Spinal muscular atrophy with an overlapping syndrome — “double trouble” or a potentially better outcome?

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To the Editors:

Spinal muscular atrophy (SMA) is one of the most frequent autosomal recessive childhood diseases. It is caused by mutations of the \textit{SMN1} gene [1, 2]. SMA patients present with progressive muscle weakness and atrophy [3]. SMA coexisting with another genetic entity is extremely rare, and poses a diagnostic challenge. These so-called “double trouble” cases demand a carefully tailored approach and multidisciplinary management. Here, we present two new cases of SMA overlapping with hereditary spastic paraplegia and Noonan syndrome, as well as a follow-up to our previously reported patient with SMA and Charcot-Marie-Tooth 1A [4].

We present the case of a 17-year-old girl with a history of progressive walking difficulties since the age of five. When she was four, her parents first noticed a tendency towards tiptoe walking. There was a history of progressive walking difficulties in several family members from her father’s side (Pedigree 1) who presented with pure spastic paraplegia. Molecular testing revealed the c.1729-2A>G point mutation in the spastin gene (\textit{SPAST}), confirming the diagnosis of hereditary spastic paraplegia (HSP). This mutation was present in our proband as well. However, in the neurological examination, she manifested additional symptoms. Moderate proximal weakness of her lower and upper limbs was observed. She had an increased muscle tone in her lower limbs, with brisk ankle reflexes and pes cavus (Fig. 1), but her knee reflexes were absent. Finger and tongue tremors were reported. Her nerve conduction study results were normal. Concentric needle electromyography revealed some neurogenic changes (supplementary Fig. 2). A genetic test confirmed homozygous deletion of exons 7 and 8 of the \textit{SMN1} gene and three copies of the \textit{SMN2} gene.

We present the case of a 20-year-old man who had been delivered by caesarean section in the 36th week of gestation (premature rupture of the membranes). In his first days of life, he had some breathing difficulties, manifested cyanosis, and was...
Table 1. Summary of Noonan syndrome features present in patient

<table>
<thead>
<tr>
<th>Dysmorphic features</th>
<th>Hypertelorism, ptosis, low-set ears, high forehead, triangular face, broad neck, widely spaced nipples</th>
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<tbody>
<tr>
<td>Cardiac defects</td>
<td>Pulmonary valve stenosis</td>
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<td>Musculoskeletal defects</td>
<td>Short stature (postnatal onset), pectus excavatum, scoliosis</td>
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<td>Neurological defects</td>
<td>Learning difficulties, mild developmental delay</td>
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<td>Ocular abnormalities</td>
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<td>Bleeding diathesis</td>
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<td>Neonatal features</td>
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diagnosed with pulmonary stenosis. The patient underwent balloon plastic surgery a few months later. He had some dysmorphic features: hypertelorism, low-set ears, a high forehead, a broad neck, bilateral ptosis, widely spaced nipples, and a high arched palate (supplementary Fig. 3). His motor milestones were reported as normal; however, from the start he could not keep up with his peers. When he was 17, a diagnosis of Noonan syndrome was established and confirmed through genetic testing. He carries the c.922A>G (Asn308Asp) mutation in PTPN11 gene, de novo in its origin. He was referred to our centre for evaluation of proximal muscle weakness at the age of 17. Since the age of six there had been a tendency towards tiptoe walking and some difficulties with climbing stairs. On examination, he presented with hypotonia, proximal weakness more prominent in the lower than in the upper limbs, a waddling gait, Gower’s sign, and bilaterally absent knee reflexes. Neither finger nor tongue tremors were observed. His nerve conduction study was normal, whereas his electromyography and muscle biopsy were consistent with neurogenic changes (supplementary Fig. 4). The clinical diagnosis of spinal muscular atrophy was confirmed by the detection of a homozygous absence of the SMN1 copy in exon 7. Interestingly, exon 7 was found to be deleted from one copy of SMN1 in one parent only — the mother (Pedigree 2). Recently, this patient has experienced decreased tolerance for motor activities, a finding initially attributed to progression of SMA. A cardiological evaluation revealed a recurrence of severe pulmonary stenosis, and now the patient is awaiting his second cardiac surgery. His neurological status is 1:1,000 live births [12]. The diagnosis is based on a clinical scoring system introduced by van der Burgt (supplementary Tab. 3) [13]. Genetic testing confirms the diagnosis in approximately 70% of cases. About half of cases are caused by a mutation in the protein tyrosine phosphatase nonreceptor type 11 (PTPN11) gene [14].

In the literature, there is one case report describing a patient with NS and Becker muscular dystrophy (BMD) with a more severe phenotype resembling Duchenne’s muscular dystrophy [15]. Hypotonia features early in NS and accounts for mild motor delays [13]. Children with NS start walking independently on average at around 21 months [16]. One study assessed motor function in 19 children with NS aged 6 to 11. They showed reduced grip and muscle strength. The mean distance in a six-minute walking test (6MWT) differed from reference values (p < 0.001) [17]. One of the factors influencing their physical activity was congenital heart disease. The intensity of physiotherapy in our patient had also to be reduced because of significant pulmonary stenosis. That further compromised his motor functions, already impaired by SMA.

Coincidences of SMA and another genetic disorder are very rare. The symptoms of anterior horn dysfunction should keep physicians away from using Occam’s razor in the diagnostic process. With the emergence of pharmacological treatment in SMA, heightened attention is needed when a patient presents with such symptoms complicated by the coexistence of another genetic disease.

Diagnosing SMA should lead to a therapeutic intervention [19–22]. Other medical problems should be attended to as required. We hope that opportunities to change the course of SMA in overlapping syndromes may turn “double trouble” into “single trouble” cases.

Legend and abbreviations

Pedigree 1: SMA — spinal muscular atrophy; SPG4 — spastic paraplegia 4
Pedigree 2: SMA — spinal muscular atrophy; NS — Noonan syndrome

Pedigree 3: SMA — spinal muscular atrophy; CMT1A — Charcot-Marie-Tooth disease type 1A

Table 2. Summary of the patients’ clinical details

Table 3. NS criteria adapted from van der Burgt [12, 13]

Figure 2. Electromyography results — Case 1. Amp — amplitude; Dur — duration; Poly — polyphasia; uV — microvolt; rel.SD — relative standard deviation; ms — milliseconds; min — minimum; max — maximum

Figure 3. Patient with Noonan syndrome and SMA. Note hypertelorism, ptosis, low-set ears, triangular face, widely spaced nipples, and proximal muscle wasting of upper limbs

Figure 4. Electromyography results — Case 2. Amp — amplitude; Dur — duration; Poly — polyphasia; uV — microvolt; rel.SD — relative standard deviation; ms — milliseconds; min — minimum; max — maximum

Figure 5. Nerve conduction study — Case 3. Lat — latency; Amp — amplitude; CV — conduction velocity; F-M — F wave; uV — microvolt; ms — milliseconds; SD — standard deviation; APB — abductor pollicis brevis muscle; Be — below; Ab — above; elb — elbow; ADM — abductor digiti minimi muscle; AHB — abductor hallucis brevis muscle; EDB — extensor digitorum brevis muscle

References