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Editor
Asst. Prof. Dr. Ayhan GULER

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PREFACE

Dear scientists, Our age is the information age. It is now a definite conclusion that the countries that produce information will survive in the future. This is why; As scientists, we have to do our best to prevent our country from falling behind in this race. During the pandemic process of all countries, we should not fall behind in the development of vaccines and the efforts to contain the epidemic. We must help and guide young researchers in this regard.

We know that we are better than many countries in the world in the field of health. The way to circumvent this pandemic with the least damage is to raise awareness of our people correctly. In this period when face-to-face education is not possible, we should use all kinds of scientific research and meetings to inform our society in the most accurate and fastest way online. It is also pleasing that our healthcare personnel and scientists, who are working under difficult conditions nowadays, can also continue their scientific activities. I hope this will set an example for the younger generation.

I would like to thank all of my colleagues and publishing house for their devotion.

Ast. Prof. Dr. Ayhan GÜLER

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ALZHEIMER'S DISEASE

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Epidemiology

Alzheimer's disease (AD) is a very common neurodegenerative disease in which memory impairment, memory loss, speech disorders are seen in the early stages of the disease, patients can not perform ordinary physical activities and have difficulty in communicating in the last stages (Corrêa-Velloso et al., 2018).

In 2005, the number of people with dementia worldwide was 24.3 million, with AD patients accounting for about 70% of this cases (Ferri et al., 2005; Reitz et al., 2011). As of 2010, there were approximately 4.7 million people diagnosed with AD in the United States, and this figure is expected to reach 13.8 million by 2050 (Hebert et al., 2013).

Age is a factor that causes a significant increase in the prevalence of AD; 3% of individuals between the ages of 65-74, 18.7% of individuals between the ages of 75-84 and 47.2% of individuals over the age of 85 are affected by the disease (Evans et al., 1989). Owing to the association of AD with aging, the increase of the elderly population leads to be this disease a global problem (Robinson et al., 2017). In addition to aging, there are additional risk factors such as the being of ApoE e4 allele, obesity, cerebrovascular disease, hypertension, diabetes, dyslipidemia, smoking and brain damage (Mayeux&Stern, 2012).

Average life expectancy in AD varies between 4 and 14 years (Small&Mayeux, 2010). In 2017, AD ranked fifth as the cause of death in people over the age of 64 in America (Soria Lopez et al., 2019).

Dementia causes extremely high costs worldwide. The social cost of dementia was estimated to be around 315.4 billion US dollars in 2005 (Wimo et al., 2007).

Developing preventive strategies to delay the onset of the disease is important in reducing the economic and social effects caused by the disease (Brookmeyer et al., 2007).

Etiology and Genetics

Significant developments occurred in the 1990s and early 2000s in terms of determine in genetic risks for AD (Bondi et al., 2017). Ballard et al. suggested that about 70% of AD cases may be associated with genetic factors (Ballard et al., 201 1).

AD is divided into early-onset AD (EOAD) and late-onset AD (LOAD). In addition, EOAD is called presenile AD and LOAD is called sporadic AD. EOAD, which occurs before the age of 65, constitutes 5% of all AD events worldwide. LOAD occurs in individuals over 65 years of age and constitutes the remaining 95% of AD incidence (Mayeux R. 2003; Selkoe&Schenk, 2003).

In both LOAD and EOAD, there is an overproduction and/or impaired clearance of amyloid β (Aβ), a cleavage product of amyloid precursor protein (APP) (Robinson et al., 2017). EOAD is generally caused by mutations in the APP, presenilin 1 (PSEN1) and presenilin 2 (PSEN2) genes, while the LOAD is caused by a polymorphism in the apolipoprotein E (ApoE) gene (Giri et al., 2016).

Mutations of the APP gene constitute approximately 15% of EOAD cases, while mutations of the PSEN1 gene constitute 80% , and mutations of the PSEN2 gene constitute 5% (Calero et al., 2015).

There are three ApoE alleles in the population, consisting of the ε2, ε3, and ε4 alleles, defined at different frequencies. The most important risk factor for LOAD among these alleles is the ε4 allele (Strittmatter et al., 1993). The ε2 allele is known to reduce the risk of developing AD (Karch&Goate, 2015). The most prevalent allele in the population is the ε3 allele (Strittmatter et al., 1993). Having ε4 allele does not always cause Alzheimer's disease (Small&Mayeux, 2010). In LOAD, the ε4 allele increases risk by 3 times, while two duplicate increases risk by 12 times (Karch&Goate, 2015). Ethnicity is a factor affecting the prevalence of the ε4 allele; the prevalence is determined as 9% in Japanese and 20% in African-Americans (Myers et al., 1996).

Also, it has been determined that triggering receptor expressed on myeloid cells 2 (TREM 2) is a risk factor for AD development. (Jonsson et al., 2013; Guerreiro et al., 2013).

Pathophysiology

In 1906, Alois Alzheimer, in the autopsy of Auguste Deter detected abnormal deposits, which he called plaques and neurofibrillary tangles. Auguste Deter had symptoms such as paranoia, aggression, and memory loss. "Alzheimer's disease" expression was first used in 1908 by Emil Kraepelin, a colleague of Alzheimer's, in the textbook Psychiatrie (Hippius,&Neundörfer, 2003).

Intracellular neurofibrillary tangles and extracellular neuritic plaques consisting of Aβ constitute the distinctive feature of AD (Erkkinen et al., 2018).

According to the "Amyloid Cascade Hypothesis", the main cause of AD is the cerebral accumulation of Aβ. The impaired clearance accompanying this increased accumulation constitutes the remaining process of the disease, including the formation of tau tangles (Hardy&Selkoe, 2002).

APP is cleaved by secretase enzymes called α, β and γ, resulting in Aβ peptides. There are two main pathways for APP metabolization: the non-amyloidogenic pathway mediated by α-secretase and γ-secretase and the amyloidogenic pathway mediated by β- and γ-secretase. The solubles APPα molecule formed by cleavage of APP by α-secretase has possible neuro protective function. In the abnormal amyloidogenic pathway, APP is first cleaved by β-secretase and then γ-secretase, resulting in Aβ fragments. The 40 amino acid form (Aβ 40) followed by the 42 amino acid form (Aβ 42) are the predominantly produced forms of Aβ peptides (Zhang et al., 2012).

Another important pathological feature for AD is neurofibrillary tangles (NFTs) formed by hyperphosphorylated forms of microtubule associated protein tau (MAPT) (Hardy&Higgins, 1992). Hyperphosphorylation of tau leads to loss of its function on microtubules and development of cytotoxicity resulting in cell death (Alonso et al., 2010).

It was determined by Braak and Braak (1991) that the distribution of NFTs and neuritic plaques were differed neuroanatomically (Braak&Braak, 1991).

In AD, there is an inverse relationship between the presence of Lewy bodies, which are frequently seen in postmortem examination, especially in neocortical regions, and the presence of NFTs and Aβ plaques; neocortical Lewy bodies are seen at higher frequency in patients with fewer neurofibrillary tangles or lower BRAAK stages (Small&Mayeux, 2010).

In patients with AD, reduced cholinergic activity caused by deficiencies in the choline acetyltransferase enzyme has been demonstrated (Whitehouse, 1998). As a result of determining the relationship of acetylcholine with memory and learning, AD's cholinergic hypothesis has emerged. Neurodegenerative cascade is a feature that occurs in the final stages of cholinergic depletion (Briggs et al., 2016).

Excitotoxicity resulting from overexposure to glutamate neurotransmitter or overexcitation of the N-methyl-D-aspartate (NMDA) receptor is important in terms of neuronal loss in AD (Lipton, 2005).

Neuroinflammation is an event that occurs as an inflammatory response in the central nervous system (CNS) with the accumulation of glial cells and is important in terms of AD pathophysiology (Morales et al., 2014).

Not only genetic factors but also lifestyle and environmental factors are effective on the development of AD (Robinson et al., 2017). Since it is not possible to change the course of the disease with only drug interventions, practices that are thought to have protective effects such as exercise, diet, and cognitive stimuli should be encouraged (Silva et al., 2019).

Clinical Aspects

Alzheimer's cognitive symptoms mainly include deficiencies in short-term memory, visual and executive dysfunction (Apostolova, 2016). Alzheimer's Disease is the most common type of dementia. The incidence increases with age. Alzheimer's disease can rarely be seen in young individuals (Zvěřová, 2018). First diagnosis is very important for patients. Since it is a disease that is difficult to diagnose, treatment is usually started late. It is necessary to know the clinical features in terms of diagnosing the disease and following the patients.

Alzheimer's disease consists of 3 stages as mild, moderate and severe. Alzheimer's is characterized by memory problems. A short-term memory loss is the most typical initial symptom for Alzheimer's disease. Later, changes in personality and behavior, impairment of verbal communication, impairment in visuospatial tasks and motor dysfunction are observed in the patients (Zvěřová, 2019).

It should be emphasized that the symptoms of Alzheimer's disease do not belong to the aging process.

Diagnosis

Appropriate laboratory tests such as serum B12, folate, thyroid parameters, blood cell count, serum electrolytes and liver function tests should be checked. In addition to these, physical examination findings and family histories should also be taken into consideration. Cerebrospinal fluid analysis and electroencephalogram may also rule out other diagnoses (Mantzavinos & Alexiou, 2017).

Studies also reveal the importance of the nerve growth factor precursor protein (Counts et al., 2018).

Brain imaging techniques are of great importance in the diagnosis of Alzheimer's patients (Eskildsen et al., 2015). The definitive diagnosis can be made by biooxidation or tissue examination at autopsy.

In the table below, the characteristics of DSM (diagnostic and statistical manual of mental disorders) and IWG-2 (International Working Group),

which are among the Alzheimer's disease diagnosis criteria, are listed (Baker, 2016).

Table 1. Alzheimer's Disease Diagnostic Criteria (DSM and IWG-2)

DSM	**IWG-2**
Genetic mutation, or all of the following:	Episodic memory impairment and pursuit of either:
Memory and learning decline plus another cognitive decline	Decrease in Aβ42 in CSF plus increase in P-tau or T-tau
Continuous gradual cognitive decline	Increased tracer retention in amyloid PET
neurodegenerative or cerebrovascular disease or other condition contributing to cognitive decline	Autosomal dominant mutation signs and symptoms of cerebrovascular disease

Treatment

Cholinergic activity is low in the brains of Alzheimer's patients. Therefore, the treatment is aimed to prevent the destruction of acetylcholine. Cholinesterase inhibitors are widely used in therapy.

It has been reported that Tau protein accumulates in the brains of patients. This situation is thought to cause the accumulation of senile plaques (Briggs et al., 2016).

Overexposure to glutamate or its NMDA receptor overexcitation plays an important role in the progression of the disease. This causes calcium accumulation in cells and increases neuronal loss (Letter, 2008).

Insulin levels are low in the serobrospinal fluids of Alzheimer's patients (Craft et al., 1998). Low insulin may increase the accumulation of Tau and neurofibrillary tangles.

The Apo gene is a genetic risk factor for Alzheimer's disease (Corder et al., 1993).

Clinical benefit has been observed in patients with mild to moderate Alzheimer's disease with the use of vitamin E, and vitamin E can be added to combined therapies.

When the above hypotheses are considered, cholinesterase inhibitors (Donepezil, Galantamine, Rivastigmine), N-methyl-D-aspartate inhibitors (Memantine) and combined therapies are planned for the treatment of Alzheimer's disease.

Treatment details are given Table 2 (Epperly et al., 2017).

Table 2. Medications

Medications	**Dose**	**Adverse Effect**
Cholinesterase Inhibitors		
Donepezil	5 mg daily	appetite, Atrioventricular block, nausea, vomiting, hypertension
Galantamin	8 mg daily	appetite, Atrioventricular block, nausea, vomiting, hypertension
Rivastigmin	3 mg daily	appetite, Atrioventricular block, nausea, vomiting, hypotension, abdominal pain, myocardial infarction
N-methyl-D-aspartate inhibitors		
Memantin	5 mg daily	Confusion, constipation, diarrhea, acute kidney injury
Combined Therapy		
Donepezil/ Memantin	7mg / 10mg daily	appetite, nausea, vomiting, syncope
Vitamin E	2000 IU daily	Haemorrhage

Clinical Trials

Since the pathophysiology of Alzheimer's disease is not fully elucidated, the search for alternatives to the applied treatments continues. Clinical drug trials are classified as Phase I, Phase II, Phase III and Phase IV. In phase III studies, it is planned as multicenter, multinational, randomized and double blind. It takes 3-4 years on average. The main

purpose of this phase is to demonstrate efficacy and to monitor side effects. The following table lists the ongoing phase III trials in Alzheimer's disease (2020).

Table 3. Ongoing Clinical Trials in Alzheimer's Disease (Phase III)

Identifier	**Drug**	**Location**
NCT03887455	Ban2401 Placebo	Phoenix, Arizona, United States
NCT04520412	Gv-971 Placebo	New York, United States
NCT04339413	Gantenerumab	San Diego, California, United States
NCT03444870	Gantenerumab Placebo	California, United States
NCT03446001	TRx0237 16 mg/day Placebo TRx0237 8 mg/day	Phoenix, Arizona, United States
NCT03283059	Octohydroaminoacridine Succinate Aricept Placebo	Shanghai, China
NCT03197740	Donepezil patch Aricept Tab	Seoul, Korea, Republic of
NCT04229927	Bpdo-1603	Incheon, Korea, Republic of
NCT04468659	Ban2401 Placebo	United States
NCT03594123	Brexpiprazole	Miami, Florida, United States
NCT03116126	Guanfacine Placebo	London, United Kingdom
NCT03548584	Brexpiprazole Placebo	Los Angeles, California, United States

NCT04464564	Avp-786 Placebo	San Diego, California, United States
NCT04408755	 Avp-786 Placebo	Miami, Florida, United States
NCT03108846	Escitalopram Placebo	Little Rock, Arkansas, United States
NCT03393520	Placebo Avp-786	Little Rock, Arkansas, United States
NCT03790709	Anavex2-73 Anavex2-73 Placebo	New South Wales, Australia
NCT03724942	Brexpiprazole	Shirakawa, Japan
NCT03980730	Azeliragon Placebo	Arizona, United States
NCT02446132	Avp-786	Arizona, United States
NCT03691519	Omega-3 treatment Placebo	Toulouse, France
NCT04121858	Brain safe app Attention control app	Indianapolis, Indiana, United States
NCT02719327	İcosapent ethyl Other: placebo	Wisconsin, United States
NCT03486938	Placebo Agb101	Phoenix, Arizona, United States
NCT04314934	Anavex2-73	New South Wales, Australia
NCT01760005	Gantenerumab Solanezumab Matching Placebo	Alabama, United States

NCT04604600	Amyloid PET	Taipei, Taiwan
NCT03620981	Brexpiprazole Placebo	Shirakawa, Japan
NCT03860857	Amyloid PET scan Tau PET scan using MK-6240 Neurocognitive testing MRI	California, United States
NCT03090516	Ginkgo biloba dispersible tablets Donepezil Ginkgo biloba dispersible tablets and Donepezil	Jiangsu, China
NCT03969732	Amyloid PET T807 PET	Taipei, Taiwan
NCT03682185	Attention-control condition Timed activity ıntervention	Pennsylvania, United States
NCT03451591	Isosorbide mononitrate xl Cilostazol Ismn xl and cilostazol Neither ısmn nor cilostazol	Lothian, United Kingdom

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THE RELATIONSHIP BETWEEN TUBERCULOSIS AND TLR

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1. Introduction

Mycobacterium tuberculosis (Mtb) continues to be the leading bacterial agent that causes death in humans with its antigen and virulence factors. In the report published recently by the World Health Organization, it has been reported that significant progress has been made in the definition and treatment of Tuberculosis (TB) cases. However, it has been reported that not enough progress has been made to reach the United Nations target of ending the TB epidemic by 2030 and TB continues to be the disease responsible for the high global loss of life that still kills 1.5 million people annually (WHO, 2019). The pathogenesis of Mtb and the host mechanisms that prevent infected individuals from developing the disease are not fully understood (Schorey & Schlesinger, 2016). Toll-like receptors (TLRs) contain a specially engineered family of pattern recognition receptors, which recognize widely conserved pathogen-associated molecular components (PAMPs) expressed by microorganisms and are involved in the immune response to eliminate intracellular invasive microorganisms (Kawai & Akira, 2011; Brennan & Gilmore, 2018).

TLRs are expressed on a variety of immune cells, such as monocytes, macrophages, dendritic cells and epithelial cells, which are members of innate immunity, and are natural immune receptors responsible for the recognition of a wide variety of molecules that lead to transcription of proinflammatory genes through a complicated signaling (Khalilullah, 2014). Lipoproteins are recognized by TLR1, TLR2 and TLR6, while double-stranded RNA TLR3, lipopolysaccharides (LPS) TLR4, flagellin TLR5, single-stranded RNA TLR7 and TLR8 are recognized by DNA TLR9 (Akira & Takeda, 2004). The TLR signaling system also provides the secretion of antimicrobial peptides, chemokines, and inflammatory cytokines (Kawai & Akira, The role of pattern-recognition receptors in innate immunity, update on Toll-like receptors, 2010). Within the TLR family, TLR2 and TLR4 are responsible for the detection of Mtb, an intracellular pathogen, and TLR2 plays a key role in this responsibility (Basu, Shin, & Jo, 2012; Yu, Zeng, & Xie, 2014). TLR2 offers a broad substrate specifically for foreign particles such as bacterial cell wall components, and in addition to lipopeptides of bacterial origin, it also shows the ability to recognize cell elements such as lipoteichoic acid and generate a specific response (Stamm, Collins, & Shiloh, 2015). With this specific response, TLR2 has a primary role in the realization of immune

reaction against infection and in the detection of Mtb. TLR4 are cells responsible for recognizing lipopolysaccharide (LPS), cell wall lipids, glycoproteins and protein secretions. In addition, signal pathways originating from myeloid differentiation 88 (MyD88) also occur through TLR4 stimulation (Shin, Yuk, Lee, Lee, & Son, 2010). Mtb's particularly thick cell wall provides some degree of protection against host immune detection, while also harboring specific antigens that can induce a TLR response (Kleinnijenhuis, Oosting, Joosten, & Netea, 2011).

2. Mycobacterium tuberculosis

2.1. History

Tuberculosis disease started with the history of humanity and although there have been numerous studies about the disease, it has taken its place in the history as a chronic infectious disease that threatens humanity throughout the history of medicine (Comas, Coscolla, Luo, Borrell, & Holt, 2013). The oldest historical evidence of the disease has been demonstrated by paleopathology studies in the remains of female and child skeletons discovered in the submerged underwater city called Atlit-Yam in Israel 9000 years ago (Hershkovitz, Donoghue, Minnikin, & Besra, 2008). 5500 years ago, evidence of spinal TB or Pott's disease was shown in ancient Egyptian mummies (Taylor, Murphy, Hopkins, & Rutland, 2007). Detection of bacterial DNA in lung lesions of mummies of 1000 years old humans found in Peru has shed light on the role of TB in the evolutionary process (Salo, Aufderheide, Buikstra, & Holcomb , 1994). German physicist scientist Heinrich Hermann Robert Koch identified the TB bacillus in the lung lesions of his 32-year-old patient who died of TB in 1882, and after this discovery, he received the Nobel Prize in Medicine in 1905. The tuberculin used was administered to the patients at a dose of 12,000 times the tuberculin dose that is still used today, but it caused high fever, recurrent coughs and anorexia again. In 1903, Von Pirgued proposed the term allergy for the reactions of tuberculin in TB cases and in 1907 made the tuberculin skin test (TDT) clinically applicable. The first tuberculosis vaccine was developed as a Bacillus Calmette-Guerin (BCG) vaccine at the Lille Pasteur Institute in 1921 by researchers Calmette and Guerin (Richter, Brown-Elliott, & Wallace; Tille, 2007). oral BCG vaccination for the first time in Turkey Prof. Dr. It was applied by Refik Güran in 1926 and BCG production was started in Refik Saydam Hıfzısıhha Center in 1931.

2.2. Epidemiology

According to the 2018 Global TB Report of the World Health Organization (WHO), about 2 billion people (1⁄4 of the world population) are infected with TB bacilli, approximately 10 million people develop active TB disease annually and 1.3 million people a year are due to TB

(WHO, 2019). It is estimated that he died. When the age distribution of infected individuals is examined, it is stated that 80% of them are 50 years and older in developed countries and 77% of them are 50 years old and under in developing countries. Up to 1 million of 10 million active TB patients annually are pediatric patients (<15 years old), and it is estimated that around 239,000 children die annually (Dodd, Yuen, Sismanidis, Seddon, & Jenkins, 2017). In 2016, 1.3 million people from TB died among people negative for Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome (HIV / AIDS). The number of HIV-positive people who died due to TB disease is 374,000 (Espert, Beaumelle, & Vergne, 2015). TB mortality is 3% per year and the incidence decreases by 2% each year. Until 2020, "End TB Strategy" has to increase by 4-5% every year to reach its first milestone (WHO, 2019).

2.3. Classification

Mycobacterium is the only genus in the order Actinomycales that belongs to the Mycobacteriaceae family. The common characteristics of more than 100 species in this genus are high lipids in their cell walls, acid and alcohol resistance, slow reproduction, and the G + C ratio in their genomes in the range of 61-71%. Due to the high similarity of DNA sequences, species that are close to each other are grouped as complex. The mtb complex includes ten species, namely M. tuberculosis, M. bovis, M. africanum subtype I, II, M. caprae, M. canettii, M. pinnipedii, M. microti, M. mungi, and M. orygis. Mycobacteria other than the M. tuberculosis complex are called Non-TB Mycobacteria (TDM) and most of them are not pathogens. Ernest Runyon, the growth rate of mycobacteria (growth times <7) days and according to the colony morphology they form in solid media: Photochromogen mycobacteria (they form orange yellow pigment when exposed to light), Scotochromogen mycobacteria (form orange yellow pigment in the dark and light), Non-chromogenic mycobacteria (They do not form pigment), Fast growing mycobacteria (they are non-pigmented or they produce very little pigment) divided into four groups (Richter, Brown-Elliott, & Wallace) (Tille, 2007).

2.4. General features

Mycobacterium genus bacteria are obliged to aerobe (or microaerophile) and incubated at 37 ° C. Unlike immobile, sporeless, encapsulated and other bacteria, there is 60% lipid in the cell walls. The lipid-rich structure of their cell walls gives these bacteria a hydrophobic feature. Because of this lipid layer, mycobacteria are not stained by the gram staining method, but they are considered gram positive (ghost staining, ghost). The shape of the bacteria varies from coccobacillus to rod. It is also the cause of a worldwide common and pathogenic chronic infectious disease, the main host of the Mtb bacillus being human.

Although the shape of the colonies varies between species, they are S-type (colony with smooth surface), R-type (colony with irregular edges) and filamentous. Colonies are pigmented or not. In solid media, they usually form colonies at 37 ° C in 18-21 days, their growth accelerates in an environment with 5% CO2. When Tween-albumin is incubated at 37 ° C in liquid medium, it can form a cord factor with the appearance of branched bacilli within 10-15 days. TB bacillus secretes niacin into the environment, it can be differentiated from other species by the niacin test, its pyrazinamidase activity and niacin accumulation are positive, it reduces nitrate to nitrite, and catalase activity is low or absent (Richter, Brown-Elliott, & Wallace) (Tille, 2007; Van Ingen, Rahim, Mulder, Boeree, & Simeone, 2012; Kumar, 2016)

2.5. Cell Structure

The cell structure of mycobacteria consists of the cytoplasm, the cell membrane surrounding the cytoplasm, and a lipid-rich cell wall surrounding them. There is a single naked chromosome in the cytoplasm. The cell membrane contains two layers of polar phospholipids. Various proteins, phosphatidylinositol, mannose and lipoarabinomannans are in this region. The innermost layer on the cell membrane is the peptidoglycan (murein) layer. It provides the shape and rigidity of the cell. The layer adjacent to the peptidoglycan layer is the layer of arabinogalac. This layer contains the major cell wall polysaccharides arabinose and galactose. Mycolic acids, which are covalently bonded to the terminal arabinose units in the side chains of arabinogalactans, are responsible for the thickness of the cell wall and the acid-alcohol resistance of the cell. Mycosides are found in the outermost layer. Cord factor, sulfatides, vax D and Purified Protein Derivative (PPD), which have an important role in pathogenesis, are located in this layer. Also, there are porin proteins in the cell Wall (Tille, 2007; Richter, Brown-Elliott, & Wallace; Van Ingen, Rahim, Mulder, Boeree, & Simeone, 2012; Kumar, 2016; Winn WC, 2006).

