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Vascular Perfusion Abnormalities in Infants with Spinal Muscular Atrophy

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Abstract

Spinal muscular atrophy (SMA) is an important cause of death in children and SMA type I, also known as *Werdnig-Hoffman disease*, is the most severe form of this disease. We report 2 cases of infants with SMA I in whom a distal necrosis developed, a feature not previously reported. Poor perfusion, autonomic dysfunction, and position-dependent factors may all play a role in the development of this complication.

Spinal muscular atrophy (SMA) type I is associated with profound muscular weakness and death in infancy in most cases. Currently, it is the most common inherited fatal disease in infants. Historically, the infantile form of SMA was almost uniformly fatal by 2 years of age, with a 50% mortality rate by 7 months and a 90% mortality rate by 12 months of age. However, recent studies have demonstrated that an increasing percentage of infants with type I SMA are living beyond 2 years with proactive nutritional and respiratory care.^{1,2}

As the care of infants with SMA type I improves and longevity increases, apparently sporadic observations may gain clinical and pathophysiological importance. Long-term observations on such children to date are few. In this article, we present instructive case histories of 2 infants with clinically significant and severe vascular perfusion abnormalities.

Serious digital perfusion abnormalities resulting in tissue necrosis were noted in 2 infants with confirmed SMA type I whose illustrative cases are outlined in more detail below. Parents of both children gave formal written consent for this description.

Case Summaries

Case 1, a female infant, first child of unrelated parents, was born by cesarean section after normal pregnancy with no fetal movements felt from the second trimester onward. At birth she was noted to have arthrogryposis and respiratory difficulties and was intubated immediately. By the end of the first month a tracheostomy and gastrostomy were performed. The patient had frequent episodes of hyperhidrosis. Diagnostic confirmation was initially via muscle biopsy; the patient was subsequently determined to have homozygous deletion of SMN and NAIP. At age 3 months she had generalized weakness, hypotonia, absent deep tendon reflexes, facial paresis, and tongue fasciculations. At age 4 months a blue color was

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noted on the tip of her first left foot digit. The color became purple and then black. This occurred progressively in almost all digits of both feet (Figure 1) along the following 2 weeks and by 4 weeks also involved finger digits. The patient did not appear to have pain or discomfort, and no apparent infection, exposure to medication, or cardiovascular event preceded these signs. The results of diagnostic evaluations including venous Doppler and coagulation studies were all normal. Echocardiography demonstrated an atrial septal defect and an asymmetric ventricular hypertrophy. Empiric treatment included aspirin, heparin, pentoxifylline, diosmine, and local care with antiseptics. Over the following weeks the lesions wax and waned, with the appearance of new lesions in more proximal locations (feet, knees, and arms). After an initial indolent course, slow improvement occurred over the ensuing 6 months (Figure 2). Finally all the lesions healed, without further recurrence over the subsequent 10 months.

Case 2 a female infant, first child of unrelated parents, was diagnosed with SMA with 2 copies of SMN2 and was put on ventilation at age 2 months. At age 5 months she began to manifest a bluish discoloration under the nails of her fingers, hands, and then feet. Distal phalanges turned swollen, red, and warm. After 10 days the color evolved to purple and black, then to tissue necrosis. No apparent infection, medication exposure, or cardiovascular event preceded onset of symptoms. Again, the results of diagnostic evaluation including venous Doppler scanning, coagulation studies, and echocardiography were normal. Treatment, started 2 weeks after the onset of symptoms, included aspirin, heparin (for 5 weeks), pentoxifylline, and diosmine, as well as local care with antiseptics. Symptoms improved over a period of 3 months. Normal nail growth followed, and the child has remained without recurrence of symptoms for 3 years.

Discussion

We describe a novel clinical feature, digital necrosis, in 2 children with SMA type I whose survival has been significantly extended because of invasive ventilation and supportive care. Unfortunately, we were unable to determine a clear cause for these symptoms and signs, which subsequently resolved in each case over a prolonged period of several months. However, investigators have recently described similar abnormalities in a mouse model with SMA treated with trichostatin A, resulting in significantly extended survival.³ Possible contributing factors might include autonomic dysregulation, coagulopathy, vasculitis, other primary or secondary vascular abnormality, or infection.

