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Lumbosacral ventral spinal nerve root atrophy identified on MRI in a case of spinal muscular atrophy type II

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ABSTRACT

Spinal muscular atrophies are rare genetic disorders most often caused by homozygous deletion mutations in *SMN1* that lead to progressive neurodegeneration of anterior horn cells. Ventral spinal root atrophy is a consistent pathological finding in post-mortem examinations of patients who suffered from various subtypes of spinal muscular atrophy; however, corresponding radiographic findings have not been previously reported. We present a patient with hypotonia and weakness who was found to have ventral spinal root atrophy in the lumbosacral region on MRI and was subsequently diagnosed with spinal muscular atrophy. More systematic analyses of imaging studies in spinal muscular atrophy will help determine whether such findings have the potential to serve as reliable diagnostic markers for clinical evaluations or as outcome measure for clinical trials.

1. Introduction

Spinal muscular atrophies (SMAs) are a category of inherited motor neuron diseases characterized by degeneration of anterior horn cells, and varying degrees of muscle atrophy and weakness, which leads to numerous multi-organ system complications [1]. Most cases are caused by homozygous deletions of *SMN1* on chromosome 5q13.2 [2]; a number of rare subtypes have been linked to other loci and genes [1]. Four clinical subtypes of SMA are generally recognized, with the first three accounting for the vast majority of cases. SMA type I is the most severe and common form and is distinguished from the others by the inability of affected children to gain the capacity to sit; it typically presents before 6 months of age. Children with SMA type II are able to sit during some portion of the clinical course, but never walk; they usually present between 6 and 18 months. SMA type III is a milder form of the disease in which affected children are able to walk; onset of symptoms is usually after 18 months. Novel treatments recently approved or under development are dramatically altering the therapeutic options and prognoses for affected individuals [3–5].

Degeneration of anterior horn cells is the pathological hallmark of SMA, and ventral nerve root atrophy is found in gross pathological studies of post-mortem spinal cord tissue from patients affected by 5q SMA as well as other subtypes [6–10]. Despite the prominence of these pathological features, previous studies of spinal imaging in SMA have reported normal findings in the lumbosacral spine or did not inspect the lumbosacral spine [11–14]. We present a patient with SMA whose diagnosis was prompted by the identification of atrophic ventral nerve roots on lumbosacral spine MRI.

2. Case report

A male infant was born via Caesarian section with no complications, a diagnosis of ankyloglossia and an unremarkable family history. At two months of age, he was evaluated by an otolaryngologist for difficulties with latching for both breastfeeding and bottle feeding, and a frenotomy was performed. He sat independently at 6 months, crawled at 7 months and stood and cruised at 12 months. Other developmental domains were intact and family history was non-contributory. At 19 months of age, he was evaluated in pediatric neurology clinic for hypotonia and motor delays. He had not walked consistently and tended to sway his hips when crawling. On physical examination at that time, weight was 8.01 kg (< 1st percentile), height 76 cm (< 1st percentile), and head circumference 47.4 cm (31.99 percentile). Pupillary responses and extraocular movements were normal, with no tongue fasciculations noted. Reflexes were essentially absent, muscle tone was diffusely reduced, and he had generalized weakness, more pronounced in the lower extremities. He was able to rise from a prone position to a sitting position. The reported swaying of the hips while crawling was

