

# Orthopaedic Manifestations of Alagille Syndrome

## A Report of Two Cases and an Updated Literature Review

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### Abstract

**Case:** Case 1 is a 6-month-old female who presented for evaluation of asymptomatic vertebral anomalies in the setting of jaundice and cardiac murmur; she was diagnosed with Alagille syndrome (AGS). Her spine has been monitored clinically. Case 2 is a 10-year-old female who sustained a pathologic femur fracture in the setting of known AGS, requiring operative stabilization and optimization of her bone mineral density.

**Conclusions:** Pediatric orthopaedists care for children with AGS both in management of congenital musculoskeletal anomalies and in treatment of pathologic fractures. Familiarity with the current AGS literature is necessary for provision of optimal multidisciplinary care.

Alagille syndrome (AGS) is a rare, multisystem genetic disorder. Neonatal jaundice with conjugated hyperbilirubinemia is typically the first clinical sign. Additional diagnostic criteria include dysmorphic facies, congenital heart disease, ophthalmologic defects, and axial skeleton anomalies. As children with AGS age, multiorgan involvement and associated nutritional deficiencies commonly lead to the development of metabolic bone disease, which may be complicated by pathologic fracture. Awareness of the clinical entity of AGS, its unique orthopaedic manifestations, and contemporary management is needed to enable providers to optimize musculoskeletal care for affected children.

The patients' families were informed that data concerning their cases would be submitted for publication, and they provided consent.

### Case Reports

**C**ASE 1. A 6-month-old female was referred for evaluation of asymptomatic vertebral anomalies. She was the product of a full-term, uncomplicated pregnancy, with multiple hemivertebrae identified on prenatal ultrasound. Postnatally, she was found to have a cardiac murmur associated with atrial septal defect and jaundice with hyperbilirubinemia. Clinical genetics evaluation raised suspicion of AGS. Genome sequencing revealed nonsense mutation Q147X in the *JAG1* gene. Liver biopsy suggested a relative paucity of bile ducts (although this finding may be subtle initially with progression over time); there was no significant ductular proliferation, with marked hepatocellular and cana-

licular cholestasis noted. The liver function test results are described in Table I.

Physical examination revealed a well-appearing infant with mild pruritus. Her spine was midline, without cutaneous manifestation of spinal dysraphism. Passive motion of the spine

**TABLE I** Liver function test values for case 1, a female infant who presented with jaundice, cardiac murmur, and vertebral anomalies identified on prenatal ultrasound and was subsequently diagnosed with AGS\*

Test Name	Reference Range and Units	Value
Total protein	4.8-7.8 g/dL	5.8
Albumin	3.5-5.0 g/dl	3.6
Globulin	2.3-3.5 g/dl	<b>2.2</b>
A/G ratio	1.0-2.2	1.6
AST	0-79 U/L	60
ALT	0-34 U/L	<b>54</b>
Alkaline phosphatase	50-400 U/L	<b>407</b>
Total bilirubin	<1.20 mg/dl	5.01
Bilirubin, direct	<0.20 mg/dl	<b>3.68</b>

\*AGS = Alagille syndrome, ALT = alanine aminotransferase, and AST = aspartate aminotransferase. Bold entries are values occurring outside the normal reference range. These abnormal values supporting the diagnosis of Alagille syndrome.

**Disclosure:** The **Disclosure of Potential Conflicts of Interest** forms are provided with the online version of the article (<http://links.lww.com/JBJS/A884>).

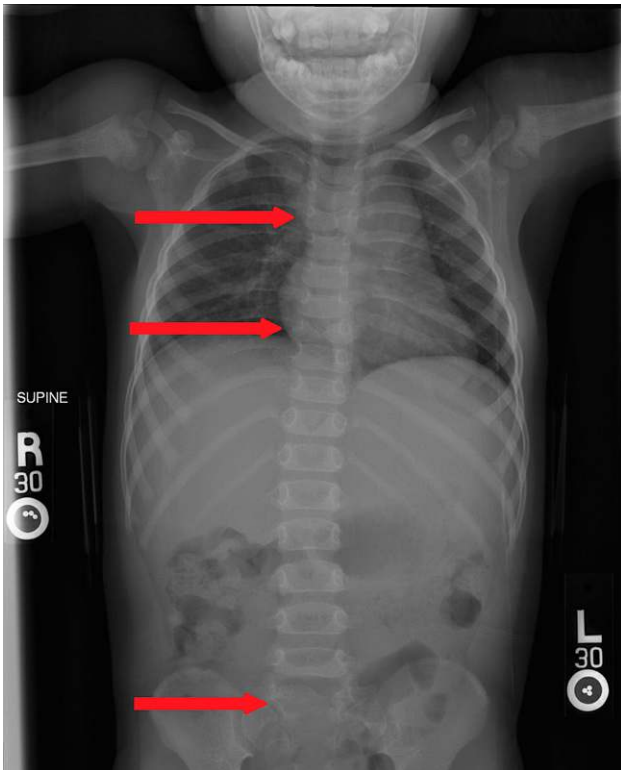


Fig. 1  
Anteroposterior radiograph of the spine taken at 18 months of age demonstrating butterfly vertebrae at T4, T8, and S1 (arrows).

was unrestricted. Neuromuscular examination was normal. Anteroposterior (AP) radiograph of the spine demonstrated butterfly vertebrae at T4, T8, and S1. The remainder of the axial skeleton was unremarkable (Fig. 1). Advanced imaging was deferred, and expectant management was initiated. The family was counseled to follow-up with gastroenterology, cardiology, and ophthalmology services, and a referral to endocrinology was made.

