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Review Article

Encephalitis: Diagnostic and Management Challenges

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Abstract

Encephalitis is a condition characterized by inflammation of the brain which may be caused either by direct infection of the brain parenchyma or as a post-infective process with a more increasingly recognized association with autoimmune etiologies. Establishing etiology is a crucial first step alongside initiating appropriate management. This article will explore the taxing issues clinicians face whilst investigating such cases and their therapeutic challenges.

Keywords: Encephalitis, challenges, infectious, autoimmune

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Introduction

Encephalitis remains a global disease burden with a prevalence of 1.9 to 14.3/ 100 000 people per year.[1] The term is occasionally interchanged with encephalopathy, both of which have similar manifestations of disorientation, confusion and cognitive impairments. However, the main difference is the presence of brain parenchymal inflammation in encephalitis whilst encephalopathy merely describes a clinical state of altered mental status with or without brain inflammation. Recognition of a case of suspected encephalitis along with searching out the causative etiology often presents a rather challenging issue for most clinicians. Knowledge of different causative pathogens and non-infective processes play a vital role when formulating a differential diagnosis. Another limitation presents when decisions for initiating therapy are to be made. Careful judgment is needed when choosing the most definitive treatment regimen with the ever-present knowledge that any delays may affect the prognosis greatly.

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Determination of Encephalitis:

Encephalitis may present a diverse clinical picture. Infective encephalitis commonly has a prodrome of fever, headaches, respiratory or gastrointestinal symptoms followed by altered mentation ranging from a depressed level of consciousness to coma. Focal signs such as aphasia, ataxia, paresis, involuntary movements or even seizures, cranial nerve deficits, personality changes and hallucinations may be seen. Physicians may also come across unique features such as temperature dysregulation, features of raised intracranial pressure or autonomic instability. Presence of these varying signs might mislead one's perception to consider several differentials and thus result in carrying out excessive testing.

Establishing encephalitis relies heavily on optimal patient history, focusing on whether an infectious agent is accountable or if a non-infective inflammatory process is at play. The determination of encephalitis is based on the criteria (Table-1) established by the International Encephalitis Consortium (IEC) guidelines[2] that includes the major criterion of clinical presentation with altered mental status lasting more than 24 hours with no alternative causes, along with at least two minor criteria, such as documented fever (≥ 38' C) within 72 hours before or after presentation and new onset seizures or focal neurological findings among others.

Table 1: International Encephalitis Consortium (IEC) diagnostic criteria for encephalitis.

Major criterion (required)
▪ Patients presenting to medical attention with altered mental status (defined as decreased or altered level of consciousness, lethargy or personality change) lasting ≥ 24 hours with no alternative cause identified.
Minor criteria (2 required for possible encephalitis, ≥3 required for probable or confirmed encephalitis)
▪ Documented fever ≥ 38`C (100.4`F) within the 72 hours before or after presentation. ▪ Generalised or partial seizures not fully attributable to a preexisting seizure disorder. ▪ New onset of focal neurologic findings. ▪ CSF leukocyte count ≥ 5/mm³ ▪ Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset. ▪ Abnormality on EEG that is consistent with encephalitis and not attributable to another cause.

Risk factor evaluation should focus on both documented and undocumented exposures, such as travel to zones with prevalence for endemic diseases, travel-related vaccinations or chemoprophylaxis, exposure to animals, pets, insects or ill- contacts, freshwater exposure and high-risk sexual activity. The occupation of an individual may be overlooked, yet is important, especially when there is a need to exclude toxin and chemical exposures. An individual's past medical history and previous immune status may be unknown or certain aspects may be unintentionally under-evaluated, especially regarding alcoholism and recreational drug use.

Infectious Encephalitis:

There are a variety of pathogens responsible for infectious encephalitis, each of which depends on a range of factors such as geographical distribution, seasonal variation, vector presence and host reservoirs. In addition, consideration of host factors like immunocompromised states, age and genetic make-up of individuals should be considered. Pathogens commonly associated with encephalitis are viral, bacterial, parasitic and fungal. Viruses, such as HSV 1 and 2, VZV, Arbovirus (Dengue, Zika and Chikungunya) and Enterovirus, have most commonly been attributed. However, other re-emergents such as West Nile Virus, Japanese Encephalitis virus, Nipah virus, Tick-borne encephalitis, Measles, Rabies and Ebola have also been included.

Japanese encephalitis virus, transmitted by the mosquito Aedes aegypti was previously a major concern of viral encephalitis for many Asian countries including Bangladesh, however with the successful implementation of intensive surveillance and vaccination programmes, particularly in parts of India, occurrences have declined.[3] The rickettsial bacterium, Orientia tsutsugamushi (Scrub typhus) transmitted by the bite of a mite has now a rising prevalence.[4] Global climate changes and ecological disruptions have allowed for the expansion of vectors such as mites, ticks and mosquitoes which have contributed to the rise in the number of outbreaks of other arboviral illnesses around the world.

