Research Priorities in Acute Encephalitis Syndrome (AES)

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Abstract

Acute encephalitis syndrome (AES) is a constellation of clinical signs and/or symptoms, i.e. acute fever, with an acute change in mental status and/or new onset of seizures that signifies acute inflammation of brain cells. Although viruses have been identified as the major etiological agents for this syndrome, a range of pathogens including acute bacterial or parasitic infection have also been attributed. In Asia, the major identified cause of acute encephalitis is Japanese Encephalitis (JE) virus. JE affects over 50,000 people annually, leading to 8-30% mortality and 50-60% disability, with children bearing the brunt of the disease. These outbreaks affect over 5,000 people annually in India, most of them being children. Many are left permanently disabled and as many as 700 people die each year. The Eastern region of Uttar Pradesh has been especially hard hit with a recurring outbreak in the rainy season each year, the primary cause of which remains uncertain. Although ICMR research institutions like National Institute of Virology (NIV), Enterovirus Research Centre, Mumbai, Vector Control Research Centre (VCRC), National Institute of Epidemiology (NIE), Centre for Research in Medical Entomology (CRME) etc are engaged in research activities dealing with various aspects of the disease, but have achieved limited success in identifying the aetiological agents. Therefore, there is a need to define research priorities in India to conduct focussed research that identifies the etiological agents for better management and treatment of AES cases to help reduce the morbidity as well as mortality associated with AES.

Keywords: AES, Acute encephalitis syndrome, JE, JE surveillance programme, viral aetiology, encephalitis, AES subgroups, altered sensorium, diagnostic algorithm, Arboviruses, functional, social and economic impact.

Background

Acute encephalitis syndrome (AES) is a constellation of clinical signs and/or symptoms, i.e. acute fever, with an acute change in mental status and/or new onset of seizures. These clinical signs suggest that the patient has acute inflammation of the brain and are used by clinicians to identify patients with acute encephalitis. Viruses are regarded as the most important cause of the acute encephalitis syndrome worldwide. However, the syndrome can be associated with a range of pathogens, including acute bacterial or parasitic infection. Where population based studies have been undertaken, the incidence ranges between 3.5 and 7.4 cases per 100,000 patient-years. Acute encephalitis can be associated with severe complications, including impaired consciousness, seizures, limb paresis or death. In Asia, the major identified cause of acute encephalitis is Japanese Encephalitis (JE) virus. JE affects over 50,000 people annually, leading to 8-30% mortality and 50-60% disability, with children bearing the brunt of the disease burden. The clinical characteristics and outcomes in paediatric JE patients hospitalized with acute encephalitis syndrome (AES) are still poorly understood.

The classification of AES was based on the World Health Organization's (WHO) definition. The results of the JE testing, undertaken as part of the JE surveillance programme, were related to the identified cases. The AES cases, based on the results of their microbiological and serological tests, were classified as AES of suspected viral
aetiology (Confirmed JE, non-JE and JE Status unknown) and AES of non-viral aetiology (AES-bacterial or parasitic aetiology). AES of suspected viral aetiology was defined by fulfilling the definition for AES (above) and having a discharge diagnosis of suspected viral encephalitis or meningo-encephalitis, supported by a CSF cell count < 1000 cells/mm³ with a lymphocyte predominance and no positive identification of non-viral pathogens (e.g. bacteria or parasites) in the CSF or blood. 

While Acute Encephalitis Syndrome (AES) occurs worldwide, it is especially prevalent in Asian countries with a high burden of the mosquito-borne disease Japanese encephalitis (JE). India introduced vaccination for JE in several states during 2006, resulting in a drop in cases. However, several areas of the country continue to experience large outbreaks of encephalitis that may be due in part to JE as well as other infectious and non-infectious diseases. These outbreaks affect over 5,000 people annually in India, most of them being children. Many are left permanently disabled and as many as 700 people die each year. The Eastern region of Uttar Pradesh has been especially hard hit with a recurring outbreak in the rainy season each year, the primary cause of which remains uncertain. Although ICMR research institutions like National Institute of Virology (NIV), Enterovirus Research Centre, Mumbai, Vector Control Research Centre (VCRC), National Institute of Epidemiology (NIE), Centre for Research in Medical Entomology (CRME) etc are engaged in research activities dealing with various aspects of the disease, but with limited success in identifying the aetiological agents. Hence, there is need for defining the research priorities in AES to undertake targeted research to define the problem and biomedical research related to control and better management of the disease. Some of the research priorities are discussed in this article.

Epidemiology

Despite being a rare condition, encephalitis is of public health importance worldwide because it has high morbidity and mortality. Yet, many details about its epidemiology have yet to be elucidated. 

