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Case report

Longitudinal assessments in discordant twins with SMA

Marika Pane [a,b], Leonardo Lapenta [a,b], Emanuela Abiusi [c], Roberto de Sanctis [b], Marco Luigetti [d], Concetta Palermo [b], Domiziana Ranalli [a,b], Stefania Fiori [c], Francesco Danilo Tiziano [c], Eugenio Mercuri [a,b,*]

[a] *Paediatric Neurology, Catholic University, Rome, Italy*
[b] *Centro Clinico Nemo, Policlinico Gemelli, Rome, Italy*
[c] *Institute of Genomic Medicine, Catholic University, Rome, Italy*
[d] *UOC Neurologia, Fondazione Policlinico Gemelli, Rome, Italy*

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Abstract

We report longitudinal clinical and neurophysiological assessments in twins affected by spinal muscular atrophy (SMA) with discordant phenotypes. The boy had the homozygous deletion of *SMN1*, a typical type 1 SMA course, and died at the age of eight months. His twin sister, asymptomatic at the time of the diagnosis in her brother, had the same genetic defect but she developed clinical and electrophysiological signs of type 2 SMA. The reduction of tendon reflexes was the first clinical sign at the age of 4 months, followed within few weeks, by a mild decrement in the amplitude of the compound motor action potentials. After the age of 9 months, she showed a sudden clinical and electrophysiological deterioration. Among molecular tests, we determined *SMN2* copy number, *SMN2* and *Plastin 3* transcript levels in peripheral blood, and observed no relevant differences between twins.

Keywords: Spinal muscular atrophy; Modifiers; Phenotypes; CMAP; Twins

1. Introduction

Spinal muscular atrophy (SMA) is a common recessive neuromuscular disorder characterized by the degeneration of spinal motor neurons with subsequent muscle weakness and atrophy, and is due to the homozygous mutations in the survival motor neuron 1 gene (*SMN1*) [1]. The clinical spectrum ranges from profound generalized weakness and inability to sit unsupported, observed in the most severe form (type 1), to proximal muscle weakness in ambulant patients as observed in type 3 [2,3]. The clinical and prognostic variability is likely modulated by genetic, epigenetic and extrinsic factors, which are partly still unknown. *SMN2* copy number has been reported to be one of the main modifiers of SMA severity [4]. Within type 1 SMA, for example, patients with 2 *SMN2* copies have overall more severe phenotypes compared to those with 3 or more *SMN2*. However, *SMN2* copy number assessment is not sufficiently predictive of the phenotypic severity in individual patients, since the clinical variability may be very wide even in the presence of the same copy number.

Some studies have reported that SMA siblings may show discordant clinical phenotypes [4,5].

We report clinical, molecular and neurophysiological findings in twin infants, a boy and a girl, with discordant phenotypes, respectively. The girl, affected by type 2 SMA, was diagnosed pre-symptomatically, following the onset of symptoms in her type 1 twin brother. This allowed observation of the onset and the progression of both clinical and neurophysiological signs.

2. Case report

We report clinical, molecular and neurophysiological findings in a boy with a typical type 1 SMA course, and in his twin sister who was subsequently diagnosed with type 2 SMA. They were conceived by egg-donation. Delivery was uncomplicated with normal perinatal and neonatal course. The boy was first seen at the age of 4 months by a pediatrician who noticed hypotonia and weakness, and referred him for a tertiary care assessment. On our examination, we observed severe hypotonia and weakness, bell-shaped chest, with no head control. Some distal movements were preserved in the upper limb, as

* Corresponding author. Pediatric Neurology, Catholic University, Largo Gemelli 8, 00168 Rome, Italy.
E-mail address: eumercuri@gmail.com (E. Mercuri).

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Table 1
Clinical, neurophysiologic and genetic characteristics of the patients.

