Letters to the Editor

**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. 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. Orbital-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.

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 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)

**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 | Iwama Kazuhiro et al.,[4] 2018 | Previous reported cases | Guissart Claire et al.[3] 2015 |
|--------------------------------|--------------------------------|--------------------------|-------------------------------|
| Reference                      | Case 1                          | Patient 1                | Patient 1                     | Patient 2                     | Patient 3                     |
| Genetics                       |                                 |                          |                               |                               |                               |
| Gene                           | SLC9A1                          | SLC9A1                   | SLC9A1                        | SLC9A1                        | SLC9A1                        |
| Mutation                       | Non-sense                       | Deletion                 | Missense                      | Exon 3                        | Exon 3                        |
| 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. His288Serfs*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           | 20 months                     | 16 months                     |
| Age of presentation            | 17 years                        | 8 years and 10 months    | 3 years and 1 month           | 22 years                      | 21 years                      |
| Gender                         | Male                            | Male                     | Female                        | Female                        | Male                          |
| Ethnic Origin                  | Indian                          | Chinese                  | Turkish                       | Turkish                       | Turkish                       |
| Consanguinity                  | Yes                             | No                       | Yes                           | Yes                           | Yes                           |
| Family history                 | Absent                          | Present                  | Present                       | Present                       | Present                       |
| Clinical Phenotype             |                                 |                          |                               |                               |                               |
| Symptom at onset               | Delayed walking                 | Delayed walking          | Delayed walking               | Deafness                      | Deafness                      |
| Developmental milestones       | Mental retardation, all         | Mild delay in speech and | Motor milestone delay         | Delayed walking until 2 years | Delayed walking until 18     |
|才 usually affected             | walking                         | delay                    |                               | months                        | months, with aid              |
| Seizures                       | Yes                             | No                       | No                            | No                            | Yes but EEG normal            |
| Ataxia                         | Yes, Progressive                | Yes                      | Yes                           | Present since walking         | Present since walking         |
| Ocular symptoms                | Horizontal and upbeat Nystagmus | Oculomotor apraxia       | Oculomotor apraxia            | Absent                        | Absent                        |
| Hearing impairment             | Absent                          | Absent                   | Profound                      | Profound                      | Severe                        |
| Speech                         | Slurred speech                  | Mild delay (slurred speech) | Within normal range         | Normal                        | Normal                        |
| Limb weakness                  | No                              | No                       | No                            | No                            | No                            |
| Areflexia                      | Present                         | Not described            | Not described                 | Upper and lower limbs areflexia | Upper and lower limbs areflexia |
| Other features                 | Dysmorphic facies, hypotonia of | -                        | Cafe-au-lait spots on left    | Cafe-au-lait spots on left    | Short stature -3SD at         |
|                               | extremities                     |                          | thigh                         | thigh                         | 16 years                      |
| Investigations                 |                                 |                          |                               |                               |                               |
| Brain MRI (age at MRI)         | Mild cerebellar atrophy         | Mild cerebellar atrophy (5 years) | Not done                     | Normal                        | Mild Vermian Atrophy          |
| Auditory evoked potentials     | Bilateral absent wave forms     | Normal                   | Normal                        | Lack of response at 100dB    | Lack of response at 100dB     |
| Sensory Evoked potentials      | Normal                          | Not done                 | Not done                      | Decreased                     | Decreased                     |
| VEP                            | Normal                          | Not done                 | Not done                      | Not done                      | Not done                      |
| NCS                            | Mild reduction in conduction    | Not done                 | Not done                      | Normal                        | Not Done                      |
| velocities                     |                                 |                          |                               |                               |                               |
| EEG                            | Not done                        | Not done                 | Not done                      | Normal at 14 years            | Not done                      |
| Nerve or muscle biopsy         | Not done                        | Not done                 | Not done                      | Normal                        | Not done                      |
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.[1] 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.[1] 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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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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