2.6. Pathogenesis

The immune response against Mycobacterium tuberculosis complex consists of the mutual interaction of natural and adaptive responses. Infection begins as a result of ingestion of droplet nuclei containing bacteria of 1-5 μm size by the sensitive host via the respiratory tract. The first place where the bacteria will settle after ingestion is the lungs (Mathema, Kurepina, Fallows, & Kreiswirth , 2008; Ahmad, 2011). For an effective immune response against tuberculosis, macrophages, dendritic cells, CD4 + T cells, CD8 + T cells, CD1 restricted cells and cytotoxic T cells and cytokines produced by these cells are required. Among these components, CD4 + T cells and IFN-gamma have the most important roles (Ahmad, 2011). Tuberculosis can occur in two forms as primary and

secondary tuberculosis. Primary TB is when the susceptible host is infected with bacteria taken by the respiratory tract for the first time. In this picture, the infection is mild and asymptomatic. After mycobacteria are ingested, they are recognized and phagocytosed by macrophages and dendritic cells in the alveoli, but bacteria also apply different strategies to prevent the host immune response thanks to some virulence factors they have (Mehta , Karls, White, Ades, & Quinn , 2006). Granuloma is a prison created for bacteria in terms of host, a wall separating the infection from other parts of the body and an environment that enables the bacteria to infect and proliferate in cells that make phagocytosis (Pai & Sotgiu, 2016). The formation of granuloma is important for the primary infection to be limited and not to spread. Bacteria confined within the lesion pass into dormant state here. However, if any weakening of the host defense occurs, bacteria may be reactivated and secondary TB picture may be seen. If this picture progresses, pulmonary TB, life-threatening meningitis and miliary TB can be seen. Secondary TB, the other form of tuberculosis, is the most common picture in the population and the main factor in TB spread among individuals.

2.7. Laboratory Diagnosis of Tuberculosis

The first step in the diagnosis of tuberculosis is microscopic diagnosis since it gives results in a short time. Carbolfuksin and Fluorochrome dyes are used for microscopic examination. Solid media egg-based media: Löwenstein-Jensen medium (LJ), American Trudeau Society (ATS) and Petragnani media are included in this group. the most commonly used medium for primary isolation lj (Richter, Brown-Elliott, & Wallace; Tille, 2007; Kumar, 2016; Van Ingen, Rahim, Mulder, Boeree, & Simeone, 2012). Agar-based media: Middlebrook 7H10 and Middlebrook 7H11 media are included in this group. Liquid media: Middlebrook 7H9 and Dubos tween albumin media are the most commonly used liquid media for mycobacteria isolation. Dubos-Tween albumin is used in more mycobacteria with the relevant dilution experiments. due to longer time required for isolation of up to six weeks of mycobacteria is intended to reduce the duration diagnosis using molecular methods. Therefore, DNA hybridization, amplification and reverse hybridization-based amplification, amplification and restriction enzyme analysis or DNA sequencing, DNA microarray and real-time polymerase chain reaction (GZ-PCR) based methods have been developed (Ahmad, 2011; Richter, Brown-Elliott, & Wallace; Tille, 2007; Van Ingen, Rahim, Mulder, Boeree, & Simeone, 2012). The tests used as an indirect method in the diagnosis of tuberculosis and used to detect latent TB are interferon gamma tests (IGST). Interferon gamma release tests are not affected by BCG vaccine (Pai & Sotgiu, 2016).

3.Toll-Like Receptors (TLR)

The Toll gene was first described in Drosophila melanogaster in 1985 by Christiane Nüsslein-Volhard, Eric Weischaus et al. Transcription of the drosomycin gene is similar to mammalian IL-1R signaling pathway transcription. Toll-Like Receptors (TLRs) were first described in humans in 1994 by Nomura et al. Since the role of the toll gene in the immune response in Drosophila was not known at that time, it was thought that this receptor played a role in the development of mammals. However, in 1997, it was shown by Janeway and Medzhitov that TLR can also activate the acquired immune system in humans. TLRs are type 1 transmembrane proteins formed by dendritic cells and macrophages, which are members of the innate immune response (Kundakçı & Pirat, 2012). The extracellular domain, which contains three leucine-rich repeats (LRR: leucine-rich repeats), consists of three parts: the transmembrane domain and the cytoplasmic Toll / IL-1 receptor (TIR) domain, which is the beginning of the signaling pathways. As a result of both human and mouse studies of mycobacterial infections, the presence of potential TB susceptibility or resistance loci, including genes involved in toll-like receptor signaling, have been identified. In humans, TLRs contribute to the recognition of pathogens by the immune system and shape the development of the acquired immune response (Wu, Hu, Li, Jiang, & Xu, 2015). Natural and acquired immune systems recognize microbial agents differently and generate response. There are millions of lymphoid cell surface molecules formed by complex gene rearrangements in acquired immunity. Native immunity receptors are much less numerous and these receptors are called "pattern recognition receptors" (PRR: pattern recognition receptors) (Palm & Medzhitov, 2009).

3.1. Toll-like Reseptor Family Members

TLR functions as an essential part of the innate immune system. TLRs recognize pathogen-dependent molecular patterns that activate signaling events that control stimulating immune responses that stimulate the expression of effector molecules. Due to the polymorphic nature of TLR genes, there are genetic variations in the genes encoding these receptors that have an important impact on the pathogenesis of inflammatory diseases. To date, 13 TLR receptors have been identified, expressing 10 TLRs (TLR1-10) in humans and 12 TLRs (TLR1-TLR9, TLR11-TLR13) in mice. TLRs are located on the cell surface or in intracellular compartments such as endoplasmic reticulum, endosome, lysosome. Researchers divided TLRs into two groups according to their cellular location. The first group TLR 1, 2, 4, 5, 6 are all synthesized on the cell surface and recognize their lipid structures. TLRs in the second group are found in 3, 7, 8, 9 intercellular regions and recognize nucleic acids derived from the genome of microorganisms (McGettrick & O'Neill, 2010). It is

related to the recognition of 2, 4, 6, 8 and 9 MTBs from TLR family. It forms a heterodimer with TLR1 or TLR6 of TLR2. Of these, TLR1, 2, 4, 5, 6, 10 on the cell surface; TLR3 is located in the intracellular compartment of 7, 8, 9. TLR4 is located in both the plasma membrane and the endolysosome (Botos, Segal, & Davies, 2011). Human genetic studies have shown that variants of TLR pathway genes, including TLR1, TLR2, TLR4, and TIRAP, regulate cellular immune response and may affect susceptibility to M. tuberculosis in different populations (Wu, Hu, Li, Jiang, & Xu, 2015).

TLR1: also referred to as CD281, recognizes the specific pathogen-associated molecular pattern and gram-positive bacteria. Studies have also shown that TLR1 is functionally related to TLR2 and TLR1 supports TLR2 in distinguishing small differences between lipopeptides. TLR1 and TLR2 (as a heterodimer) are found on the surface of macrophages and neutrophils and recognize peptidoglycan and lipoproteins. TLR1 is usually expressed in neutrophils, B cells, monocytes, and natural killer (NK) cells (Farhat, Riekenberg, & Heine, 2008). There are studies on TLR1, but a specific ligand has not been detected and the function of this receptor is still unclear.

TLR2: also called CD282, has an important role in the recognition of many PAMPs related to bacteria, parasites, fungi and viruses. It has been stated that genetic variants generally associated with TB are associated with the presence of a single nucleoid polymophism in the TLR2 gene Arg753Gln (Oliveira-Nascimento, Massari, & Wetzler, 2012). As a result of the recognition of gram-negative and gram-positive bacterial lipoproteins by TLR2, it has been shown that the cells involved in the immune system are activated and TLR2 is thought to be the receptor responsible for recognizing bacterial lipoproteins. TLR2s recognize the peptidoglycan layer of gram positive bacteria, while TLR4 recognizes the LPS structure of gram negative bacteria. In some studies, it has been shown that cells that cannot create an immune response to leptospiral lipopolysaccharide need both CD14 and TLR2 to achieve this. Although the lipopolysaccharide structure of Porphyromonas gingivalis is different from other Gram-negative bacteria, this structure is also recognized by CD14 and TLR2. TLR2 enlarges the specificity pool by creating functional heterodimers of other TLRs. It has been demonstrated that the TLR2 / 6 heterodimer interacts with peptidoglycan and zymosan (yeast), but the heterodimer of TLR2, in which it recognizes the bacterial lipoprotein structure together, has not been identified yet. In a study, it was shown that TLR2 and TLR6 are absolutely necessary for the detection of MALP-2, a diacylelipoprotein isolated from mycoplasma, by the immune system (Müştak & Esendal, 2007).

TLR3: As a result of viral replication, double stranded RNA (dsRNA) is formed in infected cells, which can stimulate the immune system, and ultimately type 1 interferon production is stimulated. Since this dsRNA is not a host cell element, it is considered as a pathogen associated molecular template (PAMP). The decrease in immune response against viral RNA copy in TLR3 defective mouse experiments showed that this receptor plays a role in the recognition of dsRNA by the cell. In addition, other molecules such as protein kinase R are thought to induce interferon production like dsRNA (Müştak & Esendal, 2007).

TLR4: It is the most researched and functional receptor group in humans by forming a complex with the LRR protein known as MD-2. TLR4 is one of the most important receptors in innate immunity and is expressed in macrophages, endothelial and smooth muscle cells, trachea epithelium, and cardiomyocytes. CD14 is a glycoprotein located on the cell surface and is responsible for binding the lipopolysaccharide molecule to the cell surface. CD14 is found on the surfaces of mononuclear phagocytes and has no intracytoplasmic region. Due to this feature, CD14 cannot perform signal transduction, indicating that the remaining two molecules are involved in lipopolysaccharide signal transduction. This function of TLR4 has been demonstrated by positional cloning of the gene involved in lipopolysaccharide recognition in mice. Each component in the CD14, TLR4 and MD-2 complex is required for effective cell-cell lipopolysaccharide signal activation. Since MD-2 does not have a transmembrane part, the extracellular part of TLR4 is used for cell activation (Müştak & Esendal, 2007). TLR4 induces a series of kinase pathways and transcription factor activation to create innate immunity against microorganisms. In TLR4 signaling, myeloid differentiation factor 88 (MyD88) dependent pathway and MyD88 independent pathway are involved. Signal cascades in dependent pathways cause the synthesis of chemokines, reactive oxygen species (ROS) and natural immune system elements such as pro-inflammatory cytokines (Jahantigh, Salimi, Alavi-Naini , & R, et al, 2013; Ozbayer C, 2014).

TLR5: TLR5 and TLR9 recognize only one molecule. Despite this, TLR2, TLR4 and TLR6 can respond to different microorganisms. Bacterial flagellin in a pure protein structure, one of the main molecules that make up the bacterial flagella, is recognized by TLR5. After the binding of flagellin with TLR5, an inflammatory response such as TNF-α occurs (Müştak & Esendal, 2007).

TLR6: Monocyte is expressed on the cell surface of immature dendritic cells (iDC) and neutrophils. In a study, this relationship between TLR2 and TLR6 was detected in Chinese hamster ovary cells. TNF-α production was found to be significantly increased against the peptidoglycan structure

found in the cell wall of Staphylococcus aureus in macrophages with TLR6 defects. While TLR6 defective macrophages do not respond to mycoplasmal lipopeptide MALP-2, it has been shown that they produce normal levels of cytokine response against synthetic bacterial lipopeptide (BLP). It is known that mice with TLR2 defects do not respond to MALP-2 and BLP. Studies have shown that the inhibition of TLR2 and TLR6 interrupts the macrophage response against Gram-positive bacteria and yeasts (zymosan). This result shows that these structures are recognized by TLR2 and TLR6 (Müştak & Esendal, 2007). TLR6 is more closely related to TLR1 and TLR2.

TLR7: It recognizes several structures belonging to the imidazoquinoline family. In this family, imiquimod and R-848 (resiquimod) are low molecular mass compounds and have strong antiviral and antitumor activities. Cytokines such as IFN-α and IL-12 are stimulated by the activity of immiquimod. R-848 is similar to imiquimod in function and is under development. In addition, TLR7 has been shown to be able to recognize other synthetic chemical structures such as loxoribine and broprimine (Müştak & Esendal, 2007).

TLR8: It is phylogenetically similar to TLR7 and, together with TLR7, is involved in the immune response against R-848, an imidazoquinoline compound. R-848 derived from HIV, VSV (Vesicular Stomatitis Virus) and influenza A virus recognizes bacterial RNA and ssRNA. The level of TLR8 increases as a result of bacterial infection (Ma, ve diğerleri, 2007).

TLR9: Unmethylated 2'-deoxyribo cytidine phosphate-guanosine (CpG), which is frequently found in bacteria, is responsible for recognizing DNA motifs by the immune system (Haas, Metzger, Schmitz, & et al, 2008). These structures have been found to stimulate B cell proliferation and activate dendritic cells and macrophages. Due to differences in the sequence of amino acids in the extracellular region of TLR9, the optimal response to the CpG-DNA motif in mice and humans is different.

TLR10: It is the last member of the human TLR family and its ligand is unknown. TLRs are expressed in innate immune system cells such as dendritic cells and macrophages, as well as in cells that do not belong to the immune system such as fibroblasts and epithelial cells. TLR4 was the first to be determined as a receptor for lipopolysaccharide, an outer membrane component of gram-negative bacteria in humans (Müştak & Esendal, 2007; Bauernfeind, Ablasser, Bartok, & Kim, 2011).

4. Mtb-TLR Relationship

The natural immune system plays the first and most important role in host defense against MTB. They play a role in recognition by many classes of PRRs, including cell wall glycolipids, Node-like Receptors, C-type

lectin receptors and TLRs found in mycobacteria. The importance of TLR4, TLR6 and TLR2 in recognizing MTB has been demonstrated by studies. In a study conducted in South Africa and Uganda, it was shown that it performed full exon sequencing in 4 genes (TLR2, TLR4, TLR6 and TIRAP) in the TLR pathway (Baker, Qiu, Randhawa, & et al, 2012). Significant differences in haplotype frequency were observed in different populations in TLR2 and TLR6. In a study in South India, they investigated the effect of TLR1, TLR2, TLR4, TLR6, TIRAP and TLR9 polymorphisms on PTB resistance and susceptibility in healthy and patient populations. In relation to TLR9 polymorphisms, the frequencies of alleles and genotypes are similar in healthy subjects and patients. T allele frequency is significantly higher among patients compared to healthy subjects.In another study conducted in India, they reported the severe susceptibility of the disease to PTB with its polymorphisms with TLR4 Asp299Gly and Thr399I (Najmi, Kaur, Sharma, & Mehra, 2010).

5. Discussion and Conclusion

TB, thought to begin with the history of humanity, is an infectious disease caused by the intracellular pathogen M. tuberculosis. The infection of a person with TB depends on the number of infectious patients in the community, and most importantly, the duration and type of contact with sick people (Abdella, Abdissa, Kebede, & Abebe, 2015). While socioeconomic status was held responsible for the development of TB disease until recent years, it has been shown that genetic factors have an important role as environmental factors in line with the molecular results obtained as a result of family and twin studies. TLRs play an important role in identifying microorganisms and initiate the immune response in acquired immunity. TLRs represent a primitive host defense mechanism against microorganisms; It plays an important role in pathogen recognition and initiation of inflammatory and immune responses. TLR2 is capable of recognizing a variety of microbial components and is the primary means of macrophage activation in response to mycobacteria. For example, Mycobacterium bovis Bacillus Calmette-Guérin has been used in the treatment of bladder cancer for nearly 40 years. This intravesical injection used in treatment activates TLR2 and TLR4 signaling in dendritic cells (Vu, Calzadilla, Gidfar, & Calderon, 2017). In a meta-analysis study, it was stated that the TLR2 gene was detected between Caucasian and Asians according to ethnicity. According to the results of the study, it was emphasized that people with TLR2 rs5743708 gene polymorphism are at a risk for TB disease (Guo & Xia, 2015).

In another study, it was aimed to investigate the relationship between TLR polymorphisms and the development of infection and it was emphasized that polymorphism is a risk factor for TB infection (Biyıkli, Baysak, Ece, & Oz, 2016). It has been shown that TLR4 is an important

component of innate immunity against chronic M. tuberculosis infection and TLR4 mutant mice are more susceptible to M. tuberculosis when infected with aerosolized M. tuberculosis compared to controls (Vu, Calzadilla, Gidfar, Calderon, & Mirsaedi, Toll like receptors in mycobacterial infection, 2017). In a study conducted in Iran, it was emphasized that TLR4 gene region polymorphisms may affect the risk of TB development (Jafari, Nasiri, Sanaei, & Anoosheh, 2016). While a statistically significant relationship was found between the presence of TLR4 gene region polymorphism and TB in studies conducted abroad (only for the Asp299Gly gene region), a significant relationship was not found between TLR4 and TB disease in studies conducted in our country. It is thought that a significant relationship between the development of TB infection and the presence of polymorphism can be determined by investigating the polymorphisms in this gene region in more patients and control groups. In order to reveal the clinical course of TB, it is important to determine the polymorphisms in the gene regions that are associated with susceptibility or resistance to this disease. Therefore, it is necessary to show a genetic predisposition to this disease with studies on these polymorphisms both in our country and around the world. With the results of these studies, the interaction between the host immune system and the immunopathogenesis of the disease can be elucidated, and it will be possible to develop new vaccines that are more effective than the BCG vaccine. It will be possible to fight more effectively against TB by carrying out such genetic predisposition studies on more individuals in different countries in people of different ethnic origin.

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SUDDEN HEARING LOSS: A CURRENT APPROACH TO ETIOLOGY, DIAGNOSIS AND TREATMENT

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1. Introduction

Sudden hearing loss (SHL) is a problem today as well as a focus of interest for Ear, Nose and Throat (ENT) specialists throughout the world in terms of its treatment methodology and outcomes. SHL is sensorineural hearing loss with a sudden onset and without a clear etiological root (Moskowitz et al., 1984). Wilson defines SHL as sensorineural hearing loss (SNHL) that develops in less than three days and is of 30 dB or greater over three consecutive frequencies (Moskowitz et al., 1984). It was first identified in 1944. It constitutes 1% of all SNHL patients and although its incidence was reported as 5-20/10,000, the incidence of SHL is actually higher than the estimates due to the fact that spontaneous improvements occur over a short time. Approximately 32-65% of SHL patients recover spontaneously (Matthew et al., 2008). There is no difference in terms of gender and it is a pathology that can develop at any age (Lazarini and Camargo, 2006). Hearing loss is generally unilateral. 4-17% of the cases may be bilateral. Right and left ears are equally affected (Anadolu et al., 1993).

Ear fullness is a common complaint in SHL patients. Tinnitus accompanies the clinical picture 70% of the time in patients with SHL. There are different studies reporting tinnitus as a good or poor prognostic factor (Lazarini and Camargo, 2006). It is seen in 40% of patients with imbalance or vertigo complaints of varying grades, and the presence of vertigo is a poor prognostic factor. Moreover, there are several studies in the literature in which reports indicate a poorer prognosis in patients under 18 and above 40 years of age (Wilson et al., 1980; Bozkurt et al., 2014). Consulting a physician and starting treatment early increases the correction potential of the hearing loss (Aydoğdu et al., 2017).

2. Etiology

Many diseases and factors have been shown to cause SHL; however, an etiological cause could not be determined in 88% of patients despite diagnostic tests and, consequently, they were considered idiopathic (Matthew et al., 2008). This kind of sudden hearing loss is called Idiopathic SHL. Specific etiology can be identified in only 10% of cases.

2.1. Viral Causes

Studies which aimed to explain the etiology of SHL revealed that viruses played a role in many cases. Among the results supporting viral SHL; a history of upper respiratory tract disease up to one month before the onset of the hearing loss has been found in approximately 28% of patients who presented with SHL (Mattox and Lyles, 1989), increased viral titers in Serology studies and viral labyrinthitis on the temporal bone in postmortem studies also support the viral theory.

Viral agents reach the inner ear in three different ways. 1) Viremia; hematogenous involvement might occur. Inner ear involvement mostly occurs in this way. 2) Spread through the cochlear aqueduct; this kind of spread is observed especially in meningitis. 3) Direct spread occurs through direct transmission of viruses in otitis media patients (Çelik, 2007).

Serologic studies have shown that viruses such as HSV, CMV, Mumps, Measles, Influenza, Parainfluenza, Adenoviruses and HIV have caused SHL in patients (Matthew et al., 2008; Lazarini and Camargo, 2006).

2.2. Vascular Causes

SHL might occur as a result of full or partial occlusion of cochlear blood flow. Sudden onset, occurring in individuals with known vascular disease and manifesting in animal model experiments are the findings that support the vascular theory. As the inner ear is supplied by the labyrinthine-internal auditory artery terminal branches of AICA (anterior inferior cerebellar artery), hearing loss might develop which may be associated with hypoxia relating to occlusion causes such as hemorrhage, thrombosis and hypercoagulation. Vascular causes include sickle cell anemia, polycythemia vera, diabetes, arteriosclerosis, Buerger's disease, microembolus and hypercoagulation syndromes (Viirre and Baloh, 1996). However, there are some opinions that do not accept the vascular theory due to the lack of a significant increase in patients with diabetes, a failure to show spontaneous recovery, the incidence in younger people and the fact that hearing loss is generally limited to a few frequencies (Einer et al., 1994).

2.3. Traumatic Causes

Approximately 30% of SHLs are attributed to traumatic causes.

2.3.1. Temporal Bone Fractures: In head traumas, development of a transverse fracture particularly in the temporal bone may cause SHL. Hearing loss may also develop in other temporal bone fractures, although with a limited possibility. Hearing loss may occur when the cochlea or labyrinthine is affected by concussion in head traumas without a fracture (Matthew et al., 2008).

2.3.2. Barotraumas: Barotrauma is a temporary or permanent dysfunction in the inner ear in consequence of sudden changes in atmospheric pressure. Causes such as sudden diving or strong sniffing might lead to this condition.

2.3.3. Acute Acoustic Traumas: This is a condition characterized by hearing loss at high frequencies caused by a noise such as a very severe explosive sound.

2.3.4. Perilymphatic Fistulas: Sudden hearing loss caused by barotrauma, head traumas, heavy lifting or the development of iatrogenic fistula may create this condition which is characterized by ringing in the ears and dizziness.

2.4. Bacterial Causes

Some bacterial infections might lead to SHL by causing otitis or meningitis. Hearing loss is generally bilateral or in the form of deep loss. As a cause of syphilis disease T. Pallidum accounts for less than 2% of SHL cases. Hearing loss may develop at any stage of syphilitic disease. B. Burgdorferi, which is a cause of Lyme disease, may also lead to SHL and hearing loss can be bilateral.

2.5. Ototoxic drugs

There are many drugs and chemicals that have an ototoxic action. In particular, the aminoglycoside group of antibiotics are ototoxic (Koçyiğit, 2017). Among these antibiotics; streptomycin, tobramycin and gentamicin have more vestibulotoxic effects. On the other hand, amikacin, kanamycin and neomycin have more cochleotoxic effects. Moreover, cases related to ototoxicity were reported in those who were exposed to cisplatin and carboplatin as antineoplastic agents (Strauss et al., 1983), loop diuretics (Rybak, 1993), salicylates, deferoxamine (Olivieri, 1986), kinin (Jung et al., 1993) and toxic materials like arsenic, mercury, lead, zinc and manganese (Schwartz and Otto, 1987). Also, there are many organic solvents that cause hearing loss. Among these solvents; styrene, hexene, carbon disulfide and toluene may cause SHL. Carbon monoxide is also a toxic agent which may cause SHL. Ototoxic drugs generally cause hearing loss at high frequencies by affecting the outer hair cells (Kanda et al., 1995).

2.6. Neoplasias

Cerebellopontine angle tumors account for around 1% of SHL cases. While the cause is usually acoustic neuroma; meningioma, hemangioma, arachnoid cysts and metastatic tumors can be among the factors that occur with less frequency. Also, SHL has been reported in some leukemia cases (Saunders et al., 1995).

2.7. Autoimmune diseases

Although the role of autoimmunity in the etiology of SHL is not yet clear, the occurrence of SHL cases in autoimmune diseases such as Systemic Lupus Erythematosus, Antiphospholipid Syndrome, Rheumatoid Arthritis, Scleroderma, PAN, Behçet's disease and Cogan's syndrome support the autoimmune theory. The benefits of glucocorticoid treatment and the detection of cross-reactive antibodies in the circulation of patients with SHL would suggest that the cause may be autoimmune conditions (Rossini et al., 2017).