Other bacteria, Borrelia burgdorferii (Lyme disease) and Mycoplasma pneumoniae are also listed as pathogens. Fungi and parasites such as Cryptococcus neoformans and Histoplasma capsulatum and Neurocysticercosis, as well as free-living amoebae (Naegleria fowleri) have also been documented as causes of neuroinvasive disease, especially in immunocompromised patients like HIV/AIDS. The most commonest infective cause has been found to be related to viral etiologies, as reported in a prospective study carried out in the USA, The California Encephalitis Project, between 1998 to 2000 on 334 patients, which aimed to establish epidemiological and clinical features of encephalitis in California, reporting 9% cases of confirmed or probable viral agent, followed by bacterial (3%), and parasitic (1%) causes. However, in 10% cases were attributed to non-infectious causes and in 62% cases the etiology remained unexplained.[5] Some patients may exhibit recent evidence of serological

infection however have no evidence on cerebrospinal fluid (CSF) analysis. This may be due to minimal or no involvement of meninges, thus the agent will remain undetectable in CSF specimens. Another explanation may be the host response to previous infection, instead leading to post-infectious encephalitis where no pathogen is present in CSF or CNS tissue.

Autoimmune Encephalitis:

Due to the overlap of symptoms and the relative lack of localized neurological impairments, especially among the different types itself, autoimmune encephalitis had been a disorder that was largely misunderstood. Over the last decade there has been an increased recognition, testing and appreciation of the condition with the discovery of more pathogenic autoantibodies. A clinical presentation commonly consists of a subacute onset (days to weeks), progressively reduced level of consciousness with fluctuations sometimes ending in coma. There may be associated memory impairment, particularly impaired retention of new memory, as well as abnormal behaviors, aggression, fear or compulsive behaviors. Abnormal movements such as dystonia and chorea may also occur early in the disease. Seizures may be a common presentation and can occur during any stage of the disease and may even progress to intractable status epilepticus. Understanding the disease pathophysiology greatly helps when carrying out relevant testing and eventually deciding on the appropriate treatment modality. There are several forms of the condition, one group consists of paraneoplastic disorders which are associated with antibodies to intracellular antigens, such as Anti-Hu, which are strongly associated with cancer and tend to have poorer prognosis.[6] In contrast, another group of the disorder have autoantibodies to extracellular epitopes of ion channels and receptors, such as CSF IgG antibodies against the GluN1 subunit of the N-Methyl-D-Aspartate (NMDA) receptor.[7] Anti -NMDAR encephalitis patients present more frequently with episodes of psychosis and memory impairment initially, followed later by abnormal movements, seizures with altered levels of cognition. Ovarian teratomas have been commonly associated in females of reproductive age and response to immunotherapy is generally good, however it may take several months to achieve full effects, and few may have persistent deficits.[8] An important advancement has been the recognition that some HSV encephalitis patients rarely develop anti-NMDAR encephalitis secondarily as a post-infectious complication a few weeks afterwards, where there is a positive CSF NMDAR- antibody and negative HSV PCR.[9] Therefore, careful consideration is needed when such a patient worsens after an infectious encephalitis, to evaluate for the possibility of an autoimmune aetiology. Prior to being moved to the medical care unit, many NMDAR encephalitis patients with initial catatonic symptoms first undergo a psychiatric evaluation or are admitted to psychiatric facilities, thus delaying diagnosis and treatment.[10] Serotonin syndrome and neuroleptic malignant syndrome frequently exhibit similar symptoms to autoimmune encephalitis. In contrast, patients with anti-NMDAR encephalitis may initially present with psychosis and be treated with neuroleptics. Later, however, these patients may experience catatonia, rigidity, autonomic instability, and altered level of consciousness; this pattern of symptoms may lead to the incorrect diagnosis. Therefore, each case of suspected neuroleptic malignant syndrome should include autoimmune encephalitis in the differential diagnosis. Another non-infectious encephalitis is acute demyelinating encephalomyelitis (ADEM) which is a demyelinating disorder following an infection or vaccination primarily seen in pediatric populations. It is characterized by varying degrees of encephalopathy and other neurological symptoms such cranial nerve palsies, ataxia, hemiparesis, myelopathy, or optic neuritis. The exclusion of other 'medical mimics' of encephalitis syndromes is also important, for example, in thiamine deficiency which leads to Wernicke's encephalitis, which is commonly seen in alcoholics and individuals with impaired absorption.