Infection is the most common cause identified, with viruses being the most important known aetiological agents. Incidence varies between studies but is generally between 3.5 and 7.4 per 100,000 patient-years. Encephalitis affects peoples of all ages; however, incidence is higher in the paediatric population. Although both sexes are affected, most studies have shown a slight predominance in males. Encephalitis occurs worldwide; some aetiologies have a global distribution (herpesviruses) while others are geographically restricted (arbo-viruses). Although definite epidemiological trends are evident, it is difficult to make generalisations as few population-based studies exist. Most cases are not reported to health authorities, and many possible pathogens are implicated but in most cases a cause is never found. Defining the causal relationship between a microbe and encephalitis is complex. Over 100 different infectious agents may cause encephalitis, often as one of the rarer manifestations of infection. The gold-standard techniques to detect causative infectious agents in encephalitis in life depend on the study of brain biopsy material; however, in most cases this is not possible. A better understanding of the epidemiology of this devastating disease will pave the way for better prevention and control strategies.

Quality of AES Surveillance

Robust surveillance system is crucial for any disease control programme. As part of the effort to control Japanese encephalitis (JE), the World Health organisation (WHO) is producing a set of standards for JE surveillance. The surveillance consists of identifying patient with acute encephalitis syndrome (AES), and then classifying patients according to the results of laboratory diagnostic tests. AES is defined as the acute onset of fever and change of mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) and/ or new onset of seizures (excluding simple febrile seizures) in a person of any age at any time of the year. As with all surveillance standards, the document includes performance targets (PT) that give an indication of the quality of the surveillance. The annual incidence of a disease syndrome that one would expect to be reported provides a vital indication on whether the surveillance is active. For example in the polio eradication surveillance standards, an annual rate of non-polio acute flaccid paralysis cases of 1 per 100,000 children is the minimum that should be reported to show that surveillance is active. A performance target for the minimum annual incidence of AES has not been defined for the Japanese encephalitis surveillance standard. Performance target for the incidence rate (IR) of AES has not been defined by WHO due to lack of data. There are no studies that specifically address the incidence of AES. There is urgent need to work out the minimum annual incidence of AES that should be reported per 100,000 people to...
show that the overall surveillance programme is active. In India, quality of surveillance for AES, including laboratory testing is necessary for understanding the epidemiology and aetiology of AES, planning, interventions, and developing policy.

**Defining clinical AES subgroups**

AES is caused by several different viruses, bacteria, fungi, parasites, spirochetes etc. More than 100 different pathogens have been recognised as the causative agents of AES like JE, herpes simplex, varicella zoster, epstein barr virus, mumps, measles, enteroviruses, influenza, adenoviruses, echoviruses, mycoplasma pneumoniae. Currently, AES has been categorized into the following categories:

- **Confirmed JE:** A suspected case, which is shown to have IgM antibodies (≥ 40 units) specific to JE virus in a single (CSF and/or serum) sample (or a rise in titres among paired samples) as detected by IgM-capture ELISA.

- **Non-JE:** A suspected viral case, which is shown to have an absence of IgM antibodies specific to JE virus, based on a negative test for a single sample collected after the ninth day of illness or no change in titres in paired samples collected at least seven days apart.

- **JE Status unknown:** A suspected viral case which was either not tested for anti-JE IgM antibodies or had samples tested that were collected too early in illness course to confidently rule out JE (as defined above).

- **AES of unknown viral aetiology:** A suspected viral case which was not confirmed as JE; this group included both of the categories described above, i.e. non-JE, and JE Status unknown.

- **AES of non-viral aetiology:** was defined by fulfilling the definition for AES (above) and either; (a) having a documented discharge diagnosis of suspected bacterial meningitis or meningoc-encephalitis, supported by a CSF cell count > 1000 cells/mm³ or a pleocytosis with a polymorph predominance and a raised CSF protein (≥ 0.45 g/L) 

  or (b) having a positive identification of non-viral pathogen in CSF or blood. A positive identification of a non-viral pathogen was fulfilled by a positive Gram stain or bacterial culture from CSF; a positive bacterial culture from blood; a positive Widal test for Salmonella typhi; or observation of asexual Plasmodium falciparum parasites in peripheral blood smears.

Confirmed JE cases may be compared to AES cases of unknown viral aetiology (non-JE and JE status unknown). As the later group also contained patients that did not have a confirmed negative test for JE, a further analysis needs to be undertaken, comparing JE against non-JE cases.

The rates of many clinical features and laboratory parameters may be similar on admission between confirmed JE, confirmed non-JE and JE status unknown. Importantly, the rates of many recorded neurological features were comparable between the patient groups. However, there was a significantly higher prevalence of patients presenting with focal neurological deficits at admission among confirmed JE patients compared to AES cases of unknown viral aetiology. Among AES patients of suspected viral aetiology, presence of a focal neurological deficit at admission had a positive predictive value of 32% (sensitivity 54%) for JE. Absence of a focal neurological deficit at admission had a negative predictive value of 89% (specificity 77%) for the patients not having JE. Besides, a change in patterns of clinical manifestations was observed in AES patients admitted in BRD Medical College Hospital, Gorakhpur. Evidences of hepatitis, renal failure, and pericarditis have been reported in significant number of cases (personal communication). There is need for classification of AES cases based on presenting symptoms and signs so that non-JE cases may be aetiologically investigated further on the basis of leads derived from clinical presentations.

