

SCA3 Presenting as an Isolated Axonal Polyneuropathy

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Objectives: To highlight an unexpected clinical presentation and to review the associated polyneuropathy phenotypes of SCA3.

Design: Clinical follow-up.

Setting: Neurological referral center.

Patient: Middle-aged man with no family history for SCA3.

Results: Presentation with an isolated axonal, distal, symmetric, sensorimotor polyneuropathy for 6 years before developing a cerebellar syndrome prompting genetic testing for SCA3.

Conclusion: SCA3 can present with an isolated axonal, distal, symmetric, sensorimotor polyneuropathy.

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SCA3 (OR MACHADO-JOSEPH disease) is an autosomal dominant cerebellar ataxia (ADCA I) due to CAG repeat expansions in *ataxin3*. Patients with SCA type 3 have the latest onset and slowest progression with cerebellar ataxia and polyneuropathy, with or without progressive external ophthalmoplegia or pyramidal signs.¹ We describe a patient with a unique presentation of an axonal distal sensorimotor polyneuropathy for 6 years before developing a cerebellar syndrome leading to the diagnosis of SCA3. We also review SCA3-associated polyneuropathy phenotypes.

REPORT OF A CASE

A 52-year-old man had leg weakness for 6 months and no family history for SCA3. His mother had diabetes mellitus and died at 86 years. His father's age of death and details were unknown. The facial and cranial nerves were normal. He had distal lower limb weakness. Arm reflexes were sluggish, the knee jerks were brisk, ankle jerks were absent, and plantar responses were mute. Results of the sensory examination were unremarkable. Results of the following tests were either negative or normal: complete blood cell count, erythrocyte sedimentation rate, liver and thyroid function, VDRL, human T-lymphotrophic virus 1, serum protein electrophoresis, rheumatoid factor, antinuclear antibody,

Kveim, chest radiograph, and levels of glucose, urea, electrolytes, vitamin B₁₂, folate, extractable nuclear antigen, antineutrophil cytoplasmic antibody, and cerebrospinal fluid. Electrophysiology showed absent (medians, ulnars, and surals) or small (radial, 4.6 μV) sensory nerve action potentials, absent soleus H-reflexes, normal motor conduction velocities and F-wave latencies (medians, ulnars, and common peroneal nerves), no conduction block, small lower limb compound muscle action potentials, and distal denervation in the upper and lower limbs consistent with an axonal sensorimotor polyneuropathy.

Six months later he reported cramps in his hands and legs. He had fasciculations in the biceps, triceps, thighs, and calves. There was now distal weakness in the upper and lower limbs. Reflexes were brisk with absent ankle jerks, an extensor right plantar, and no sensory signs. A year later, he reported worsening weakness of the upper and lower limbs. Reflexes were now diminished with flexor plantar responses. Sensory examination results remained normal. A sural nerve biopsy specimen confirmed a moderately severe axonal neuropathy affecting myelinated and unmyelinated axons, with some regeneration and secondary demyelination and remyelination. There was no vasculitis, abnormal infiltrates, or Schwann cell hyperplasia.

Two years later he walked with a cane. There was more distal weakness of the upper and lower limbs. All reflexes were ab-

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Table. Peripheral Neuropathy in SCA3 CAG Repeat Length, Clinical and Electrophysiological Data

