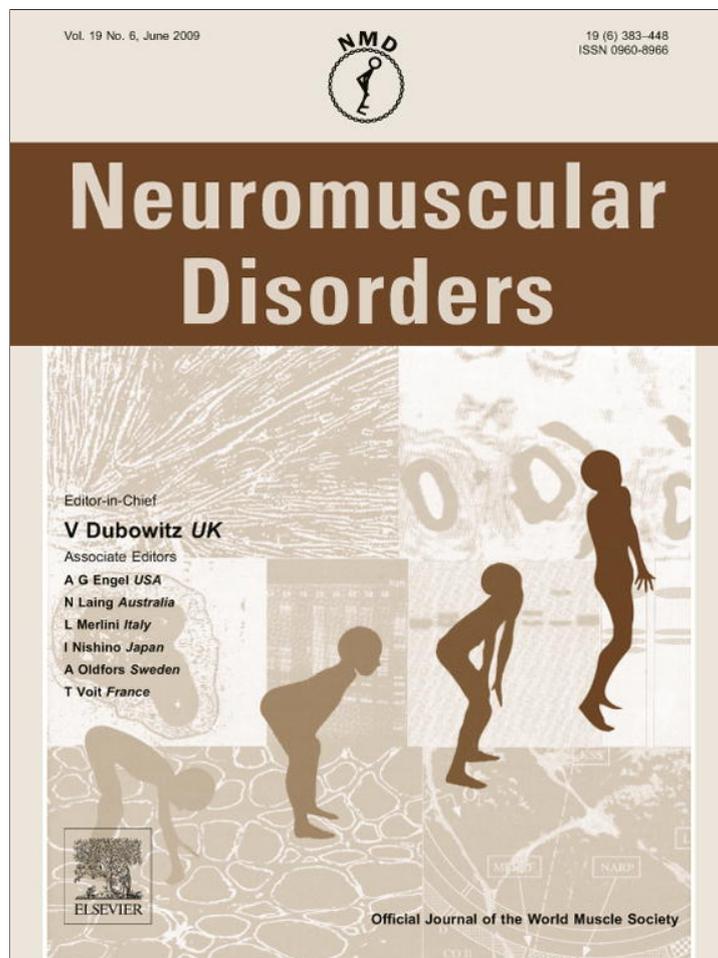


Provided for non-commercial research and education use.
Not for reproduction, distribution or commercial use.



This article appeared in a journal published by Elsevier. The attached copy is furnished to the author for internal non-commercial research and education use, including for instruction at the authors institution and sharing with colleagues.

Other uses, including reproduction and distribution, or selling or licensing copies, or posting to personal, institutional or third party websites are prohibited.

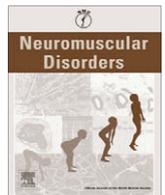
In most cases authors are permitted to post their version of the article (e.g. in Word or Tex form) to their personal website or institutional repository. Authors requiring further information regarding Elsevier's archiving and manuscript policies are encouraged to visit:

<http://www.elsevier.com/copyright>



Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd

Case report

Cranial nerves palsy as an initial feature of an early onset distal hereditary motor neuropathy – A new distal hereditary motor neuropathy phenotype

J. Haberlová^{a,*}, K.G. Claey's^b, P. De Jonghe^{c,d}, P. Seeman^a^a DNA laboratory, Department of Child Neurology, Second School of Medicine, Charles University Prague, 15200 Prague 5, Czech Republic^b Institut de Myologie, Groupe Hospitalier Pitié-Salpêtrière, Paris, France^c Neurogenetics Group, Department of Molecular Genetics, Flanders Interuniversity Institute for Biotechnology, University of Antwerp, Antwerpen, Belgium^d Department of Neurology, University Hospital Antwerp, Antwerpen, Belgium

ARTICLE INFO

Article history:

Received 26 February 2009

Received in revised form 15 March 2009

Accepted 20 March 2009

Keywords:

Distal hereditary motor neuropathy

Cranial nerve palsy

Slow progression

Autosomal dominant inheritance

ABSTRACT

Distal hereditary motor neuropathy is a heterogeneous group of disorders characterised by a pure motor axonal neuropathy. It is occasionally associated with additional signs such as facial weakness, vocal cord paralysis, weakness of the diaphragm, and pyramidal signs. Although predominantly the inheritance is autosomal dominant, all types of inheritance have been described. Here we report a Czech family with cranial nerves palsy as an initial feature of a non progressive infantile onset dominant distal hereditary motor neuropathy. This family may represent a new subtype of distal hereditary motor neuropathy.

