Post-Infective Rhombencephalitis with Bilateral Olivary Hypertrophic Degeneration

Dear Editor,

Scrub typhus, caused by *Orientia tsutsugamushi*, is endemic in various parts of South Asia, including numerous cases reported from various parts of India.[1,2] Pathologically, it is characterized by disseminated vasculitis involving the cardiovascular, gastrointestinal, lymphoreticular, and central nervous system (CNS).[1] Neurologic manifestations are myriad and include meningoencephalitis, cranial neuropathies, plexopathies, myelitis, and cerebellitis.[3] Lesions of the dentato-rubro-olivary pathway (DROP) lead to hypertrophic degeneration of the olivary nucleus, regarding which currently, there is limited literature in the pediatric population. We report the first case of pediatric hypertrophic olivary degeneration (HOD) secondary to a scrub typhus–induced brainstem demyelination.

Majumder *et al*.[4] reported a 7-year-old boy of Bengali ethnicity, who presented with acute-onset ataxia, dysarthria, and respiratory distress, preceded by fever, in February 2021. Initial presentation was with lower limb weakness and walking difficulty, followed by spastic quadriparesis and respiratory failure, which necessitated intubation. Following demonstration of scrub typhus IgM antibodies (enzyme-linked immunosorbent assay [ELISA]) in the serum and cerebrospinal fluid (CSF), the patient was commenced on intravenous azithromycin (10 mg/kg/day) and pulse methylprednisolone (30 mg/kg/day for 5 days). Magnetic resonance imaging (MRI) of brain revealed hyperintensity of medulla on T2-weighted sections with corresponding hypointensity on T1-weighted images and no restriction on diffusion-weighted image (DWI) [Figure 1]. Primary demyelination was ruled out after the patient tested negative for relevant serum antibodies (anti-aquaporin 4 IgG and anti-myelin oligodendrocyte glycoprotein [anti-MOG] IgG antibodies). The patient responded to immunotherapy, and a diagnosis of scrub typhus–induced rhombencephalitis was made. Over the next few weeks, corticosteroids were gradually tapered and stopped.

The patient was followed up after 2 years by the authors and was found to be ataxic, with signs of cerebellar involvement [Video 1]. Repeat MRI of brain showed a residual T2/fluid-attenuated inversion recovery (FLAIR) hyperintensity of bilateral inferior olive (IO) nuclei, with enlargement, suggestive of HOD [Figure 1]. No contrast enhancement or diffusion restriction was noticeable. CSF examination was unremarkable. Serum analysis for antibodies against synaptic and neuronal cell surface antibodies were negative, as were the vasculitis profiles. Primary demyelination was ruled out after the patient tested negative for anti-aquaporin 4 and anti-MOG antibodies (IgG) in serum as well as the absence of oligoclonal bands (OCB) in CSF. Clinical deficits (i.e., ataxia) persisted despite the monophasic nature of the initial illness. The patient was not started on immunotherapy owing to absence of signs of active disease as suggested by lack of contrast enhancement on imaging. Symptomatic therapy with amantadine (50 mg orally twice daily) was started and the child has remained clinically stable on subsequent follow-up, without any adverse effects or clinical deterioration.

Scrub typhus, caused by *O. tsutsugamushi* and transmitted via the bite of larval form of trombiculid mite, is endemic in various parts of India. It is characterized by febrile illness, lymphadenopathy, and a hallmark "eschar."[1] Neurologic manifestations have been reported to be present in one-fifth of patients.[5] There have been only a handful of reports of acute demyelinating encephalomyelitis (ADEM)/rhombencephalitis following scrub typhus[6-8] [Table 1]. Focal vasculitis due to endothelial cell dysfunction, and extensive perivascular lymphocytic infiltration, as well as aberrant immune responses have been proposed as a possible pathophysiology of rickettsial CNS manifestations.[8,9]

Presently, there is a dearth of literature on the incidence and prevalence of HOD in children, as most data is in the adult population. Bilateral HOD is exceedingly rare. Previous reports of pediatric HOD have been secondary to trauma, surgery, or tumors.[10] HOD is a consequence of interruption of inputs to and from IO in the medulla, which is a part of the Guillain–Mollaret triangle (GMT), also consisting of the contralateral dentate nucleus (DN) and ipsilateral red nucleus (RN).[10] Inputs to IO originate from the contralateral DN, passing through the brachium conjunctivum or superior cerebellar peduncle (SCP), decussating at the caudal midbrain, passing through the ipsilateral RN, and reaching IO through the central tegmental tract (CTT). Efferents from IO are carried by the inferior cerebellar peduncle (ICP), crossing the midline and synapsing at the contralateral DN, thereby forming a disynaptic closed circuit, that is, DROP[10] [Figure 2].