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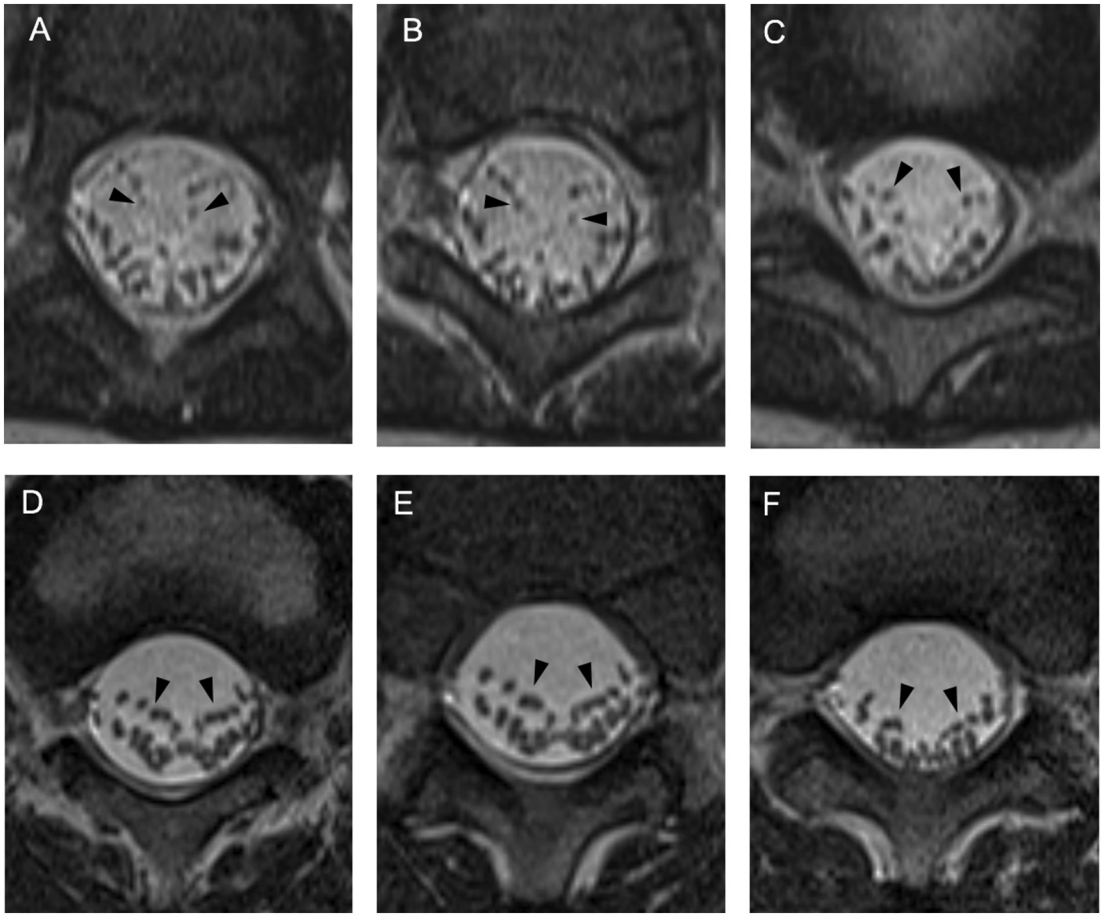

Fig. 1. Representative axial lumbar spine MR T2 weighted images of patient with SMA type 2 and unaffected age-matched control. Significant bilateral atrophy of the ventral roots (arrowheads) can be seen at the level of L2 (A), L3 (B) and L3–L4 (C) in the patient with SMA type 2. Significant size asymmetry is also present between of dorsal and ventral roots in the SMA case. A healthy age-matched control demonstrates normal diameter and distribution of ventral roots (arrowheads) at the levels of L2 (D), L3 (E), and L3–L4 (F). There is no significant asymmetry between size of dorsal and ventral roots in the normal patient.

confirmed on examination. He was able to walk only with assistance and locked his knees when he did so.

CK levels were measured to be 131, 171, and 126 U/L [reference range < 160]. Brain MRI performed at 19 months showed no intracranial abnormalities, but the lumbar spine MRI revealed significant symmetric atrophy of lumbosacral ventral roots in the dural sac when compared to a normal age matched control case. Significant size differences were also noted between ventral and dorsal roots in the SMA case but not the healthy control case (Fig. 1, 2). All MR imaging was T2 weighted and performed using a 1.5 Tesla Magnetom Avanto (Siemens Healthcare Sector, Erlangen, Germany) with dedicated high resolution multichannel spine matrix coils and parallel imaging techniques. Nerve conduction studies and electromyography showed normal left median and sural sensory responses, normal left median motor study, low-amplitude left peroneal compound motor action potential with a normal conduction velocity, and evidence for chronic reinnervation on needle examination of the left deltoid and tibialis anterior. The diagnosis of SMA was suspected in light of these findings. CK levels were measured to be 131, 171, and 126 U/L [reference range < 160]. Multiplex ligation-dependent probe amplification performed at a clinical genetics laboratory showed 0 copies of *SMN1* and three copies of *SMN2*, confirming the diagnosis of SMA. Based on the clinical course, the most appropriate subtype designation was determined to be SMA type II.

Since diagnosis, the patient received 4 loading doses of nusinersen at the standard dose administered intrathecally according to the standard protocol. At 29 months, he was pulling to stand and cruising, and was able to walk with the assistance of a walker. His parents reported significantly increased strength and motor activity since starting the treatment.

