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REVIEW ARTICLE

Presentation, diagnosis, and treatment of meningitis and encephalitis; a detailed review

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ABSTRACT

The infection of the central nervous system (CNS) is a medical emergency as it could lead to mortality and severe complications. The arrival of infectious organisms to the CNS cause meningitis and encephalitis based on the causative organism. Thus, this study aimed to highlight the presentation, diagnosis, and treatment of meningitis and encephalitis. An online research process was used to obtain articles related to the current subject. The research process involved was searching through scientific websites using several keywords to obtain all possible articles related to the current subject. Almost 75 articles were obtained, and according to the inclusion criteria, only 21 articles were included in this review, whereas 54 articles were excluded. The causes of meningitis and encephalitis could be bacterial, viral, or fungal; the diagnosis could be done using culture, polymerase chain reaction (PCR), and imaging could differentiate between meningitis, encephalitis, and other mimic conditions. Prompt treatment should be considered to avoid severe complications and outcomes, including mortality.

Keywords: Meningitis, encephalitis, presentation, diagnosis, treatment, management.

Introduction

The infection of the central nervous system (CNS) is a medical emergency; it has rapid progression to death and occurs among 40% of the patients. Survivors of CNS infections experience long term deficits of neurological function [1,2]. The infections of CNS are varied in causes, presentation, and prognosis [3]. The challenge for CNS infections is the isolated nature of the CNS and its protective barriers. The main protective feature of the CNS is the blood-brain barrier, which restricts the pathogen from reaching the cerebrospinal fluid (CSF) from the blood [3]. The presence of neurovascular space is involved in the infection and it is often a spectrum extending from the meninges to the encephalon [3]. The infectious organism that cause meningitis and progress to encephalitis is also known as meningoencephalitis [3]. The infection of CNS is presented as meningitis or encephalitis [4]. The meninges are triple layered membranes that are enveloping the CNS and are composed of the pia mater, arachnoid space, and dura mater. Meningitis is the inflammation of the leptomeninges and CSF within the subarachnoid space, which exists between the arachnoid layers and the pia matter [5]. The causes of inflammation varies; however, acute meningitis could be caused by primary infectious agents, including bacteria, viruses, and fungi [1]. Encephalitis is caused by an invasion of a pathogen or microorganism to the brain parenchyma and is presented with encephalopathy and evidence of inflammation of the CNS [6]. Meningitis and encephalitis required prompt diagnosis and management to prevent accompanied morbidity and mortality [7]. Thus, this study aimed to highlight the presentation, diagnosis, and treatment of both meningitis and encephalitis.

Materials and Methods

The online searching process was used to obtain articles focusing on the current subject through the scientific website, including Google scholar. Several keywords

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were used to obtain all possible articles related to the current subject, such as "Meningitis, encephalitis, presentation, diagnosis, treatment, and management." Through the searching process, the articles with titles not related to the current subject were neglected. Almost 75 articles were obtained after the exclusion of repeated articles, and articles that does not focus on the current subject, along with the articles that were published in 2015 and before 2015, and articles that mentioned the same information and studies; thereby, 21 articles were included which were published between 2016 and 2020 and were related to the current subject.

Discussion

Meningitis

Meningitis represents a challenge for physicians; its etiology ranged from benign to life-threatening [8]. A total of 1.3 million cases of meningitis were reported annually and globally [9]. European studies reported an incidence of 7.6/100,000 adults, 5.2/100,000 children with the age of one to 14 years, and 70/100,000 children younger than 1 year [10,11].

In the US, enterovirus was responsible for 50.9% meningitis cases among hospitalized adults, whereas bacteria was responsible for 13.9%, herpes simplex virus (HSV) was responsible for 8.3%, and the fungal infection was responsible for only 2.7% [12]. Meningitis caused by a bacterial infection could result in significant morbidity and mortality due to severe inflammation. The inflammation could result in significant edema of the surrounding structures and therefore causing an increase in the intracranial pressure [13]. The pathologic bacteria involved in meningitis vary by vaccination state, recent trauma, and age [14]. *Streptococcus pneumonia* was the main cause of bacterial meningitis in adults and children globally [15].

Streptococcus pneumonia and *Neisseria meniginitidis* were the most common organisms responsible for meningitis in adults, whereas *Listeria monocytogenes* was particularly most common among the elderly [3]. Other studies [16] reported that young adults and children were at higher risk of *N. meningitidis* meningitis, whereas older patients were at higher risk of *S. pneumonia* meningitis.

