesions, adhesions and scar tissues. Laparoscopic surgery (using a small camera to visualize inside the body) allows doctors to keep incisions small.

Discuss your treatment options with a health care provider. Treatments are based on individual preferences and effectiveness, side effects, long-term safety, costs and availability. Raising awareness can help people to be diagnosed early. Early treatment can slow or halt the natural progression of the disease and reduce the long-term symptoms. In addition to talking to their doctor, people may find additional advice and emotional assistance in local patient support groups.

Some treatments are associated with side effects, and endometriosis-related symptoms can sometimes reappear after therapy ends. The choice of treatment depends on effectiveness in the individual, adverse side effects, long-term safety, costs, and availability. Most current hormonal management is not suitable for persons suffering from endometriosis who wish to get pregnant, since they affect ovulation.

Success in reducing pain symptoms and increasing pregnancy rates through surgery are often dependent on the extent of disease. In addition, lesions may recur even after successful eradication, and pelvic floor muscle abnormalities can contribute to chronic pelvic pain. Secondary changes of the pelvis, including the pelvic floor, and central sensitization may benefit from physiotherapy and complementary treatments in some patients. Treatment options for infertility due to endometriosis include laparoscopic surgical removal of endometriosis, ovarian stimulation with intrauterine insemination (IUI), and in vitro fertilization (IVF), but success rates vary.

Challenges and priorities

In many countries, the general public and most front-line healthcare providers are not aware that distressing and life-altering pelvic pain is not normal, leading to a normalization and stigmatization of symptoms and significant diagnostic delay. Patients who could benefit from medical symptomatic management are not always provided with treatments due to limited awareness of endometriosis among primary healthcare providers. Due to diagnostic delays, prompt access to available treatment methods, including non-steroidal analgesics (painkillers), oral contraceptives and progestin-based contraceptives is often not achieved. Due to limited capacity of health systems in many countries, access to specialized surgery for those who need it is sub-optimal. In addition, and especially in low and middle-income countries, there is a lack of multi-disciplinary teams with the wide range of skills and equipment needed for the early diagnosis and effective treatment of endometriosis. Although primary health care professionals should play a role in screening and basic management of endometriosis, tools to screen and accurately predict patients and populations who are most likely to have the disease are lacking. In addition, many knowledge gaps exist, and there is need for non-invasive diagnostic methods as well as medical treatments that do not prevent pregnancy.

Addressing these issues is the current focus of endometriosis response.

WHO response

The World Health Organization recognizes the importance of endometriosis and its impact on people's sexual and reproductive health, quality of life and overall well-being. WHO aims to stimulate and support the adoption of effective policies and interventions to address endometriosis globally, especially in low and middle-income countries. WHO is partnering with multiple stakeholders, including academic institutions, non-state actors and other organizations that are actively involved in research to identify effective models of endometriosis prevention, diagnosis, treatment, and care. WHO recognizes the importance of advocating for increased awareness, policies and services for endometriosis, and collaborates with civil society and endometriosis patient support groups in this regard. WHO is also collaborating with relevant stakeholders to facilitate

and support the collection and analysis of country- and region-specific endometriosis prevalence data for decision making.

3. Leishmaniasis

Key facts

- There are 3 main forms of leishmaniases: visceral (the most serious form because it is almost always fatal without treatment), cutaneous (the most common, usually causing skin ulcers), and mucocutaneous (affecting mouth, nose and throat).
- Leishmaniasis is caused by protozoan parasites which are transmitted by the bite of infected female phlebotomine sandflies.
- The disease affects some of the world's poorest people and is associated with malnutrition, population displacement, poor housing, a weak immune system and lack of financial resources.
- An estimated 700 000 to 1 million new cases occur annually.
- Only a small fraction of those infected by parasites causing leishmaniasis will eventually develop the disease.

Overview

Leishmaniasis is caused by a protozoa parasite from over 20 *Leishmania* species. Over 90 sandfly species are known to transmit *Leishmania* parasites. There are 3 main forms of the disease:

- **Visceral leishmaniasis** (VL), also known as kala-azar, is fatal if left untreated in over %95 of cases. It is characterized by irregular bouts of fever, weight loss, enlargement of the spleen and liver, and anaemia. Most cases occur in Brazil, east Africa and India. An estimated 50 000 to 90 000 new cases of VL occur worldwide annually, with only 25–45% reported to WHO. It has outbreak and mortality potential.
- **Cutaneous leishmaniasis** (CL) is the most common form and causes skin lesions, mainly ulcers, on exposed parts of the body. These can leave life-long scars and cause serious disability or stigma. About 95% of CL cases occur in the Americas, the Mediterranean basin, the Middle East and central Asia. It is estimated that 600 000 to 1 million new cases occur worldwide annually but only around 200 000 are reported to WHO.
- **Mucocutaneous leishmaniasis** leads to partial or total destruction of mucous membranes of the nose, mouth and throat. Over 90% of mucocutaneous leishmaniasis cases occur in Bolivia (the Plurinational State of), Brazil, Ethiopia and Peru.

