Understanding the etiology and epidemiology of meningitis and encephalitis: now and into the future

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Meningitis and encephalitis are important causes of morbidity and mortality worldwide. Meningitis is one of the four largest contributors of neurological disability-adjusted life years (DALY) globally.[1] In the U.S., from 2000-2010, there were approximately seven encephalitis hospitalizations per 100,000 population.[2] The international consortium for encephalitis stated that specific etiologies are found in <50% of cases of encephalitis.[3] Although several studies have assessed the frequency of various pathogens in encephalitis in countries such as the USA, France, Australia and England, large-scale studies of this nature had previously not been carried out in Asian populations.[4] A review of the infectious causes of encephalitis, in 2016, found herpes simplex virus (HSV) to be the most frequently reported pathogen (in 65% of studies), followed by Varicella-zoster virus (VZV) and Enteroviruses, with important regional differences, such as the Japanese encephalitis virus (JEV) in Asia.[5]

In *The Lancet Regional Health – Western Pacific*, Wang and colleagues report the results of a nationwide surveillance study across China, looking for viral and bacterial pathogens in patients with acute meningitis or encephalitis.[6] This large study, spanning a decade, is an important contribution towards understanding the etiology and epidemiology of meningitis and encephalitis.

Wang et al[6] studied 11 different bacterial and viral etiologies (enterovirus, HSV, JEV, Mumps virus, Neisseria meningitidis, Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae type b, Escherichia coli, Mycobacterium tuberculosis, and Streptococcus suis) and assessed their relative frequencies, demographics, and time trends. They identified certain factors that were predictive of the type of pathogen detected. The most important one was age; enterovirus was more common in children (age <18 years), and HSV and JEV were more frequently detected in adults (age >18 years). For bacterial infections, Streptococcus pneumoniae was more common in children aged <5 years, Neisseria meningitidis in children between ages 5-18 years, and Staphylococcus Aureus in adults. The pathogen spectrum also showed geographical and seasonal variations. There were some differences in the pathogens detected in hospitalized patients versus outpatients. Additionally, population density and gross domestic product, which are often reflective of socioeconomic status, affected pathogen circulation. The authors also analyzed the year-to-year variation of detected pathogens, which showed, except for JEV, a decrease in the number of infections with viruses.[6]

On joinpoint analysis, the authors found an increasing turnpoint at 25 years of age for JEV, hence, they advocated for a booster vaccine for this at the age of 25.[6] Similarly, a previous study showed the benefit of meningitis B vaccinations in preventing Neisseria meningitidis infections, demonstrating the key role of vaccinations in meningitis infection prevention.[7]

It is notable that an infectious cause was identified in only 30% of patients in this study.[6] This could be due to a limitation of the study being that many pathogens that may cause meningitis or encephalitis were not assessed for (e.g., bacteria: listeria monocytogenes, leptospirosis; fungi: cryptococcus neoformans; viruses: human immunodeficiency virus and VZV). Moreover, novel techniques such as metagenomic next generation sequencing, by assessing for a wide range of etiologies in an unbiased manner, may allow identification of infectious agents not initially considered on the differential diagnosis.[8] It also warrants emphasis that autoimmune causes of meningoencephalitis and encephalitis are increasingly recognized, and in some regions, like the USA, may equate to that of infectious encephalitis.[9] Indeed, when systematically evaluated in the California encephalitis project, it was found that the prevalence of anti-NMDA receptor encephalitis exceeded that of infectious encephalitis in younger individuals.[10]

Identification of an autoimmune etiology of meningitis or encephalitis is crucial given the potential for reversibility with immunotherapy and lack of response to empiric antimicrobial treatments. Furthermore, in some scenarios, detection of a neural antibody may be an indication of an underlying malignancy. Thus, further studies in large populations are needed to assess the frequency of autoimmune etiologies of encephalitis and meningitis.

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The study by Wang and colleagues[6] is important for the Chinese, as well as the global population. Knowledge of the etiology and epidemiology of infectious meningitis and encephalitis can help clinicians better test for the pathogens that are more likely to be causative.

It can also guide public health policies, such as vaccination programs, targeting the disease vectors and improving crowded living conditions. Surveillance testing also helps to monitor antimicrobial resistance patterns, through PCR testing and for early detection of emerging novel pathogens.

Additional research should address pathogen detection in sterile sites only (like cerebrospinal fluid) versus those from non-sterile sources. Moreover, it would also be useful to separate the pathogens detected in meningitis from encephalitis as, despite some overlap, the clinical presentations can be different. This could help narrow down the organisms a clinician should consider testing with each phenotype. Lastly, future studies should determine what impact the infection prevention measures imposed during the COVID-19 pandemic had on the epidemiology of meningitis and encephalitis.

Declaration of interests

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Author contributions

Both authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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