Come To Your Senses: Atypical Polyneuropathy

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Clinical History

35 year old female was referred to the neurology clinic for evaluation of an abnormal gait. She reported slow but progressive changes in her gait over the course of the last ten years. Her changes ranged from a sense of feeling off-balanced to shooting pain down each leg She felt that her pain originated in her low back and radiated posteriorly down each leg without any accompanying numbness, weakness, or bowel and bladder involvement. Of significance is her longstanding hearing impairment, requiring hearing aids at age 12 and then cochlear implants in her early 30's. She also had visual changes which resulted in bilateral cataract removal. Her family history is notable for reported hearing loss and diabetes. No other family member has her additional constellation of symptoms (i.e. gait disturbance, cataracts etc.). Her parents immigrated from Egypt and are reported first cousins.

There had been no reported trauma to her low back, and previous CT imaging of her brain and spine were reportedly unremarkable.

Physical Exam

>She had symmetric hyporeflexia. Reflexes were graded as 1/4 in her bilateral biceps, triceps, brachioradialis, and achilles. Patellar reflexes were 2/4. Plantar reflexes showed a downgoing response and Hoffman's reflex was absent bilaterally.
> Sensory exam showed diminished light touch, pinprick and temperature in a stocking distribution. Vibratory sense was absent at the toes and was diminished in a gradient in her lower legs. Position sense was intact. Romberg testing was negative.
>Gait was spastic.

Pertinent negative exam findings:
-Her mental status and cranial nerves were normal.
-Normal muscle bulk and tone throughout her upper and lower extremities.
-Range of motion was intact.
-Motor strength was 5/5 and symmetric in all extremities.
-Finger-to-nose, heel-to-shin, and rapid alternating movements were intact.

Pre-Test Differential Diagnosis

CMT, mitochondrial disease, storage disease, Refsum disease, structural spine disease, nutritional deficiency (B12, copper, zinc excess), toxic etiologies (HTLV, HIV), multiple sclerosis.

Workup

Electrodiagnostics

Nerve Conductions	Distal Latency	Peak Latency	Amplitude	Conduction Velocity (m/sec)
Right Median CMAP	4.3		7.8	
	11.6		5.8	26
Right Median SNAP		5	7	36
Right Radial SNAP		3.7	14	27
Right Ulnar CMAP	4		6.6	
	9.2		4.5	30
	12.3		5.9	32
Right Ulnar SNAP		5.2	14	33
Left Peroneal CMAP (EDB)	8.8		0.4	
	21.7		0.5	23
Right Peroneal CMAP (EDB)	6.6		1.1	
	19.7		0.3	22
Left Tibial CMAP	8		0.1	
	25.7		0	20
Right Tibial CMAP	8.7		0.1	
	28.7		0.1	16
L Sural SNAP	No Response			
R Sural SNAP	No Response			

There was significant slowing of the conduction velocity in all nerves tested, in near uniform fashion, including her asymptomatic RUE. There was conduction block at the R peroneal nerve. These findings were consistent with a demyelinating, length-dependent, sensorimotor neuropathy.

Needle EMG of the right arm and leg was unremarkable.

Eye Exam

She was referred to an ophthalmologist. Her exam showed trace temporal pallor OU, mid-to-far peripheral vision loss OU, and findings consistent with retinitis pigmentosa.

Imaging

We repeated CT imaging of her brain and spine; brain imaging was negative. CT of her spine showed mild degenerative changes and minimal narrowing of the spinal canal (bilateral L5/S1 foraminal stenosis, mild central canal stenosis at C5-6). We were unable to do MRI due to her cochlear implants.

Genetic Testing

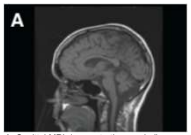
A Charcot Marie Tooth Panel was negative. Further genetic studies revealed a homozygous mutation for the G176E variant in the ABHD12 gene.

Diagnosis and Discussion

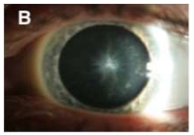
Our patients clinical history and genetic testing results were consistent and she was diagnosed with PHARC: Polyneuropathy, Hearing Loss, Ataxia, Retinitis Pigmentosa, Cataracts.

