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Meningitis: Bacterial, Viral and Fungal Disease

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Abstract

Meningitis is an atypical infection, affecting the membranous coverings of the brain and spinal cord-meninges. Meningitis may be of different types depending upon the causative agents, including bacteria, viruses and fungi, and are commonly referred to as bacterial, viral and fungal meningitis, respectively. There are several viruses, such as Enteroviruses, Herpes Simplex Virus-2 (HSV-2) and Varicella-zoster virus, which have been known to cause meningitis. The viral meningitis is the prevalent type of meningitis and typically disappears without treatment. Various bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* and *Listeria monocytogenes*, have been shown to cause meningitis. Bacterial meningitis is the most acute type and could be life-threatening. It is contagious and might be transmitted by prolonged close contact with an infected person. The rare form of the disease is fungal meningitis. Fungus, namely, *Cryptococcus neoformans*, has been mainly reported to cause fungal meningitis. It typically encounters people with the feeble immune system. In this review article, the three forms of meningitis, as well as the symptoms of the disease, which vary with age, have been discussed.

Keywords: Meningitis; Bacteria; Fungi; Viruses; Meninges; Pneumococcal meningitis; Herpes simplex virus-2

Abbreviations: HSV-2: Herpes Simplex Virus-2; EVs: Enteroviruses; CSF: Cerebrospinal Fluid; VZV: Varicella-Zoster Virus; PCR: Polymerase Chain Reaction; HIV: Human Immunodeficiency Virus; MMR: Mumps, Measles and Rubella; AIDS: Acquired Immunodeficiency Syndrome; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; EEG: Electroencephalogram; Hib: Haemophilus Influenzae b; EDTA: Ethylenediaminetetraacetic Acid

Introduction

Meningitis is an acute inflammation of the meninges-membranous envelopes covering the brain and the spinal cord. It could be caused by bacteria, viruses, or fungi. The most common causes are viruses and bacteria, with viruses accounting for up to half of the cases [1]. In viral meningitis, there is an inflammation of the meninges and the subarachnoid space-fluid-filled space between the meninges. The viral type could disappear without treatment. Whereas, the bacterial form of the disease is the most severe type and could be life-threatening. It is associated with high mortality. In patients who survive, there is a high risk of permanent disability [2]. The approximate prevalence of bacterial meningitis is 0.7-0.9/100,000 people per year in developed countries [3].

Fungal meningitis is the rare form of the disease and usually occurs when the fungus enters the intrathecal space by rupturing the blood-brain barrier. It mainly affects people with a weak immune system. While major fungal pathogens, including *Cryptococcus neoformans*, *Coccidioides immitis* or *Histoplasma capsulatum*, could cause infections in individuals, *Cryptococcus neoformans* has been reported to be the main pathogen. Cryptococcal meningitis has been reported to be the most common type of fungal meningitis, with nearly 70.1% of cases [4].

Viral Meningitis

Viral meningitis is the most prevalent type of meningitis, which takes place due to a viral infection. It is usually mild and gets treated on its own. It is also known as aseptic meningitis. Nearly 50% of the cases of viral meningitis are caused by common seasonal

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viruses. Viruses could be transmitted by close contact with an infected person's cough, saliva or faecal matter. A mosquito bite could also transmit some of the viruses [5].

Viral meningitis could infect any person at any age, but its highest rates are in young children, and the prevalence diminishes with age. A study published in 1986 reported that the annual prevalence of viral meningitis was 219 per 100,000 infants (<1-year-old) and 27.8 per 100,000 children under 14 years old [6,7]. Another study reported that the rate of viral meningitis was 7.6 per 100,000 in people aged 16 and above, which was much lower than that reported in children [6,8].

There are several viruses that may cause meningitis. Enteroviruses are mostly responsible for causing meningitis at all ages. Viruses, namely, Herpes Simplex Virus type 2 and Varicella-zoster virus, are also reported to be the cause of meningitis [6,8].

Enteroviruses (EVs)

EVs are the common viruses that invade the body through the mouth and then travel to the brain and neighbouring tissues and multiply there. These viruses are mainly found in mucus, faeces and saliva. These could be transmitted through immediate contact with an infected person or even an object [9]. Coxsackie A and B viruses, echoviruses and polioviruses are some of the viruses that hold within the enteroviruses and could give rise to symptoms of viral meningitis. Among these, coxsackie B viruses and echoviruses are the cause of the majority of the meningitis cases caused by enteroviruses [6,10]. People with feeble immunity, especially children, are mainly vulnerable to enteroviruses [6].