Streptococcus agalactia and *Escherichia coli* (*E. coli*) were responsible for most of the meningitis in neonates. Whereas in children older than the neonatal stage, the most commonly involved organisms include *S. pneumonia* and *N. meningitidis* [17]. *Streptococcus agalactia* group B was the major cause of neonatal meningitis, and it was usually acquired from the mother during vaginal delivery [17].

Listeria monocytogenes ranked third in the causes of neonatal meningitis, following *S. agalactia* group B and *E. coli* [4]. The epidemiology of *N. meningitidis* (meningococcus) varied between geographic regions [4]. Viral meningitis was less severe compared to bacterial meningitis [3]. Meningitis caused by viruses was usually caused by herpes simplex virus type 2 (HSV-2) or enteroviruses [4], and varicella-zoster virus. Non-polio enteroviruses account for more than 85% of all viral meningitis cases [3].

Symptoms and clinical presentation

Presentation of viral and bacterial meningitis could be similar, but bacterial meningitis is more ill-appearing [8]. The time taken from the onset of symptoms to the presentation for the medical care tends to be longer in viral meningitis compared with bacterial meningitis, with 47% of bacterial meningitis patients presented after less than 24 hours of symptoms [18], whereas patients with viral meningitis have median presentation after duration of 2 days from the onset of symptoms [19].

Clinical symptoms include nuchal rigidity, fever, and altered mental state; these symptoms were present in fewer than half of the patients [1]. The full triad of nuchal rigidity, fever, and altered mental state was rarely present, making it hard to diagnose meningitis [3]. Almost less than one-half of patients were presented with all of the three symptoms [20]. A combination of two previous symptoms occurred among 95% adults with bacterial meningitis [20]. A large proportion of cases with meningococcal infection experienced petechial rash [1], patients with meningitis caused by other meningeal pathogens could experience similar rashes [17].

The presentation varies in young children; in children, the signs and symptoms were often non-specific, and they included hyper or hypotonia, poor feeding, and irritability [17]. Common historical signs of meningitis patients include vomiting, neck pain, and headache [21].

The presence of symptoms alone was poorly sensitive, with pooled sensitivity for headache and vomiting/nausea of 50% and 30%, respectively. However, the absence of neck stiffness, altered mental status, and fever exclude meningitis [21].

The presentation of patients varies with the age of the patient. Older patients were less likely to have neck stiffness and headache, but they were more prone to suffer focal neurologic deficits and altered mental status [22].

Diagnosis and diagnostic tools

The clinical signs and symptoms are poorly sensitive in indicating meningitis, so patients presented with symptoms concerning for meningitis should undergo immediate lumbar puncture and CSF evaluation [8]. Lumbar puncture is the hallmark of the diagnostic procedure for meningitis. Although serum markers could show the presence of inflammation, none could accurately diagnose meningitis [3]. Most of the patients should perform lumbar puncture without a potentially fatal delay [4].

Clinical investigations of meningitis include investigations of CSF, blood culture, and imaging of the brain [4]. CSF culture is the gold standard for diagnosis and identification of the pathogen. The culture is diagnostic among 70%-85% of cases before exposure to an antibiotic; the sensitivity is reduced by 20% following antibiotic pretreatment [23]. Abnormal findings of CSF are shown in 88% of bacterial meningitis cases, whereas 25% of the patients with meningitis caused by Listeria infections, 2% of adults with meningitis, and 6% of neonates showed normal CSF [1,17]. It was suggested that CSF lactate differentiates between viral and bacterial meningitis, but lactate also increased in patients with encephalitis [17]. Prompt identification of the causative agent is necessary in order to reduce the duration of hospitalization and antibiotic therapy [24].

It should be noted that CSF culture is time-consuming, so polymerase chain reaction (PCR), as a novel method for identification of the pathogen, is a rapid method that is performed through amplification of the pathogen‘s gene and matches its products [25]. PCR is a sensitive, specific, and rapid technique; its sensitivity was reported to be above 90% for most of the organisms implicated in meningitis, as reported in a multicentre study [26].

The blood culture shows positivity in 40%-100% of patients with meningitis who were not able to have lumbar puncture because of signs of brain shift, elevated intracranial pressure, space-occupying lesions, and anticoagulant treatment [1,26].

The performance of brain imaging before lumbar puncture is a common practice now. Brain image is required for patients who suffered seizures, altered mental state, focal neurological signs, or immunocompromised patients [1]. According to the European Society of Clinical Microbiology and Infectious Diseases, there are clinical criteria for performing head Computerized Tomography (CT). In the absence of Glasgow coma score <10 and focal neurological deficits other than cranial nerve palsies, it is safe to perform lumbar puncture without head CT performance [17].

