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Case Series

Acute encephalitis syndrome with the cause hidden in plain sight – A case series

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ABSTRACT

Acute encephalitis syndrome (AES) is one of the important life-threatening presentations in children with a case fatality rate of 12.6%. The most common etiology in India is viral encephalitis. However, one of the emerging yet treatable causes is scrub typhus, which is endemic in many parts of India including Tamil Nadu and Puducherry. It is a vector borne disease which has myriad presentations, one among those being AES. This is a case series of four such cases noted over the first 6 months of 2022. All the patients presented with symptoms of fever and alteration of sensorium without any seizures. Examination revealed generalized lymphadenopathy, hepatosplenomegaly, and abnormal central nervous system findings. A thorough examination revealed the classical eschar in all the cases. Based on the examination findings, oral doxycycline was started in all the patients along with supportive treatment while awaiting results, which later revealed to be scrub ELISA positive. After 48 h, due to inadequate defervescence and improvement in sensorium, IV azithromycin was added in two patients and oral doxycycline was changed to injectable in other two patients. All of them recovered without any complications or sequelae. Early identification and initiation of appropriate antibiotics are essential for a positive outcome. In endemic areas, children with AES should be thoroughly examined for signs of scrub typhus including eschar. In our patients, parenteral doxycycline or azithromycin was found to be more effective than oral doxycycline in resolution of fever and neurological abnormalities. If AES is suspected to be due to scrub typhus, parenteral therapy may be preferred over oral.

Keywords: Scrub meningoencephalitis, Acute encephalitis syndrome, Acute encephalitis in children, Scrub typhus complications, Central nervous system infections

INTRODUCTION

Acute encephalitis syndrome (AES) is an acute neurological dysfunction and is one of the important causes of intensive care unit admission in children. With a case fatality ratio of 12.6%, it is a common cause of mortality or morbidity in the form of neurological sequelae. It may be caused by various microorganisms including viruses, bacteria, protozoa, and mycobacteria. In India, the most common etiological agents are viruses, Japanese encephalitis (JE), and Herpes virus.[1] One of the emerging causes is scrub typhus, due to increased urbanization and deforestation of rural areas.[2] The significance of identifying the cause of AES as scrub typhus is more as there is specific treatment available in the form of antibiotics.

Scrub typhus is a rickettsial infection caused by arthropod-borne, Gram-negative, obligately intracellular bacillus – *Orientia tsutsugamushi*. It is a febrile disease characterized by focal or disseminated vasculitis and perivasculitis with a wide clinical spectrum ranging from fever of unknown origin to multiorgan dysfunction syndrome (MODS) secondary to diffuse vasculitis.

Outbreaks of scrub typhus are usually seen after the monsoon season and it is endemic in many parts of southeast and south Asia. Usually, scrub typhus presents with fever, headache, hepatosplenomegaly, lymphadenopathy, and the classic inoculation eschar. Complications may be seen in the form of myocarditis, pneumonia, acute kidney injury, liver enzyme derangement, shock, and meningo-encephalitis.[3]

Incidence of AES following scrub infection is 13.6%.[2] The neurological involvement is usually in the form of meningitis or encephalitis and may present with alteration in sensorium, seizures, and meningeal signs with less likelihood of focal deficits. The findings in cerebrospinal fluid (CSF) and neuroimaging are non-specific.[4] Serological identification using IgM ELISA aids in the diagnosis of scrub typhus.

This case series highlights the importance of maintaining a high index of suspicion of the possibility of scrub typhus as a cause of AES, and early initiation of treatment. In all the four cases, thorough examination revealed an eschar and oral doxycycline was started presumptively. All the patients recovered without any sequelae.

CASE SERIES

Case 1

A 9-year-old boy presented with complaints of fever and abdomen pain for 3 days and vomiting for 2 days. On examination, child was febrile, with the right axillary lymphadenopathy, hepatomegaly, and an eschar in the right axilla. Central nervous system (CNS) findings included altered sensorium without focal deficit or meningeal signs.

On investigating, complete blood counts (CBC) showed leucopenia and thrombocytopenia with elevated liver enzymes. Dengue serology and scrub typhus ELISA were sent, out of which scrub ELISA came positive. In view of poor sensorium, lumbar puncture was done and the CSF analyzed was found to have pleocytosis with normal sugar and protein levels. Neuroimaging done was normal.

The child was treated empirically with oral doxycycline for 3 days, but persisted to have altered sensorium and fever spikes. Hence, IV azithromycin was given, but the child developed allergic reaction so was changed to IV doxycycline which was given for 5 days. The child improved symptomatically and was discharged. On follow-up, the child had completely recovered without sequelae.

Case 2

A 5-year-old boy was brought with complaints of fever, cough, and cold for 4 days, facial puffiness and abdomen distention for 1 day. On examination, the child was febrile with altered sensorium, facial puffiness, generalized lymphadenopathy, and hepatomegaly. Eschar was noticed in the scrotum. No focal deficit or meningeal signs were noted.

On investigation, CBC showed thrombocytopenia with normal counts. Liver enzymes were elevated. Scrub typhus ELISA was reactive. Lumbar puncture was done due to poor sensorium and CSF showed lymphocytic pleocytosis.