Transmission

Leishmania parasites are transmitted through the bites of infected female phlebotomine sandflies, which feed on blood to produce eggs. Some 70 animal species, including humans, can be the source of *Leishmania* parasites.

WHO regional specificities

WHO African Region

Cutaneous Leishmaniasis is highly endemic in Algeria whereas in west Africa the epidemiological information is scarce. In east Africa all forms are endemic with outbreaks of visceral leishmaniasis occurring frequently.

WHO Region of the Americas

Cutaneous leishmaniasis is the main form and the epidemiology is complex, with several animals being the source of the parasite, and numerous types of sandflies and multiple *Leishmania* species in the same geographical area. Brazil is the main country endemic for VL in that region.

WHO Eastern Mediterranean Region

This region accounts for 80% of the cutaneous leishmaniasis cases reported worldwide. Visceral leishmaniasis is highly endemic in Iraq, Somalia, Sudan and Yemen.

WHO European Region

Cutaneous and visceral leishmaniasis are endemic. Imported cases are common, coming mainly from Africa and the Americas.

WHO South-East Asia Region

Visceral leishmaniasis is the main form of the disease, which is also endemic for cutaneous leishmaniasis.

Post-kala-azar dermal leishmaniasis (PKDL)

Post-kala-azar dermal leishmaniasis (PKDL) is usually a sequel of visceral leishmaniasis that appears as macular, papular or nodular rash usually on face, upper arms and trunk. It occurs in east Africa (mainly in Sudan) and on the Indian subcontinent, where 5–10% of patients with kala-azar are reported to develop the condition. Although uncommon, it has also been reported from Brazil and also in HIV coinfected VL cases caused by *L. infantum*. It usually appears 6 months to 1 or more years after kala-azar has apparently been cured but can occur earlier. People with PKDL are considered a potential source of *Leishmania* infection.

Leishmania-HIV co-infection

People living with HIV and who are infected with leishmaniasis have high chances of developing the full-blown disease, high relapse and mortality rates. Antiretroviral treatment reduces the development of the disease, delays relapses and increases the survival. As of 2021, *Leishmania*-HIV coinfection has been reported from 45 countries. High coinfection rates are reported from Brazil, Ethiopia and the state of Bihar (India). In 2022, WHO published new treatment recommendations for *Leishmania*-HIV coinfected patients in east Africa and South-East Asia.

Major risk factors

Socioeconomic conditions

Poverty increases the risk for leishmaniasis. Poor housing and domestic sanitary conditions (lack of waste management or open sewerage) may increase sandfly breeding and resting sites, as well as their access to humans. Sandflies are attracted to crowded housing because it is easier to bite people and feed on their blood. Human behaviour, such as sleeping outside or on the ground, may increase risk.

Malnutrition

Diets lacking protein-energy, iron, vitamin A and zinc increase the risk that an infection will progress to a full-blown disease.

Population mobility

Epidemics of leishmaniasis often occur when many people who are not immune move into areas where the transmission is high.

Environmental and climate changes

The incidence of leishmaniasis can be affected by changes in urbanization, deforestation or the human incursion into forested areas.

Climate change is affecting the spread of leishmaniasis though changes in temperature and rainfall, which affect the size and geographic distribution of sandfly populations. Drought, famine and flood also cause migration of people into areas where the transmission of the parasite is high.

Diagnosis and treatment

People suspected of suffering from visceral leishmaniasis should seek medical care immediately. In visceral leishmaniasis, diagnosis is made by combining clinical signs with parasitological or serological tests (such as rapid diagnostic tests). In cutaneous and mucocutaneous leishmaniasis serological tests have limited value and clinical manifestation with parasitological tests confirms the diagnosis.

The treatment of leishmaniasis depends on several factors including type of disease, concomitant pathologies, parasite species and geographic location. Leishmaniasis is a treatable and curable disease, which requires an immunocompetent system because medicines will not get rid of the parasite from the body, thus the risk of relapse if immunosuppression occurs. All patients diagnosed with visceral leishmaniasis require prompt and complete treatment. Detailed information on the treatment is available in the WHO technical report series 949, Control of leishmaniasis and the latest guidelines published on HIV-VL in east Africa and South-East Asia and the guideline for the treatment of leishmaniasis in the Americas.