In a study by Michael et al. [27], it was reported that unnecessary head CT resulted in significant delays in lumbar puncture performance and led to a decrease in the utility of CSF culture that is required for antibiotic determination in the treatment.

The leukocyte differential count could hint toward the etiology of meningitis, where bacteria tend to generate neutrophilic predominance, whereas viral causes tend to generate lymphocytic predominance. However, these patterns in the differential cell count are still non-specific [3].

The treatment

Bacterial meningitis treatment

Empiric therapy. The initiation of meningitis treatment is based on the abnormal CSF differential or clinical suspension. Patients with concern for septic shock or sepsis should be started on empiric therapy of broad-spectrum antibiotics and antivirals before lumbar puncture performance to avoid the delay in treatment [28]. The patient should administrate antibiotics within 1 hour of arrival to the hospital; delayed administration of antibiotics is an important cause of death of patients with bacterial meningitis [1]. The addition of acyclovir should be done, if there is a concern for HSV meningitis or encephalitis [8]. The choice of initial antibiotic therapy varies between nations and is affected by the local community prevalence of pathogens. Penicillin is no longer an appropriate empiric therapy for meningitis because of reduced susceptibility of bacteria to penicillin [17]. The treatment protocols should be conservative as the inappropriate antibiotic choice that could lead to severe consequences [4]. The length of treatment varies according to the organism identified [8].

Specific therapy. This therapy is based on the drug sensitivity determined by the microbiological analysis, where the medication is determined according to the causative organism detected [4].

Adjunctive therapy. This therapy is added to the specific therapy administered by the patient to avoid particular complications [4]. These adjunctive therapies include (1) Rifampicin, as shown by the multicenter study from France, was beneficial as adjunctive therapy to standard empiric meningitis protocol [29]. (2) Induced hypothermia and glycerol therapy were associated with a lower survival rate in a randomized study on bacterial meningitis, so it is not recommended [29]. (3) Intracranial pressure-targeted treatment improved the outcomes of bacterial meningitis patients in one study, but its role in routine practice is still unidentified [1]. (4) Anticonvulsant therapy has no role in prophylaxis for patients with meningitis if there are no seizures [17]. (5) Corticosteroids were reported to be beneficial for children with munities during the period when the predominant pediatric pathogen was Haemophilus influenzae serogroup B; [30] after vaccination eliminated H. influenza as a significant pathogen, this benefit was no longer evident [31]. Corticosteroids are used as meningitis adjunctive therapy to reduce the inflammatory response [8]. Corticosteroids‘evidence is heterogeneous and limited to specific bacteria [8]. It was recommended that bacterial meningitis could be treated with corticosteroid in high-income countries, either before or together with the first antibiotic dose. However, corticosteroid therapy has been associated with increased mortality among patients with Listeria meningitis [32].

Viral meningitis treatment

The treatment of viral meningitis is supportive. Acyclovir is often used for the treatment of adults, but currently, there is no study that reported significant benefit in meningitis treatment [3]. Viral meningitis is milder than bacterial meningitis; it has a benign course unless complicated

with myelitis or encephalopathy. Recurrent episodes of aseptic meningitis should be rapidly investigated for HSV-2 [33]. Most viral meningitis patients could be treated at home with analgesics, and they should return rapidly to the hospital if their condition deteriorates [4].

Pleconaril became available for the treatment of enteroviral meningitis in 2006 [33], but it wasn't approved by the Food and Drug Administration in the United States because of its poor cost-benefit and modest effect relationship [34]. However, pleconaril was found to be promising in the treatment of chronic meningoencephalitis in immunocompromised patients [34]. Suppression of the virus using valaciclovir doesn't prevent the HSV-2 meningitis relapse [4].

Encephalitis

Encephalitis is inflammation of the brain parenchyma with global or focal dysfunction regardless of meningitis involvement, causing a neurological disturbance, and it might become life-threatening [35,36]. Inflammation is caused by invasion of microorganisms or pathogens [3]. Encephalitis is characterized as an acute infective encephalopathy with at least three features; seizures, fever, CSF pleocytosis (leukocytes less than $5*10^6$/l), focal neurological signs, abnormal magnetic resonance imaging (MRI) findings, and electroencephalogram [37,38]. The viral infection is responsible for the large majority of encephalitis cases 20%-50%, with HSV being the most responsible virus [3]. Almost one-half of the remaining percent showed no identifiable causes [3].

