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Peripheral circulation disturbances in two consecutive children with spinal muscular atrophy and literature review

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Spinal muscular atrophy is a progressive and severe hereditary (autosomal recessive) neuromuscular disease characterized by lower motor neuron degeneration in the spinal cord and brainstem causing a clinical picture of progressive muscle atrophy and weakness of skeletal and respiratory muscles. There is an ongoing discussion on the extent to which other tissues might be affected in patients with SMA. Several animal models and some case reports or small case series report involvement of other organ systems, such as peripheral nerve, brain, muscle, heart, vascular system, and pancreas. Recent literature reviews identified a number of cases with vascular abnormalities. We present two consecutive cases of patients diagnosed with SMA who developed peripheral circulation disturbances and combine the findings with a thorough review the literature.

Key words: spinal muscular atrophy, peripheral circulation disturbances, children

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Introduction

Spinal muscular atrophy (SMA) is a progressive and severe hereditary (autosomal recessive) neuromuscular disease characterized by lower motor neuron degeneration in the spinal cord and brainstem causing a clinical picture of progressive muscle atrophy and weakness of skeletal and respiratory muscles. It is one of the most common causes of infantile mortality with an estimated incidence of 1:6000 - 1:11,000 newborns. It is caused by a homozygous mutation, deletion, or rearrangements in the survival motor neuron 1 (*SMN1*) gene on chromosome 5q13 [1,2]. These mutations are responsible for a dysfunctional SMN protein. SMN protein is ubiquitously expressed in all cells. The human genome also contains the *SMN2* gene, which is a SMN1 paralog and differs only in few nucleotides, the most crucial of which is a C to T transition in exon 7 causing the skipping of this exon in a large proportion of SMN2 transcripts. Consequently, SMN2 mainly produces a non-functional protein, which is rapidly degraded [3]. It is important to note that SMN2 expression accounts for only a small proportion of the full-length fully functional SMN protein and thus only partially compensates for the loss of SMN1. Even though the number of SMN2 copies is not essential to diagnose SMA, it is an important positive modulator of the severity of SMA phenotype: in fact, the disease severity appears to

be inversely proportional to the *SMN2* gene copy numbers and SMN protein levels despite the mechanisms of disease progression are not clear yet. SMA can be classified into five clinical types ranging from SMA 0 or 1 – the most severe and devastating types – to milder subtypes SMA 3 and SMA [4], based on age of onset and severity [4]. There is an ongoing discussion on the extent to which other tissues might be affected in patients with SMA [5,6]. Several animal models and some case reports or small case series report involvement of other organ systems, such as peripheral nerve, brain, muscle, heart, vascular system, and pancreas [7]. Recent literature reviews identified a number of cases with vascular abnormalities [8-10]. It is known that populations of neurons, astrocytes, and vascular endothelial cells constitute the so-called neurovascular unit (NVU), in which neuronal and synaptic metabolism is closely coupled to capillary blood flow by astrocyte-mediated vasodilator control. Various neurodegenerative disorders, such as Alzheimer's disease and amyotrophic lateral sclerosis, are characterized by a disruption in NVU [11]. The loss of motor neurons of anterior horn induces metabolic stress in neighboring astrocytes. These events lead to a reduction in the control of capillary blood flow [12]. *SMN1* gene provides instructions for making the SMN protein and plays a role as translational regulator [13]. Among the peripheral circulation disturbances, the Raynaud's phenomenon-like clinical pictures and more generally paroxysmal vasospasms of the extremities are relatively common, but often unrecognized clinical syndromes causing reversible color changes, from white (arterial spasm) to blue (resultant cyanosis) and red (reactive arteriolar dilation) as a result of vasospasm.

We present two consecutive cases of patients diagnosed with SMA who developed peripheral vascular abnormalities.

Patients

Patient 1

A 13-year-old girl with spinal muscular atrophy type 3 (homozygous deletion of exons 7 and 8 in the *SMN1* gene with 3 copies of *SMN2;* Revised Hammersmith Scale: 52/66; Revised Upper Limb Module scale: 34/37) treated with nusinersen with a good clinical response, presented with changed skin color on her feet. Acrocyanosis and sweating affected her feet only. No edema, arthritis, fever or other changes occurred. The patient did not complain pain or discomfort, and no apparent infection, previous traumas or cardiovascular event preceded these signs. Feet became suddenly and temporarily purple (Fig. 1A-B) for about 10 minutes, and then showed an almost spontaneous resolution (Fig. 1C), resembling a Raynaud's phenomenon-like clinical picture. The physical examination revealed trophic changes of nails indicating a probable chronic onset. This phenomenon occurred both in clinostatism, when the girl was in bed, and in orthostatism (for example, under the shower – Fig. 1D). Clinical evaluation, including venous and arterial Doppler scanning, coagulation studies, serological parameter for autoimmune diseases and echocardiography was unremarkable. The patient had no known family and personal history for vascular abnormalities. Our patient did not exhibit a certain trigger, but multiple risk factors: chronic immobility and inconsistent prolonged sitting on wheelchair, limb contractures, external compression (i.e. due to unsuitable orthoses or wheelchair cushions), neuromuscular disease itself, emotional stressdue to invasive therapies (lumbar punctures for intrathecal nusinersen administration). She is now clinically monitored for this. No symptomatic therapy was started.

