Optic Neuritis, Miller Fisher Syndrome, and Guillain Barre Syndrome Overlap Secondary to Scrub Typhus in a North Indian Girl

Sir,

Scrub typhus is an important tropical infection in India. Seizures, altered sensorium, and acute cerebellitis are the most common neurological features of Scrub typhus. The neurological complications are considered secondary to vasculitis or immune-mediated phenomenon.[1-3] Scrub typhus accounts for 15-20% of cases of acute encephalitis in India.[2] In addition, Guillain Barre syndrome (GBS), acute transverse myelitis, opsoclonus myoclonus ataxia syndrome, optic neuritis, ocular flutter, and ophthalmoplegia are other neurological complications associated with Scrub typhus.[4-7] We report a 9-year-old girl with Optic Neuritis, Miller Fisher syndrome (MFS) and GBS overlap following Scrub typhus.

A 9-years-old girl presented with a history of fever, headache, vomiting, abdominal pain, and respiratory distress for five days. The parents also noticed periorbital puffiness and rash over the face since day 2 of illness. Anthropometry showed weight of 25 kg (between 0 and -1 SD WHO growth chart), height of 145 cm (at +2SD WHO growth chart), and occipitofrontal circumference of 54 cm (between mean to +2SD). On day five of illness, examination showed pallor, facial puffiness, petechial rash over face and trunk, and tachypnoea with respiratory distress. Her systemic and neurological examination was unremarkable. For suspected tropical infection, she was initiated on intravenous doxycycline and ceftriaxone. Investigations revealed anaemia (Hb-8.8 g/dl), thrombocytopenia (Platelet count-66,000/µl), hyponatremia (Serum sodium 127 meq/L), hypoalbuminemia (Serum albumin 2.5 g/dl), elevated C-reactive protein (27 mg/dl, normal <10 mg/dl). Peripheral smears for malaria aµnd dengue serology were negative. The Scrub typhus IgM ELISA was positive (In Bios International Inc., Seattle, WA; optical density (OD) value, 3.29; OD value of >0.5 was considered diagnostic). Nested PCR performed using the DNA extracted from the whole blood, and was amplified to detect Orientia tsutsugamushi DNA oligonucleotide primers (sequences of a gene encoding for the 56-kDa antigen of a Gilliam strain of Orientia tsutsugamushi) was positive.

During the hospital stay, she developed right-sided 3rd and 7th nerve palsy, left-sided 6th nerve palsy, encephalopathy, and seizures on day 8 of illness. She was intubated and ventilated because of worsening sensorium and poor respiratory efforts. Contrast-enhanced MRI brain was normal. Intravenous methylprednisolone for five days was given for suspected encephalitis; she responded well and was extubated on day 14 of illness. Lumbar cerebrospinal fluid (CSF) analysis revealed 7 cells, 84 mg/dl (normal value:<40 mg/dL) protein, and 53 mg/dL glucose (Blood glucose: 77 mg/dL). Repeat serum and CSF Scrub typhus IgM ELISA were negative at day 14 of illness. She received intravenous doxycycline for 10 days.

Post-extubation, she developed tremulousness of arms, slurring of speech, and appendicular weakness. She developed bilateral lower motor neuron type facial palsy, near-complete ophthalmoplegia with dilated pupils (preserved left eye adduction), quadriparesis, hypotonia, areflexia, and cerebellar signs. She had appendicular weakness with an MRC sum score of 38. She was noted to have profound bilateral vision loss once her sensorium improved and was diagnosed with bilateral optic neuropathy. Nerve conduction study suggested the presence of bilateral symmetrical motor axonal poly neuropathy with preserved sensory responses. A diagnosis of Optic Neuritis with MFS-GBS overlap was considered. The MRI of the brain, optic nerves, spine and MR venography were unremarkable. Visual evoked potentials showed the absence of waveforms in both eyes. Serum NMO and MOG antibodies were negative. Serum biotinidase levels and serum B12 were normal.

For MFS-GBS overlap with optic neuritis, she received IVIG at 2 gm/kg, followed by five cycles of plasmapheresis given. She had a gradual and complete recovery in motor weakness, cerebellar signs, and ophthalmoparesis by two months; however, there was minimal improvement in vision. She was subsequently treated with intravenous cyclophosphamide for optic neuropathy, but she did not show much response. At six months follow up, she was ambulatory, able to climb stairs, speak well, and can perceive light in both eyes with bilateral optic atrophy.

