

Massive Ribs Fractures Due to
Artriohepatic Dysplasia (Alagille
Syndrome): A Case ReportMohammed J Aboud¹, Manal M Kadhim², Shaima Mohammed³ and Noor Abudi⁴¹Consultant pediatric Surgery, the Maternity and Child Teaching Hospital, Iraq²Department of Microbiology, Al Qadisiya University, Iraq³Pediatrics Specialists, the Maternity and Child Teaching Hospital, Al Diwaniya, Iraq⁴Doctor, the Maternity and Child Teaching Hospital, Al Diwaniya, Iraq

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Abstract

Alagille Syndrome (ALGS) is a rare multisystem congenital disorder, with a minimum incidence of approximately 1:30,000 live births. Several of the characteristics of Alagille syndrome may result in patients having an especially high risk of fracture. Case presentation; a 6-months-old girl admitted to pediatric surgery unit with jaundice since one month of age, progressive abdominal distention. She had been diagnosed with biliary atresia at the age of 1 month on the base of clinical diagnosis; she was malnourished with stunted growth. She had most of the features of Alagille syndrome. Chest radiographs showed generalized decreased in bone density with multiple ribs fractures on the left side, with pulmonary consolidation in the left middle and lower zone. Osteodystrophy (hepatic cause) was enrolled based on the fact that there was no evidence or history of trauma (child abuse by the family was not considered). Our study is one of a few reports to document ribs fracture in children with AGLS.

Introduction

Alagille syndrome (ALGS) is a rare multisystem congenital disorder, with a minimum incidence of approximately 1:30,000 live births. It is an autosomal dominant disease that arises from mutations in the Jagged1 (JAG1) gene (approximately 60% of cases are caused by de novo mutations), which encodes a ligand for Notch receptors [1,2]. The majority of the mutations detected result in protein truncation and haploinsufficiency is the presumed mechanism of pathogenesis. The Notch signaling pathway regulates proliferation and differentiation of a variety of cell types during development. Defects in the pathway are associated with embryonic angiogenic abnormalities and are presumed to impair bile duct formation, although its exact function in liver and biliary tree development is unknown [3]. The most common symptoms associated with this syndrome are cholestasis with the obstruction or slowing of biliary flow, congenital heart disease (pulmonary artery stenosis) and butterfly-shaped vertebrae, anterior chamber eye defects and dysmorphic faces. One of the main diagnostic features of this syndrome is bile duct paucity (liver histology pointed to an increased portal tract-to-bile duct ratio), which is more common later in infancy and childhood [4-6]. Ductular proliferation is present in a small number of infants with such syndrome, leading to significant diagnostic confusion. Because of the variability in the early histopathology of the liver in this syndrome, a number of patients have been misdiagnosed as having biliary atresia [7,8]. In the majority of cases, individuals with ALGS present in infancy with cholestasis (conjugated hyperbilirubinemia with high GGT, increased serum bile acids, and elevated cholesterol and triglycerides), which manifest as jaundice, intense pruritus, xanthomas (fatty deposits on the extensor surfaces) and failure to thrive due to fat malabsorption [9-11]. Several of the characteristics of Alagille syndrome may result in patients having an especially high risk of fracture. The majority of patients suffer from chronic cholestasis [12], which can have a variety of adverse effects on bone metabolism. Hyperbilirubinemia inhibits osteoblast proliferation and induces osteoporosis. Most importantly, cholestasis leads to a deficiency of intestinal bile acids. This deficiency ultimately interferes with the absorption of vitamins and minerals that are critical to bone development, including calcium, vitamin D and vitamin K [13].

We report a case of a 6-months-old girl with marked hyperbilirubinemia from birth who presented with a massive pathological fracture of the ribs.

Ethics Statement

Written informed consent was obtained from the patient parent who participated and managed in this report for publication of this case and any accompanying images. The scientific and health committee in our Health directorate office approved this publication.

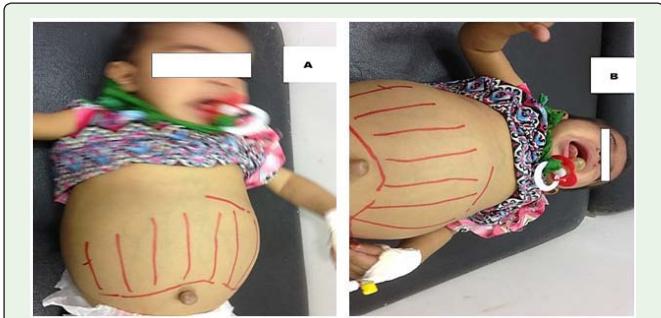


Figure 1 A and B: The patient on the initial clinical assessment with massive hepatomegaly and hyperbilirubinemia.