Patient 2

An 8-year-old girl with spinal muscular atrophy type 2 - having a homozygous deletion of exons 7 and 8 in the SMN1 gene with 3 copies of SMN2; Revised Hammersmith Scale: 8/66; Revised Upper Limb Module scale: 24/37 – treated with nusinersen with a good clinical response, presented a first vascular episode characterized by changed skin color of her legs and feet bilaterally. Mild edema was reported before that. The patient did not report any associated pain or discomfort. Her legs and feet suddenly and temporarily turned purple but this gradually and spontaneously disappeared residing a mottled reticulated vascular pattern with a purplish lace-like discoloration of the skin (Fig. 2). This phenomenon occurred mostly in clinostatism. Clinical evaluation, including cardiological exam, coagulation studies, serological parameter for autoimmune diseases and echocardiography was unremarkable. Venous and arterial Doppler scanning showed reduced flow velocity in the arterial circulation as per peripheral vasoconstriction without acute vascular diseases. The patient had no known family and personal history for vascular abnormalities. Like patient 1, this patient neither exhibited specific triggers but multiple risk factors: chronic immobility and excessive supine position, limb contractures, external compression (i.e. due to unsuitable orthoses or wheelchair cushions), neuromuscular disease itself, emotional stress due to invasive therapies (lumbar punctures for intrathecal administration of nusinersen). We decided to closely follow-up the clinical picture without starting any therapy.

Discussion

We described two children with SMA (one case of type II and one case of type III) and peripheral vascular

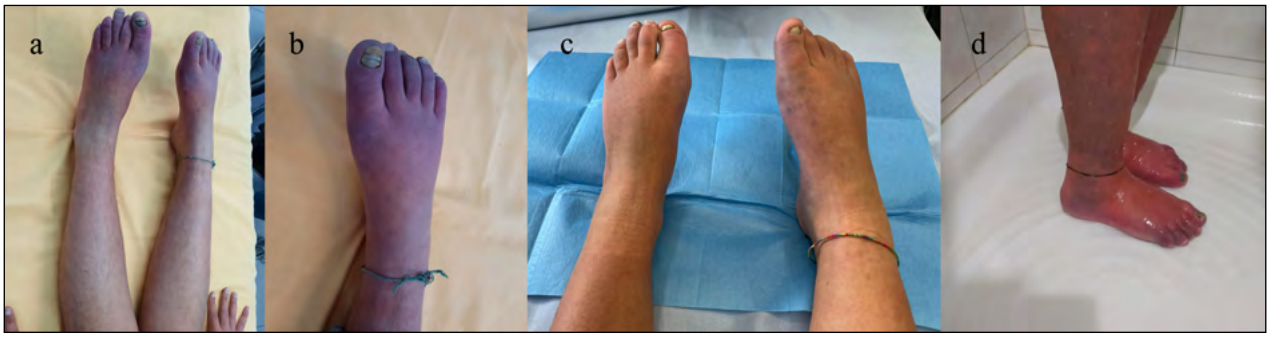

Figure 1. Feet temporarily purple (A,B). Spontaneous resolution (C). Feet under the shower (D).

abnormalities. There are very few data in the literature about this phenomenon: only four other cases of SMA associated to vascular diseases have so far been reported [9,10]. In particular, digital necrosis is reported in two patients and thrombotic occlusions of small vessels are described in other two cases [10]. Both patients (1 female, 1 male) with digital necrosis had the most severe subtype of SMA, SMA 1 with only one SMN2 copy. The male began to show progressive digit necrosis at 4 months without pain reaction; at 6 months, a skin biopsy showed necrosis of the epidermis and upper dermis and thrombotic occlusion of small vessels. Other causes for distal necrosis such as diabetes, autoimmune disorders, infections and coagulation defects were excluded. The girl developed skin necrosis on all digits and toes from the age of 3 months, which could not be accounted for by medical interventions, heart defect, or other conditions. In this case, skin biopsy revealed nonspecific vasculitis without structural defects of the dermis. With regards to two female patients with thrombotic occlusions of small vessels, one was found to have homozygous deletion of SMN and NAIP, the other one was diagnosed with SMA with 2 copies of SMN2. In the first case, at age 4 months a blue color was noted on the tip of the patient's first left foot digit which became purple and then black. In the following weeks, this spread to almost all digits in both feet and finger digits without causing pain or discomfort, and with no apparent infection. Diagnostic evaluations, including venous Doppler and coagulation studies, were all unremarkable with the exception of echocardiography which revealed atrial septal defect and asymmetric ventricular hypertrophy. Empiric treatment with aspirin, heparin, pentoxiphylline, diosmine, and local care with antiseptics was administered. Over the following weeks the lesions wax and waned and healed, and the following 10 months were event-free. In the second case, at age 5 months, the child's palms and fingers as well as nails turned bluish. In the following days, the color evolved to purple and black, then tissue necrosis started without apparent infection, medication exposure, or cardiovascular event. Again, the diagnostic evaluation was unremarkable. Treatment was started 2 weeks after the onset of symptoms including aspirin, heparin, pentoxiphylline, and diosmine, as well as local care with antiseptics. Symptoms improved over a period of 3 months, followed by normal nail growth.