Type 1 SMA (boy)							
		Ulnar CMAP					
AGE (in months)	EMG	Latency	Amplitude	CHOP	DTR	SMN transcripts *	PLS3 *
4				12	absent		
5	fp, psw +++	3,1 ms	0,3 mV	9	absent	fl: 130.9 ± 8.6 del7: 118.4 ± 8.8	4.7 ± 0.3
6	fp, psw +++	3.1 ms	0.3 mV	-	absent		
8	fp, psw +++	2,5 ms	0,4 mV	5	absent		
9	-	-	-	2	absent		

Type 2 SMA (girl)							
		Ulnar CMAP					
AGE	EMG	Latency	Amplitude	CHOP	DTR	SMN transcripts *	PLS3 *
5	normal	2,0 ms	5,7 mV	64	reduced?	fl: 134.0 ± 5.4 del7: 180.4 ± 3.0	17.9 ± 1.8
6	normal	2,0 ms	5,7 mV		absent		
8	fp, psw +	2,1 ms	4,3 mV	60	absent		
9	fp, psw ++	2,1 ms	4,0 mV	49	absent		
12	fp, psw +++	2,0 ms	1,7 mV	46	absent		
18	fp, psw +++	2,8 ms	0,7 mV	32	absent	fl: 216.5 ± 7.5 del7:161.6 ± 9.2	
26	-	-	-	4 (HFMSE)	absent		
32	-	-	-	4 (HFMSE)	absent		
39	-	-	-	4 (HFMSE)	absent		

CMAP = compound motor action potential; EMG = electromyography; fp = fibrillation potentials; psw = positive sharp waves; DTR = deep tendon reflexes; HMFSE = Hammersmith functional motor scale-expanded.
* transcript levels are expressed number of molecules/ng of total RNA.

well as more limited distal sub-gravity movements in the lower limbs. There were also tongue fasciculation, distal tremors. Reflexes were not elicitable. There were feeding difficulties and paradoxical pattern of breathing.

Genetic investigation for SMA was performed by Restriction Fragment Length Polymorphism- Polymerase Chain Reaction (RFLP-PCR) for *SMN1* exon 7 and 8. For *SMN2* copy number, Relative real time PCR was used. The analyses showed homozygous deletion of the *SMN1* gene and 2 *SMN2* copies.

The boy was assessed monthly, and showed progressive weakness, with loss of scores on the CHOP INTEND motor scale (Table 1), increased swallowing difficulties and respiratory distress. The compound motor action potential (CMAP) of the right median nerve at 5 and 8 months of age showed markedly reduced values already on the first assessment. The parents agreed to have nasogastric tube feeding placed, but declined any other pro-active support. The boy died at 8 months of age due to respiratory failure.

Even if the neurological examination of the twin sister was considered normal at the same age of her brother's diagnosis, the genetic test was performed due to a slight reduction of tendon reflexes. The two sibs were identical at the SMN locus: *SMN1* homozygous deletion, 2 *SMN2* copies, same haplotype at Ag1-CA and C212 polymorphic markers (albeit DNA sample of the biological mother was not available).

Following diagnosis, the girl also had longitudinal neurological end electrophysiological assessments. Within a few weeks after the first visit, deep tendon reflexes were completely lost. At 4 months she was completely asymptomatic, she had normal muscle tone and good head and trunk control, full spontaneous antigravity movements with no distal tremor or tongue fasciculation. Deep tendon reflexes were reduced, and, within a few weeks, absent. Feeding and breathing were unremarkable. At the age of 6 months she was able to roll both sides completely and to lift both her arms above the head. She acquired the ability to sit unsupported at the age of 6 to 7 months. Minimal signs of clinical deterioration were noticed by the age of 8 months with difficulties in rolling smoothly. At the same age she showed some deterioration also on CMAP and sporadic fibrillation potentials and positive sharp waves appeared at electromyographic examination (EMG).

After the age of 9 months there was a more marked progressive functional loss with the typical pattern of hypotonia and functional impairment compatible with a type 2 SMA (see Table 1). Rolling became more difficult and the score of the CHOP INTEND motor scale showed a progressive reduction. Details of the examinations, using the CHOP and the Hammersmith's Functional Motor Scale – Expanded Module (HFMSE) are reported in Table 1. At 12 months, CMAP showed a sharp reduction; concomitant diffuse signs