Case Presentation

A 6-months-old girl admitted to pediatric surgery unit with jaundice since one month of age, progressive abdominal distention, dyspnea and tachypnea and in recent few days prior to admission she developed an attack of coffee ground vomiting associated (sometimes with clear bloody streaks). She was fed breast milk. She had been diagnosed with biliary atresia at the age of 1 month on the base of clinical diagnosis and accordingly she treated with vitamins D and K. On admission and initial evaluations, she was malnourished with stunted growth (height: 46.5 cm, <3rd centile; weight: 3.4 kg, < 3rd centile). She had most of the features of Alagille syndrome, including a characteristic face, raised peripheral pulmonary vascularity, venous overload with evidence of heart failure (by echocardiography assessments), massive hepatomegaly and hyperbilirubinemia (Figure 1 A,B). Blood tests revealed anemia (hemoglobin, 7.2 g/dL). Blood film revealed microcytic hypochromic anemia with leukocytosis and lymphocytosis. Liver dysfunction with high serum bilirubin 8.2 mg/dl (direct 6.7 mg/dl), and high serum alkaline phosphatase 212 IU/L. Total serum cholesterol (269.8 mg/dL), (251.5 mg/dl) of triglyceride and serum calcium was (5.8 mg/dl). Serum creatinine was (1.2 mg/dl) and serum albumin (2.8 g/dl). Urine and serum chromatography screening tests for acylcarnitine, amino acids and organic acids were negative. Thyroid function test was normal. Chest radiographs showed generalized decreased in bone density with multiple ribs fractures on the left side, hemivertebrae in the lower thoracic region, with pulmonary consolidation in the left middle and lower zone (Figure 2 A,B). Bilateral wrist joint X-ray reported signs of Richet (Figure 3). A plain skeletal radiography of the lower limbs revealed osteoporotic changes. Abdominal ultrasonography US revealed mild increased in liver and spleen size, thin wall gallbladder with mild dilatation of intra and extrahepatic biliary ducts. Right ectopic hydronephrosied (solitary kidney) was noticed in the US study done for urological assessment. A three-dimensional



Figure 3: Left wrist joint X-ray reported signs of Richet.

Computerized Tomography Scan (CT-Scan) of the chest submitted multiple fractures more announced on the left side. The ribs were osteoporotic, with cortical thickening, there appeared to be at high risk of pathological fractures (Figure 4 A-C). Osteodystrophy (haptic cause) was enrolled based on the fact that there was no evidence or history of trauma (child abuse by the family was not considered) and the baby suffered from prolong cholestasis. The patients arranged for genomic DNA study, the polymerase chain reactions PCR were enrolled; the PCR product was analyzed by direct sequencing using a Big Dye Terminator v3.1 Cycle Sequencing Kit in an ABI PRISM 310 Genetic Analyzer (Life Technologies Corporation, California-United States). The DNA heteroduplex post PCR analysis submitted mutations in the JAG1 gene. Ophthalmological consultation carried out, the report revealed posterior embryotoxon, diagnosed by a slit-lamp examination. The patient arranged for a multidisciplinary

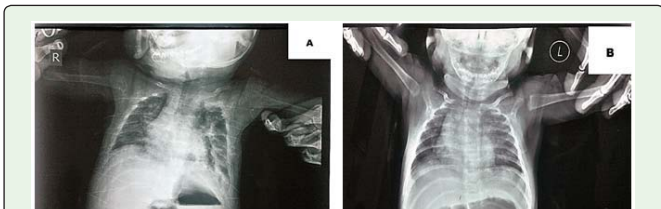


Figure 2 A and B: Chest x-ray decreased in bone density with multiple ribs fractures on the left side, hemi vertebrae in the lower thoracic region, with pulmonary consolidation in the left middle and lower zone.

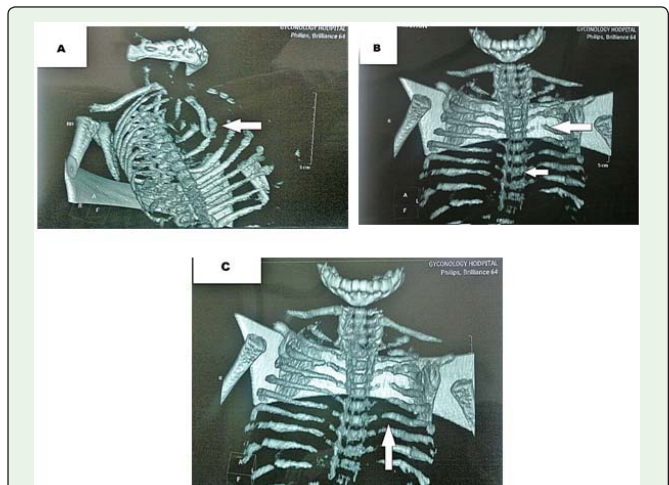


Figure 4 A-C: A- Three-dimensional CT-Scan of the chest with multiple fractures more announced on the left side (white arrow). B-The ribs and vertebrae were osteoporotic (white arrows). C- Cortical thickening at high risk of pathological fractures (white arrow).

approach. Dietary input and supplementary feeding were initiated with the continuation of vitamins, especially D and K. As the family noticed the recent development of pruritus made the baby irritable, choleretic agents (ursodeoxycholic acid) were started accordingly in dose (5-10 mg/kg/day) and for improving bile flow. Anti-failure measurement prescribed for cardiac consequences. The lack of liver transplantation advances, technology, and protocol (despite that the patient criteria's and indications were not suggested), this made the policy of the biliary diversion surgery under considerations. Genetic counseling offered to parent for the future planning their own family.