Herpes Simplex Viruses (HSVs)

There are two types of HSVs, namely, HSV-1 and HSV-2. After enteroviruses, HSVs are the second most common viruses responsible for viral meningitis in kids and adults. The HSV-1 is mainly related to encephalitis in the brain (inflammation of the brain), whereas HSV-2 causes meningitis [11]. HSV-2 is considered to be the most prevalent cause of Mollaret's meningitis, responsible for nearly 84% of cases [12]. Mollaret's meningitis is recurrent, benign, aseptic meningitis and is commonly referred to as recurrent benign lymphocytic meningitis. It is the unusual disease specified by 3-5 episodes of benign meningitis, hanging around for 2-5 days before recuperation [11,13]. HSV-2 mainly develops due to genital infection and is procured through sexual contact. A total of 36% of women and 13% of men with the primary genital infection have been reported to develop meningitis. However, HSV-2 meningitis could also occur in the absence of genital herpes symptoms [6,11,14,15]. A study reported that 82% of the assessable patients with HSV-2 detected in the cerebrospinal fluid (CSF) and recurrent meningitis neither had any history of genital herpes nor had active lesions at the time of presentation [16].

Varicella-zoster virus (VZV)

VZV is known to cause chickenpox (varicella). It is regarded as the rare cause of viral meningitis, especially during reactivation. In the United States, VZV is responsible for nearly 11% of the total cases of viral meningitis [17]. VZV is always not necessarily associated with cutaneous symptoms. Echevarría et al. [18] conducted a Polymerase Chain Reaction (PCR) analysis of the CSF samples of 21 patients suffering from aseptic meningitis. They found that 55% of those patients lacked skin contusions.

Gnoni et al. [17] reported a case of VZV meningitis in a 29-year-old Caucasian female who presented at the hospital with headache, photophobia and chills for 5 days. Before the appearance of these symptoms, she was healthy and immunocompetent. On performing CSF's polymerase chain reaction analysis, the authors detected aseptic meningitis caused by the VZV infection. There was no shingles rash eruption on physical examination. As a treatment, she was given oral valacyclovir 2 g Q6H after receiving two days of IV acyclovir. The authors stated this case to be the first reported case of a patient with VZV-associated meningitis successfully treated with oral valacyclovir.

Other viruses

Other viruses, such as mumps virus, measles virus, poliovirus, HIV, West Nile virus, have also been reported to cause meningitis. Meningitis might be a common complication before vaccination. Usually, a vaccine shot for Measles, Mumps and Rubella, called as Mumps, Measles and Rubella (MMR) vaccine, is given at a younger age, thus minimizing the possibility of meningitis. Before the introduction of the MMR vaccine, the most common cause of viral meningitis was reported as mumps in the UK [19]. A study published in 2005 reported that young men seemed to be at a higher risk of mumps-associated meningitis [20]. In rare cases, Morbilli virus known to cause measles, could also cause meningitis [11]. Unusually, a virus causing polio affects the brain and spinal cord, resulting in symptoms associated with meningitis [21]. HIV might cause meningitis during the initial stages of the infection. Although viral meningitis is rarely caused by HIV, it is imperative that adults with idiopathic viral meningitis undergo an HIV test. The reason is that if the HIV responsible for viral meningitis is not identified at an early stage, it might remain undiagnosed with no symptoms until the patient encountered an advanced disease (or Acquired Immunodeficiency Syndrome (AIDS)). The risk of transmission of HIV is also greater in the initial stages [6,19]. Each year, when the insect inhabitants are inflated, arthropod viruses, such as West Nile virus, account for a small number of meningitis cases [11].

Symptoms

Infants suffering from viral meningitis commonly present symptoms, such as fever, irritability, refusal to eat, drowsiness, rash and fatigue. The commonly reported symptoms of viral meningitis in children and adults are fever, headache, stiff neck, sensitivity to light, drowsiness, nausea, irritability, vomiting, poor eating, fatigue and altered mental status [11,22].

The most common clinical symptoms exhibited by the Enterovirus (EV)-positive meningitis patients have been reported to be fever, vomiting and nausea [23]. EV-positive meningitis might also be associated with localised vesicles in hand, foot and mouth, herpangina and maculopapular rash [6]. The complications associated with HSV-2 meningitis are urinary retention, constipation, motor weakness, paresthesias and back, buttock, perineal or lower extremity pain [14,15]. Fever and vomiting are typically associated with mumps meningitis, and approximately half of the cases also express swelling of the salivary gland. HIV meningitis is commonly associated with fever, lymphadenopathy, sore throat or a rash [24]. Meningitis caused by other viruses are either asymptomatic or cause mild illness with the usual presentation of clinical symptoms associated with the virus causing disease. The majority of immunocompetent people with mild viral meningitis conventionally recuperate on their own within 7-10 days [22].

Diagnosis

As the symptoms of viral meningitis are identical to those of bacterial meningitis, the proper identification of a viral cause is favourable in reducing the use of antibiotics and decreasing the length of hospital stay. The useful reported investigations to diagnose the suspected viral meningitis include the analysis of CSF (microscopy, immunoassays, protein and glucose concentration measurement, PCR), lumbar puncture, CT or MRI head scan with contrast enhancement and EEG [6,11,24].