PHARC was first described by Fiskerstrand et al in 2008.[1] At that time they were attempting to genetically characterize a neurological disorder that resembled Refsum disease in a Norwegian family. Further research in 2010 led them to the conclusion that there is a mutation in the ABHD12 gene that caused a clinical syndrome that they termed PHARC.[2] It is an autosomal recessive disease which often becomes apparent in the late teens. Multiple case reports have now been published showing various mutations in the ABHD12 gene causing clinical pictures consistent with PHARC. Examples of typical findings are shown below.

Clinical Features

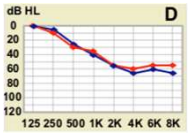


A. Sagittal MRI demonstrating cerebellar atrophy in a 50 yo F who developed ataxia, jerky eye movements and hand tremors at the age of 18.

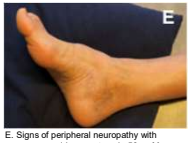


B. A star-shaped cataract in a 24 yo M who developed cataracts at age 15.

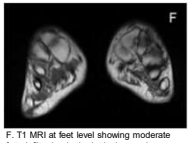
C. Fundus of a 56 yo M showing bone-spicule shaped pigment deposits, pallor of the optic disc, attenuation of the retinal vessels, and maculopathy.



D. Audiogram of a 16 yo M showing sensorineural hearing loss of both right (red curve) and left (blue) ears, around 60 dB in the higher frequencies.



E. Signs of peripheral neuropathy with pes cavus and hammertoes in 56 yo M.



F. T1 MRI at feet level showing moderate fatty infiltration in the intrinsic muscles of the feet.

Pathophysiology

There is a great deal of variability in the presentation of symptoms; as there is variability amongst the gene mutations leading to inactive ABHD12. Despite the variability that exists within gene mutations, it is posited that all of the homozygous mutations result in complete loss-of-function of the ABHD12 enzyme. Reduction in ABHD12 results in increased levels of endocannabinoid arachidonoyl glycerol 2-AG, which has important functions in synaptic plasticity and neuroinflammation. The effects of long-term increased levels of this metabolite have not been investigated. Endocannabinoid signaling is tightly regulated and appears to be important for many physiological processes including neurotransmission and inflammation.

Clinically, PHARC shares many overlapping features with Refsum disease (i.e. progressive vision loss, degenerative nerve disease, and ataxia). In contrast, Refsum often includes additional dermatologic features (ichthyosis) and anosmia, which PHARC patients do not exhibit. Furthermore, PHARC patients do not have elevated phytanic acid levels, and their peroxisomal functioning is normal.

Refsum disease is, principally, a defect in lipid metabolism which results in impaired myelination of the nervous system; it is by definition a leukodystrophy. Similarly, it is inherited as an autosomal recessive trait.

Treatment Considerations

Unlike in cases of Refsum disease where avoidance of dietary triggers high in phytanic acid can be of therapeutic benefit (i.e. dairy products, beef, lamb, some seafood), PHARC does not share this consideration. As it stands, management is primarily supportive.

Looking forward, there is interest in its association with endocannabinoid receptors; ABHD12's relationship with 2-AG, and subsequently CB1 and CB2, could lend itself towards potential areas of intervention.

Conclusion

Polyneuropathy, Hearing Loss, Ataxia, Retinitis Pigmentosa, and Cataracts (PHARC) is a neurodegenerative disease that is caused by mutations in the ABHD12 gene and often indolent in its progression. It tends to involve both the central and peripheral nervous system; and is highly variable in degree and timing of symptom presentation. There are overlapping features with Refsum disease, and genetic testing for PHARC should be sent when patients present with this clinical constellation of symptoms. Treatment is supportive at this time.

References

(1) Fiskerstrand et al, A Novel Refsum-like Disorder That Maps to Chromosome 20. Neurology 2009;72;20-27

(2) (A-E); Fiskerstrand et al, Mutations in ABHD12 Cause the Neurodegenerative Disease PHARC: An Inborn Error of Endocannabinoid Metabolism. The American Journal of Human Genetics 87, Sep. 10 2010.

(3) F; Fraquet et al, Phenotypical Features of two Patients Diagnosed with PHARC Syndrome and Carriers of a New Homozygous Mutation in the ABHD12 Gene, Journal of the Neurological Sciences 387 (2018).

(4) Novel ABHD12 Mutations in PHARC Patients: The Differential Diagnosis of Deaf-Blindness.

(5) Functional validation of ABHD12 mutations in the Neurodegenerative Disease PHARC.

(6) OMIM