No. of Patients/ Sex	Age at Presentation	CAG Repeat Length	Follow-up, y	EMG & Nerve Conduction	PN Phenotype		Additional Features, %		Source
					Sensory or Sensorimotor/ Distal/Symmetry	Ataxia/ Pyramidal/ Extrapyramidal	PEO	Other	
3/M	53, 50, 67 (At time of report)	53 ^a	13 ^b	2 Denervation, 2 absent/red SNAPs, and 1 red CMAPs	3 SM/Y/Y	33/66/66		3 RLS; 2 fascics	van Alfen et al ¹¹
Mean of 18 (10 PN) ^c	41.7 (27-56)	...	7.9 ± 4.8	10 red SNAPs, 2 red MNCVs	10 SM/Y/Y	100/28/	78		Abele et al ⁵
Mean of 14 (8 PN) ^c	18-54	69-90	...	NCV slowing in 2 of 3 families	9 ^b /Y/Y	100/64/21.4	43		Chakravarty et al ¹²
Mean of 22 (6 PN) ^{b,c}	34 (9-60)	62-80	6 (1-21)	Not done	6 ^b /Y/Y	82/59/18	45		Giunti et al ⁹
2/M, 2/F	35, 62, 64, 65	62, 62, 65, 66	1-11	2 Red SNCVs, 2 red MNCVs, 1 normal	3 SM, 1 S/Y/Y	75/25/		3 Cramps, 3 fascics	Colding-Jorgensen et al ¹³
2/M, ^b 1/F ^b	32, 35, 50		5-18	Chronic denervation, red/absent sural SNAPs	2 SM, 1 S/Y/Y	75/50/50	75		Kinoshita et al ¹⁴
Mean of 58 (31/F, 27/M)	37.8 ± 11.3	63-82	9.1 ± 5.9	Red SNAPs and CMAPs, normal or red NCVs	58 SM/Y/Y		Klockgether et al ⁸
Mean of 13 (7 PN) (5/M, 2/F)	42.5 (24-60)	68-77	2-26	6 SM, 1S	5 SM, 1 S, 1 NSym /Y, 1 NSym /Y, 1 NSym		Kubis et al ⁷
1/M, 2/F	40, 42, 50	66, 67, 69	2, 9, 14	2 Abnormal, 1 normal	.../Y/Y	100/100/66	33		Lau et al ³
2/M, 1/F	18, 35, 44	72, 75, 78	6, 19, 22	Absent SNAPs, red CMAPs	2 SM, 1S/Y/Y	100/100/	100		Lin and Soong ⁶
Mean of 21 (5 PN) ^c	30.1 (21-60)	...	21-60	Not done	5 SM/Y/Y	95/76/38	62		Takiyama et al ¹⁵
Mean of 8 (3/M, 5/F)	47 (38-56)	67.9 (61-72)	9.1 (1-21)	4 SM, 3 neuronopathy, 1 normal	4 SM, 3 S/Y/Y		van de Warendburg et al ⁴
2/M	50, 62	54, 62 ^a	10-24	1 Absent/red SNAPs & CMAPs, 1 not done	SM, S/1N, 1Y/1N, 1Y	100//		1 Fascics	van Schaik et al ¹⁰
M	52	62	13	Absent SNAPs, small CMAPs, normal MCVs and F-waves, chronic denervation	SM/Y/Y	100/100/			Present case
116/173 PN/total cases					9 S, 99 SM 1 NSym 18 ...//				

Abbreviations: CMAP, compound muscle action potential; ellipses, unknown; EMG, electromyography; fascics, fasciculations; MNCV, motor nerve conduction velocity; N, no; NCV, nerve conduction velocities; red, reduced; PEO, progressive external ophthalmoplegia; PN, polyneuropathy; RLS, restless leg syndrome; S, sensory; SM, sensorimotor; SNAP, sensory nerve action potential; SNCV, sensory nerve conduction velocity; Y, yes.

^aNot pathologically expanded.

^bSex distribution unavailable.