2.8. Metabolic causes

Metabolic conditions such as Diabetes Mellitus, lipid metabolism disorders, thyroid dysfunctions and metabolic disorders of the liver may cause SHL (Oiticica and Bittar, 2010).

2.9. Neurological diseases

Sudden hearing loss may rarely develop in neurogenic diseases such as Multiple Sclerosis and migraine (Atula et al., 2016).

2.10. Psychogenic causes

The SHL picture can be observed also as a conversion reaction.

3. Diagnosis and Evaluation

Anamnesis: A detailed anamnesis upon the admission of the patient is the initial and the most significant step towards the diagnosis and treatment of SHL. In anamnesis, the patient is asked when hearing loss began, the history of trauma or noise exposure, the use of ototoxic drugs, the presence of comorbidities and whether the patient has pain, tinnitus, vertigo or a neurological deficit accompanying the hearing loss or not (Matthew et al., 2008, Lorenzi et al., 2003).

Otologic surgery and ear tests: The condition of the auricle, the external auditory canal, the tympanic membrane and the middle ear is assessed. A neurological examination of the cranial nerves is performed. SHL is diagnosed with basic audiologic tests, otoacoustic emission and auditory brainstem response (ABR) tests in non-cooperative patients.

Laboratory tests: Blood pressure, hemogram, sedimentation, biochemical values, coagulation tests, thyroid function tests and the lipid profiles of patients who are diagnosed with SHL should be evaluated. Checking autoantibodies by taking autoimmune disease into consideration as well as treponemal antibody tests in the case of suspected syphilis should be undertaken. Neutrophil to Lymphocyte ratios and Platelet to Lymphocyte ratios which are considered novel prognostic parameters in patients with SLH can also be evaluated (Wang et al., 2013).

Radiological Tests: Computed Tomography (CT) and Magnetic Resonance (MR) imaging can be ordered to evaluate the temporal bone. CT is more useful in the differential diagnosis of temporal bone traumas and fistula. Gadolinium MR is gold standard in the diagnosis of retro-cochlear pathology such as acoustic neuroma (Bozkurt et al., 2014).

Bilateral SHL, mild hearing loss, lack of accompanying vestibular symptoms, an ascending curve in audiograms, the early commencement of treatment, development in younger people and lack of comorbidities are good prognostic factors. Pediatric and elderly patients, severe hearing loss, the late commencement of treatment and the presence of vestibular symptoms and systemic diseases are among the poor prognostic factors (Wang et al., 2013, Karakurt et al., 2014).

4. Treatment Methods

Numerous types of treatments have been administered for SHL. This variety in treatment protocols stems from the differing etiological factors and uncertainties in diagnosis (Matthew et al., 2008). Some of the treatment methods include corticosteroids, antivirals, vasodilators, hemodilution drugs, diuretics, hyperbaric oxygen therapy, ozone therapy and combined therapies. As most of the patients are idiopathic, treatment is generally initiated empirically. Today, the most popular drugs which are thought to be most effective in the treatment of SHL patients are corticosteroids (Stachler et al., 2012).

4.1. Corticosteroids

It is thought that hearing loss is associated with the immune process (Dornhoffer et al., 1997). Therefore, corticosteroids have been used in treatment. Corticosteroids are still the most commonly used drugs in the treatment of idiopathic SHL (Aoki et al., 2006). In the literature, it has been reported that rates of improvement ranged from 49% to 89% with the use of systemic steroids in treatment (Chandrasekhar, 2001). A very significant trial which indicated the efficacy of steroids and was conducted by Wilson et al. (Wilson et al. 1980) was a double-blind and placebo-controlled study. However, it was shown in another double-blind, placebo-controlled study in 2001 that steroids were not superior to the placebo in effect (Cinamon et al., 2001). A Cochrane database searching study concluded that the impact of steroid treatment in SHL was unclear. Moreover, the use of steroids is contraindicated in patients with ulcers, diabetes, active bacterial infections and renal or heart failure (Dornhoffer et al., 1997). Intratympanic steroid (ITS) treatment was considered because of the side effects of systemic steroids and to further increase steroid concentration in the perilymph. ITS can be used with three different protocols. It can be used with systemic steroids, as rescue therapy in patients who cannot benefit from systemic steroids and as primary therapy in patients who are

not prescribed systemic steroids (O'Malley et al., 2008). In their study, Gianoli and Li (Gianoli and Li, 2001) found that ITS provided a hearing benefit of 44% in patients who were not able to benefit from systemic steroids. Another study by Ho Guan-Min et al. (Guan-Min et al., 2004) reported that intratympanic treatment provided an improvement of 54% in patients who showed no improvement following the use of systemic steroids. Arastou et al. (Arastou et al., 2013) compared systemic steroids alone to a combination of systemic and intratympanic steroid and demonstrated that the combined therapy was more effective. The possibility of administering ITS to patients for whom systemic steroids are contraindicated, an ability to treat only the affected ear and attaining high concentrations in the perilymph are among the significant advantages of ITS treatment. On the other hand, the disadvantages of ITS treatment include the development of complications such as tympanic membrane perforation, pain, vertigo and otitis (O'Malley et al., 2008).

4.2. Antiviral treatment

The fact that viral causes play a role has been shown in many cases in the studies on the etiology of SHL. Consequently, antiviral treatments were trialed in these patients. However, findings which support the viral theory are unclear (Merchant et al., 2008). In a study by Seltzer and Mark (Seltzer and Mark, 1991), signs of inflammation were observed in magnetic resonance imaging (MRI) during SHL and a decrease in these signs and symptoms supported the presence of viral inflammation. However, a study by Tucci et al. (Tucci et al., 2002) trialed steroid+valacyclovir and steroid+placebo in two separate groups and found no significant difference. In a double-blind, randomized study by Westerlaken et al. (Westerlaken et al., 2003) in 91 patients, steroids alone and steroid+acyclovir were compared and no difference was observed in terms of recovery. Uri et al. (Uri et al., 2003) demonstrated that adding antiviral drugs to steroid treatment did not change the outcome. Even though there is no clear clinical trial indicating the benefits of antiviral treatments in SHL, a combination of steroid+antiviral therapy is recommended in treatment due to there being less side effects and more potential benefits (Matthew et al., 2008).

4.3. Hyperbaric oxygen therapy:

Hyperbaric oxygen therapy (HBOT) was used in SHL treatment for the first time in 1979. It is thought that HBOT corrects ischemia-induced hearing loss by partially increasing oxygen pressure in the inner ear. Narozny et al. administered steroid and vasoactive drugs in one group and administered HBOT in addition to these drugs in another group, and found a significant difference in the latter group in terms of hearing gain (Narozny et al., 2004). In their study conducted with 465 patients, Liu et

al. (Liu et al., 2011) revealed that adding HBOT to steroid treatment significantly contributed to recovery. Desloovere et al. (Desloovere et al., 2006) advocated that HBOT was successful in rescue therapy. Again in a study by Muzzi et al. (Muzzi et al., 2010), HBOT was administered to patients who did not benefit from medical treatment and it was seen to be successful. However, some authors asserted that HBOT had no benefits. In a study in 276 patients, Suzuki et al. (Suzuki et al., 2012) stressed their findings that steroid+ITS was superior to steroid+HBOT. Satar et al. (Satar et al. 2006) demonstrated in their study that HBOT had no additional benefits for the success of medical treatments.

The studies showed that HBOT could be used as a combined treatment or as rescue therapy in patients who did not benefit from medical therapies. While many studies in this regard highlight the benefit of HBOT, its efficacy has not been definitively proven as yet (Bennett et al., 2007). It is recommended that HBOT be started in the first three days to increase its effectiveness and it can be maintained for up to three months (Kanda et al., 1995).

4.4. Ozone Therapy

In recent years, ozone therapy has been used for the treatment of SHL as well as for many other diseases. A double-blind, placebo-controlled study asserted that ozone therapy had clear benefits for patients with SHL in pure tone audiometry, speech discrimination scores and subjective hearing gain (Ragab et al., 2009).

4.5. Vasoactive Drugs

Vasodilators, anticoagulants and hemodilution agents are vasoactive drugs used in the treatment of SHL. A disorder in microcirculation in the inner ear may cause sudden hearing loss. There is a negative correlation between hearing thresholds and cochlear blood flow (Ihler et al., 2012). Vertebrobasilar insufficiency, atherosclerosis, thrombosis, and carotid occlusive diseases accompanying SHL should be considered particularly in patients over 50 years of age (Castro et al., 2007). Vasoactive agents increase tissue perfusion by affecting microcirculation in the inner ear. Vasoactive drugs such as Pentoxifylline and Prostaglandin E1 were administered in addition to steroids (Suzuki et al., 2008). While some authors indicate the efficacy of such drugs in treatment, there are other authors who suggest that they do not have any significant effect (Ogawa et al., 2002).

It was seen in the studies conducted with this group of drugs that they were used in combination with steroids; however, there is insufficient data relating to use as a single agent. Considering the overall studies, the efficacy of vasoactive drugs in the treatment of SHL has not been proven.

4.6. Diuretics

When SHL is thought to be induced by endolymphatic hydrops, diuretics can be added to the treatment protocol. Thiazide diuretics are preferred in the foreground due to the ototoxic effects of many diuretic drugs.

4.7. Urografin (Diatrizoate Meglumine)

It is an intravenous contrast medium that is used for radiological imaging. Coincidentally, Morimitsu noticed the effect on hearing. According to Morimitsu's theory on Urografin treatment, SHL is caused by a fracture or defect in the blood-cochlea barrier, the cortic organ and stria vascularis and causes a decrease in endocochlear DC potentials. Urografin allows the Na pump to operate actively by filling the pores of the impaired membrane with its configuration and molecular size, thus creating normal potentials (Morimitsu, 1977). On the other hand, Bhat et al. emphasized that substantial amounts of histamine were released to the plasma during injections of Urografin and histamine had an important place in the treatment of SHL (Emmett and Shea, 1979). Still, the use of Urografin is limited due to the fact that Urografin treatment can only be administered intravenously and raises the possibility of a contrast agent reaction.

4.8. Surgical therapy

In cases with suspected hearing loss associated with perilymph fistula, surgery (exploratory tympanotomy) is recommended to correct complaints related to hearing and balance and to prevent complications such as meningitis. Detected fistulas are closed with a graft like fascia, etc. and this procedure contributes to the improvement with SHL. Another cause that requires surgery is Acoustic neuroma. If it causes hearing loss, surgical therapy is recommended.

Conclusion

Although there are many studies on the treatment of SHL, a treatment protocol is still unclear. It is difficult to focus on a certain treatment group because of the uncertainty of SHL etiology. Antivirals, vasoactive drugs, hyperbaric oxygen and, particularly, steroids are the most common treatment options. As SHL can be improved also without any treatment, it is difficult to understand to what extent recovery depends on the treatment administered. Therefore, there is still no treatment protocol with proven certainty for SHL. Larger studies are needed relating to both etiology and treatment.

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COVID-19: WHAT CAN BE SAID ABOUT IT?

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Introduction

Coronaviruses are enveloped and positive sense, single-stranded RNA (+ss RNA) (Kramer, Schwebke, & Kampf, 2006) viruses ranging from 60 nm to 140 nm in diameter with spike like projections on its surface that range from 9 nm to 12 nm giving the virions a crown (solar corona) like appearance under the electron microscope; hence the name coronavirus (Figure1) (Cassady & Whitley, 2016) (Goldsmith et al., 2004). Coronaviruses (CoV) constitute a large family of viruses that is found in nature and can cause respiratory, enteric, hepatic and neurological diseases in humans and animals.

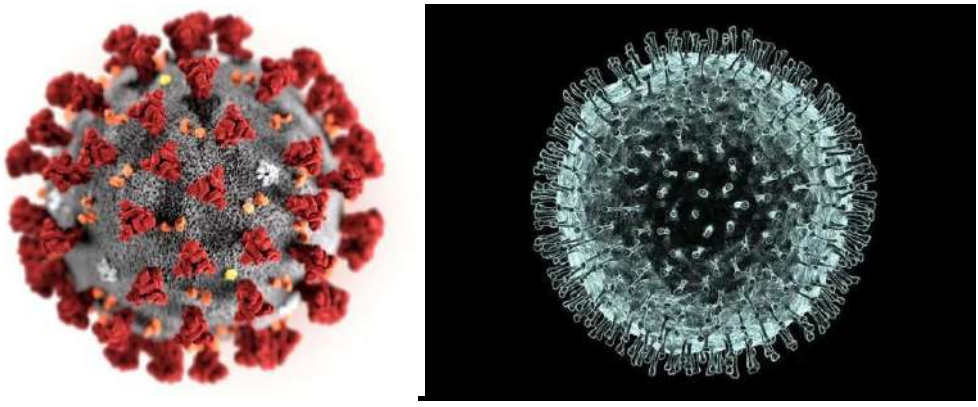

Figure 1. The appearance of Coronavirus.

Classification

The SARS-CoV-2, taxonomically, is currently part of the species of the SARS-related coronaviruses that belong to the subgenus Sarbecovirus. Together with the subgenera Embecovirus, Hibecovirus, Merbecovirus, and Nobecovirus, that are part of the genus Betacoronavirus (order Nidovirales; suborder Cornidovirineae; family Coronaviridae; subfamily Coronavirinae) (Gorbalenya et al., 2020; Rodriguez-Morales et al., 2020). The family consists of two subfamilies, Coronavirinae and Torovirinae and members of the subfamily Coronavirinae are subdivided into four genera: (a) Alphacoronavirus contains the human coronavirus HCoV-229E and

HCoV-NL63; (b) Betacoronavirus contains HCoV-OC43, Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), HCoV-HKU1, and Middle East Respiratory Syndrome coronavirus (MERS-CoV); (c) Gammacoronavirus includes viruses of whales and birds and; (d) Deltacoronavirus includes viruses isolated from pigs and birds (Burrell, Howard, & Murphy, 2016). SARS-CoV-2 belongs to Betacoronavirus together with two highly pathogenic viruses, SARS-CoV and MERS-CoV. While α and β genera can infect mammals, they are responsible for respiratory infections in humans and enteritis in animals. γ and δ genera tend to infect birds (Zhu et al., 2020). While coronavirus affects the respiratory, gastrointestinal and cardiovascular systems in animals, it mostly causes respiratory and gastrointestinal system diseases in humans (Saif, 2004). Human Coronaviruses (HCoV) were first described in the 1960s, and there are 7 Coronaviruses known to cause illness in humans. Human Coronaviruses 229E (alpha Coronavirus), NL63 (alpha Coronavirus), OC43 (betacoronavirus) and HKU1 (betacoronavirus) cause typical mild/moderate respiratory tract diseases in humans. It is known that Human Coronavirus OC43 and NL63 are more common in children, cause epidemics in winter, and 229E is rare (Heimdal et al., 2019; Saatçı, 2020).

Except for coronaviruses that usually cause mild/moderate upper respiratory tract infections, coronavirus infections (MERS-CoV, SARS-CoV) that cause epidemics and severe infections from time to time have also been reported. MERS-CoV (betacoronavirus, Middle East Respiratory Syndrome) was first detected in September 2012 in Saudi Arabia and affected 27 countries, with confirmed 2494 cases and 858 (34%) deaths. It has been established that MERS-CoV is transmitted to humans from dromedary camels that are intermediate carriers. Bats are the main source (Bakanlığı,2020). SARS-CoV (betacoronavirus, Severe Acute Respiratory Syndrome) is first seen in February,2003 in Guangdong province of China. The origin of SARS-CoV is bats and is crossed over to humans via palm civets (Memish, Perlman, Van Kerkhove, & Zumla, 2020). This virus affected 8422 people mostly in China and Hong Kong and caused 916 deaths (mortality rate 11%) before being contained (Chan-Yeung & Xu, 2003). The 7th and the last member of the family is the newly found 2019-nCoV (2019-novel coronavirus), which is close to bat betacoronavirus.

Pneumonia caused by this Coranavirus has been called "Novel Coronavirus Infected Pneumonia (NCIP)" (Yeşil & Hacımustafaoğlu; Zhu et al., 2020).

While this New Coronavirus is called 2019-nCoV by the World Health Organization, as of February 11, 2020, it has been named SARS-CoV-2 by the International Virus Taxonomy Committee Coronavirus Working Group due to some genetic and clinical similarities (Gorbalenya et al., 2020). In addition, on the same date, it was announced in the "Nature"

newsletter with the recommendation of WHO that the term COVID-19 means "Coronavirus disease in 2019" will be used for the disease caused by 2019-nCoV (Yeşil & Hacımustafaoğlu). There is 79% similarity between SARS-CoV and SARS-CoV-2, and 59% similarity and less relationship between MERS-CoV and SARS-CoV-2. The structure of the receptor-binding gene region is very similar to the structure of SARS-CoV and it has been shown that the virus uses the same receptor, angiotensin converting enzyme 2 (ACE2) for cell entry (Dikmen, KINA, Özkan, & İlhan, 2020; R. Lu et al., 2020; Zhou et al., 2020).

Origin

On 31st December 2019, 27 cases of pneumonia of unknown etiology were identified in Wuhan City, Hubei province in China (Lu, Stratton, & Tang, 2020). Wuhan is the most populous and the capital city in Central China with a population exceeding 11 million. These patients most notably presented with clinical symptoms of dry cough, dyspnea, fever, sore throat and bilateral lung infiltrates on imaging. Most of cases have spontaneously resolved. However, some have developed various fatal complications including organ failure, septic shock, pulmonary oedema, severe pneumonia, and Acute Respiratory Distress Syndrome (ARDS) (Chen, 2001). 54.3% of those infected with SARS-CoV-2 are male with a median age of 56 years. Notably, patients who required intensive care support were older and had multiple co-morbidities including cardiovascular, cerebrovascular, endocrine, digestive, and respiratory disease. Those in intensive care were also more likely to report dyspnea, dizziness, abdominal pain, and anorexia (Bai et al., 2020; H. Lu et al., 2020). Many of the initial cases had a common exposure to the Huanan wholesale seafood market that also traded live animal species including poultry, bats, marmots, and snakes (Sohrabi, Alsafi, O'Neill, et al., 2020). The surveillance system (put into place after the SARS outbreak) was activated and respiratory samples of patients were sent to reference labs for etiologic investigations. On the same date, China notified the outbreak to the World Health Organization and on 1st January of 2020, the Huanan seafood market was closed. On 7th January, the virus was identified as coronavirus that had >95% homology with the bat coronavirus and > 70% similarity with the SARS-CoV. Environmental samples from the Huanan wholesale seafood market had been analyzed and tested positive, pointing that the virus originated from there (Singhal, 2020a). The number of cases started increasing exponentially, some of which did not have exposure to the live animal market, suggestive of the fact that human-to-human transmission was occurring (Chaolin Huang et al., 2020). The first fatal case was reported on 11th Jan 2020. The massive migration of Chinese during the Chinese New Year fueled the epidemic. In other provinces of China, and in other countries (Thailand, Japan and South Korea in quick succession)

cases were reported in people who were returning from Wuhan. Transmission to healthcare workers caring for patients was described on 20th January,2020. By 23rd January, the 11 million population of Wuhan was placed under lock down with restrictions of entry and exit from the region. Soon this lock down was extended to other cities of Hubei province. Cases of COVID-19 in countries outside China were reported in those with no history of travel to China suggesting that local human-to-human transmission was occurring in these countries (Bastola et al., 2020).

Although phylogenetic analysis suggests that bats may be the original host of SARS-CoV-2, the intermediate animal through which it crossed over to humans is uncertain. Pangolins and snakes are the current suspects (R. Lu et al., 2020; Wong, Cregeen, Ajami, & Petrosino, 2020).

History of important events of Covid-19 Outbreak

We can list the important developments in the time period from the first day of Covid-19 to 30th November 2020 in chronological order as follows (Budak & Korkmaz, 2020; Muccari, Chow, & Murphy, 2020):

Dec. 31, 2019: Chinese officials in Wuhan in China's central Hubei province confirmed dozens of cases of pneumonia from an unknown cause.

Jan. 7, 2020: The outbreak was identified as a new coronavirus.

Jan. 11: China reported its first known death from an illness caused by the coronavirus. The patient was a 61 years old man in Wuhan.

Jan. 20: A World Health Organization situation report detailed the first confirmed cases outside China in Thailand, Japan and South Korea.

Jan. 21: The United States announced its first confirmed coronavirus case, a man in his 30s in Washington state.

Jan. 23: China placed Wuhan, a city of 11 million people, under quarantine orders. All flights and trains departing from the city were cancelled, and buses, subways and ferries within the city were suspended.

Jan. 30: WHO declared the outbreak as a global Public Health Emergency of International Concern (PHEIC) as more than 9,000 cases were reported worldwide, including 18 countries beyond China (Jiang et al., 2020).

Jan. 31: The White House announced that it would ban entry for most foreign nationals who had travelled to China within the last 14 days.

Feb. 1: Princess Cruises confirmed that a passenger who sailed aboard the Diamond Princess from Yokohama, Japan, on January 20 and disembarked in Hong Kong on January 25 had tested positive for the virus.

Feb. 2: The first coronavirus death reported outside China (a 44 year old Wuhan resident) who died in the Philippines.

Feb. 4: The Diamond Princess cruise ship was quarantined in Yokohama with about 3,700 people, including passengers and crew, onboard.

Feb. 7: Dr Li Wenliang, a Chinese doctor who issued a warning about the coronavirus outbreak before it was officially recognized, died in Wuhan. Li became a hero in China and his death sparked a wave of public mourning.

Feb. 8: The first U.S. citizen died from COVID-19 in Wuhan.

Feb. 9: The death toll in mainland China rose to 811, surpassing the number of fatalities from the SARS outbreak in 2003.

Feb. 11: WHO announced that the disease caused by the new coronavirus will be known by the official name of COVID-19.

Feb. 14: Egypt confirmed its first coronavirus case, becoming the first country in Africa to be affected by the outbreak.

Feb. 14: The first coronavirus death was recorded outside Asia. The patient was an 80 years old Chinese tourist who died in France.

Feb. 20: South Korea reported its first coronavirus death, as the country's number of confirmed cases rose to 104. It was the ninth confirmed death from the virus outside mainland China.

Feb. 24: Italy became the worst-hit country in Europe as cases spiked. Health officials announced the sixth death from the virus.

Feb. 24: The U.S. stock market plummeted over coronavirus fears, after the Dow Jones Industrial Average experienced the worst day in two years.

Feb. 26: California announced the first case in the U.S. with no clear source of exposure.

Feb. 26: Brazil confirmed its first coronavirus case, the first in Latin America.

Feb. 28: Iran reported 34 deaths out of 388 confirmed coronavirus cases, making it the country with the highest number of deaths from the virus outside China.

Feb. 29: President Donald Trump announced additional travel restrictions involving Iran and increased warnings about travel to Italy and South Korea.

Feb. 29: The first recorded coronavirus death in the U.S., a man in his 50s in Washington state.

March 3: Patients infected by the coronavirus wait to be transferred from Wuhan No. 5 Hospital to Leishenshan Hospital, the newly built hospital for COVID-19 patients, in Wuhan.

March 6: Vice President Mike Pence announced that 21 people aboard the Grand Princess, a cruise ship being held off the coast of California, tested positive for the coronavirus.

March 8: Italy issued a lockdown to quarantine around 16 million people in the country's northern Lombardy region, as confirmed cases surpassed 5,800 and more than 230 people died from the virus. The area sealed off includes Milan and Venice.

March 9: Ireland cancels St. Patrick's Day festivities over coronavirus concerns.

March 10: Italy's prime minister announced that the lockdown placed on millions in the Lombardy region will be extended to the entire country to curb the virus' spread.

March 10: Iran's health officials reported a spike of almost 900 new cases, bringing the country's total number of confirmed cases to 8,042 with 291 deaths.

March 10: Chinese President Xi Jinping visited Wuhan for the first time since the virus emerged in December. The visit came as people gradually returned to work in other parts of China.

March 11: The World Health Organization declared that the coronavirus outbreak "can be characterized as a pandemic," which is defined as worldwide spread of a new disease for which most people do not have immunity.

March 11: The NBA suspended all basketball games after a player for the Utah Jazz preliminarily tested positive for COVID-19, the disease caused by the new coronavirus.

March 11: The Oscar-winning actor Tom Hanks and his wife, Rita Wilson, announced that they tested positive for the coronavirus. They announced on Instagram that they are being isolated and observed in Australia, where Hanks was in pre-production for a film.

