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ORIGINAL PAPERS

Epidemiological and Clinical/Bioevolutive Aspects on Viral Meningitis – the Possible Relevance of the Oxidative Stress Status ?

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Abstract. *Meningitis is the inflammation of the meninges associated with an abnormal number of cells in the cerebrospinal fluid. It is a disease caused by an infection of the cerebrospinal fluid or brain. Identification of the pathogen requires rapid diagnostic methods for rapid treatment, in order to minimize hospitalization, mortality and associated complications. The aim of this study was to update and future identify the etiology of viral meningitis in adult and pediatric patients, and to create new management strategies for the diagnosed cases. Even more, we are lately increasingly interested in the relevance of the oxidative stress in the matter mentioned above, and we will describe here some aspects about that.*

Key words: *Meningitis, viral meningitis, West Nile virus, diagnostic, PCR.*

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Introduction

Meningitis is the inflammation of the meninges associated with an abnormal number of cells in the cerebrospinal fluid (CSF). [1] Meningitis can have both infectious (viral, bacterial, fungal) and non-infectious causes (chemical reactions, drug allergies, cancers, sarcoidosis). Viral and bacterial meningitis are characterized by an acute onset of fever, headache, photophobia and neck stiffness, often accompanied by nausea and vomiting. At the first presentation,

there are no reliable clinical indicators to differentiate between viral and bacterial meningitis, so all suspected cases should be monitored in hospital. [2][3][4] Viral causes of meningitis have become more common as vaccinations have decreased the prevalence of bacterial meningitis, and viral meningitis has become the most common form of meningitis in many countries. [5] Viral meningitis usually has an acute onset with fever, headache, photophobia, stiff neck with nausea and vomiting.[6] Appropriate and timely evaluation is critical because there are no reliable baseline clinical indicators to differentiate the bacterial etiologies from the viral ones. Viral meningitis is usually a self-limiting disease with a good prognosis.[1] Enteroviruses (Coxsackie or Echovirus groups) are the most common cause of viral meningitis in all ages. [7][8] Herpesviruses that cause meningitis include herpes simplex virus (HSV) 1 and 2, varicella-zoster virus (VZV), cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6. Other viral causes include adenoviruses, lymphocytic choriomeningitis (LCMV), influenza, parainfluenza virus and epidemic mumps. [5] [8] Arboviruses are caused by viruses that are spread to humans by the bite of an arthropod, commonly a mosquito or tick. In the last 50 years, the unprecedented occurrence of arbovirosis epidemics has changed the perception of their contribution to global mortality. Arboviruses that can cause viral meningitis include West Nile virus (WNV), Zika, Chikungunya, Dengue, LaCross, Saint Louise encephalitis, Powassan, and Eastern equine encephalitis virus. [6] It is highly important to obtain a detailed travel history in patients with suspected viral meningitis because many viruses have specific geographic distributions.[9] In about 80% of cases the infection produces no symptoms, the rest are Nile fever-like, a self-limiting disease with flu-like symptoms. Approximately 1 in 150 infections progress to neuroinvasive disease: meningitis, encephalitis, or acute flaccid paralysis.[16] Management of severe West Nile virus disease remains supportive only. Patients with severe meningeal symptoms require headache therapy, antiemetic therapy, and hydration for associated nausea and vomiting. [17][18][19] Most viruses that cause meningitis have no specific treatment other than supporting vital functions through management that includes fluids, acid-base balance and pain control. [5][6][10] Patients should be observed for neurologic and neuroendocrine complications, including seizures, cerebral edema. Because of the difficulty in initially differentiating viral from bacterial meningitis, empiric antibiotic therapy is usually indicated until the diagnosis of bacterial meningitis is ruled out. [10]

The prognosis for viral meningitis without associated encephalitis is generally good. [11] Viral meningitis usually has a quick recovery. Children and teenagers are often sick for more than a week, but usually make a full recovery. Adults with enteroviral meningitis may have symptoms for several weeks, but the disease is usually less severe than in children. [10]

Enteroviral meningitis usually has a benign course, while enterovirus encephalitis can lead to long-term neurological sequelae. Significant morbidity and mortality are found in enteroviral meningitis in newborns and immunocompromised patients. Some enterovirus subtypes, such as EV71 and EV68, are associated with more severe neurological disease and long-term complications. The most common and severe complications of enteroviral meningitis are meningoencephalitis, myocarditis and pericarditis. [12] [13] In children, neurologic complications of enteroviral infection may include acute flaccid paralysis and rhombencephalitis. [14] [12] Some studies have noted sleep impairment as a long-term sequela of meningitis [15].

Current relevance

Viruses are one of the major causes of human infectious diseases. Identifying the causative pathogen remains a challenge still. Many clinical syndromes such as viral meningitis/encephalitis or febrile illnesses require a rapid and extensive differential diagnosis. This results in a more extensive use of diagnostic tests, starting with the most common pathogens and ending with the least common ones. This approach is time consuming and associated with considerable costs and may require weeks until we have a final result. Rapid diagnosis is essential in order to initiate treatment specific to the causative organism and a diagnostic test with the ability to highlight potential pathogens in a single assessment would be a tremendous improvement

Future perspectives

Right now, there are lots of efforts to establish a quick and correct diagnosis, and in the same time to compares the frequency of viral meningitis among adults and the children. Rapid diagnosis and treatment of meningitis reduces mortality and the possibility of neurological sequelae but may be delayed by the atypical onset of the disease, the uncertainty of performing lumbar puncture or the low sensitivity of microbiological diagnosis. The patient's medical history and clinical examination alone are sometimes not sufficient to rule out or confirm the diagnosis. Theoretically, the diagnosis can be obtained in a few hours by lumbar puncture and PCR, but the long period of time until the lumbar puncture is performed, to which is most often added the impossibility of carrying out the analysis by PCR, explains why in many cases the causative agent of viral meningitis is not identified. In the flow of specialized publications in Romania and especially in the North-Eastern region of Romania, the data on the etiology of viral meningitis with enteroviruses and West Nile are limited, there are relatively few studies, something that will be fixed by the doctoral research.

