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Evaluation of paediatric cases suffered from acute encephalitis syndrome in DMCH

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Abstract
Acute encephalitis syndrome (AES) is a serious public health problem in India. It is characterized as acute-onset of fever and a change in mental status (mental confusion, disorientation, delirium, or coma) and/or new-onset of seizures in a person of any age at any time of the year. The disease most commonly affects children and young adults and can lead to considerable morbidity and mortality. Hence based on above findings the present study was planned for Evaluation of Paediatric Cases Suffered from Acute encephalitis syndrome in to DMCH.
The present study was planned in Department of Pediatrics, Darbhanga Medical College and Hospital Darbhanga, Bihar. Total 20 cases of Acute Encephalopathy Syndrome were enrolled in the present study. After admission, detailed history was taken and management of fever, raised ICT and seizure were carried out simultaneously. Clinical examinations were done. Urgent supportive management, and blood samples were sent for different baseline biochemical tests. Blood and urine samples were sent for culture and sensitivity in all cases by maintaining proper aseptic technique. Neuroimaging and CSF analysis were performed in all cases of fever with altered sensorium.
The data generated from the present study concludes that AES is a major illness affecting children of Bihar as well as other parts of country with significant morbidity and mortality. Its control is very important from public health aspect as it has significant impact on resources of state, nation and public exchequer. Most importantly, the chance of lifelong sequalae leaves scarring on the face of survivor, their family and society.

Keywords: paediatric cases, acute encephalitis syndrome, AES, DMCH, etc

Introduction
Encephalitis, an inflammation of the brain parenchyma, presents as diffuse and/or focal neuropsychological dysfunction. Although it primarily involves the brain, the meninges are frequently involved (meningoencephalitis).
From an epidemiologic and pathophysiologic perspective, encephalitis is distinct from meningitis, though on clinical evaluation both can be present, with signs and symptoms of meningeal inflammation, such as photophobia, headache, or stiff neck. It is also distinct from cerebritis. Cerebritis describes the stage preceding abscess formation and implies a highly destructive bacterial infection of brain tissue, whereas acute encephalitis is most commonly a viral infection with parenchymal damage varying from mild to profound.
Although bacterial, fungal, and autoimmune disorders can produce encephalitis, most cases are viral in origin. The incidence of encephalitis is 1 case per 200,000 population in the United States, with herpes simplex virus (HSV) being the most common cause. Considering the subacute and chronic encephalopathies, the emergency department (ED) physician is most likely to encounter toxoplasmosis in an immune-compromised host.
The relatively common acute arboviral encephalitides vary widely in epidemiology, mortality, morbidity, and clinical presentation, and no satisfactory treatment exists for these infections. However, attempts to distinguish these acute arboviral encephalitides from the treatable acute viral encephalitides due to herpes simplex or varicella are important.
Herpes simplex encephalitis (HSE), which occurs sporadically in healthy and immune-compromised adults is also encountered in neonates infected at birth during vaginal delivery and is potentially lethal if not treated. Varicella-zoster virus encephalitis (VZVE) is life threatening in immune-compromised patients. Swift identification and immediate treatment of HSE or VZVE can be lifesaving. From a risk-benefit standpoint, most authorities recommend initiating ED treatment with acyclovir in any patient whose central nervous system (CNS) presentation is suggestive of viral encephalitis, especially in the presence of fever, encephalopathy, or focal findings, and in all neonates who appear ill for whom a CNS infection is being considered.
Portals of entry are virus specific. Many viruses are transmitted by humans, though most cases of HSE are thought to be reactivation of HSV lying dormant in the trigeminal ganglia. Mosquitoes or ticks inoculate arbovirus, and rabies virus is transferred via an infected animal bite or exposure to animal secretions. With some viruses, such as varicella-zoster virus (VZV) and cytomegalovirus (CMV), an immune-compromised state is usually necessary to develop clinically apparent encephalitis.
In general, the virus replicates outside the CNS and gains entry to the CNS either by hematogenous spread or by travel along neural pathways (eg, rabies virus, HSV, VZV). The etiology of slow virus infections, such as those implicated in the measles-related subacute sclerosing pan encephalitis (SSPE) and progressive multifocal leukoencephalopathy

(PML), is poorly understood [1].