March 11: Trump announced a new restriction on many foreign travelers from 26 countries in Europe, except for Ireland and the United Kingdom, for the next 30 days.

March 13: The World Health Organization said Europe "has now become the epicenter" of the pandemic, with more reported cases and deaths than the rest of the world combined, beyond China.

March 14: Spain recorded a spike of nearly 2,000 new cases. With more than 3,800 total confirmed cases and at least 84 deaths, the country enacted a partial lockdown restricting people from leaving their homes unless to go to work, the pharmacy or a hospital.

March 15: The White House announced that the European travel ban would be extended to include the U.K. and Ireland.

March 15: Iran reported a big jump of 1,365 new cases in the past 24 hours, bringing the country's total number of confirmed cases to 12,729, while the death toll rose to 611.

March 15: The number of new cases imported into mainland China from overseas surpassed the number of locally transmitted new infections for the first time, according to the country's National Health Commission.

March 15: The Centers for Disease Control and Prevention released guidelines recommending "that for the next 8 weeks, organizers (whether groups or individuals) cancel or postpone in-person events that consist of 50 people or more throughout the United States."

March 16: Wall Street plunged again, as the Dow Jones Industrial Average sank by 3,000 points and the S&P 500 and Nasdaq were down by around 12 percent by the closing bell.

March 16: Germany sealed its borders with France, Austria, Switzerland, Luxembourg and Denmark to curb the virus' spread. The border controls only allow through goods and people who work in neighboring nations and thus commute across state lines.

March 16: Italy announced that confirmed cases rose to nearly 28,000, an increase of more than 3,000 from the day before, while the death toll hit 2,158. The government said it plans to spend 25 billion euros ($28 billion) to tackle the epidemic, while Italian officials said they expect more than 90,000 people will become infected by the end of April.

March 16: Canada announced plans to close the border to noncitizens, as the country's number of confirmed cases rose to 339 with one death. The border restrictions include some exceptions, including for U.S. citizens.

March 16: U.S. researchers administered the first shot to the first person in a test of an experimental coronavirus vaccine. Even if the trials go well, health officials warned that a vaccine would not be widely available for at least 12 to 18 months.

March 16: France imposed stringent restrictions on people's movement for two weeks, with president Emmanuel Macron saying people should only leave their homes for essential activities. The order came after the country already shut down restaurants, bars, ski resorts and closed schools.

March 17: The European Union announced a 30-day ban on most non-essential incoming travel.

March 18: Canada and the U.S. agreed to close its borders to all "non-essential traffic."

March 18: Belgium announced plans to lock down the country, becoming the fourth nation in Europe to enact a nationwide quarantine, after Italy, France and Spain.

March 18: The WHO announced an international trial to gather data about which treatments are most effective for the coronavirus. Participants in the so-called solidarity trial include Argentina, Canada, France, Norway, South Africa, Spain, Switzerland and Thailand.

March 18: Italy reported its deadliest day of the coronavirus outbreak after deaths rose by 475, the biggest one-day jump. Nationwide, Italy recorded more than 35,713 confirmed cases and 2,978 deaths, as the country tightened restrictions on residents leaving their home.

March 19: China reported no new domestic cases for the first time since the start of the epidemic. There were 34 new confirmed cases, but they were registered as "newly diagnosed imported cases."

March 19: Australia and New Zealand announced plans to close their borders to all foreigners.

March 19: The death toll in Spain, the second worst affected country in Europe, saw its death toll soar by 209 over a 24-hour period, bringing the country's total number of deaths to 767 and total confirmed cases to 17,147.

March 19: Italy overtook China as the country with the most coronavirus-related deaths, registering 3,405 fatalities.

March 19: The Cannes Film Festival, set to be held in May, was postponed until an as-yet-decided time in late June or early July.

March 19: China exonerated Dr. Li Wenliang, the doctor who was reprimanded for warning about the coronavirus outbreak and later died of the disease.

March 20: The U.S. announced plans to close the border with Mexico to all "nonessential travel." Acting Homeland Security Secretary Chad Wolf said all immigrants who lack proper entry documentation will be turned away.

March 20: Death toll in Italy surpassed 4,000, after 627 more deaths were announced from the previous day. It was the biggest day-to-day increase in the country, as Italy neared the end of its second week of a nationwide quarantine.

March 21: Sri Lanka imposed a countrywide curfew over the weekend, as other South Asian countries accelerated efforts to stop the virus' spread.

March 21: China administered its first clinical trials of coronavirus vaccines to volunteers, according to local media reports.

March 21: Jordan ordered a nationwide curfew, limiting the mobility of its 10 million citizens and closing all shops indefinitely.

March 21: Coronavirus cases in Switzerland jumped 25 percent in just 24 hours. The country's confirmed cases rose to 6,113 with at least 56 deaths.

March 22: The International Olympic Committee announced that they expect to make a decision about the upcoming Tokyo Games within four weeks.

March 22: Canada announced that it will not send athletes to the Olympics later this year if the games are not delayed because of the pandemic. Australia similarly announced plans to pull out of the games the next day (local time).

March 23: Spain's coronavirus death toll topped 2,000, more than doubling in just three days. The country, the second hardest hit in Europe, had 33,090 confirmed cases and 2,182 deaths.

March 23: The Iraqi government extended a ban on travel in and out of Baghdad to March 28. The government also extended its ban on all flights in and out of the country's airports, as the number of confirmed cases rose to 233 cases and 20 deaths.

March 23: Convicted rapist and disgraced movie mogul Harvey Weinstein, 68, tested positive for coronavirus.

March 23: The World Health Organization said more than 300,000 cases were reported from almost every country in the world. Johns Hopkins University, which cited slightly different numbers, reported that global coronavirus infections were on track to reach 350,000.

March 23: The U.K. issued a three-week national lockdown, with strict new measures to limit people's movement. Prime Minister Boris Johnson said the lockdown will be enforced by police.

March 24: Chinese authorities announced that travel restrictions in and out of the city of Wuhan will be lifted on April 8.

March 24: Japan's prime minister Shinzo Abe announced that the Tokyo 2020 Olympics will be postponed, adding that the games will be held by the summer of 2021.

March 24: France entered a two-month state of emergency, part of an emergency law that was passed to give the government special powers to enforce the countrywide lockdown that began two weeks ago.

March 24: The U.K.'s death toll jumped by 25 percent, after 87 new fatalities were reported in the past 24 hours, the country's highest daily increase.

March 25: The WHO warned that the U.S. could become the global epicenter of the coronavirus pandemic. The country recorded 54,810 coronavirus cases, including 781 deaths.

March 25: Prince Charles, 71, who is first in line to the British throne, tested positive for coronavirus.

March 25: Spain surpassed China in nationwide deaths from coronavirus, becoming second only to Italy. Spain reported 738 new deaths in the past 24 hours, bringing the country's total number of fatalities to 3,434.

March 26: New Zealand started a one-month mandatory lockdown to slow the spread of the virus.

March 26: Russia announced plans to ground all international flights, with exceptions for repatriation flights bringing Russian citizens home and those with special government approval.

March 26: U.S. coronavirus cases surpassed China. The U.S. reported at least 82,474, with more than 1,100 deaths, while China reported 81,961 cases and more than 3,000 deaths.

March 27: Britain's Prime Minister Boris Johnson tested positive for coronavirus.

March 27: Coronavirus cases in the U.S. surpassed 100,000, the most in the world. More than 1,500 deaths were also reported nationwide.

March 27: Italy recorded its deadliest day of the coronavirus pandemic, after the country reported 919 new deaths in the past 24 hours. The country had more than 86,000 confirmed cases and 9,134 total deaths nationwide.

March 28: Italy surpassed China in the number of confirmed coronavirus infections, with 86,498 cases. Italy trailed the United States, which had nearly 104,837 confirmed cases, while China recorded 81,394 cases.

March 28: The U.S. Food and Drug Administration authorized the emergency use of a new, rapid coronavirus test that could give patients results in less than 15 minutes.

March 28: An infant, younger than a year old, who tested positive for coronavirus died in Illinois, state health officials announced.

March 29: The city of Wuhan, China, reopened subways and long-distance train service.

March 29: Spain recorded 838 deaths overnight, the biggest surge in fatalities for the country in the past 24 hours. Spain had 78,797 confirmed cases and a total of 6,528 deaths, the second highest in Europe after Italy.

March 30: The Tokyo 2020 Olympic Games were rescheduled for July 2021. The games are now scheduled to open July 23, 2021, and close Aug. 8, 2021.

March 31: Italy's National Institute of Health said the outbreak was reaching a plateau in the country, as Italy's death toll rose to more than 12,000.

April 1: Wimbledon tennis tournament was cancelled.

April 1: The death of a 6-week-old baby was linked to the coronavirus, in what was thought to be one of the youngest coronavirus-related fatalities of the pandemic.

April 4: More than 150 crew members of a U.S. Navy aircraft carrier whose captain was relieved of command after raising concerns about the coronavirus tested positive. More than 1,500 sailors on the USS Theodore Roosevelt were moved ashore after a letter written by Capt. Brett Crozier was leaked.

April 5: U.K. Prime Minister Boris Johnson was taken to the hospital for tests, more than a week after he tested positive for coronavirus.

April 6: British Prime Minister Boris Johnson was transferred to the intensive care unit at a London hospital after his COVID-19 symptoms worsened.

April 6: The coronavirus death toll in the U.S. surged past 10,000.

April 6: China reported its first day with no coronavirus deaths since the outbreak began.

April 7: The Israeli government imposed a complete nationwide lockdown over the Jewish Passover holiday.

April 8: Britain's Prime Minister Boris Johnson remained in intensive care, but was "responding to treatment," according to a spokesperson.

April 9: Second coronavirus vaccine trial began in the U.S.

April 9: British Prime Minister Boris Johnson was moved out of the intensive care.

April 10: Turkey's coronavirus death toll topped 1,000.

April 10: The World Health Organization warned that a premature lifting of lockdown restrictions by countries fighting the coronavirus could spark a "deadly resurgence."

April 12: British Prime Minister Boris Johnson left the London hospital.

April 13: The U.S. Food and Drug Administration cleared the first saliva test to diagnose COVID-19. The test initially will be available through hospitals and clinics affiliated with Rutgers University in New Jersey.

April 14: President Trump announced plans to halt funding for the World Health Organization, accusing the agency of "severely mismanaging and covering up" the coronavirus crisis. Trump previously threatened to cut off funding after the WHO criticized his response to the epidemic.

April 15: Organizers of the Cannes Film Festival announced that the event will not take place this year in "its original form" due to the pandemic.

April 16: Officials across the U.S. are racing to provide coronavirus tests to diagnose infections and to identify recovered patients with antibodies that may help others battle the disease.

April 16: The president of the European Commission (the executive branch of the European Union) offered an apology to Italy on Thursday, saying the country did not receive adequate help at the beginning of the coronavirus pandemic.

April 16: While hand-washing with soap and water has been advocated worldwide to keep the coronavirus at bay, some 74 million people in the Middle East lack access to a sink, soap or basic water facilities at home, a United Nations report found.

April 17: Comic-Con 2020 was canceled for the first time in its 50-year history.

April 17: NBA Commissioner Adam Silver announced the league will withhold 25 percent of player pay starting with their May 15 checks. Silver added that games that were not played due to the pandemic will not be rescheduled and said it remains impossible to make any decisions about whether to resume the remainder of the season.

April 20: Iran lifted some of its lockdown restrictions, allowing some shops and inter-city roads to open.:

April 20: The NYC Pride March was cancelled for the first time in a half-century, along with all in-person events leading up to the annual June event.

April 20: Oil prices plunged into negative territory as global demand plummeted.

April 20: Robert Redfield, director of the Centers for Disease Control and Prevention, warned that a second wave of the coronavirus is bound to be much worse next winter.

April 21: Spain's San Fermin bull run was cancelled because of the pandemic. The event has only been cancelled four other times in history: in 1937 and 1938 for the Spanish civil war, in 1978 following clashes between police and Basque nationalists, and in 1997 after the assassination of a Spanish politician by the ETA separatist group.

April 24: The Food and Drug Administration cautioned against prescribing hydroxychloroquine, an antimalarial touted by President Trump, to COVID-19 patients outside of hospital settings or clinical trials.

April 24: The number of coronavirus deaths in the U.S. topped 50,000.

April 25: China reported no new coronavirus deaths for the tenth consecutive day.

April 25: The U.K.'s coronavirus death toll surpassed 20,000, making it the country with the fifth-highest virus death toll in the world, after the U.S., Italy, Spain and France.

April 25: China announced that there are no remaining coronavirus cases in the hospitals in Wuhan, the city where the global pandemic began.

April 25: The Africa Centers for Disease Control and Prevention announced that there were more than 30,000 reported cases of coronavirus on the continent of Africa. South Africa had the continent's most COVID-19 cases with 4,361 reported cases, followed by Egypt, Morocco and Algeria.

April 27: U.K. Prime Minister Boris Johnson returned to work after recovering from COVID-19.

April 27: Russia said it surpassed China in the number of confirmed coronavirus cases since the outbreak began. Russia reported a total of 87,147 infections across the country, with significant day-on-day growth over the past two weeks.

April 27: The head of the World Health Organization warned that the coronavirus pandemic was "far from over," expressing concern about growing outbreaks in Africa, Eastern Europe, Latin America and some Asian countries.

April 27: JetBlue Airways became the first U.S. airline to announce that all passengers will have to wear a face covering on flights.

April 28: The total number of coronavirus cases in the U.S. reached 1 million.

April 29: The results of a large study hinted at the potential benefit of an experimental COVID-19 drug called remdesivir. Gilead Sciences, which makes the drug, said full results would be published "in the coming weeks."

April 30: South Korea reported no new domestic virus cases for the first time since February, according to the Korea Centers for Disease Control and Prevention.

April 30: The World Health Organization said it is “urgently” investigating a potential link between the coronavirus and Kawasaki syndrome, an illness of unknown cause that primarily affects children under 5.

April 30: A Navy hospital ship, the USNS Comfort, departed New York City, a month after it was sent to relieve stress on local hospitals. The Comfort treated just 182 people as a surge in cases in the city fell short of the worst-case projections.

April 30: Russia's Prime Minister Mikhail Mishustin tested positive for the coronavirus. Mishustin informed President Vladimir Putin of the result during a video conference.

May 1: The Food and Drug Administration granted emergency use authorization for remdesivir, the drug that has shown promise in early clinical trials to help people with severe COVID-19.

May 1: The NBA postponed its draft lottery and combine because of the coronavirus pandemic. No new dates were set.

May 2: China’s central province of Hubei, where the coronavirus was first detected, lowered its emergency response level from the highest to the second highest, in the latest relaxation of lockdown restrictions.

May 3: South Korea reported no new coronavirus deaths for the first time since February.

May 4: Swiss drug maker Roche won emergency approval from the U.S. Food and Drug Administration for an antibody test to determine whether people have ever been infected with the coronavirus.

May 5: The World Health Organization said that a report that COVID-19 had emerged in December in France, sooner than previously thought, was "not surprising," and urged countries to investigate any other early suspicious cases.

May 5: Researchers at Pfizer and New York University said they are working on a never-before-tried coronavirus vaccine that could be available by September.

May 6: A 57-year-old man from El Salvador became the first person to die from COVID-19 in Immigration and Customs Enforcement detention.

May 7: The World Health Organization said that the coronavirus could kill between 83,000 and 190,000 in Africa in its first year if not contained.

May 8: China's National Health Commission said it supports and will participate in the World Health Organization global initiative to develop COVID-19 vaccines.

May 8: The U.S. Food and Drug Administration authorized the first test that uses saliva, rather than an uncomfortable nasal swab, to diagnose COVID-19.

May 8: New York Gov. Andrew Cuomo said that the state has 73 cases of children developing symptoms like Kawasaki disease, a rare but potentially dangerous complication thought to be linked to the coronavirus.

May 8: The National Institute of Allergy and Infectious Disease began a trial looking at the effects of remdesivir combined with a second drug, called baricitinib, on treating COVID-19.

May 8: Roy Horn, half of the famed magic and entertainment duo Siegfried & Roy, died of complications related to coronavirus at the age of 75.

May 8: Thousands of cyclists took over streets in the center of the Slovenian capital, Ljubljana, to protest coronavirus restrictions put in place by Prime Minister Janez Jansa's government.

May 9: Two more children in New York state died of an inflammatory syndrome believed to be related to the coronavirus, raising the toll to three.

May 9: White House officials said Dr. Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, and Dr. Robert Redfield, director of the Centers for Disease Control, will self-quarantine after possible exposure to COVID-19.

May 11: Russia confirmed more than 2,000 COVID-19 deaths, as the country's outbreak grew to become the world's third largest. Russia's total number of confirmed cases rose to 221,344, surpassing Italy and the U.K.

May 11: The WHO warned that summer heat waves that are expected to hit Europe in the coming months will add to the risks facing those already vulnerable to coronavirus outbreak.

May 12: Kremlin spokesman Dmitry Peskov told Russian state news agencies that he has been hospitalized after testing positive for COVID-19. Peskov followed Prime Minister Mikhail Mishustin, who announced he was heading to a hospital on April 30 after testing positive.

May 12: USA Gymnastics postponed all "premier events" until 2021 because of the coronavirus epidemic.

May 13: A 28-year-old sumo wrestler became the youngest person to die from the coronavirus in Japan, the country's Ministry of Health announced.

May 14: The first confirmed coronavirus case was detected in a Bangladesh camp, home to more than 1 million Rohingya refugees fleeing Myanmar.

May 14: An experimental coronavirus vaccine from Oxford University appeared to be effective at preventing COVID-19, according to findings from a small study in six monkeys. The preliminary findings were posted on the preprint server bioRxiv.

May 14: The CDC issued a health alert to physicians about what has emerged as a rare but potentially deadly condition linked to COVID-19 in children. The illness, known as "multisystem inflammatory syndrome in children" or MIS-C, has been reported in at least 19 states and Washington, D.C.

May 15: A model by the World Health Organization's regional office for Africa predicted that approximately 22 percent of Africa's one billion population (or around 220 million people) will be infected in the first year of the coronavirus epidemic.

May 15: Chinese officials said all 11 million residents of Wuhan will be tested for the coronavirus, in a bid to avoid a second wave of infections. The country marked one month without any reported deaths from the disease.

May 15: The medical journal The Lancet published a sharply worded editorial condemning the Trump administration's coronavirus efforts and calling on voters to choose a new president.

May 18: A COVID-19 vaccine candidate developed by Moderna showed it can prompt an immune response in the human body and was also found to be safe and well-tolerated in a small group of patients.

May 19: The World Health Organization's annual meeting finished, ending amid tensions between the United States, China and the WHO itself. In a letter to WHO Director-General Tedros Adhanom Ghebreyesus, President Trump threatened to make permanent a temporary funding freeze

on American donations as he accused the agency of helping China cover up the coronavirus outbreak.

May 19: The Lancet, a British medical, rebutted claim by President Trump that the World Health Organization consistently ignored reports of the virus spreading in China in early December.

May 20: More than 100,000 cases were reported to the World Health Organization in 24 hours, the Director-General Tedros Adhanom Ghebreyesus said during a news conference. The announcement came as the total number of coronavirus cases worldwide neared 5 million.

May 20: International Olympic Committee President Thomas Bach said he agreed that the rescheduled Tokyo 2020 Olympics would have to be cancelled if the Games cannot take place in summer 2021.

May 20: The Chinese city of Wuhan, where the coronavirus pandemic was first detected, implemented a five-year ban on the trade of illegal wildlife and the consumption of wild animals.

May 21: British-Swedish pharmaceutical company AstraZeneca received more than $1 billion in funding from the U.S. Health Department's Biomedical Advanced Research and Development Authority to develop a coronavirus vaccine in collaboration with the University of Oxford.

May 22: An experimental coronavirus vaccine under development at the University of Oxford progressed to advanced stages of human trials.

May 22: A new study published in The Lancet found that hydroxychloroquine, a drug that President Trump said he was taking as a preventive strategy and has publicly touted, does not help COVID-19 patients, and may increase deaths.

May 22: Two children in Washington State were diagnosed with a rare and potentially deadly COVID-19-linked condition known as Multisystem Inflammatory Syndrome in Children, or MIS-C.

May 24: The Vatican announced that the Vatican Museums will reopen on June 1 after a three-month lockdown that had drained the Holy See's finances.

May 24: Muslims around the world began celebrating Eid al-Fitr, a holiday marking the end of the fasting month of Ramadan, with millions under strict stay-at-home orders.

May 25: Syria reported 20 new coronavirus cases, the country's largest single-day increase to date.

May 25: Doctors in Austria announced that they completed a lung transplant on a COVID-19 patient, the first to be done in Europe.

May 25: The World Health Organization announced that it was suspending a trial of hydroxychloroquine in treating COVID-19, saying fears of the drug's potential danger is causing it to "err on the side of caution."

May 25: A second person in U.S. Immigration and Customs Enforcement custody died from COVID-19 complications.

May 26: The CDC reported that more than 62,000 doctors, nurses and other health care providers on the front lines of the U.S.'s COVID-19 crisis had been infected, and at least 291 had died.

May 26: The World Health Organization said the Americas had emerged as the new epicenter of the coronavirus pandemic.

May 28: The World Health Organization announced the creation of a foundation for new sources of funding. WHO General Director Tedros Ghebreyesus said it would ease a potential financial shortage and that funds will go towards all of the agency's projects, including vaccine research and preparing for future pandemics.

May 29: New Zealand celebrated one week without a new coronavirus case in the country.

June 1: Gilead Sciences Inc. said its antiviral drug remdesivir showed improvement in patients with moderate COVID-19 in a late-stage study.

June 1: Eli Lilly started the first COVID-19 antibody treatment trials in humans. The treatment uses what are known as monoclonal antibodies made from people who were sick with the coronavirus. They are meant to work as natural antibodies do in the body by blocking the virus.

June 2: A report from Public Health England found that black and Asian ethnic minorities in England are up to twice as likely to die after contracting COVID-19 than white British people. People of Chinese, Indian, Pakistani and Caribbean ethnicity were at between 10 percent to 50 percent higher risk of death, the report said.

June 3: The Director-General of the World Health Organization said in a news briefing that the spread of COVID-19 is still escalating globally, with more than 100,000 cases reported for each of the past five days, but new cases in Europe continue to decline.

June 3: New research from the University of Minnesota Medical School found that hydroxychloroquine was no better than a placebo at preventing symptoms of COVID-19 among people exposed to the virus.

June 3: An autopsy found that George Floyd, who died during an arrest in Minneapolis on May 25, had coronavirus.

June 4: The medical journal The Lancet on Thursday retracted a large study on the use of hydroxychloroquine to treat COVID-19 because of potential flaws in the research data. The study published two weeks ago, found no benefit to the drug and suggested its use may even increase the risk of death.

June 5: Friday prayers at mosques in countries across the Middle East were permitted, after restrictions put in place to slow the spread of the coronavirus were lifted.

June 5: The World Health Organization broadened its recommendations for the use of masks during the coronavirus pandemic and said it is now advising that in areas where the virus is spreading, people should wear fabric masks when social distancing is not possible, such as on public transportation and in shops.

June 8: The WHO said new coronavirus cases had their biggest daily increase ever on June 7, as more than 136,000 new cases were reported worldwide. The agency said the pandemic had yet to peak in central America and urged countries to press on with efforts to contain the virus.

June 9: A WHO expert clarified that the coronavirus can be spread by people who show no symptoms, a day after sparking widespread confusion by saying that such asymptomatic spread of COVID-19 was "very rare."

June 10: Starbucks announced that it lost as much as $3.2 billion in revenue because of the coronavirus pandemic.

June 11: The Defense Department's largest biomedical lab, the Walter Reed Army Institute of Research in Maryland, selected a lead COVID-19 vaccine candidate for additional research as well as two backup vaccine candidates.

June 17: The World Health Organization announced that it will update its clinical guidance for COVID-19 following the University of Oxford's announcement of results from a trial on the steroid dexamethasone. WHO officials stressed, however, that the drug should only be used in severe cases under close clinical supervision.

June 17: The World Health Organization halted research on whether hydroxychloroquine could be an effective treatment for COVID-19. Multiple studies had shown that the drug, an anti-malarial medicine also used to treat lupus and rheumatoid arthritis, had no impact on the coronavirus.

June 28: Global death toll from COVID-19 surpassed 500,000 and the number of confirmed cases worldwide topped 10 million.

July 3: The number of confirmed coronavirus cases worldwide surpassed 11 million.

