Pontine Tegmental Cap Dysplasia: A Rare Brainstem Malformation Mimicking Hereditary Sensory Autonomic Neuropathy

Dear Editor,

Pontine tegmental cap dysplasia (PTCD) is a rare hindbrain malformation with heterogeneous clinical manifestations and distinctive imaging findings. PTCD is characterized by hypoplastic ventral pons with tegmental cap at the dorsal pons on magnetic resonance imaging (MRI) and ectopic transverse pontine fibers in the dorsal pons on diffusion tensor imaging (DTI).[1,2] We report a case of PTCD in a young child presenting with developmental delay, corneal opacities, nonhealing oral ulcers, and sensorineural deafness, with absence of sweat and tears, mimicking hereditary sensory autonomic neuropathy (HSAN) type II or type III.

A 13-month-old girl, first born of consanguineous parentage, with smooth perinatal transition presented to us with delay in attainment of developmental milestones. At the time of presentation, she was able to sit in a tripod position with support, babble, and had attained rolling over corresponding to a developmental age of 5–6 months. The child was excessively irritable in the initial 3 months of life, with an episode of unprovoked tonic seizure at 5 months of age. From 6 months of age, parents noticed fluffy opacities in the eyes (right followed by left), which progressively increased and led to visual impairment. She also had recurrent nonhealing oral ulcerations. Eventually, parents also observed that the child had poor response to sound, with absence of tears and sweat. There was no history of regression of previously attained milestones or any associated movement abnormalities. There were no ulcers over the extremities or self-mutilation behavior. There was no similar history in siblings. On examination, the head circumference was 44 cm (-2 to -3 z-score, World Health Organization [WHO]), there was corneal clouding in both eyes (left > right), visual acuity was 20/400 in the right eye and finger movement perception in the left eye, and mucosal ulcers were found on the lower lip; also, absent corneal and conjunctival reflex, absent sensations over the face, absent menace reflex, and absence of response to the sound of bell bilaterally were noted. Motor examination showed normal tone, power, and preserved reflexes [Figure 1a and b]. The child had global developmental delay and bilateral trigeminal, facial, auditory, and autonomic neuropathy. Based on the clinical deficits the localization was considered to be at the brainstem or cranial nerves, with the possible etiology being HSAN or brainstem malformation/tumors. Complete hemogram, lipid profile, renal, hepatic, and thyroid function tests, ammonia, and

lactate were normal. Tandem mass spectroscopy and urine for metabolite abnormalities were negative. Brain MRI showed an abnormal brainstem and cerebellar peduncle morphology suggestive of PTCD [Figures 2–5]. Nerve conduction study showed sensorimotor axonal neuropathy in all the tested nerves (motor- median, ulnar, and common peroneal nerves; sensory- median and ulnar nerves). Starch–iodine test for the presence of sweat production revealed no production of sweat even after 2 h [Figure 1c]. Hearing assessment showed absent otoacoustic emissions in the right ear and doubtful presence in the left ear. X-ray spine was normal. Electroencephalography was normal. Whole exome sequencing showed no overt pathogenic/likely pathogenic variants in the well-established genes that are monogenic causes of PTCD and HSAN. A final diagnosis of PTCD was considered. The child was treated symptomatically with lubricating eye drops and rehabilitation measures.

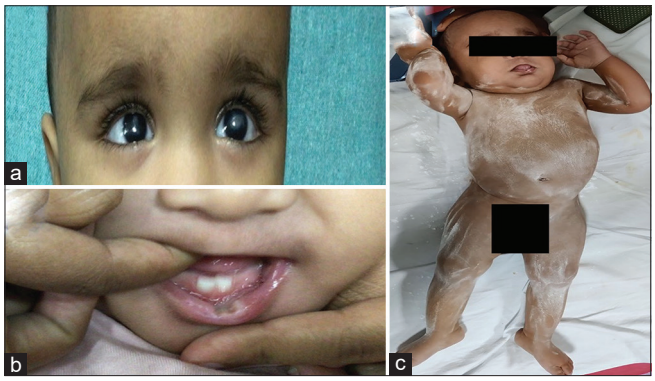

Figure 1: (a) Corneal clouding in both eyes. (b) Nonhealing oral ulcer in the lower lip. (c) A negative starch–iodine test even after 2 h of topical application (70% alcohol, povidone-iodine, and starch)

