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Pathologic Lower Extremity Fractures in Children with Alagille Syndrome

Christina B. Bales, MD^{1,4}, Binita M. Kamath, MBBChir^{1,4}, Pedro S. Munoz¹, Alexander Nguyen¹, David A. Piccoli, MD^{1,4}, Nancy B. Spinner, PhD^{2,4}, David Horn, MD^{3,4}, Justine Shults, PhD⁵, Mary B. Leonard, MD^{1,4,5}, Adda Grimberg, MD^{1,4,*}, and Kathleen M. Loomes, MD^{1,4,*}

¹Department of Pediatrics, at The University of Pennsylvania School of Medicine Philadelphia, Pennsylvania

²Department of Pathology and Laboratory Medicine, at The University of Pennsylvania School of Medicine Philadelphia, Pennsylvania

³Department of Orthopaedic Surgery at The University of Pennsylvania School of Medicine Philadelphia, Pennsylvania

⁴The University of Pennsylvania School of Medicine Philadelphia, Pennsylvania

⁵Department of Biostatistics and Epidemiology The University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.

Abstract

Objectives—In this retrospective study, we aimed to determine the incidence and distribution of fractures in patients with Alagille syndrome, one of the leading inherited causes of pediatric cholestatic liver disease.

Methods—Surveys regarding growth, nutrition, and organ involvement were distributed to patient families in the Alagille Syndrome Alliance or The Children's Hospital of Philadelphia research database. Patients with a history of fracture were identified by their response to one question, and details characterizing each patient's medical, growth, and fracture history were obtained through chart review and telephone contact.

Results—Twelve of 42 patients (28%) reported a total of 27 fractures. Patients experienced fractures at a mean age of 5 years, which contrasts with healthy children, in whom fracture incidence peaks in adolescence. Fractures occurred primarily in the lower extremity long bones (70%) and with little or no trauma (84%). Estimated incidence rate calculations yielded 399.6 total fractures/10,000 person years (95% CI = 206.5, 698.0) and 127.6 femur fractures/10,000 person-years (95% CI = 42.4, 297.7). There were no differences in gender, age distribution or organ system involvement between the fracture and no-fracture groups.

Correspondence to: Kathleen M. Loomes, M.D.; Division of Gastroenterology and Nutrition; The Children's Hospital of Philadelphia; 1010 Abramson Research Center; 3615 Civic Center Boulevard; Philadelphia, PA 19104. Telephone: 267-426-7223; Fax: 267-426-7814; lloomes@email.chop.edu.

*Drs. Grimberg and Loomes declare joint responsibility for senior authorship

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Conclusions—Children with Alagille syndrome may be at risk for pathologic fractures, which manifest at an early age and in a unique distribution favoring the lower extremity long bones. While this preliminary study is limited by small sample size and potential ascertainment bias, the data suggest that larger studies are warranted to further characterize fracture risk and to explore factors contributing to bone fragility in these children.

Keywords

Alagille syndrome; fracture; osteomalacia

Introduction

Alagille Syndrome (AGS) is an autosomal dominant disorder associated with mutations in *JAG1*, which encodes a ligand in the Notch signaling pathway (1,2). A smaller group of patients have mutations in the gene encoding the Notch2 receptor (3). The syndrome occurs in at least 1 in 70,000 live births and is one of the leading causes of inherited pediatric cholestatic liver disease (4). In addition to cholestasis, which is related to a paucity of intrahepatic bile ducts, patients with AGS can present with cardiac, ocular, renal, vascular, and skeletal abnormalities. Organ involvement and specific clinical manifestations are highly variable, with differences observed even among patients harboring identical *JAG1* mutations (5).

Certain skeletal manifestations are considered cardinal features of AGS (6). Approximately 70% of patients have sagittal cleft or “butterfly” vertebrae (7), and some may have a decreased interpedicular distance in the lumbar vertebrae (8). Abnormal fusions between adjacent ribs, vertebrae, and forearm bones are also described (8,9). Collectively, these findings are not associated with functional compromise. However, some patients suffer significant morbidity as a consequence of bone fractures. Case studies document multiple recurrent fractures in some patients (10,11), and poor healing and/or marked post-fractural deformities in others (12,13). Indeed, one study of 10-year outcomes in an AGS cohort reported that 6 of 8 patients referred for liver transplantation experienced recurrent and/or poorly healing bone fractures (11).