Once across the blood-brain barrier, the virus enters neural cells, with resultant disruption in cell functioning, perivascular congestion, hemorrhage, and a diffuse inflammatory response that disproportionately affects gray matter over white matter. Regional tropism associated with certain viruses is due to neuron cell membrane receptors found only in specific portions of the brain, with more intense focal pathology in these areas. A classic example is the HSV predilection for the inferior and medial temporal lobes.

In contrast to viruses that invade gray matter directly, acute disseminated encephalitis and postinfectious encephalomyelitis (PIE), most commonly due to measles infection and associated with Epstein-Barr virus (EBV) and CMV infections, are immune-mediated processes that result in multifocal demyelination of perivenous white matter.

The cause of encephalitis is usually infectious in nature. Viral agents, such as HSV types 1 and 2 (the latter much more common in neonates than adults), VZV, EBV, measles virus (PIE and SSPE), mumps virus, and rubella virus, are spread through person-to-person contact. Human herpesvirus 6 may also be a causative agent [2]. The CDC has confirmed that WNV can be transmitted by means of organ transplantation and via blood transfusions.

Important animal vectors include mosquitoes and ticks, which spread the arbovirus group, and warm-blooded mammals, which are vectors for rabies and lymphocytic choriomeningitis (LCM).

Bacterial pathogens, such as Mycoplasma species and those causing rickettsial disease or catscratch disease, are rare and invariably involve inflammation of the meninges out of proportion to their encephalitic components. Encephalitis due to parasites and fungi other than Toxoplasma gondii are covered elsewhere. Noninfectious causes include the demyelinating process in acute disseminated encephalitis.

The prognosis is dependent on the virulence of the virus and the patient's health status. Extremes of age (< 1 y or >55 y), immune-compromised status, and preexisting neurologic conditions are associated with poorer outcomes.

Untreated HSE has a mortality of 50-75%, and virtually all untreated or late-treatment survivors have long-term motor and mental disabilities. The mortality in treated HSE averages 20%, and the neurologic outcome correlates with the neurological disability present at the time of the first dose of acyclovir or comparable antiviral agents. Approximately 40% of survivors have minor-to-major learning disabilities, memory impairment, neuropsychiatric abnormalities, epilepsy, fine-motor-control deficits, and dysarthria.

Outcomes in arboviral JE and EEE are catastrophic, similar to untreated HSE, with high mortality and severe morbidity, including mental retardation, hemiplegia, and seizures. Other arboviruses cause substantially less morbidity and mortality. For example, St Louis encephalitis and WNE have a mortality rate of 2-20%, the higher rates found in patients older than 60 years. Long-term sequelae with St Louis encephalitis include behavioral disorders, memory loss, and seizures.

WEE is associated with few deaths and much less morbidity, although developmental delay, seizure disorder, and paralysis occasionally occur in children, and postencephalitic Parkinsonism may occur in adults. CE is typically associated with mild illness, and most patients make a full recovery; however, the minority of patients with severe disease have a 25% chance of focal neurologic dysfunction. Death rates from WEE and LAC are less than 5%.

PIE secondary to measles is associated with a mortality rate approaching 40% of cases, with a high rate of neurologic sequelae in survivors. SSPE is uniformly fatal, although the disease course may last anywhere from several weeks to 10 years.

VZVE has a mortality of 15% in immune-competent patients and virtually 100% in immune-suppressed patients. The mortality for EBV encephalitis is 8%, with substantial morbidity found in approximately 12% of survivors.

Rabies encephalitis and acute disseminated encephalitis are virtually 100% fatal, although there are rare survivors reported in the medical literature.

Encephalitis is inflammation of the brain. Severity is variable. Symptoms may include headache, fever, confusion, a stiff neck, and vomiting. Complications may include seizures, hallucinations, trouble speaking, memory problems, and problems with hearing.

