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Clinical Profile & Outcome of Viral Encephalitis in Pediatric Department in Government General Hospital, Guntur

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Abstract: ***Background: Encephalitis is an acute inflammatory process affecting the brain. Viral infection is the most common and important cause, with over 100 viruses implicated worldwide. Viral encephalitis is an important cause of mortality and morbidity in children. The etiological agents are varied, it may be sporadic like herpes simplex encephalitis (HSE) or epidemic such as Japanese B encephalitis (JE). Pediatricians who treat these children should be aware of when to suspect encephalitis, how to manage a child with suspected encephalitis, as specific antiviral therapy is lifesaving in some diseases like Herpes encephalitis and these should be diagnosed without delay. For some cases of encephalitis like JE, effective vaccine is available. Moreover, optimum supportive care is of paramount importance in the management of suspected encephalitis due to any etiology for optimum outcome in the affected children. There is no Indian data on the incidence of encephalitis due to various viral agents. There are numerous lacunae in our knowledge, problems in epidemiological investigations, lack of diagnostic facilities, as well as difficulties in managing these critically ill children in smaller centers in our country resulting in high mortality and morbidity with permanent neurological sequelae in the surviving children. Japanese encephalitis (JE) is the main cause of epidemic viral encephalitis in many countries of Asia including India with nearly 68 000 clinical cases every year. The disease in Southern India affects children below 15 yr of age whereas in Northern India, all age groups are affected. Although symptomatic JE is rare, the case-fatality rate among those with encephalitis can be as high as 30%. Permanent neurologic or psychiatric sequelae can occur in 30%–50% of those with encephalitis. There is no cure for the disease. Treatment is focused on relieving severe clinical signs and supporting the patient to overcome the infection. Safe and effective vaccines are available to prevent JE. WHO recommends JE vaccination in all regions where the disease is a recognised public health problem. Since there is no data available from our area regarding the incidence and severity of vaccine preventable cases of JE, inspite of several cases of encephalitis getting admitted every year, we undertook this observational study to determine the incidence, clinical features & severity of viral encephalitis and the contribution of JE to the burden of encephalitis in our region so that effective preventive steps by various strategies including vaccination for JE can be undertaken to control this devastating disease which is having a long lasting effect on the neuro-motor system of children in their formative years of growth & development. Materials and Methods: Type of Study: It was an observational hospital based study. Inclusion Criteria: All the children who were admitted in Pediatric ward, GGH/Guntur Over a period of 1 year with clinical features of fever, seizures, altered sensorium were included in the study. Exclusion Criteria: Cases which turned out to be positive for Bacterial / TB Meningoencephalitis, febrile seizures were excluded from study. Investigations: CSF analysis, Fundus examination, Monteux test, Chest X - ray, CT Brain, MRI Brain, EEG, Virological studies at VBRI, Hyderabad. Results: Total of 105 cases of viral encephalitis were studied which were admitted in the Pediatric Department, GGH/Guntur from October 2009 – January 2011. Out of 105 cases, 52.38 % were males and 47.62 % were females. Very few cases were seen in infancy, predominant age group being 05 – 08 yrs. Out of 105 cases, 75 cases were seen from the months of September – November (71.42%), youngest age being admitted was 6 months old child. Majority of cases were reported from rural areas accounting for 86.66 % of cases when compared to urban areas. Among presenting features, fever was present in all cases (100 %), altered sensorium and seizures were next common presenting features. CSF analysis was done in 90 cases, pleocytosis was seen in 75.58 %, elevated protein levels was seen in 70.93% and globulins was positive in 11.42 %. CT Brain was done in all cases which was reported normal except for 12 cases which showed diffuse cerebral oedema. MRI Brain showed bilateral thalamic hyper intensities in T2 weighted images in 10 cases, out of which two cases were also sero-positive for Japanese Encephalitis. Two cases showed temporal lobe involvement characteristic of herpes encephalitis. Conclusions & Recommendations: Vulnerable areas for viral encephalitis in our district especially for epidemic cases of JE, the predominant age groups affected with viral encephalitis, most common season for occurrence of viral encephalitis due to JE epidemics and the predominant clinical features of suspected viral encephalitis were determined and these would be an aid to pediatricians in the evaluation and management of children with suspected viral encephalitis admitted in the hospital and assist the public health authorities in acute encephalitis surveillance so that appropriate steps can be undertaken to minimize the burden of this neurological disease in the vulnerable pediatric population.***