Prevention and control

Preventing and controlling the spread of leishmaniasis is complex and requires many tools. Key strategies include:

- **Early diagnosis and effective prompt treatment** reduce the prevalence of the disease and prevents disabilities and death. It helps to reduce transmission and to monitor the spread and burden of disease. There are highly effective and safe anti-leishmanial medicines particularly for visceral leishmaniasis, although they can be difficult to use. Access to medicines has significantly improved thanks to a WHO-negotiated price scheme and a medicine donation programme through WHO.
- **Vector control** helps to reduce or interrupt transmission of disease by decreasing the number of sandflies. Control methods include insecticide spray, use of insecticide-treated nets, environmental management and personal protection.
- **Effective disease surveillance** is important to promptly monitor and act during epidemics and situations with high case fatality rates under treatment.
- **Control of animal reservoir hosts** is complex and should be tailored to the local situation.
- **Social mobilization and strengthening partnerships** – mobilization and education of the community with effective behavioural change interventions must always be locally adapted. Partnership and collaboration with various stakeholders and other vector-borne disease control programmes is critical.

WHO response

WHO's work on leishmaniasis control involves:

- supporting national leishmaniasis control programmes technically and financially to update guidelines, ensure access to quality-assured medicines, design disease control plans, surveillance systems, and epidemic preparedness and response systems;

- monitoring disease trends and assessing the impact of control activities through the web-based global surveillance system which will allow for raising awareness and advocacy on the global burden of leishmaniasis and promoting equitable access to health services;
- developing evidence-based policy strategies and standards for leishmaniasis prevention and control, including capacity building such as online courses at Neglected Tropical Diseases (openwho.org);
- strengthening collaboration and coordination among partners and stakeholders;
- promoting research including safe, effective and affordable medicines, as well as diagnostic tools and vaccines; and
- supporting the South-East Asia Region, the only one with an initiative for the elimination of visceral leishmaniasis as a public health problem through 2022–2026, defined as less than one case per 10 000 inhabitants at the district level in Nepal and subdistrict level in Bangladesh and India. As per NTD road map 2023 milestone, only one country has been validated for elimination as public health problem. The region launched Regional strategic framework for accelerating and sustaining elimination of kala-azar in the South-East Asia Region 2022–2026.

4. Pneumonia in children

Key facts

- Pneumonia accounts for 14% of all deaths of children under 5 years old, killing 740 180 children in 2019.
- Pneumonia can be caused by viruses, bacteria or fungi.
- Pneumonia can be prevented by immunization, adequate nutrition, and by addressing environmental factors.
- Pneumonia caused by bacteria can be treated with antibiotics, but only one third of children with pneumonia receive the antibiotics they need.

Overview

Pneumonia is a form of acute respiratory infection that affects the lungs. The lungs are made up of small sacs called alveoli, which fill with air when a healthy person breathes. When an individual has pneumonia, the alveoli are filled with pus and fluid, which makes breathing painful and limits oxygen intake.

Pneumonia is the single largest infectious cause of death in children worldwide. Pneumonia killed 740 180 children under the age of 5 in 2019, accounting for 14% of all deaths of children under 5 years old but 22% of all deaths in children aged 1 to 5 years. Pneumonia affects children and families everywhere, but deaths are highest in southern Asia and sub-Saharan Africa. Children can be protected from pneumonia, it can be prevented with simple interventions, and it can be treated with low-cost, low-tech medication and care.

Causes

Pneumonia is caused by several infectious agents, including viruses, bacteria and fungi. The most common are the following.

- *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia in children.
- *Haemophilus influenzae* type b (Hib) is the second most common cause of bacterial pneumonia.
- Respiratory syncytial virus is the most common viral cause of pneumonia.
- In infants infected with HIV, *Pneumocystis jiroveci* is one of the most common causes of pneumonia, responsible for at least one quarter of all pneumonia deaths in HIV-infected infants.

Transmission

Pneumonia can be spread in several ways. The viruses and bacteria that are commonly found in a child's nose or throat can infect the lungs if they are inhaled. They may also spread via air-borne droplets from a cough or sneeze. In addition, pneumonia may spread through blood, especially during and shortly after birth. More research needs to be done on the different pathogens causing pneumonia and the ways they are transmitted, as this is of critical importance for treatment and prevention.