Causes of encephalitis include viruses such as herpes simplex virus and rabies as well as bacteria, fungi, or parasites. Other causes include autoimmune diseases and certain medications. In many cases the cause remains unknown. Risk factors include a weak immune system. Diagnosis is typically based on symptoms and supported by blood tests, medical imaging, and analysis of cerebrospinal fluid.

Certain types are preventable with vaccines. Treatment may include antiviral medications (such as acyclovir), anticonvulsants, and corticosteroids. Treatment generally takes place in hospital. Some people require artificial respiration. Once the immediate problem is under control, rehabilitation may be required. In 2015, encephalitis was estimated to have affected 4.3 million people and resulted in 150,000 deaths worldwide [3].

Acute encephalitis syndrome (AES) is a serious public health problem in India. It is characterized as acute-onset of fever and a change in mental status (mental confusion, disorientation, delirium, or coma) and/or new-onset of seizures in a person of any age at any time of the year. The disease most commonly affects children and young adults and can lead to considerable morbidity and mortality.

Viruses are the main causative agents in AES cases, although other sources such as bacteria, fungus, parasites, spirochetes, chemicals, toxins and noninfectious agents have also been reported over the past few decades.

Japanese encephalitis virus (JEV) is the major cause of AES in India (ranging from 5%-35%).Herpes simplex virus, Influenza A virus, West Nile virus, Chandipura virus, mumps, measles, dengue, Parvovirus B4, enteroviruses, Epstein-Barr virus and scrub typhus, S. pneumoniae are the other causes of AES in sporadic and outbreak form in India. Nipah virus, Zika virus are also found as causative agents for AES. The etiology in a large number of AES cases still remains unidentified.

AES due to JEV was clinically diagnosed in India for the first time in 1955 in the southern State of Madras, now Tamil Nadu. During 2018, 10485 AES cases and 632 deaths were reported from 17 states to the National Vector Borne Diseases Control Programme (NVBDCP) in India, with a case fatality rate around 6 per cent. AES cases were reported mainly from Assam, Bihar, Jharkhand, Karnataka, Manipur,

Meghalaya, Tripura, Tamil Nadu, Uttar Pradesh [4].

Acute Encephalitis Syndrome (AES) has a very complex etiology. Causative agents of AES include a wide variety of viruses, bacteria, protozoa, fungi, and non- infectious agents. While Japanese encephalitis virus (JEV) is a leading cause of acute encephalitis syndrome in India (ranging from 5-35%), the etiology in a large number of cases however remains unidentified. In India during 2018, 15% of cases of AES were found positive for infection due to JEV.

Herpes simplex virus, Influenza A virus, West Nile virus, Chandipura virus, mumps, measles, dengue, Parvovirus B4, enteroviruses and scrub typhus, S. pneumoniae are the other causes of AES in sporadic and outbreak cases in India. In many cases, however, no etiological agent is determined. Tick-borne encephalitis virus – TBEV, Zika virus, Nipah virus are also found positive in AES cases.

Some are the zoonotic disease, that transmitted from animals to humans via mosquitoes (e.g. Japanese encephalitis virus, and West Nile virus) or ticks, (Tick-borne encephalitis virus), while for other flaviviruses humans are the natural hosts; these include dengue virus (DENV), and Zika virus (ZIKV).

Although AES cases other than JE continue to be reported throughout the year, there is an overall increase of total AES cases since the month of June, peak during July- August and decline in September- October.

The AES cases in Muzaffarpur, Bihar and adjoining litchi producing districts have been observed mostly during April to June particularly in children who are undernourished with a history of visiting litchi orchards. In 2014, a relationship between consumption of litchi and AES was postulated by National Centre for Disease Control, Delhi (along with Centre for Disease Control US) in acute encephalitis in children, in Muzaffarpur [5].

Hence based on above findings the present study was planned for Evaluation of Paediatric Cases Suffered from Acute encephalitis syndrome Admitted to DMCH.