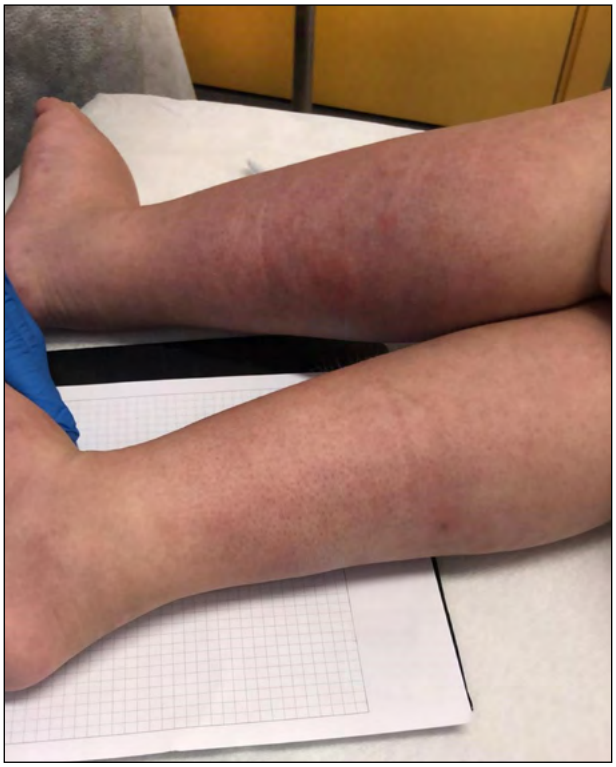

Figure 2. Mottled reticulated vascular pattern with a lace-like purplish discoloration of the skin.

These findings suggest a probable relationship between innervation and vascularization in motor neuron disease, yet there is limited evidence. One study carried in a mouse model for human SMA type I shows that in mice treated successfully with trichostatin A, long-living mice developed tissue ischemia with a black discoloration

of the tail and digits. Histological examination showed tissue necrosis and thrombosis of small vessels. The investigators thought that it could be an adverse effect of trichostatin A, however vascular dysfunction was also observed in non-treated SMA mice, suggesting that vascular alterations could be caused by SMN protein deficiency [14]. SMA type I has recently been reported to be causally related to congenital heart defects mostly in the presence of one *SMN2* gene copy, therefore it was assumed that there could be an association between heart defects and vascular alterations, but these perfusion abnormalities were also found in the subject without heart defect [15]. Araujo et al. believe that autonomic nervous system abnormalities, which are found in severely paralyzed infants surviving mechanical ventilation over a longer period of time, could influence perfusion and suggest that symptomatic treatment or passive movements or regular posture change could reduce vascular dysfunction [9]. In SMA I patients, chronic hypoperfusion associated with sympathetic hyperactivity was observed, which causes metabolic stress with accelerated loss of anterior horn motor neurons, triggering a vicious circle with further regression of capillaries and astroglial dysfunction [12,16,17]. The NVU is therefore a critical therapeutic target for treating SMA I [18].

Conclusions

Although there is limited data in the literature about the possible correlation of SMA and perfusion alterations, it can be hypothesized that several pathophysiological mechanisms are – directly and indirectly – linked to SMA. Furthermore, SMN protein would play a central role not only in the neuronal system but also in vascular and metabolic functions, while the number of *SMN2* gene copy – besides determining the clinical phenotype - could also influence the degree of involvement of other organs and systems. However, further studies are required to understand the function of SMN in the neurovascular unit and other observations will hopefully provide more significant data.

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Conflict of interest statement

The Authors declare no conflict of interest.

Authors' contributions

GF, MF and AT acquired the clinical data, reviewed the literature, and drafted the manuscript; AT designed the study, oversaw data acquisition, supervised the initial drafting, and critically revised the manuscript; MD and MCO contributed to manuscript writing analyzed the clinical data and critically revised the manuscript. All Authors contributed to the interpretation of results and reviewed the final manuscript.

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