

Sensory Neuropathy in Spinocerebellar Ataxia Type 14: A Novel Phenotype

Dear Sir,

Spinocerebellar ataxias (SCA) are a group of autosomal-dominant disorders presenting as progressive cerebellar ataxia. Apart from the cerebellum, there is involvement of brainstem, basal ganglia, and cerebral cortex. SCA14 is caused by missense, deletion mutations in the exon 4 of the protein kinase C gamma gene (*PRKCG*). SCA14 has an incidence of 1–4% of all autosomal-dominant cerebellar ataxias. Patients present chiefly with slowly progressive cerebellar ataxia.^[1] There are no reports of SCA14 from India. Hereby, we report a 32-year-old male patient who presented with symptoms suggestive of sensory neuropathy. Brain magnetic resonance imaging (MRI) showed cerebellar atrophy. Whole exome sequencing showed a heterozygous missense mutation in the *PRKCG* gene suggestive of SCA14.

A 32-year-old male presented with burning paresthesia in both feet of 7 months duration and imbalance while walking of 4 months duration. The symptoms were insidious in onset and gradually progressive. The symptoms started as a burning sensation in both soles, moderate in intensity, continuous, with no specific aggravating factors but relieved on foot immersion in water. He was started on gabapentin for the same by local doctor and there was partial relief in symptoms. One month later, the patient developed numbness in both feet, which progressed over 1 month to involve both legs below the knees and was static till the present admission. He started developing imbalance while walking which was more in the dark and on the closure of eyes with the washbasin phenomenon. At the time of presentation to us 7 months after initial symptom onset, he was using a cane to walk. There was slippage of footwear

as he was not aware. His family members had noticed mild slurring of speech. There were no sensory symptoms, motor weakness in upper limbs, or decreased vision and hearing. There were no systemic symptoms. His father had a history of mild gait unsteadiness at the age of 60 years with no upper limb or speech involvement. Systemic examination was unremarkable. Neurological examination showed normal cognition, mild scanning dysarthria, depressed deep tendon reflexes, normal motor power, and absent sensation to all modalities in both lower limbs below the knee with impaired proprioception. There was no nystagmus, titubation, or upper and lower limb incoordination. Romberg sign was positive and sensory ataxic gait. Our patient had sensory ataxic neuropathy of lower limbs with dysarthria and a family history of gait ataxia in the proband father. A differential diagnosis of vasculitic neuropathy, a variant of chronic inflammatory demyelinating polyradiculoneuropathy, B12 deficiency-related polyneuropathy, paraproteinemic and paraneoplastic-related neuropathy. Complete blood counts, renal, hepatic, and thyroid functions were normal. Serum blood glucose, vitamin B12, folate, copper, vitamin E levels, and angiotensin-converting enzymes were normal. Serological test for human immunodeficiency virus, hepatitis B surface antigen, and venereal disease research laboratory was non-reactive. The Vasculitis profile was negative. Serum protein electrophoresis did not show a monoclonal band. The serum paraneoplastic antibodies profile was negative. Nerve conduction studies showed absent sensory nerve action potentials in sural and superficial nerves with preserved motor action potential. Brain MRI showed diffuse cerebellar and vermian atrophy [Figure 1]. Spine MRI with plexus was normal. Sural nerve biopsy showed features of chronic axonopathy. Cerebrospinal fluid analysis was normal. He was started on 1 gram of intravenous methylprednisolone but had worsening of burning paraesthesia; hence, it was discontinued. He had good relief with gabapentin 600mg/day. In view of significant cerebellar atrophy with gait ataxia in father, genetics was sent. Whole exome sequencing showed heterozygous missense variant in exon 4 of the *PRKCG* gene (c. 383G>A; p.Gly128Asp) resulting in the

amino acid substitution of aspartic acid for glycine at codon 128. This variant was classified as pathogenic by the ClinVar database [VCV000013246.3]. Sanger sequencing was not done.