July 7: The WHO acknowledged "emerging evidence" of the airborne spread of the coronavirus, after a group of scientists wrote a letter urging the global body to update its guidance on how the respiratory disease is spread.

July 24: CDC: One-third of COVID-19 patients who weren't hospitalized have long-term illness.

August 3: The WHO warned there may never be a 'silver bullet' for Covid-19.

August 14: The CDC suggested recovered COVID-19 patients have protection for 3 months.

August 30: The U.S. recorded its six millionth Covid-19 case.

Oct. 2: President Trump announced that he tested positive for Covid-19.

Oct. 15: The U.S. reached eight million Covid-19 cases.

Oct. 20: The world crossed the 40 million case mark.

Oct. 21: The CDC changed guidance on close contacts, emphasizing the importance of wearing masks.

Nov. 15: Eleven million Covid-19 cases counted in the U.S.

Nov. 16: Moderna announced its Covid-19 vaccine candidate, said it's 94.5 percent effective.

Nov. 18: Pfizer announced its leading coronavirus vaccine candidate would be submitted for FDA approval "within days."

Nov. 18: The U.S. counted its 250,000th Covid-19 death.

Nov. 19: The CDC warned Americans not to travel on Thanksgiving.

Nov. 20: Donald Trump Jr. tested positive for Covid-19.

Nov. 23: AstraZeneca announced its coronavirus vaccine can be around 90 percent effective.

Nov. 30: Moderna said it would submit its vaccine to the FDA for approval.

Clinical Manifestations

The incubation period (the time from exposure to symptom onset) for Covid-19 is 1-14 days, approximately 5.2(2-7) days and 97.5% of individuals who develop symptoms will do so within 11.5 days of infection (Alhazzani et al.; Lauer et al., 2020; Li et al., 2020; Rothan & Byrareddy, 2020).

Disease in neonates, infants and children has also been reported to be significantly milder than their adult counterparts (Singhal, 2020a).

The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days. This period is dependent on the age of the patient and status of the patient's immune system. It was shorter among patients >70 years old compared with those under the age of 70 . The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, hemoptysis, hypoxemia, diarrhea, dyspnea, acute cardiac injury, and lymphopenia (Carlos, Dela Cruz, Cao, Pasnick, & Jamil, 2020; Ren-LL & Wu, 2020; Wang, Tang, & Wei, 2020; X. Yang et al.,2020). These are systemic disorders. Respiratory disorders are rhinorrhea, sneezing, sore throat, pneumonia, ground-glass opacities, RNAaemia, Acute Respiratory Distress Syndrome. Clinical features revealed by a chest CT scan presented as pneumonia, however, there were abnormal features such as RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of grand-glass opacities that led to death (X. Yang et al., 2020). In some cases, the multiple peripheral ground-glass opacities were observed in subpleural regions of both lungs (Lei, Li, Li, & Qi, 2020) that likely induced both systemic and localized immune response that led to increased inflammation.

The median (interquartile range) interval from symptom onset to hospital admission is 7(3-9) days (Garg, 2020). The median age of hospitalized patients varies between 47 and 73 years, with most cohorts having a male preponderance of approximately 60% (Alhazzani et al.; Docherty et al., 2020; Safiya Richardson et al., 2020). Among patients hospitalized with COVID-19, 74% to 86% are aged at least 50 years (Garg, 2020).

COVID-19 has various clinical manifestations. In a study of 44,672 patients with COVID-19 in China, 81% of patients had mild manifestations, 14% had severe manifestations, and 5% had critical manifestations (defined by respiratory failure, septic shock, and/or multiple organ dysfunction. A study of 20,133 individuals hospitalized with COVID-19 in the UK reported that 17.1% were admitted to high-dependency or intensive care units (ICUs) (Docherty et al., 2020).

Although only approximately 25% of infected patients have comorbidities, 60% to 90% of hospitalized infected patients have comorbidities (Grasselli et al., 2020; Novel, 2020). The most common comorbidities in hospitalized patients include hypertension (present in 48%-57% of patients), diabetes (17%-34%), cardiovascular disease (21%-28%), chronic pulmonary disease (4%-10%), chronic kidney disease (3%-

13%), malignancy (6%-8%), and chronic liver disease (<5%) (Wiersinga, Rhodes, Cheng, Peacock, & Prescott, 2020).

The most common symptoms in hospitalized patients are fever (up to 90% of patients), dry cough (60%-86%), shortness of breath (53%-80%), fatigue (38%), nausea/vomiting or diarrhea (15%-39%), and myalgia (15%-44%) (Chey, 2020; X. Yang et al., 2020). Patients can also present with nonclassical symptoms, such as isolated gastrointestinal symptoms. Olfactory and/or gustatory dysfunctions have been reported in 64% to 80% of patients.(Lechien et al., 2020; Spinato et al., 2020). Anosmia or ageusia may be the sole presenting symptom in approximately 3% of patients.

Complications of COVID-19 include impaired function of the heart, brain, lung, liver, kidney, and coagulation system. COVID-19 can lead to myocarditis, cardiomyopathy, ventricular arrhythmias, and hemodynamic instability (Hendren, Drazner, Bozkurt, & Cooper Jr; Long, Brady, Koyfman, & Gottlieb). Acute cerebrovascular disease and encephalitis are observed with severe illness (in up to 8% of patients) (Helms et al., 2020; Mao et al., 2020). Venous and arterial thromboembolic events occur in 10% to 25% in hospitalized patients with COVID-19 (Marcel Levi, Jecko Thachil, Toshiaki Iba, & Jerrold H Levy, 2020; Middeldorp et al., 2020). In the ICU (Intensive Care Unit), venous and arterial thromboembolic events may occur in up to 31% to 59% of patients with COVID-19 (Klok, Kruip, & Meer, 2020).

Approximately 17% to 35% of hospitalized patients with COVID-19 are treated in an ICU, most commonly due to hypoxemic respiratory failure. Among patients in the ICU with COVID-19, 29% to 91% require invasive mechanical ventilation (Docherty et al., 2020; Myers, Parodi, Escobar, & Liu, 2020). In addition to respiratory failure, hospitalized patients may develop acute kidney injury (9%), liver dysfunction (19%), bleeding and coagulation dysfunction (10%-25%), and septic shock (6%) (Y.-T. Chen et al., 2020; Marcel Levi et al., 2020).

Approximately 2% to 5% of individuals with laboratory confirmed COVID-19 are younger than 18 years, with a median age of 11 years. Children with COVID-19 have milder symptoms that are predominantly limited to the upper respiratory tract, and rarely require hospitalization. It is unclear why children are less susceptible to COVID-19. Potential explanations include that children have less robust immune responses (e.g. no cytokine storm), partial immunity from other viral exposures, and lower rates of exposure to SARS-CoV-2. Although most pediatric cases are mild, a small percentage (<7%) of children admitted to the hospital for COVID-19 develop severe disease requiring mechanical ventilation. A rare multisystem inflammatory syndrome similar to Kawasaki disease has recently been described in children in Europe and North America with

SARS-CoV-2 infection. This multisystem inflammatory syndrome in children is uncommon (2 in 100 000 persons aged <21 years) (Götzinger et al., 2020; Levin, 2020; Riphagen, Gomez, Gonzalez-Martinez, Wilkinson, & Theocharis, 2020; Whittaker et al., 2020).

Transmission

It was observed that the main spread of Covid-19 infection was person-to-person contact (Özdemir & Pala, 2020). This infection can be seen in all age groups and is transmitted through droplets scattered after sneezing or coughing. It cannot be transmitted by the droplet more than two meters away and cannot remain suspended in the air too much. Under suitable weather conditions, SARS-Cov-2 can survive on surfaces, but can be cleaned with disinfectants such as sodium hydrochloride and hydrogen peroxide. Infection is transmitted by person-to-person droplet inhalation or contact with eyes, nose and mouth after touching virus-contaminated places (McIntosh, Hirsch, & Bloom, 2020). Typically, respiratory viruses are most contagious when a patient is symptomatic (Sohrabi, Alsafi, O'Neill, et al., 2020). Asymptomatic and presymptomatic carriers can also transmit SARS-CoV-2 (Bai et al., 2020; Wei et al., 2020). Presymptomatic transmission is thought to be a major contributor to the spread of SARS-CoV-2. Although studies have described rates of asymptomatic infection, ranging from 4% to 32%, it is unclear whether these reports represent truly as symptomatic infection by individuals who never develop symptoms, transmission by individuals with very mild symptoms, or transmission by individuals who are asymptomatic at the time of transmission but subsequently develop symptoms (Byambasuren et al., 2020; Park et al., 2020; Tabata et al., 2020). Individuals can be released from isolation based on clinical improvement. The Centers for Disease Control and Prevention recommend isolating for at least 10 days after symptom onset and 3 days after improvement of symptoms (Control & Prevention, 2020).

Although viral nucleic acid can be detectable in throat swabs for up to 6 weeks after the onset of illness, several studies suggest that viral cultures are generally negative for SARS-CoV-2 8 days after symptom onset (He et al., 2020; Sun et al., 2020; Wölfel et al., 2020).

In pregnancy, a study of nine pregnant women who developed COVID-19 in late pregnancy suggested COVID-19 did not lead to substantially worse symptoms than in non-pregnant persons and there is no evidence for intrauterine infection caused by vertical transmission (H. Chen et al., 2020; Harapan et al., 2020).

CoVid-19 is not a super-hot spreading virus (spread by one patient to many others) (Lu, 2020). The Basic Reproductive Number (R0) has been estimated with varying results and interpretations. R0 measures the average number of infections that could result from one infected individual

in a fully susceptible population (Bauch & Oraby, 2013). Studies from previous outbreaks found R0 to be 2.7 for SARS (Riley et al., 2003) and 2.4 for 2009 pandemic H1N1 influenza (Y. Yang et al., 2009). One study estimated that that basic reproductive number (R0) was 2.2 (95% CI: 1.4–3.9) (Li et al., 2020). However, later in a further analysis of 12 available studies found that R0 was 3.28 (Liu, Gayle, Wilder-Smith, & Rocklöv, 2020). Because R0 represents an average value it is also important to consider the role of super spreaders, who may be hugely responsible for outbreaks within large clusters but who would not largely influence the value of R0 (Kucharski & Althaus, 2015). During the acute phase of an outbreak or prepandemic, R0 may be unstable (Bauch & Oraby, 2013).

The incidence of SARS-CoV-2 infection is seen most often in adult male patients with the median age of the patients was between 34 and 59 years (Bai et al., 2020; Chang et al., 2020; Chaolin Huang et al., 2020; D. Wang et al., 2020). SARS-CoV-2 is also more likely to infect people with chronic co-morbidities such as cardiovascular and cerebrovascular diseases and diabetes (Nanshan Chen et al., 2020). The highest proportion of severe cases occurs in adults ≥60 years of age, and in those with certain underlying conditions, such as cardiovascular and cerebrovascular diseases and diabetes (Bai et al., 2020; D. Wang et al., 2020). Severe manifestations maybe also associated with co-infections of bacteria and fungi (Nanshan Chen et al., 2020).

Diagnosis

Diagnosis of Covid-19 is typically made using real-time Reverse Transcription-Polymerase Chain Reaction (rRT-PCR) testing via nasal and oropharyngeal swab (Wiersinga et al., 2020). However, because of false negative test result rates of SARS-CoV-2 PCR testing of nasal swabs, clinical, laboratory, and imaging findings may also be used to make a presumptive diagnosis.

Reverse transcription polymerase chain reaction–based SARS-CoV-2 RNA detection from respiratory samples (e.g. nasopharynx) is the standard for diagnosis. However, the sensitivity of testing varies with timing of testing relative to exposure. One modeling study estimated sensitivity at 33% 4 days after exposure, 62% on the day of symptom onset, and 80% 3 days after symptom onset (Kucirka, Lauer, Laeyendecker, Boon, & Lessler, 2020; Nandini Sethuraman, Sundararaj Stanleyraj Jeremiah, & Akihide Ryo, 2020; Wenling Wang et al., 2020). Factors contributing to false-negative test results include the adequacy of the specimen collection technique, time from exposure, and specimen source. Lower respiratory samples, such as bronchoalveolar lavage fluid, are more sensitive than upper respiratory samples. SARS-CoV-2 can also be detected in stool, and in severe cases in blood, but not in urine (Singhal, 2020b; Wenling Wang

et al., 2020). Saliva may be an alternative specimen source that requires less personal protective equipment and fewer swabs but requires further validation (Williams, Bond, Zhang, Putland, & Williamson, 2020).

Whether and how frequently second infections with SARS-CoV-2 occur remain unknown. Whether presence of antibody changes susceptibility to subsequent infection or how long antibody protection lasts are unknown. IgM antibodies are detectable within 5 days of infection, with higher IgM levels during weeks 2 to 3 of illness, while an IgG response is first seen approximately 14 days after symptom onset. Higher antibody titers occur with more severe disease (Guo et al., 2020; Nandini Sethuraman et al., 2020; J. Zhao et al., 2020).

Laboratory Findings

Elevated serum C-reactive protein (increased in>60% of patients), lactate dehydrogenase (increased in approximately 50%-60%), alanine aminotransferase (elevated in approximately 25%), and aspartate aminotransferase (increased in approximately 33%) . Approximately 75% of patients had low albumin (Rodriguez-Morales et al., 2020). The white cell count is usually normal or low. The most common hematological abnormality is lymphopenia (lymphocyte count<1000 has been associated with severe disease), mild thrombocytopenia (present in approximately 30% of patients) and elevated D-dimer values (present in 43%-60% of patients) are common (N. Chen et al., 2020; Guan et al., 2020; M. Levi, J. Thachil, T. Iba, & J. H. Levy, 2020; Tang, Li, Wang, & Sun, 2020; Thachil et al., 2020). Procalcitonin level is usually normal but a high procalcitonin level may indicate a bacterial co-infection. However, most of these laboratory characteristics are non-specific and are common in pneumonia. More severe laboratory abnormalities have been associated with more severe infection (Guan et al., 2020; C. Huang et al., 2020; Wu et al., 2020). D-dimer and, to a lesser extent, lymphopenia seem to have the largest prognostic associations (Wu et al., 2020).

Imaging

Chest X-ray usually shows bilateral infiltrates. CT (Computed Tomography) is more sensitive and specific. The characteristic chest computed tomographic imaging abnormalities for COVID-19 are infiltrates, sub-segmental consolidation and diffuse, peripheral ground-glass opacities (P. Huang et al., 2020). Ground-glass opacities have ill-defined margins, air bronchograms, smooth or irregular interlobular or septal thickening, and thickening of the adjacent pleura (Shi et al., 2020). Early in the disease, chest computed tomographic imaging findings in approximately 15% of individuals and chest radiograph findings in approximately 40% of individuals may be normal.

Treatment

The first step is to ensure adequate isolation to prevent transmission to other contacts, patients and healthcare workers. Mild illness should be managed at home with counseling about danger signs. The usual principles are maintaining hydration and nutrition and controlling fever and cough. In hypoxic patients, provision of oxygen through nasal prongs, face mask, high flow nasal cannula (HFNC) or non-invasive ventilation is indicated. Mechanical ventilation and even extra corporeal membrane oxygen support may be needed. Renal replacement therapy may be needed in some. Antibiotics and antifungals are required if co-infections are suspected or proven. The following classes of drugs are being evaluated or developed for the management of COVID-19: antivirals (e.g. remdesivir, favipiravir), antibodies (e.g. convalescent plasma, hyperimmune immunoglobulins), anti-inflammatory agents (dexamethasone, statins), targeted immunomodulatory therapies (e.g. tocilizumab, sarilumab, anakinra, ruxolitinib), anticoagulants (e.g. heparin), and antifibrotics (e.g. tyrosine kinase inhibitors). The role of corticosteroids is unproven; while current international consensus and WHO advocate against their use, Chinese guidelines do recommend short term therapy with low-to-moderate dose corticosteroids in COVID-19 ARDS (Russell, Millar, & Baillie, 2020; J. P. Zhao et al., 2020). There is, as of now, no approved treatment for COVID-19. It is likely that different treatment modalities might have different efficacies at different stages of illness and in different manifestations of disease. Viral inhibition would be expected to be most effective early in infection, while, in hospitalized patients, immunomodulatory agents may be useful to prevent disease progression and anticoagulants is recommended for all hospitalized patients to prevent thromboembolic complications (M. Levi et al., 2020; Thachil et al., 2020).

More than 200 trials of chloroquine/hydroxychloroquine, compounds that inhibit viral entry and endocytosis of SARS-CoV-2 in-vitro and may have beneficial immunomodulatory effects in-vivo, have been initiated, but early data from clinical trials in hospitalized patients with COVID-19 have not demonstrated clear benefit (Sanders, Monogue, Jodlowski, & Cutrell, 2020; W. Tang et al., 2020).

Prognosis

Hospital mortality from COVID-19 is approximately 15% to 20%, but up to 40% among patients requiring ICU admission. Hospital mortality ranges from less than 5% among patients younger than 40 years to 35% for patients aged 70 to 79 years and greater than 60% for patients aged 80 to 89 years (S. Richardson et al., 2020). Because not all people who die during the pandemic are tested for COVID-19, actual numbers of deaths from COVID-19 are higher than reported numbers.

Protection and Vaccine Trials

COVID-19 is a potentially preventable disease. The relationship between the intensity of public health action and the control of transmission is clear from the epidemiology of infection around the world (Chu et al., 2020; Jüni et al., 2020; Pan et al., 2020). Continued interventions will be required until effective vaccines or treatments become available. In general, these interventions can be divided into those consisting of personal actions (e.g. physical distancing, personal hygiene, and use of protective equipment), case and contact identification (e.g. test trace-track-isolate, reactive school or workplace closure), regulatory actions (e.g. governmental limits on sizes of gatherings or business capacity; stay-at-home orders; proactive school, workplace, and public transport closure or restriction; cordon sanitaire or internal border closures), and international border measures (e.g. border closure or enforced quarantine). A key priority is to identify the combination of measures that minimizes societal and economic disruption while adequately controlling infection. Optimal measures may vary between countries based on resource limitations, geography (e.g. island nations and international border measures), population, and political factors (e.g. health literacy, trust in government, cultural and linguistic diversity).

The evidence underlying these public health interventions has not changed since the 1918 flu pandemic (Markel et al., 2007). Mathematical modelling studies and empirical evidence support that public health interventions, including home quarantine after infection, restricting mass gatherings, travel restrictions, and social distancing, are associated with reduced rates of transmission (Jüni et al., 2020; Pan et al., 2020; Xiao, Tang, Wu, Cheke, & Tang, 2020).

A human vaccine is currently not available for SARS-CoV-2, but approximately 120 candidates are under development. Approaches include the use of nucleic acids (DNA or RNA), inactivated or live attenuated virus, viral vectors, and recombinant proteins or virus particles (Lurie, Saville, Hatchett, & Halton, 2020; Thanh Le et al., 2020). The SARS-CoV-2 S protein appears to be a promising immunogen for protection, but whether targeting the full-length protein or only the receptor-binding domain is sufficient to prevent transmission remains unclear (Lurie et al., 2020). Other considerations include the potential duration of immunity and thus the number of vaccine doses needed to confer immunity (Lurie et al., 2020; N. Sethuraman, S. S. Jeremiah, & A. Ryo, 2020). More than a dozen candidate SARS-CoV-2 vaccines are currently being tested in phase 1-3 trials.

Other approaches to prevention are likely to emerge in the coming months, including monoclonal antibodies, hyperimmune globulin, and convalescent titer.

Covid-19 in Turkey and in the World

The first Covid-19 patient was detected on March 11,2020 in Turkey and the first death was reported on March 17,2020. From 20 May 2020 the daily number of confirmed cases decreased but it started to increase from the date 19 August. The number of deaths started to increase since September. The number of total confirmed cases from the beginning of outbreak reported by WHO on December 3rd,2020 in Turkey is 520,167 and deaths are 14,316. According to WHO data, the total number of cases worldwide on the same date was 64,350,473 and the number of deaths was 1,494,668. USA leads with 13,759,500 cases and 271,233 deaths.

Cases have been reported on all continents except Antarctica, and the number of cases and deaths continue to increase in many countries.

Conclusion

The novel virus outbreak has been challenging all the world for nearly one year. From the beginning until today more than 64 million people worldwide had been infected and almost 1.5 million people died of SARS-CoV-2. Many aspects of transmission, infection, and treatment remain unclear. The main thing is to avoid disease by social distancing, wearing surgical masks, being careful about hygiene and minimal contacts with others. It should not be forgotten that, "to avoid of an illness is better than to be cured". "Stay at Home" has become a right motto in all over the world during this pandemic. Therefore, nobody should go out without any need.

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ROLE OF HYSTEROSCOPY IN MODERN GYNAECOLOGY

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Hysteroscope is a minimally invasive instrument that can be used to diagnose and treat intrauterine and endocervical problems. Hysteroscopic polypectomy, myomectomy, and endometrial ablation are just a few of the mostly performed procedures. Given their safety and efficacy, diagnostic and operative hysteroscopy have become norm in gynecologic practice.

The invention of hysteroscopy is rooted in the work of Pantaleoni, who first reported uterine endoscopy in 1869.[1] However, at that time, instrumentation was elementary, and dilatation of the uterine cavity was insufficient. In 1925, Rubin first used CO2 to expand the uterus.[1] Around the same time, Gauss was tring with the use of fluids to achieve uterine expansion.Hysteroscopy did not become usefull until the 1970s. By the mid-1980s, hysteroscopic procedures had almost change dilation and curettage (D&C) for diagnosing intrauterine pathology. [2]

1.Equipment

Hysteroscopes

The telescope involvs of 3 parts: the eyepiece, the barrel, and the objective lens. The focal length and angle of the distal tip of the instrument are main for visualization (as are the fiberoptics of the light source).

Angle options include 0°, 12°, 15°, 25°, 30°, and 70°. A 0° hysteroscope supply a panoramic view, but an angled one might improve the view of the ostia in an abnormally shaped cavity.

Hysteroscopes are presents in different styles, including rigid and flexible-hysteroscopes,contact-hysteroscopes,and microcolpo-hysteroscopes. The diameter of every instrument varies and is a main consideration. The requirement of a sheath for input-outflow of distention media increases the format of the hysteroscope.

Surgical instruments

Surgical instruments are present in both rigid and flexible forms to be inserted through the operating channels of the scopes. Models of surgical instruments and their uses are listed below:

Scissors - To incise a septum, cut a polyp, or lyse synechiae

Biopsy forceps - To take directed biopsy for pathologic review

Grasping instruments - To take off foreign bodies

Roller ball, barrel, or ellipsoid - To make endometrial ablation and/or desiccation (This instrument is used with a resectoscope.)

Loop electrode - To resect a fibroid or polyp or endometrium (This instrument is used with a resectoscope.)

Scalpel - To resect or coagulate tissue, with high power density (This instrument is used with a resectoscope.)

Vaporizing electrodes – To devastat endometrial polyps, fibroids, intrauterine adhesions, and septa; also used for endometrial ablation (This instrument is used with a resectoscope.)

Morcellator – To resect and remove endometrial polyps or fibroids

2.Energy sources and uses

Monopolar and bipolar electricity, laser energy, each of have uses in hysteroscopy.

Monopolar cautery

The resectoscope is a appropriated instrument often used with a monopolar, double-armed electrode and a trigger device for usage in hypotonic, nonconductive media, such as glycine. It resect and coagulates tissue by means of contact desiccation with resistive heating. [3] The depth of thermal damage is depend on several factors: endometrial thickness; speed, pressure, and duration of contact during motion; and power setting. [4, 3]

A thin electrode can cut tissue, whereas one with a large surface area, such as a ball or barrel, is best appropriated for coagulation. [5]

Bipolar cautery

The Versa Point system uses bipolar circuitry for electrosurgery, which can be used in isotonic conductive media. This system contain a spring tip for hemostatic vaporization of wide areas, a ball tip for precise vaporization, and a twizzle tip for hemostatic resection and morcellation of tissue. There is also a cutting loop like to traditional resectoscopy. [3]

Bipolar resectoscopes have been invented by both Karl Storz and Richard Wolf Medical Instruments Corporation. The latter has designed the Princess a 7 mm resectoscope — the smallest bipolar resectoscope available. Also, the Chip E-Vac System can be used with bipolar and monopolar energy.

Laser techniques

Several fiberoptic lasers are available for gynecologic use, as well as potassium-titanyl-phosphate (KTP), argon, and Nd:YAG lasers. They all have various wavelengths, though the KTP and argon lasers have analogue properties.

