Evolving neuromuscular phenotype in a patient with a heterozygous CHCHD10 p.G66V mutation

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Evolving neuromuscular phenotype in a patient with a heterozygous CHCHD10 p.G66V mutation

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Dear Sirs,

Divergent phenotypes in different individuals carrying an identical genetic defect are well known to occur in several neuromuscular disorders. Another related issue is that the same individual may get different diagnoses depending on the accuracy and interpretation of the clinical assessment. In some cases such a diagnostic odyssey may lead to harmful treatments or to misguided and far-reaching decisions by the patient. We report on a male patient with late-onset spinal motor neuronopathy (LOSMoN/SMAJ [1], OMIM #615048) with three different clinical diagnoses during the disease course.

The first symptoms were lower limb fasciculations, which emerged at the age of 37 years. Examined at age 39, fasciculations were generalized, and sensation was normal. Electromyography/nerve conduction studies and muscle biopsy showed neurogenic abnormalities (Table 1). The most likely clinical diagnosis was considered to be amyotrophic lateral sclerosis (ALS) despite absent upper and lower limb tendon reflexes. A central motor conduction study was not performed. Over the following 4 years, disease progression was very slow, and the patient only experienced some difficulties in running. The diagnosis at this stage (age 44) was reevaluated and considered to be consistent with adult-onset spinal muscular atrophy, and the previous ALS diagnosis was revoked. Over the next two decades, concomitant with the slowly progressive muscle weakness, the patient developed loss of vibration sense in the lower extremities despite normal lower limb sensory nerve action potential values (Table 1), indicating possible dorsal column pathology. Sensory evoked potentials at age 61 were unobtainable from the lower limbs (tibial nerve) and normal from the upper limbs. Similar sensory features have in some of the LOSMoN/SMAJ patients led to a diagnosis of CMT2 [2]. At this stage, the patient had Medical Research Council (MRC) 3–4/5 strength in proximal limb muscles, but ankle dorsiflexors and peroneal muscles had full strength (MRC 5/5). Spirometry values remained normal. The patient is still ambulant at the age of 62 years without walking aids. We identified the LOSMoN/SMAJ mutation pG66V in the CHCHD10 gene in this patient, thus confirming the final diagnosis [1].

Because detailed long-term follow-up studies of patients with neuromuscular disorders are not frequently published, it is unclear if the phenotypic heterogeneity reported in the literature actually means the existence of distinct phenotypes, or if it in some cases reflects the accumulation of additional abnormalities in the same individual over time, as recently shown for the *HSPB8* mutation p.K141E [3] causing a distal hereditary motor neuropathy and a myopathy. Based on our clinical experience with more than 60 patients, in some cases over a 30 year time period, the phenotype caused by the p.G66V mutation in CHCHD10, is relatively uniform and recognisable, and the expansion of the phenotype to include typical CMT2 and ALS, although recently reported in the literature, has not been well substantiated. Indeed, the patients carrying a p.G66V mutation initially labelled as familial ALS [4], had a phenotype typical of LOSMoN/SMAJ, as described in detail [1]. It is also unclear whether the recently reported CMT2 patients with p.G66V mutation had a typical CMT phenotype, because sensory findings in these patients were mild or absent and CMAP values were not described [2].

In conclusion, we suggest that the phenotypic heterogeneity observed in some patients with identical genetic mutations may be due to the fact that clinical examinations have been performed at different ages and stages of the disease and due to variable accuracy of assessment. Follow-up data on previously diagnosed patients is needed to take these realities into account in order to avoid labelling the same disease confusingly with many different names.

Ethics committee approval and informed consent were obtained for this study. The authors declare that they have no relevant conflicts of interest.

EMG/NCS results	**Age 39**	**Age 51**	**Age 59**
Left median CMAP	3,8 mV (-1,0 SD)	4,6 mV (-1,4 SD)	ND
Ulnar CMAP	ND	Left 5,1 mV (-1,5 SD)	Right 5,3 mV (-1,4 SD)
Right peroneal CMAP	6,3 mV (0,3 SD)	4,2 mV (-0,8 SD)	3,3 (-1,1 SD)
Right per sup SNAP	5,3 µV (0,8 SD)	**0,9 (-2,6 SD)**	ND
Right sural SNAP	10,0 µV (-0,9 SD)	3,4 µV (-1,4 SD)	2,6 µV (-1,5 SD)
Right radial SNAP	17,5 µV (-0,1 SD)	**5,6 µV (-3,0 SD)**	**2,2 µV (-4,9 SD)**
Right ulnar SNAP	13,0 µV (-0,3 SD)	ND	**1,0 µV (-5,9 SD)**
Clinical sensory findings	Normal sensation	Normal sensation (age 44)	**Absent vibration sensation in lower limbs**
EMG	**Chronic neurogenic abnormalities proximodistally in UL and LL**, bulbar muscles normal	**Chronic neurogenic abnormalities proximodistally in UL, LL and trunk**, bulbar muscles normal	**Chronic neurogenic abnormalities proximodistally in UL and LL**, bulbar and thoracic muscles not examined

Table 1. Electrophysiological findings of the patient compared with age-, sex- and height-matched control values of the laboratory.

Sensory abnormalities were more profound in the upper than lower limb, suggesting a non-length-dependent process and unlike a typical polyneuropathy. In EMG, chronic neurogenic abnormalities refer to fibrillation, increased motor unit action potential size and reduced interference pattern. Fasciculation potentials were detected in several muscles in all EMG sessions and nerve conduction velocities were always normal. Abnormal findings in bold. Per sup= superficial peroneal nerve, SD= standard deviation, ND=not done, UL= upper limb, LL= lower limb. NCS=nerve conduction studies. CMAP=compound muscle action potential. SNAP=sensory nerve action potential.

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