

Profile of Neurological Manifestations in Children Presenting With Rickettsial Disease

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Objective: To study the profile of neurological manifestation of rickettsial disease in children. **Methods:** Review of hospital records was done in a tertiary care hospital for the period from January to December, 2020. Data of all the children fulfilling the inclusion criteria i.e., clinical criteria and serology were retrieved from the hospital records. **Results:** Of the total 7974 children admitted over this period, 178 were diagnosed with rickettsial disease wherein 54 (33.3%) had neurological involvement. Convulsions (59%), altered sensorium (56%), headache (44%), meningeal signs (37%), ataxia, (11%), lateral rectus palsy (7.5%) and stroke (7.5%) were the major neurological manifestations. Cerebrospinal fluid (CSF) analysis done in 30 (55%) children showed pleocytosis [median (IQR) cells 15 (3.75, 50)] with lymphocyte predominance [median (IQR) lymphocytes 11.5 (3, 38.75)] and elevated proteins [median IQR 41.5 (29.75,61)]. Neuroimaging abnormalities noticed were cerebral edema ($n=7$), cerebellar hyperintensities ($n=5$), basal ganglia infarcts ($n=2$) and hippocampal hyperintensities ($n=1$). **Conclusion:** Early recognition of rickettsial infection as a cause of neurological manifestation would facilitate early specific management.

Keywords: Cranial nerve palsy, Meningoencephalitis, Stroke.

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Rickettsial diseases are one among the re-emerging causes of acute undifferentiated febrile illness in several parts of India [1]. Vasculitis is the basic pathogenic mechanism and is responsible for the various manifestations [1,2]. Variable prevalence (28-80%) of neurological manifestations has been reported in rickettsial diseases [3-11]. Early recognition and treatment of rickettsial infection with neurological manifestations is important to prevent the morbidity and mortality associated with the disease.

METHODS

We conducted a review of hospital records of children admitted to a tertiary care hospital in Bangalore between January and December, 2020. 'Rickettsial disease' was the keyword used to search the data in the electronic patient records. Children less than 18 years of age with score more than 14 as per RGA (Rathi Goodman Aghai) scoring system [3], and defervescence of fever within 48 hours of beginning of doxycycline treatment, or positive Weil-Felix test with a single titer above 1:80 or positive IgM/IgG ELISA for scrub typhus (optical density >0.5) with neurological involvement (in the form of headache or irritability or seizures or altered mental status or meningeal signs or focal neurological

deficits or cerebrospinal fluid abnormalities or neuroimaging abnormalities) were included in the study. Children with established alternative etiology of fever were excluded from the study.

A total of 7974 children (<18 year) were admitted in the institution during the study of which 178 had rickettsial disease (RD); 54 of these fulfilled the inclusion criteria. We analyzed the demographic profile, clinical presentations, laboratory investigations, neuroimaging, complications and hospital - outcome in these children. Patients having drowsiness, confusion, stupor, delirium, coma with Glasgow Coma Scale (GCS) score of less than 13 or AVPU scale indicating altered sensorium were treated in the pediatric intensive care unit. A serum sample was sent for Weil-Felix test to the central hospital laboratory (Turnover time 24 hours). Weil felix test was done by Cromatest febrile serodiagnostic (LiNEAR chemicals), Inbios scrub typhus Detect (IgM and IgG ELISA kits).

All children with RD were treated with oral doxycycline 5 mg/kg/day for 5-7 days. Intravenous (IV) doxycycline was used in those for whom oral intake was not possible. Azithromycin 10 mg/kg/day for 7-10 days was used in children who did not respond to oral/IV doxycycline within

4 days of initiation of treatment. All children with neurological involvement were initially treated with IV ceftriaxone, which was stopped if serology was positive for RD. Other symptomatic therapies like antipyretics, anti-cerebral edema measures, intravenous fluids and anti-convulsants were used as per the clinical scenario. Out of 54 children included in our study, CSF analysis was done in only 30 children and neuroimaging (computerized tomography, CT and magnetic resonance imaging (MRI) was done in 22 children only.

Data analysis: Data was collected on a pretested proforma from the hospital patient records and transferred to Microsoft Excel sheet. Mean and standard deviation was tabulated for linear parameters, frequency tables were tabulated for nominal data and analyzed.

RESULTS

Out of 178 children treated as rickettsial disease, 54 (33.3%) had neurological manifestations. Out of 54 children 29 (54%) were males. Mean age of our study population was 7.3 years (SD: 3.62, Median: 7) with youngest child being 1 year and oldest child being 15 years. 51 (94%) children presented between months of August to January, highest incidence being seen in September ($n=15$, 27.85%), October ($n=10$, 18.5%) and December ($n=10$, 18.5%).

Fever was present in all the children included in our study with mean duration of 6 days (SD: 3.7 days). Two third (66.7%, $n=36$) of the children presenting with neurological manifestations had fever for 4 days or more. Only 14 (26%) children with neurological manifestation had rashes, out of which two children developed purpura fulminans. Hepatomegaly was noted in 40 (74%) children while hepatosplenomegaly was noted in 9 (17%) children. Edema was present in 30 (55%) children at presentation. Though ophthalmological examination details of all the children could not be retrieved, subconjunctival hemorrhage, petechiae, keratitis, optic disc edema and macular edema were major findings while retinitis with vascular changes were noted in few.

