100 adults with spinal muscular atrophy at the dawn of treatment: A bone health focus

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ABSTRACT

INTRODUCTION: As disease-modifying treatments for spinal muscular atrophy (SMA) are implemented, comorbidities in adults including osteo-pathologies are increasingly recognised. Guidance for managing such issues is incomplete.
We present data on bone health from, to our knowledge, the UK's largest single-centre adult SMA cohort.

OBJECTIVES: We aimed to quantify the following in our cohort:
1. Fracture incidence and location
2. Implementation of bone density scanning
3. Vitamin D status and supplementation

METHODS: Retrospective case note review was performed for 100 adult patients (51% male; 49% female, average age 32), at the National Hospital for Neurology and Neurosurgery from 2022-2025. SMA subtypes were SMA3 (N=55), SMA2 (N=44) and SMA1 (N=1). Where available ethnicities were: White (N=57), Asian (N=13), Black (N=4), Mixed (N=2) and Other (N=4).

RESULTS: Fracture incidence was 25% (N=25), of which 85% (N=29) affected the lower limb(s). Most fractures (80%) (N=20) occurred in SMA3 patients. 50% (N=10) of SMA3 patients with a history of fractures, subsequently lost the ability to walk.
Bone density scans were recorded in 40% (N=10) of patients who had fractures (90% of scans occurred post fracture), and in 17% (N=13) of non-fracture patients.
Of the overall cohort, 39% (N=39) were vitamin D deficient or insufficient, and 60% (N=60) were prescribed cholecalciferol.

CONCLUSIONS: The high fracture rate is particularly pertinent, given that lower limb fractures can accelerate ambulation loss in SMA3 patients. Consistency in bone-density scanning is lacking and generally reactive to fracture occurrence. This highlights the importance of bone health considerations in adult SMA patients.

Keywords: Spinal muscular atrophy, Fractures, Bone, Neuromuscular disease

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive inherited neuromuscular disease characterized by degeneration of alpha motor neurons in the spinal cord. SMA is caused by loss-of-function mutations of the survival of motor neuron 1 (*SMN1*) gene, typically (>95% of cases) a deletion of exons 7 and 8.[1,2] SMA incidence is around 1 in 10,000 live births and the average carrier frequency of *SMN1* pathogenic mutations varies from 1:40 to 1:60 worldwide.[2]

SMN1 encodes the SMN protein, which is ubiquitously expressed in all cells.[1] The *SMN2* gene is highly homologous to *SMN1*. The only functional difference between *SMN1* and *SMN2* is a synonymous transition leading to alternative splicing of *SMN2* exon 7 encoding an SMN protein from *SMN2* of limited function instead of the full-length protein. Previous clinical studies have shown that the *SMN2* copy number is negatively correlated with disease severity and a higher level of functional SMN protein is associated with milder phenotypes.[3]

Consequently, the clinical features of SMA are heterogeneous, with all patients experiencing varying degrees of severity of progressive muscle weakness, hypotonia and mobility impairment with respiratory and bulbar muscle weakness in more severe cases.[4] SMA patients have, therefore, historically been characterized by their clinical phenotype, and age of disease onset into subtypes.[1-5]

Until recently, SMA was symptomatically managed with musculoskeletal, nutritional and respiratory support. However, the advent of several disease modifying therapies has changed the landscape of treatment in SMA. This includes Zolgensma (gene therapy for infants under 2 years with SMA1, 2 and 3) and Nusinersen and Risdiplam (for children and adults with SMA 1, 2 and 3) both of which act to increase SMN protein expression via the modulation of SMN2 pre-mRNA splicing.[6,7] Nusinersen and Risdiplam were recently licenced in the UK, and a health service treatment programme makes both available for all those with SMA types 1-3 who are not in the final stages of disease

(i.e. when daily ventilation use exceeds 16 hours). The initial data is promising, demonstrating not only reduced disease progression but also improved motor function scores.[8] Along with this demonstratable reduction of disability, it may be anticipated that these treatments could increase life-expectancy in the more severe forms of SMA. As these therapies are being increasingly implemented worldwide, this has led to an increasing awareness of the extent of comorbidities in SMA patients, both in paediatric and adult populations.[9]

One of these comorbidities is poor bone health. In SMA lower limb muscle weakness results in reduced loading leading to osteoporosis and gait difficulties increasing risk of falls and fractures.[10] Fractures result in loss of function and deformity which negatively impact on quality of life. Additionally, there is evidence that the SMN protein has a role in bone re-modelling. In *SMN1* gene mouse knock-out models, both an osteoporotic phenotype and increased osteoclast activity (on histochemical staining), have been demonstrated, thus further increasing the potential for osteoporosis and fracture.[11]

