Distal hereditary motor neuropathy with vocal cord paresis: from difficulty in choral singing to a molecular genetic diagnosis

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Keywords:
Hereditary motor neuropathy, Peripheral neuropathy, Spinal muscular atrophy,

Abstract

Patients presenting with distal weakness can be a diagnostic challenge and the eventual diagnosis is often dependent upon accurate clinical phenotyping. We present a case history of a mother and daughter with a rare form of distal hereditary motor neuropathy (DHMN) type 7 in whom the diagnosis was made evident by initial difficulty in singing, due to early vocal cord dysfunction. We draw attention to this rare form of neuropathy, which has now been identified in two apparently unrelated families in Wales. The clinical presentation of this family is typical of DHMN7, and we have identified the common truncating mutation in the SLC5A7 gene. Advances in genetic analysis of these rare conditions broadens our understanding of the potential molecular mechanisms and may allow more directed therapy.

Case History

A 52 year old lady (proband) and her 20-year-old daughter had been keen singers, the daughter performing with the winning choir at the national Eisteddfod at age 10. At 12-13 years of age both noticed a change in their voice when singing, the daughter describing the change "as if her voice was breaking like a boy's at puberty". At age 15, the mother was reviewed by an ear nose and throat (ENT) consultant who diagnosed a vocal cord nodule and she was referred for speech therapy; however, by age 17, she was re-referred to ENT by her music college due to hoarseness of her voice. At that time, she was diagnosed with a benign thymic tumor and had a partial thymectomy. Despite this her voice problem progressed with deterioration and fatigue more prominent towards the end of the day. A more recent review by ENT revealed a persistent glottis chink with poor opposition of vocal cords due to bilateral vocal cord paralysis.

Motor problems in the proband were noticed after her first pregnancy at age 27, at which time she struggled with tasks such as doing up her baby's clothes or making up bottles of milk. Motor problems in the daughter were noticed earlier at age 14 with hand cramps especially when writing, difficulty with retrieving money from a purse and in using a knife and fork. Both have experienced a gradual deterioration in hand function and in addition have noticed pain in their feet after walking, cramps in the calf muscles and poor balance. Examination of the proband, 50 years after onset, revealed a hoarse voice but otherwise normal cranial nerves. She had bilateral severe wasting and weakness of all small hand muscles, more prominent at the thenar eminence (fig 1), with retained proximal strength, sensation and reflexes. She had high foot arches with clawing of the toes and distal weakness most apparent on dorsiflexion, inversion and eversion. Both proband and daughter have retained independent mobility. Nerve conduction studies showed normal sensory action potentials and sensory and motor conduction velocities with F wave latencies in the normal range. Motor action potentials were small and EMG showed changes of distal chronic denervation consistent with a motor neuropathy.

Considering a familial cause of distal motor neuropathy, other members of the family were reviewed (fig 2). The proband's mother had some mild weakness of the first dorsal interossei on the right, but no wasting or weakness in the hands. It was noticed that her foot arches were high with some clawing of the toes but no weakness. The maternal aunt had relatively high arches with toe clawing, but no wasting or weakness. The proband's father died in 1993 due to unrelated causes, but was reported to have had thenar wasting in the right hand which had been attributed to a war injury. There were no reported problems in the left hand, feet or voice. The clinical phenotype was identified to be consistent with distal hereditary motor neuropathy (DHMN) type 7. The proband had genetic analysis which identified the pathogenic c.1497delG mutation in the SLC5A7 gene, which leads to a frameshift mutation and premature truncation of the presynaptic choline transporter. Genetic testing was not performed in any of the proband's relatives.

Discussion

Differential diagnosis of distal weakness

When considering distal limb weakness without sensory loss, it is important to establish the exact pattern of weakness at disease onset. For example, the typical split hand appearance of amyotrophic lateral sclerosis (ALS) with predominant thenar wasting, compared to the asymmetric onset of a mononeuritis multiplex. Both conditions characteristically generalise to become more symmetric with disease progression. Inclusion body myositis (IBM) and myotonic dystrophy (MD) can present with weakness of finger flexion, but are distinguished by the pattern of weakness in the lower limbs (predominantly distal calf weakness in MD compared to quadriceps weakness in IBM). The pattern is again different in the typical foot and finger drop seen in Laing myopathy.

The next stage is to determine the pathological region of interest, be it spinal cord, nerve or muscle (table 1). Information from sensory examination and blood tests (in particular creatine kinase), may help point towards a neuropathic, myopathic or dystrophic process. This can be aided by extending the physical examination with neurophysiology. Preservation of sensory and motor nerve studies is a good indication of normal peripheral nerve function, although very proximal conduction block can be missed. Again, a normal EMG from a single muscle does not exclude a myopathic process and it is important to ensure thorough neurophysiological examination in clinically affected and unaffected muscle groups. Distal chronic denervation with normal sensory studies point to a diagnosis of distal motor neuropathy. Distinguishing myopathies from hereditary motor neuropathy (HMN) is of particular importance when discussing prognosis and cardiac screening which is necessary in many of the myopathies.

