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Unsolved mystery of amplifier host as a cause of Japanese Encephalitis in Acute Encephalitis Syndrome cases: Need to implement testing protocol including simultaneous testing of viral RNA, viral IgG and IgM antibodies in the amplifier host sera.

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Abstract

Clinically diagnosed cases of Acute Encephalitis Syndrome (AES) in the paediatric age group were reported by DMO, Mayurbhanj in September, 2015 . DMET, Odisha deputed a STF Team to district Mayurbhanj to undertake detailed investigation. Out of the 6 blood samples , 3 samples (I indoor patient and 2 random samples collected from children in contact with the positive cases in village) were positive for JE IgM through Bios ELISA kit. The team suggested remedial actions on containment, preventive measures to be initiated at field level and followed up the effect of coordinated and prompt steps taken by the government. 56 serum samples of the animal hosts (pigs) were found to be negative by Japanese Encephalitis (JE) (IgM) Capture ELISA for JE infection. After initiation of vector control measures like IRS and Fogging , use of mosquito nets and JE vaccination in 2017 in the affected villages, except for only one positive case reported at RMRC, BBSR, no further case of JE has been reported till date. As the mystery of amplifier host remains unsolved, there is a need to implement simultaneous testing of viral RNA, viral IgG antibody and viral IgM antibody in the sera of suspected amplifier host.

Keywords- JE; AES; JE vaccination; animal host –pigs; simultaneous testing of viral RNA, viral IgG and IgM antibodies

Introduction

Acute Encephalitis Syndrome (AES) is defined as 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) in a person of any age at any time of year (1).

AES can result due to infections with either viruses, bacteria, fungus, parasites, spirochetes or chemical/ toxins etc (2). Amongst these etiologies, Japanese Encephalitis (JE) over the years has emerged as one of the major public health problems in the country (3).

Viral encephalitis including JE presents with clinically similar neurologic manifestations including a prodrome of fever, headache, nausea, diarrhoea, vomiting, and myalgia lasting for few days (1-5 days), followed by irritability, altered behaviour, convulsions and coma. The progression of disease is rapid. Signs of raised intra cranial tension are commonly present in acute stage of illness. The patient may develop difficulty of speech and other neurological deficits like ocular palsies, hemiplegia, quadriplegia and extrapyramidal signs in the form of dystonia,

choreoathetosis and coarse tremors (2). Specific anti-viral drug for AES including Japanese Encephalitis is not available till date and cases are managed symptomatically. Directorate of NVBDCP have issued a set of technical operational guidelines to be used by all the personnel engaged in Prevention and Control of JE/AES.(2)

AES including JE are reported mainly from Assam, Bihar, Karnataka, Tamil Nadu and Uttar Pradesh. These states contributes approximately 80% of cases and deaths respectively with a case fatality rate ranging from 20 to 25%.(2). In Odisha, a state in eastern India, only one outbreak of JE was reported from Rourkela city of Sundergarh district in 1989. Since then, sporadic cases of JE have been diagnosed in hospitalized children from 1992 to 1995. Thereafter, in 2012, JEV infection was reported from Malkangiri district of Odisha after two decades of last report (4, 5,6,7) . In 2014, a sharp increase in the number of JE cases were observed in Assam, and in the same year , 51% of the total JE cases from India were reported from the Assam itself (8).

JE vaccination was introduced in India, in 2006, following large outbreaks of JE in some districts of Eastern UP and Bihar. Since then, many vaccination campaigns have been carried out in high risk districts of the country (10). Live attenuated SA-14-14-2 vaccine against Japanese encephalitis (JE) was introduced in the routine immunization under Universal Immunization Program in the 181 endemic districts of India. Recently, the Government of India has announced the introduction of one dose of JE vaccine for adults in endemic districts. The policy to mass vaccinate adults has raised several concerns. There is lack of authentic data on effectiveness of currently employed SA-14-14-2 JE vaccine.

In September, 2015 , clinically diagnosed cases of AES in the paediatric age group were reported by DMO, Mayurbhanj. Out of the 12 admitted cases in the IPD , DHH , four cases died , while others recovered. RMRC virology and entomology team investigated the AES cases in Mayurbhanj district by testing serum/ CSF for JE and got the positive cases confirmed at NIV, Pune. Subsequently as per the request of Director of Public Health, the DMET, Odisha deputed a STF Team to district Mayurbhanj to undertake detailed investigation and suggest remedial actions on containment and preventive measures to be initiated at field level for better case management and to follow up the effect of coordinated and prompt steps taken by the government .