^cData of those with neuropathy only not available separately.

sent except for the knee jerks. The right plantar was again extensor; the left plantar was equivocal. There was impaired pin-prick sensation in the left foot. A second autoimmune screen, including the levels of antigliadin, antiendomysial, antineuronal antibodies, and vitamin E were normal. Magnetic resonance imaging of the lumbosacral spine disclosed no abnormality. Three years later he reported poor balance resulting in falls. He had an ataxic gait out of proportion to the polyneuropathy and used a walker. There were broken smooth-pursuit eye movements, no nystagmus, and a mild intention tremor of the limbs. Computed tomography of the brain showed atrophy of the cerebellar hemispheres with preservation of the pons and olives. Magnetic resonance imaging showed no cervical cord pathology. Genetic analysis revealed an

expanded CAG trinucleotide repeat (62) in *ataxin3*. A year later, nerve conduction study results showed a more severe polyneuropathy with absent sensory nerve action potentials in the upper and lower limbs, unrecordable lower limbs, and smaller upper limbs, compound muscle action potentials, and more severe distal denervation in the limbs.

COMMENT

Our patient presented with a progressive axonal, distal, symmetric, sensorimotor polyneuropathy. A cerebellar syndrome developed 6 years later. We have not found a similar presentation of SCA3 in the literature. Chronic idiopathic

axonal polyneuropathy, considered initially, is a diagnosis of exclusion²; the earlier onset and progression of the severe polyneuropathy in our patient also argue against this diagnosis.² The known association of polyneuropathy and SCA3, long follow-up, and low incidence of SCA3 make a chance association between these 2 unlikely. In retrospect, the right extensor plantar response recorded 1 year after presentation signaled a multiple system disorder. It was not confirmed 1 year later. After a further 2 years, it was extensor again. However, the patient returned for follow-up 3 years later; by then he also had ataxia.

Patients with SCA3 who develop a polyneuropathy may present with a late-onset ataxic syndrome.³ Patients with symptoms or signs of a polyneuropathy may have electrophysiological evidence of an axonal sensorimotor polyneuropathy, a motor or sensory neuropathy, or normal findings.⁴ Reduced sensory nerve action potentials were seen in 13 of 17 patients with SCA3; only 56% had absent or reduced reflexes and vibration sense.⁵ Myelinated and unmyelinated fibers are decreased in number and relatively hypomyelinated with a smaller mean axon size, consistent with distal axonopathy.⁶

There is an inverse correlation between CAG trinucleotide repeat length and onset of disease in SCA3.⁷ The polyneuropathy appears late and correlates with shorter CAG trinucleotide repeat length. There is an inverse correlation between age and compound muscle action potentials or sensory nerve action potentials in SCA3, with decline at a more rapid rate than in normal aging.⁸ Conduction velocity slowing was not correlated with CAG repeat length.⁸ CAG repeat expansions in *ataxin3* have a bimodal distribution, with populations of normal (<41) and disease-causing expansions (>62).⁹

A male with a progressive, severe, asymmetric proximal polyneuropathy from age 50 years with no central nervous system or cerebellar signs, a family history of SCA3, and a 54-repeat trinucleotide expansion is recorded.¹⁰ He had non-insulin dependent diabetes, and IgG-κ monoclonal gammopathy. Two relatives with ataxia and peripheral neuropathy or pyramidal signs had SCA3 CAG trinucleotide repeat expansions within the pathogenic range.¹⁰ The proband's intermediate-range 54 repeats may not be unequivocally related to his isolated polyneuropathy, particularly with its predominantly proximal and asymmetrical phenotype. There are no reports of such a phenotype in the 116 other cases of polyneuropathy and SCA3 (Table). CAG repeats within the intermediate range (53-54) have only been reported to be associated with disease in 4 members of 1 other pedigree¹¹; 2 had a polyneuropathy plus other features but without data excluding other causes of polyneuropathy.

SCA3 published polyneuropathies are sensorimotor in 85.3% (99 of 116 patients) and sensory in 7.8% (9 of 116 patients). All those with polyneuropathy and a pathologically expanded CAG repeat had distal symmetrical presentations (Table).

SCA3 should be considered a rare differential diagnosis of an axonal, distal, symmetric, sensorimotor polyneuropathy of unknown etiology in a middle-aged patient despite the absence of a positive family history. However, genetic investigation of such an unusual oc-

currence would be impractical unless it had clear therapeutic or genetic counseling implications.

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