Distinguishing distal hereditary motor neuropathy types

DHMN has previously been referred to as spinal CMT, distal spinal muscular atrophy (SMA) and as a neuronopathy rather than neuropathy. The confusion in nomenclature relates to the uncertainty regarding the site and nature of the major pathogenic lesion. It is becoming increasingly understood that different molecular abnormalities can result in diverse phenotypes in individuals with a variable degree of involvement of the cell body and axon, and that HMN is the most accurate nomenclature for these conditions.

DHMN is characterised by progressive wasting and weakness in the lower and upper limbs without sensory impairment; however, the phenotypic features are variable and have been used to define 7 main disease subtypes (table 2). More recently, the number of genes causing an HMN phenotype has expanded with increasing recognition of allelic disorders such as with the Alanyl-tRNA synthetase (AARs) gene (MIM phenotype number 613287) which can cause a phenotype consistent with HMN or CMT2N. There is vast variability in the prognosis between HMN types, enhancing the relevance to families of making an accurate diagnosis.

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Autosomal dominant DHMN with vocal paresis (DHMN7) has been described in two families from Wales who were later demonstrated to be related by genealogy[1]. The typical presentation is of a slowly progressive weakness affecting mainly the hands with onset in late teens to early twenties. Lower limb involvement is less prominent and mobility is usually retained. Voice change can be the presenting feature, but is frequently under reported – unless the patient is a keen singer. The family reported here has been followed in the Departments of Neurology and Genetics at the University Hospital of Wales and the Royal Gwent Hospital from 1994 to 2015. Genetic analysis from affected Welsh families indicated linkage to chromosome 2q14 in 2001[1]. Recently, whole exome sequencing has led to the identification of a pathogenic frameshift mutation in SLC5A7 in one family, which encodes the presynaptic choline transporter involved in synaptic acetylcholine synthesis at the neuromuscular junction[2]. Although the DHMN with vocal cord paresis phenotype is suggestive of DHMN7/SLC5A7 mutation, similar features have been described in patients with TRPV4 mutations(table 2)[3,4]. These families have varying phenotypes including hereditary motor and sensory neuropathy 2c[5,6], scapuloperoneal SMA[7] and congenital non-progressive SMA. In some of these families clinical or neurophysiological sensory features can be helpful in pointing to a TRPV4 mutation. In patients with prominent upper limb DHMN,clinicians should also consider mutations in the BSCL2 and GARS genes (table 2); especially relevant in patients who are not keen singers and may have delayed recognition of vocal cord problems.

Key points

1. Precise phenotypic characterisation of distal weakness is essential for guiding diagnostic tests
2. Accurate genetic diagnosis of DHMN types is essential for guiding prognosis.
3. Advances in genetic understanding of rare disease subtypes will guide development of directed therapy.
4. DHMN7 has a characteristic presentation with vocal cord problems and hand weakness.

Acknowledgements

We are grateful for the opportunity to have reviewed the clinical notes and investigations of Dr John Graham and Prof Sir Peter Harper and to the family members reported.

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Table 1: Differential diagnosis of distal weakness

Pathological region	Diagnosis		Key notes
Spine	Cervical myelopathy		Always rule out multi-level spinal disease
Anterior horn cell	ALS		Can present with predominantly distal weakness, particularly associated with split hand appearance
Nerve	Compressive		If multiple compression palsies, consider HNPP (chromosome 17p deletion)
	Metabolic		In particular uraemic and diabetic related.
	Inflammatory	GBS	Typical changes on nerve conduction studies confirm peripheral nerve involvement
		MMN	Conduction block on nerve conduction studies.
		Vasculitic	Often presenting with mononeuropathies.
	Inherited	CMT	For in depth review see Rossor AM et al [8].
		HMN	See table 2
Muscle	Distal myopathy	Laing distal myopathy	MYH7 (MIM 160500). Prominent weakness in ankle and finger extension.
		Welander distal MD	TIA1 (MIM 604454). Commonly presents with upper limb weakness first.
		Nonaka distal myopathy	GNE (MIM 605820). Prominent anterior lower leg weakness in persons of Japanese descent.
	Myotonic dystrophy 1		DMPK trinucleotide repeat on chromosome 19 (Phenotype MIM 160900). Distal weakness and myotonia
	FSHMD		Chromosome 4q35 (MIM 158900). Often affects facial muscles first, then anterior calf, then scapulohumeral muscles.
	LGMD	2b: dysferlinopathy / Miyoshi distal MD	Dysferlin 2p13.2 (MIM 253601). Prominent posterior calf and biceps weakness. Very high CK.
		1a: myotilin	Chromosome 5q31 (MIM 159000). Can also get dysarthria and dysphagia and cardiac involvement.
		2l: anactamin	Chromosome 11p14 (MIM 611307). Prominent lower limb involvement first.
	Myofibrillar myopathies	Desmin-related: chromosomes 2q35 and 11q	Prominent lower limb involvement first with progression to arms and respiratory muscles. (MIM 601419)
	IBM		Weakness of long finger flexors and dysphagia. Typical

