Congenital third cranial nerve palsy with prenuclear dysinnervation involving otolithic pathways: Underpinnings of a novel congenital cranial dysinnervation disorder

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A 10-year-old boy with unilateral cryptorchidism and renal aplasia displayed features of unilateral congenital pupil sparing third cranial nerve palsy with exotropia manifesting novel dysinnervation encompassing synergistic divergence with upshoot, convergence on attempted upgaze, gaze-evoked phasic conjugate torsion, and gaze-evoked nystagmus. Congenital third nucleus/nerve hypoplasia with secondary dysinnervation is classified as congenital cranial dysinnervation disorder (CCDD). It is speculated that miswiring between prenuclear structures, otolithic pathways, interstitial nucleus of Cajal (INC), nucleus prepositus hypoglossi, and third and sixth nerve nuclei likely resulted in this novel dysinnervation. Cryptorchidism and renal aplasia if seen may point towards an overlapping phenotype with Duane-radial ray syndrome and acro-renal-ocular/IVIC syndromes.

Key word: Congenital cranial dysinnervation disorder, congenital third nerve palsy, cryptorchidism, gaze-evoked conjugate torsion, renal agenesis, synergistic divergence, vestibular nystagmus

Congenital cranial dysinnervation disorders (CCDDs) with fibrosis as cardinal feature share great genotypic and phenotypic heterogeneity affecting cranial nerve nuclei or nerves.[1] Synergistic divergence (SD), another CCDD is characterized by paradoxical abduction of the affected eye on attempted horizontal gaze to contralateral side affecting the sixth cranial nerve nuclei or nerves.[3] In CCDDs, lack of innervations and paresis are the primary events, with miswiring and a variable amount of fibrosis as a secondary event rendering the clinical picture extremely variable and heterogeneous. CCDDs involving third and fourth cranial nerve nuclei or nerves with exuberant fibrosis are eponymously classed as congenital fibrosis of extraocular muscles (CFEOMs).[3] CCDDs involving third/fourth nerves where fibrosis and paresis are admixed may present like the congenital third and fourth nerve palsies, mono-ocular elevation deficiencies, and Brown’s syndrome remain poorly delineated. About 1/3 of congenital third nerve palsies and 2/3 of fourth nerve palsies may demonstrate some hypoplasia/aplasia of the nerve and qualify to be classified as CCDDs.[10] Brown’s syndrome and fourth cranial nerve palsy may coexist in the same eye.[11] Such palsies may share features of unilateral CFEOM3 sans fibrosis with TUBB 3 and TUBB2B pathologic variants with attendant dysinnervation and CNS involvement. The present case showcases that dysinnervation may not only be peripheral involving other cranial nerves but also involve prenuclear structures like the interstitial nucleus of Cajal (INC) and medial longitudinal fasciculus (MLF) constituting otolithic pathways. That immensely broadens the turf of CCDDs and the way we look at them.

Case Report

A boy aged 10 years presented with outward deviation, abnormal ocular movements, and poor vision in the right eye since birth. The child was a known case of absent right kidney and left cryptorchidism. There was no consanguinity and the other two siblings were unaffected.

He had aided visual acuity of 20/400 and 20/20 with +3.5 DS and +1.5 DS OS. Right exotropia of >60 PD and hypotropia of 15 PD was noted. Ductions were full in the left eye but limited in the right eye (adduction limitation -4, abduction limitation -1, supraduction and infraduction limitation -3). On levoversion, synergistic divergence (SD) with an upshoot of the right eye (vertical split) occurred. On attempted upgaze right eye synkinetically adducted to a large esotropic position with no pupillary constriction/convergence retraction nystagmus, adduction was maximum on straight upgaze. On an attempted downgaze, there was SD right eye with a worse vertical split that was maximum in levo-depression. There was a large A pattern. Bilateral fundus intorsion noted in primary position, upgaze evoked grade 4 conjugate extorsion right eye, and intorsion left eye occurred [Fig. 1]. The head tilt test was unremarkable.

There was no nystagmus in primary position, in left eye gaze-evoked right beating horizontal jerk nystagmus was noted on dextroversion. On levoversion, a torsional right beating vestibular nystagmus with a see-saw movement was noted [Video 1]. On magnetic resonance imaging (MRI) of the
brain and orbits, a hypoplastic right medial rectus (MR) was found (note slightly tilted coronal view). Subtle ventricular expansion in the peritrigonal area was noted [Fig. 2a and b]. Third and sixth cranial nerves could not be visualized. Left renal agenesis and right undescended testis were revealed on abdominal ultrasound and physical examination [Fig. 2c] Forced duction test done under local anesthesia was moderately positive for the right inferior rectus (IR) with poor force generation in all directions. Linkage analysis was not done.