Admission patterns also differed between JE and non-JE patients. JE patients demonstrated a clear peak in hospital admissions rates in the months immediately following the rainy seasons each year (August and September). Non-JE patients didn’t demonstrate any clear seasonal variation in hospital admission rates. During 2014 no confirmed case of JE was admitted in BRD Medical College Hospital, Gorakhpur till June 2014 out of the total AES cases admitted. Subgrouping of the AES cases admitted during different months of the year need to be sub classified based on the predominant clinical manifestations in addition to fever and altered sensorium, which may provide clues for further investigations and diagnosis of AES cases.
Diagnostic algorithm

Algorithms for the diagnosis of AES may serve many purposes, including aiding clinicians in management of patients, standardizing evaluations for research, and facilitating public health disease surveillance. The primary goal of research and development is to develop a practical diagnostic algorithm for use by medical professionals in the initial evaluation of suspected encephalitis. In addition, the algorithm is supposed to provide a standardized approach for use in collaborative, multicentre research studies. Aetiologies that should be focused on include those that are more commonly identified, may have targeted therapies, and are of particular public health significance. The algorithm should be directed towards identification of specific infectious and autoimmune causes of encephalitis. Obtaining a comprehensive case history including recent and remote travel, animal contacts, and insect exposure and carefully characterizing presenting symptoms, signs and laboratory and neuroimaging findings are crucial to inform additional testing. Algorithm for adults and paediatric populations should be distinctively developed, because frequencies of aetiologies differ between the two age groups. Further research is needed to understand the underlying factors that lead to bad outcome in AES and JE, including a more systematic investigation of the influence of supportive measures.

Functional, social, and economic impact

During 2010 over 133,000 children with AES were reported in Asia, out of which JE accounted for approximately one quarter of cases. In most cases, no pathogen could be identified, and the management was supportive. Although JE is known to result in neurological impairment, few studies have examined the wider and long term impact of JE and AES on the patients and their families. Children with disabilities can have limited participation in everyday life and social activities. Participation is affected by motor and cognitive function, communication skills, age, gender, and environmental factors. Reduced participation has been shown to have a negative impact on the quality of life in disabled children.

Improving inclusion and participation for people with disabilities is the ultimate aim of the World Health Organization’s ‘Community Based Rehabilitation’ programme. Although there are scores for assessing the participation of children with disability in high income countries, there is no such score for use in a resource poor setting. The functional problems experienced by the children highlight their needs for long term medical support. The substantial economic costs to families suggest rationalisation of acute care costs. A positive attitude to social engagement of children with disabilities may be warranted. However, there is scanty research data available from India on these aspects.

Host Genetics

Although encephalitis is typically a rare clinical entity, it follows infection with a number of relatively common agents. Reasons for the range of disease severity remain unclear. Several general and disease specific risk modifiers have been identified including infectious dose, viral or microbial gene variation, and age related changes in anatomic barriers or body immune function. In addition, an individual genetic makeup contributes significantly to the various infectious disease susceptibility and severity. Preclinical studies have identified host cell factors that modulate the course of infection for the range of microbes. With few exceptions, however, these studies have failed to identify the human gene, variation in which, affects disease outcome. The sporadic and highly sporadic nature of encephalitis presents certain challenges. The strategy and approach to identifying genotype determinants of a given phenotypes depends largely on its allelic architecture – the number, type, penetrance and frequency of disease associated variants. Overall, the identification of genetic risk factors for encephalitis and other neuroinvasive complications of infection is a priority research and it is expected that a better understanding of encephalitis host genetics will elucidate pathogenic mechanisms, define relevant biomarkers, and suggest potential therapeutic approach. More work is clearly needed in this area.