Symptoms and clinical presentation

The clinical hallmarks of encephalitis include fever, headache, and altered mentation [4]. However, 10% of the patients do not show fever [39]. Examination and detailed history are involved in the initial evaluation because the early diagnosis and immediate treatment could improve the outcome of the patient. Physical examination includes the presence of a change in mental status and behavior, fever, seizures, and neurological deficits. The important components of the history of the patients included animal bites and exposure, contact with ill individuals, vaccinations, recent illness, the progression and the speed of the disease, recent travel, and occupation [3,4]. Autonomic instability is detected late in the course of the condition, with 88% of the patients experiencing reduced consciousness and akinesis and 76% of the patients developing seizures [40].

Diagnosis and diagnostic tools

The differentiation between encephalitis and encephalopathy is difficult because of the similarities of their clinical presentation. The evaluation of CNS inflammation is the key to early diagnosis and treatment [3]. It should be considered that some parasites such as Taenia solium, Toxoplasma, Gnathostoma, and Schistosoma could cause space-occupying lesions rather than diffuse or regional inflammation [41]. Moreover, there are several conditions that are mimic of encephalitis, including hyponatremia, hypoglycemia, hepatic encephalopathy, autoimmune disease, opportunistic infections, and stroke [42].

CSF and blood culture should be performed before the initiation of the treatment [4]. The protein and glucose content of CSF, as well as the CSF cell count, should be estimated, and the detection of bacterial, viral, and fungal presence should be done by culturing and PCR; this should be done based on the history of the patient and the exposure of the patient to possible pathogen according to the prevalence of the pathogens [4].

Normal glucose with mild elevation of protein could be found. PCR of HSV-1 and HSV-2 revealed a sensitivity and specificity of 96% and 99%, respectively. However, it could be negative early on the disease progress [43,44]. PCR could detect non-culturable enterovirus serotypes; it is also cost-effective and rapid [39].

CSF serology could be helpful in case of the likelihood of infection by a flavivirus, syphilis, or Cryptococcus if the patient's history revealed exposure to such pathogens. PCR assessment using a stool and respiratory specimen might be informative [4]. Imaging might be required as electroencephalography to exclude epilepsy and encephalopathy, CNS imaging such as MRI as the preferable imaging, especially among immunosuppressed patients, and chest X-ray if there is an infection with tuberculosis, melioidosis, or cryptococcosis [45].

The treatment

Supportive therapy

Close observation of the patient could be done by intensive care to control seizures, and intracranial pressure, to maintain the balance of electrolytes and fluid, and circulatory and respiratory support [4].

Empiric therapy

The median time from the onset of the symptoms to hospital admission is 3-3.5 days, so antiviral treatment should be initiated as soon as possible [39]. The patients should receive intravenous acyclovir until the results of specific investigations are obtained [46]. A high dose of acyclovir of 10 mg/kg intravenously every 8 hours should be used [39]. In the case of confirmation of encephalitis, acyclovir therapy should be continued for 14-21 days [46]. As relapse occurs in 5% of the patients, treatment should be continued for additional 7 days [47]. If meningeal signs are accompanied, antibiotics should be given to the patient, including amoxicillin, with ceftriaxone intravenously until the bacterial cultures are revealed [46].

Adjunctive therapy

Animal models with herpes encephalitis showed that adjunctive corticosteroid therapy could be beneficial.

Rapamycin and artesunate were proven to be useful as adjuncts to valacyclovir therapy in mice with herpes encephalitis [48].

Conclusion

The clinical symptoms of meningitis and encephalitis are similar. The causes of these conditions can be bacterial, viral, or fungal. However, the majority of meningitis cases return to bacterial causes, whereas the majority of encephalitis cases return to viral causes. The diagnosis using culture, polymerase chain reaction, and imaging could differentiate between meningitis, encephalitis, and other mimic conditions. Also, encephalitis could be accompanied by meningitis. Prompt treatment should be considered to avoid severe complications and outcomes, including mortality. In the case of meningitis, the initiation of antibiotics is done before the result of the culture obtained to avoid any delay; then, the specific antibiotic is chosen. Whereas in the case of encephalitis, acyclovir is initiated until the results of culture and PCR obtained to continue specific therapy.

List of Abbreviations

CNS	Central nervous system
CSF	Cerebrospinal fluid
E. coli	*Escherichia coli*
HSV-2	Herpes simplex virus type 2
MRI	Magnetic resonance imaging

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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