3.Media

The use of media is important for panoramic inspection of the uterine cavity. The medium opens the possible space of the otherwise narrow uterine cavity. Intrauterine pressures needed to efficiently view the endometrium are proportional to the muscle tone and thickness of the uterus. The refractive index of each medium affects enlargement and visualization of the endometrium.

Gases

Carbon dioxide (CO2) is quickly absorbed and easily cleared from the body by respiration. The refractory index of CO2 is 1.0, which allows for excellent clarity and widens the field of view at low enlargement . The gas easily flows through slim channels in small-diameter scopes, making it helpful for office-based diagnostic hysteroscopy. However, this technic offers no way to clear blood from the scope.

With CO2, a hysteroscopic insufflator is necessary to regulate flow and limit maximal intrauterine pressure. (Note that laparoscopic insufflators are not secure.) A flow rate to 40-60 mL/min at a maximum pressure of 100 mm Hg is commonly accepted as safe. Pressures and rates upper than this can result in cardiac arrhythmias, embolism, and arrest. [6]

Fluids

The advantage of fluid over gas is the symmetric distention of the uterus with fluid and its effective potency to flush blood, mucus, bubbles, and small tissue fragments out of the visual areas. Both low-viscosity and high-viscosity fluid media can be used for extension. A pressure of 75 mm Hg is usually enough for uterine distention; seldom is more than 100 mm Hg required, and pressures higher than this can increase the risk of intravasation of medium. [1]

A lot delivery systems are established to suit the many media used for uterine distention and to accurately record volumes of inflow and outflow. This recording is significant because fluid can leave the uterus by means of intended efflux systems, cervical or tubal leakage, or intravasation. Preventing excess absorption of hypotonic fluids is necessary for patient safety.

0.9% sodium chloride solution and lactated Ringer solution

Normal sodium chloride solution and lactated ringer solution are isotonic, permeable, low-viscosity fluids that can be used for diagnostic hysteroscopy and for limited operative procedures.

Two major minus associated with these solutions include their miscibility with blood, which hides visibility with bleeding, leading to the need for increased volumes to clear the operative area, and their excellent conductivity, which blocke procedures that use standard monopolar electrosurgery.

5% Mannitol, 3% sorbitol, and 1.5% glycine

The hypotonic, nonconductive, low-viscosity fluids 5% mannitol, 3% sorbitol, and 1.5% glycine increase visualization when bleeding occurs. They convenientional for diagnostic as well as operative hysteroscopy. (5% mannitol can be used only with monopolar operative procedures.)

All overdose a risk of volume overload and hyponatremia from intravascular absorption (particularly > 2 L). Therefore, careful fluid monitoring is necessary during their use. When intravasation of 5% mannitol occurs, it stays in the extracellular compartment; treatment of this condition is stoping the procedure and administering diuretics. [1] 3% sorbitol is broken down into fructose and glucose and therefore has an added risk of hyperglycemia when absorbed in excess. Use 1.5% glycine with caution in patients with bad hepatic function because glycine is metabolized to ammonia.

Dextran 70

The only high-viscosity medium available, Dextran 70 is a nonelectrolytic, nonconductive fluid that useful in all types of procedures. It is immiscible with blood and minimally leaks through the cervix and tubes, allowing for perfect visibility during surgical procedures.

Like the other nonelectrolytic fluids, however, stop absorption of more than 500 mL to avoid fluid overload. With each 100 mL of Dextran 70 absorbed, the intravascular volume rise by 800 mL. [1, 7] Allergic reactions and anaphylaxis, fluid overload, disseminated intravascular coagulopathy, and destruction of tools are adverse effects of this medium.

4.Indications

Abnormal uterine bleeding

Infertility

Intrauterine adhesions

Müllerian anomalies

Polyps and fibroids

Sterilization

Proximal tubal obstruction

Intrauterine devices-Hysteroscopy can be applied to take off an intrauterine device (IUD) under correct visualization after sonography-guided retrieval fails. [8]

Figure : Hysteroscopic myomectomy

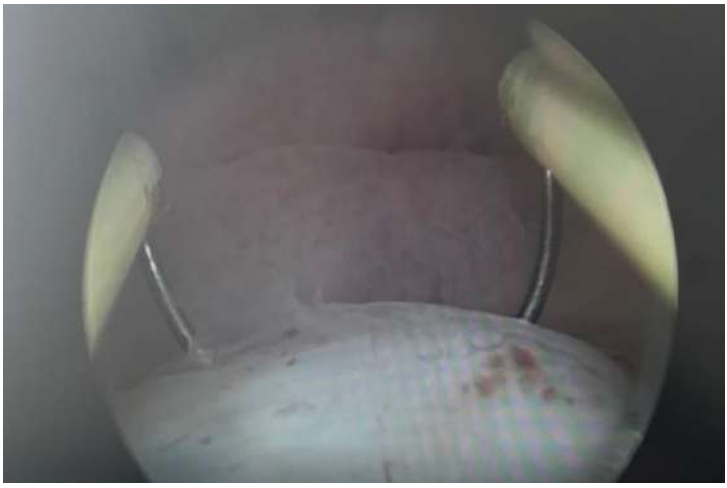

Table. Thickness of the Uterine Wall

Location	Mean, mm	Range, mm
Anterior wall	22.5	17-25
Posterior wall	21	15-25
Fundus	19.5	15-22
Isthmus	10	8-12
Corpus	5.5	4-7

5.Contraindications

In general, hysteroscopy is avoided in patients with the this findings:

Active cervical or uterine infection

A large uterine cavity, longer than 10 cm in length (clinically similar to a 12-wk pregnant uterus)

Serious medical conditions precluding surgery

Pregnancy

Concerns and contraindications for hysteroscopy depend on the operation planned. For endometrial ablation, considerations include a wish for future fertility, atypical endometrial hyperplasia or endometrial cancer, and undiagnosed abnormal bleeding. Polypectomy and myomectomy, subject include transmural lesions, use of hypotonic media in patients with hyponatremia, use of glycine in patients with liver disease, and use of sorbitol in patients with severe diabetes.

Moreover, if the uterus is deeper than 12 cm, the cavity may not distend properly. [9] If lesions are larger than 2 cm, patients must be informed about possibility of a staged procedure, increased fluid deficit, and blood loss.

Contraindications to transcervical sterilization with Essure include current pregnancy or pregnancy within 6 weeks of the scheduled procedure, current or recent lower pelvic infection, allergy to contrast, hypersensitivity to nickel, or patients in who only one microinsert can be fixed (tubal occlusion or uterine abnormalities block proper visualization).

6.Summary

Hysteroscopy can be an highly well tolerated and effective instrument to diagnose and treat uterine disorder. It is often underutilized because of surgeon concern and inadequate training. It is essential that the surgeon understands and is ready to solve the potential complications as they can be severe and life-threatening. With proper training and education, one can limit and avoid complications.

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VACCINE, VACCINE REJECTION

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Vaccine

Vaccination is to obtain artificial immunity by giving weakened viruses or bacteria or their antigenic particles to the body called vaccines. The vaccine protects people from infectious diseases that increase morbidity and mortality or cause permanent sequelae in the body(Kutlu,2017). Vaccination ensures individual immunity and therefore social immunity. If the number of vaccinated individuals in the community increases, the probability of unvaccinated individuals to encounter the disease factor, the rate of the disease in that society decrease. This is called Herd Immunity(Fine, Eames, & Heymann, 2011).

Vaccination is the best cost-effective method of protection. Each unvaccinated individual increases the likelihood that any newborn, infant, or child who has not been vaccinated may encounter the causative agent and therefore the morbidity, mortality, sequelae of that disease may be seen in that population (Dube, Vivion, & MacDonald, 2015; Fine et al., 2011; Helps, Leask, & Barclay, 2018).

In the report published by the World Health Organization(WHO) in March 2018, 2-3 million deaths are prevented every year with global immunization. In the last few years, the global immunization rate is around 85% and is over 90% in developed countries. It is stated that by increasing the immunization rates, 1.5 million deaths per year can be prevented(Gür, 2019).

Immunization practices in Turkey started in the 1930s by the smallpox vaccine. Smallpox was eradicated from the world in the early 1980s as a result of widespread vaccination supported by WHO. The last known case was seen in Somalia in 1977. The smallpox vaccine, which was previously mandatory for all countries, was ended in the 1980s. However, the smallpox vaccine is still administered to military personnel (eg US soldiers in Iraq) in some countries(Özmert, 2008).

The first mass vaccination program in Turkey started in 1981 and is called "The Expanded Immunization Program". Initially, vaccination against 5 diseases was expanded against 7 diseases in 2005 and 13 diseases in 2013 to a total of 20 doses. These vaccines protect against hepatitis B, tuberculosis, diphtheria, pertussis, tetanus, poliomyelitis, measles, rubella, mumps, chickenpox, hepatitis A, pneumococcus, H.influenza type B

infections (Table 1)(Genelgesi, 2009) are applied free of charge to all children by the Ministry of Health of the Republic of Turkey.

Table 1: Turkish Republic Ministry of Health National Childhood Vaccination Schedule (2020).

	After birth	End of 1st month	End of 2nd month	End of 4th month	End of 6th month	End of 12th month	End of 18th month	End of 24th month	48th month	13 years old
Hep-B	I	II			III					
BCG			I							
CPV			I	II		B				
DaBT-İPA-Hib			I	II	III		B			
OPV					I		II			
Chickenpox						I				
MMR						I			II	
Hep-A							I	II		
DaBT-İPA									B	
Td										B

Hep-B:Hepatitis B Vaccine
BCG:Bacille Calmette-Guerine Vaccine
CPV: Conjugate Pneumococcal Vaccine
DaBT-IPV-Hib:Diphteria, Acellular Pertussis, Tetanus, Inactivated Polio, Haemophilius influenza tybe B Vaccine (Quintette Combination Vaccine)
OPV: Oral Polio Vaccine
Chickenpox:Chickenpox Vaccine
MMR: Mumps, Measles, Rubella Vaccine
Hep-A:Hepatitis A Vaccine
DaBT-IPV:Diphteria, Acellular Pertussis,Tetanus, Inactivated Polio (Quatro Combination Vaccine)
Td:Adult type Diphteria-Tetanus Vaccine
B:Booster Vaccination (Reinforcement)

As a result of the successful implementation of vaccination programs, WHO explained that polio is eradicated in Turkey in 2002 and maternal and neonatal tetanus are eradicated in 2009 that have high mortality rates(Organization, 2009). The rate of application for each vaccine in the routine performed since 2009 in Turkey is over 95%(Özceylan, Toprak, & Esen, 2020).

Vaccine Rejection

According to the data for each antigen, the vaccination rate in 2007 remained at 95% in Turkey. Although vaccination was mandatory before 2007, the vaccination rates were around 75%. The reasons for this are; insufficient record keeping, geographical location, and climatic conditions, insufficient legal measures, and payments to healthcare professionals. This can be defined as difficulty in reaching the vaccine, not a vaccine rejection. But in the world in the 1990s and in Turkey since 2010 the "anti-vaccine" concept has emerged(Bozkurt, 2018). This concept means that, despite the proven positive effects of vaccination, some parents have hesitation or refusal to vaccinate their children. Anti-vaccine is vaccine hesitation or vaccine rejection. Vaccine Hesitancy is to delay in getting or not having one or more vaccines despite reaching vaccines. Vaccine Rejection is the case of not having all vaccinations of their own will(Group, 2013). The basis of this concept goes back to 1853 England. That year, during the smallpox epidemic in England, the state forced the public to be vaccinated without informing them, and those who refused to be vaccinated were punished or prisoned. As a result, there have been social reactions(Boom & Cunningham, 2014). Especially since the early 2000s, anti-vaccination has increased all over the world. Upon this, WHO established a group called "Vaccine Hesitancy Working Group" in 2012 to investigate vaccine rejection(Group, 2013). As a result of their work, this group prepared a joint report with Unicef in which vaccine hesitation and vaccine rejection were defined differently(Larson et al., 2015).

The vaccine refusal in Turkey began to be seen only sporadically since 2010 but increased by a law case in 2015. After a prosecutor living in Ordu did not vaccinate his twins, the City Family Health and Social Directorate went to law for the health measure of children. The father also filed a counter-lawsuit for the violation of individual rights and the obligation to obtain consent and won the case. Thereupon, the press and social media portrayed this incident as the "victory of the prosecutor who did not vaccinate their twins", thus, groups led by "religious and philosophical active" people increased their discourse against vaccination.

Since then, some parents have not had their children vaccinated with their consent. According to the Turkish Republic Ministry of Health data, the number of these parents was 183 in 2011, 980 in 2013, 5400 in 2015, 12000 in 2016, and 23000 in 2018 (Figure 1)(Gür, 2019).

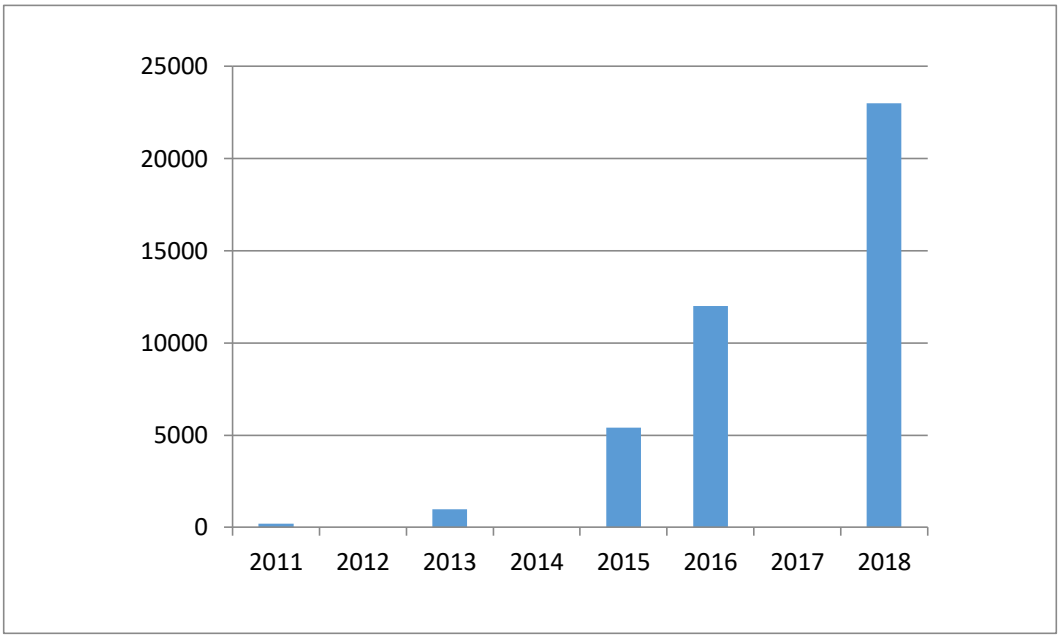

Figure 1: Number of vaccine rejectors in Turkey by years.

Although diphtheria, measles, rubella, whooping cough(pertussis), mumps, tetanus, hepatitis B, and pneumococcal vaccination rate was 98% in Turkey in 2016, it regressed to 96% in 2017. The BCG vaccination rate has also decreased from 96% to 93%.

WHO has collected the reasons for vaccine rejection under the main headings: individual, contextual, social, and organizational(Group, 2013).

The reasons for vaccine rejection in studies conducted abroad:

1. Chemicals contained in vaccines are toxic and cause some diseases,

2.Because of the high income of vaccine producing companies, it is malicious,

3. The immunity acquired by passing the disease instead of vaccination is better,

4. Alternative and complementary medicine is more effective and has fewer side effects,

5. Vaccines harm children whose immune systems are not yet fully developed,

6. No studies proving the efficacy and reliability of vaccines,

7. Studies are reporting side effects of vaccines,

8. The statements of some religious and philosophical people and doctors that vaccines are harmful and their children should not be vaccinated(Hausman, Ghebremichael, Hayek, & Mack, 2014).

Due to the confidentiality of personal information in Turkey, the Ministry of Health does not provide contact information of families who refuse vaccines, there is no study on vaccine rejection. There are some studies about vaccine hesitation(Bozkurt, 2018). For example, the tetanus vaccination rates of pregnant women and children in Şanlıurfa Harrankapı in 2004 were investigated and the reason for the low vaccination rate was determined ignoring the vaccine (21%), not being able to have it due to temporary agricultural work (27%), and thinking that the vaccine is harmful (21%)(Gülgün et al., 2014; Kurçer, Şimşek, Solmaz, Dedeoğlu, & Gülel, 2005). In 2007, a study investigating the approaches of healthcare professionals working in a chest diseases hospital to influenza vaccine was conducted, and the most important reasons for not getting vaccinated: not believing the necessity of the vaccine (64.5%), fear of its side effects (39.1%), preferring other prevention methods (% 40.9)(Sari, Temocin, & Kose, 2017). The main reason for vaccine hesitation and rejection is that the chemicals it contains can cause health deterioration(Hausman et al., 2014). Mercury (thimerosal) comes first among these chemicals. Mercury is claimed to cause autism. Claims that "vaccines cause autism" were first raised in 1998. Surgeon Andrew Wakefield published an article in the respected British medical journal The Lancet, claiming that the measles-mumps-rubella (MMR) vaccine causes autism. In the following period, with counter-articles published in the peer-reviewed academic medical journal, British Medical Journal, Wakefield's study was revealed to be inaccurate and did not reflect the facts, and the doctor was dismissed from the professional interest(Smith, 2017). By weight 49.6% of thimerosal is mercury and when it is metabolized, thiosalicylate and ethyl mercury occur. Ethyl mercury is an organomercurial compound and should be evaluated separately from toxic methyl mercury. Thimerosal contained in vaccines has the capacity to kill microorganisms that may be encountered and prevent the growth of fungi. Also, thimerosal is used in some vaccines to inactivate the antigen. Concentration rate between 0.001% - 0.01% thimerosal is effective in eradicating many pathogens(Egan & Baylor, 1999). Mercury is a common element in the universe, and most of the mercury found in water, soil, plants, and animals are in the form of inorganic mercury salt. Mercury is found primarily in the form of ethyl mercury (organomercurial) in foods found in water. Organic forms of mercury are more easily absorbed and eliminated than inorganic forms. Seafood consumption causes exposure to methyl mercury. Ethyl mercury is eliminated by stool in 7-10 days after it becomes inorganic in the body, while methyl mercury is eliminated in 50 days, it is said it also has toxic effects on brain and kidney tissue(Mahaffey, 1998). However, there is no

study to prove this claim(Ball, Ball, & Pratt, 2001). Despite this, the US government announced in 2001 that it removed mercury from vaccines in order not to decrease vaccination rates(Offit, 2007). In Turkey, the Ministry of Health announced that mercury has been removed from vaccines since 2009. However, parents believe that vaccines still contain mercury. Another element found in vaccines and accused of toxicity is aluminum, which is thought to be a substance that damages the nervous system by parents, thus causing neurodevelopmental problems and autoimmune diseases in children(Miller, 2016). According to the Biological Evaluation and Research Center, there is information that if the amount of aluminum in vaccines does not exceed 850 µg, there is no harm, and this level of aluminum increases the antigenicity and effectiveness of the vaccine(Baylor, Egan, & Richman, 2002). In a laboratory study, encephalitis was reported in some sheep vaccinated with a vaccine containing aluminum and mercury(Haley, 2005; Luján et al., 2013). However, it is known clinically that the vaccine prevents many cases of meningitis and encephalitis. While the number of meningitis due to H.influenza type B in Turkey in 2005 was 28 and 0 since 2012(Bozkurt, 2018). In the last 20 years, the most measles cases in the USA were seen in 2014, most of which were found to be vaccine rejection(Control & Prevention, 2014). In Europe, the number of measles cases increased in 2011 and 85% of them were found to be unvaccinated(Cottrell & Roberts, 2011). According to ECDC (European Center for Disease Prevention and Control) 2017 data, the number of measles cases detected in Europe is 3 times of 2016 and the vast majority of this was reported from Romania and Italy.Vaccine rejectors were 87% of these individuals. 35 patients died of measles in the measles epidemic in Europe due to vaccination refusal(Bozkurt, 2018). Another issue is the idea that diseases can be protected by alternative and complementary medicine better than vaccines. In some studies conducted in Australia, it has been observed that vaccine rejectors resort to alternative medicine methods. Studies have shown that complementary medicine methods are more natural, do not contain chemicals, do not have side effects, and are reliable methods that are not worried about money of large pharmaceutical companies(Attwell, Ward, Meyer, Rokkas, & Leask, 2018; Chow, Danchin, Willaby, Pemberton, & Leask, 2017). These alternative and complementary methods (acupuncture, aroma therapy, homeopathy, naturopathy, cupping, leech therapy methods, phytotherapy) may help but not replace medical protection or treatment(Pedersen, 2013).

The side effects of vaccines are another cause for concern. In the study of parents who refused vaccines in Venezuela, the side effects of vaccines and the idea that it is unnecessary to give more than one vaccine came to the fore(Wong, Wong, & AbuBakar, 2020). Chemicals added to increase the effectiveness of vaccines and prevent them from deteriorating may

cause side effects ranging from simple pain to anaphylaxis, but these side effects are also observed to be much less frequent and milder than the effects of vaccines(Özen & Doğan, 2012). Considering the benefit-harm balance, studies are in favor of vaccines(Argüt, Yetim, & Gökçay, 2016).

In the rejection of vaccines, propaganda such as "vaccine-induced diseases" rather than "vaccine-prevented diseases" especially in social media groups formed by mothers was very effective(Bozkurt, 2018).

Another issue is the orientation of religious and philosophical people or groups. In a study conducted in Nigeria, it was emphasized that religious and traditional leaders should be emphasized in the polio eradication program in eliminating concerns over the polio vaccine(Taylor et al., 2017).

In other studies, it has been shown that religious beliefs and religious leaders in Africa, Afghanistan, and India are effective in vaccine rejection. According to the analysis of WHO "Vaccine Hesitations Working Group" in 2015 (Jarrett, Wilson, O'Leary, Eckersberger, & Larson, 2015), the fact that people defined themselves as more knowledgeable and increased awareness is at the forefront of trust questions about vaccines, and if we ignore the availability of vaccines, the guidance of religious and philosophical active people is a difficult problem to solve and it needs dialogue.

Upon the rapid increase in vaccine rejection cases in the world and reaching dangerous levels; WHO included "anti-vaccination" at the top of the 10 global health problems that it plans to resolve in 2019(Organization, 2019).

The vaccination rates of the states that follow a voluntary vaccination policy in the world are not behind the states that follow a mandatory vaccination policy. Although vaccination is compulsory in the USA, flexibility has been provided with articles such as "religious, medical, philosophical exemption"(Bozkurt, 2018; Padda, Kaur, Kaur, & Jhajj, 2012). However, there are 5 states in the USA that do not accept this flexibility. While voluntary vaccination programs are implemented in the UK, Canada, and Sweden, the government implements positive financial incentives for healthcare providers and healthcare servers to keep vaccination rates high. In Australia, the state pays money to parents who have their children vaccinated. In Belgium and Poland, vaccination refusals are punished with imprisonment or high fines. Although Turkey implements mandatory vaccination, the vaccine against the rejection of a regulation is not available(Avcı, 2017).

Result

The reason for the increasing vaccination rejection in our country in recent years should be well known and our citizens should be well informed that these reasons are actually unwarranted and unscientific. Family physicians, who have better and more frequent contact with families, have the greatest task in this regard. In the event of vaccination that cannot be made, performance is deducted from the salary of family physicians. In order to make a very positive contribution to public health, family physicians should follow up the vaccinations regularly and try to persuade them to be vaccinated by meeting with vaccine rejectors.

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ATHLETES' PERFORMANCE: A PERSPECTIVE OF SPORT PSYCHOLOGY

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1. Introduction

Sport is a set of physical, mental and spiritual activities that are competitive, socializing, and integrative which aims to satisfy a person's unconscious desires, such as defeating and being able (Şahin, 2002). Sport also allows a person to have a healthy and happy, good moral and balanced personality before a person and society, taking into account their developmental characteristics. An important function of sports is ensuring the adaptation of the individual to society and ensuring the health of the soul and body (Duman and Kuru, 2010).

An athlete is an active sports member who gives himself/herself to sports within certain rules with or without tools, individually or collectively participates in a competitive; located within communal and cultural phenomenon; has a physical and moral side, gains material and spiritual satisfaction from his/her work (Erkal, 1981).

