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Auditory neuropathy spectrum disorder in hypomyelinating leukodystrophy—A case study

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1. Introduction

Leukodystrophy is one of a group of disorders characterized by degeneration of white matter in the brain. The basic defect in this disorder is directly related to the synthesis and maintenance of myelin membranes. When damage occurs to white matter, immune responses may lead to inflammation in the central nervous system along with loss of myelin. Characteristics of leukodystrophy include decreased motor function, spasticity, muscle rigidity, and eventual degeneration of the senses of vision and hearing. The majority of the leukodystrophies involve the inheritance of a recessive, dominant, or X-linked trait while some are the result of spontaneous mutation rather than genetic inheritance (although involving a defective gene).

Though the degeneration of white matter can be seen on an MRI, identification of leukodystrophy remains a challenge. Hypo myelinating leukodystrophies (HLD) are identified by a paucity of myelin development. MRI typically shows variable signal (that is, hyper-, hypo-, or isointense) on T1-weighted imaging and mild hyper intensity on T2-weighted imaging of the white matter compared to gray matter signal. This is distinct from other leukodystrophies in which more hypo intense T1-weighted and more severe hyper intense T2-weighted white matter imaging signals are seen, usually in a more geographic or localized distribution [1].

Kohlschütter and Eichler [2] reported that boys with X-ALD may have normal brainstem auditory evoked responses (BAER) in the first decade of life, but BAERs later become abnormal in the course of the disease when demyelinating lesions extend to the brainstem and spinal cord. Even patients with a normal MRI may have an abnormal neurophysiologic pattern identical to that seen in adrenomyeloneuropathy patients (evidently milder in terms of abnormalities); in such cases, usually BAERs are first to be abnormal [3]. Feldman et al. [4] also suggested that abnormal BAERs can be of help in the early diagnosis of the disorder.

Dramatically improving BAERs over a 10-year period have been reported in persons affected with HLD [5]. Hypomyelinating disorders like Pelizaeus–Merzbacher disease (PMD) may show normal wave I without subsequent waves and thus BAERs are of particular value in the early diagnosis of the disorder [6,7]. BAERs are typically absent in PMD [1]. Therefore, Pouwels et al. [1] believe that BAERs can serve as an objective marker for identification of PMD. However, the validity of this observation needs to be established.

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A number of researchers have reported hearing and speech related problems in persons with HLD; absence of language acquisition and evidence of brainstem dysfunction on auditory testing [8]; deafness in 1–3 year old children with leukodystrophy [9]; and learning disability and variable delay in auditory evoked potentials in 7 unrelated patients with leukodystrophy [10]. Van Der Knaap et al. [10] also reported very poor speech development and decreased hearing (not a consistent feature) in another series of 11 unrelated patients with leukodystrophy. Simons et al. [11] reported that 10 out of their 11 patients with HLD had some sort of speech delay and dysarthria.

In a retrospective comparative study of neurophysiologic results from 10 patients with PMD-like disease (PMLD1; 608804) and 8 with classic PMD, Henneke et al. [12] found that BAERs were significantly worse in patients with classic PMD. Waves III–V which are generated in the pons and midbrain were absent in all patients with PMD, but were clearly recordable in patients with PMLD1. Investigations of auditory acuity were not available. Henneke et al. [12] concluded that BAER is a helpful tool to differentiate between PMLD1 and PMD.

The clinical onset of HLD is frequently insidious, and the symptoms then slowly progress. It can be seen from the above review that many investigators have reported abnormalities of speech and hearing in children with HLD. Most of the investigators have talked of either abnormalities of BAERs or sensorineural hearing loss (general observation only). However, the specific nature of the hearing defect in this clinical population has not been described. We report here a patient with HLD in whom a diagnosis of auditory neuropathy spectrum disorder (ANSD) was made based on detailed audiological investigations.