Discussion

Alagille syndrome (also known as arteriohepatic dysplasia) is a rare disease, frequently the prolonged jaundice is the most frequent symptom [14]. The familial nature of this syndrome has been identified from early studies. Researchers studied five families and discussed the possible dominant inheritance and variable expressivity of this disorder [15]. Alagille et al, found that 3 out of 15 patients had sibs with neonatal cholestasis [16]. Additional families were reported with multiple affected members consistent with an autosomal dominant pattern of inheritance with low penetrance and variability of expression. Genetic evaluation for JAG1 mutations is currently available on both a research and commercial sides. At this time, the molecular screening for Notch receptors is primarily a research test and still performed commercially at limited centers. The diagnosis may be difficult because of the variable and broad expression of the clinical manifestations. Ideally, three of five major clinical signs: cholestasis, ophthalmologic abnormalities, the characteristic facial features (prominent forehead, deep-set eyes with moderate hypertelorism, pointed chin and straight nose with a bulbous tip), congenital heart disease (commonly stenosis of the peripheral/pulmonary arteries) and skeletal abnormalities (commonly butterfly vertebrae). Renal and vascular (often in the head and neck) abnormalities considered as important manifestations [5,17]. The submission of these observations with the liver biopsy and histology (showing bile duct paucity and increased portal tract-to-bile duct ratio), have led to an expansion of the phenotypic criteria of the syndrome such that three of seven characteristic clinical criteria's are sufficient for a clinical diagnosis [17,18]. Despite of the liver biopsy may confirm the clinical images; recently the presence of cholestasis considered sufficient [14]. The most important issue associated with this syndrome is cholestasis (the slowing or obstruction of the biliary flow). The lack or deficiency of intestinal bile acids ultimately interrupts the absorption of vitamin D, this vitamin is hydroxylated at the carbon 25 position to form 25-hydroxyvitamin D, this occurs primarily in the liver [19]. This mechanism generally associated with failure of endochondral ossification. Multiple spontaneous fractures of both the ribs and long bones have been noticed in infants with chronic liver disease and chronic cholestasis, pointed to the generalized skeletal demineralization or rachitic changes [20]. Exposure to and high accumulation of the levels of bilirubin inhibits the proliferation of osteoblasts in cell cultures. Despite the underlying mechanism, causing osteoporosis secondary to hyperbilirubinemia still not so clear, patients with primary biliary cirrhosis and osteoporosis have higher serum bilirubin levels than those without osteoporosis [21]. In our patient, long-term hyperbilirubinemia clearly identified with her systemic osteoporosis. Researchers announced; in patients with ALGS, the fracture sites deteriorated despite treatment, and all of

the patients eventually succumbed [22]. The underlying urological pathologies associated ALGS, made the patients also suffer from renal tubular acidosis, this form an additional risk of osteomalacia [23]. The genetic disruptions in Notch signaling in ALGS may alter skeletal integrity as well as skeletal morphology. Despite the bone fragility has never been improved a genetically determined feature of this syndrome, a recent evidence suggests that Notch signaling plays a critical role in inducing normal skeletal microstructure at the various stages of development [24-26]. Report of 10-year outcomes in an AGLS submitted that 6 of 8 patients referred for liver transplantation experienced recurrent, poorly and delayed healing bone fractures [8]. Poor solubilisation and absorption of dietary lipids, essential fatty acids, and fat-soluble vitamins; causing malnutrition inducing high risk of growth failure with additional depletion in skeletal mass and bone density (osteopenia) [7]. A study reported; the age at the time of fracture in chronic liver disease ranged from 3 to 16 months after birth (our case was diagnosed at age of 6 months), and the patients with severe cholestasis have a risk of bone fracture despite the administration of the essential minerals and vitamins.

Conclusion

Infants with AGLS presenting with cholestatic jaundice have to be followed in a serious way because of the high risk of complications of the liver disease associated cholestasis. The pediatrician should maintain a high index of suspicion for and in considering traumatic fractures in such patients. Careful radiological attention is also important to avoid missing unsuspected fractures on skeletal x-ray images. Our study is one of a few reports to document ribs fracture in children with AGLS.

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