Along with the developments experienced over time, especially with the influence of communication tools and technology, interest in sports has also increased. The use of expanding sports as a means of propaganda and advertising has also made sports a commercial phenomenon. For this reason, the traditional approach to sports has been changed and improvements have been made to existing applications and thus sport has been kept up to date. Important elements such as athletes' training programs, performance levels, productivity, motivation, and personality characteristics have been discussed in more detail (Doğan, 2005).

Sports, which have a sociocultural function along with physical, cognitive, emotional and psychological dimensions, interact with many branches of science because of this feature. Psychology, one of these branches of science, is of great importance because it is the subject of human behavior (Aracı, 2006; Erden, 2007).

Psychology, which can be defined as knowledge of the soul through the combination of the words Psyche (soul) and logos (knowledge) is he science that helps us to understand our behavior and the inner world behind it (Morgan, 1981). According to another definition, psychology is a science that studies a person's behavior in his social and physical environment in relation to various relationships (Balkış Baymur, 2016).

One of the main goals of psychology is to try to understand why and how an individual behaves. Questions asked by psychology are, 'How does thinking and dreaming occur?, How does a person learn?, What differences exist between people in terms of intelligence, ability and personality?, To what extent does the environment and society affect a person and in what situations do they become incompatible with the human environment?' (Morgan, 1981; Balkış Baymur, 2016).

In the science of psychology, where behavior is studied, various areas of psychology have emerged due to the presence of more than one behavior. Sports psychology is a field of psychology that covers the study of the behavior of individuals engaged in sports or exercise activities from a scientific point of view and the application of acquired knowledge (Weinberg and Gould, 2015).

2. Sports Psychology

Sports psychology focuses on behavior in sports environments, the behavior of athletes, coaches, managers, referees and fans is considered in psychological phenomena and principles (Başer, 1998). Alderman (1980) defined sport psychology as "the effect of sport on human behavior". On the other hand, Gill (1986), expressed sports psychology as "the subfield of sports and exercise science that tries to find answers to questions about human behavior in the sports environment".

Cox (1994) defined sports psychology as a field that includes the application of the principles of psychology to the sports environment, while the American Psychological Association (APA) expressed sports psychology as the study of the psychological foundations of physical activity and the application of the principles and rules of psychology to the sports environment (Cox, 1994; APA, 1996).

The basic scope of sports psychology is all activities involving movement behavior and sports actions. Sports psychology investigates not only compliance with the laws of movement and action of sports activities, but also the effect and contribution of psychological conditions in increasing sportive success.

This approach means that the activities in the whole physical education process are psychologically correct and in compliance with the principles (Rakuvalvy, 1980)

Performance athletes have become the center of attention of psychology over time. Psychologists thought that they could obtain detailed information about the direction and management of the human behavior from the studies that reach the limit of spiritual overloads. Likewise, psychologists realize that athletes can achieve higher performance if they

care about psychological knowledge. In this sense, sports psychology must also examine the psychological conditions beside the athletehes performance. Sports psychology analyzes the psychological processes of athletes during training and competition and pay dividends to achieve high performance (Bauman, 1994)

The two main goals of sports psychology are to determine the impact of psychological factors on motor performance and the impact of participation in physical activity on a person's psychological development (Weinberg and Gould, 2015).

Three main features of sports psychology are:

- Sports psychology is a science.
- Sports psychology includes competing athletes' behavior, as well as physical activity studies for exercise, free time, and fitness.
- Sports psychology is also a profession which is as theoretical as it is practical (Moran, 2004).

Sports psychology also has implications for improving performance, accelerating learning, and eliminating psychic barriers to performance (Mahoney and Suinn, 1986; May, 1986).

3. Preparing Athletes For Competition From A Psychological Point Of View

In order for athletes to achieve the desired performance, psychological preparation, as well as physical, bio-mechanical, tactical and social preparation, must be planned and implemented. The lack of even one of these elements can lead to failure in achieving peak performance (Brewer, 2009; Konter, 1998). During long-term journeys spent in organizations such as international camps, World Championships, Olympic preparation camps and the Olympics, the sports psychologist should prepare to meet the complex multifaceted requirements of athletes and coaches (Koruç and Bayar, 2006)

3.1. Prerequisites of Psychological Preparation (From The Point of View of the Coach and Sports Psychologist)

- Getting to know the coach himself, his athletes and other people; having sufficient knowledge and skills in matters such as communication, interpersonal relationships, motivation, training and sports.
- The coach has sufficient technical and tactical knowledge and can use this information both in training and during and after the competition,

- Knowledge of methods of eliminating elements that hinder the performance of the coach,
- Giving seminars and courses through the sports psychologist (Doğan, 2005).

3.2. Psychological Preparation of Athletes

Psychological preparations applicable to amateur or professional athletes consist of two stages:

3.2.1. General Psychological Preparation

At this stage, the necessary preliminary information is given and, in a sense, the competition is rehearsed. The scheme allows athletes to focus on the competition by using images or videos. At the same time, increasing the level of motivation and eliminating elements that may affect performance are aimed at ensuring that athletes are psychologically and physically ready and can maintain this situation (Weinberg and Gould, 2015).

3.2.2. Special Psychological Preparation

At this stage, covering the preparations made specific to the sports industry, special motivation, special tactical and technical studies and special places and conditions are provided. Some situations that require special psychological preparation are as follows:

- If the competition is for a record,
- If competitors are previously encountered athletes,
- If the competition is important in terms of prestige,
- If the competition determines the position of the athlete or team at the national or international level,
- If a competition is being held for the first time,
- If the competition takes place in front of a large audience,
- If the competition is a show (Doğan, 2005).

4. Impact of Psychological Conditions on Sports Injuries

A disability is a trauma that results in temporary or sometimes permanent physical disability and the deterioration of some motor functions. A sports disability leads to a number of psychological problems as well as physical dysfunction. Isolation, frustration, anxiety and depression are common mental states in athletes with disabilities. Athletes

who experience significant life stress and have not been able to develop strategies to cope with this are likely to have disabilities.

In addition to physical factors, social, psychological and personality factors are also effective in the formation of disability.

- **Physical Factors:** Physical factors such as fatigue, muscle imbalance and ongoing stress are the main causes of disability.
- **Social factors:** The desire of athletes with mild disability or pain to continue playing is among the potential causes of sports disability. Friends, parents, team mates and coaches have influence in the formation of this desire.
- **Psychological factors:** The stress factor is at the center of sports injuries. Especially in cases where there is a potential for stress to occur, the formation of disability is affected by how threatening the athlete perceives the situation to be. Threat elements cause muscle tension and changes in attention and focus, causing a sense of anxiety in the athlete. In this case, the likelihood of disability also increases (Weinberg and Gould, 2015).

5. Some Features That Should Be Found In Athletes In Terms Of Psychology

Cox (1994) listed some features that should be found in athletes:

- Personality traits suitable for sports,
- An internal focus to control success and failure,
- High self-confidence and belief in ultimate success,
- Internal motivation,
- Strong dominance of goal orientation for sporting success,
- Full concentration on the current task,
- Ability to control emotion and arousal,
- Strong skills to cope with the difficulties that are encountered,
- Setting goals and making plans to achieve these goals,
- Ability to use inner speech, imagination, self-control and other psychological methods for confidence and motivation,
- Mental endurance (Cox, 1994).

6. Psychological Preparation For Athletes Before, During and After The Competition

As a result of selecting athletic candidates according to their abilities, and implementing a training program and motivation, athletes are ready to compete. The outcome of the competition is very difficult to predict in advance because there is more than one factor that can affect the outcome. Two types of factors affecting athletes' performance can be mentioned:

- **Internal factors:** personality, perception and motivation levels, ability and psychomotor skills and training performance.
- **External factors:** opponents' status, spectators, referees, weather conditions, and the technical and tactical characteristics of the sports branch.

All these internal and external factors can positively or negatively affect performance and result in, as well as cause, psychological pressure on the athlete (Başer, 1998).

In a psychological sense, competitions can be studied in three stages.

6.1. Before the Competition

Before the competition, a number of changes occur in the athlete depending on his/her individual characteristics (knowledge, experience, and skills) and the nature of the game (the importance level of the game, the degree of difficulty). If the effects of these resulting changes are felt about an hour before the game, the main pre-start situation is beginning, and the pre-start situation begins a minute or two before the start of the game (Başer, 1998)

Some physiological changes are observed in the control of the autonomic nervous system in the pre-start state. These changes include an increase in the number of heart beats, an acceleration of breathing, an increase in blood sugar levels, and the secretion of the hormone adrenaline. In the case of the pre-start, with the presence of internal and external factors, a state of tension can also be observed in athletes with an upset balance in the nervous system (Doğan, 2005).

- **Insufficient Motivation:** Insufficient motivation, which occurs in situations such as underestimating the opponent and trivializing the game, occurs in athletes in the form of reluctance, lethargy, fatigue, avoiding the fight, combative behavior and quitting the competition.
- **Over-motivation:** the importance of the competition and the possible loss of prestige that will be experienced in the event of

failure, as well as what will be achieved in the event of success, will cause psychological pressure on athletes. Along with this situation, emotions such as tension, anxiety, and excessive ambition prevail in the athlete. Excessive motivation can also cause various physiological effects, such as increased heart rate, tremor, sweating, and novelization (Doğan, 2005).

6.2. During the Competition

Low levels of arousal and start laziness are observed in athletes due to insufficient motivation. In the case of start laziness, athletes experience insufficient energy, a reluctance to fight, impaired integrity in movements, difficulties in decision-making, and decreased creativity (May, 1986)

In over-motivated athletes, the state of start flurry occurs. In cases where there is a rush to start, there is an excessive state of arousal in athletes. A decrease in creativity and the softness of movements as well as irregular movements, and technical and tactical incompetence, are among the consequences of the state of start flurry (Doğan, 2005)

During the competition, the athlete is prepared according to the tactics given by the coach; he fights, performs his movements as he wishes, uses his fitness at the optimum level, is creative and is affected by internal and external factors at the minimum level (Weinberg and Gould, 2015)

6.3. After the Competition

The post-competition process is also very important. Even if all the necessary conditions are met before and during the competition, the results may not be as expected. For this reason, especially young athletes may be adversely affected by this situation due to failure (Doğan, 2005)

Determining the measures to be taken with the studies carried out after the competition is an effort that will also be beneficial for the planning of the next competition. It is important to make various evaluations and arrangements by determining the right and wrong things before and after the competition. In addition, it is necessary to have a scientific perspective while making these evaluations.

In the post-competition period, the most critical task and responsibility falls on the coaches. The criticism of the trainers should be constructive and the dose should be adjusted well. In addition, the support of the coach, family, friends and managers to the athletes should continue (Başer, 1998; Weinberg and Gould, 2015).

7. Elimination of Psychological Factors that Negatively Affect Athletes

Efforts to eliminate factors affecting performance can be considered in the form of psychological skills training, autogenic training, progressive relaxation, systematic desensitization, yoga and psychotherapy.

7.1. Psychological Skills Training

Psychological skills include elements such as stress, thought, concentration, motivation, psycho-energy and goal setting management, arousal control, imagery, self-confidence configuration, self-awareness development, and leadership and communication (Anderson, Miles, Robinson, Mahoney., 2004).

Psychology skills training refers to the consistent and systematic study of mental or psychological skills in order to increase performance, pleasure, and personal satisfaction in sports or physical activity.

As with physical skills, psychological skills can be trained and developed. Again, psychological skills training, such as physical training, must be programmed for pre-season, sequence, and post-season (Carron and Brawley, 2008).

Psychological skills training has three main objectives:

- To improve physical and psychological performance,
- To accelerate skills learning,
- To eliminate psychological barriers that adversely affect performance (Mahoney and Suinn, 1986; May, 1986).

7.2. Autogenic Training

In autogenic training, a type of relaxation is achieved using a controlled relaxation technique. This technique occurs by bringing a person to a sleeping position, ensuring a balance between the sympathetic and parasympathetic nervous systems (Yılmaz, 2019).

7.3. Progressive Relaxation

The main purpose of these exercises is to bring tension to the optimal level. The exercises focus on a specific muscle group and the muscle groups are systematically contracted and relaxed. These exercises provide benefits in terms of reducing stress, maintaining breathing and sleep patterns (Doğan, 2005).

7.4. Systematic Desensitization

In this method, the idea prevails that encountering the factors that make up fear has a significant effect on defeating fear (İkizler and Karagözoğlu, 1997). Accordingly, the factors caused by negative emotions are arranged in increasing severity and these factors are confronted in a concrete form. After each respective emotional negative is confronted, and the effect of this negative emotion is eliminated, there is a move to the next negative factor. In this way, a solution is obtained by eliminating the negatives encountered (Öztürk, 2016).

7.5. Yoga

In this method, the goal is to increase one's satisfaction by raising awareness (Manaf, 2013). In this way, as the mind calms down, body awareness increases and anxiety decreases. Yoga also increases people's quality of life (Smith, Hancock, Blake-Mortimer, Eckert, 2007)

7.6. Psychotherapy

Psychotherapy is a method of helping a person with a problem and healing a person using various methods. In this method, benefits and support are provided to individuals who experience stress, impaired interpersonal relationships and mental disorders by using indoctrination, persuasion behavior and ways to change the personality (Öztürk, 2016).

8. Conclusion

"High performance and success in sports come not only with physical, technical and tactical preparation, but also with psychological preparation and regulation of social life. Performance in sport is a whole, and it is necessary to capture harmony in this integrity" (Konter, 2006). In this context, it is very important to provide psychological support and service to athletes in an adequate and accurate way before, during and after the competition to achieve the desired performance. The focus of sports psychology is to improve the athlete's self-development, to increase own value, to control behavior and have impulse control (Cantor, Markus, Niedenthal, Nurius., 1996)

Various studies have been conducted on the relationship between sports and other branch of science. In these studies, the phenomenon of sports psychology has emerged among many hypotheses on the definition of sports psychology (Dimmock and Gucciardi, 2008) When the studies conducted in the field of sports sciences were examined, it was concluded that sports psychologists have increased the performance of athletes with their studies on mental processes and mental training (Feltz and Landers 1983) In their studies in the field of sports psychology, Borkovec, Shadick,

and Hopkins (1991) drew attention to the anxiety experienced by athletes and emphasized the need for a sports psychologist to work in this field.

The state of anxiety can be considered as the totality of uncontrolled and negative thoughts by the athlete. At this point, it helps athletes to gain insight into the situations in which they experience anxiety and how to deal with it. Partington and Orlick (1987) also revealed that the positive relationships that athletes establish with psychologists have contributed positively to their performance on the development of sports psychology.

In today's, where sports gain importance day by day, it is critical to increase the share of sports psychology and to provide psychological support by people who have been trained in the field. In this sense, it is important to carry out studies that will benefit the emergence of potential performance or increase current performance in developing sports psychology programs (Martin and Toogood,, 1997)

On the other hand, it would be the right approach to focus on both preventive and rehabilitative psychological studies at the point of preventing injuries that affect success and performance in sports. At this point, important duties and responsibilities fall to coaches, sports psychologists and educators. It is believed that studying all aspects of psychological factors, in which the personality characteristics of athletes also have a very significant share, and conducting more extensive research in this area will make important contributions to sports science, which is an cumulative process.

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SEXUAL DYSFUNCTION IN DIABETIC WOMEN

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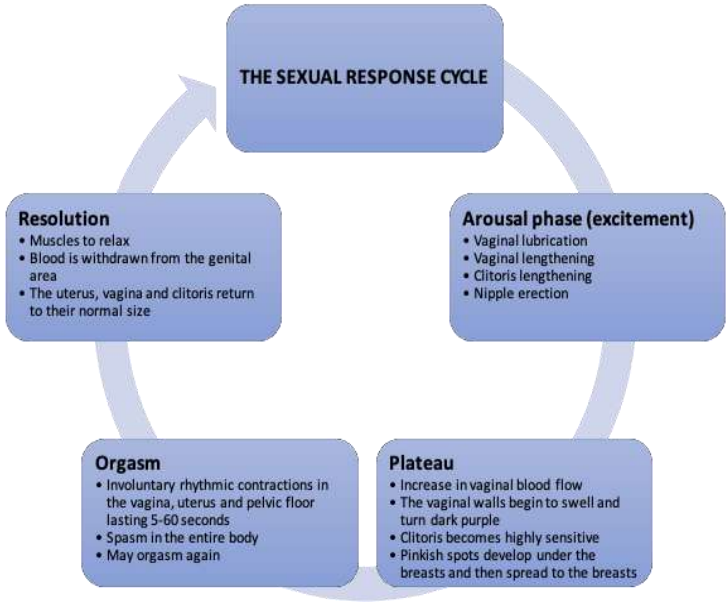
Introduction

Sexual health has been described as "A state of physical, emotional, mental and social well-being in relation to sexuality" by the World Health Organization (Organization vd., 1975). Although reproductive function is important for the well-being of the psychological and social situation, sexual health remains a neglected issue. Sexual dysfunction (SD) can develop due to many reasons. Psychosocial, metabolic, vascular problems and multiple drug use are the main reasons. Coexistence of more than one reason is common in SD (Meeking vd., 2013). Given that diabetes affects many systems and causes physical and psychological complications, it is not surprising that sexual health is significantly affected by diabetes. It has known that known the negative effects of diabetes on the sexual function and health of people with diabetes in both sexes (Rahmanian vd., 2019). Diabetes is one of the major causes of SD in both men and women, it occurs twice as often and starts 10-20 years earlier than those without diabetes. For this reason, it is very important for the healthcare team and the diabetes nurse that follows the diabetics to know the impact of diabetes on male and female sexual functions, early recognition of problems that may occur, timely treatment planning and educating the patient and their family (Meeking vd., 2013; Phillips & Wright, 2009; Rubin vd., 2004; Shifren vd., 2008; Williams & Pickup, 2004).

Female Sexual Response Cycle

Sexual functions are focused on reproduction and sexual pleasure (physical and psychological pleasure). The sexual response has 4 phases in the cycle; First, it starts with the arousal phase, continues with plateau, orgasm, and finally ends with the resolution phase. The sexual response cycle in women is related to both the intensity and duration of the response, and can be of numerous variations (Lipshultz vd., 2016; Rao & Nagaraj, 2015). Female sexual response cycle is in figure 1.

Figure 1: Female Sexual Response Cycle



Sexual Dysfunction in Diabetic Women

SD is an important problem affecting the quality of sexual life of women with diabetes. Studies have reported that SD in women with diabetes has seen between 20-80%, and women with diabetes have a higher feeling of vaginal dryness and less sexual desire than those without diabetes. The most common SD disorders are desire, arousal, lubrication, dyspareunia, and orgasm. In addition, it has been reported that women with type 2 diabetes have higher rates of SD compared to type 1 diabetes due to their older age, the presence of chronic diseases, severe complications, and higher rates of menopause and depression (Celik vd., 2015; Gupta vd., 2018; Mazzilli vd., 2015; Williams & Pickup, 2004).

Etiology of Sexual Dysfunction in Women with Diabetes

SD in women is a multidimensional health problem with physiological, biological, psychological, social and cultural components (Bargiota vd., 2011). Etiological factors include aging, endocrinological disorders, cardiovascular diseases, hypertension, neurological diseases and other chronic diseases, pelvic pain syndromes, concurrence of genitourinary diseases, menopause, pregnancy, high number of births, obesity, drugs (antineoplastic, antidepressants and antihypertensives), major surgical operations, radiotherapy, psychiatric diseases (depression,

anxiety, past sexual trauma, sexual harassment, relationship between spouses), financial difficulties, workplace conditions, education background, physical inactivity (Bargiota vd., 2011; Maiorino vd., 2014; Rahmanian vd., 2019; Rao & Nagaraj, 2015; Woodard & Diamond, 2009).

Physiopathology of Sexual Dysfunction in Women with Diabetes

Diabetes can affect all organ systems, leading to SD. The pathogenesis of SD in women with diabetes includes hyperglycemia, recurrent genital infections, neurological and vascular damage, psychosocial disorders, and hormonal changes (Bargiota vd., 2011; Corona vd., 2020; Kizilay vd., 2017; Schram vd., 2009). It is known that somatic sensory system is affected by diabetes and the most deteriorated parts of genitalia in diabetic women are introits vagina, labia minor and clitoris (Elyasi vd., 2015).

Hyperglycemia

When blood sugar stays high for a long time, mucosal secretion decreases, and the frequency of urogenital infections increases. Genital arousal disorder in diabetic women might be correlated neurovascular change due to hyperglycemia and vascular deterioration in genital area with impaired genital response to sexual stimuli (Corona vd., 2020). In these cases, pain, vaginal dryness, itching, and discharge may occur in the pelvic area, which can lead to vaginal discomfort and dyspareunia (Maiorino vd., 2014; Meeking vd., 2013; Rutherford & Collier, 2005).

Diabetes-related Vascular and Neurological Dysfunction

Long-term high blood sugar leads to structural and functional alterations in the genital system, resulting in impaired sexual response. As a result of vascular disorders such as atherosclerosis and endothelial dysfunction, insufficiency occurs in the clitoral and vaginal vessels and blood flow to the genital area decreases (Maiorino vd., 2014). Diabetic neuropathy causes alterations in the vaginal wall, pelvic floor dysfunction and weakening of muscle tone (Park vd., 2002). Autonomic nervous system damage caused by neuropathy disrupts the orgasm process and causes prolongation of the arousal and desire phase. Neuropathy can inhibit nitric oxide activation and affect vascular response during sexual stimulation. Painful sexual intercourse is also seen due to lack of lubrication (Rutherford & Collier, 2005).

Hormones

It is known that systemic endocrine function is adversely influenced by diabetes in both men and women (Rutherford & Collier, 2005). Many hormones must be at normal levels for sexual activity. Diabetes causes SD by affecting these systems. Neurotransmitters such as serotonin,

dopamine, epinephrine, norepinephrine, histamine, opioids and gamma aminobutyric acid play a role in regulating sexual functions. Estrogen is effective in protecting the integrity of the vaginal tissue and providing clitoral and vaginal blood flow. Androgens are thought to be particularly important for their effects on libido. It has been shown that the sexual problems experienced by women with diabetes are associated with alters in androgen and estrogen levels. Neuropathy and vascular changes together with increased serum androgens especially in women with type 2 diabetes are likely to have a negative effect on sexual function and sexuality. Psychological problems that occur with changes in these hormones cause SD in women (Çiftçi & Yeni, 2014; Maiorino vd., 2014; Rutherford & Collier, 2005).

Psychological Factors

Depression is one of the main determinants of SD in women with diabetes (Enzlin vd., 2003, 2009). Diabetic women with SD were reported to be twice as depressed as women without diabetes (Elyasi vd., 2015). In addition, the development of diabetes and its complications can affect the sexual performance of women by causing loss of self-confidence, deterioration of health status and related social life, and decrease in quality of life (Enzlin vd., 2002; Ogbera vd., 2009; Rutherford & Collier, 2005; Schram vd., 2009).

Definition and Classification of Female Sexual Dysfunction

Female sexual dysfunction (FSD) was defined as "disruption of the process determining the sexual response cycle and pain in sexual intercourse" in the consensus meeting held by the American Foundation for Urological Diseases in 1998. Also, it is divided into four categories as sexual desire disorders, sexual arousal disorders, orgasm disorders and sexual pain disorders. In 2000, the classification was changed by adding the expression "causing personal distress" as a new diagnostic criterion in the consensus. At the meeting in 2004, the definitions regarding the FSD were revised again (R Basson vd., 2000; Rosemary Basson vd., 2010).

Definitions for Sexual Dysfunction

Hypoactive sexual desire disorder: Lack or absence of sexual interest or sexual desire that cannot be explained by advanced age and long-term relationship; lack of sexual thoughts or fantasies and willingness to respond to sexuality.

Subjective sexual arousal disorder: Significant diminished or absence of feelings of sexual arousal (sexual excitement and pleasure), despite the presence of peripheral arousal response such as vaginal lubrication or other signs of sexual arousal.

Genital sexual arousal disorder: Impaired or absence of genital sexual arousal. The decreased in peripheral response, such as vaginal lubrication, despite subjective sexual arousal response to sexual stimuli.

Combined genital and subjective arousal disorder: The absence of affective sexual arousal (sexual excitement and pleasure), and markedly diminished peripheral arousal responses despite all kinds of sexual stimulation. There is also impaired vulval swelling and lubrication.

Persistent sexual arousal disorder: It is the involuntary, spontaneous, and unwanted genital stimulation response that lasts for hours or days in the absence of sexual desire or interest and does not end despite orgasm.

Female orgasm disorder: Inability to orgasm despite sufficient sexual arousal or excitement with any type of stimulation, there is a significant decrease in orgasm intensity, marked delay of orgasm.

