Lichtenstein–Knorr Syndrome: A Rare Case of Ataxia with Sensorineural Hearing Loss

Sir,

Lichtenstein–Knorr syndrome is a juvenile-onset form of cerebellar ataxia and sensorineural hearing loss. It was first described in 1930 by Lichtenstein and Knorr.[1] To date, only five cases with two variants causing Lichtenstein and Knorr phenotype have been described (literature search in PubMed, Google Scholar, OMIM database). Here, we describe a novel homozygous solute carrier family (*SLC9A1*) mutation in a 17-year-old boy who presented with ataxia and hearing loss leading to a diagnosis of Lichtenstein–Knorr syndrome.

A 17-year-old boy, born out of consanguineous marriage, presented with a history of mental sub-normality, difficulty in walking from three years of age, and seizures from eight years of age. The child had an uneventful perinatal period. He had a delay in milestones involving all domains. The child started walking at the age of three years. However, the mother noticed swaying to either side, recurrent falls, and incoordination of both upper limbs. It was progressive in nature, associated with explosive quality of speech. Subsequently, from the age of eight years, child developed recurrent seizures. Semiology was unresponsiveness that lasted for a few seconds. He was initiated on carbamazepine, following which seizures were controlled. The patient remained seizure-free for one year. However, he started having recurrent episodes despite being on medications. Hence, phenytoin and clobazam were added outside. At the age of 10 years, he developed progressive hearing impairment in both ears. The other siblings were normal. The difficulty in walking and speech disturbances increased from the age of 16 years. There was no significant family history. No history of visual disturbances, weakness of limbs. On examination, child was conscious and following simple commands. Orbito-frontal circumference was 51 cm. Formal cognitive assessment could not be done. He had low set ears, notched incisors, malaligned teeth, and wide epicanthic fold. Parents and siblings did not have dysmorphism. Fundus examination was normal.

Eye movements assessment showed multi-directional nystagmus. Bilateral sensorineural hearing loss was present. He had hypotonia of all limbs, deformities of right elbow and wrist in the form of flexion deformity, power of 5/5, areflexia, and flexor plantar response. There was bilateral incoordination of limbs, dysdiadochokinesia, and gait ataxia. Laboratory parameters showed hemoglobin of 11.6 gm%, total leucocyte count of 4700/mm3. He had low serum B12 levels (180 ng/L). His serum ammonia, lactate, and copper levels were within normal limits. Renal function test, liver function test, thyroid function test, and lipid profile were normal. Urine screening for abnormal metabolites and saline dilutional test for acanthocytes were negative. Magnetic resonance imaging (MRI) of brain revealed cerebellar atrophy [Figure 1 and Table 1]**.** Nerve conduction studies showed a mild decrease in conduction velocities. Brainstem auditory evoked response showed absent waveforms. Visual evoked potential (VEP) of both eyes was normal. He had received vitamin E supplements outside for about a year with no response. He received vitamin B12 supplements. In view of these clinical and investigation findings, a diagnosis of autosomal recessive cerebellar ataxia (ARCA) with sensorineural hearing loss and seizures was considered. ARCA can be sub-classified into congenital like Joubert syndrome, metabolic, that is, Ataxia with vitamin E deficiency, Abetalipoproteinemia, Refsum's disease, deoxyribonucleic acid repair defects, and degenerative types. Most of them have infantile-onset. Few manifest symptoms from adolescence. The clinical clue in our patient was SNHL. Deafness is a feature of Refsum's disease. However, our patient did not have retinitis pigmentosa and other features of Refsum disease. Hence, commonly described ARCAs were ruled out clinically.[2] We proceeded to genetic testing after counseling the family.

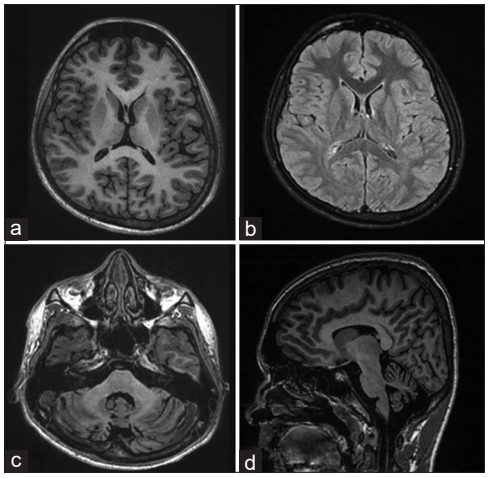

Figure 1: MRI T1 (a) and T2 FLAIR axial (b) show normal cerebral parenchyma; reveals cerebellar atrophy in T2 FLAIR axial (c) and T1 sagittal image (d)

