Tongue fasciculations in an infant with spinal muscular atrophy type 1

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Introduction
Spinal muscular atrophy (SMA) is a neuromuscular disorder characterized by degeneration of the α-motor neurons, leading to symmetrical muscle weakness and atrophy mainly of the lower limbs [1]. Here, we report on an infant with SMA type 1 with a rare compound heterozygosity of the survival of motor neuron 1 gene (SMN1) and characteristic fasciculations of the tongue.

Case Report
A 4-month old, Caucasian boy with an unremarkable antenatal history (first child of nonconsanguineous, healthy parents, no polyhydramnios) was admitted to our hospital due to dyscataposia and mucus congestion with suspicion of a pulmonary infection. The parents denied fever, cough, or sneezing. A mild muscular hypotonia was observed by the family’s pediatrician during standard examinations by age 1 month. Our examination revealed a poor sucking reflex, failure to thrive, proximal and peripheral muscular weakness with a bell-shaped chest and areflexia. Lower limbs were more strongly affected than upper limbs. On inspection, fasciculations of the tongue were observed – most prominently at the periphery of the tongue (Video S1). Magnetic resonance imaging (MRI) of the brain showed a mega-cisterna magna (MCM, Fig. 1). During hospitalization, the infant

Key Clinical Message
Muscular hypotonia in infants may be associated with several conditions, such as spinal muscular atrophy (SMA). We report on an infant with tongue fasciculations and a rare mutation of the SMN1 gene. The presence of tongue fasciculations in combination with a thorough history may be suggestive of SMA.

Keywords
Mega-cisterna magna, neuromuscular disease, point mutation, tongue fasciculation.
required mechanical ventilation for respiratory failure. Clinical and neurophysiological examinations were suggestive of the neuromuscular disorder SMA type 1. Molecular genetic testing showed a rare compound heterozygosity for a point mutation c.815A>G (p.Y272C) in exon 6 of the \textit{SMN1} gene (OMIM 600354) on the paternal allele and a deletion of \textit{SMN1} exon 7 and 8 on the maternal allele, in the presence of two copies of the \textit{SMN2} gene (OMIM 601627) confirming the diagnosis of SMA. At parental request the infant was extubated and provided with palliative care. Shortly thereafter, the infant succumbed to respiratory insufficiency.

**Discussion**

Spinal muscular atrophy is a heterogeneous neuromuscular disorder and the second most common lethal, autosomal recessive disease in Caucasians after cystic fibrosis [2]. Three clinical subtypes depending on age of clinical onset and maximum motor function have been identified [1]. Type 1 (Werdnig-Hoffmann, OMIM 253300) – the most severe and common type of SMA – has an early onset and progressive unrelenting course resulting in death due to respiratory insufficiency within the first 2 years [2]. Characteristic clinical features include profound hypotonia, symmetrical paralysis, little or no head control and areflexia [1, 3]. Fasciculations and atrophy of the tongue affect roughly one-third to one-half of patients with SMA, and may be noted during the first months of life, as in our patient [3]. Fasciculations of the tongue may also be seen in neonates with other medical conditions such as hypoxic-ischemic injury (HIE), Mobius syndrome, and storage disorders (Pompe disease) [3]. Usually, these distinct clinical entities can be differentiated from SMA by taking a detailed birth history (e.g., for HIE) or taking into account other characteristic clinical findings (e.g., macroglossia in Pompe disease). In addition to tongue involvement, fasciculation of the eyelids may also be seen in children with SMA. Several studies in infants have found an association between cerebrospinal fluid space abnormalities such as ventricular dilatation and congenital myotonic dystrophies [4]; such abnormalities, like dilatation of the cisterna observed in our patient, may not result in serious complications and remain in most of the cases uninvestigated. MCM is a controversial entity which is generally thought to be an anatomic variant with no clinical significance but may constitute part of several malformation syndromes such as Dandy Walker complex (DWC). To the best of our knowledge, there is only one reported association between SMA type I and Blake’s pouch cyst, which along with MCM is regarded as a less severe malformation included in the DWC [5].

Spinal muscular atrophy is caused by mutations in the \textit{SMN1} gene [6]. The vast majority of patients display a homozygous absence of \textit{SMN1} exons 7 or 8 or exon 7 only, whereas only a few (approximately 4%) show compound heterozygosity for a point mutation on one and a deletion on the other chromosome [2]. Unfortunately, in patients who do not present a homozygous disruption of the \textit{SMN1} gene, adversities in terms of diagnosis, prognosis and genetic counseling still occur. c.815A>G (p.Y272C), a missense mutation in a highly conserved region in exon 6 of \textit{SMN1} [6–8], accounts for approximately 20% of SMA patients with compound heterozygosity for a point mutation [2, 6]. p.Y272C is found to result in almost complete reduction in the self-oligomerization capacity [9], which suggests it to be a severe mutation [8] and is in agreement with our case.

In conclusion, muscular hypotonia is a common clinical sign in infants and may be associated with several conditions including neuromuscular disorders, connective tissue disorders, metabolic diseases, or even prematurity. The presence of tongue fasciculations, although not pathognomonic, and in combination with a thorough history, may be suggestive of SMA diagnosis. More genotype-phenotype associations are needed to achieve better genetic counseling.
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Conflict of Interest
None declared.

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Supporting Information
Additional Supporting Information may be found in the online version of this article:
Video S1. Tongue fasciculations in infant with spinal muscular atrophy