2. Report of a case

A 26-months old girl NM was brought to the outpatient clinic of the Department of Neurology with the complaints of abnormal movements of eye and head since birth, and delayed developmental milestones. She was the second child born to third degree consanguineous parents. She was born at term after an uneventful pregnancy and delivery (birth weight of 3 Kg). Birth cry was delayed and therefore, the baby was kept in neonatal ICU for a day. Then the parents were counselled and discharged. At one year, mother noticed that the child was not able to hold her neck. The doctors at the local hospital advised the parents to carryout physiotherapy. Parents did not suspect any problem relating to speech-language or hearing in their child.

Examination at the Neurology outpatient clinic of the National Institute of Mental Health & Neurosciences showed an active playful child. All anthropometric measurements were below the third centile for age. Neurological examination revealed roving eye movements in the primary position which became exaggerated on horizontal and vertical gaze. Extra ocular movements were full. She could fix and follow light. Ophthalmological examination revealed normal optic disc and retina. Motor system examination showed bilateral pyramidal signs in the form of spasticity, brisk reflexes and extensor plantar response. Tremulousness of bilateral upper limbs on reaching out for objects was noted. Titubation of the head was present at rest.

She was evaluated for routine hematological and biochemical studies which revealed normal results. Tandem mass spectrometry revealed normal amino acids and acyl carnitine profiles. Urine was negative for abnormal metabolites. She had a normal thyroid function, and normal levels of S. Homocysteine, Vitamin B12, uric acid, serum ammonia, and serum lactate. Nerve conduction studies showed normal compound muscle action potentials from median, ulnar and common peroneal nerves and sensory nerve action potential from sural and median nerves. The child could stand with support, transfer objects from one hand to another, babble a little and respond to sound though inconsistently.

Review of the MRI of the brain done at 22 months of age (Fig. 1) showed presence of myelination confined to the posterior limbs of the internal capsule, pericentral area, brain stem, genu and splenium of the corpus callosum on both T1 weighted and T2 weighted images. There was no evidence of myelination in lobar white matter. Basal ganglia and thalamus showed hypo intensity on T2 weighted images. The findings were suggestive of hypo myelination. Based on the results of clinical, MRI and metabolic

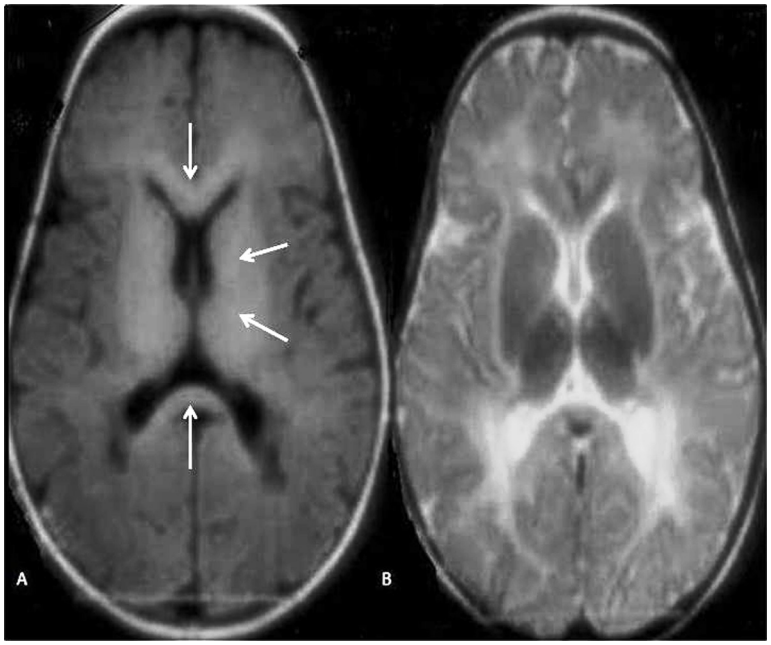

Fig. 1. MRI brain at the age of 22 months: T1 weighted image (A) demonstrating hyper intensity only in the anterior and posterior limb of internal capsule, genu and splenium of the corpus callosum. T2 weighted image (B) demonstrates diffuse hyper intensity of the white matter suggesting hypomyelination.