Keywords: Japanese Encephalitis, Mosquito borne, Thalamic infarcts Acyclovir, JE vaccine

1. Introduction

Viral encephalitis is an important cause of mortality and morbidity in children. The etiological agents are varied,It may be sporadic like herpes simplex encephalitis (HSE), or epidemic such as Japanese B encephalitis (JE). Japanese encephalitis (JE) is the most important cause of epidemic cases of viral encephalitis in Asia for which effective vaccine is available. It is a mosquito-borne flavivirus related to dengue, yellow fever and West Nile viruses. The first case of JE was documented in 1871 in Japan.The annual incidence of clinical disease varies both across and within countries, ranging from <10 to >100 per 100 000 population. A recent literature review estimates nearly 68 000 clinical cases of JE globally each year, with up to 20 400 deaths due to JE (Bulletin of WHO, October 2011). JE primarily affects children. Most adults in endemic countries have natural immunity after childhood infection, but individuals of any age may be affected. 24 countries in the WHO South-East Asia and Western Pacific regions have endemic JE transmission, exposing more than 3 billion people to risks of infection. JE was 1st recognized in India in 1955 when cases of encephalitis from North Arcot Districts of TN and neighbouring districts of AP admitted in CMC Vellore were

serologically diagnosed as JE. Since 1972, JE has spread to newer areas and now epidemics of JE have been reported from several states in India. The spread of JE in new areas has been correlated with agricultural development and intensive rice cultivation supported by irrigation programmes.JE is transmitted to humans through bites from infected mosquitoes of the *Culex*species (mainly *Culextritaeniorhynchus*). The virus exists in a transmission cycle between mosquitoes, pigs and/or water birds (enzootic cycle). The disease is predominantly found in rural and peri-urban settings, where humans live in closer proximity to these vertebrate hosts. Major outbreaks of JE occur every 2-15 years. In most temperate areas of Asia, the Japanese Encephalitis Virus (JEV) is transmitted mainly during the warm season, when large epidemics can occur. In the tropics and subtropics, transmission can occur year-round but often intensifies during the rainy season and pre-harvest period in rice-cultivating regions during which vector populations increase.

Most JE virus infections are mild (fever and headache) or without apparent symptoms, but approximately 1 in 250 infections results in severe disease characterized by rapid onset of high fever, headache, neck stiffness, disorientation, coma, seizures, spastic paralysis and death. The clinical disease can be divided into 3 stages: the prodromal febrile stage, acute encephalitic stage marked by CNS involvement and continuing fever, late stage marked by either recovery or persistent symptoms of irreversible neuronal injury leading to transient or permanent sequelae. Although symptomatic JE is rare, the case-fatality rate among those with encephalitis can be as high as 30%. Permanent neurologic or psychiatric sequelae can occur in 30%–50% of those with encephalitis. There is no cure for the disease. Treatment is focused on relieving severe clinical signs and supporting the patient to overcome the infection. Safe and effective vaccines are available to prevent JE. WHO recommends having strong prevention and control activities, including JE immunization in all regions where the disease is a recognized public health problem, along with strengthening surveillance and reporting mechanisms. Individuals who live in or have travelled to a JE-endemic area and experience encephalitis are considered a suspected JE case. To confirm JE infection and to rule out other causes of encephalitis requires a laboratory testing of serum or preferentially cerebrospinal fluid and efforts are undertaken to expand laboratory-based surveillance. In view of large number of Viral Encephalitis cases being admitted in our hospital every year and known endemicity of JE with yearly epidemics occurring in several parts of our state, we undertook this observational study with an aim to know the incidence &etiology of Viral Encephalitis focusing on total number of JE patients out of all encephalitis cases, in relation to age, sex, geographical distribution and seasonal variation, to study the clinical manifestations and to know the mortality, morbidity, neurological sequelae so that necessary recommendations can be made to the public health authorities for controlling this deadly disease especially the JE cases through vaccine introduction and large-scale JE vaccination campaigns.

2. Materials and Methods

Type of Study: It was an observational hospital based study. *Inclusion Criteria:* All the children who wereadmitted in the Pediatric ward over a period of one year with clinical features of fever, seizures, altered sensorium were included in the study. *Exclusion Criteria*: Cases which turned out to be positive for Bacterial / TB meningoencephalitis, febrile seizures were excluded from study. *Investigations* : CSF analysis, Fundus examination, Monteux test, Chest X - ray, CT Brain, MRI Brain, EEG, Virological studies at VBRI, Hyderabad.

