Influenza and Epstein-Barr virus encephalitis in children: could we be missing them and why?

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We note the case of influenza A encephalopathy reported in the *Hong Kong Medical Journal* in 2020, involving an unvaccinated 10-year-old child who presented with high fever, convulsions, and altered consciousness.[1] The patient was successfully treated with anticonvulsants, oseltamivir, and hypertonic saline and mannitol to control cerebral oedema. The electroencephalogram showed diffuse slow-wave activity.[1] Although Hong Kong offers a free seasonal influenza vaccination programme for children aged 6 months to under 12 years (those attending primary school), uptake remains relatively low (50%-60%),[2] and several paediatric influenza-related deaths are reported annually in the city, primarily among unvaccinated children.[3]

A diagnosis of influenza encephalitis is made after exclusion of all other possible causes, following confirmed detection of influenza virus in a respiratory sample, but only very rarely by detection of influenza RNA in the cerebrospinal fluid (CSF). Clinical presentation can be variable, including fever, seizures, meningism, photophobia, excessive sleepiness, disorientation, agitation, altered personality, and leg paresis. Electroencephalogram findings can show diffuse slowing or generalised spike-wave activity, while magnetic resonance imaging may be normal or show multiple focal lesions.[4]

This form of 'indirect' diagnosis in viral encephalitis is not unique to influenza. Among other viral encephalitis—such as West Nile virus, Japanese encephalitis virus, and tick-borne encephalitis viruses—diagnosis is often confirmed by serology or seroconversion as the virus may have already cleared from the CSF by the time patients with neurological symptoms present. Concerning influenza encephalitis, virus detection in a respiratory sample by polymerase chain reaction is a common diagnostic approach. Treatment of influenza in otherwise healthy children is often not required; whether treated or not, the clinical outcomes of presumed influenza encephalitis are generally good, especially when oseltamivir and neurosupportive treatment are promptly instituted.[5]

A practical diagnostic distinction has been made between acute influenza encephalitis—occurring within a few days of confirmed infection and influenza encephalopathy, which occurs within 3 weeks after diagnosis, after respiratory symptoms have resolved.[4,6] Clinical treatment is essentially the same.[7,8]

Another underrecognised cause of encephalitis is Epstein-Barr virus (EBV), the usual cause of glandular fever in teenagers and young adults. An important differential diagnosis is streptococcal pharyngitis or tonsillitis. We have encountered unwell teenagers with tonsillitis, cervical lymphadenitis, atypical lymphocytosis, and normal inflammatory markers but negative rapid throat streptococcal antigen test results. Prompt diagnosis of EBV glandular fever can help avoid unnecessary antibiotics (personal communication). Epstein-Barr virus is a herpesvirus that becomes latent in B lymphocytes after primary infection, which is often asymptomatic. Reviews of EBV encephalitis suggest it is more common than previously thought, particularly in children.[9-13] As with influenza, most cases resolve spontaneously with few sequelae, and the diagnostic criteria remain poorly defined.

In EBV encephalitis, EBV DNA is more frequently detected in CSF polymerase chain reaction, particularly in cases that involve reactivated EBV infection.[9] However, such EBV DNA–positive CSF results are often interpreted and dismissed as benign 'bystander' EBV reactivations assumed to play no role in the current illness.

Similar to influenza encephalitis, EBV encephalitis presents with a wide range of symptoms, including headache, fever, nausea, vomiting, tonsillitis, myalgia, and neurological manifestations such as cerebellar syndromes, tonic-clonic seizures, meningism, hypotonia, myalgia, psychiatric disorders, and cognitive, sensory or visual impairments. Brain imaging may show white matter changes in the cerebellum, basal ganglia, frontal lobe, and cerebral cortex, and electroencephalogram findings may be normal or indicate diffuse slowing.[9] However, none of these features is specific to EBV encephalitis and may also be found with other viral causes.

Diagnosis of EBV encephalitis is therefore often made by exclusion when no other pathogen is identified. Where treatment has been initiated, intravenous acyclovir or ganciclovir (although neither is licensed for EBV treatment) has been used, with or without corticosteroids—or corticosteroids alone, often with good outcomes.[9] Although the direct efficacy of acyclovir and ganciclovir against EBV encephalitis is doubtful, they may help suppress concurrent reactivation of herpes simplex virus (HSV)–1, which could otherwise lead to more severe HSV-1 encephalitis.

Acute encephalitis due to dual or simultaneous coinfections by EBV and influenza is theoretically possible and may cause diagnostic dilemma. However, a PubMed review of literature does not identify any report. In any case, treatment will essentially be the same by using specific antiviral medications for both viruses.