At the time of the initial report by Majumder *et al.*,[4] this was the first documented case of medullary demyelination following scrub typhus. Sanverdi *et al*.[10] reported a series of four pediatric patients with bilateral HOD, three of whom had posterior fossa surgery. A diffuse demyelinating lesion affecting both the central tegmental tract (CTT) on one side and the brachium conjunctivum on the other, might have been responsible for the bilateral nature of olivary degeneration in the present case. Since HOD is a dynamic process, the importance of follow-up brain imaging with high-resolution (1.5 T and above) MRI cannot be overemphasized.

Para- and post-infectious CNS demyelination is a well-recognized public health burden, particularly in the pediatric age group.

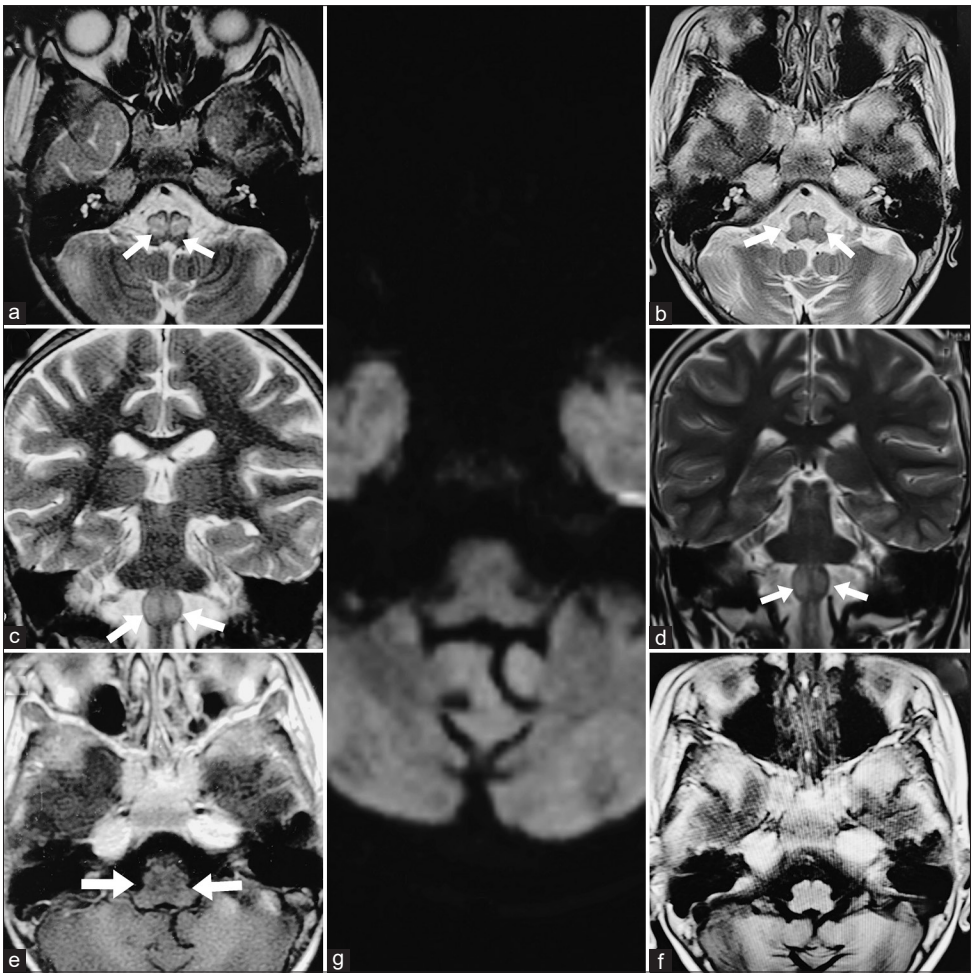

Figure 1: Panel on left: (a) Initial T2-weighted axial and (c) coronal MRI showing diffuse hyperintensity of the medulla oblongata (white arrows); (e) T1-weighted postcontrast sequence showing subtle hypointensity of the medulla without any enhancement (white arrows). Panel on right: (b) Axial and (d) coronal T2-weighted MRI at follow-up after 2 years showing hyperintensity of bilateral inferior olive nuclei with slight enlargement (white arrows); (f) axial T1 contrast sequence of the medulla showing no signal change or contrast enhancement. Center: (g) DWI axial sequence showing no restriction. DWI = diffusion-weighted image, MRI = magnetic resonance imaging

Table 1: Comparison of studies depicting scrub typhus induced acute demyelinating encephalomyelitis (ADEM)/rhombencephalitis

Study	Age (years)/sex	Clinical presentation	Brain imaging	Treatment	Outcome
Chen *et al*., 2005[6]	77/male	ADEM	T2-weighted hyperintensity in the periventricular white matter	10-day course of minocycline followed by high-dose corticosteroid	Limited improvement
