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Skeletal involvement in Joubert syndrome: From low bone mineral density to severe secondary osteoporosis

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SUMMARY: Joubert syndrome (JS) is a rare ciliopathy characterized by neurological and multisystem manifestations; however, skeletal involvement remains poorly recognized. We report two genetically confirmed pediatric patients with JS illustrating different degrees of bone impairment. The first patient, a 2.5-year-old boy with a TMEM67 mutation, presented with severe hypotonia, profound immobility, multiple fractures, and markedly reduced bone mineral density (DXA Z-score −5.875), fulfilling the criteria for secondary osteoporosis and requiring bisphosphonate therapy. The second patient, a 5-year-old girl with an OFD1 mosaic mutation, showed delayed motor development and reduced bone mineral density (DXA Z-score −2.2) without fractures and was managed conservatively. These cases demonstrate the broad spectrum of skeletal manifestations in JS, ranging from low bone mineral density to severe secondary osteoporosis. Reduced mobility and chronic hypotonia may contribute to impaired bone mineralization. Increased awareness and early bone health surveillance, including fracture assessment and densitometric evaluation, may facilitate timely diagnosis and improve management of bone complications in patients with Joubert syndrome.

Keywords: Joubert syndrome, secondary osteoporosis, low bone mineral density, hypotonia, pediatric osteoporosis, fractures

1. Introduction

Skeletal involvement in Joubert syndrome (JS) remains underrecognized, despite well-described neurological and multi-organ manifestations of this ciliopathy (*1-3*). Importantly, bone mineralization abnormalities in JS may range from asymptomatic low bone mineral density (BMD) to severe secondary osteoporosis with fractures. Here, we present two pediatric patients illustrating this phenotypic spectrum and highlight the clinical implications for bone health monitoring.

JS (OMIM 213300) is a rare neurodevelopmental disorder characterized by cerebellar and brainstem malformations, including the molar tooth sign on neuroimaging (*2,4*). Hypotonia and delayed motor development are common and may contribute to reduced mechanical loading, a known risk factor for impaired bone mineralization (*5*). However, skeletal complications remain insufficiently described in clinical practice (*3,4*).

In pediatric populations, it is important to distinguish between low BMD and osteoporosis. According to International Society for Clinical Densitometry (ISCD) criteria, pediatric osteoporosis requires both a clinically significant fracture history and low BMD (Z-score ≤ −2.0), whereas reduced BMD alone does not establish the diagnosis (*6,7*).

We present two genetically confirmed patients with JS and contrasting skeletal phenotypes (Table 1).

The first patient (Figure 1A), a 2.5-year-old boy with a TMEM67 mutation, presented with severe hypotonia, inability to sit independently, and markedly reduced mobility. He developed multiple fractures during infancy, accompanied by progressive skeletal deformities (Figure 1B), including rib and humeral abnormalities. DXA revealed profoundly decreased BMD (Z-score −5.875). Based on the combination of fracture history and densitometric findings, secondary osteoporosis was diagnosed, and bisphosphonate therapy was initiated (*7-9*).

In contrast, the second patient, a 5-year-old girl with an OFD1 mosaic mutation, demonstrated milder neurological involvement and achieved independent ambulation, albeit delayed. Despite the presence of dysmorphic skeletal features and mild spinal abnormalities, she had no history of fractures. DXA revealed reduced BMD (Z-score −2.2), but she did not meet criteria for osteoporosis and was managed conservatively with monitoring (*10,11*).

These cases illustrate the broad phenotypic spectrum of skeletal involvement in JS, ranging from severe

Table 1. Comparative clinical characteristics of the two patients

Parameter	Patient 1	Patient 2
Age	2.5 years	5 years
Genotype	TMEM67	OFD1 (mosaic)
Neurological severity	Severe hypotonia	Moderate hypotonia
Mobility	Non-ambulatory	Independent walking (delayed)
Fracture history	Multiple fractures	None
Skeletal deformities	Severe (thorax, humeri, spine)	Mild (genu valgum, spine curvature)
DXA (Z-score)	−5.875	−2.2
Diagnosis	Secondary osteoporosis	Low BMD
Treatment	Bisphosphonates	Observation