Material and Methods

The STF team reported to CDMO, Baripada on 20.10.15, visited the DHH, DPMU, IDSP cell , NVBD cell to collect data. During the visit the team members interacted with CDMO and Addl Director, Paediatric Specialist(DHH), Program Managers of DPMU, IDSP and NVBD cell, Incharge staff nurse of paediatric ward, 3 indoor paediatric patients with symptoms suggestive of AES , villagers, ASHA, and AWW. The STF team then proceeded to the 2 affected villages in Kosta block (one village with patient discharged from DHH and other village with a child death within 10 days. During the visit, the STF team interacted with the family members of affected patients in the affected villages, PHEO and MO incharge of CHC, Kosta block of Baripada. Information regarding presence of mosquitoes, animal hosts(pigs and ducks) in the affected villages and measures initiated by the District Health Authorities in coordination with Block Health Authority was gathered. During this visit, 6 blood samples (2 from patients admitted in DHH , Mayurbhanj with suspected AES and 4 from field collection) was sent to RMRC through district authority for testing of JE IgM through Bios ELISA kit (In Bios International , USA). A detailed report along with suggestions on preventive and remedial measures was submitted to the government. As per the suggestion given in the report to the government , and subsequent steps taken by the Government of Odisha, the

veterinary department sent 56 serum samples of the animal hosts(pigs) to NIV Pune on 28.10.2015 to test for Japanese Encephalitis (JE) antibody . Subsequently, the results of these tests, further steps taken by the government and the net result of measures initiated by the District Health Authorities in coordination with Block Health Authority was obtained from the DMO, Mayurbhanj .

Results

During the field visit of the affected villages in Kosta block (one village with patient discharged from DHH and other village with a child death within 10 days), it was found that one of the discharged patients was having residual neurological deficit. During interaction with the villagers, it was found that increased mosquito population was felt by the villagers following rainy season. There was presence of animal hosts (pigs and ducks) in the affected villages . As per the results of the investigations obtained from DMO, Mayurbhanj, out of the 6 blood samples collected, and sent to RMRC through district authority for testing of JE IgM through Bios ELISA kit , 3 samples (I indoor patient and 2 random samples collected from children in contact with the positive cases in village) were positive for JE IgM (chart 1). All the 56 serum samples of pigs were found to be negative for JE infection by Japanese Encephalitis (JE) (IgM) Capture ELISA (table 1).

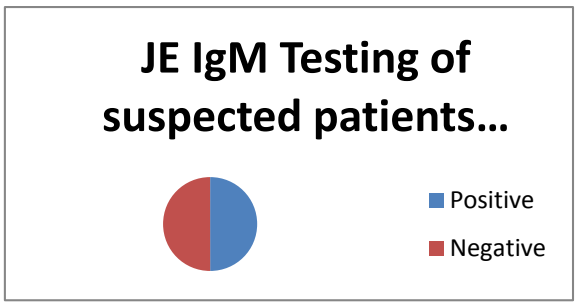

Chart 1: Testing of JE IgM through Bios ELISA kit , 3 samples (I indoor patient and 2 random samples collected from children in contact with the positive cases in village) were positive for JE IgM.

Table 1 : Animal (Pig) sera tested for JE by (IgM) Capture ELISA

Result of JE (IgM) Capture ELISA	No of samples
Positive	0
Negative	56
Total	56

Public health measures was initiated by the District Health Authorities in coordination with Block Health Authority. Vector control measures like IRS and Fogging was done in the affected villages in response to confirmation of JE case and death. Households having mosquito nets in the affected villages got them treated with insecticide. Awareness was created regarding mosquito control and use of bed nets in these villages. After mass vaccination against JE in 2017, only one positive case in serum was reported at RMRC, BBSR. No further case has been reported till date.