The most common neurological manifestations were convulsions (59%), altered sensorium (56%), headache (44%), irritability and signs of meningeal irritation (37%),

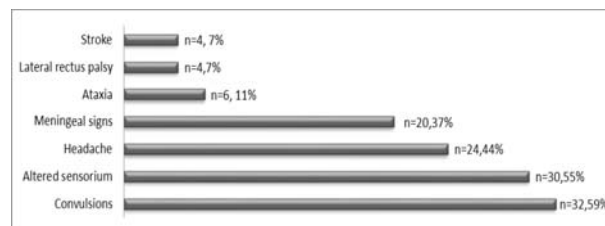


Fig. 1 Neurological features in rickettsial disease.

ataxia (11%). Lateral rectus palsy was noted in 4 children (7.5%) with three of them showing unilateral right sided involvement while one had bilateral lateral rectus palsy. Right sided hemiparesis was noted in three children while left hemiplegia was noted in one child. Other less common neurological manifestations were titubation, dysdiado-kinesia, nystagmus, Slurred speech, dysphagia, dysdiado-kinesia and dysmetria suggesting cerebellar involvement. Spectrum of neurological manifestations in rickettsial disease is depicted in **Fig. 1**.

Anemia, thrombocytopenia and leukocytosis were the major hematological parameters noted while hypoalbuminemia, elevated liver enzymes and elevated C-reactive protein (CRP) were the major biochemical abnormalities (**Table I**). Among the children with elevated liver enzymes, 35 (65%) children had aspartate aminotransferase (AST) elevated more than alanine aminotransferase (ALT), 7 (13%) had ALT elevated more than AST, while 8 (15%) had isolated AST elevation. CSF analysis was done in only 30 children. Elevated protein [median (IQR) 41.5 (29.75) mg/dL], pleocytosis [median (IQR) 15 (3.75,50) cells per high power field] with CSF sugar being normal [median (IQR).53 (46,61) mg/dL] were the notable features in the CSF examination. Cell count was zero in 8 children while lymphocytic predominance [median (IQR) 11.5 (3,38.75)] was noted in 22 children with 17 children showing 100% lymphocytes.

Weil-Felix test was done in all the patients, and 32 (59%) were positive for the test (25 OXK, 6 OX2 and OX19, 1 OX2). Six children tested positive for IgM antibodies while 3 tested positive for IgG antibodies to scrub typhus. Majority (63%) of the children included in our study serologically (positive OXK titers, positive IgM/IgG for scrub typhus) belonged to scrub typhus group. Two children were positive for both OXK by Weil Felix test and IgM for scrub typhus.

Table I Laboratory Profile in Children With Neurological Manifestations (N=54)

Parameter	Value
Hemoglobin (g/dL)	9.31 (1.26)
Total counts ($\times 10^9/L$)	19.56 (2.34)
Neutrophils (%)	65 (16)
Lymphocytes (%)	28 (16)
Platelet count ($\times 10^9/L$) ^a	56 (66)
Serum sodium (meq/L)	132 (4)
Serum albumin (g/dL)	2.55 (0.45)
Aspartate aminotransferase (U/L) ^a	152 (107.5)
Alanine aminotransferase (U/L) ^a	114.5 (102.75)
C-reactive protein (U/L)	80.6 (27.24)

All values in mean (SD) or ^a median (IQR).

WHAT THIS STUDY ADDS?

- Association of stroke, cerebellar involvement and lateral rectus palsy in rickettsial disease.

Neuroimaging was done in 22 (41%) children (MRI in 10). Cerebral edema was the most common feature in CT brain which was seen in 7 children, one child showed white matter hypo densities, while CT was normal in 2 children. MRI was normal in 4 children while 5 (4 being positive for IgM scrub typhus) children showed signal changes in cerebellar hemispheres, cerebellar atrophy, two children with stroke showed basal ganglia infarcts and one child showed bilateral hippocampal hyperintensities.

Out of 54 children, 16 children required mechanical ventilation as part of management. Poor sensorium was the most common indication for ventilator support while associated respiratory distress was also noted in 2 children and mean duration of ventilation was 7 days. One child on ventilator support died of refractory septic shock while 15 children recovered from illness. Acute kidney injury was noted among 3 children who eventually recovered. Two children developed purpura fulminans out of which one child had auto amputation of toes bilaterally, while other developed septic shock with ARDS (acute respiratory distress syndrome) with AKI (acute kidney injury) requiring ventilator support but recovered eventually.

DISCUSSION

Neurological involvement in rickettsial diseases occurs typically following bacterial dissemination through the bloodstream and infective vasculitis caused by them. Rickettsia affects small blood vessels, creating central nervous system nodules consisting of glial cells and mononuclear cells around gray matter capillaries. These changes rarely progress to thrombotic occlusion and micro-hemorrhages, thus explaining the rapid reversibility of most neurologic signs [6].