3. Discussion

On a microscopic level, SMA is associated with motor neuron apoptosis, empty cell beds, glial cell bundles, and aberrant migration of motor neurons to the spinal roots [15]. Surviving motor neurons in the anterior horn often appear swollen and chromatolytic and express accumulations of vesicles, mitochondria, phosphorylated neurofilaments, and ribosomes. Atrophy of the ventral nerve roots has been documented in gross pathology of SMA types I [8], II [6], and III [9] with corresponding evidence of anterior horn cell loss and relative sparing of the dorsal roots [6,8,9]. Similar findings of atrophic ventral roots with unaffected posterior roots have been noted in autopsies of those with X-linked SMA [7] and autosomal dominant congenital SMA as well [10]. These studies do not, however, consistently address whether these findings are present throughout the rostro-caudal extent of the spinal cord. Of note, gross pathological examination in autosomal dominant congenital SMA has shown atrophic lumbosacral ventral roots appearing < 0.5 mm in diameter, significantly smaller than dorsal roots from the same specimens [10]. Mean ventral nerve root cross-sectional area has previously been found to be approximately 0.61 mm^2 (approximately 0.9 mm in diameter) in a healthy 3–53 month age cohort [16]. In our SMA case, we also observed ventral roots that were significantly smaller than dorsal roots at the same spinal level. Precise

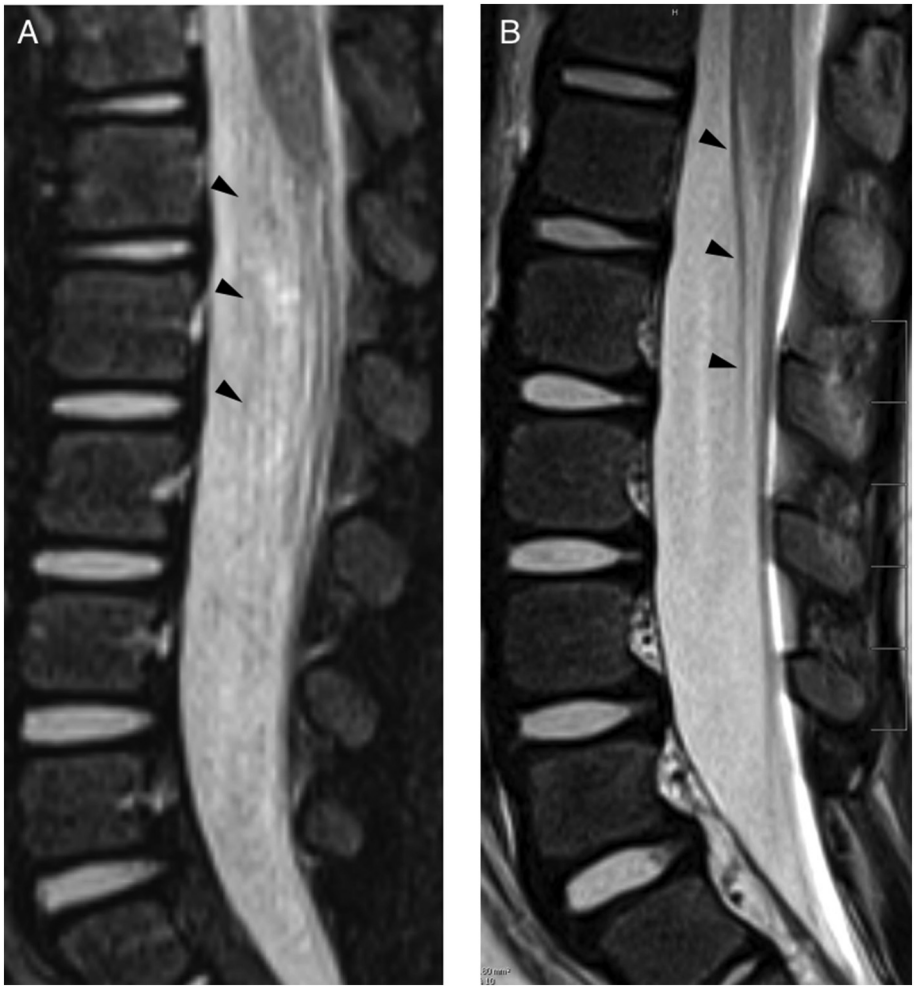

Fig. 2. Representative sagittal lumbosacral spine MR T2 weighted images of patient with SMA type 2 and unaffected age-matched control at the midline. Ventral spinal roots of the patient with SMA type 2 are barely appreciable in the midsagittal view (A; arrowheads). In a healthy age-matched control, ventral roots are clearly visible (B; arrowheads).

measurement of root diameter in this case, however, is difficult due to resolution of MR imaging used. Discrepancy in dorsal and ventral root size may provide the clearest indicator of root atrophy in SMA across patients and imaging modalities.