On clinical exome sequencing, a novel homozygous splice site proximal variant c. 1573C>T in exon 6 of the *SLC9A1*(chr1:27429716G>A) that results in a stop codon and premature truncation of the protein at codon 525 (p. Gln525Ter; ENST00000263980.3) was detected [Figure 2]. The p.Gln525Ter variant has not been reported in the 1000 genomes, ExAC, gnomAD, and NHLBI ESP databases. The insilico prediction of the variant on Variant Effect Predictor, Ensembl release 87 (SIFT version - 5.2.2; PolyPhen - 2.2.2); LRT version - November, 2009 release from dbNSFPv3.1 and Mutation Taster2 based on build NCBI 37/Ensembl 69 predicted this variant as pathogenic. The reference genome is conserved across species. Based on the above evidence and according to American College of Medical Genetics (ACMG) guidelines the *SLC9A1* variation is classified as a pathogenic variant. Segregation analysis was performed in the unaffected parents and sibling by Sanger sequencing. The variant was in a heterozygous state in the unaffected parents and unaffected sister [Figure 2]**.** The phenotype of the proband is matching with the phenotype caused by pathogenic variants in the gene.

Lichtenstein–Knorr syndrome is an autosomal recessive neurologic disorder characterized by severe progressive sensorineural hearing loss and progressive cerebellar ataxia. The onset of symptoms is usually in childhood or young

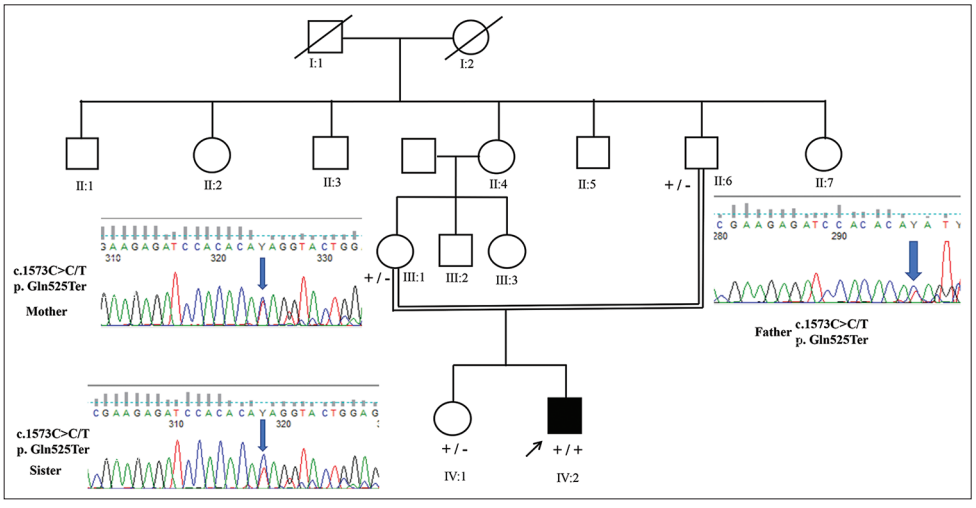

Figure 2: Pedigree chart and segregation analysis of sister and parents

Table 1: Clinical, imaging, and genetic findings of cases reported

Case	Reported in this article	Previous reported cases				
		Iwama Kazuhiro *et al*.,[4] 2018		Guissart Claire *et al*.[3] 2015		
Reference	Case 1	Patient1	Patient2	Patient 1	Patient 2	Patient 3
Genetics						
Gene	SLC9A1	SLC9A1		SLC9A1	SLC9A1	SLC9A1
Mutation	Non-sense	Deletion		Missense	Missense	Missense
Location	Exon 6	Exon 1		Exon 3	Exon 3	Exon 3
Nucleotide change	c. 1573C >T	c. 862del		c. 913G>A	c. 913G>A	c. 913G>A
Amino acid change	p. Gln525Ter	p.Ile288Serfs*9		p.Gly305Arg	p.Gly305Arg	p.Gly305Arg
Zygosity	Homozygous	Homozygous		Homozygous	Homozygous	Homozygous
Inheritance	AR	AR		AR	AR	AR
Demographics						
Age of onset	3 years	2 years and 6 months	1 year and 6 months	20months	16 months	12 months
Age of presentation	17 years	8 years and 10 months	3 years and 1 month	22 years	21 years	17 years
Gender	Male	Male	Male	Female	Female	Male
Ethnic Origin	Indian	Chinese	Chinese	Turkish	Turkish	Turkish
Consanguinity	Yes	No	No	Yes	Yes	Yes
Family history	Absent	Present	Present	Present	Present	Present
Clinical Phenotype						
Symptom at onset	Delayed walking	Delayed walking	Delayed walking	Deafness	Deafness	Deafness
Developmental milestones	Mental retardation, all milestones affected	Mild delay in speech and walking	Motor milestone delay	Delayed walking until 2 years	Delayed walking until 18 months	Delayed walking until 5 years, with aid
Seizures	Yes	No	No	No	Yes but EEG normal	No
Ataxia	Yes, Progressive	Yes	Yes	Present since walking	Present since walking	Present since 3 years
Ocular symptoms	Horizontal and upbeat Nystagmus	Oculomotor apraxia	Oculomotor apraxia	Absent	Absent	Absent
Hearing impariment	Present	Absent	Absent	Profound	Profound	Severe
Speech	Slurred speech	Mild delay (slurred speech)	Within normal range	Normal	Normal	Sign language
Limb weakness	No	No	No	No	No	No
Areflexia	Present	Not described	Not described	Upper and lower limbs areflexia	Upper and lower limbs areflexia	Upper and lower limbs areflexia
Other features	Dysmorphic facies, hypotonia of extremities	-	-	Cafe-au-lait spots on left thigh	Cafe-au-lait spots on left thigh	Short stature -3SD at 16 years
Investigations						
Brain MRI (age at MRI)	Mild cerebellar atrophy	Mild cerebellar atrophy (5 years)	Not done	Normal	Mild Vermian Atrophy	Not done
Auditory evoked potentials	Bilateral absent wave forms	Normal	Normal	Lack of response at 100dB	Lack of response at 100dB	Lack of Vwave at 110dB
Sensory Evoked potentials	Normal	Not done	Not done	Decreased	Decreased	Decreased
VEP	Normal	Not done	Not done	Not done	Not done	Not done
NCS	Mild reduction in conduction velocities	Not done	Not done	Normal	Normal	Not Done
EEG	Not done	Not done	Not done	Not done	Normal at 14 years	Not done
Nerve or muscle biopsy	Not done	Not done	Not done	Not done	Normal	Not done