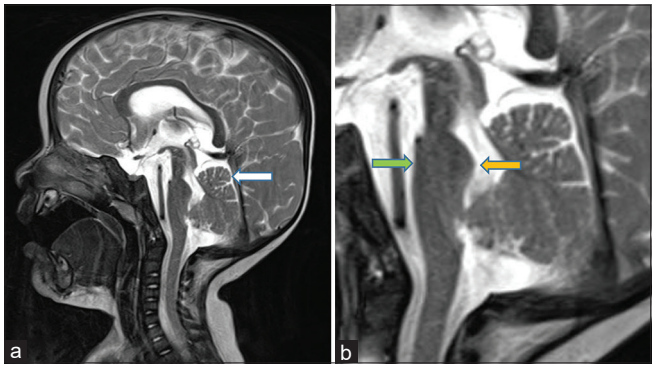

Figure 2: (a and b) MRI brain T2W sagittal images highlighting flattening of the ventral pons (green arrow) and thinning of the isthmus with dysmorphism of the dorsal upper pons (cap like) bulging (orange arrows) and protruding in the fourth ventricle. Mild cerebellar vermian hypoplasia and corpus callosum hypoplasia are seen. MRI = magnetic resonance imaging, T2W = T2 weighted

PTCD is a rare hindbrain malformation, with only 50 patients reported till date in the literature.[1,2] The term was first proposed by Barth *et al*.[1] in the year 2007 in four unrelated children who presented with corneal anesthesia (1/4), sensorineural deafness (4/4), swallowing difficulty (2/4), ataxia (2/4), and bony abnormalities (4/4). Though the presence of ventral pons hypoplasia and cerebellar atrophy has earlier been described in pontocerebellar hypoplasia, congenital disorders of glycosylation, Moebius syndrome, and Joubert syndrome, imaging differed in these patients. In addition to ventral pons hypoplasia and cerebellar atrophy, the unique findings described in PTCD are the presence of cap-like projection from the middle third of the tegmentum of dorsal pons into the fourth ventricle, vermian hypoplasia, abnormalities in the cerebellar peduncles often giving rise to a molar tooth appearance, distorted appearance of the medulla oblongata, and absent inferior olivary prominences.[1,2]

Studies on DTI show absent transverse pontine fibers in the ventral pons, aberrant transverse fibers in the tegmental cap projecting from the dorsal pons, and reduced or absent decussation of the superior cerebellar peduncle.[3,4] Based on this, the possible mechanisms implicated in the development of PTCD are defective axonal guidance, neuronal migration, or ciliary dysfunction during the embryonic stage.[1,2] Mutational studies on *DCC* and *NTN1* genes, which are responsible for axonal guidance, have been negative.[1] In a report by Macferran *et al*.,[5] a 2q13 microdeletion consisting of the gene *NPHP1* implicated in Joubert syndrome has been reported to

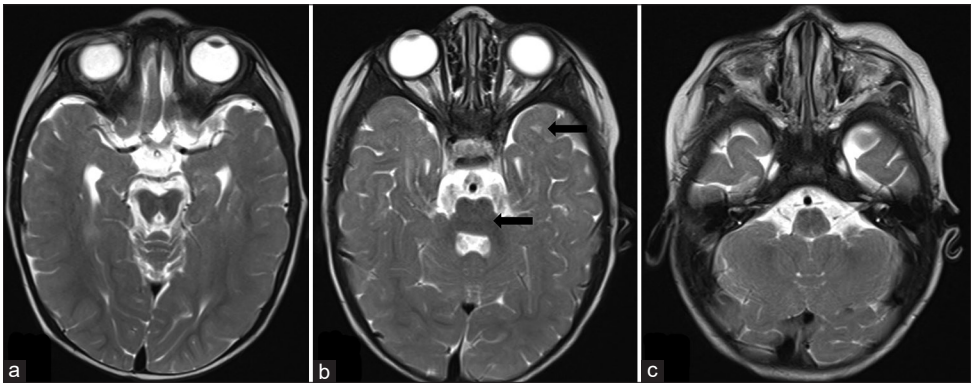

Figure 3: (a–c) MRI brain T2W axial images showing hypoplastic middle cerebellar peduncle with globular dysmorphic pons. Subcortical white matter signal changes in the cerebral hemisphere. MRI = magnetic resonance imaging, T2W = T2 weighted

be associated with PTCD. Nonetheless, the same has not been replicated. Though a strong genetic role has been attributed to PTCD, no single definitive gene has been described to be associated with PTCD.

The clinical manifestations of PTCD reflect the involvement of structures in the hindbrain.[1,2,6] The onset can be in the neonatal period, which is usually severe, or in early childhood and often sporadic. The clinical hallmarks are the presence of involvement of cranial nerves (V, VI, VII, and VIII), developmental delay, cognitive impairment, and cerebellar symptoms like hypotonia, ataxia, and oculomotor apraxia. Cranial nerve symptoms described are corneal anesthesia, blepharitis, lack of facial sensations, impaired facial expressions, squint, and sensorineural hearing loss. Skeletal abnormalities (fused lumbosacral vertebrae, hemivertebrae, and acetabular dysplasia) have been reported in most of the patients. In addition, gastrointestinal (dysphagia, reflux disease, imperforated anus) and renal anomalies (horseshoe kidneys) and cardiac involvement (mild atrial septal defect) can also be seen. There have been reports of complete absence of vestibulocochlear nerves and presence of accessory auditory canal for the facial nerve on imaging in majority of cases.[7] Dysautonomia in the index child can probably be due to brainstem malformation itself.

