SACS Gene Deletional Mutation Presenting as an Isolated Nonprogressive Sensory Motor Axonal Neuropathy: A Case Report

To the Editor,

Autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) caused by the mutation of the SACS gene is an early-onset neurodegenerative disease with a high prevalence among French-Canadians in the Charlevoix–Saguenay region of Quebec. Spastic ataxia of the Charlevoix–Saguenay type (OMIM#270550) is caused by homozygous or compound heterozygous mutations in the SACS gene (OMIM*604490).[1-3] The classical phenotype consists of a triad of cerebellar ataxia, peripheral neuropathy, and pyramidal tract signs with a significant disability on disease progression. However, there are atypical presentations of ARSACS, which are dominated by peripheral neuropathy, leading first to the diagnosis of a complicated form of Charcot–Marie–Tooth disease and thus delaying the correct clinical diagnosis of ARSACS.[4]

We present here a case of a young male with isolated sensory-motor axonal neuropathy who remained stable without any clinical progression over 7 years due to homozygous mutation of the SACS gene resulting from a four base pair deletion at exon 10 in chromosome 13. To the best of our knowledge, no such atypical case has been reported from the Indian subcontinent. In patients with sensory-motor axonal non *Charcot-Marie-Tooth* (CMT)-type pathology and myelinated retinal nerve fibers on fundoscopy, an atypical presentation of SACS gene mutation should be considered in the clinical workup.

A 25- year-old man from the Eastern Indian Province, born out of the nonconsanguineous marriage without any siblings and normal family history, had lower limb sensory symptoms of pain and paresthesia over several years, with a similar intensity without any gradual progression of the sensory symptoms. The patient did not have any speech difficulty, visual problems, or cognitive change. On examination, the speech, tone, and gait of the patient were found to be normal. The patient did not show ataxic symptoms, and the results were found to be normal when the patient underwent finger–nose–finger, finger–finger, and knee–heel shin tests. Moreover, the patient could also walk in tandem normally without any difficulty. Investigations with a 1.5 tesla magnetic resonance (MR) scan for the brain did not reveal any cerebellar atrophy or brainstem hyperintensities. The nerve conduction study showed that the patient had severe sensory-motor axonal neuropathy with reduced compound muscle action potentials (CMAPs) and conduction velocities in the median, ulnar, and tibial nerves in the absence of CMAPs in peroneal nerves bilaterally. Sensory nerve action potentials (SNAPs) in the median, ulnar, and sural nerves were also found to be absent in the patient. Then, the patient underwent a left sural nerve biopsy that showed unremarkable epineural connective tissue and nerve vasculature. The fiber loss was uniform and chronic and of mild-to-moderate density involving both large and small fibers with occasional regenerating clusters. No onion bulbs were noted. Overall, the histopathology suggested a non CMT type of axonal neuropathy. Ophthalmology evaluation revealed normal visual acuity with a moderate degree of myelinated retinal nerve fibers in a radiating pattern from the optic disc bilaterally [Figure 1]. Evaluation for Friedreich's ataxia with the GAA repeats by triplet-primed PCR and GAA-PCR was found

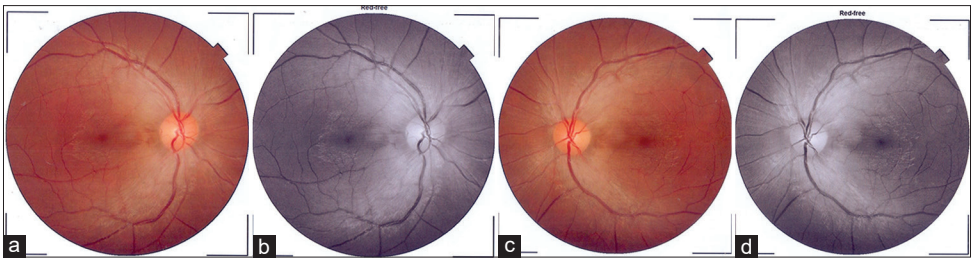

Figure 1: (a) Right eye normal retinal blood vessels. (b) Right eye optic disc with myelinated nerve fibers. (c) Left eye normal retinal vessels. (d) Left eye meylinated retinal nerve fibers

to be negative. The patient underwent clinical exon sequencing done by medgenome laboratories in India, which revealed a pathogenic mutational variant of homozygous four base pair deletion in exon 10 of the SACS gene (chr13:23909222_23909225delTTTT; Depth: 121x) that resulted in a frameshift and premature truncation of the protein 22 amino acids downstream to codon 2930 (p.Lys2930AsnfsTer22; ENST00000382298). The patient was given a confirmed diagnosis of isolated axonal neuropathy due to SACS gene mutation as a phenotypic presentation of the homozygous four base pair deletion in exon 10. Over a follow-up until December 2019, the patient remained independent of activities of daily living (ADL) without any progressive cerebellar features and stable sensory symptoms.

J. Baets *et al.* in their study reported 7 out of 17 patients with predominantly neuropathic disorders, who later developed pyramidal and cerebellar signs on disease progression; however, in our case study, the patient remained neurologically stable for 7 years of follow-up. Five of their patients had atypical age of onset after 20 years, with one patient developing neuropathy after 40 years of age.[4]

The causative gene SACS is located on chromosome 13q12.126 and consists of one giant 12,800-bp exon and 8 smaller upstream exons. Larger-scale genomic deletions comprising SACS and adjacent genes have been documented well, but recently, screening of copy number variations in SACS has identified a partial deletion of exons 3–5. Our case also has a homozygous four base pair deletion of exon 10, resulting in the frameshift and premature truncation of the protein. The observed variant has not been reported in the 1000 genomes, ExAC, and internal databases of medgenome labs.

In a recent study, K Vill *et al.* have described nine isolated neuropathic cases in suspected CMT cases among six unrelated families. The genetic evaluation showed biallelic mutations, either in a homozygous or in a compound heterozygous state along with a case of an 8,581-bp genomic deletion encompassing SACS exons 3 and 4 (our case has homozygous deletions in exon 10).[5]

The case reported by Agarwal *et al.* falls into the "classical" category with a triad of neuropathy, pyramidal signs, and cerebellar ataxia with MRI findings and retinal changes.[6] This highlights the importance of our case as being the first case of atypical isolated neuropathic case of ARSACS from the Indian subcontinent.

In another case report, single base-pair deletion has been reported as 6543delA in two related Japanese patients with a speculative conclusion that myelinated nerve fibers are not caused by the loss of function of the SACS gene.[7] We can clearly see in our patient that retinal nerve fiber myelination is seen in the deletional mutations for exon 10.

It can be postulated that this documented-specific mutation is associated with a less virulent form of the disease and has predominantly isolated neuropathic presentation with asymptomatic retinal changes and without any MRI or cerebellopontine abnormalities. We can conclude that clinically in a workup for a sensory-motor nonCMT axonal neuropathy, one must undergo a fundus examination (which may give a clinical clue about myelinated fibers), which may further strengthen to consider SACS gene mutation genetic evaluation for the diagnosis of ARSACS.

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.

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