© 2009 Elsevier B.V. All rights reserved.

1. Introduction

Distal hereditary motor neuropathy (dHMN) is a clinically and genetically heterogeneous group of disorders characterized by progressive, pure motor axonal neuropathy. Occasionally dHMN can combine with additional features such as facial weakness, vocal cord paralysis, diaphragm weakness or pyramidal signs. Inheritance predominantly is autosomal dominant, but autosomal recessive or X linked recessive inheritances have also been reported. Over the last six years mutation in six different genes for autosomal dominant and one gene for autosomal recessive inheritance have been identified. Here we report a Czech family with cranial nerves palsy as an initial feature of a non progressive infantile onset dominant dHMN. Gene testing had excluded mutation in *HSP 22*, *27*, *GARS*, *BSCL2*, *SETX*, *VAPB* and *DCTN1* genes. This family may represent a new subtype of dHMN with slow progression.

2. Patients

A 28-year-old Czech woman and her 6-month-old daughter were similarly affected since early infancy. Family history is negative. Her perinatal history is normal, however, since the age of 4 months the mother presented with horizontal nystagmus, facial weakness with bilateral eye closing weakness, dysphagia and quadruhyperreflexia.

At the age of 8 months stridor and dyspnoea by bilateral recurrent nerve palsy with live threatening vocal cord paresis was reported and was later treated by a chordectomy at the age of 10 years. During the first decade of life she developed mild distal muscular atrophy predominantly in her hands, which was most pronounced at the thenar muscles and in her legs maximally at the distal flexors. The muscular weakness progressed slowly during the second and third decade of life. Currently she is still able to work as a dressmaker. Objectively there is bilateral facial weakness with bilateral eye closing weakness, tongue atrophy with fasciculation, palatal palsy, absent gag reflex, severe dysphonia and mild distal muscular atrophy predominantly of hands, hyperreflexia C5–8 and L2/4, areflexia L5/S2, mild pes cavus. Nystagmus has disappeared and mental development is normal. At the age of 28 she gave birth to a daughter. The pregnancy and delivery were normal.

Brain and spinal cord MRI at the age of 17 years were normal. Electrophysiological examination (Table 1) showed signs of axonal neuropathy. Motor nerve conduction velocity (MNCV) in the hands and legs was repeatedly normal. There was, however, very low amplitude of compound muscle action potentials (CMAP). Sensory NCV (SNCV) as well as sensory nerve action potential (SNAP) was repeatedly normal. EMG showed a discrete interference pattern (IP), with some of the motor unit action potentials (MUPs) having a high amplitude. Electronystagmography showed abnormalities compatible with a central lesion. Somatosensory, visual and auditory evoked potentials were normal. Muscle biopsy at the age of 11 years was observed by immunohistologic techniques and

* Corresponding author.

E-mail address: jana.haberlova@gmail.com (J. Haberlová).

Table 1

	Sensory nerves		Motor nerves	
	SNAP (uV)	CV (m/s)	CMAP (mV)	CV (m/s)
<i>Electrophysiological findings of 28-year-old mother</i>				
n.medianus	37	58	0.8	48
n.ulnaris	50	53	0.9	56
n.tibialis	–	–	0.8	44
n.peroneus	–	–	0.3	50
n.suralis	45	54.8	–	–
Needle EMG	m.TBA	Discrete IP, few chronic neurogenic MUPS		
	m.vastus medialis	Discrete IP, normal MUPS		
<i>Electrophysiological findings of 7-month-old daughter</i>				
n.peroneus	–	–	0.2	42 (35)*
n.suralis	6	33 (30)*	–	–
Needle EMG	m.TBA	Discrete IP, normal MUPS		

SNAP – sensory nerve action potential; CMAP – compound motor action potential; CV – conduction velocity; IP – interference pattern; MUPS – motor unit action potentials. * Normal age matched values.

showed mild signs of neurogenic atrophy. Sural nerve biopsy at the same age observed by immunohistologic techniques was normal.

