Cervical Dystonia with Cerebellar Ataxia in KCNA1 Mutation: A Phenotypic Expansion

Dear Sir,

The KCNA1 gene encodes the voltage-gated potassium (K^+) channel Kv1.1 α-sub-units, and the mutation has been primarily linked to episodic ataxia type 1 (EA1). Some patients have EA1 with epilepsy or de novo epilepsy without EA1 in this mutation. It has also been associated with hypomagnesemia, paroxysmal dyskinesia, and myokymia.[1] EA1 is characterized by intermittent ataxia, dysarthria, and myokymia precipitated by the exercise, emotional stress, temperature, and sudden movement. However, persistent cerebellar ataxia with dystonia as a phenotype of KCNA1 gene mutation has not been described. Here, we report a 20-year-old lady who presented with cervical dystonia followed by persistent cerebellar ataxia. Genetic analysis showed heterozygous missense mutation in the KCNA1 gene.

A 23-year-old lady born out of consanguineous parentage with normal perinatal history and developmental milestones had presented with the history of abnormal posturing of the head in the form of head turn to the right for 3 years. The abnormal posturing was persistent, with an increase in severity on anxiety and walking. There was no diurnal variation. After 1 month, the patient developed walking difficulty in the form of imbalance and tremulousness of both hand on target-oriented activities. There were no speech, visual, and hearing disturbances. There were no seizures and myoclonus and behavioral changes. The family history was non-contributory. Systemic examination was unremarkable. Neurological examination showed normal cognition, vision, and cranial nerves. There was bilateral horizontal gaze-evoked nystagmus. She had anterior sagittal shift (a combination of anterocollis and retrocaput), left horizontal shift of the head, right laterocaput, and left laterocollis with dystonic tremors during both rest and walking, worsening on walking. There was no null point. The muscle tone, power, and reflexes were normal. There was bilateral impaired finger–nose–finger coordination, heel–knee coordination, dysdiadochokinesia, and impaired tandem gait with gait ataxia [Videos 1,2,3]. Sensory examination and plantar responses were normal. Complete blood counts and renal, hepatic, and thyroid function tests were normal. Slit lamp examination did not show Kayser–Fleischer rings. Peripheral smear for acanthocytes was negative. The serum vasculitis profile, copper, and ceruloplasmin were normal. Brain magnetic resonance imaging (MRI) was normal. Genetic analysis showed a novel heterozygous missense variant (p. Arg295Cys) in exon 2 of the KCNA1 gene (NM_000217.3). The missense variant KCNA1 (NM_000217.3): c. 883C > T (p. Arg295Cys) has not been reported previously as a benign variant to our knowledge. The p. Arg295Cys variant is novel (not in any individuals) in gnomAD. The p. Arg295Cys variant is novel (not in any individuals) in 1 kG. The p. Arg295Cys missense variant is predicted to be damaging by both SIFT and PolyPhen2. As the clinical phenotype of the proband almost matches with that of the disorder caused by pathogenic variants in the gene KCNA1, this variant was classified as likely pathogenic according to the American College of Medical Genetics (ACMG) guidelines. The patient received botulinum toxin (100 units) for rotational torticollis and had moderate improvement for 3 months. She was treated with tetrabenazine (75 mg/day), trihexyphenidyl (10 mg/day), and acetazolamide (750 mg/day). There was no improvement in gait ataxia.

The KCNA1 gene encodes the voltage-gated Kv1.1 potassium channel. The gene mutation primarily causes EA1 with myokymia and with/without epilepsy. The ataxia because of KCNA1 gene mutation is because of the lower availability of Kv1.1 channels in the cerebellum and hippocampus. This low functional reserve of Kv1.1 renders the cerebellum and hippocampus especially vulnerable to Kv1.1 deficits. In EA1, there is hyper-excitability of basket cells in the cerebellum because of the Kv1.1 dysfunction, leading to excessive inhibition of Purkinje cells and subsequent motor deficits.[2] The KCNA1 gene mutation causing cervical dystonia and persistent cerebellar ataxia is rare. Our patient had a peculiar phenotype wherein she had cervical dystonia as the initial symptom, followed by the development of cerebellar ataxia which was non-episodic unlike in EA wherein the ataxic attacks are precipitated by the exercise, emotional stress, temperature, and sudden movement with normality in the inter-ictal period. She did not have myokymia. We found a novel heterozygous missense variant (p. Arg295Cys) in exon 2 of the KCNA1 gene (NM_000217.3). EA1 is mainly caused by missense genetic mutations. There are 47 KCNA1 mutations identified in EA1 patients that are pathogenic or likely pathogenic.[3] Hyperthermia associated with EA1 has been reported in two patients with different KCNA1 mutations in the voltage-sensing domain. KCNA1 mutations have been associated with myokymia or neuromyotonia without ataxia and paroxysmal kinesigenic dyskinesia.[1] Lee *et al*.[4] (2021) reported another phenotype with KCNA1 gene mutation wherein a patient aged 51 years had progressive cerebellar syndrome with generalized myoclonus. Brain MRI showed cerebellar atrophy. They found a novel heterozygous mutation of KCNA1: a frameshift mutation of c. 791del (p. Pro264LeufsTer 10) (NM_000217.2). Demos *et al*.[5] (2009) reported persistent cerebellar dysfunction with cerebellar atrophy in a family with KCNA1 gene mutation c. 1222G > T (p. Val408Leu). Rogers *et al*.[6] (2018) reported four cases of infantile epileptic encephalopathy and cognitive impairment because of de novo KCNA1 variants.

KCNA1 channelopathy has broad phenotypic variability which is influenced by the location and nature of the mutated amino acid residue. EA1 is the most common phenotype of KCNA1 channelopathy. However, this case reports an expansion in the clinical phenotype of KCNA1 channelopathy in the form of dystonia and persistent cerebellar ataxia without episodic variability.

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.

Rohan R. Mahale, Jayanth S. S, Debayan Dutta, Manu S. G, Hansashree Padmanabha, Pooja Mailankody

Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, Karnataka, India

Address for correspondence: Dr. Rohan R. Mahale, Department of Neurology, NIMHANS, Bangalore - 560 029, Karnataka, India.
E-mail: rohanmahale83@gmail.com

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