		appearance on muscle biopsy.
Metabolic	Debrancher enzyme deficiency type III	Autosomal recessive metabolic disease affecting liver, muscles and heart.
	Phosphorylase b kinase deficiency	Glycogen storage disorder type IX affecting liver and muscles and causing stress induced hypoglycaemia and ketoacidosis.
Nemaline myopathy		Rods on gomori trichrome stain of muscle biopsy

ALS: amyotrophic lateral sclerosis. HNPP: hereditary neuropathy with liability to pressure palsies. GBS: Guillain-Barre syndrome. MMN: multifocal motor neuropathy. CMT: Charcot Marie Tooth. HMN: hereditary motor neuropathy. MIM: refers to the MIM phenotype number. MD: muscular dystrophy. FSHMD: facioscapulohumeral muscular dystrophy. LGMD: limb girdle muscular dystrophy. IBM: inclusion body myositis.

Table 2: Distal hereditary motor neuropathies

Type	MIM phenotype no.	Inheritance	Gene	Phenotype
HMN1	182960	AD	Linked to 7q34-36	Symmetrical juvenile onset lower limb weakness
HMN2A	158590	AD	HSPB8	Symmetrical progressive lower limb weakness
HMN2B	608634	AD	HSPB1	Symmetrical distal weakness progressing from lower to upper limbs
HMN2C	613376	AD	HSPB3	Symmetrical distal weakness progressing from lower to upper limbs
HMN2D	615575	AD	FBX038	Symmetrical progressive weakness starting distally in calf muscles.
HMN4 / DSMA3	607088	AR	Linked to 11q13	Distal weakness with progression to truncal and diaphragmatic weakness
HMN5A	600794	AD	GARS	Symmetrical progressive weakness with upper limb predominance. Gene defect also causes CMT2D with similar phenotype.
HMN5A	600794	AD	BSCL2	Same phenotype as BSCL2 mutation, but also causes Silver syndrome which has an overlapping phenotype with spasticity
HMN5B	614751	AD	REEP1	Weakness predominantly affecting intrinsic hand muscles but also lower legs. Overlap with SPG31 (610250)
HMN6 / SMARD1	604320	AR	IGHMBP2	Infantile onset with diaphragm paralysis and respiratory failure.
SMARD2 / SMAX[9]		XR	LAS1L	Infantile onset with diaphragm paralysis and respiratory failure.
SMAX3	300489	XR	ATP7A	Distal weakness with prominent gait disorder
HMN7A	158580	AD	SLC5A7	Distal weakness with upper limb predominance and vocal paresis
HMN7B	607641	AD	DCTN1	Distal weakness with upper limb predominance, facial weakness and vocal paresis
Congenital non-progressive SMA	600175	AD	TRPV4	Distal lower limb weakness with vocal paresis. Overlapping phenotype with SPSMA and CMT2C
HMN-Jerash type / DSMA2	605726	AR	SIGMAR1	Distal weakness with some pyramidal features
DHMN with pyramidal features/ JALS4	602433	AD	SETX	Distal weakness with some pyramidal features
DSMA4	611067	AR	PLEKHG5	Distal weakness progressing proximally with associated respiratory failure.
DSMA5	614881	AR	DNAJB2	Symmetrical progressive distal weakness predominantly in lower limbs

HMN / CMT2N	613287	AD	AARS	Distal weakness in lower limb. Allelic with Early Infantile Epileptic Encephalopathy 29.
HMN / CMT2	137200	AR	HINT1	Distal weakness with little sensory loss. Associated neuromyotonia.

HMN: hereditary motor neuropathy. AD: autosomal dominant. DSMA: distal spinal muscular atrophy. AR: autosomal recessive. SMARD: spinal muscular atrophy with respiratory distress. XR: X- linked recessive. SPSMA: scapuloperoneal spinal muscular atrophy.CMT: Charcot Marie Tooth. SPG spastic paraplegia. JALS juvenile amyotrophy lateral sclerosis

Figure 1: Images of the proband demonstratingsevere upper limb wasting apparent in hands, most prominently in the thenar eminence bilaterally, with wasting of intrinsic foot muscle but no true pes cavus deformity.

Figure 2: Family history