MME GENE MUTATION CAUSING SPINOCEREBELLAR ATAXIA AND AXONAL POLYNEUROPATHY: CLINICAL CASE

R. Collin, J. Dellatte, JF. Kaux, FC. Wang
Physical Medicine, Rehabilitation, Sport Traumatology and Electrophysiology department, CHU Liège, Liège, Belgium

Abstract

We describe **spinocerebellar ataxia (SCA)** with **late onset, progressive, sensorimotor polyneuropathy (PNP)** in a 56-year-old patient. The involvement of six other family members lead to a genetic analysis which shows a **mutation of the membrane metalloendopaptidase (MME) gene**. This gene codes for **neprylisin (NEP)** which is a membrane protein. Several studies have shown the impact of MME gene mutations on the incidence of late-onset axonal sensorimotor PNP. The interest of this clinical case is the description of a new MME gene mutation, responsible for a late-onset, slowly progressive, inherited PNP affecting mainly motor axons.

Introduction

SCA is **chronic progressive disease** that results from neuronal loss or dysfunction in the cerebellum and spinal cord. **Different genetic subtypes** has been described from SCA1 to SCA42. **PNP** are sometimes **associated** with SCA, axonal and/or demyelinating, according to the genetic subtype.

Purpose

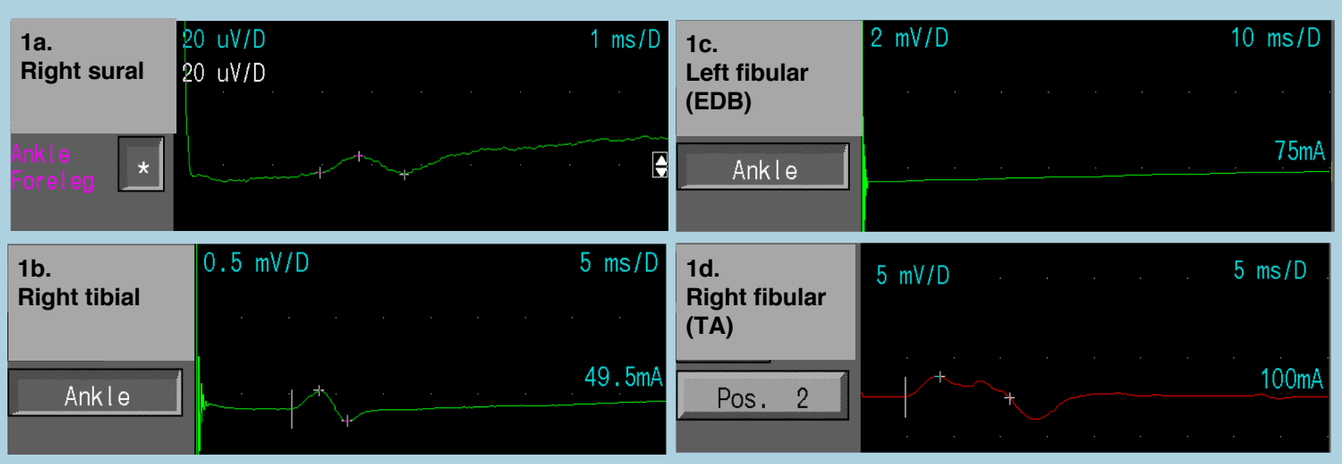
A **56-year-old woman** suffers **ataxic gait** and lower limbs **neuropathic pain**. The clinical examination shows **pectus carinatum**, **pes cavus**, **distal amyotrophy**, **distal hypoesthesia** and **areflexia** in the lower limbs. Three years later, patient develops hypometric saccades and dysarthia suggesting a **cerebellar syndrome**. Three sisters, one brother, and two nieces, present a cerebellar syndrome and a PNP over several years. Some have a pectus carinatum. These familial clinical features lead to a **genetic study** on 28 family members. The results show a **mutation of the MME gene** in the **7 affected subjects.**

Method

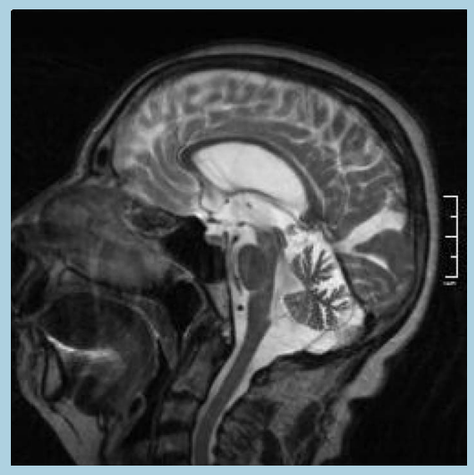
The diagnosis is performed by several electrophysiological examinations, brain MRI and molecular genetic study of the patient and his family.

