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Low bone mineral density and fractures are highly prevalent in pediatric patients with spinal muscular atrophy regardless of disease severity

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Abstract

Patients with Spinal Muscular Atrophy (SMA) are at risk for poor bone health. The prevalence of fractures, low areal bone mineral density (aBMD; Z-score ≤−2.0) of the lateral distal femur and of osteoporosis by SMA subtype is not known. We aimed to describe the natural history of bone health in patients with SMA prior to bisphosphonate treatment. We reviewed data from 85 eligible patients with SMA ages 12 months to 18 years, seen at a single institution between January 2005 and July 2016. Fracture history was reported at annual clinic visits. aBMD was obtained from dual energy x-ray absorptiometry scans of the lumbar spine, total body, and lateral distal femur. 85% of patients had aBMD Z-scores ≤−2.0 SD and were progressively lower with worsening SMA severity. Longitudinal aBMD Z-scores of the lateral distal femur decreased with age. Fractures occurred in 38% (32/85) of patients with the femur being the most common location (25 of 57 fractures). Thirteen percent of patients fulfilled criteria for osteoporosis. Low aBMD and femur fractures are highly prevalent in all SMA subtypes from a young age; however, few patients met the criteria for osteoporosis. Poor bone health may be an under-recognized comorbidity of SMA.

Keywords: Osteoporosis; Children; Dual energy x-ray absorptiometry

1. Introduction

Spinal Muscular Atrophy (SMA), an autosomal recessive neuromuscular disease due to mutations in the survival motor neuron gene 1 (*SMN1*), affects 1 in 6000–10,000 live births and is the leading cause of death due to a genetic mutation in infants [1,2]. This degenerative disease of the spinal cord and lower brainstem motor neurons causes progressive proximal muscle weakness, resulting in varying degrees of hypotonic immobility and respiratory compromise. While there are no genotype–phenotype correlations, clinical severity is associated with the number of copies of a rescue gene, *SMN2* [3]. Patients are typically characterized by their clinical phenotype: patients with SMA Type 1 (SMA1) never sit independently; those with SMA Type 2 (SMA2) can sit but never stand or walk independently; and those with SMA Type 3 (SMA3) walk independently with a later loss of mobility [3,4]. SMA Type 4 is an adult-onset disease with mild muscle weakness [4].

Without intervention, survival of the most severely affected children is poor, with most patients dying before 24 months of life [5]. Advances in medical care have led to improved survival and quality of life [6]. However, these children now face complications due to chronic immobility that also impact those with milder SMA phenotypes.

A major complication of chronic immobility is poor bone health. Weight-bearing activity during growth is an important stimulus for bone mass accrual [7–9]. Children who have limited weight-bearing activity are at risk for poor bone accrual and a marked decrease in peak bone mineral density (BMD) [10–13]. Children with SMA also have low muscle mass, which may lead to lower mechanical loading forces on the osteocyte. Additionally, data from mouse models suggest a direct interaction of *SMN* with modulators of osteoclast activity,

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leading to altered bone remodeling and impaired bone mineralization [14,15]. Low BMD increases risk for all types of fractures and development of osteoporosis [16,17].

Despite these known risk factors, there is limited published literature on bone health in patients with SMA. Retrospective studies report a widely variable (9.3%–46%) fracture prevalence in pediatric patients with SMA, with the distal femur being the most common fracture location [18–21]. Analyses of BMD in these children have been inconclusive. Some studies report normal bone mineral parameters [22,23], whereas others found bone density in pediatric patients with SMA was lower than expected for age [24,25] and lower than in patients with other neuromuscular conditions [25]. No study has reported the prevalence of fractures or low BMD (Z-score ≤−2.0) by SMA subtype, prevalence of low BMD of the lateral distal femur (an important fracture location in non-ambulatory children), nor prevalence of osteoporosis in this population. Thus, the degree and extent of poor bone health among children and adolescents with SMA is not known.

In this study, we aimed to describe, by SMA subtype, the natural pattern of bone mineralization at multiple skeletal sites, and determine the prevalence of low BMD and fractures in pediatric patients with SMA. We also aimed to determine the prevalence of osteoporosis using the diagnostic criteria established in the 2013 International Society for Clinical Densitometry (ISCD) pediatric position statement.