Arboviruses

In recent years, there has been a dramatic global resurgence of epidemic arboviral diseases, including those that cause encephalitis. This has been caused by a number of demographic and societal changes that have created ideal conditions for the increased movement and transmission of vector-borne diseases. Increased population growth; increased movement of people, animals, and commodities via modern transportation, uncontrolled urbanization, and changes in agricultural practices all contribute to increased geographic spread, human exposure, and infection by these zoonotic viruses. Most arboviruses of medical importance belong to three families:
Flaviviridae, Togaviridae and Bunyaviridae. Japanese encephalitis virus (JEV) is the leading cause of mosquito borne encephalitis globally and continues to expand its range. Tick- borne encephalitis virus (TBEV) is the most common arthropod transmitted viral infection of humans worldwide, both in developing and developed countries and increasing numbers of cases of neuro- invasive disease have been documented. West Nile virus (WNV) has re- emerged as an important cause of encephalitis in the United States and Europe, and there has been recognition of dengue and chikungunya viruses as causes of neurological complications. The arboviruses that cause meningoencephalitis in humans are found in nearly all parts of the world. Each virus has a geographic distribution that is usually limited by the ecological parameters governing its transmission cycle. Important limiting factors include temperature, rainfall patterns, and the distribution and population densities of the arthropod vectors and the vertebrate reservoir hosts. Most of the arboviruses are found in the tropics, where the flora and fauna are diverse. In the immediate future, therefore, vector control will be required to interrupt transmission of most emergent/ resurgent vector- borne diseases. Environmentally safe insecticides and research on alternative approaches (such as biological control) are needed. Integrated vector control strategies must be developed and implemented in endemic/ enzootic- disease areas. In addition to economic support for research, human resources are needed to develop and implement sustainable prevention programs. A vector control strategist should have sound knowledge of the bionomics, distribution, seasonal prevalence, vectorial capacity, insecticide susceptibility status, and role of arthropods in diseases transmission coupled with the knowledge of identification features of the incriminated vectors for formulating effective control strategies. Once armed with this knowledge, the choice of effective vector management tools may be exercised; the range and sophistication of control methods is impressive.

Diagnosis of arbovirus borne encephalitis is challenging. For most arboviruses serologic testing of serum and CSF is preferred to molecular testing, since the peak of viraemia typically occurs prior to symptoms onset. For example, in patients with WNV infection associated with neuroinvasive diseases, CSF PCR is relatively insensitive compared to WNV IgM. The cumulative percentage of seropositive patients increases approximately by 10% during the first week of illness suggesting, the need for repeat testing if the suspicion for the disease is strong in those with initially negative results. Notably, arboviruses IgM antibodies may be persistently detectable in the serum and less commonly, in CSF, many months after acute infection. Therefore, if possible, documentation of acute infection by seroconversion and/ or 4- fold or greater rises in the titre using paired sera should be advocated. There is strong need for generation of data on prevalence/ circulation of neuroinvasive arboviruses in the community by conducting serosurveillance, using IgM antibodies titre in cumulative samples. Besides there is also need for study of evolution of vectors in relation to ecological changes over the years in order to understand interaction between vectors and their hosts.

**Conclusion**

Acute encephalitis syndrome (AES) is challenging to diagnose, manage, and study. It is a syndrome of multiple aetiologies and pathogeneses. Pathogenetic mechanisms for the parenchymal inflammation of encephalitis range from direct infectious to immune- mediated; however, specific mechanisms within each of these groups are diverse and often incompletely understood. Despite greater than 100 known causes, in most cases of encephalitis neither a pathogenetic mechanism nor aetiology is identified. Accurate and complete case ascertainment of encephalitis cases is made difficult by the complexity of the syndrome, difficulties in distinguishing it from non- encephalitis mimics, and the lack of standard clinical case definitions. There is no standard laboratory diagnostic algorithm for encephalitis in the country, although few laboratories test for JE, herpes simplex virus (HSV), varicella zoster virus (VZV) and enteroviruses nucleic acid sequences in the cerebrospinal fluid (CSF) of immunocompetent patients.

For sporadic and epidemic causes of infectious encephalitis, it is not understood why only a minority of individuals exposed to an infection develop encephalitis – the majority of encephalitic patients are not immunosuppressed. Host and pathogen- related factors are likely to be important. Host factors are increasingly implicated in encephalitis. Alleles in the innate immune effectors TLR3 and UNC93B have been identified that mediate susceptibility to herpes encephalitis in children. Further studies to address both pathogen neurovirulence and host susceptibility could increase our understanding of the pathogeneses of encephalitis, perhaps even providing potential targets for novel treatment.
strategies. A standard diagnostic algorithm for laboratory investigation is needed incorporating testing for infectious and antibody-associated causes. Such a development should be combined with improved access to specialist diagnostic tests performed in centres participating in rigorous quality control programmes.

Research on acute encephalitis syndrome needs to broaden its focus beyond the pathogen and shift to the big picture that includes knowledge gaps related to pathogen, host–pathogen interaction, host immune system interaction, laboratory diagnosis, disease surveillance, immunization, health care delivery, and access as well as community perceptions and knowledge. Disease surveillance is the corner stone of response to emerging disease threats. Risk assessment and outbreak preparedness are imperative. Basic, translational and operational research efforts to develop more effective and advanced tools to combat the resurgence the arboviruses or develop more effective and advanced tools to understand the changing pattern and epidemiology of different diseases is imperative.

References