Several disease characteristics of AGS may place patients at an especially high risk of fracture. The majority of patients suffer from chronic cholestasis (7), which can have a variety of adverse effects on bone metabolism. 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. A subset of AGS patients also suffer from renal tubular acidosis (7), which can further increase the risk of osteomalacia. Finally, patients with AGS have genetic disruptions in Notch signaling that may alter skeletal integrity as well as skeletal morphology. Although bone fragility has never been considered a genetically determined feature of AGS, recent evidence suggests that Notch signaling plays a critical role in establishing normal skeletal microstructure at various stages of development (14,15).

While studies have examined surrogate markers of skeletal fragility in patients with AGS (16), there are no studies of fracture epidemiology in this potentially high-risk population. In this retrospective study, we determined the incidence and distribution of fractures in AGS patients who responded to a broader survey regarding growth and organ system involvement.

Methods

Data Collection

Written surveys, entitled “The Children’s Hospital of Philadelphia Alagille Syndrome Growth Study,” were mailed to patient families over a 2-year time period between 2005 and 2007. All

families were registered with the Alagille Syndrome Alliance or The Children's Hospital of Philadelphia (CHOP) research database. The study was approved by the Institutional Review Board of The Children's Hospital of Philadelphia. The surveys asked parents to submit growth chart information and to answer a series of "yes/no" questions about organ system involvement in their affected children. Patients with prior fractures were identified by a positive response to a single question regarding a history of "broken bones".

Parents who reported that their child had previously suffered one or more fractures were contacted via telephone for additional details. Specifically, they were asked to recount the total number of fractures sustained, the patient's age at the time of each fracture, the specific bone (s) fractured, and the potential mechanism of injury in each case. Mechanisms of injury were then classified according to the modified Landin criteria published by Clark and colleagues (17). Parents were also asked to recall whether each fracture was a new entity or a recurrence at a previous fracture site. Information collected via survey and telephone was cross-referenced and confirmed with medical records from referring institutions, where possible. The CHOP research database was also searched for available *JAG1* mutation analysis information on each patient.

Statistical Analyses

Age and sex-specific Z-scores (standard deviation scores) for height and Body Mass Index (BMI) were calculated from data extrapolated from submitted growth charts using National Center for Health Statistics 2000 Center for Disease Control growth data (18). For patients with a history of fractures, individual Z-scores were calculated at the time of first fracture. For patients without a history of fractures, height and BMI z-scores were calculated at the mean age of fracture occurrence in this study (i.e., 5 years).

The Student's t-test was performed to detect differences between the fracture and non-fracture groups with respect to mean age at the time of questionnaire and mean calculated height and BMI z-scores. Pearson's chi-square analysis was used to determine whether the 2 groups differed with respect to gender, *JAG1* mutation type, organ system involvement, and surrogate markers of disease severity (i.e., history of either biliary diversion or liver transplantation). The Wilcoxon rank sum analysis (Mann-Whitney test) was also used to determine whether the number of fractures per subject differed according to organ involvement.

Finally, fracture incidence rates in the sample were calculated by dividing the number of patients with a fracture by the total number of person-years of follow-up. The resulting rates were standardized to yield an estimated fracture incidence rate per 10,000 person-years, with 95% confidence intervals determined based on the Poisson distribution. To maintain consistency with larger-scale epidemiologic studies of fracture rates in children, only the first fracture was used in the calculation of incidence rates for patients who reported multiple fractures. All analyses were performed with the STATA data analysis system (StataCorp, College Station, TX).

Results

Four hundred and ninety-five surveys were mailed, and 93 were returned undelivered due to inaccurate address listing. Of the remaining 402 surveys, 42 were completed and returned with associated parental consent, yielding a completion rate of 10 percent. The study group was comprised of 24 males and 18 females, ranging in age from 1 to 35 years (mean 10 years) at the time of survey completion.