Viral encephalitis is inflammation of the brain caused by a virus.[14] Diagnosis is based on symptoms, travel history, and investigations such as histology, imaging, and lumbar puncture. Many viruses can cause encephalitis.[15] These viruses often replicate outside the central nervous system before triggering diverse forms of viral encephalitis. Differential diagnosis helps rule out non-infectious encephalitis.[14] Some viruses have characteristic symptoms of infection that may aid diagnosis.[16] A broad differential diagnosis should be considered, including infectious and non-infectious aetiologies (eg, malignancy, autoimmune or paraneoplastic encephalitis, abscess, tuberculosis, drug reactions, vascular or metabolic disease).[15-17] It may not always be possible to distinguish viral encephalitis from immune-mediated inflammatory central nervous system diseases (eg, acute disseminated encephalomyelitis and immune-mediated encephalitis) in children.[18] Symptoms usually occur acutely, with fever, stiff neck, headache, altered mental status, photophobia, vomiting, confusion, and, in severe cases, seizures, paralysis, or coma.[16,18] Most cases are mild.[15] Neuroimaging and lumbar puncture are essential[14]; computed tomography or magnetic resonance imaging can identify increased intracranial pressure and the risk of uncal herniation. Cerebrospinal fluid should be analysed for opening pressure, cell counts, glucose, protein, and immunoglobulin G and immunoglobulin M antibodies. Polymerase chain reaction testing for HSV-1, HSV-2, and enteroviruses is also recommended. Where indicated, brain biopsy and body fluid specimen cultures may assist. Electroencephalogram findings are abnormal in over 80% of viral encephalitis cases, and continuous monitoring may be needed to identify non-convulsive status epilepticus.[15,18]

Thus, if clinical outcomes are generally good with current non-specific supportive management protocols, even in the absence of a specific cause, there may be little additional value in defining a precise diagnosis. Brain biopsy to confirm the exact cause is usually unnecessary. Treatment is usually supportive, with antivirals such as acyclovir for herpes simplex encephalitis. Where specific treatment (eg, oseltamivir for influenza) is available, it should be used because it may alleviate encephalitic symptoms. Furthermore, once a diagnosis of encephalitis is made, the clinical team can avoid extensive investigation for other causes, reassured that most cases resolve with appropriate supportive care and good outcomes.

In conclusion, infection or infection-associated encephalitis and encephalopathy can often be managed empirically. A definitive diagnosis can support targeted antiviral therapy and reduce unnecessary investigations, provided the diagnosis is robust. We propose a flowchart to guide frontline physicians and paediatricians in the diagnosis and management of these conditions (Fig). Because it is often impractical or impossible to confirm the presence of the causative infectious agent in the brain parenchyma, there is limited relevance in labelling the condition as encephalitis or encephalopathy. The term acute cephalic syndrome (ACS) may be more appropriate. The cardinal symptom of ACS is an altered or fluctuating mental state. Irrespective of whether the aetiology is infectious, para-infectious, or non-infectious, the ABCDE approach should aid physicians during initial management of patients with ACS.

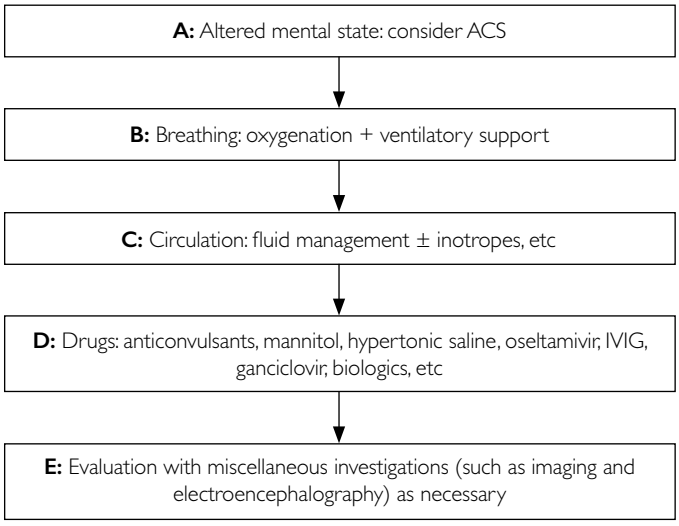

FIG. Acute cephalic syndrome management using an ABCDE approach
Abbreviations: ACS = acute cephalic syndrome; CBC = complete blood count; CRP = C-reactive protein; IVIG = intravenous immunoglobulin; NPS = nasopharyngeal swabs; PCR = polymerase chain reaction

Author contributions

Both authors contributed equally to the concept or design, acquisition of data, analysis or interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. Both authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As an editor of the journal, KL Hon was not involved in the peer review process. The other author has declared no conflicts of interest.

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