At 18 months of age, she returned for follow-up. At this point, she was ambulating independently, and musculoskeletal examination remained unremarkable. AP spinal radiograph demonstrated the unchanged appearance of multiple butterfly vertebrae without associated curvature. Recommendations for longitudinal optimization of bone health in consultation with gastroenterology, endocrinology, and nutrition services were reinforced. Given the unlikelihood of her vertebral anomalies becoming symptomatic or posing a progressive structural problem, she is to be followed up clinically.

CASE 2. A 10-year-old female with AGS (previously identified genetic defect in the *NOTCH2* gene) presented with acute right thigh pain and inability to ambulate after a low-energy fall 2 days prior. Physical examination demonstrated a young girl of short stature with mild jaundice and a prominent forehead, deep-set eyes, and depressed nasal bridge. Focused evaluation of the right lower extremity demonstrated intact skin and obvious thigh deformity with soft compartments. She had painless passive motion of the ipsilateral hip and tenderness localized to the distal thigh. Distal neurovascular function was intact. Orthogonal radiographs of the right hip, femur, and



Fig. 2



Fig. 3

**Fig. 2** Lateral radiograph of the right femur demonstrating diffuse osteopenia and a comminuted short spiral fracture of the distal femur at the metaphyseal-diaphyseal junction, with associated shortening and malangulation. **Fig. 3** Anteroposterior radiograph of the right femur taken on postoperative day 10, demonstrating fracture reduction and fixation with a submuscular plate.

knee revealed diffuse osteopenia and an isolated, comminuted spiral fracture of the distal femur at the metaphyseal-diaphyseal junction with shortening and malangulation (Fig. 2).

After preoperative medical evaluation, she underwent closed reduction and internal fixation of her fracture using a submuscular plate and a minimally invasive technique the following day (Fig. 3). Her postoperative course was uneventful; she was discharged home on postoperative day 2 with protected weight bearing using a walker and endocrinology follow-up for optimization of bone health. Bone mineral density Z-scores for the lumbar spine, femoral neck, and hip were significantly lower than age-matched peers ( $-2.6$ ,  $-2.5$ , and  $-2.2$ , respectively). Recommendations for oral calcium and vitamin D supplementation, complemented by PediaSure, were reinforced. By week 6, she was ambulating independently. By week 12, she was back to unrestricted baseline low-impact activity, with radiographs demonstrating fracture healing. More than a year after sustaining her fragility fracture, she remained pain-free and fracture-free. The plate has thus far remained in situ, and serial radiographs have not demonstrated development of distal femoral valgus deformity.

### Discussion

AGS is a multisystem genetic disorder characterized by cholestatic liver disease, congenital cardiac defects, musculoskeletal deformities, ophthalmologic abnormalities, and characteristic facies<sup>1</sup>. Its incidence has been estimated at 1:30,000 to 1:70,000 live births<sup>2,3</sup>. AGS is inherited in an autosomal-dominant fashion, with variable penetrance and phenotypic expression; de novo mutations are common, occurring in 50% to 70% of patients with AGS<sup>1-4</sup>.

The majority (97%) of AGS cases result from mutations in the *JAG1* gene, whereas ~1% is associated with the *NOTCH2* gene<sup>3-7</sup>. Both genes play a role in the Notch signaling pathway, which is involved in the segmentation of the axial skeleton during fetal development. This pathway additionally plays a central role in controlling bone metabolism throughout life by regulating osteoblast and osteoclast differentiation and function<sup>8</sup>. Mutations in this pathway contribute to various musculoskeletal disorders, including Hajdu-Cheney syndrome, spondylocostal dysostosis, and osteosarcoma<sup>3,8</sup>.

AGS presents with cholestasis and conjugated hyperbilirubinemia in the first year of life<sup>2</sup>. The diagnosis may be made with a liver biopsy demonstrating a paucity of interlobular bile ducts plus 3 of 5 major clinical features (Table II)<sup>1-3,9</sup>. Genetic testing is useful for diagnostic confirmation. Other organ systems may be affected: renal complications including renal tubular acidosis (RTA) occur in 23% to 40% of patients with AGS<sup>9,10</sup>. The incidence of growth retardation is estimated to be ~90%<sup>9</sup>.

