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Variable sensory nerve conduction parameters in late onset Friedreich ataxia

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There is increasing recognition of “late-onset” Friedreich ataxia (LOFA)¹, presenting later than age 25 years². We describe 3 genetically confirmed patients with variable sensory nerve conduction study (S-NCS) parameters (table), who underwent genetic testing, because Friedreich ataxia (FA) is a common cause of ataxia in the UK.

Patient 1: A 49 year old man presented with a 5 year history of difficulty walking and upper limb incoordination. A few months prior to presentation, his speech had changed. Examination revealed mild optic disc pallor, cerebellar dysarthria, and gait and lower limb ataxia. Ankle jerks were absent, and plantar responses were extensor. There was no limb weakness or spasticity. Vibration sense was impaired to the sternum. Fibular motor nerve conduction studies (M-NCS) demonstrated a borderline compound muscle action potential from the extensor digitorum brevis muscle. Other M-NCS were normal. Electrocardiogram and echocardiogram were normal.

Patient 2: The 45 year old sister of patient 1 reported balance problems beginning at age 39 years. Examination demonstrated optic disc pallor, cerebellar dysarthria, and pseudoathetosis. Ankle jerks were absent, plantar responses were extensor, and she had gait and limb ataxia. Sensory examination was normal. There was no limb weakness or spasticity. M-NCS were normal, as were blink reflex tests. Electrocardiogram and echocardiogram were normal.

Patient 3: A 68 year old woman presented with a 10 year history of a slowly progressive gait disorder with subsequent cerebellar dysarthria and upper limb incoordination. Examination demonstrated a mild cerebellar dysarthria speech, non-smooth pursuit eye movements without nystagmus, and limb and gait ataxia. Plantar responses were down going. There was no weakness or spasticity. M-NCS and the blink reflex were normal. Electrocardiogram demonstrated a left bundle branch block (LBBB). Echocardiogram was normal. The patient subsequently developed a non-ST elevation myocardial infarction.

In FA a relationship exists between trinucleotide expansion size and clinical phenotype. The number of repeats inversely correlates with age of ataxia onset, and with the occurrence of cardiomyopathy^{1,5}. In keeping with this, none of our patients had firm evidence of cardiac involvement related to FA. The LBBB in patient 3 was likely secondary to ischemia.

The classic nerve conduction findings in FA are of an early and severe sensory neuropathy^{3,2} with significantly reduced or absent sensory nerve potentials also reported in LOFA⁴. A single study has reported expansion size to be inversely related to sensory nerve action potential amplitude in the median and tibial nerves.⁶ Differences in phenotype between early and LOFA have been documented, with lower limb spasticity and retained tendon reflexes more common in the latter². In LOFA, normal S-NCS velocities (but not amplitudes) were reported in one small series with small GAA expansions⁷. Normal S-NCS were reported in a very late onset patient who presented with spastic tetraparesis⁸. In our patients, the 2 with the larger GAA expansions had abnormal S-NCS, consistent with previous reports⁶. Overall, in LOFA, S-NCS may be variable, and clinicians should consider genetic testing in patients with late onset ataxia and normal nerve conduction studies.

Abbreviations

Late-onset Friedreich ataxia - LOFA

Friedreich ataxia – FA

Sensory nerve conduction study – S-NCS

Motor nerve conduction studies – M-NCS

Electrocardiogram – ECG

Left bundle branch block – LBBB

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Table. Genetic and sensory nerve data.

Patient	GAA expansion size	Median SNAP (L/R)		Ulnar SNAP (L/R)		Radial SNAP (L/R)		Sural SNAP (L/R)		Fibular SNAP (L/R)		Interpretation
		Amp. (μ V)	C.V (m/s)	Amp. (μ V)	C.V. (m/s)	Amp. (μ V)	C.V (m/s)	Amp. (μ V)	C.V (m/s)	Amp. (μ V)	C.V (m/s)	
1	~ 300 repeats	ND/NR	-/-	ND/1.2	-/60	ND/0.7	-/57	ND/NR	-/-	ND/NR	-/-	Sensory ganglionopathy
2	~ 300 repeats	NR/NR	-/-	NR/NR	-/-	NR/NR	-/-	3.2/1.9	43/47	1.1/NR	38/-	Sensory ganglionopathy
3	~ 100 repeats	12.7/11.2	57/54	8.9/8	55/59	47.4/44.1	67/65	17.2/13.8	53/52	29.6/23.5	57/57	Normal

SNAP; sensory nerve action potential, L; Left, R; Right, NR; no response, ND; not done;

C.V, conduction velocity. Median and ulnar studies - orthodromic, radial, fibular and sural -

antidromic. The reported GAA expansion size is the smaller of the two expanded alleles.