Treatment

There is no specific treatment recommended for viral meningitis, and the majority of immunocompetent patients recuperate on their own within 7-10 days. For the management of the disease, intake of plenty of fluids has been recommended. Pain and fever could be controlled with analgesics and antipyretics, respectively [11,25]. A few studies have reported the usage of oral and/or intravenous antiviral drugs to treat viral meningitis. HSV-2 meningitis has been reported to be treated with antiviral agents, such as acyclovir and valacyclovir [26,27]. A 29-year-old Caucasian female suffering from VZV meningitis has been reported to be successfully treated with oral valacyclovir [17].

Bacterial Meningitis

Bacterial meningitis is the most severe type and could be life-threatening. It is significantly associated with high rates of morbidity and mortality. Thus, the condition demands rapid identification and treatment [28]. In patients who survive, there is a high risk of permanent disability, such as brain damage, hearing loss and learning disabilities. The main bacteria responsible for meningitis include *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* and *Listeria monocytogenes* [29]. The approximate prevalence of bacterial meningitis is 0.7-0.9/100,000 people per year in developed countries [3]. The data reported that children in the age group of five years, adults in the age group of 14 to 25 years and older people above 55 years are mainly affected by bacterial meningitis [30-32].

The bacteria causing meningitis vary depending on age, vaccination status and recent trauma. Newborns are at higher risk of *Streptococcus pneumoniae*, *Escherichia coli* and *Listeria monocytogenes*, whereas *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* are responsible for causing meningitis in children. Adults are at higher risk of *Neisseria meningitidis* and *Streptococcus pneumoniae*. Whereas the older population is at higher risk of *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Listeria monocytogenes*. In the developed world, the risk of *Haemophilus influenzae* to cause meningitis has been nearly eradicated due to vaccination. Similarly, due to vaccination, there has been a substantial reduction in the rates of other meningitis-causing bacteria, namely, *Neisseria meningitidis* and *Streptococcus pneumoniae* [28,29].

The bacteria for meningitis have been observed in the rear part of the nose and also in the throat. From these parts, they travel to the brain through blood [33]. The bacteria might invade the body of humans through cough, sneeze, saliva and kissing. Their survival time is not too long outside the body (i.e., in the atmosphere) [34]. Generally, the bacteria do not spread through water, swimming pool and building. When an individual suffers from septicaemia, i.e., blood poisoning, the bacteria multiply within the blood itself [9]. It has also been found that many times, bacteria for meningitis may survive within the body without any visible symptoms. In such cases, generally, the body develops antibodies against the bacteria using its defence system. On the weakening of the defence system of the body, the individual is suffered from meningitis [35].

The bacteria for meningitis have a capsular structure, which slows down the process of phagocytosis. The bacterial capsular structure has serovars made of polysaccharides. There are different types of serovars, such as serovar A, serovar B and serovar C. These serovars trigger the immune reaction in the body [36]. An endotoxin has also been found in these bacteria. Vaccines for bacterial meningitis are also available, which mostly have serovar A and serovar C, exhibiting strong immunogenic properties. People are generally advised to take a vaccine shot, especially if they plan to visit a place prone to bacterial meningitis [37].

Predisposing factors

Although bacterial meningitis could encounter any individual of any age, certain factors increase the risk for the disease. These factors include age, socioeconomic factors, large gatherings, genetic variation of the host, group setting, travelling to meningitis-prone places, working with pathogens causing meningitis and underlying medical conditions associated with enhanced vulnerability to bacterial infections in people [29,38].

Streptococcus pneumoniae

Meningitis caused by *S. pneumoniae* is referred to as pneumococcal meningitis. It is responsible for two-thirds of meningitis cases in Europe and the United States. It is mainly present in the human nasopharynx, where it leads to colonization. Young children have the highest carriage rates of *S. penumoniae*. The carriage rates might increase in a crowded environment, such as hospitals, daycare centres, shelters, etc. It is mainly transmitted by coughing and sneezing [39]. This bacterium is also found in the respiratory tract and might travel to the middle ear via the bloodstream, leading to deafness. It might also encounter the dura mater of the meninges, causing epileptic seizures [9]. Individuals suffering from sickle cell anaemia, thalassemia, diabetes, or who underwent spleen removal are more prone to pneumococcal meningitis [40]. The pneumococcal conjugate vaccine was introduced in 2000. Since then, the rates of pneumococcal meningitis in children and adults have reduced. The vaccine not only protects immunized children but also provides herd immunity by reducing the transmission of *S. pneumoniae* from immunized children [41].

Neisseria meningitidis

Meningitis caused by *N. meningitidis* is referred to as meningococcal meningitis. In the United States, this bacterium is common and a pertinent cause of community-acquired meningitis among children and adults. If it is not identified at an early stage followed by a treatment, it could be detrimental with a high fatality rate [42]. Meningococcal disease is associated with pronounced morbidity, including hearing loss, cognitive dysfunction, visual impairment, developmental delays, motor nerve deficits, behavioural problems, educational difficulties, limb loss and seizure disorders [43]. It is mainly transmitted by close or lengthy contact with the infected patient. It could be spread by respiratory and throat secretions [44]. Following the routine use of meningococcal vaccination, the occurrence of meningococcal meningitis has diminished. In the United States, the prevalence of the disease is less than 1 case per 100,000 per year. In adolescents, the estimated number of cases per year is 1.2 million. Infants (less than a year old) are at the highest risk of the disease, with 5.38 cases per 100,000 [42]. Although the development of vaccines against the disease is highly significant, the infection is still being reported in both developed and developing countries due to the absence of universal vaccine coverage and the increasing incidences of antibiotic resistance [43].