There is no definitive treatment for PTCD. Supportive care is in the form of rehabilitation, and protection of neurotrophic cornea with lubricating eye drops, patches, or tarsorrhaphy.[6] The role of cochlear implantation has been conflicting.[7,8] Prognosis of PTCD is poor if onset is the neonatal period or if there is severe brainstem dysplasia on imaging (beaked angular brainstem). However, the presence of tegmental cap on imaging reflects mild disease. Lately, the emphasis is on prenatal diagnosis with ultrasonography and fetal MRI, with a few reports demonstrating diagnosis of PTCD as early as 22 weeks of gestation.[9]

Our index child presented to us with developmental delay, neurotrophic lesions in the cornea and oral mucosa, sensorineural deafness, and autonomic involvement in the form of absence of sweat and tears. Hence, upfront, a clinical diagnosis of HSAN type II or III was considered. Eventually, imaging clinched the diagnosis to be a brainstem malformation, and it was identified to be PTCD. As there is no definitive etiology identified till date, the role of fetal MRI would be crucial in recognizing this entity antenatally.

PTCD is a rare hindbrain malformation with characteristic clinical and imaging findings (ventral pons hypoplasia with dorsal pons tegmental cap). Often, it can be mistaken for HSAN clinically or other brainstem malformations (pontocerebellar hypoplasia, Joubert syndrome, Moebius syndrome) on imaging. Our case also expands the phenotype of PTCD with autonomic involvement. The awareness of the entity has to be increased among the clinicians, and the role of fetal MRI needs to be discussed for subsequent conceptions.

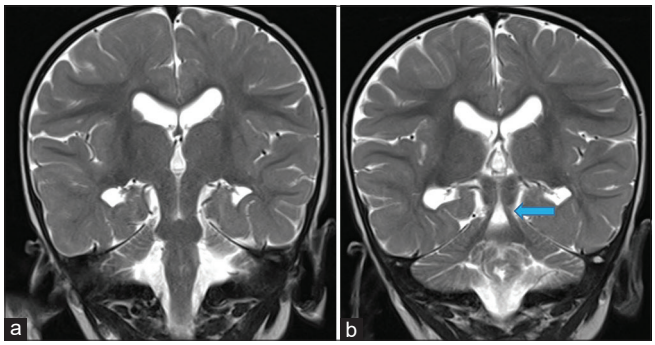

Figure 4: (a and b) MRI brain T2W coronal images showing "molar tooth" appearance of the elongated superior cerebellar peduncles running laterally (arrows) and the dorsal band crossing the midline and likely joining the middle cerebellar peduncles. MRI = magnetic resonance imaging, T2W = T2 weighted

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

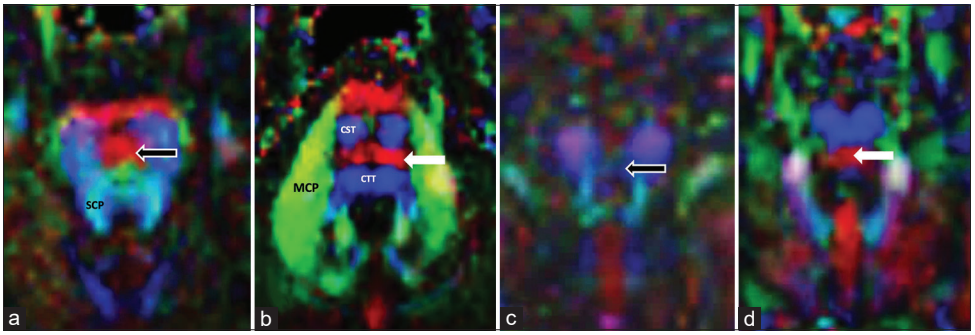

Figure 5: Diffusion tensor imaging (six direction) (a and b) demonstrates normal decussation of SCP (black arrow), and normal relation of CST, CTT and traverse pontine fibers (white arrow); (c and d) Imaging In pontine tegmental cap dysplasia in index child, showing no evidence of SCP decussation (black arrow) and abnormal ventral orientation of transverse pontine fibers in the pons due to faulty migration (white arrow). [CST= Corticospinal tract, CTT= central tegmental tract, SCP = superior cerebellar peduncle]

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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