Her 6-month-old daughter had a normal perinatal history. She has never been able to suck and since the age of 4 months she has had horizontal nystagmus, bilateral facial weakness with eye closing weakness, slight stridor, and hyperreflexia at the legs. Nerve conduction studies (Table 1) showed normal MNCV and SNCV, significantly decreased CMAP and normal SNAP. With EMG a discrete IP was visualized, and MUPS were normal. Somatosensory evoked potentials were normal. Brain MRI at the age of 14 months showed no structural changes, only unspecific mild gliosis in occipital and periventricular regions.

Genetically *SMN1* gene deletion was excluded in the mother during her childhood. After the occurrence of similar phenotype in the daughter, *HSP 22, 27, GARS, BSCL2, SETX, VAPB* and *DCTN1* genes, that are associated with different types of dHMN, were screened by direct sequencing, but no mutation was found. All genes were sequenced on their all coding exons and exon–intron boundaries.

3. Discussion

We described a family with dHMN that started as cranial nerve palsies with vocal cord paresis (incomplete paresis of n.VII, VIII, IX, X, XI, XII) in early infancy. This novel phenotype does not fit to any previously published entity. The muscle weakness appears during the first decade of life, predominantly in the hands. The progression is slow, inheritance is probably autosomal dominant with a de-novo mutation in unidentified gene in the mother.

Vocal cord paresis is a prominent feature in some form of dHMN, however, these are clinically distinct from the disorder present in this family. Firstly, there is dHMN with vocal cord paresis caused by mutations in the dynactin gene (*DCTN1*). In contrast to our

patients, the facial weakness is mild and the onset of muscle weakness is during the second or third decade of life [1]. In distal spinal muscular atrophy with vocal cord paresis, linked to chromosome 2q14, hand weakness appears later, during the second decade of life, and there is no other cranial nerve involvement [2,3].

The second group of disorders to be considered are rare variants of bulbospinal SMA. There is a variant of Fazio-Londe disease with AD inheritance [4,5], but the distinction is that in our case there is distal muscle weakness and atrophy. The other variants of bulbospinal SMA are Brown-Vialetto-van Laere disease [5,6], but all reported patients had deafness and onset of the disorder is later in life.

To conclude, this family with novel phenotype of dHMN may represent a new disease entity with multiple cranial nerve palsies as an initial symptom and with vocal cord paresis which can be life threatening. Together with similar families our findings may contribute to finding a new causal gene for dHMN and to learn more about the pathogenesis of dHMN.

References

- [1] Puls I, Oh SJ, Sumner CJ, et al. Distal spinal and bulbar muscular atrophy caused by dynactin mutation. *Ann Neurol* 2005;57:687–94.
- [2] McEntagart M, Norton N, Williams H, et al. Localization of the gene for distal hereditary motor neuropathy VII (dHMN-VII) to chromosome 2q14. *Am J Hum Genet* 2001;68:1270–6.
- [3] Young ID, Harper PS. Hereditary distal muscular atrophy with vocal cord paralysis. *J Neur Psychiat* 1980;43:413–8.
- [4] Gomez MR, Clermont V, Bernstein J. Progressive bulbar paralysis in childhood. Report of a case with pathologic evidence of nuclear atrophy. *Arch Neurol* 1962;6:317–23.
- [5] Van den Berg-Vos RM, Van den Berg LH, Visser J, et al. The spectrum of lower motor neuron syndromes. *J Neurol* 2003;250:1279–92.
- [6] Hawkins SA, Nevin NC, Harding AE. Pontobulbar palsy and neurosensory deafness with possible autosomal dominant inheritance. *J Med Genet* 1990;27(3):176–9.