Discussion

Clinically diagnosed cases of AES in the paediatric age group were reported by DMO, Mayurbhanj in September, 2015. DMET, Odisha deputed a STF Team to district Mayurbhanj to undertake detailed investigation. The STF team reported to CDMO, Baripada and interacted with the key stakeholders and then proceeded to the 2 affected villages and collected blood samples from suspected JE cases and their close contacts . Out of the 6 blood samples , 3 samples (I indoor patient and 2 random samples collected from children in contact with the JE positive cases in village) were positive for JE IgM through Bios ELISA kit. The asymptomatic contact with serological tests positive for (IgM) JE can be explained by the fact that most human infections are asymptomatic or result in only mild symptoms. Only, a small percentage of infected

persons develop inflammation of the brain (encephalitis), with symptoms ranging from sudden onset of headache, high fever, disorientation, coma, tremors, convulsions and about 1 in 4 cases are fatal(9) .

56 serum samples of the animal hosts(pigs) were found to be negative for JE infection by Japanese Encephalitis (JE) (IgM) Capture ELISA. This can be due to several reasons. One reason may be that JE , a mosquito borne zoonotic viral disease, is maintained in animals, birds and pigs. Birds particularly belonging to the family Ardeidae (eg. Cattle egrets, pond herons etc) act as the natural hosts. In the transmission cycle, pigs & wild birds act as the reservoirs of infection and are also called as amplifier hosts. Man and horse are dead end hosts .The virus does not cause any disease among its natural hosts and thus they remain asymptomatic of JE infection. JE is transmitted to a healthy person through the bite of vector culex vishunii that after biting an infected host bites a healthy person after an incubation period ranging from 5 to 14 days (11). According to the guidelines, as the pigs are amplifying host for JE virus, thus ,monitoring of IgM antibody titre in 5-8 months old piglets helps in determining viral activity. Since there was a presence of ducks also, they could have been the natural host /amplifier host but their sera was not tested.

The other reason for the sera testing negative for IgM antibody for JE could be the fact that since the natural course of any viral infection is characterized by the appearance of the following markers in chronological sequence- viral RNA/ DNA, viral antigens and subsequently viral antibodies. Thus assays meant to detect IgM antibodies, may miss detecting the infections before seroconversion i.e. in the “window period” and also when tested after disappearance of IgM from the sera (12). Since in this case , all the 56 serum samples of pigs were found to be negative for JE infection by Japanese Encephalitis (JE) (IgM) Capture ELISA, there is a need to implement testing protocol including simultaneous testing of viral RNA, viral IgG and IgM antibodies in the amplifier host sera.

The team suggested remedial actions on containment, preventive measures to be initiated at field level and followed up the effect of coordinated and prompt steps taken by the government. After initiating vector control measures like IRS and Fogging , use of mosquito nets and after JE vaccination in 2017 in the affected villages, only one positive case in serum has been reported at RMRC, BBSR. No further case has been reported till date.

Strength of the study

AES including JE are reported mainly from Assam, Bihar, Karnataka, Tamil Nadu and Uttar Pradesh. These states contributes approximately 80% of cases and deaths respectively with a case fatality rate ranging from 20 to 25%.(2). To the best of our knowledge very few studies have been done especially in Odisha to evaluate the net result of measures initiated by the Health Authorities and follow up status especially after the introduction of JE vaccine. In this context, the current study becomes highly relevant as it gives a platform to analyze the results of the tests done on suspected amplifier host , and the net result of measures initiated by the District Health Authorities in coordination with Block Health Authority as obtained from the DMO, Mayurbhanj, Odisha.

Limitation of the study

All the 56 serum samples of pigs were tested for JE infection by Japanese Encephalitis (JE) by (IgM) Capture ELISA. The testing protocol did not include testing of viral RNA, viral IgG in the pig sera.

Future research implicated

Despite all the preventive and remedial actions taken, the mystery of the amplifier host could not be solved. All the 56 serum samples of pigs were tested for JE infection by Japanese Encephalitis (JE) by (IgM) Capture ELISA. The testing protocol did not include testing of viral RNA,

viral IgG in the pig sera. In order to be better equipped to prevent future JE outbreaks, further studies are needed and the testing protocol should include simultaneous testing of viral RNA, viral IgM and viral IgG in the amplifier host sera.

Author's contribution

Dr Nidhi Prasad was the principal investigator and the main author of this article .

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Conflicts of interest

There were no conflicts of interest

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