Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2020, Volume 54
DOI: 10.5603/PJNNS.a2020.0060

ISSN 0028–3843

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

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Key words: spinal muscular atrophy, hereditary spastic paraplegia, Noonan syndrome, CMT1A, SMA coexistence

Introduction

Spinal muscular atrophy (SMA) is one of the most frequent autosomal recessive childhood diseases. It is caused by mutations of the *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].

Case report 1

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 (*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 *SMN1* gene and three copies of the *SMN2* gene.

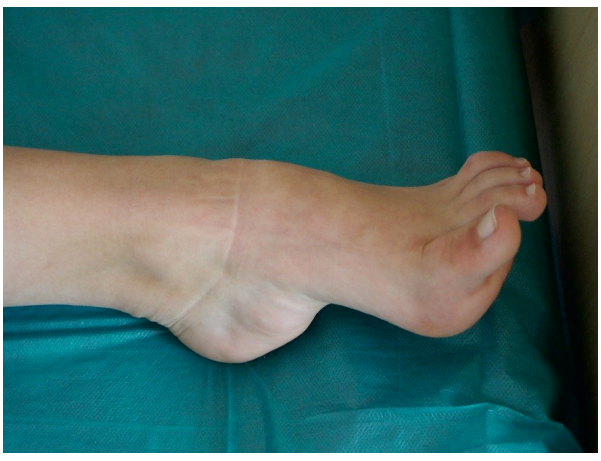

Figure 1. Foot deformity in patient with spinal muscular atrophy and hereditary spastic paraplegia

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Table 1. Summary of Noonan syndrome features present in patient

Dysmorphic features	*Hypertelorism, ptosis, low-set ears, high forehead, triangular face, broad neck, widely spaced nipples*
Cardiac defects	*Pulmonary valve stenosis*
Musculoskeletal defects	*Short stature (postnatal onset), pectus excavatum, scoliosis*
Neurological defects	*Learning difficulties, mild developmental delay*
Ocular abnormalities	*Nystagmus, myopia*
Bleeding diathesis	*Easy bruising*
Neonatal features	*Dorsal limb lymphedema*

Case report 2

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 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 reoccurrence of severe pulmonary stenosis, and now the patient is awaiting his second cardiac surgery. His neuromuscular performance is stable. The features of NS syndrome in our patient are summarised in Table 1.

Case report 3

Table 2 shows summary of the patients' clinical details. See supplementary files.

Discussion

To the best of our knowledge, there is no modern report of a coincidence of HSP and SMA, nor of NS and SMA.

SMA + HSP

Hereditary spastic paraplegia (HSP) is a heterogenous group of diseases with a prevalence of 1.8/100,000 [9]. Progressive lower limb spasticity and muscle weakness are its most prominent features. Most frequently, the first symptoms occur in adulthood. Our understanding of the genetic background spectrum has expanded considerably in recent decades. Mutations of over 70 distinct loci have been identified, with the spastin gene mutation being the most common cause of HSP that is classified as familial spastic paraplegia 2 (FSP2) [10]. In spastic paraplegia 4 (SPG4) spasticity may be accompanied by a reduced vibration in the legs. Theoretically, a mild spasticity may be beneficial in patients with SMA. Also, a lower motor neuron lesion may ameliorate an increased muscle tone. Such an additive effect has been reported in SPG4 coexisting with facioscapulohumeral muscular dystrophy [11]. Most probably, that positive effect could be merely temporal due to progressive spasticity and SMA-related weakness.

SMA + NS

Noonan syndrome (NS) is a common heterogenic disorder featuring characteristic facial features, a high incidence of congenital cardiac defects, short stature, chest deformities as well as cryptorchidism in males, mild intellectual deficits, bleeding tendencies, and many others. The estimated incidence of NS 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.

SMA + CMT

See supplementary files.

Conclusion

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.

Clinical implications/future directions

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

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