3. Results

Out of 105 encephalitis cases, peak incidence was from September – December. Following table shows the distribution of cases in relation to various months of year.

Table 1

Month	*Number Of Cases*	*Percentage*
August	5	4.76
September	31	29.52
October	25	23.80
November	19	18.09
December	10	9.52
January	4	3.80
Remaining months	11	10.47

Out of 105 cases, 75 cases were seen from the months of September – November (71.42%), youngest age being admitted was 6 months old child. Following table shows the age distribution cases.

Table 2

Age (In Years)	Number Of Cases	Percentage
00 – 04	28	17.14
05 – 08	44	41.9
09 – 12	33	31.4

Sex Predilection: Out of 105 cases, 52.38 % were males and 47.62 % were females. Following table shows the area wise distribution of cases.

Table 3

Area	Number Of Cases	Percentage
Rural	91	86.66
Urban	14	13.66

Following table shows the distribution of cases as per presenting features in relation to various age groups.

Table 4

Presenting Feature	*Age Groups (in years)*			*Total*
	00 – 04	05 – 08	09 -12	
Fever	28 (17.14%)	44 (41.9%)	33 (31.42%)	105 (100 %)
Headache	8 (7.6%)	35 (33.33%)	29 (27.61%)	72 (68.57%)
Vomiting	6 (5.7%)	25 (23.8%)	20 (19.04%)	51 (68.57%)
Altered sensorium	27 (25.71%)	41 (39.04%)	30 (28.51 %)	98 (93.33%)
Seizures	24 (22.85%)	38 (36.19%)	23 (21.90%)	85 (80.95%)

Following table shows the details of clinical signs.

Table 5

Clinical Sign	*Number of Cases*	*Percentage*
Speech disturbance	10	9.52
Cranial nerve involvement	18	17.14
Motor deficit	38	36.19
Cerebellar signs	4	3.80
Involuntary movements	8	7.61
Meningeal signs	81	77.14
Papilledema	14	13.33

Following table shows thenumber of deaths in relation to duration of onset of symptoms.

Table 6

Days	*Number Of Cases Died*	*Percentage*
01 – 07	17	53.13
08 -14	9	28.13
15 – 26	6	18.75

Following table shows the mortality incidence in accordance with age.

Table 7

Age	*Total Cases*	*Number Of Cases Died*	*Percentage*
00 – 04 yrs	28	9	8.57
05 – 08 yrs	44	16	15.23
09 – 12 yrs	33	7	6.67

4. Discussion

Viral encephalitis is an important cause of mortality and morbidity in children. Viral agents responsible for sporadic encephalitis include Varicella zoster virus, Mumps, Human herpes virus 6 and 7, Epstein Barr virus, and most importantly, *Herpes simplex* virus. Herpse simplex virus encephalitis (HSE) is the most common cause of sporadic fatal viral encephalitis, with an incidence of 1-3/million in western countries [1]. Not much information is available regarding proportion of AES cases due to HSE in the Indian setting. In untreated patients, mortality is high (70%), which is decreased to 30% in treated patients in a timely manner with the antiviral drug Acyclovir (risk of sequelae of around 11%) [2].

Acute encephalitis syndrome (AES) is a term used by WHO for syndromic surveillance in the context of Japanese encephalitis (JE) [3]. Acute Encephalitis Syndrome is defined **c**linically as a person of any age, at any time of year with the acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma, or inability to talk) AND/OR new onset of seizures (excluding simple febrile seizures).Acute encephalitis syndrome is a medical and neurological emergency, requiring immediate consideration of key issues including immediate life support, identification of cause, and when available, institution of specific therapy.

Japanese encephalitis (JE) is the most important cause of epidemic cases of viral encephalitis in Asia. Approximately 3 billion people and 60 per cent of the world population live in JE-endemic regions, and there are approximately 50,000 cases and 15,000 deaths per annum notified from wide geographical range (4-6). Increase in population density, deforestation and increase in irrigation of agricultural areas may contribute to the rise in JE incidence[7]. The disease was 1st recognized in Southern India in 1955. Since 1972, JE has spread to newer areas. The disease in Southern India affects children below 15 yr of age whereas in Northern India, all age groups are affected. World studies report the mortality due to JE ranging from 23 to 36 per cent and 18 per cent of cases end up with complications[8,9]. Some studies say that infection may also result in residual sequelae in 30-60 per cent of the cases[9].In the absence of specific antiviral therapy, JE is managed by symptomatic and supportive therapies and preventive measures. Purified formalin inactivated mouse brain derived vaccine and live attenuated vaccine (SA 14-14-2) are available; the latter is reported to be safe, effective and cheap.