To minimize the possibility of diagnostic error the study deliberately focuses on cases with meningitis proven by the classical method of serology and PCR. We will try to optimize the protocol of diagnosis and follow-up of patients with viral

meningitis with enteroviruses and West Nile, given the fact that in the specialized literature there are few studies about their frequency among children versus adults.

The importance of the use of PCR as a diagnostic method that should be included in the protocol for use in suspected cases of viral meningitis will be highlighted, which associated with the clinical examination, lumbar puncture, will lead to early diagnosis and implicitly to rapid therapeutic intervention.

So basically, our group will be following these main aspects: Considering the fact that in the N-E area of Romania, there is no study on the frequency of viral meningitis with enteroviruses and arboviruses, we propose to synthesize the information related to viral meningitis appearing in the literature and to correlate it with the data provided by the groups of patients included in study, to assess the frequency of viral meningitis with enteroviruses and West Nile in the area of Moldova. Also, the main purpose of our future work will be to identify cases of viral meningitis caused by enteroviruses and West Nile virus using molecular investigations, clinical, paraclinical, imaging examinations, which will facilitate the diagnosis and quantification of cases of viral meningitis, with a view to the economic use of resources, decrease in medication consumption and reduction in hospitalization rate.

We will also be interested in revealing the importance of early diagnosis of viral meningitis from the first symptoms, the frequency of cases of West Nile virus infection in our area in recent years calls for more thorough screening of cases of viral meningitis and also the characterization of the type of viral meningitis according to age, sex, symptoms, comorbidities, seasonality, neurological sequelae and the evolution over time of the patients included in the study.

The relevance of the oxidative stress status

In a study conducted by the Gaziantep University Faculty of Medicine Infectious Diseases Clinic, oxidative and nitrosative stress were evaluated both in cerebrospinal fluid and blood samples in patients with meningitis. In this study took part thirty-seven patients with bacterial meningitis, thirty patients with tuberculous meningitis and thirty with viral meningitis. [16].

The diagnosis of bacterial meningitis was made based on some important clinical features such as acute onset of headache, fever and signs of meningeal irritation, but also based on the laboratory diagnosis which was made by the examination of cerebrospinal fluid. Patients with viral meningitis had similar clinical features with bacterial meningitis (fever, acute headache and meningeal irritation), negative cerebrofluid stain and culture, but positive PCR for viral pathogens. Diagnosis of tuberculous meningitis was made based on the detection of Mycobacterium tuberculosis in the cerebrospinal fluid.

The cerebrospinal examination in patients with bacterial meningitis revealed pleocytosis especially neutrophilic, whilst patients with viral meningitis had mainly lymphocytes.

When an infection occurs, our immune system produces reactive oxygen and nitrogen species. It has been established that when bacteria enter the subarachnoid space, activated PMNs create reactive oxygen and nitrogen species as part of the host's inflammatory response.

In the same study, tyrosine nitration has been found to be enhanced at the cellular level in bacterial meningitis, particularly in the arteries of the brain and inflammatory cells. The presence of the lipid peroxidation marker 4-hydroxynonenal in these cells suggests that reactive nitrogen species may be involved in oxidative brain damage. Furthermore, it was shown that the condition deteriorated when CSF fluid included high levels of nitrotyrosine. [16].

Reactive oxygen species and nitrogen species are thought to mediate the breakdown of the blood brain barrier in bacterial meningitis. Additionally, it has been discovered that antioxidant therapy stops the blood brain barrier from deteriorating.

In the study it was concluded that oxidative and nitrosative stress markers are not a quick and accurate biomarker for the diagnosis of bacterial meningitis, but oxidative stress is at least partially responsible for the severe neurological dysfunction found in meningitis, particularly bacterial meningitis. [16].

In another study included in The Tropical Medicine and Infectious Disease it is told that the West Nile virus infection can be asymptomatic, but in some cases can lead to West Nile Fever or more severe pathologies as meningitis, encephalitis or flaccid paralysis. About 10% of neurological presentations, also known as West Nile Neuroinvasive Disease, result in death. Amongst patients that survived West Nile Neuroinvasive Disease, there were several that reported significant neurological sequelae such as abnormal reflexes, muscle weakness or chronice fatigue, that persisted for years after the infection. When compared to asymptomatic patients, it was found that patients with West Nile Fever and West Nile Neuroinvasive Disease had a significantly higher total oxidant status. In contrast to asymptomatic, West Nile Fever and West Nile Neuroinvasive Disease appear to have a higher total oxidant status, an indicator that summarizes the overall oxidative capability in a sample. [17]

Conclusions

We theoretically described here some epidemiological and clinical/bioevolutive aspects on viral meningitis. The modifications of the oxidative stress status seems to exert an interesting role in the management / chronicity of aspects mentioned above

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