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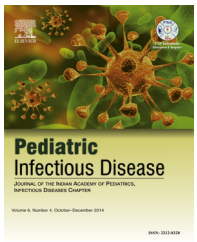

Neurological manifestations of Rickettsial infections in children

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ABSTRACT

Background: Neurological manifestations in patients with Rickettsial diaseases are increasingly being reported from various parts of India but still Rickettsial diseases as a cause of central nervous system (CNS) infections are underdiagnosed.

Aim: Main objective of this case series is to report neurological manifestations in patients of Rickettsial diseases so as to increase awareness amongst pediatricians.

Methods: Study design was a retrospective analysis of children (birth to 16 years) hospitalized in Smile Institute of Child Health and Orbit Children Hospital, which are secondary referral centres catering to children in five districts of central India, with diagnosis of Rickettsial disease from August 2014 to July 2015. Diagnosis of Rickettsial infections was made by clinical features, IgM antibodies by ELISA, prompt response to Doxycycline and exclusion of differential diagnoses.

Results: Out of 62 patients, who were diagnosed as having Rickettsial diseases, 51 patients had neurological involvement. Out of 51 patients with diagnosis of Rickettsial disease having symptomatic neurological involvement, 21 (41%) had neurological manifestation as the main presenting feature while remaining presented with non-neurological manifestations of Rickettsial diseases too along with neurological manifestations. Youngest patient was 23 days old neonate. Various neurological manifestations seen were headache (90%), irritability (61%), meningeal signs (21%), altered mental status (23%), seizures (17%), papilloedema (6%), focal neurological deficits (13%), cerebrospinal fluid (CSF) abnormalities (76%) and neuroimaging abnormalities (35%).

Conclusions: Myriads of neurological manifestations were seen with varying range of severity. Pediatricians should be aware of neurological manifestations seen in Rickettsial infections and should have high index of suspicion for Rickettsial diseases in febrile patients having neurological features specially in endemic areas.

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1. Introduction

Rickettsial diseases are one of the most incapacitating, covert, notoriously difficult to diagnose, reemerging infections of the present time reported from various parts of India and rest of the world. They present with fever, rash, edema, eschar, systemic features and various life threatening complications. Therapy is easy and affordable with dramatic results and needs to be started on clinical suspicion, as there is no specific test for early diagnosis.[1] Variable prevalence (28–80%) of neurological manifestations in Rickettsial diseases are reported.[2,3] Various clinicopathological syndromes seen are aseptic meningitis, acute encephalitic syndrome, meningoencephalitis, postinfectious demyelination and cerebral infarcts. We report a series of 51 patients with Rickettsial diseases having symptomatic neurological involvement.

2. Methods

We conducted a retrospective review of children admitted in our centers over a period of one year (from August 2014 to July 2015).

Inclusion criteria:

a) age <16 years and
b) neurological involvement (in the form of headache or irritability or seizures or altered mental status or meningeal signs or papilloedema or focal neurological deficits or CSF abnormalities or neuroimaging abnormalities) and
c) having more than one clinical features compatible with Rickettsial disease (fever, rash, edema, hepatosplenomegaly, lymphadenopathy, eschar and history of tick exposure and defervescence of fever within 5 days of beginning doxycycline treatment) and
d) positive IgM antibody to spotted fever or scrub typhus (titer > 1:64) by ELISA.

Exclusion criteria:

a) patients not hospitalized and/or
b) established alternative etiology of fever.

51 patients were qualified for the review. Their clinical, CSF and neuroimaging features were collected. CSF was done in all but neuroimaging (MRI) was done in only 17 patients due to financial constraints. IgM ELISA for spotted fever (Panbio, Brisbane, Australia) and IgM ELISA for scrub typhus (InBios international, Seattle, USA) were done and considered positive with a titer of 1:64 or more. ELIZA was done after day 5 of illness. All cases were treated with oral or nasogastric doxycycline 5 mg/kg/day for 7–10 days. Other symptomatic therapies like antipyretics, IV mannitol, IV fluids and anticonvulsants were used as per the clinical scenario. Antibiotics, antimalarials and antivirals were started empirically at the time of admission in 18 (35%) patients, whose diagnosis was uncertain at initial presentation and were promptly withdrawn once the positive report of ELIZA was available.

Various neurological manifestations were noted and their incidence was calculated. Patients having drowsiness, confusion, stupor, delirium or coma were classified as altered mental status. History of headache was elicited only in patients 6 years of age and above.