Haemophilus influenzae

H. influenzae type b (Hib) has always been considered to cause severe infections in the brain and spinal cord, leading to meningitis [45]. It could be spread by coughing or sneezing when in close contact. It usually enters the body from the lungs and airways and then travels to the blood and,subsequently, to the brain area [45,46]. Before the introduction of the Hib vaccine, Hib was the leading cause of *H. influenzae* meningitis in children younger than 5 years old [47]. With the introduction of the Hib conjugate vaccine, the total number of cases of Hib meningitis has decreased substantially. However, it has been reported that Hib conjugate vaccine is not fairly potent among HIV-positive patients, and there might be an association between the high incidence of HIV infection and the perseverance of Hib meningitis [47]. Post the reduction in the rates of Hib infections due to vaccination, the other serotypes have been considered as potential pathogenic agents in children under 5 years old. Cardoso et al. reported a case of an immunocompetent 1-year-old boy with *H. influenzae* type f meningitis [48].

Listeria monocytogenes

In the elderly population, *L. Monocytogenes* is the third most prevailing cause of bacterial meningitis after *S. pneumoniae* and *N. meningitidis* [49]. *L. Monocytogenes* are intracellular bacteria that is transmitted to humans through ingestion of contaminated food, particularly food with long shelf life, such as ready-to-eat products, deli meats and soft cheeses. Pregnant women, newborn children, older population and individuals with the impaired immune system are at higher risk of this bacterium. Although listeria meningitis is scarcely reported in immunocompetent children with no history of immunological disorders, it could progress rapidly and might be associated with a high mortality rate. A recent study reported the case of a previously healthy, immunized, a 16-month-old girl who was diagnosed with listeria meningitis [50].

Other bacteria

Bacteria like *Escherichia coli* and *Streptococcus agalactiae* (also known as Group B *Streptococcus*) mostly infect kids. Although rare cases of infections caused by these bacteria have been reported, they could be fatal compared to other bacterial infections. Premature babies and babies in whose birth women experienced issues are at higher risk of infections caused by these bacteria. *E. coli* is mostly found in the intestine and is responsible for urinary infection and diarrhoea. There are very few cases reported on the *E. coli* meningitis. *S. agalactiae* is mainly found in the vagina of pregnant women and could infect newborn either during labour pain or before the delivery.

Tubercle bacillus may also cause meningitis, which is referred to as TB meningitis. This bacterium mostly infects older people. People suffering from tuberculosis are also prone to this infection. This bacterium first infects the lungs and then travels to the brain *via* the blood stream. Due to the slow multiplicity rate of this bacterium, sometimes, it is difficult to detect its infection [51,52].

Symptoms

Adults and teenagers suffering from bacterial meningitis commonly present the following symptoms:

- High fever with cold hands and feet
- Vomiting
- Diarrhoea
- Headache
- Stiffness of the neck and sometimes up to the extent that the person is unable to bend the chin
- Laziness
- Pain in joints and muscles
- Pain in the abdomen
- Loss of balance/giddiness
- Unconsciousness/fits
- Perplexity

Young children suffering from the disease generally present the following symptoms [53]:

- High fever with cold hands and feet
- Vomiting
- Not able to eat any food
- Weeping or binge
- Yellowness and emptiness on the face
- Stiffness in the neck and back
- Laziness
- Softness and light swelling in the head

However, the presence of all the symptoms at a time is not necessary. The patient might exhibit a few symptoms associated with the disease at a time [53].

S. pneumoniae infection might cause a petechial rash. Pneumococcal meningitis is likely to be associated with seizures, focal neurologic findings and altered consciousness [54].

Individuals infected with *Neisseria meningitidis* might suffer from septicaemia, i.e., blood poisoning, leading to tissue damage, organ failure or even death. The symptoms associated with this are petechial rashes, which, subsequently, turn into blood spots. If these rashes are associated with septicaemia could be confirmed by pressing them using glass, which should not result in the fading of rashes. If they fade a little, dark colour would be resumed soon. On the dark coloured skin, sometimes it becomes difficult to observe rashes associated with the disease. In that case, the palm and soles of feet must be examined, which generally turn yellowish. Rashes might also appear in parts of eyes that remain covered with eyelids [55].

The symptoms of listeria meningitis are not specific and are similar to other types of meningitis (viral or bacterial). Some common signs and symptoms include fever, headache, vomiting, diarrhoea and altered mental status. In some cases, abducens nerve palsy and nystagmus have also been reported as the initial signs of the disease [50].