The protein kinase C gamma enzyme comprises two domains—catalytic domain and regulatory domain. Most of the mutations are located in the regulatory domains C1 and C2, with C1 harboring the largest cluster of pathogenic *PRKCG* variants. The first mutation was identified in the *PRKCG* gene in 2000. *PRKC* regulates Purkinje cells dendritic growth and calcium permeability and the elimination of climbing fiber synapses as it is abundantly expressed in the Purkinje cells. Chen *et al.*^[2] (2003) from USA reported first case of mutations in *PRKCG* gene. Yabe *et al.*^[3] (2003) reported missense mutation in 11 affected members of a Japanese family. Five patients had axial myoclonus as the initial symptom. Subsequently, SCA 14 cases were reported from France, Portugal, Norway, and Netherlands.^[4-6] Most of the mutations are missense or deletion but Shirafuji *et al.*^[7] (2019) first reported nonsense mutation in the *PRKCG* gene with patient presenting with cerebellar ataxia, deafness, cognitive impairment, and cerebellar atrophy. SCA 14 commonly presents



Figure 1: Brain MRI (A) axial T2-weighted image showing atrophy of cerebellum (white arrow)

Table 1: Brief summary of reported SCA 14 cases

	Phenotype	Genotype	MRI
Chen <i>et al.</i> (2003)	Pure cerebellar ataxia without anticipation, AD inheritance	Missense mutations in exon 4 (H101Y, S119P, G128D) in the Cys2 region of the C1 domain	Not available
Yabe <i>et al.</i> (2003)	Progressive gait, limb ataxia, dysarthria, nystagmus, axial myoclonus	Missense mutation in exon 4 (Q127R)	Cerebellar atrophy
Alonso <i>et al.</i> (2005)	Slowly progressive cerebellar ataxia	Missense mutation in exon 4 (H101Q) in the Cys2 region of the C1 domain	Cerebellar and cerebral atrophy
van de Warrenburg <i>et al.</i> (2003)	Slowly progressive cerebellar syndrome, mean age at onset of 40.8 years, focal dystonia, hyporeflexia	Missense mutation in exon 4 (G118D) in C1 domain	Cerebellar atrophy
Koht <i>et al.</i> (2012)	Cerebellar ataxia, reduced vibration in lower limb, spasticity	Missense mutation in exon 5 (H139Q)	Cerebellar atrophy
Shirafuji <i>et al.</i> (2019)	Cerebellar ataxia, deafness, cognitive impairment, seizures	Nonsense mutation in exon 4 (R76X) in C1 domain	Cerebellar atrophy
Present case	Sensory neuropathy of lower limbs with sensory ataxia, areflexia, and scanning dysarthria	Missense mutation in exon 4 (G128D) in C1 domain	Cerebellar atrophy

as slowly progressive cerebellar ataxia with onset in the thirties but variable from childhood to the seventh decade. However, cognitive impairment, sensory impairment, pyramidal signs, axial myoclonus, tremor, and focal dystonia have been reported. Recently, De Michele *et al.*^[8] (2022) reported a novel phenotype of SCA14 wherein one patient had episodic ataxia, another had spastic paraparesis, and two children with feeding difficulties and developmental delay. Most of the mutations are in exon 4 but Sun *et al.*^[9] (2023) reported a novel mutation in exon 11 which is in the catalytic domain and the patient had episodic ataxia with speech and cognitive disorder since early childhood. Chelban *et al.*^[10] (2018) reported one patient with a mutation in exon 11 who had dystonia, severe neuropathy in the lower limb apart from the cerebellar ataxia. Our patient had a heterozygous missense variant in exon 4 of the *PRKCG* gene (c.383G>A; p.Gly128Asp). The mutation lies in the C1 domain. The patient had presented with sensory neuropathy of the lower limbs with nerve conduction studies showing sensory axonopathy of the lower limbs with mild dysarthria. Protein kinase C gamma plays a role in long-term hyper-excitability in nociceptive neurons. Activation of PKCγ has been reported to cause hyperalgesia in diabetic neuropathy. The burning paresthesia in our patient may be due to abnormal activation of PKCγ in nociceptive neurons. The reported cases of SCA14 are summarized in Table 1.

SCA14 usually presents with chronic slowly progressive cerebellar ataxia. Mild cognitive involvement, spasticity, impaired vibration in lower limbs, dystonia, and myoclonus have been reported. However, the presenting symptom as severe sensory neuropathy of lower limbs has not been reported. This is the first report of SCA14 from India. SCA 14 should be considered in patients with sensory neuropathy with imaging evidence of cerebellar atrophy.

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.

Saraswati Nashi, Raviprakash Singh, Deepak Menon, Faheem Arshad, Suvarna Alladi, Rohan R. Mahale

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

Address for correspondence: Dr. Rohan R. Mahale, Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, Karnataka, India. E-mail: rohanmahale83@gmail.com

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