Most common presenting features in our study were seizures and altered sensorium, similar to previous studies from India [7,11]. The clinical manifestations in this study showed higher prevalence of seizures and meningeal signs compared to previous studies [8-10], possibly due to the tertiary-care government healthcare setting of our hospital. Other reasons could be enrolment of only Rocky Mountain spotted fever cases in one study [10], and smaller sample size in the other [8]. CSF findings reported here are also in consonance with the literature [12,15]. MRI in six children with rickettsial disease showed signal changes in bilateral cerebellar hemisphere, which is a new addition to the existing literature [12]. We also report a child with rickettsial

encephalitis (Weil-Felix test OXK positive 1:320 titer) with features of raised ICP and isolated 6th cranial nerve involvement. This suggests that cranial nerves can be separately affected by the vasculitis process of RD, as previously suggested by Wai, et al. [14].

As it is a retrospective study, complete data of neurological manifestations, neuroimaging and diagnostic tests of all the children were not available. RD was considered based on Weil Felix test, RGA scoring and response to doxycycline, and only limited children were diagnosed based on confirmatory test.

Rickettsial disease should be considered as etiological agent in acute neurological manifestations, in the appropriate setting, especially in children presenting from endemic areas for these infections.

Contributors: KRA: data collection; SBC: data compilation, statistical and results analysis, discussion writing; MA: introduction and discussion editing; KNV: Discussion and editing of neurological data; KSS: proof reading and editing; GVB: formulation of research methodology, editing of results and proofreading of manuscript. All authors approved the final version of manuscript, and are accountable for all aspects related to the study.

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NEWS IN BRIEF

New way to deliver mRNA Vaccines

Needles – Not only children even some adults are also afraid of needle prick. This fear of needle results in low acceptance and adherence with injectable drugs and vaccines. A team of researchers from the Massachusetts institute of technology (MIT) have developed a capsule to deliver injectable drugs directly in the mucosal layer of stomach. In the initial two years, during trials the team had been successful in delivering large molecules like monoclonal antibodies into the stomach mucosa without degradation. Recently they have successfully delivered 150 micrograms of RNA in the stomach of pigs without degradation, which is more than the mRNA present in the COVID-19 vaccines in use at present. Subsequently, the research team documented a successful production of reporter protein by stomach cells. The researchers are now planning to create a systemic immune response in humans, including activation of B- and T-cells, by delivering mRNA vaccines using their capsule. The success of this modality might abolish the need of injection for the delivery of vaccines/drugs in near future, thus helping us to reach our vaccination targets.

(*Matter 31 January, 2022*)

Nano- and Micro-plastics: Danger to our future generations

Recently there are articles on 'Plasticenta' i.e., presence of microplastic particles in human placenta. Plastic, a synthetic material made of polymers, become an integral part of our present day lifestyle due to its features like light weight, durability, chemical and thermal resistance, and low cost. Globally, environmentalists are worried about the impact of plastic and its degradation products on our environment. But what about its effect on our own health? Nano- and micro-plastic particles are <1000 μm and <1000 nm in size respectively, inside human body these particles can cross through the biological barriers, cause inflammatory reactions in sensitive areas and acts as carriers of various toxic chemicals causing long term effects on human health. As pregnancy, infancy, and childhood are sensitive

periods of vulnerability to environmental toxicants exposures. In a recent paper from the Norwegian University of Science and Technology, authors studied the effects of exposure to nano- and microplastics (NMPs) through placental transfer, breastmilk, ingestion, inhalation, and dermal absorption on the health of the newborns and children. Their findings showed that there is a lack of substantial data regarding the effect of NMPs on the health of infants and children, yet they have given recommendations for the policymakers, industry as well as for the families. The important ones includes the appropriate measures to reduce the exposure of the children to NMPs – through steps like removal of the youth involved in plastic waste collection and e-waste burning, reducing the contact of plastic with food items intended for children, regular wet-cleaning of our homes, and careful choice of safer personal care products and building materials etc.

(*Environmental Health Perspectives 26 January, 2022*)

Vaccine against Zika Virus

Since 2015-16, when an outbreak was reported from Brazil, American and African region no treatment is available for Zika virus or its associated disease. It was declared as a public health emergency of international concern by WHO along with the guidelines to prevent its spread. But now a ray of hope has emerged in the form of Zika virus vaccine, which is the result of the collaboration between the Texas Biomedical Research Institute's Southwest National Primate Research Center (SNPRC), Trudeau Institute and Walter Reed Army Institute of Research (WRAIR), where the vaccine is under development. The initial test results of the purified, inactivated Zika vaccine (ZPIV) candidate in non-pregnant animal models, showed its effectiveness in clearing the virus from their blood. While on testing in pregnant mice and marmosets, the vaccine prevented fetal malformations and generated neutralizing antibodies in 80% and 90% cases, respectively. In Phase 1 human trials, it has shown to be safe and able to elicit a protective immune response. Though its, quite early but the results have shown that ZPIV is both potent and durable, and it also has the potential to prevent the harmful consequence of Zika virus infection during pregnancy.

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