Motor neurography		A (mV)	DL (ms)	CV (m/s)	F (ms)
Right median	1999	7.9	3.7		25.3
	2001	7.3	3.5		25.5
	2003	8.3	3.7	48	29.0
Right tibial	1999	**0.4**	6.5		
	2001	**0.1**	13.3		
	2003	**0.1**	10.3		
Left fibular (EDB)	1999	**0.7**	6.8		
	2001	**0.2**	5.5		
	2003	**0**	0		
Right fibular (TA)	1999	**3.1**	3.5		
	2001	**2.2**	3.3		
	2003	**1.4**	3.3		
Sensitive neurography		A (mV)	DL (ms)	CV (m/s)	
Right radial	1999	**13**	2.6	57	
	2001	**/**			
	2003	**/**			
Superficial fibular	1999	**6.4**	2.9	46	
	2001	**5**		50	
	2003	**3.5**		40	
Right sural	1999	**5.5**	4.6	39	
	2001	**/**			
	2003	**5**		48	

▲Fig. 2 : ENMGs show a subacute axonal sensorimotor PNP progressive over several years. A = amplitude; DL = distal latency; CV = conduction velocity; F = F waves; EDB = extensor digitorum brevis muscle; TA = tibialis anterior muscle.



◀ **Fig. 1** : **ENMG 2003** : right sural (**1a**), right tibial (**1b**), left fibular (EDB) (**1c**), right fibular (TA) (**1d**).



▶ **Fig. 3 : Brain MRI** : cerebellar vermis atrophy.

Results

Electroneuromyography (ENMG) demonstrates a **subacute axonal sensorimotor PNP**, mostly motor rather than sensitive, progressive over several years. Indeed, the ENMG shows a predominantly **distal** decrease in the **amplitude** of sensory responses (radial, fibular, sural) (Fig. 1a), and even more of the **motor** responses: tibial and fibular-EDB > fibular-TA > median nerves (Fig 1b,c,d). ENMG reports **subacute neurogenic** muscle involvement over several years confirming a progressive active axonal loss (Fig. 2). **Sensory evoked potentials** attest defect especially in the lower limbs. **Brain MRI** shows a cerebellar vermis atrophy (Fig. 3). Finally, familial genetic study identifies **mutation of the MME gene**, which codes for **neprilysin**. The mutation is a substitution of guanine by adenine on chromosome 3q25.2, inducing a replacement of cysteine by tyrosine at 143 position (p.C143Y). The consequence is a rupture of a disulfide bridge. This mutation, not previously described, defines a new disease: **SCA43** (1).

Conclusion

1. The MME gene encodes NEP which is a membrane metalloendopeptidase, one of the most prominent beta-amyloid (Aß)-degrading enzymes, expressed in the peripheral and central nervous systems. The **pathogenesis** due to the loss of function of NEP is still **unclear.** But amyloid deposit is not found on biopsies (2).

2. In this family, the p.C143Y MME mutation transmitted according to the autosomal dominant mode, is responsible for the phenotype of **SCA43**, **associated** to **late-onset axonal sensorimotor PNP.**

3. Two recent studies (3,4) show a **late-onset axonal sensorimotor PNP**, without central nervous system involvement, in patients with other MME gene mutations. **Different MME mutations** induce **several phenotypes**, ranging from AR-CMT2T to SCA43.

Contact: rcollin@chuliege.be

1. Depondt C. et al.; MME mutation in dominant spinocerebellar ataxia with neuropathy; Neurol Genet. 2016, 2(5), e94.
2. Pareyson D. et al.; New developments in Charcot–Marie–Tooth neuropathy and related diseases; Curr Opin Neurol. 2017; 30(5):471-480.
3. Higuchi Y. et al.; Mutations in MME Cause an Autosomal-Recessive Charcot–Marie–Tooth Disease Type 2; Ann Neurol. 2016; 79(4):659-72.
4. Auer-Grumbach M. et al.; Rare Variants in MME, Encoding Metalloprotease Neprilysin, Are Linked to Late-Onset Autosomal-Dominant Axonal Polyneuropathies; Am J Hum Genet. 2016; 99(3):607-623.