The most common orthopaedic manifestation of AGS at the time of presentation is vertebral anomaly, occurring in 51% to 66% of patients<sup>9,11</sup>. Butterfly vertebrae are classically described<sup>11,12</sup>. These anomalies, named for their appearance with a central sagittal cleft, result from failure of fusion of the anterior vertebral arches in one or more vertebrae, typically at the thoracic level<sup>11</sup>. Other reported axial skeleton manifestations include fusion of adjacent vertebrae, decreased interpedicular distance, twelfth rib absence, pointed C1 anterior processes, spina bifida occulta, craniosynostosis, and hemivertebrae<sup>12,13</sup>. Hemivertebrae may be evident on prenatal ultrasound; if present in conjunction with other abnormalities, this finding may aid in the early diagnosis of AGS<sup>14,15</sup>. Deformities of the appendicular skeleton including radioulnar synostosis and distal phalangeal hypoplasia have also been described<sup>3,16</sup>.

Orthopaedic management of AGS-associated musculoskeletal anomalies is dependent on the specific abnormality. Butterfly vertebrae, the most common finding with AGS, do not typically require intervention, as compensatory midline growth of the adjacent vertebrae and intervertebral disks serves to keep the spine balanced<sup>17</sup>. As a result, butterfly vertebrae have traditionally been believed to be of little symptomatic or structural significance, without the need for ongoing follow-up<sup>3</sup>. That said, several recent case reports have raised the possibility of an association between butterfly vertebral defects and back pain in the adult population, suggesting that the presence of a butterfly vertebra might not be entirely benign over time<sup>17-19</sup>. Hemivertebrae have the potential to pose structural spinal problems such as progressive congenital scoliosis and should be recognized and monitored accordingly.

Metabolic bone disease is common and may be complicated by pathologic fracture<sup>4</sup>. Children with AGS have a 3-fold increase in total fracture incidence when compared with a healthy pediatric population, with 25% of patients with

TABLE II Classic criteria for a diagnosis of AGS\*

System/Presenting Feature	Description
Hepatobiliary	Jaundice with conjugated hyperbilirubinemia and cholestasis
Dysmorphic facies	Broad forehead, deep-set eyes, prominent ears, and straight nose with the bulbous tip and pointed chin
Cardiac	May present as pulmonary artery stenosis, pulmonary atresia, ASD, VSD, and TOF
Musculoskeletal	Axial skeleton anomalies; "Butterfly" vertebrae most common; also hemivertebrae, fusion of adjacent vertebrae, and spina bifida occulta
Ophthalmologic	Anterior chamber defects, most commonly posterior embryotoxon

\*AGS = Alagille syndrome, ASD = atrial septal defect, TOF = tetralogy of Fallot, and VSD = ventricular septal defect.

AGS sustaining a pathologic fracture in childhood<sup>4,20</sup>. In addition to a higher overall fracture rate, fractures in children with AGS differ from the normal population in terms of both age distribution and anatomic location<sup>4</sup>. Fractures occur at an average age of 5 years in AGS with 93% of fractures occurring before age 10<sup>4</sup>; by contrast, fractures occur at an average age of 11 years and 14 years in healthy females and males, respectively<sup>20</sup>. In addition, 70% of AGS fractures occur in the long bones of the lower extremities in contrast to healthy children who are more likely to suffer upper extremity fractures<sup>4,20</sup>. Estimates of femur fracture incidence are 2.5 per 10,000 person-years in the healthy pediatric population and 127.6 per 10,000 person-years in the pediatric AGS population, a 50-fold increase<sup>4,20</sup>.

Increased fracture risk may be partially explained by differences in bone metabolism. Children with AGS have both decreased bone area and decreased bone mineral content compared with healthy controls<sup>21</sup>. These deficiencies are likely multifactorial in etiology: malabsorption, hyperbilirubinemia, RTA, growth hormone receptor insensitivity, and disruption of the Notch signaling pathway have all been identified as possible contributors to osteopenia and increased fracture risk seen in these patients<sup>4,9,22-26</sup>. Sustained efforts to medically optimize bone health with monitoring and supplementation combined with counseling patients and their families regarding the importance of regular participation in low-impact physical activities may mitigate this risk.

For children with AGS who present with pathologic fracture, initial orthopaedic management consists of fracture reduction and stabilization once this can be safely accomplished. Ensuring that patients receive appropriate multidisciplinary medical management is essential for optimizing future bone health. Fracture nonunion and recurrent fractures have both been reported in the AGS population; some authors

have described the use of adjunctive methods of healing such as low-intensity pulsed ultrasound stimulation<sup>4,5,27</sup>.

Pediatric orthopaedists may care for children with AGS both in the evaluation of musculoskeletal anomalies that are present from birth and in the treatment of pathologic fractures that occur secondary to the disease. Therefore, increased awareness of the clinical entity of AGS and its orthopaedic manifestations is essential to the provision of high-level multidisciplinary musculoskeletal care for affected children. ■

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