Whether primary autonomic nervous system dysfunction is an integral part of the phenotype in SMA remains unclear at this time. However, parents of children with SMA report a number of symptoms suggesting autonomic nervous system involvement. In addition to complaints of coolness and poor perfusion of distal extremities, parents frequently report excessive sweating of the palms, soles, and back, particularly during sleep. Resting tachycardia is virtually universal in infants with SMA type I, and SMA type I children are particularly vulnerable to episodes of symptomatic bradycardia, especially when stressed or ill.¹

There is an integral and codependent relationship between innervation and vascularization in motor neuron disease.⁴ Clinical and pathologic autonomic dysfunction has been documented in diverse motor neuron disorders, including amyotrophic lateral sclerosis, spinal muscular atrophy with respiratory distress type 1, and dominantly inherited proximal SMA associated with vesicle-associated membrane protein/synaptobrevin-associated membrane protein B mutations.^{5–10} In addition, angiogenic factors, including specific isoforms of vascular endothelial growth factor, have been demonstrated to exert clear neuroprotective effects in motor neuron disease models, including both amyotrophic lateral sclerosis and X-linked

spinobulbar muscular atrophy animal models.⁴ Because vascular patterning closely follows that of innervation, it seems intuitively evident that these systems would be integrally connected and codependent and that vessel caliber and quantity in disorders with neurogenic atrophy would be diminished. This would seem to be especially true in disorders with congenital or early infantile onset of symptoms occurring during critical periods for growth and development of vascular networks.

Autonomic dysfunction in infants with SMA, particularly sympathetic dysfunction, has been hypothesized to be a primary source of the vascular perfusion abnormalities in infants with SMA.¹¹ Arai et al¹¹ performed autonomic investigations in a small cohort of children with SMA, including 7 infants with type I, 2 infants with type II, and 1 child with type III, and compared them with results obtained in healthy children. Investigations included finger cold–induced vasodilation, sympathetic skin response, and R-R interval variation. They noted that the amplitudes of sympathetic skin response to sound stimulation were absent or low in 6/6 subjects with SMA studied, although possible technical artifact from excessive sweating was not specifically discounted. The mean sympathetic response latency and amplitude did not differ significantly from healthy children. Finger cold–induced vasodilation was abnormal in 6 of 10 patients, with findings supporting sympathetic hyperactivity in some cases and hypoactivity in others. No significant difference was found in the mean R-R interval variation. Arai et al¹¹ documented autonomic dysfunction in 3 cases of SMA type I on long-term mechanical ventilation, and demonstrated sympathetic-vagal imbalance on R-R interval analysis, as well as abnormalities in finger cold–induced vasodilation. One case showed significant blood pressure and heart rate fluctuation, as well as a high plasma concentration of norepinephrine during tachycardia.

Parents of infants and children with SMA type I frequently report that their child's hands and feet are "cold and clammy," that the tips of fingers and toes are intermittently blue or pale, that their skin is "blotchy," or that they become "pale and sweaty," particularly when stressed or ill. It is a feature of children with SMA type I that they never attain the ability to sit independently, remaining confined to bed rest. It is well known that baroreflex control of sympathetic nerve activity responds to gravity and that prolonged bed rest results in decreased tolerance for maintaining cardiovascular stability in an upright posture.¹² Prolonged bed rest triggers cardiovascular and neurohumeral changes resulting in natriuresis and diuresis, leading to a persistent decrease in circulatory blood volume and orthostatic intolerance, which cannot be restored by replacement of plasma volume alone. The resulting chronic contraction of plasma volume undoubtedly places them at some increased risk for dehydration and distal vascular thrombosis. Immobility of limbs either to lack of normal muscular contraction or to absence of passive limb movement also promotes venous stasis and lymphedema, additional risk factors for thrombosis.

We were unable to identify any studies of patients with SMA with pathologic findings clearly documenting autonomic nervous system abnormalities. Thus whether sympathetic innervation is primarily impaired remains unclear, but it seems likely given the significant proportion of children with suggestive clinical symptoms and signs. With regard to documented small-vessel abnormalities, data are also scarce. We were able to find only a single report documented abnormalities, characterized only as "thinning of the basement membrane" of small arterial vessels in muscle in specimens from a single subject with SMA.¹³ Further studies, particularly skin biopsy, looking for small fiber density and autopsy are clearly needed with regard to these issues.

Other causes for distal necrosis such as diabetes, sickle cell disease, infection, inflammatory conditions such as in autoimmune disorders and intravascular coagulation, have all been excluded in those 2 children. Given that necrosis is quite an uncommon finding in infants

and young children and has not been reported to date in other infants with SMA, it seems likely that the cause of the observed vascular perfusion abnormalities in the described patients is multifactorial. Parallel observations and additional studies of such phenomenon in SMA mouse models may help to clarify pathogenesis of these symptoms and determine possible relevance to treatment interventions in SMA.

The complete inability to move their limbs against gravity or voluntarily to change their position puts these children at significant risk for postural-dependent factors. We would therefore recommend special attention to passive movement and regular posture change, as well as careful assessment of hydration status, to help diminish the likelihood for the development of significant vascular perfusion abnormalities reported here.

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Figure 1.
Digital necrosis.

Figure 2.
The same patient after follow-up.