The child was treated initially with oral doxycycline, then changed to parenteral azithromycin after 2 days as he persisted to have high grade fever and poor sensorium. On day 2 of IV antibiotic, the child improved symptomatically and was discharged without any sequelae after completing 7-day course.

Case 3

A 5-year-old female child was brought with complaints of fever and vomiting for 3 days. On examination, the child was febrile with altered sensorium, facial puffiness, generalized lymphadenopathy, hepatosplenomegaly, and an eschar in axilla.

On investigation, CBC showed leucopenia with thrombocytopenia. CSF analysis showed pleocytosis. As child's sensorium was persistently poor, neuroimaging was done which was normal. The child was initially started on oral doxycycline. However, as the child persisted to have fever spikes and poor sensorium, antibiotics were changed to parenteral azithromycin for 5 days. The child responded well and improved symptomatically, hence was discharged without sequelae.

Case 4

A 11-year-old female child was brought with complaints of fever 4 days, headache and chest pain for 1 day. On examination, the child was febrile, pale, with altered sensorium, lymphadenopathy, hepatomegaly, and an eschar over the abdomen.

On investigation, CBC showed anemia, leukocytopenia, and thrombocytopenia with elevated liver enzymes. Scrub ELISA was reactive, and dengue serology and WIDAL were negative. The child was started on oral doxycycline. As the child developed warm shock, inotrope dopamine was given. Chest x-ray showed bilateral infiltrates; hence, oxygen support was given. Antibiotic was changed to parenteral doxycycline after 48 h of oral. Lumbar puncture was done and CSF analyzed showed pleocytosis with lymphocytic predominance. Neuroimaging was done, which was normal. Parenteral azithromycin was added in view of persistent fever spikes. The child improved symptomatically and was hemodynamically stable, hence was discharged after 5 days of IV azithromycin.

The clinical presentation, examination findings, and management of all patients are summarized in [Table 1].

Table 1: Examination and management details of all four cases.

Investigations	Case 1	Case 2	Case 3	Case 4
Age	9 years	5 years	5 years	11 years
Gender	Male	Male	Female	Female
Fever	+	+	+	+
Altered sensorium	+	+	+	+
Seizures	-	-	-	-
Lymphadenopathy	+	+	+	+
Eschar	+	+	+	+
Meningeal signs, focal deficit	-	-	-	-
TLC	3300	8500	8700	2100
PLT count	88000	35000	20400	111000
SGOT	90	306	131	118
SGPT	52	216	71	54
Scrub typhus ELISA	+	+	+	+
Dengue	-	-	-	-
CSF findings				
Sugars	113	64	32	44
Protein	23	12	43.2	26
Cells	46	14	121	30
Cultures growth	Nil	Nil	Nil	Nil
Neuroimaging	Normal	-	-	Normal

DISCUSSION

Scrub typhus is a vector-borne zoonotic disease that is causing a public health burden in endemic regions. It is a neglected tropical disease affecting rural population with management made difficult due to lack of awareness about the complications and outcome.[1,5] Scrub typhus can affect all age groups but is rare among neonates. As the organism enters into the human body, it targets the endothelial and reticuloendothelial cells leading to vasculitis and perivasculitis. Scrub typhus has wide variation in clinical presentation such as fever, classical eschar at the bite site, lymphadenopathy, hepatosplenomegaly, and maculopapular rash.[4] Because such findings are non-specific in children and have varied etiology in tropical and subtropical regions, a high index of suspicion is needed for diagnosis. If left untreated or misdiagnosed, or there is a delay in treatment, it can lead to complications such as MODS which is an important cause for morbidity and mortality in scrub typhus.[2]

AES is characterized as acute onset of fever, change in mental status, and seizures. Etiologies of AES include neurotropic viruses such as Herpes Simplex virus or JE virus, cerebral malaria, dengue, and scrub typhus. JE is the most common cause in India (5–35%), but has declined recently with vaccines.[1] If the causative organisms are viruses such as JE virus or dengue, treatment is mainly supportive. However, scrub typhus and malaria have specific drugs or antibiotics available, making their identification important to initiate appropriate treatment.

CSF analysis in scrub encephalitis shows low-to-normal sugars, mild-to-moderate rise in proteins, and lymphocytes on smear. Similar pattern is seen in subacute tubercular meningitis; hence, it is an important differential diagnosis of scrub typhus meningoencephalitis. Neurological involvement in scrub typhus includes cerebral edema, ischemic changes, hyperintensities in putamen, and thalamus in magnetic resonance imaging.[4]

Tetracycline or doxycycline and chloramphenicol are recommended treatment for scrub typhus. Chloramphenicol is not preferred due to its systemic adverse effects. Alternate drugs include azithromycin, roxithromycin, and rifampicin. Usually, there is good response and outcome following early initiation of oral doxycycline. However, in our patients with scrub typhus who presented with AES, response to oral doxycycline was inadequate, whereas patients rapidly improved with parenteral (IV) doxycyline or azithromycin.

CONCLUSION

Scrub typhus can also cause AES apart from other organisms. Treatment with parenteral azithromycin and doxycycline has equal efficacy on outcome and was found to more efficacious than oral doxycycline in our patients. Early suspicion of scrub typhus by thorough examination to identify the eschar, lymphadenopathy, and organomegaly in addition to the CNS examination will aid the diagnosis and treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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