Introduction

- Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (**ARSACS**) is the 2nd most common cause of recessive ataxia worldwide after Friedrich's ataxia & characterized by progressive cerebellar ataxia, spasticity and peripheral neuropathy

Case Report

- **HISTORY**: Here, we report a family of 2 siblings born of 3rd degree consanguineous marriage. The elder sibling, a **38-year-old lady**, presented with an **insidious** onset & **progressive unsteadiness** while walking **since the 1st decade** of life which progressed gradually & by the 3rd decade of her life, she required support to stand & walk. She also had **undue pauses between syllables** while speaking. She had **clumsiness of hands** due to which her hands would shake while writing or taking a water glass to her mouth.

•By the 3rd decade of life, she had new difficulties in the form of **tightness** of her legs, due to which she had to drag them to walk. She also had **numbness** of feet.

•**EXAMINATION**: she had an MMSE of 22/30, bilateral horizontal gaze evoked **nystagmus**, dysmetric saccades & broken pursuits & ataxic type dysarthria.

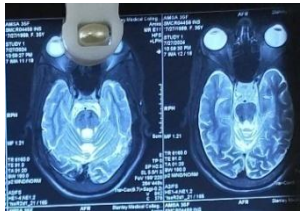
•She had **spasticity** of both lower limbs, normal strength in upper limbs with mild distal more than proximal weakness in both lower limbs. Abdominal reflex was absent bilaterally; plantar reflex was withdrawal bilaterally. All deep tendon reflexes were **brisk** except absent ankle jerks.

•There was a **graded loss of all modalities of sensation in both lower limbs**.

•She had impaired finger nose test & heel knee test on both sides with stance & gait **ataxia**.

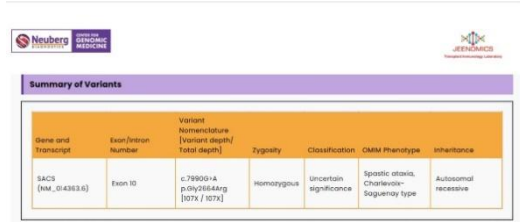
•SIBLING:

•Earlier, her 35 yr old **younger brother** was admitted with sudden onset paraplegia with sensory loss below subcostal region & urinary retention after he sustained a fall. MRI revealed a hematomyelia & he underwent a decompression laminectomy . On probing, he also reported that he had **unsteadiness** while walking since the 2nd decade of his life & clumsiness of hands & slurred speech. He had MMSE 24/30, bilateral horizontal gaze evoked nystagmus with dysmetric saccades, broken pursuits & ataxic dysarthria. He had spasticity of both lower limbs, normal strength in upper limbs & distal more than proximal weakness in both lower limbs. Plantar response was extensor bilaterally &all deep tendon reflexes were brisk except absent ankle jerks.
All modalities of sensations were reduced below sub costal margin.



• INVESTIGATIONS:

- Her routine hematological & biochemical investigations (including lipid profile) & thyroid function test were normal, viral markers were negative. Her cardiac & ophthalmologic evaluation & hearing assessment were normal. **MRI brain** showed **superior vermian atrophy** & **pontine linear hypointensities**. **NCS** showed severe sensory-motor axonal neuropathy of all 4 limbs with secondary demyelinating changes. With a clinical diagnosis of early onset cerebellar ataxia with spasticity & peripheral neuropathy, with positive family history, a whole exome sequencing was sent & it showed homozygous mutation in **SACS gene**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Summary of Variants

Gene and Transcript	Exon/Intron Number	Variant Nomenclature [Variant depth/ Total depth]	Zygosity	Classification	OMIM Phenotype	Inheritance
SACS (NM_014363.6)	Exon 10	c.7990G>A p.Gly2664Arg [107X / 107X]	Homozygous	Uncertain significance	Spastic ataxia, Charlevoix-Saguenay type	Autosomal recessive

Discussion

•ARSACS should be suspected in patients with a gradually progressive cerebellar ataxia- gait unsteadiness appearing as early as 12- 18 months or later, along with spasticity of both lower limbs & peripheral neuropathy.
•Brain MRI shows a vermian atrophy with upper predominance with or without atrophy of cerebellar hemispheres & hypointense stripes in bilateral paramedian pons.
•Diagnosis is established in patients with these clinical findings by molecular genetic testing showing biallelic pathogenic variants in SACS gene.
•Additional findings include thickened retinal hypermyelinated fibres which are seen as yellow streaks radiating from the edge of optic disc on fundus examination.
•In addition to this triad, some individuals have additional features such as hearing loss, intellectual disability, myoclonic epilepsy & urinary disturbances.
•Management includes neurological & hearing evaluation, gait & speech therapy and genetic counselling

Conclusion

•While approaching ataxia, age of onset, progression, family history, medical background & involvement of systems other than cerebellar are important.
•In **recessively inherited ataxias**, we must find a laboratory biomarker (eg, vitamin E level in Ataxia with Vitamin E Deficiency) or a signature clinical finding (eg, telangiectasia in Ataxia Telangiectasia, tendon xanthomas in CerebroTendinous Xanthomatosis) or a classical radiologic feature (eg, T2 hypointense pontine linear abnormalities in ARSACS) to narrow the differential diagnosis.

References:
http://doi.org/10.1212/WNL.0000000000009886
http://www.ncbi.nlm.nih.gov/books/NBK1255/
Bradley and Daroffs Neurology in Clinical Practice

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