Methodology

The present study was planned in Department of Pediatrics, Darbhanga Medical College and Hospital Darbhanga, Bihar. Total 20 cases of Acute Encephalopathy Syndrome were enrolled in the present study. After admission, detailed history was taken and management of fever, raised ICT and seizure were carried out simultaneously. Clinical examinations were done. Urgent supportive management, and blood samples were sent for different baseline biochemical tests. Blood and urine samples were sent for culture and sensitivity in all cases by maintaining proper aseptic technique. Neuroimaging and CSF analysis were performed in all cases of fever with altered sensorium.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Detailed systemic and neurological examination were done to identify the probable cause and to assess the severity of neurological damage. Baseline investigations were done as per protocol and special investigations like NS1 antigen, IgM antibody against dengue, scrub typhus, serum and CSF IgM for Japanese Encephalitis (JE) virus, CSF PCR for Herpes Simplex Virus (HSV) and Varicella Zoster Virus (VZV), Widal test, geneXpert for Tuberculosis (TB), HIV Elisa, HIV DNA PCR and neuroimaging were done as per facility available. Patients were managed symptomatically until a definite cause was identified and then treated accordingly.

Results & Discussion

Acute encephalitis is the clinical diagnosis of children with acute onset of symptoms and signs of inflammatory lesions in the brain. Changes in sensorium, seizures and upper motor neuron type of altered muscle tone point to cerebral dysfunction. Brain tissue would show the pathology, but at the bedside, inflammation is surmised from pleocytosis of the cerebrospinal fluid (CSF) to predominantly lymphocytes, since the aetiology is mostly non-pyogenic infection [1]. The clinical picture usually consists of a prodromal phase (one to three days) with fever, malaise and headache and an encephalitic phase with continued fever, decreasing level of consciousness, seizures, abnormal movements or paralysis. Signs of meningeal inflammation are absent or minimal. Many children may succumb, but others recover through a post-encephalitic phase, the fortunate ones more or less completely, but others with sequelae of cognitive deficiencies, muscle paralysis, abnormal movements, etc.

Acute encephalopathy and acute meningitis - pyogenic, tubercular, fungal or viral - are other examples of acute central nervous system (CNS) diseases due to infectious or non-infectious aetiologies that can and must be differentiated from acute encephalitis. In acute encephalopathy, brain pathology is non-inflammatory, often biochemical; hence, CSF shows no pleocytosis. Onset is often without prodromal phase and tends to be in the morning hours, the child having been well the previous evening. Changes in sensorium, seizures and upper motor neuron-type muscle tone abnormalities and abnormal movements point to cerebral dysfunction. Encephalopathy occurring in clusters is often conflated with acute encephalitis outbreak [7, 9]. Acute meningitis is diagnosed when the clinical presentation points to meningeal inflammation - with fever, headache, neck rigidity, positive Kernig and Brudzinski signs and high pleocytosis in CSF. In pyogenic meningitis, CSF cells are predominantly polymorphonuclear leucocytes, while in most others, these are predominantly lymphocytes. While viral meningitis is often self-limited, bacterial and fungal meningitis will progress to severe brain dysfunction and death, if left untreated. When features of encephalitis and meningitis co-exist, the disease is called meningoencephalitis [6].

Table 1: Demographic Details

Parameters	No. of Cases
Age	
Less than 1 year	3
1 – 3 years	2
3 – 7 years	10
7 – 10 years	5
Sex	
Male	14
Female	6
Locality	
Rural	16
Urban	4

Table 2: Clinical signs

Clinical Sign	No. of Cases
Speech disturbance	8
Cranial nerve involvement	14
Motor deficit	16
Cerebellar signs	5
Involuntary movements	6
Meningeal signs	18
Papilledema	10

Table 3: Death occurrence

In Days	No. of Death
Within 1 week	2
Within 2 weeks	1
Within 3 weeks	1
Total	4

The present study demonstrates that most of the cases of AES were from rural area and from low socio economic group and maximum patients were admitted in the post monsoon season that is in the months of September to November. The most common age group affected were 1-5 yrs, males. Most of the patients presented with fever with altered sensorium, seizures, vomiting, loose stools and breathlessness. These findings were consistent with studies by Bokade *et al*. [10], Dongol *et al*. [11], Bandyopadhyay *et al*. [12], Saumyen De *et al*. [13].