In contrast to the well-documented pathological abnormalities, to our knowledge radiographic studies have not previously shown corresponding findings at the ventral nerve roots. One prior study focusing on the cervical cord reported unremarkable MRI findings in multiple SMA subtypes [12]. Another study reported broadly unremarkable findings in the spines of individuals with SMA who had onset of symptoms at birth [13]. We have found only one published report of spinal cord anatomical changes in SMA, and that study focused on intramedullary findings rather than changes at the nerve roots. This study described a means of morphometrically indexing neurodegeneration of motor neurons in the cervical spinal cord of patients with SMA types III or IV using 3 T MRI [11].

In our patient, the atrophy of lumbosacral ventral roots correlated with the clinical features and the genetic diagnosis of SMA. Previous studies may have been insensitive to such spinal nerve root anatomical changes because they did not have access to newer MRI technologies with higher magnetic field strengths, multi-channel coils or parallel imaging hardware. Newer MRI technology may have contributed to the detection of intramedullary abnormalities in a recent study [11]. An additional factor may have been the inherent challenges in detecting spinal cord and nerve lesions on MRI, due to the small diameters of the spinal cord and nerves, hyper dynamic CSF motions in the dural sac reducing the spatial resolution of MRI at the lumbar spine, and the overall tendency for lesions in this region to be small. These issues are exacerbated in young children, not only due to small body sizes, but also the higher incidence of excessive motion artifact in the absence of sedation. One factor facilitating visualization of the spinal roots at the level of the dural sac is the grouping and isolation of the nerve roots in this compartment.

The need to diagnose SMA promptly and track clinical progression has been heightened in the wake of the recently approved therapy and ongoing clinical trials of other novel therapies. The diagnosis of SMA was traditionally made via electromyography studies, which still have utility in urgent situations or cases of unusual presentations. Genetic testing is now the standard diagnostic test modality. In cases where children with motor delays and hypotonia undergo spine MRI, special attention should be paid to the ventral nerve roots to detect signs of atrophy. Routine newborn screening for SMA is not currently recommended by the United States Health Services and Advisory Administration [17]. However, in light of recent therapeutic developments, efforts to initiate newborn screening for SMA are underway in several states, thus diagnostic needs for this disease may be largely met in the coming years. Our observations do, however, have potential implications for outcome measures in both clinical trials and routine clinical practice. MRI is non-invasive and yields consistent, reproducible results. Longitudinal data regarding progression of ventral nerve root atrophy could provide a baseline against which to measure experimental therapies. The main barriers to the use of spine MRI for

the SMA population include cost, sedation requirements for younger children, and movement artifact that may occur more often in unsedated children compared to adults. Outcome measures in recent trials for SMA treatments have relied mainly on survival and functional motor assessments, supplemented by electrophysiologic measures and sometimes post-mortem pathological studies [3–5,18,19]. Other biomarkers have been proposed, such as leg muscle MRI, serum SMN protein levels, and serum leptin [18,20–23]. Ventral nerve root diameter may merit further investigation as a potential biomarker.

Evaluation of lumbosacral nerves in the dural sac with 2D routine spine imaging can be problematic due to CSF artifacts and slice thickness. We saw CSF artifact around the conus medullaris which slightly obscured evaluation of the ventral roots, but in the inferior portion of the lumbar region differentiation of ventral roots was clearer due to absence of CSF artifacts (Fig. 1A, B, C). We believe that more advanced techniques in 3D high resolution T2 weighted imaging, such as CISS and T2-SPACE imaging, will be more efficient for evaluation of these structures for this indication in future studies. These advanced imaging techniques were used not during the course of routine imaging of our patient.

This case illustrates that spine MRI may be helpful for evaluation of ventral nerve root atrophy in SMA. The next step would be to analyze additional spine MRI data, both retrospectively and prospectively, to determine how consistently these findings are present in SMA, and to explore the potential use of advanced high-resolution spine MRI as a non-invasive biomarker for monitoring disease progression and responses to novel therapies.

Disclosures

PBK serves as a consultant for AveXis, co-edited a textbook on pediatric electromyography for Springer, and is an associate editor for Muscle & Nerve.

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