Despite these risk factors, there is as yet no consensus on guidelines regarding managing and maximising bone health in adults with SMA.[10]

We aimed to quantify bone health specific parameters in, to our knowledge, the largest single centre adult SMA patient cohort in the UK. We aimed to quantify:

1. Fracture incidence, location and incidence categorised by SMA subtype
2. Implementation of bone density scanning and bisphosphonate prescription
3. Vitamin D status and supplementation.

Table 1: Classification of spinal muscular atrophy subtypes.

Type	Onset	Motor Function
1	0-6 months	Never sit
2	<18months	Sit never stand
3	>18 months	Exceed the ability to sit
4	>18 years	Walk unaided

Methods

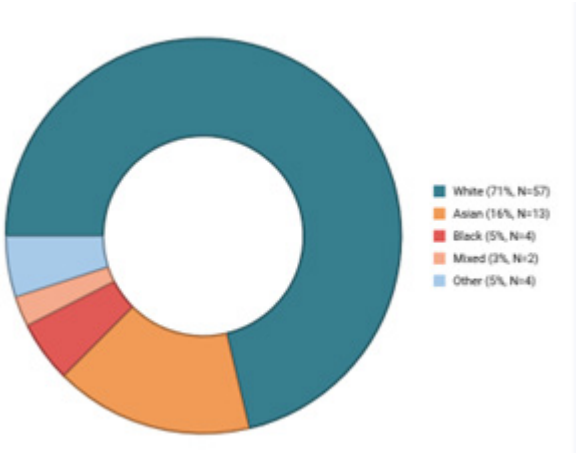
Retrospective case note review of 100 adult patients at the National Hospital for Neurology and Neurosurgery with genetically confirmed SMA was performed. When data was missing GP records were reviewed. This project is registered with the Queen Square Clinical Audit & Quality Improvement Subcommittee.

The average age of the cohort was 32 years old (range 17-67 years old), and 87% (N=87) of patients were on disease modifying treatment. Of the patients on disease modifying treatment, 77% (N=67) were on Risdiplam and 23% (N=20) on Nusinersen. The remainder of the cohort demographics are shown in table 2 and figure 1. Ethnicity data were available for (N=80) patients.

Table 2: Cohort demographics for 100 adult spinal muscular atrophy patients

Characteristics	Male (N = 51)	Female (N= 49)	Totals (N= 100)
SMA subtypes			
SMA1	0	1	1
SMA2	20	24	44
SMA3	31	24	55

Figure 1: Ethnicities (where available, N=80) of cohort of 100 adult spinal muscular atrophy patients



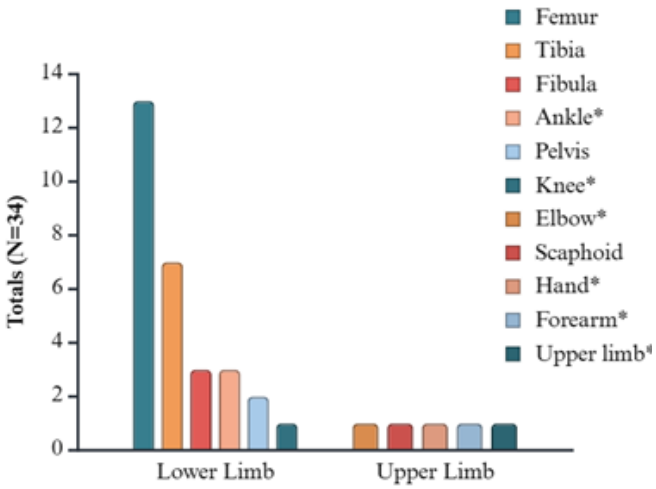
Results

Fracture incidence, location and incidence categorised by SMA subtype

Across the whole cohort 25% (N=25) had at least one fracture reported. Eight patients had a history of fracture in more than one bone, in two of these cases the fractures occurred on separates episodes, in the remaining six cases, multiple bones were fractured in one episode. 85% (N=29) of the overall fractures occurred in lower limbs. A more detailed breakdown of fracture location is shown in figure 2.