adulthood.[3] To date, recessive *SLC9A1* related pathogenic variants causing Lichtenstein–Knorr syndrome has been reported in five patients from two families [Table 1].

Our patient developed ataxia and hearing loss beginning in early childhood and progressed till the age of 17 years, like patient 3 of Guissart, Claire *et al*.[3] 2015. He also had seizures with developmental delay and mental retardation unlike other reported cases.

The SLC9A1 is responsible for Na^+/H^+ exchange transport (NHE1).[4,5] NHE1 is a ubiquitous protein that transports one Na+ into the cell in exchange for one H + against its electrochemical gradient.[5,6] In the spontaneous mouse mutant, analysis of mutant mouse tissues revealed progressive neuronal degeneration in three regions: vestibular nuclei, cochlear nuclei, and most prominently deep cerebellar nuclei. These sites of pathology correlate with the clinical presentation of our patients, similar to the three patients of family C in Guissart *et al*.[3] Despite the fact that the SLC9A1 mouse models did not present hearing loss, NHE1 was shown to have an important role in the inner ear by regulating the pH of the endo-lymphatic sac, which is essential for the normal hearing function. It has been shown that changes in the pH of the endolymph cause hearing loss.[7] This is the first detailed explanation of recessive *SLC9A1* related Lichtenstein–Knorr Syndrome from South Asia.

Further studies of SLC9A1 in ataxia/hearing loss patients will uncover the full spectrum of this unique disorder. In patients with suspected autosomal recessive ataxia, sensorineural hearing loss, and neuropathy are clues for diagnosis. Clinical phenotyping helps us curtail investigations, do specific genetic analysis, and prognosticate the illness.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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.

Nagabushan Hesarur[1#], Mainak Bardhan[1#], AshokVardhanReddy Taallapalli[1], Saraswati Nashi[1], Gautham A. Udupi[2], Girish B. Kulkarni[1]

Departments of [1]Neurology and [2]Human Genetics, National Instituute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, India
[#]Equal Contribution

Address for correspondence: Dr. Saraswati Nashi, Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru - 560 029, Karnataka, India.
E-mail: nandanashi@gmail.com

References

1. Lichtenstein H, Knorr A. On some cases of progressive hearing loss in hereditary ataxia. German J Neurol 1930;114:1-28.
2. Palau F, Espinós C. Autosomal recessive cerebellar ataxias. Orphanet J Rare Dis 2006;1:1-9. doi: 10.1186/1750-1172-1-47.
3. Guissart C, Li X, Leheup B, Drouot N, Montaut-Verient B, Raffo E, *et al*. Mutation of SLC9A1, encoding the major Na+/H+ exchanger, causes ataxia–deafness Lichtenstein–Knorr syndrome. Hum Mol Genet 2015;24:463-70.
4. Iwama K, Osaka H, Ikeda T, Mitsuhashi S, Miyatake S, Takata A, *et al*. A novel SLC9A1 mutation causes cerebellar ataxia. J Hum Genet 2018;63:1049-54.
5. Sardet C, Franchi A, Pouysségur J. Molecular cloning, primary structure, and expression of the human growth factor-activatable Na+H+ antiporter. Cell 1989;56:271-80.
6. Bell SM, Schreiner CM, Schultheis PJ, Miller ML, Evans RL, Vorhees CV, *et al*. Targeted disruption of the murine Nhe1 locus induces ataxia, growth retardation, and seizures. Am J Physiol 1999;276:C788-95.
7. Son EJ, Moon IS, Kim SH, Kim SJ, Choi JY. Interferon-γ suppresses Na+–H+ exchanger in cultured human endolymphatic sac epithelial cells. J Cell Biochem 2009;107:965-72.

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