**Discussion**

The clinical presentation simulates congenital unilateral pupil sparing third nerve palsy with novel dysinnervation with sixth nerve in the form of SD with vertical splits and prenuclear structures involving otolithic pathways manifesting as gaze-evoked ipsilesional phasic conjugate torsion, gaze-evoked horizontal jerk and torsional vestibular nystagmus, upgaze evoked convergence, down gaze-evoked divergence with vertical splits, all conforming to a novel CCDD.[13]

The presentation can be conflated as a non-fibrotic paretic form of unilateral congenital fibrosis of the extraocular muscle (CFEOM3).[1] Central nervous system involvement comprising dysgenesis of the corpus callosum, anterior commissure, corticospinal tracts, basal ganglia, malformations of cortical development, polymicrogyria, and microgyria are reported with CFEOM3 phenotypes with TUBB3, TUBB2B pathogenic variants along with dysinnervations like synergistic divergence.[1-3] TUBB3 and TUBB2B phenotypes are caused by pathogenic variants in beta tubulins. Microtubules are composed of tubular proteins and are vital for generation migration and differentiation of neurons, the three processes that are vital for the development of the vertebrate brain. Functional properties are determined by the microtubule cytoskeleton and are essential for intracellular transport and cell division in all eukaryotes.[6]

Developmental brain anomalies in basal ganglia, optic nerve hypoplasia, pituitary gland malformations, hypoplasia of the midbrain and corpus callosum, ventricular dilatation, de-Morsier syndrome, and the absence of septum pellucidum have also been reported in association with congenital third nerve palsies drawing proximity to CFEOMs.[7] INC, a prenuclear structure, is lying just rostral to third nerve nuclear complex and caudal to riMLF. The INC vital for vertical gaze holding projects to both third, fourth nerve nuclei, ipsilateral cerebellum, vestibular nuclei, and nucleus prepositus hypoglossi (NPH) in the medulla, the structures vital for horizontal gaze holding. Acquired inhibitory lesions of INC produce vertical gaze-evoked and ipsilesional beating torsional nystagmus, impaired smooth pursuit, and contralesional tonic ocular tilt reaction (OTR).[8] An acquired phasic OTR is due to an increase in neural activity and is ipsilesional.[9] Conjugate torsion is an integral part of OTR and together with ipsilateral hypotropic eye fulfills two of the three criteria for OTR constituting incomplete OTR.[9]

Novel gaze-evoked ipsilesional (right) conjugate torsion seen in this child may constitute incomplete phasic OTR due to excitatory involvement of INC likely resulting from dysinnervation. Vestibular nystagmus in the form of an

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**Figure 1:** (a) Nine gaze montage showing limited ocular rotations right eye with right eye convergence on upgaze, synergistic divergence and upshoot on left and down gaze. (b) Fundus torsion in primary position (above) and upgaze evoked conjugate torsion (below)

**Figure 2:** (a) MRI showing medial rectus hypoplasia. (b) Mild peritrigonal hydrocephalus. (c) Abdominal ultrasound showing left renal aplasia and right cryptorchidism
ipsilesional beating gaze-evoked torsional nystagmus on the left gaze may also betrayed dysinnervation at the level of the INC and ipsilesional beating gaze-evoked horizontal jerk nystagmus likely shows dysinnervation in the otolithic pathways between INC and NPH.

Hypoplasia of ipsilateral MR is invariably found in SD, which may show hypoplasia/aplasia of the abducens nerve. Hypoplasia may result in dysinnervation of ascending interneurons in MLF. Convergence in upgaze with vertical splits in the left and downgaze likely arose from dysinnervation simultaneously involving vertical and horizontal vectors in INC, riMLF, and MLF.

Cryptorchidism has been reported with bilateral CFEOM3. Acro-renal-ocular syndromes may have overlapping features with Duane-radial ray syndromes. The presence of hitherto unreported renal aplasia and cryptorchidism in congenital third nerve palsy attests to the complex underpinnings of this CCDD.

**Conclusion**

Gaze-evoked torsional and horizontal jerk nystagmus, gaze-evoked conjugate torsion, synergistic divergence, vertical splits in downgaze unequivocally betray dysinnervation between otolithic pathway including INC, riMLF, MLF, and right sixth and third nerve nuclei. The novel prenuclear and internuclear dysinnervation in the setting of congenital third nerve palsy may have some remote parallels in a likely CFEOM3 phenotype from a TUBB3/TUBB2B pathogenic variants with brain anomalies and underscores the expanding turf of CCDD phenotypes with a variable blend of paresis and fibrosis. Congenital third, fourth nerve palsy, Brown’s syndrome, Monocular Elevation Deficiency (MED), and CFEOMs may just be a continuum of the clinical spectrum with nature and extent of fibrosis and paresis determining the clinical picture. Advances in imaging and genetics are likely to fix the missing pieces of the jigsaw.

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**Conflicts of interest**

There are no conflicts of interest.

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