Bhat *et al*., 2015[7]	6/female	Cerebellitis	T2/FLAIR hyperintensity in bilateral superior cerebellum	Not specified	Not specified
Didel *et al*., 2017[8]	6/male	Cerebellitis	Focal, unilateral T2 hyperintensity in the cerebellar hemisphere	Oral doxycycline	Good recovery
Present case	7/male	Brainstem demyelination (rhombencephalitis)	Diffuse medullary T2/FLAIR hyperintensity followed by bilateral hypertrophic olivary degeneration	Parenteral doxycycline and pulse methylprednisolone	Recovery with residual cerebellar ataxia

ADEM=Acute disseminated encephalomyelitis, FLAIR=Fluid-attenuated inversion recovery

A knowledge of epidemiology, high index of suspicion, and understanding of its ability to masquerade various systemic ailments is requisite for the timely diagnosis and management of scrub typhus and its potential complications. Owing to its ubiquitous nature of involvement, it is necessary to keep a low threshold for testing for *O. tsutsugamushi* in cases of new-onset CNS-demyelinating/vasculitic events. Survivors of brainstem demyelination should be meticulously followed up. Olivary hypertrophy is an exceptional consequence of brainstem insults, which may manifest after a variable period of latency. Despite the dearth of evidence, one might presume that mechanisms such as synaptic reorganization and neuroplasticity might be

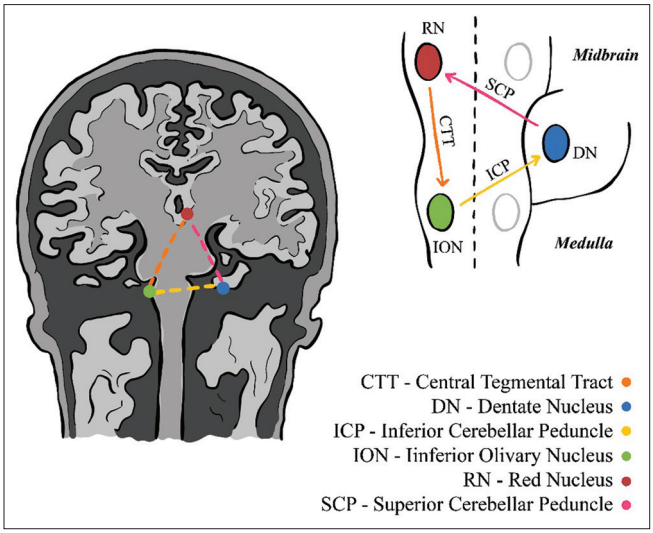

Figure 2: Artistic illustration of Guillain–Mollaret triangle on T2-weighted MR image (left) with schematic representation of the nuclei and tracts. MR = magnetic resonance

at play following neurotropism of *O. tsutsugamushi,* leading to olivary degeneration.

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Conflicts of interest

There are no conflicts of interest.

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