In our study, we tried to know the incidence &etiology of Viral Encephalitis, its relation to age, sex, geographical distribution and seasonal variation, the clinical manifestations and tried to look at the mortality, morbidity and neurological sequelae to make the necessary recommendations to the public health authorities. We also tried to find out the JE positivity among the clinical acute encephalitis syndrome (AES) cases referred to our centerbasesd on serology and imaging studies and looked at other details like rural vs urban predominance, duration of hospital stay and clinical outcome with respect to timing of presentation to the hospital and duration of stay in the hospital.

This data would be useful to pediatrician in the evaluation and management of children with suspected viral encephalitis admitted in the hospital and assist the public health authorities in acute encephalitis surveillance to formulate a policy in our region to minimize the burden of this devastating neurological disease in the high risk pediatric population through effective preventive measures.

Most of the encephalitis cases in our study were referred from nearby districts especially from the rural areas. Cases reported from rural areas accounting to 86.66 % when compared to urban areas. In our study, males were predominantly affected than the females. Out of 105 cases, 52.38 % were males and 47.62 % were females. The major burden of JE in many studies is observed in children. In our study, only few cases were seen in age group 00 – 01 yr, predominant age group affected being 05 – 08 yrs. Majority of the cases were reported soon after monsoon*i.e.* during August September, October, November and December months. Upsurge of cases during the rainy season (monsoon) has been shown earlier[17]. Out of 105 cases, 75 cases were seen from the months of September – November (71.42%), youngest age being admitted was 6 months old child. Cases started to appear in the month of August and peaked during September, October, November, December months and started to decline from January i.e coinciding with the end of harvest season.

Symptomatic JEV infection manifests with nonspecific febrile illness, aseptic meningitis or encephalitis. Encephalitis manifests with altered sensorium, seizures and focal neurological deficit. Acute flaccid paralysis may occur

due to anterior horn cell involvement. A wide variety of movement disorders especially transient Parkinsonian features and dystonia (limb, axial, orofacial) are reported in 20-60% patients. JE mainly affects thalamus, corpus striatum, brainstem and spinal cord as revealed by MRI and on autopsy studies. Among presenting features in our study, fever was present in all cases (100 %), altered sensorium and seizures were next presenting features. Motor deficit was seen in majority of our cases, the other presentations being cranial nerve involvement, speech disturbance, cerebellar signs and involuntary movements. 22 cases out of 105 encephalitis cases expired (20.95% mortality). World studies also show high mortality in viral encephalitis with the mortality due to JE ranging from 23 to 36 per cent and 18 per cent of cases end up with complications[8,9].

Diagnosis of JE depends on a high degree of clinical suspicion and confirmation by serology or culture. CSF analysis, CT and MRI also play an important role[4]. Laboratory diagnosis of JE is by IgM capture ELISA, which has high sensitivity and specificity. In our study, CSF analysis was done in 90 cases. Among those cases pleocytosis was seen in 75.58 %, elevated protein levels was seen in 70.93 % and globulin was positive in 11.42 %. CT Brain was done in all cases which showed normal except for 12 cases which showed diffuse cerebral oedema. MRI Brain was done which showed bilateral thalamic hyper intensities in T2 weighted image in 10 cases, out of which two cases were also sero positive for Japanese Encephalitis. 2 cases showed temporal lobe involvement characteristic of herpes encephalitis. When all the sera were analyzed at VBRI, Hyderabad, it was seen that only 2 cases were positive for Japanese Encephalitis.

As per WHO criteria **Laboratory-confirmed JE is defined as a** suspected case that has been laboratory-confirmed as JE [2]. **Probable JE is defined as a** suspected case that occurs in close geographic and temporal relationship to a laboratory-confirmed case of JE, in the context of an outbreak. Hence, among the encephalitis cases in our centre, we presumed JE to be more common than HSV. It was suspected based on seasonal occurance of cases, clustering of cases in a particular region and positive findings on imaging studies pointing towards JE than HSV. Of the 105 suspected viral encephalitis cases admitted during the study period, JE was confirmed with positive serology in only 2 cases. A positive MAC ELISA in CSF or serum is the accepted standard for diagnosis as JEV infection[12,13]. JE was confirmed in our study when either IgM was positive in serum or CSF or in both. In a study in Nepal, JEV positivity of 17.7 per cent was noted[1]. Rayamajhi *et al*[14,15] found 61.7 per cent of laboratory confirmed JE cases in one study and 86.2 per cent cases in another study. Akiba *et al*[16] had found laboratory confirmed JE in 78 per cent of cases.