Dyspareunia: Persistent or recurrent pain during vaginal intercourse.

Vaginismus: The woman does not allow the penis or other object to enter the vagina persistently or repeatedly, despite the desire for vaginal intercourse.

Sexual aversion disorder: Woman's excessive anxiety or disgust at any sexual activity expectation or attempt (Rosemary Basson vd., 2004; Giraldi & Kristensen, 2010).

Diagnosis of Sexual Dysfunction in Women with Diabetes

It is very difficult for both the patient and the healthcare worker to evaluate sexual function and dysfunction. Limited experience with sexual functions, personal taboos about sexuality, privacy issues, and humiliation problems make it difficult to explain sexual problems. Initially, it is essential to distinguish between psychogenic and organic causes of SD (Lipshultz vd., 2016; Young, 2010).

Sexual History: The first step in evaluating sexual function is to take a detailed and systematic sexual and medical history. The effects of religious and social beliefs on sexuality should be evaluated and discussed with their partner. Situations that have an effect on sexuality should be evaluated and discussed with their partner using targeted questioning regarding individual characteristics, psychosocial status, sexual history, medical history (glycemia, complications, diabetes treatment, etc.), other chronic diseases, mental condition, drugs used, smoking and alcohol use, sedentary life style, gynecological history, abuse or other traumatic sexual experiences (Gupta vd., 2018; Kingsberg & Janata, 2007; Rahmanian vd., 2019). Diabetic neuropathy for the lower urinary tract findings and the presence of repeated urinary infections can

be questioned regarding findings, such as nocturia, incontinence, pain during intercourse, and others (Pop-Busui vd., 2017).

Application of Sexual Questionnaires: Sexuality questionnaires play a complementary role in the diagnosis and treatment of FSD. These questionnaires are especially used to identify people with SD, evaluate the severity of SD, satisfaction after therapy, and the effect of sexuality on people's quality of life (Gupta vd., 2018). The most commonly used validated scales that evaluate female sexual function and its disorders;(Bargiota vd., 2011; Jones, 2002; Young, 2010).

- The Female Sexual Function Index (FSFI)
- The Brief Index of Sexual Functioning for Women (BISF-W)
- The Sexual Interest and Desire Inventory (SIDI)
- The Female Sexual Distress Scale (FSDS)
- The Derogates Interview for Sexual Function (DISF/DISF-SR)
- The Profile of Female Sexual Functioning (PFSF)
- Brief form Profile of Female Sexual Functioning (B-PFSF)
- The Short Personal Experience Questionnaire (SPEQ)

Physical Examination: Examination includes the inspection and palpation of the internal and external genital organs, as well as the evaluation of the neurological and vascular system. Labia, skin turgor, thickness, clitoris, vaginal entrance are observed with the vaginal examination. It should be observed vaginal discharge. During vaginal examination urethra, rectum, uterus, adnexa, and pelvic floor muscle tone and prolapse are evaluated. Also, vaginal depth and sensitivity, vaginal mucosal integrity, and secretions are examined (Gupta vd., 2018; Kingsberg & Janata, 2007; Pasqualotto vd., 2005).

Laboratory tests: Mandatory tests for every patient include fasting glucose, hemoglobin A1c, lipid profile, testosterone, and estrogen level. If necessary, prolactin, follicle-stimulating hormone, luteinizing hormone, thyroid-kidney-liver function tests, and complete urine tests may be requested (Kingsberg & Janata, 2007). Vaginal cultures and Pap smear should be evaluated along with physical examination. Clinical suspicion should guide the use of imaging modalities such as Computed Tomography scan (CT) and ultrasonography (Pasqualotto vd., 2005).

Specific diagnostic tests: Special diagnostic tests are used to diagnose SD and to determine the pathophysiological mechanism (vascular, hormonal, and neurological components). These tests; genital blood flow measurement (clitoris and vagina blood flow), vascular evaluation, vaginal compliance measurement, genital sensitivity test (biothesiometry-vibration test) (Kingsberg & Janata, 2007).

Treatment of Sexual Dysfunction in Women with Diabetes

There is currently no specific treatment strategy for diabetic women with impaired sexual function. Treatment is determined by the cause and the general state of health. Also, women with sexual problems are managed by a multidisciplinary team trained in diabetes and sexuality. During the treatment/care of patients, the age of patients, previous operations and chronic diseases, and complications due to diabetes are taken into consideration. Therapeutic possibilities for SD in diabetic women apply to metabolic control with optimal diabetic control, lifestyle changes, psychotherapy, follow-up and treatment of depression and selected medications when appropriate (Maiorino vd., 2014).

The adoption of a healthy lifestyle, metabolic control, and the other therapeutic treatments may reduce insulin resistance and blood glucose level, endothelial dysfunction, and oxidative stress, all of these are desired goals for diabetic patients. These changes would further help decrease and prevent SD in women with diabetes. Estrogen preparations may prevent atherosclerosis in the pelvic arteries by creating vasodilation and increase blood flow in the clitoris, vagina, and urethra in postmenopausal women. Mechanical vibrators, simple lubricants or topical estrogens are recommended for women with arousal disorders and orgasm problems. Clitoral vacuum devices increase clitoral blood supply and autonomic reflex and restore the decreased vaginal lubrication to normal levels. Treatment approaches for SD in women with diabetes are summarized in table 1 (Gupta vd., 2018; Meeking vd., 2013; Price, 2017).

Table 1: Treatment of Sexual Dysfunction in Women with Diabetes

Genital infection	▪ Genital infection treatment ▪ Genital hygiene training
Menopause	▪ Hormone replacement therapies (estrogen, androgen)
Libido decreased	▪ Evaluation of depressive diseases ▪ Psychosexual support for all kinds of self-image issues ▪ Estrogen / Androgen replacement
Dyspareunia (painful sexual intercourse)	▪ Investigation and treatment of the underlying cause ▪ Providing vaginal lubrication ▪ Cognitive-behavioral psychotherapy
Lack of desire or vaginismus	▪ Cognitive and behavioral psychotherapies

Arousal or orgasm disorders	▪ Clitoral vacuum device ▪ Psychosexual support
Decreased vaginal lubrication	▪ Training to ensure adequate pre-intercourse lubrication ▪ Water-based vaginal lubrication ▪ Hormone replacement therapy ▪ PDE-5 (phosphodiesterase type-5) inhibitors treatment
Metabolic control	▪ Individual diabetes treatment ▪ Optimal glycemic control ▪ Blood pressure control ▪ To maintain lipids within the normal range
Lifestyle changes	▪ Quitting alcohol and smoking ▪ Healthy diet planning ▪ The regular exercise program, increased physical activity ▪ Control of body weight
Psychological	▪ Sex education, sexual experiences ▪ Sexual therapy (individual or couple) ▪ Elimination of stress factors ▪ Relaxation exercises (yoga, etc.) ▪ Concentration / mindfulness exercises
Depression	▪ Specific antidepressant therapy

The Role of The Nurse in Sexual Dysfunction

Since SD is a multidisciplinary subject, it requires interdisciplinary cooperation. Nurses are often involved in counseling and rehabilitating patients. The nurses have an essential role in the early diagnosis of sexual problems, who help individuals or couples to develop a health plan that includes their sexual health. For this reason, it is important and necessary for diabetes nurses, who play an important role in the team, to notice individual sexuality, to be comfortable with sexuality issues, to be a good listener, not to have a judgmental attitude, to have developed counseling skills, and to have knowledge about sexuality and sexual function (Karakoyunlu & Öncel, 2009; Rosen vd., 2000; Trisha, 2014).

- Nurses should be aware that the patient may have a sexual problem, and the patient should be encouraged to explain and discuss by asking questions.
- The nurse should be aware of the beliefs, values and attitudes of the society and culture in which the individual lives.

- The nurse takes the first history by talking to the individual / couple, fills in the necessary forms, and then performs a physical examination and, if necessary, diagnostic tests based on the story.
- A comfortable environment is provided while interviewing and the privacy of the individual is protected. Whenever possible, the sexual partner should be included in the consultation.
- During the interviews, open-ended questions should be asked clearly, and effective listening methods should be used. Patients should be encouraged to ask questions, if they feel uncomfortable about sexuality and sexual functions.
- Reasons preventing satisfaction from sexual activity and interests, attitudes and knowledge about sexuality are evaluated / diagnosed.
- The effects of chronic diseases on sexual functionality are discussed, and planning is made for the treatment and care of existing diseases.
- If SD is related to drug therapy, alternatives are examined / case management can be chosen.
- While discussing sexual health with patients of childbearing age, the patient's cultural and religious beliefs about contraception should be taken into consideration.
- The nurse cooperates with primary caregivers, physicians or mental health specialists/consultants specialized in this subject during the training process on sexual function functions, and can refer the patient to support groups if necessary (Karakoyunlu & Öncel, 2009; Rosen vd., 2000; Trisha, 2014).

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THE EFFECT OF TOXIC STRESS ON BRAIN DEVELOPMENT IN EARLY CHILDHOOD PERIOD

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1. Introductıon

"Early childhood" covers the 0-8 age period in a child's life and is vital for his/her development. This period forms almost half of the extent that the child will progress in his developmental areas during his life. Moreover, the mental abilities, intelligence, social behaviors, and personality of the child, which have a huge impact on their lives, are seriously shaped during this period. Many studies highlight the need to support the child's developmental areas in the early childhood period with appropriate means. The foundations of language development, which is essential in social and academic life, are also laid in this period. Before children's speech skills develop, the areas related to language development in the brain actively develop in early childhood (Senemoglu, 2012; Bacanli, 2016).

Stress is described as an inevitable part of the life experienced by people of all age groups. While a certain amount of stress is deemed normal and necessary for survival, it can positively or negatively affect a young child's life. In some cases, it is considered beneficial for children to adapt to new conditions, cope with dangerous and scary situations, and help them develop necessary skills (Bilim, 2012). Experts have discovered that prolonged or excessive stress can become harmful to children and can lead to serious health issues. According to experts, when stress increases in early childhood, neurobiological factors are affected. In particular, the cortisol level, which is the stress hormone, rises above the normal level (Aksin & Ahmetoglu, 2015).

Stress is caused by internal or external influences disrupting an individual's usual well-being. These effects can lead to physiological changes as well as emotional distress. Accordingly, factors such as exposure to adverse childhood experiences, hunger, separation from the family, domestic violence, neighborhood violence, mental illness, physical/sexual abuse, divorce, a new home or school, illness and hospitalization, loss of life of a loved one, poverty, natural disasters,

terrorism, and negative discipline techniques of adults cause the child's well-being to deteriorate (Sypniewski, 2016).

2. Causes of Stress

Although stress is usually regarded as a situation that negatively affects life, it has a significant and protective meaning for humans. When people encounter a negative situation, there is also "biological feedback" against this event (Oguz, Dursun & Dursun, 2004). The concept of biological feedback is defined as the techniques that emerged in the 1960s and enabled the individual to voluntarily control his/her physiological movements. In other words, biological feedback is the person's ability to minimize stress's adverse effects by obtaining information about his/her biological process (Mongan, 2005).

The child's mind and body may have difficulties in distinguishing the dangers in some life events. In case of approaching danger or a negative situation, the child's alarm system is activated physically, mentally, emotionally, and behaviorally. Situations such as the child's constant vigilance and the presence of an undesirable situation for a long time can become tiring over time. The individual may become unable to continue his/her daily work. In Figure 1, the reasons that disrupt psychological well-being are shown.

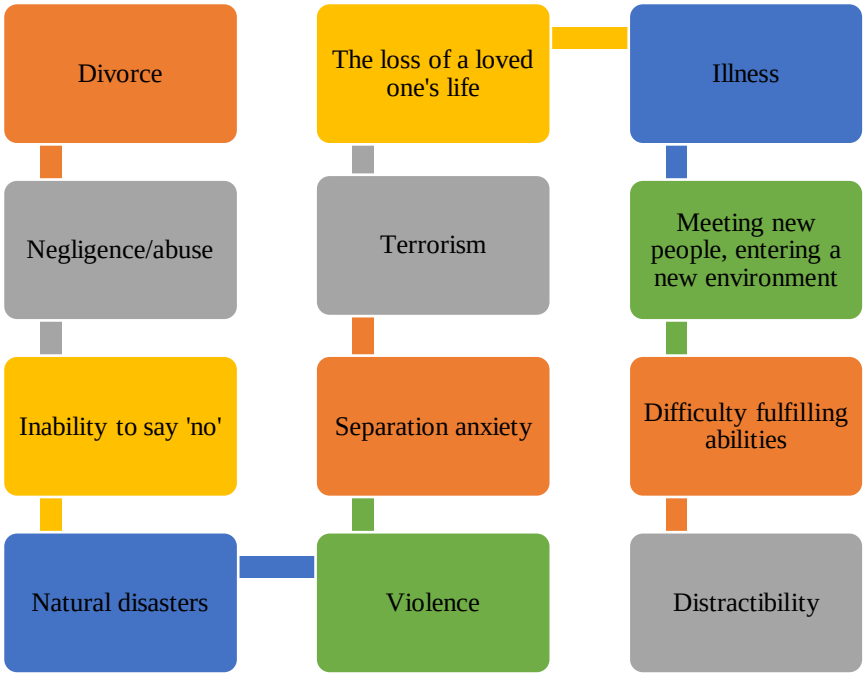

Figure-1: Causes of stres (Middlebrooks & Audage, 2008).

As seen in Figure 1, socialization and entering a new environment, which seem optimistic compared to negative situations, can affect the child's life and psychological well-being. Besides, unwanted situations such as the child's parental attitudes (extreme perfectionism), inability to spend quality time with loved ones, and peer bullying can be cited among toxic stress causes (Condon et al., 2019).

3. Stress and Brain Development

In the neonatal period, the baby's brain weight is approximately 350 grams. At the end of a year, the baby's brain weight becomes about 1.1 kilograms. At the end of the second year, the baby's brain weight reaches almost 80 percent of an adult's brain weight (Bugie, 2002). Many factors affect brain development positively/negatively in this process, which continues from the beginning of pregnancy to the nervous system's development.

Hormone systems and brain circuits are formed and activated at an early age. The body's neurobiological systems are essential for survival in early childhood and throughout life. When a child or adult is exposed to stress, the body tries to regulate this by releasing stress hormones. However, hormones that are continually increasing due to prolonged or frequent biological stress may increase the risk of future physical and mental health problems in early childhood. Since brain circuits are vulnerable in early childhood, stress factors can affect the development of necessary brain connections. Consequently, toxic stress is a factor that can alter the formation of the brain circuitry, disrupt it, and cause a small brain size in young children (Center for Disease Control and Prevention (CDC), 2016).

3.1. Stress Levels

Learning how to deal with adversity is an essential part of healthy child development. When the brain becomes aware of a potential threat, it sends signals to the body to take action (Condon et al., 2019). The body produces a series of stress hormones and neurotransmitters that prepare the mind and muscles to stimulate and respectively accelerate the heartbeat, breathing, and the immune system. If this reaction of the child in a negative situation remains for a long time, stress hormones begin to break down the body's organs and immune system in a way that can develop chronic health problems. Particularly in early childhood, brain architecture is affected adversely according to the intensity and duration of stress. In Figure 2, the stress level observed in children in early childhood is expressed.

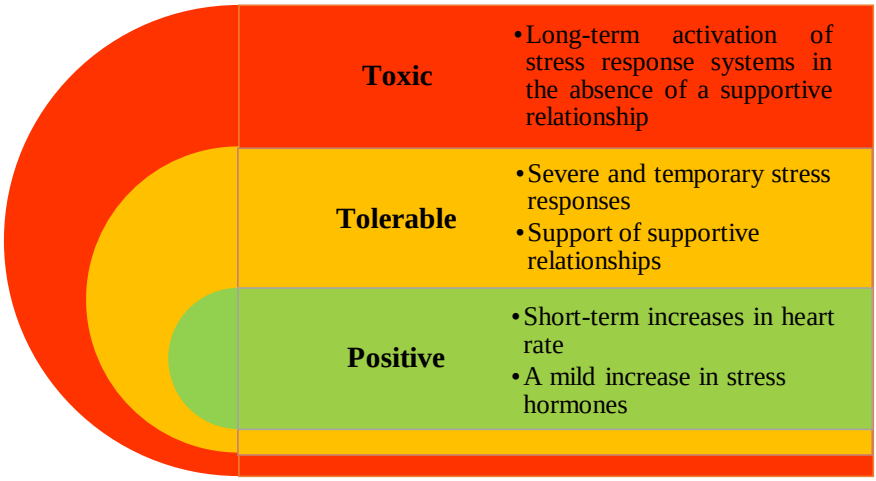

Figure-2: Early childhood stress levels (Center on the Developing Child, 2020).

Positive stress level, is a normal and important part of healthy development. It enables the child to competently deal with the undesirable situation while under threat. It also causes physiological and hormonal changes. In particular, an increase in heart rate and a slight rise in cortisol hormone level occur. The first day of school, a family wedding, or making new friends can be classified as examples of positive stressors. Such experiences allow the child to respond positively to stressful events by promoting healthy development in a supportive relationship (family support) environment (Ortiz & Sibinga, 2017).

Tolerable stress level, results from intense but short-lived negative experiences in the child's life that are often overcome. Examples of tolerable stress factors include family fights, accidents, or the death of a loved one. It is essential to realize that these types of stressors are only tolerable when appropriately managed. With the proper care of adults, children can easily cope with tolerable stress, turning it into positive stress. Yet, tolerable stress can be harmful if adult support is not sufficient in a child's coping stages (Lyness, 2013).

Toxic stress level, arises when bad experiences continue for a long time and intensely. In 1993, Bruce McEwen and E. Stellar defined it as "wear and tear on the body" when exposed to negative experiences and chronic stress (Center on the Developing Child, 2020). Examples of toxic stress factors include abuse, family separation, neglect, violence, and the child's survival without adult support. Studies have revealed that children who experience severe and prolonged abuse have smaller brain sizes. Caring

and supportive adults are required to support children in these situations. The toxic stress level of children who can receive adequate care and support from their families can turn into a tolerable stress level (Peddicord, 2009).

3.2. Toxic Stress

Toxic stress is a term adopted by pediatrician Jack P. Shonkoff and Harvard University's Center on the Developing Child to refer to chronic and extreme stress exceeding the child's ability to cope with stress due to lack of supportive care (Center on the Developing Child, 2020).

Learning to cope with mild to moderate stress is a part of normal development in children. Simultaneously, the lack of supportive relationships to buffer the effects of the increased stress response (mother/father support) and the emergence of prolonged stress situations can harm the child's physical and mental health. Prolonged toxic stress can cause the child to become more susceptible to stressful events and wear and tear of their physical systems. This wear and tear later increase the risk of physical and mental illness (Ortiz & Sibinga, 2017).

When chronic toxic stress occurs, a child's brainstem, heart, and circulatory system (blood circulation) can be damaged by overstimulation. Also, changes can occur in children's brain chemistry that leads to hyperactivity and anxiety. Thus, it has been determined that the occurrence of toxic stress in early childhood may cause changes in the child's physical, emotional, psychological, social, and behavioral characteristics (Sypniewski, 2016).

4. The Effects of Stress on Children

4.1. Physical Effects

Stress can make a child's body more vulnerable to infections, cardiovascular problems, obesity, prolonged illness, viruses, and gastrointestinal issues. It can also affect the growth and development of children, including the onset of puberty. Some of the physical cues that may indicate stress in children can be listed as eczema, acne and hair loss, worsening asthma, insomnia or hypersomnia, frequent headaches, muscle aches, vomiting, constipation, and diarrhea, and skin rashes. Besides, extreme fatigue, chest pain, tremors, cold hands and feet, getting sick often, and ulcers are other physical symptoms that occur due to stress (Ozmert, 2005).

4.2. Emotional Effects

When children cannot cope with stress, they may start to develop emotional problems. Lacking energy and motivation, they can become seriously depressed. They can develop personality traits such as violence

and disobedience. Post-traumatic stress disorder can also occur (Sypniewski, 2016).

4.3. Psychological Effects

Mood changes, increased irritability, or aggression are psychological symptoms that indicate stress in children. Examples include frustration, anxiety, guilt, emotional turmoil, and isolation from family and friends. New fears, nightmares, and even symptoms of paranoia may occur in the child. They can easily lie to others to hide their emotions. The children's' stress level is mostly due to academic reasons and excessive responsibilities related to workload (Centers for Disease Control and Prevention (CDC), (2016).

4.4. Social and Behavioral Effects

Children who are under extreme stress tend to move away from their families and friends. They may have difficulties in their adaptation to the school process and their relationships with their peers. Simultaneously, they may be distracted and react furiously towards others.

In early childhood, regression of language development, more frequent crying, restlessness, disobedience to parents, new habits, or regression behaviors such as thumb sucking, bed wetting, and nail-biting may occur (Wise, 2014).

4.5. Long-Term Effects of Stress on Children

In the Adverse Childhood Experiences (ACE) study conducted by Dr. Vincent Felitti and Dr. Robert Anda between 1995 and 1997 on 17,337 participants, it was determined that adulthood problems are associated with adverse childhood experiences (McEwen, 1998).

Researchers have discovered that a person's cumulative ACE score is strongly linked with numerous health, social, and behavioral problems throughout their lives, including substance use disorders. These factors are listed in Figure 3.

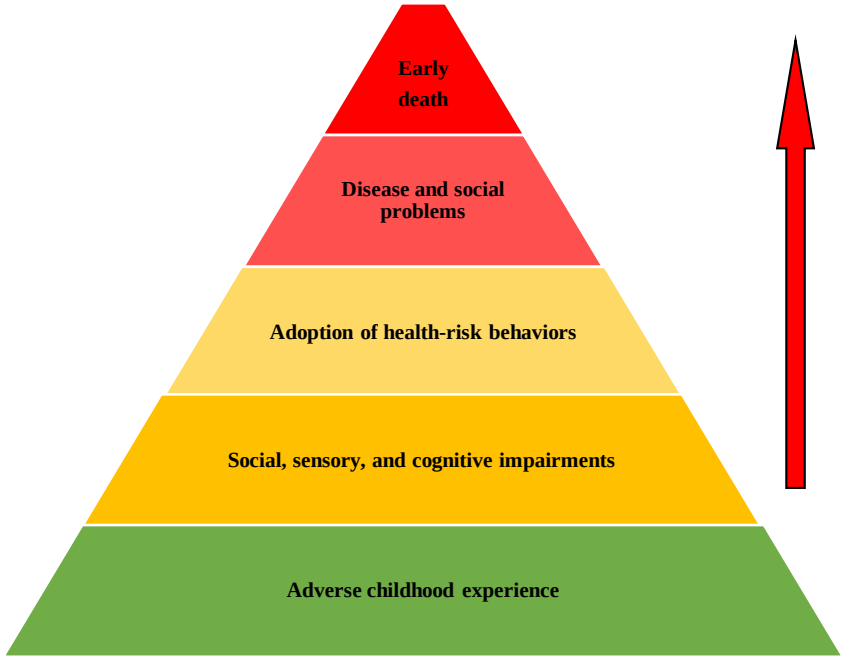

Figure-3: Adverse childhood experience results (Center for Disease Control and Prevention (CDC), 2016).

As seen in Figure 3, the ACE pyramid represents the conceptual framework that reveals how adverse childhood experiences are strongly linked with many risk factors throughout life.

5. Recommendations

5.1. Recommendations to Help Prevent Stress in Children Include

The recommendations to help prevent stress in children are as follows:

- Talking about the experience that will help children understand stress.
- Keeping communication open. This situation makes the child feel comfortable when talking to a person. The child's comfort level is vital because if the child is not comfortable and has to talk, it may not be opened at all.
- The family environment should be arranged as an environment where a child can express his / her feelings in healthy ways.
- Stress coping mechanisms should be modeled for children (such as going for a walk, playing games).
- To reveal children's creative features. For example, running, writing, reading, art activities, and playing musical instruments.
- To teach children to act and positively think when they encounter an undesirable situation to manage stress.

- To ensure that children are fed correctly.
- To ensure that children are not exposed to substance addiction or violence. (Peddicord, 2009)

5.2. Recommendations for Coping with Stress in Early Childhood Period

Some recommendations to assist children in coping with stress are as follows:

- Recognizing the child's behavior and emotions and helping him/her express what bothers him/her.
- Not preventing children when they do wrong and helping them learn by doing.
- Helping the child to think and act positively.
- To help the child develop positive habits to cope with stress.
- Being patient with the child (Lyness, 2013).

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