Presenting features

The presenting features of viral and bacterial pneumonia are similar. However, the symptoms of viral pneumonia may be more numerous than the symptoms of bacterial pneumonia. In children under 5 years of age who have cough and/or difficult breathing, with or without fever, pneumonia is diagnosed by the presence of either fast breathing or lower chest wall indrawing where their chest moves in or retracts during inhalation (in a healthy person, the chest expands during inhalation). Wheezing is more common in viral infections.

Very severely ill infants may be unable to feed or drink and may also experience unconsciousness, hypothermia and convulsions.

Risk factors

While most healthy children can fight the infection with their natural defences, children whose immune systems are compromised are at higher risk of developing pneumonia. A child's immune system may

be weakened by malnutrition or undernourishment, especially in infants who are not exclusively breastfed.

Pre-existing illnesses, such as symptomatic HIV infections and measles, also increase a child's risk of contracting pneumonia.

The following environmental factors also increase a child's susceptibility to pneumonia:

- indoor air pollution caused by cooking and heating with biomass fuels (such as wood or dung)
- living in crowded homes
- parental smoking.

Treatment

Pneumonia should be treated with antibiotics. The antibiotic of choice for first line treatment is amoxicillin dispersible tablets. Most cases of pneumonia require oral antibiotics, which are often prescribed at a health centre. These cases can also be diagnosed and treated with inexpensive oral antibiotics at the community level by trained community health workers. Hospitalization is recommended only for severe cases of pneumonia.

Prevention

Preventing pneumonia in children is an essential component of a strategy to reduce child mortality. Immunization against Hib, pneumococcus, measles and whooping cough (pertussis) is the most effective way to prevent pneumonia.

Adequate nutrition is key to improving children's natural defences, starting with exclusive breastfeeding for the first 6 months of life. In addition to being effective in preventing pneumonia, it also helps to reduce the length of the illness if a child does become ill.

Addressing environmental factors such as indoor air pollution (by providing affordable clean indoor stoves, for example) and encouraging good hygiene in crowded homes also reduces the number of children who fall ill with pneumonia.

In children infected with HIV, the antibiotic cotrimoxazole is given daily to decrease the risk of contracting pneumonia.

WHO response

The WHO and UNICEF integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD) aims to accelerate pneumonia control with a combination of interventions to protect, prevent and treat pneumonia in children with actions to:

- **protect** children from pneumonia, including promoting exclusive breastfeeding and adequate complementary feeding;
- **prevent** pneumonia with vaccinations, hand washing with soap, reducing household air pollution, HIV prevention and cotrimoxazole prophylaxis for HIV-infected and exposed children;
- **treat** pneumonia focusing on making sure that every sick child has access to the right kind of care – either from a community-based health worker, or in a health facility if the disease is severe – and can get the antibiotics and oxygen they need to get well.

Several countries including Bangladesh, India, Kenya, Uganda and Zambia have developed district, state and national plans to intensify actions for the control of pneumonia and diarrhoea. Many more have integrated diarrhoea and pneumonia specific action into their national child health and child survival strategies.

Effective diagnosis and treatment of pneumonia is critical to improve child survival. To meet the Sustainable Development Goal targets for SDG 3.2.1 (reducing child mortality), ending preventable diarrhoea- and pneumonia-related deaths is an urgent priority.

5. Tetanus

KEY FACTS

- Tetanus is acquired through infection of a cut or wound with the spores of the bacterium Clostridium tetani, and most cases occur within 14 days of infection. Tetanus cannot be transmitted from person to person.
- Tetanus can be prevented through immunization with tetanus-toxoid-containing vaccines (TTCV). However, people who recover from tetanus do not have natural immunity and can be infected again.
- The majority of reported tetanus cases are birth-associated among newborn babies and mothers who have not been sufficiently vaccinated with TTCV.
- In 2018, about 25 000 newborns died from neonatal tetanus, a 97% reduction since 1988, largely due to scaled-up immunization with TTCV.
- In 2023, 84% of infants worldwide were vaccinated with 3 doses of diphtheria-tetanus-pertussis (DTP) containing vaccine.

Overview

Tetanus is an acute infectious disease caused by spores of the bacterium *Clostridium tetani*. The spores are found everywhere in the environment, particularly in soil, ash, intestinal tracts/feces of animals and humans, and on the surfaces of skin and rusty tools like nails, needles, barbed wire, etc. Being very resistant to heat and most antiseptics, the spores can survive for years.