The average age in patients with a history of fracture was 35.44 years (18-65 years). 92% (N=23) of patients with a history of fracture were on disease modifying treatment, 76% (N=19) of these patients were on Risdiplam, and 16% (N=4) on Nusinersen. The majority of fractures occurred in SMA3 patients (N=20) (80% of all fractures). Of note, eleven patients reported a decline in motor function post fracture, of whom 50% (N=9) lost the ability to walk, one ambulant patient lost the ability to both ambulate and sit and one SMA2 patient lost the ability to sit.

Figure 2: Fracture location of (N=34) cases in a cohort of 100 adult spinal muscular atrophy patients

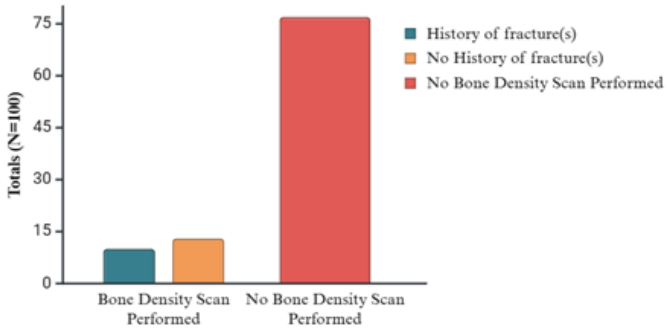


*Location of fracture not specified further. Fractures occurring in femur (N=13), tibia (N=7), fibula (N=3), ankle (N=3), pelvis (N=2), knee (N=1), elbow (N=1), scaphoid (N=1), hand (N=1), forearm (N=1) and upper limb (N=1).

Bone Density Scanning implementation and bisphosphonate prescription

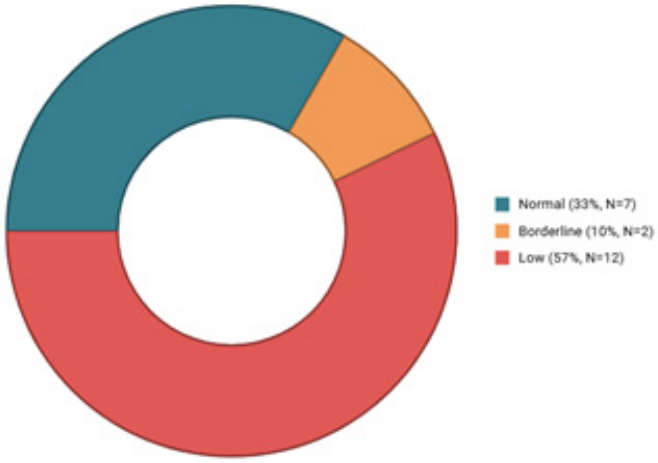
Bone density scans were performed in 23% (N=23) of the overall cohort, one further patient has also been referred but is awaiting the scan. See figure 3 for a more detailed breakdown of bone density scanning implementation. The interpretations from bone density scans (available in 21 of the 23 cases) are shown in figure 4. 4% (N=4) of the cohort were prescribed a bisphosphonate (Zoledronic acid (N=3) and Alendronic acid (N=1)).

Figure 3: Bone density scanning implementation in cohort of 100 adult spinal muscular atrophy patients.



Bone density scanning was performed in 23 patients, 10 of whom had a history of fracture, 77 patients had not had a bone density scan.

Figure 4: Interpretation of 21 bone density scans in a cohort of 100 adult spinal muscular atrophy patients.

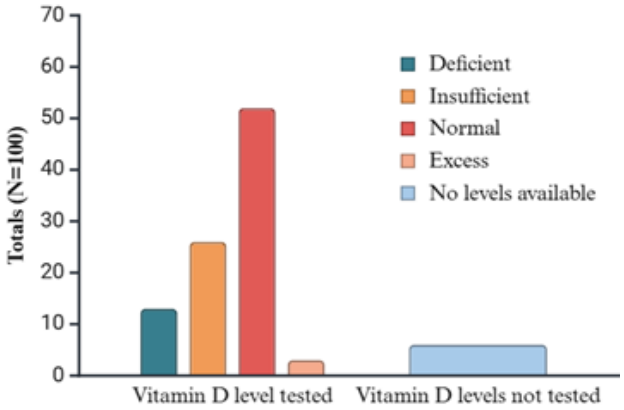


The interpretation of the bone density scans into normal, borderline and low was based on z-scores.

Vitamin D levels and supplementation

Vitamin D status was available for 94% (N=94) of the cohort. The levels are shown in figure 5. Notably, 60% (N=60) of the cohort were prescribed vitamin D replacement therapy.