3. Results

Out of 62 patients of confirmed Rickettsial infection, a total of 51 (82%) patients met the inclusion criteria. 34 (66.6%) patients had scrub typhus and 17 (33.3%) had spotted fever group Rickettsioses. Youngest was 23 days old neonate, who was referred as a case of neonatal sepsis on day 5 of illness with fever, anasarca and seizures. His blood, urine and CSF cultures were negative and had no response to conventional treatment of neonatal sepsis. CSF was suggestive of aseptic meningitis. On detailed history, mother remembered removing tick from baby's axilla, the piece of history, which she thought was unimportant. ELIZA scrub typhus was positive, all antibiotics were stopped and baby responded promptly to doxycyline. 45 (88%) patients responded well to therapy in 3–10 days with defervescence and complete recovery in neurological manifestations. 3 (6%) patients died inspite of therapy due to status epilepticus, ARDS and encephalitis respectively. 3 (6%) patients had persistent neurological deficit on discharge (deafness, Guillain_Barre syndrome and hemiparesis), all of which recovered completely within 8 weeks on follow up. Fever was seen in all patients. Of peculiar importance was the fact that 21 (41%) patients had only neurological manifestations (along with fever) as the presenting feature in them which brought them to hospital. Various neurological findings were seen in varying severity as shown in Table 1. Out of 9 patients with seizures, 5 had partial while 4 had generalized seizures (2 out of these 4 had status epilepticus). Out of 7 patients with focal neurological deficits, 2 had ataxia, 1 had hemiparesis, 1 had 3rd cranial nerve palsy, 1 had 6th cranial nerve palsy, 1 had deafness (8th cranial nerve palsy) and 1 had Guillain Barre syndrome. Guillain Barre syndrome developed on day 9 of hospitalization (day 16 of illness), when patient was about to get discharged. CSF abnormalities were seen in 39 (76%) patients and were in the form of mildly raised proteins (48–92 mg%) and pleocytosis of 10–98 cells/cumm (lymphocytic preponderance in 55% and polymorphonuclear preponderance in 45% cases). CSF glucose level was normal in all patients (except 2 (4%) who had hypoglycorrhachia). Gram stain and

Table 1 – Various neurological manifestations seen in Rickettsial diseases.

S. no.	Neurological feature	No. of patients	%
1	Headache (above 6 years of age)	28/31	90%
2	Irritability	32/51	61%
3	Meningeal signs	11/51	21%
4	Altered mental status	12/51	23%
5	Seizures	9/51	17%
6	Papilloedema	3/51	6%
7	Focal neurological deficits	7/51	13%
8	CSF abnormalities	39/51	76%
9	Neuroimaging abnormalities	6/17	35%

bacterial cultures on CSF were done in 42 and 4 patients respectively and both were normal. Various neuroimaging abnormalities noted were meningeal enhancement, sulcal effacement, abnormal hyperintense signals in gray matter on T2 and FLAIR, cerebral infarct and compressed ventricular system suggestive of raised intracranial pressure. Late neurological sequelae like depression, behavioral disturbances, learning disability described earlier[3] were not studied in this series.

4. Discussion

Neurological manifestations have long been recognized as complications of Rickettsial infections and the word "typhus" itself comes from the Greek word whose meaning – hazy or smoky – is related to the mental status of affected individuals.[4] CNS involvement in Rickettsial diseases is secondary to systemic nature of disease and infective vasculitis caused by them but direct invasion is also documented.[5] Majority of patients have neurological involvement in the form of aseptic meningitis, meningoencephalitis, acute encephalitic syndrome, cerebral infarct or postinfective demyelination like Guillain Barre syndrome or acute demyelinating encephalomyelitis.[6]

We are reporting a series of 51 patients of Rickettsial diseases who had neurological involvement from central India in Maharashtra. 82% (51/62) of Rickettsial diseases in children had neurological manifestations either at presentation or during the course of their hospitalization. Out of total 62 patients with Rickettsial diseases, 63% (39) had CSF abnormalities, while CSF abnormalities were found in 76% (39/51) patients of Rickettsial diseases who had symptomatic CNS involvement. Neurological involvement was seen at all ages, youngest being a 23 days old neonate. Four neonates were reported from Tamil Nadu, where neonatal sepsis was caused by Rickettsia and 2 of them had seizures.[7] Commonest neurological manifestations were headache, irritability and CSF abnormalities, while papilloedema was the rarest. One such study,[8] showed headache in 70%, seizures in 40%, meningeal signs in 30% and abnormal MRI in 100% cases, while comparable figures in our study were 90%, 17%, 21% and 35% respectively. Differences could be because they studied only Rocky Mountain Spotted Fever. Of peculiar interest is the fact that significant proportion (41%) of these patients presented with only neurological manifestation (with fever) in absence of characteristic clinical features of these infections like rash, edema, eschar, hepatosplenomegaly and lymphadenopathy. Majority of patients (94%) responded well to doxycycline therapy.

5. Limitations

As per the recent guidelines by ICMR, a confirmed case is one with Rickettsial DNA detected in eschar samples or whole blood by PCR Or rising antibody titers on acute and convalescent sera detected by Indirect Immune Fluorescence Assay (IFA) or Indirect Immunoperoxidase Assay (IPA). Due to nonavailability of these confirmatory tests, IgM positivity by ELISA was used as an essential criteria for diagnosis.

Further study is required to understand the long term prognosis of the neurological abnormalities seen in these patients.

6. Conclusion

Rickettsial diseases can present with various neurological features of varying severity. Their diagnosis should be considered in cases of aseptic meningitis, meningoencephalitis and acute encephalitic syndrome associated with fever of short duration without an obvious cause, specially in areas known for these infections. CSF showing mildly elevated proteins and mild pleocytosis is compatible with diagnosis but low glucose level should prompt clinician to search for alternative diagnosis. Timely diagnosis prevents morbidity, mortality and lowers economic burden on patients for unnecessary diagnostic workups and unwarranted therapies.

Contribution of authors

NR&RK were responsible for conceptualization, management of the cases and writing the article. MM contributed towards review of literature, data analysis and writing of the article.

Conflicts of interest

The authors have none to declare.

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