Diagnosis

It could be difficult to diagnose bacterial meningitis due to the non-specificity of its signs and symptoms. Lumbar puncture (CSF analysis and culture) is the classic method for the diagnosis of meningitis. PCR analysis with specimens, such as blood culture, throat swab, blood Ethylenediaminetetraacetic Acid (EDTA), and serology with baseline clotted blood must be performed in patients with suspected meningitis. The assays to analyse full blood count, urea, electrolytes, C reactive protein must also be typically performed. Sometimes, cranial computed tomography (CT) is also performed if a patient has signs of increased intracranial pressure, seizures,

hydrocephalus, etc. In such cases, CT should be performed prior to the lumbar puncture; however, the risk of increased intracranial pressure is not completely excluded by the normal CT scan result. Sometimes, the interpretation of the scan could be difficult due to the variation in the size of the lateral ventricles [56,57].

Treatment

A cohort study reported that the implementation of dexamethasone decreased the mortality from 30% to 20% in adults with pneumococcal meningitis [39]. Montassier et al. [58] reported a case of a 60-year-old woman whose blood culture was positive *for S. pneumoniae*. She was diagnosed with bacterial meningitis four days after the presentation of initial clinical symptoms. She responded favorably to intravenous ceftriaxone treatment. A recent study by de Queiroz et al. showed an anti-inflammatory and neuroprotective action of Vitamin B12 in the infant rat model of pneumococcal meningitis [3].

In 1913, Serum therapy, and, in 1937, sulphonamides were introduced for the treatment of meningococcal disease. In the 1960s, following the disclosure of resistance to sulphonamides, the first vaccines against meningococci were developed [43]. A third-generation cephalosporin antibiotic therapy has been recommended for meningococcal meningitis. The antibiotics, namely, cefotaxime, ceftriaxone and penicillin, are preferred as initial therapy in patients with a clinical diagnosis of meningococcal disease [59]. A study of 381 patients with meningococcal disease reported that the administration of penicillin reduced the mortality rate by 40% [59].

In children younger than 7 years old, vancomycin plus an expanded-spectrum cephalosporin, such as cefotaxime or ceftriaxone, is a recommended antimicrobial treatment of H. influenzae meningitis, according to the Infectious Disease Society of America. Chloramphenicol, cefepime and meropenem are some of the alternate recommended therapies. Ampicillin is recommended as standard therapy for ampicillin susceptible *H. influenzae*. A fluoroquinolone, either gatifloxacin or moxifloxacin, could also be used as an alternate agent for the treatment of adult patients with *H. influenzae* meningitis [60]. In Japan, combination chemotherapy of cefotaxime and meropenem or ceftriaxone and meropenem has been reported to be utilized for *H. influenzae* meningitis patients [61]. A 16-month-old girl with listeria meningitis has been reported to be successfully treated with intravenous ampicillin and gentamicin without any sequelae. A few studies reported the use of carbapenems alone or in combination with an aminoglycoside in treating listeria meningitis [50]. Trimethoprim-sulfamethoxazole has also been reported as a successful treatment of refractory listeria meningitis [62].

In general, bacterial meningitis must be promptly treated with intravenous antibiotics and sometimes corticosteroids. Depending on the type of bacteria causing the infection, the appropriate antibiotic(s) are prescribed by the doctor. Sometimes, a broad-spectrum antibiotic is also recommended until the revelation of the exact cause of meningitis [63].

Fungal Meningitis

Fungal meningitis is the rare form of the disease and usually occurs when the fungus enters the intrathecal space by rupturing the blood-brain barrier. It mainly affects people with a weak immune system, such as who are infected with HIV or who undergo organ transplantation or chemotherapy. Due to the slow multiplication rate of fungus, it is sometimes difficult to detect the infection. This type of meningitis does not transmit between people. Fungi causing meningitis live in the environment and could be breathed in [64]. Due to the late investigation of fungal meningitis, it is often that patients don't receive prompt medical attention. Thus, in some cases, the untreated fungal meningitis has been reported to result in systemic infections and stroke. A study reported that the most prevalent cause of death in patients suffering from fungal meningitis is haemorrhagic or ischaemic stroke [65,66].

While major fungal pathogens, including *Cryptococcus neoformans*, *Coccidioides immitis* or *Histoplasma capsulatum*, could cause infections in individuals, *Cryptococcus neoformans* has been reported to be the main pathogen. Cryptococcal meningitis has been reported to be the most common type of fungal meningitis, with nearly 70.1% of cases [67].

Cryptococcal meningitis

It could be caused by *Cryptococcus neoformans* or *Cryptococcus gattii*. Prior to 1960s, there were very few cases of cryptococcal meningitis, but during the early 1980s, when the AIDS pandemic outbroke, there was a dramatic rise in cryptococcal infections. HIV is associated with up to 79% of cryptococcal meningitis cases, constituting the largest risk factor [67]. This meningitis is the leading cause of HIV-related mortality worldwide. In addition to the high fatality, cryptococcal meningitis is also associated with high morbidity. Patients who survive from cryptococcal meningitis could suffer from irreversible blindness and deafness, as well as reversible neurocognitive impairments [68]. Nearly 30% of cryptococcal meningitis cases could occur in immunocompetent people with no underlying disease, and such infections are commonly caused by *C. Gattii* [67]. Although the availability of antiretroviral therapy for treating HIV infection has declined the long-term mortality associated with cryptococcal meningitis, in low-income countries, due to the lack of effective distribution of therapy, the overall prevalence of the disease has not decreased [68].