Diagnostic challenges:

There are a diverse range of neurodiagnostic techniques available, some of which have been recently developed in line to focus on comprehensive evaluation of meningitis and

encephalitis, further improving the rate of a etiological diagnosis. Lumbar puncture for evaluation of opening pressure and CSF analysis for microbiological evidence, molecular assays such as PCR and immunological studies for antibodies are recommended. Early and efficient detection of pathogens may be influenced by several factors, such as timing of sample collection in relation to the onset of infection and duration of symptoms, availability and accessibility of specific tests, in addition, experience of clinicians to interpret negative results. In viral encephalitis, the CSF typically shows a predominantly lymphocytic pleocytosis, protein levels may be moderately elevated or normal. It is recommended to obtain CSF gram stain and culture, CSF HSV PCR, CSF VZV PCR, CSF Enterovirus PCR. In suspected HSV encephalitis with an initial negative CSF PCR, a repeat testing is indicated in 3-7 days if there remains undiagnosed encephalitis with features suggestive of HSV.[11] When CSF and imaging fail to reveal a cause, paraneoplastic and autoimmune causes should be considered. Ideally, both serum and CSF anti-neuronal auto antibodies (such as anti- NMDAR, anti LGI1, anti- AMPAR, GAD65, GABA-A and GABA-B) should be tested, bearing in mind that absence of antibody does not rule out the disease. Further imaging should be considered to rule out occult malignancies and systemic infections.[12] Neuroimaging techniques, traditionally include CT or the more preferable Brain MRI scan, which allow to identify the areas involved and thus gives a clue to the possible causative pathogen whilst assessing the burden of involvement and presence of edema, hemorrhage or herniation. MRI sequences of T2 -weighted images, FLAIR, diffusion-weighted imaging (DWI) and post-gadolinium sequences are the most appropriate. Knowledge of specific areas of involvement may be suboptimal and thus may delay in identification of the condition. In HSV encephalitis, 90 % of abnormalities may be detected in the medial and inferior temporal lobes with cytotoxic and vasogenic edema. Whereas, in VZV encephalitis, T2 hyper intensities with restricted diffusion are observed in basal ganglia, thalamus, temporal cortex and cerebellum. Fluorodeoxyglucose-positron emission tomography (FDG- PET) scans also allow for evaluating autoimmune etiologies and assessing brain physiology.

Continuous electroencephalogram (c-EEG) has been recommended in critically ill patients with persistent altered mental status for at least 24 hours of unknown etiologies despite treatment. It detects 95% nonconvulsive seizures in patients compared to conventional EEG.[13] However, these advanced technologies are not widely available and may be restricted to tertiary centers where few specialists are trained in interpreting the results.

Emerging novel techniques have been introduced over the past decade allowing for comprehensive evaluation. Two such methods are the molecular- based assay BioFire FilmArray® Meningitis/Encephalitis (ME) panel and metagenomic Next Generation Sequencing (NGS). The FilmArray® ME panel allows multiple CSF PCR assays, especially for meningitis and encephalitis- causing pathogens, testing fourteen different microorganisms, having high sensitivity and specificity with a rapid turnaround time.[14] However there are limitations, as not all pathogens are included in the panel and remain to be unavailable in most hospital settings. Metagenomic NGS provides a more extensive method of detection for viruses, bacteria, parasitic and fungal infections by isolating and sequencing RNA or DNA in samples such as fluids and tissue, then identifying the non-human pathogen compared to known genetic sequences available on a database.[15] Although it offers an unbiased approach to pathogen identification and rules out co-infections, the occurrence of false positive results due to sample contamination can lead to wrongly identifying a cause. In addition, the method relies heavily on the presence of nucleic acids, which may not be appropriate for diagnosing pathogens that are short lived or have a low pathogen load.[16] Compliance with diagnostic guidelines also have a great impact, as evaluated in a retrospective study, where in spite of a high compliance rate in performing tests such as brain CT, blood cultures and CSF microbiology, evaluation with other available tests were not uniformly performed which contributed to the underutilization of resources.[17]

Therapeutic pitfalls:

Management may be suboptimal, possibly due to lack of awareness and experience by clinicians of current treatment guidelines for both infectious and autoimmune encephalitis. Infective encephalitis requires immediate empiric antibiotic and antiviral treatment, whereas autoimmune encephalitis may respond to high dose steroids, IVIG, plasmapheresis and immunomodulatory treatment such as rituximab and cyclophosphamide. Seizures are common sequela of encephalitis and access to anticonvulsant drugs and intensive care units play a vital role in such a situation. Challenges arise from limited availability of specific therapeutics, especially in resource-limited areas with poor health access. Other factors hampering management are in part due to the re-emergence or resurgence of infectious pathogens, which had been previously under-recognized to cause neurological disease, in addition to the geographic expansion of vector distribution and under-surveillance of encephalitis cases, thus impeding the understanding of actual disease prevalence.

Conclusion:

Encephalitis remains a global concern, despite advances in diagnostic technologies and management guidelines, it remains a condition of high mortality and morbidity. Difficulties remain in identifying etiologies, using standardized neurodiagnostic testing and promptly initiating therapy. Infectious pathogens are still the most prevalent causes of encephalitis. Autoimmune encephalitis has also become increasingly recognized yet evaluation remains a challenge. Novel techniques have allowed for etiology identification however most remain inaccessible.

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