The index case had a biphasic illness; the first phase consisted of typical with petechial rash, facial puffiness, pneumonia, anaemia, thrombocytopenia, hyponatremia, and hypoalbuminemia. In the first phase, she developed seizures, acute encephalopathy, and cranial nerves palsy. At this point, contrast-enhanced MRI brain was normal, and Scrub encephalitis was considered. She was treated with doxycycline and steroid and showed an excellent response to therapy and recovered gradually. However, by the 3rd week of illness, she developed vision loss, bilateral ophthalmoplegia, bifacial weakness, ataxia, and areflexia, suggesting a diagnosis of Optic neuritis, MFS-GBS overlap syndrome. The presence of albumin-cytological dissociation in the CSF and acute motor axonal polyneuropathy supported the diagnosis of MFS-GBS overlap syndrome. In addition, she also developed vision loss with bilateral optic neuropathy. Negative scrub typhus ELISA

at this point suggested that acute infection was adequately treated with antibiotics. We could not perform antiganglioside antibodies (IgG anti-GQ1b) in the index case.

MFS is considered a variant of GBS, and phenotypic overlap between GBS and MFS has been observed frequently and termed as MFS-GBS overlap.[8,9] Kim KW *et al*.[10] reported a case of MFS with bilateral ptosis, ophthamoplegia, facial diplegia, gait ataxia, and areflexia in a 70-year-old male, two weeks following Scrub typhus illness. CSF showed albumin-cytological dissociation and elevated titre for *O. tsutsugamushi* antibodies. Good response to IVIG was observed with complete recovery during follow-up.

Optic neuritis with Scrub typhus is very unusual, especially in children. Jessani LG *et al*.[7] reported unilateral optic neuritis with prompt response to immunosuppressive therapy with Scrub typhus. Cho *et al*.[11] reported bilateral optic neuritis associated with Scrub typhus in an eight-year-old boy during the convalescent phase with good response to steroids, and post-infectious immune-mediated neuropathy was postulated etiology.[11]

The outcome of Scrub typhus associated encephalopathy has not always been excellent. Persisting neurological deficits have been reported among cases with Scrub typhus-associated encephalitis, small vessel vasculitis, and chronic immune mediated demyelinating polyneuropathy.[3,4] In the index case, optic neuritis remained refractory to immunotherapy and progressed to optic atrophy in follow up. We believe that apart from immune mediated damage to the optic nerve, there was a component of ischemic optic neuropathy due to small vessel vasculitis secondary to Scrub typhus. The component of permanent ischemia affecting the optic nerves had possibly resulted in poor recovery of vision despite aggressive immunotherapy in this index child.

To conclude, Scrub typhus can have a myriad of neurological manifestations during the acute phase and immune-mediated complications during the convalescent phase. Early identification and treatment of various neurological complications is essential for favorable outcome.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Xu G, Walker DH, Jupiter D, Melby PC, Arcari CM. A review of the global epidemiology of Scrub typhus. PLoS Negl Trop Dis 2017;11:e0006062.
2. Jain P, Prakash S, Tripathi PK, Chauhan A, Gupta S, Sharma U, *et al.* Emergence of Orientia tsutsugamushi as an important cause of Acute Encephalitis Syndrome in India. PLoS Negl Trop Dis 2018;12:e0006346.
3. Fisher J, Card G, Soong L. Neuroinflammation associated with Scrub typhus and spotted fever group rickettsioses. PLoS Negl Trop Dis 2020;14:e0008675.
4. Gulati S, Maheshwari A. Neurological manifestations of Scrub typhus. Ann Indian Acad Neurol 2013;16:131.
5. Didel S, Basha MA, Biswal M, Suthar R, Sankhyan N. Acute cerebellitis in a child with Scrub typhus. Pediatr Infect Dis J 2017;36:696-7.
6. Kasinathan A, Suthar R, Sahu JK, Sankhyan N, Nallasamy K. Ocular flutter in Scrub typhus. J Pediatr 2019;204:315.
7. Jessani LG, Gopalakrishnan R, Kumaran M, Devaraj V, Vishwanathan L. Scrub typhus causing unilateral optic neuritis. Indian J Pediatr 2016;83:1359-60.
8. Bazán-Rodríguez L, López-Hernández JC, Jorge de Saráchaga A, Gómez-Figueroa E, Leon-Manriquez E, Briseño-Godinez ME, *et al.* Classic and overlapping Miller-Fisher syndrome: Clinical and electrophysiological features in Mexican adults. Neurol Sci 2021;42:4225-9.
9. Wakerley BR, Uncini A, Yuki N; GBS Classification Group; GBS Classification Group. Guillain-Barré and Miller Fisher syndromes--new diagnostic classification. Nat Rev Neurol 2014;10:537-44.
10. Kim KW, Kim YH, Kim BH, Lee CY, Oh MS, Yu KH, *et al.* Miller Fisher syndrome related to Orientia tsutsugamushi infection. J Clin Neurosci 2014;21:2251-2.
11. Cho HJ, Choi JH, Sung SM, Jung DS, Choi KD. Bilateral optic neuritis associated with scrub typhus. Eur J Neurol 2013;20:e129-30.

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