Symptoms

In a case presentation, patients suffering from fungal meningitis reported symptoms, such as headache, nausea, stiff neck and backache, that were in accordance with bacterial meningitis [65].

For cryptococcal meningitis, the symptoms are generally nonspecific. Often, patients have been reported to present with headache, fever, lethargic and altered mental status. Meningeal irritation and focal neurological deficits are some of the signs that might be exhibited in patients suffering from fungal meningitis but are rare. In a case report of a 23-year-old active-duty soldier, the patient had perpetuated oral intolerance, headache, weight loss and multiple syncopal events. During his stay in the hospital, he also exhibited meningeal signs, such as nuchal rigidity [69].

Diagnosis

The possibility of fungal infection could be investigated with clinical examination findings. Several clinical and laboratory practices, such as cell counts, determination of protein and glucose levels, histological stains for fungi, detection of the fungal antigen, analysis of blood cultures, etc., could also be performed to investigate the possibility of a fungal infection [70].

Cryptococcal meningitis is most commonly diagnosed with a lumbar puncture and analysis of the CSF. A head computed tomography should also be obtained prior to the lumbar puncture [69]. The diagnosis of cryptococcal meningitis in HIV-positive patients is primarily done by microscopy, culture or antigen detection. India ink is considered as the most common diagnostic tool for the identification of *Cryptococcus* in the CSF samples; however, the sensitivity of Indian ink is reported to be <86%. The cryptococcal antigen lateral flow assay has been recently developed, transforming the diagnosis of cryptococcal meningitis in settings with inadequate resources [68].

Treatment

Two weeks of intravenous amphotericin B (0.7-1.0 mg/kg/day) in combination with 100 mg/kg/day flucytosine has been recommended by the current guidelines as first-line therapy for the treatment of cryptococcal meningitis. A combination of amphotericin B and fluconazole has also been recommended for the treatment of cryptococcal meningitis [68]. Jarvis et al. [71] reported an adjunctive interferon-gamma immunotherapy for the treatment of HIV-associated cryptococcal meningitis. The authors found that the rate of clearance of cryptococcal infection was significantly increased in the CSF of the patients randomized to standard therapy plus interferon-gamma immunotherapy.

In general, fungal meningitis is treated with high doses of anti-fungal medications for a long time. Generally, the medications are given intravenously. Afterwards, oral medications are also prescribed to patients. The immune system of the patient and the fungus responsible for the infection are the factors that decide the period of the treatment [64].

Conclusion

Meningitis is an inflammation of the meninges-membranes surrounding the brain and spinal cord. It is caused by viral, bacterial or fungal infections. Viral infections are the most prevalent cause of meningitis. There are several viruses, such as Enteroviruses, Herpes Simplex Virus-2 (HSV-2) and Varicella-zoster virus, which are reported to cause meningitis. The viral meningitis is generally mild and typically disappears without treatment. Bacteria enter the bloodstream and travel to the brain and spinal cord, causing meningitis. Sometimes, bacteria directly invade meninges as a result of ear infection, skull fracture or some surgeries, giving rise to meningitis. Various bacteria, such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* and *Listeria monocytogenes*, have been shown to cause meningitis. Bacterial meningitis is more fatal compared to viral disease since viruses may be excreted from the body through the liquid. A number of vaccines have been introduced for bacterial and viral infections, minimizing the possibility of meningitis. Fungal meningitis is the most unusual form of the disease and often occurs when the fungus enters the intrathecal space by rupturing the blood-brain barrier. Fungi causing meningitis live in the environment and could be breathed in. Fungus, namely, *Cryptococcus neoformans*, has been mainly reported to cause fungal meningitis. Further research is needed in the discipline to get rid of this dreaded disease.

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REFERENCES

1. Griffiths MJ, McGill F, Solomon T. Management of acute meningitis. Clin Med (Lond). 2018;18:164-9.
2. Young N, Thomas M. Meningitis in adults: diagnosis and management. Internal Med J. 2018;48;1294-307.
3. de Queiroz KB, Cavalcante-Silva V, Lopes FL, et al. Vitamin B12 is neuroprotective in experimental pneumococcal meningitis through modulation of hippocampal DNA methylation. J Neuroinflammation. 2020;17:96.
4. Charalambous LT, Premji A, Tybout C, et al. Prevalence, healthcare resource utilization and overall burden of fungal meningitis in the United States. J Med Microbiol. 2018;67:215-27.

