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

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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 metalloendopeptidase (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 dysarthria 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 (A β)-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.