Commentary

Investigating outbreaks of uncertain aetiologies

Outbreaks of Japanese encephalitis (JE) occur in many parts of India. There is therefore a tendency to assign that aetiology to almost any outbreak of acute illness affecting the brain in children. In the absence of a systematic disease surveillance system, it is often media reports that alert the Government health services system. During the outbreak investigations, blood and cerebrospinal fluid (CSF) are collected and tested for the presence of JE virus, its antigen or antibody. Many encephalitis outbreaks in the known endemic States and districts are thus confirmed as JE. Innumerable outbreaks not confirmed as JE remain unreported.

The ‘ability’ to detect viral aetiology leads to its ‘application’ in every outbreak of acute febrile illness of children with brain involvement, whether appropriate or not. The basic problem with this approach is the assumption that all such outbreaks are due to viral encephalitis, caused by either JE or another virus. Consequently, even if the evidence is against JE virus aetiology, much effort is taken to identify a viral aetiology. This has often led investigators in directions and conclusions that later turn out to be non-replicable, hence unreliable. Epidemiology is conspicuous by its absence in such investigations. Virologists tend to classify all cases with the triad of acute onset fever, convulsions and altered sensorium in children as encephalitis. Paediatricians have however called for a distinction between encephalitis and encephalopathy, both of which may have the triad. Evolving and establishing appropriate case definition has been neglected in most outbreak-investigations. Epidemiological investigation cannot progress without knowing what is to be included and what must be excluded. Inclusion of ‘false positives’ will certainly confound the results and often mislead the conclusion.

How important is the difference between acute encephalitis and encephalopathy. Clinically encephalitis and encephalopathy have overlapping features. Both affect children, with acute onset and severe brain involvement manifested as delirium or coma and convulsions. However, for the discerning clinicians, there are also several critical differentiating features. Encephalitis is a prolonged illness (days to weeks), has slow clinical progression to brain disease, and recovery is often associated with neurological sequel. The brain pathology of inflammation is reflected in CSF pleocytosis. Encephalopathy on the other hand has abrupt onset, a very rapid progression (hours) and dramatic and complete recovery within 2-3 days. It is mostly non-infectious and without brain tissue inflammation, hence the absence of CSF pleocytosis. It is often caused by toxic or metabolic insults and brain oedema also tends to be more frequent or more pronounced. Case-fatality is often very high, usually due to extreme intracranial pressure. Innumerable failed investigations have tested children with encephalopathy for viral aetiology of encephalitis - this has not been wasteful but distracts investigators from other possible explanations and aetiologies. Thus, the mystery of undiagnosed outbreaks persists.
In some regions of India outbreaks of acute brain disease with high case-fatality occur infrequently but in western Uttar Pradesh (UP) they are an annual feature. Since media attention has been focused on such outbreaks in Saharanpur district in western UP, the mystery disease is generally assumed to be viral encephalitis - “Saharanpur encephalitis”. These cases have been regularly investigated for a viral aetiology without much success. The investigations were based on the assumption that the disease was encephalitis, but others have pointed out the lack of evidence of the inflammatory process of encephalitis. In the absence of clinical and laboratory features of inflammatory encephalitis, cases have diagnosed as acute encephalopathy, the most common of which is Reye’s syndrome. These cases therefore were provisionally classified as Reye’s syndrome. However, Reye’s syndrome is usually sporadic, and it does not usually occur in outbreaks. Hence the western UP outbreaks had to be explained clinically, pathologically and epidemiologically.

As reported in this issue, a team of investigators from 4 institutions have systematically studied the outbreak of encephalopathy syndrome in Bijnor district, western UP and have come up with a clear case definition. In addition to submitting appropriate specimens for virological testing, they proceeded to define the disease by histo-pathological examination. First they applied strict clinical criteria to select cases with uniform clinical features so that other confounding illnesses with brain involvement could be excluded. The illness was characterized by acute onset and rapid progression of unconsciousness in a previously well child; CSF without pleocytosis; no malarial parasite on blood smear; no plausible clinical diagnosis to explain the disease. Since liver involvement is common in Reye’s syndrome, they measured liver enzymes and documented gross derangement of liver function. Histopathology examination was done by a reputed liver pathologist and the conclusion was that the function derangement was due to cell necrosis without inflammation - obviously due to toxin but not virus. Brain specimens were understandably extremely difficult to obtain, but what was available confirmed non-inflammatory pathology, confirming the clinical diagnosis of encephalopathy. Then they biopsied skeletal muscles and found toxic necrosis of myocytes. Now they could add muscle enzyme rise to the case definition for further studies. Thus the “Saharanpur encephalitis” was convincingly reclassified as a catastrophic, multiorgan, non-inflammatory, cell necrosis pathology - which they have named appropriately as acute hepato-myencephalopathy.

Detection of risk factor(s) is always necessary and often sufficient to design intervention for prevention and control. The detection of male homosexual acts and intravenous drug use as risk factors of the acquired immunodeficiency syndrome was sufficient to promote preventive interventions of safe sex, condom use and clean syringe/needle years before the aetiology of a retrovirus was discovered. Back in the 18th century the epidemiologic association of one water source as the risk factor of a cholera outbreak in London was sufficient to stop its progression by disabling the hand pump. Risk factor detection requires epidemiological investigations, for which the starting point is precise case definition. This sequence is well illustrated by the diagnosis of this new syndrome of hepato-myencephalopathy in western UP. We eagerly await to see if the investigators will come up with specific risk factors through systematic epidemiologic studies, so that this fatal illness could be prevented even if its aetiology is not identified.

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References