5. https://www.healthline.com/health/aseptic-meningitis.
6. Logan SA, MacMahon E. Viral meningitis. BMJ. 2008;336:36-40.
7. Rantakallio P, Leskinen M, von Wendt L. Incidence and prognosis of central nervous system infections in a birth cohort of 12,000 children. Scand J Infect Dis. 1986;18:287-94.
8. Kupila L1, Vuorinen T, Vainionpää R, et al. Etiology of aseptic meningitis and encephalitis in an adult population. Neurol. 2006;66:75-80.
9. https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Meningitis-and-Encephalitis-Fact-Sheet.
10. Pallansch MA, Roos RP. Enteroviruses: polioviruses, coxsackieviruses, echoviruses, and newer enteroviruses. In: Knipe DM, Howley PM, Griffin DE, et al. Fields virology. 4th ed, Lippincott Williams And Wilkins, Philadelphia, 2001.
11. https://www.uspharmacist.com/article/viral-meningitis-an-overview.
12. Abou-Foul AK, Buhary TM, Gayed SL. Herpes simplex virus type 2-associated recurrent aseptic (Mollaret's) meningitis in genitourinary medicine clinic: a case report. Int Med Case Rep J. 2014;7:31-3.
13. Shalabi M, Whitley RJ. Recurrent benign lymphocytic meningitis. Clin Infect Dis. 2006;43:1194-7.
14. Corey L, Adams HG, Brown ZA, et al. Genital Herpes Simplex Virus infections: Clinical manifestations, course, and complications. Ann Intern Med. 1983;98:958-72.
15. Berger JR, Houff S. Neurological complications of herpes simplex virus type 2 infection. Arch Neurol. 2008;65:596-600.
16. O'Sullivan CE, Aksamit AJ, Harrington JR, et al. Clinical spectrum and laboratory characteristics associated with detection of Herpes Simplex Virus DNA in cerebrospinal fluid. Mayo Clin Proc. 2003;78:1347-52.
17. Gnoni M, Zaheer K, Vasser MM, et al. Varicella Zoster aseptic meningitis: Report of an atypical case in an immunocompetent patient treated with oral valacyclovir. ID Cases. 2018;13:4.
18. Echevarría JM, Casas I, Tenorio O, et al. Detection of varicella-zoster virus-specific DNA sequences in cerebrospinal fluid from patients with acute aseptic meningitis and no cutaneous lesions. J Med Virol. 1994;43:331-5.
19. https://www.meningitis.org/meningitis/causes/viral-meningitis.
20. Gupta RK, Best J, MacMohan E. Mumps and the UK epidemic 2005. BMJ 330. 2005;7500:1132-5.
21. https://kidshealth.org/ChildrensMercy/en/parents/polio.html.
22. https://www.cdc.gov/meningitis/viral.html.
23. Chen P, Lin X, Liu G, et al. Analysis of enterovirus types in patients with symptoms of aseptic meningitis in 2014 in Shandong, China. Virol. 2018;516:196-201.
24. Chadwick DR. Viral Viral meningitis. British Medical Bulletin. 2005;75 and 76:1-14.
25. https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/health+topics/health+conditios+prevention+and+treatment/infectious+diseases/viral+meningitis/viral+meningitis+including+symptoms+treatment+and+prevention.
26. Landry ML, Greenwold J, Vikram HR. Herpes simplextype-2 meningitis: presentation and lack of standardized therapy. Am J Med. 2009;122;688-691.
27. Miller S, Mateen FJ, Aksamit AJ. Herpes simplex virus 2 meningitis: a retrospective cohort study. J Neuro Virol. 2013;19:166-171.
28. Mount HR, Boyle SD. Aseptic and bacterial meningitis: evaluation, treatment and prevention. Am Fam Physician. 2017;96:314-22.
29. https://www.cdc.gov/meningitis/bacterial.html.
30. Oordt-Speets AM, Bolijn R, vanHoom RC, et al. Global etiology of bacterial meningitis: A systematic review and metaanalysis. PLOS One. 2018;13:e0198772.
31. Jayaraman Y, Veeraraghavan B, Purushothaman GKC, et al. Burden of bacterial meningitis in India: Preliminary data from a hospital based sentinel surveillance network. PLOS One. 2018;13:e0197198.
32. Zafar M, Tauseef A, Asghar MS, et al. *Escherichia coli*: a rare cause of meningitis in immune-competent adults. J Community Hosp Intern Med Perspect. 2020;10:699-72.
33. http://www.euro.who.int/__data/assets/pdf_file/0013/102316/e79822.pdf.