2. Patients and methods

We conducted a retrospective chart review of patients with a confirmed diagnosis of SMA seen at the Neuromuscular Comprehensive Care Center at Cincinnati Children's Hospital Medical Center between January 2005 and July 2016. The clinical protocol for medical care in this center includes anthropometric measurements at each visit with a segmental height used as a surrogate for standing height in non-ambulatory patients, nutritional counseling by a registered dietitian regarding appropriate dietary calcium intake and periodic monitoring of 25-hydroxyl vitamin D levels. DXA scans are ordered annually at age 3 and thereafter, whereas x-rays are ordered as needed if history or physical exam raises suspicion for fracture.

SMA subtypes were defined by classic criteria [3,4]. Patients were included in analyses if they had a clinic visit between ages 12 months and 18 years. We selected this age range to exclude congenital fractures and fractures secondary to delivery in order to refine fracture analyses while capturing the timeframe of bone accrual through childhood and adolescence. This also excluded the most severely affected children who did not survive to one year of age. Additional exclusion criteria included use of systemic glucocorticoids or valproic acid, or diagnosis of another chronic illness known to affect bone metabolism (e.g., malabsorption syndromes, inflammatory bowel disease, hypopituitarism). In order to study the natural history of bone health in this population, we excluded any data on bone health obtained 6 months or more after a bisphosphonate medication was prescribed as a change in BMD or fracture frequency would not be expected in this immediate time interval.

Data extracted from the medical records included sex, race, SMA subtype, age at SMA diagnosis, age at dual energy x-ray absorptiometry (DXA) scans, fracture history, bisphosphonate use, and age at clinical encounter. This study was approved by the Institutional Review Board at Cincinnati Children's Hospital Medical Center.

2.1. Bone mineral density

Areal bone mineral density (aBMD) was measured by DXA. All DXA scans were obtained as part of routine clinical care where the standard protocol was to obtain annual DXA scans of the lumbar spine (LS), whole body (WB), and lateral distal femur (LDF), starting at three years of age. These sites were measured in accordance with ISCD recommendations [26,27]. DXA scans were obtained prior to age 3 years in specific clinical scenarios, such as a fragility fracture. Limitations in positioning and/or spinal rod instrumentation prevented DXA scans at all sites from being obtained on each patient. Scans were acquired on a Hologic densitometer (Delphi/Discovery/Horizon) calibrated to a common manufacturer standard, and scans were analyzed using software with the same bone detection algorithms (version 12.3). LS and WB scans were acquired using standard positioning and analysis procedures. The coefficient of variation (CV) at our center is ≤1% for WB and LS BMD. LDF scans were obtained and three regions of interest (R1, R2 and R3) were identified as described by Henderson et al. [28] and Zemel et al. [29]. We included R1, composed of primarily trabecular bone, and R3, composed of primarily cortical bone, in our analyses. R2 is difficult to interpret given it is an admixture of both bony tissue types. The CV for the LDF BMD has not been reported. All scans were reviewed (by H.W.) for image quality, positioning and artifact (spinal instrumentation, ports and movement). LS aBMD Z-scores were calculated using reference data from Kalkwarf et al. [30] for ages 1–36 months, Kelly et al. [31] for ages 37–60 months, and Zemel et al. [32] for ages 5–20 years. WB BMC and aBMD Z-scores were calculated using reference data from Kelly et al. [31] for ages 37–60 months, and from Zemel et al. [32] for ages 5–20 years. LDF aBMD Z-scores were calculated for children ages ≥3 years using reference data from Henderson et al. [28]. We studied the outcomes of age-, sex-, and race-specific aBMD Z-scores for each skeletal region of interest.

2.2. Fracture history

Patients were asked about fracture history at each clinic visit and responses were recorded in the medical record. Data collected included age at fracture, number of fractures, and location of fractures. Reported fractures were confirmed when possible by review of radiographic images (by H.W.), with documentation of fracture by a radiologist or evidence of healing fracture on subsequent radiographic imaging. Fractures of the skull or of the digits were excluded as these do not usually constitute osteoporotic fractures.