Anyone can get tetanus, but the disease is particularly common and serious in newborn babies and pregnant women who have not been sufficiently immunized with tetanus-toxoid-containing vaccines. Tetanus during pregnancy or within 6 weeks of the end of pregnancy is called maternal tetanus, and tetanus within the first 28 days of life is called neonatal tetanus.

The disease remains an important public health problem in many parts of the world, but especially in low-income countries or districts, where immunization coverage is low, and unclean birth practices are common. Neonatal tetanus occurs when nonsterile instruments are used to cut the umbilical cord or when contaminated material is used to cover the umbilical stump. Deliveries carried out by people with unclean hands or on a contaminated surface are also risk factors.

In 2018, approximately 25 000 newborns died from neonatal tetanus, a 97% reduction from 1988 when an estimated 787 000 newborn babies died of tetanus within their first month of life. However, there is increased risk of tetanus in adolescent and adult males who undergo circumcision due to waning immunity and limited opportunity for receiving booster doses in males in many countries.

Symptoms and diagnosis

The incubation period of tetanus varies between 3 and 21 days after infection. Most cases occur within 14 days.

Symptoms can include:

- jaw cramping or the inability to open the mouth
- muscle spasms often in the back, abdomen and extremities
- sudden painful muscle spasms often triggered by sudden noises
- trouble swallowing
- seizures
- headache
- fever and sweating
- changes in blood pressure or fast heart rate.

In neonatal tetanus, symptoms include muscle spasms, which are often preceded by the newborn's inability to suck or breastfeed, and excessive crying.

Tetanus is diagnosed on the basis of clinical features and does not require laboratory confirmation. The WHO definition of a confirmed neonatal tetanus case is an illness occurring in an infant who has the normal ability to suck and cry in the first 2 days of life, but who loses this ability between days 3 and 28 of life and becomes rigid or has spasms.

The WHO definition of non-neonatal tetanus requires at least one of the following signs: a sustained spasm of the facial muscles in which the person appears to be grinning, or painful muscular contractions. Although this definition requires a history of injury or wound, tetanus may also occur in patients who are unable to recall a specific wound or injury.

Treatment

Tetanus is a medical emergency requiring:

- care in the hospital
- immediate treatment with medicine called human tetanus immune globulin (TIG)
- aggressive wound care
- drugs to control muscle spasms
- antibiotics
- tetanus vaccination.

People who recover from tetanus do not have natural immunity and can be infected again, and therefore need to be immunized.

Prevention

Tetanus can be prevented through immunization with tetanus-toxoid-containing vaccines (TTCV), which are included in routine immunization programmes globally and administered during antenatal care contacts.

To be protected throughout life, WHO recommends that an individual receives 6 doses (3 primary plus 3 booster doses) of TTCV. The 3-dose primary series should begin as early as 6 weeks of age, with subsequent doses given with a minimum interval of 4 weeks between doses. The 3 booster doses should preferably be given during the second year of life (12–23 months), at 4–7 years of age, and at 9–15 years of age. Ideally, there should be at least 4 years between booster doses.

There are many kinds of vaccines used to protect against tetanus, all of which are combined with vaccines for other diseases:

- diphtheria and tetanus (DT) vaccines
- diphtheria, tetanus, and pertussis (whooping cough) (DTaP) vaccines
- tetanus and diphtheria (Td) vaccines
- tetanus, diphtheria, and pertussis (Tdap) vaccines.

Neonatal tetanus can be prevented by immunizing women of reproductive age with TTCV, either during pregnancy or outside of pregnancy. Additionally, robust medical practices can also prevent tetanus disease including clean delivery and cord care during childbirth, and proper wound care for surgical and dental procedures.

In countries where national programmes have maintained high immunization coverage for several decades, tetanus incidence rates are very low.

WHO Response

The global neonatal tetanus elimination goal was launched at the World Health Assembly in 1989 to reduce neonatal tetanus as a public health problem (defined as less than one case of neonatal tetanus per 1000 live births in every district) in all countries.

The Maternal and Neonatal Tetanus Elimination (MNTE) Initiative was launched by UNICEF, WHO and the United Nations Population Fund (UNFPA) in 1999, revitalizing the goal of MNTE as a public health problem.

As of July 2023, there are 11 countries that have not achieved MNTE. Once MNTE has been achieved, maintaining elimination will require continued strengthening of routine immunization activities for both pregnant women and children, maintaining and increasing access to clean deliveries, reliable neonatal tetanus surveillance, and introduction and/or strengthening of school-based immunization, where feasible.

To sustain MNTE and protect all persons from tetanus, WHO recommends that 6 doses of tetanus-containing vaccine be given to all persons from childhood to adolescence.