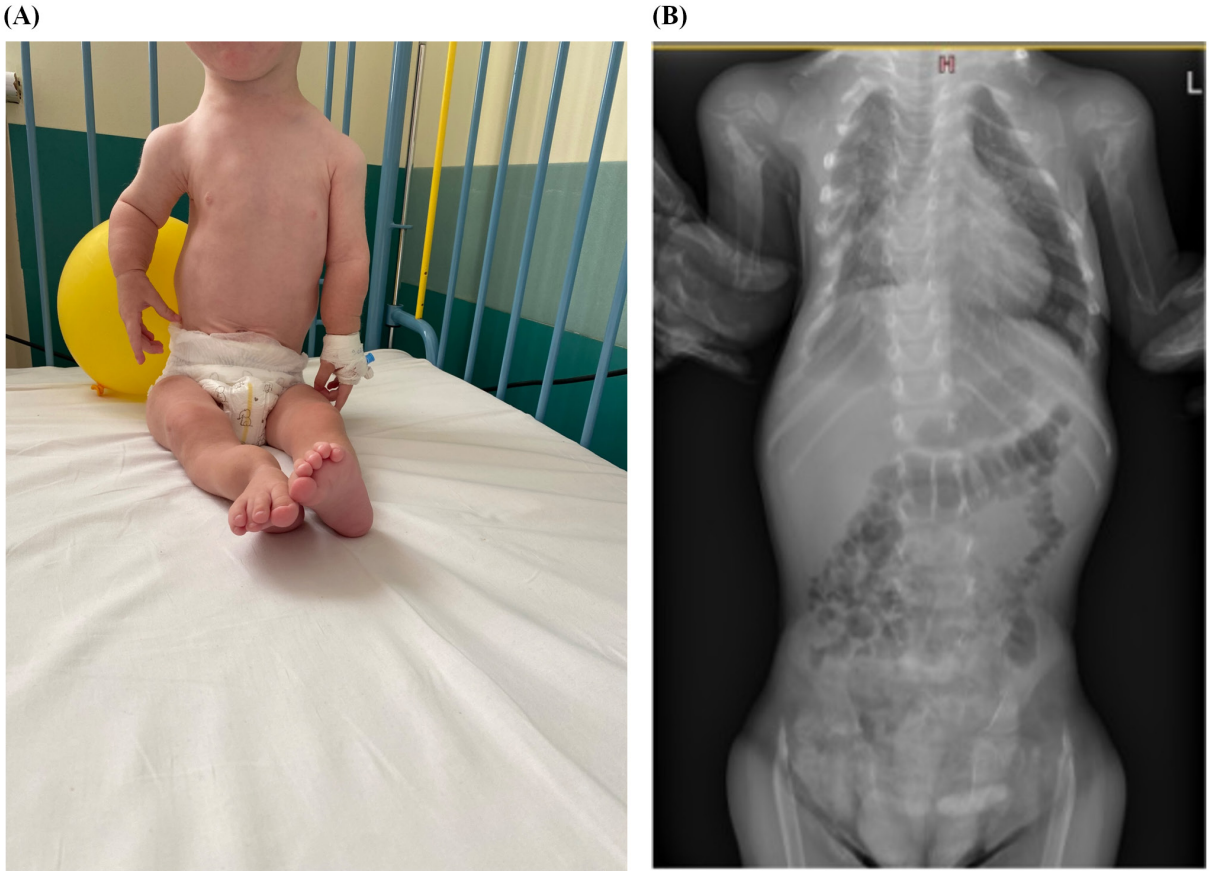

Figure 1. Skeletal manifestations in Joubert syndrome. (A) Clinical appearance of patient 1 showing severe hypotonia and skeletal deformities; **(B)** Radiographic findings demonstrating reduced bone mineralization and skeletal abnormalities associated with severe secondary osteoporosis. *Note*: Written informed consent for publication of this report and any accompanying images was obtained from the patients' legal guardians.

osteoporosis with fractures to subclinical reductions in BMD without overt complications.

2. Clinical implications

These observations highlight several important clinical considerations. Skeletal involvement in Joubert syndrome may be underestimated because fractures are not present in all patients with impaired bone mineralization. Chronic hypotonia and reduced mobility are likely major contributors to skeletal fragility, as mechanical loading plays an essential role in bone mass acquisition during childhood. In addition, nutritional deficiencies, delayed motor development, and limited physical activity may further compromise bone health. The marked difference between our two patients highlights the clinical heterogeneity of skeletal manifestations in JS.

First, skeletal complications in JS may remain clinically silent and therefore underdiagnosed, particularly in patients without a history of fractures (*3*). Second, severe hypotonia and limited mobility appear to contribute significantly to bone fragility and increase fracture risk (*10,11*). Third, reduced BMD may be present even in relatively mobile patients and may not necessarily fulfill the criteria for osteoporosis.

Given these findings, routine bone health

assessment should be considered in selected patients with JS, particularly those with significant hypotonia, delayed motor development, or reduced mobility. Such evaluation may include fracture history, biochemical assessment, and DXA measurement when feasible (*7-10*). Increased awareness among pediatricians and neurologists may allow earlier diagnosis and timely intervention aimed at preventing fractures and improving quality of life.

The potential role of ciliopathy-related mechanisms in bone metabolism remains unclear but may contribute to the observed variability in skeletal involvement (*4*). This hypothesis warrants further investigation.

3. Conclusion

Skeletal manifestations in Joubert syndrome represent a clinically relevant but underrecognized spectrum, ranging from asymptomatic low BMD to severe secondary osteoporosis with fractures. Increased awareness and appropriate monitoring may improve early detection and management of bone complications in this population.

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