A history of fever or recent illness suggests an acute infectious etiology, but other disorders in which encephalopathy maybe preceded by a febrile illness must also be considered. These include acute disseminated encephalomyelitis, Reye's syndrome, and mitochondrial and other inborn errors of metabolism [14]. History of trauma, drug/toxin exposure, dog bite, past medical illnesses, and family history must be elicited. Past history of similar illness may indicate the presence of an underlying inborn error of metabolism. Encephalitis associated with gastrointestinal symptoms include infections with enteroviruses, rotavirus and human parechovirus. Encephalitis associated with respiratory illnesses may be due to influenza viruses, paramyxoviruses and the bacteria, Mycoplasma pneumoniae; those with influenza associated encephalopathy may, in addition, have associated myositis [15].

The general physical examination may provide helpful etiological clues. Presence of pallor may indicate cerebral malaria, or intracranial bleed. Icterus could indicate leptospirosis, hepatic encephalopathy, or cerebral malaria. Skin rashes are common in meningococcemia, dengue, measles, varicella, rickettsial diseases, arboviral diseases, and enteroviral encephalitis. Petechiae are seen in meningococcemia, dengue and viral hemorrhagic fevers. Parotid swelling and orchitis point towards mumps as etiology. Mumps encephalitis, may, however, occur without parotitis [16]. In a study of 137 patients with mumps meningitis, parotitis was detected only in 37% of patients [17]. Labial herpes in young children may point towards herpes simplex virus encephalitis [18].

The neurological examination is targeted to document the level and localization of brain dysfunction. It may also provide information about the potential causes. The level of consciousness must be recorded in the form of an objective scale, such as the Glasgow Coma Scale (GCS). A modified GCS should be used for infants and young children [19]. While the GCS allows efficient, standardized communication of a child's state, a more detailed description of the child's clinical findings is often more useful for relaying detailed information and detecting changes over time.

The AES cases had a seasonal distribution—beginning in the months of April and May and peaking in June. The cases started to decline from October. A similar pattern was seen in confirmed cases of JE. In India, Karnataka has been reported to have two epidemics each year, a severe form from April to July and a milder one from September to December along with the rest of India [20]. In Nepal, cases of AES and JE started a little earlier, in April–May, and reached a peak during late August to early September, and then declined [21]. Most previous studies too reported epidemics between May and October, and mostly from the northern and eastern parts of India [22]. In UP, the reported JE cases between 1998 and 2007 were sporadic in June and peaked in September before declining. Seasonal peaks of cases of JE have occurred during July to October, coinciding with the rainy and post-rainy seasons. The onset of winter brings a decline in the cases of JE. Saxena *et al*. studied the trend of AES cases and suggested that JE was increasing in northern India, which may result in larger epidemics in the future [23]. In Tamil Nadu, of 561 AES cases reported during a study, JE was confirmed in 4.9% with an increasing trend from 4.1% in 2007 to 5.3% in 2009 [24]. The minimum reported incidence in a tropical setting for all ages was 6.34 per 100 000 population [25]. Districts of Patna, Nalanda, Jehenabad, Nawada, Gaya, Aurangabad, Vaishali, Muzaffarpur, Sheohar and East Champaran had the maximum number of cases of AES cases with an annual incidence ranging from 4.7 to 24.8 per 100 000 population. Dinesh *et al*. [26] and Mishra *et al*. [27] have also reported a similar distribution of cases.

Conclusion

The data generated from the present study concludes that AES is a major illness affecting children of Bihar as well as other parts of country with significant morbidity and mortality. Its control is very important from public health aspect as it has significant impact on resources of state, nation and public exchequer. Most importantly, the chance of lifelong sequalae leaves scarring on the face of survivor, their family and society.

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