Japanese encephalitis (JE)-epidemics have been reported in many parts of our country. The incidence of JE in recent times is showing an increasing trend. It appears that JE may become one of the major public health problems in India, considering the quantum of the vulnerable pediatric population, the proportion of JEV infections among the encephalitic children and wide scattering of JE-prone areas. Japanese encephalitis is considered as a serious disease due to the complexity of the disease and lack of specific treatment. In India, the actual JE burden could be estimated only by strengthening diagnostic facilities for JE confirmation in hospitals. However, the available records at present indicate a rising trend in JE- occurrence and expansion of the disease into JE non-endemic areas, which cannot be ignored. In our study, the incidence of JE among the suspected viral encephalitis cases has been shown to be high among paediatric group with high mortality. However, the number of confirmed positive cases was much less in our study probably due to improper response to the details of sample collection. Many problems were encountered by us in the management of children with suspected Viral Encephalitis, the most important among these were delay in informing the higher authorities, lack of easily available, low-cost microbiological testing for agents of viral encephalitis, delayed response in taking proper samples, storing & timely transport of samples. Virus isolation, even at the best of the laboratory facilities is tedious and the methods for collection, storage and transport of the samples and the precautions taken during sample collection influences the test reports to a large extent. Clotted blood sample should be taken and serum should be separated after clot retraction. Samples should be collected within 4 days after the onset of illness for isolation of virus and at least 5 days after the onset of illness for detection of IgM antibodies. A second, convalescent sample should be collected at least 10-14 days after the first sample for serology Serum should be shipped on wet ice within 48 hours or stored at for a maximum period of 7 days. In case a delay is anticipated, sera must be frozen at -20°C and should be transported to the specified laboratory on frozen ice packs. Repeated freezing and thawing can have detrimental effects on the stability of IgM antibodies. CSF sample may be stored at +4°C if delays in processing for virus culture or viral PCR will be less than 24 hrs. If greater delays are likely, CSF should be frozen at -80°C. Serum and CSF samples from all our AES cases were sent to VBRI, Hyderabad, implicating the time, method of sample collection or storage of sample could be vital factors influencing the test results with less number of cases with positive serological diagnosis in our study.

The JE cases in our study were mostly from nearby rural areas of neighbouring districts of Andhra Pradesh where JE is found to be endemic with a gradual increase in the positivity of JE cases. JE vaccination has proven to be effective in the control and prevention of JE worldwide and this has been already undertaken in phases in Andhra Pradesh. A secular trend towards declining of JE has been brought in China, Korea, and Japan with widespread use of JE vaccine. Since it is the paediatric population which is highly implicated with high mortality and morbidity in JE, augmenting the current vaccination programme throughout the country can control the infection[5,16]. However, to prevent the disease, public health measures such as vector control, widespread usage of mosquito nets, protective clothing and effective surveillance is necessary. WHO also recommendsto have strong prevention and control activities, including JE immunization in all regions where the disease is a recognized public health problem, along with strengthening surveillance and reporting mechanisms.

5. Conclusions &Recommendations for Public Health Authorities

Viral encephalitis is an important cause of mortality and morbidity in children. Japanese encephalitis (JE)-epidemics have been reported in many parts of our country. The incidence of JE in recent times is showing an increasing trend. It appears that JE may become one of the major public health problems in India, considering the quantum of the vulnerable paediatric population, the proportion of JEV infections among the encephalitic children and wide scattering of JE-prone areas and expansion of the disease into JE non-endemic areas, which cannot be ignored.

In our study, vulnerable areas for viral encephalitis especially JE, the predominant age groups affected, most common season for occurrence of majority of JE cases in the district and their clinical features were determined and intimated to the concerned authorities.Since JE cases are much more compared to encephalitis due to Herpes virus in our region and as the majority of cases were occurring from the month of September, we highly recommend anti mosquito and anti-larval measures from June itself. Preventive measures like vaccination to Japanese Encephalitis should be taken on a priority basis in high risk groups.

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