Figure 5: Vitamin D level status in cohort of 100 adult spinal muscular atrophy patients



Deficient (N=13), insufficient levels (N=26), normal levels (N=52), excess (N=3), Status not available (N=6). Ranges are as follows, deficient:< 25 nmol/L, insufficient: 25-50 nmol/L and normal >50nmol/L.

Discussion

A pertinent finding from our results is the high fracture rate in this adult SMA population. One of the widely understood risks of hereditary neuromuscular disorders is the increased risk of fractures - noted especially in Duchenne muscular dystrophy (DMD), which is "less rare" than SMA (1 in 3500 to 1 in 5000 live male births) and where the recommended use of corticosteroids for disease modification has further prompted specific bone health guidance.[13,14] In their retrospective study reviewing bone health across various hereditary neuromuscular disorders, Opsomer et al. found the highest prevalence of fractures in DMD, myotonic dystrophy and SMA patients, with results comparable to our own demonstrating most fractures affecting the lower limb.[15] They also noted that the aetiology of fractures in their cohorts was a mix of low-energy traumatic and osteoporotic fractures, with nearly 30% of their SMA cohort losing ambulation due to the fracture, thus raising the possibility of a potential complex aetiological overlap and highlighting the functional impact that fractures can have in this patient population.

We found that consistency in bone density scanning is lacking in this cohort, and generally reactive to a fracture occurring. Furthermore, where bone density scans were performed, the majority were found to have borderline or low bone density. This is particularly significant, as it was noted that most fractures in our cohort affected the lower limb - with the most commonly fractured bone being the femur - and occurred in SMA3 patients, of whom a significant proportion lost the ability to ambulate post-fracture. In all populations, low bone density increases the risk of fractures. However, in vitro, preclinical and clinical studies support the notion that there is dysregulated bone metabolism in SMA from intrinsic and extrinsic mechanisms.[10,11,16] From here, a vicious cycle can ensue- intrinsically impaired bone growth and remodelling in SMA results in a fracture, which then affects mobility and weight-bearing abilities, thus further impairing bone density and increasing risk of recurrent fractures.[16]

There is scope to optimise the management of low bone density in SMA. Current guidelines (from the pre-treatment era and focussed on children and younger people) encourage supplementation with vitamin D and/or bisphosphonates in any evidence of osteopenia or frequent fractures.[17] In our cohort, testing of vitamin D levels and supplementation with cholecalciferol were the most consistently applied actions to improve bone health. Despite this and our cohort's substantial fracture rate, only 4% were prescribed bisphosphonates. Actions to improve bone health. Despite this and our cohort's substantial fracture rate, only 4% were prescribed bisphosphonates.

This implies that treating bone health in the aftermath of fractures may not be enough alone to improve bone density and reduce future fracture risk. We advocate for a proactive and prophylactic approach to be implemented in bone health management of SMA patients. Early bone health screening to identify those at highest risk of low bone density or fractures, and a multidisciplinary approach to improve bone health would be beneficial to management. Studies auditing current clinical practices in the management of bone health in SMA patients identified the need for fracture prevention and standardised screening protocols.[18,19]

Some limitations should be acknowledged in our report. Although we present- to our knowledge- the largest single centre cohort of adult SMA patients from a range of cities in the UK, we have a limited sample size, and the majority reside in the south of England. Previous studies have noted epidemiological variation of fracture incidence in both children and adults correlating with regional differences.[20,21] Additionally, identifying the aetiology and mechanism of fractures was beyond the scope of this study. Fractures were not categorised by those deemed osteoporotic or traumatic secondary to impaired mobility.

There is a lack of consensus and research when it comes to long-term post-fracture management in in the adult SMA population. For otherwise healthy patients, standard practice in the UK is to encourage early mobilisation and physiotherapy to reduce risk of deconditioning.[22] However, in adult SMA patients, decisions regarding early mobilisation are more nuanced, and consensus is yet to be reached on mobility management post-fracture due to the inherent complexities in balancing deconditioning against the risk of further fractures in this population with progressive muscle weakness. We note the recent publication of UK orthopaedic care guidelines for DMD, including aspects of post-fracture and post-operative care, as a prompt to future such work in SMA.[23]

Ultimately, bone health is an important consideration in SMA patients given its potential long-term implications for functional disability and overall morbidity. Further research in this unique demographic of adult SMA patients, with a focus on bone health, is required in order to create robust management guidelines.

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