34. https://www.southerncross.co.nz/group/medical-library/meningococcal-meningitis-symptoms-and-treatment.
35. https://www.columbianeurology.org/neurology/staywell/document.php?id=42031.
36. Attarpour-yazdi MM, Ghamarian A, Mousaviehzadeh M, et al. Identification of serotypes of bacterial meningitis agents; implication for vaccine usage. Iran J Microbiol. 2014;6:211-8.
37. Crum-Cianflone N, Sullivan E. Meningoccal vaccinations. Infect Dis Ther. 2016;5:89-112.
38. Lundbo LF, Benfield T. Risk factors for community acquired bacterial meningitis. J Infect Dis. 2017;49:433-44.
39. Mook-Kanamori BB, Geldhoff M, Poll TVD, et al. Pathogenesis and pathophysiology of pneumococcal meningitis. Clin Microbiol Rev. 2011;24:557-91.
40. https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-3-vaccination-specific-populations/page-7-immunization-persons-with-chronic-diseases.html.
41. Hsu HE, Shutt KA, Moore MR, et al. Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. N Engl J Med. 2009;360:244-56.
42. Nguyen N, Ashong D. *Neisseria Meningitidis*. Stat Pearls. 2020.
43. Rouphael NJ, Stephens DS. *Neisseria meningitidis*: Biology, microbiology, and epidemiology. Methods Mol Biol. 2012;799:1-20.
44. https://www.cdc.gov/meningococcal/about/causes-transmission.html.
45. https://www.cdc.gov/hi-disease/index.html.
46. https://medlineplus.gov/ency/article/000612.htm.
47. McCormik DW, Molyneux EM. Bacterial meningitis and *Haemophilus influenzae* type b conjugate vaccine, Malawi. Emer Infect Dis. 2011;17:688-90.
48. Cardoso MP, Pasternak J, Giglio AE, et al. Meningitis due to *Haemophilus influenzae* type f. Einstein (Sao Paulo). 2013;11:521-3.
49. Pagliano P, Ascione T, Boccia G, et al. *Listeria monocytogenes* meningitis in the elderly: epidemiological, clinical and therapeutic findings. Le Infezioni in Medicina. 2016;2:105-11.
50. Castellazzi MM, Marchisio P, Bosis S. *Listeria monocytogenes* meningitis in immunocompetent and healthy children: a case report and a review of literature. Ital J Pediatr. 2018;44:152.
51. https://www.meningitisnow.org/meningitis-explained/what-is-meningitis/types-and-causes/tb-meningitis/.
52. Isabei BE, Rogelio HP. Pathogenesis and immune response in tuberculosis meningitis. Malayasian J Med Sc. 2014;21:1-4.
53. https://www.stanfordchildrens.org/en/topic/default?id=meningitis-in-children-90-P02528.
54. Bamberger DM. Diagnosis, initial management, and prevention of meningitis. A m Fam Physic. 2010;82:1491-8.
55. Coureuil M, Join-Lambert O, Lecuyer H, et al. Pathogenesis of meningococcemia. Cold Spring Harb Perspect Med. 2014;3: a012393.
56. Bashir HE, Laundy M, Booy R. Diagnosis and treatment of bacterial meningitis. Arch Dis Child. 2003;88:615-20.
57. Tacon EL, Flower O. Diagnosis and management of bacterial meningitis in the paediatric population: A review. Emer Med Int. 2012:320309.
58. Montassier E, Trewick D, Batard E. *Streptococcus pneumoniae* meningitis in an adult with normal cerebrospinal fluid. CMAJ. 2011;183:1618-20.
59. Nadel S. Treatment of meningococcal disease. J Adolescent Health. 2016;59:521-8.
60. Tristram S, Jacobs MR, Appelbaum PC. Antimicrobial resistance in *Haemophilus influenzae*. Clin Microbiol Rev. 2007;20:368-89.
61. Hasegawa K, Kobayashi R, Takada E, et al. High prevalence of type b β-lactamase-non-producing ampicillin resistant *Haemophilus influenzae* in meningitis: the situation in Japan where Hib vaccine has not been introduced. J Antimicrobial Chemother. 2006;57:1077-82.
62. Polat M, Kara SS, Tapisiz A, et al. Successful treatment of refractory *Listeria meningitis* and bacteremia with trimethoprim-sulfamethoxazole in an immunocompetent child. Turk J Pediatr. 2016;58:220-2.
63. https://www.mayoclinic.org/diseases-conditions/meningitis/diagnosis-treatment/drc-20350514.

64. https://www.cdc.gov/meningitis/fungal.html.

65. Arnold C. Fungal meningitis outbreak affects over 700. Lancet Neurol. 2013;12:429-30.

66. Kainer MA, Reagan DR, Nguyen DB, et al. Fungal infections associated with contaminated methylprednisolone in Tennessee. New Eng J Med. 2012;367:2194-203.

67. Charalambous LT, Premji A, Tybout C, et al. Prevalence healthcare resource utilization and overall burden of fungal meningitis in the United States. J Med Microbiol. 2018;67:215-27.

68. Abassi M, Boulware DR, Rhein J. Cryptococcal meningitis: Diagnosis and management update. Curr Trop Med Rep. 2015;2:90-9.

69. Newsome J, Nguyen D. Cryptococcal meningitis caused by *Cryptococcus neoformans* is an immunocompetent soldier. Military Med. 2014;179:e1059-61.

70. Davis JA, Costello DJ, Venna N. Laboratory investigation of fungal infections of the central nervous system. Neurol India. 2007;55:233-40.

71. Jarvis JN, Meintjes G, Rebe K, et al. Adjunctive interferon-γ immunotherapy for the treatment of HIV-associated cryptococcal meningitis: a randomized controlled trial. AIDS. 2012;26:1105-13.