Twelve patients (28%) had a history of bone fracture, with a total of 27 fractures reported. The number of fractures in each patient ranged between 1 and 7. Although 6 patients reported

multiple fractures, only one of these was attributed to recurrence at a previous fracture site. Study patient characteristics are described in Table 1. There were no differences in gender or age distribution between the fracture and no-fracture groups. Moreover, the two groups did not differ with respect to the presence of cardiac anomalies, renal disease, vertebral anomalies, or surrogate markers of liver disease severity, including a history of biliary diversion or transplantation. The 3 patients who underwent biliary diversion experienced a total of 9 fractures, 2 of which occurred before diversion and 7 of which occurred after diversion. The 3 patients who underwent liver transplantation experienced a total of 3 fractures, 1 of which occurred before transplantation and 2 of which occurred after transplantation. Children with a history of fractures had lower mean height and BMI z-scores, but the differences were not significant.

Patient age at the time of fracture ranged from 9 months to 20 years. However, the vast majority (93%) occurred at less than 10 years, with a mean age of 5 years. Fracture locations and associated mechanisms of injury are summarized in Table 2. Of note, 70% percent of fractures occurred in the lower extremity long bones, including the tibia, fibula or femur. Parents were able to recall the events surrounding 25 of the 27 reported fractures. The recalled mechanism of injury was consistent with little (SLT) or no trauma (NT) in 84% of cases (see Table 2). The estimated fracture incidence rate in our study group was 399.6 fractures per 10,000 person-years (CI = 206.5-698.0 fractures per 10,000 person-years) in the first 20 years of life. The estimated incident rate of femur fractures in this sample was 127.6 femur fractures per 10,000 person-years (CI = 41.4 – 297.7 femur fractures per 10,000 person years).

JAG1 mutation data were available on 29 patients (11 patients with fractures and 18 patients without fractures). Within the fracture group, one patient had a chromosomal deletion and 5 patients had nucleotide(s) deletions and/or insertions, which resulted in frameshift and premature protein truncation. Three patients had nonsense mutations, and two others had splice site mutations. The distribution of mutations was similar in both fracture and non-fracture groups. Overall, within the fracture group, 73% (8/11) of the mutations were predicted to be protein-truncating.

Discussion

This study shows that patients with Alagille Syndrome (AGS) may have an increased risk of bone fracture in early childhood. Estimated incidence rates in the first 20 years of life (399.6 fractures per 10,000 person-years; CI = 206.5 – 698.0) were 3 times higher than those reported in a widely-referenced pediatric population-based study (133.1 fractures per 10,000 person-years) (19). Of note, the majority of fractures in our study occurred prior to early adolescence, when fracture incidence peaks in healthy children (19). Patients in our sample sustained their first fractures at a mean age of 5.2 years, whereas boys and girls in the general population experience the highest fracture incidence rates at ages 14 and 11 years, respectively.

The anatomic distribution of fractures in our sample is striking. Unlike healthy children, who tend to fracture bones in the upper extremities (19), patients in our study experienced the highest number of fractures in the lower extremity long bones. Indeed, more than two-thirds of fractures were located in either the femur or tibia/fibula. Femur fractures, in particular, are unusual in the general pediatric population. The incidence rate in healthy children has been estimated at 2.5 femur fractures per 10,000 person-years and accounts for less than 2% of the total fracture incidence (19). In contrast, the estimated incidence rate in our sample was 127.6 femur fractures per 10,000 person-years (CI = 41.4 – 297.7) and accounted for 31% of the total fracture incidence.

We acknowledge that our findings may be limited by small sample size and survey method. The questionnaire length and cumbersome request for longitudinal growth information may have contributed to a low survey response rate, which may have introduced an ascertainment bias into our sample. It is also possible that families with more severely affected children would be more likely to participate in research and to respond to such a questionnaire. In that case, our study sample would be biased towards those patients with more severe cholestasis, who would be at a higher risk of fracture. Thus, the calculated incidence rates in our sample represent preliminary estimates. Larger studies, in which all families respond, are needed to establish accurate incidence rates.

Because incidence rates only account for the initial fracture reported for each individual, they do not capture the burden of multiple fractures incurred by certain children. Nearly half of the patients in our fracture group had more than one event. Perhaps more importantly, all of these children seemed to experience fractures after little or no trauma. In the majority of cases with preceding trauma, parents recalled their child falling from a height that was less than or equal to standing. With rare exceptions, these falls did not involve significant forward and/or downward momentum. Modern classification systems categorize this type of short-distance, low-impact fall as “slight” trauma in a graded scheme that ranges from “slight” through “moderate” and severe” (17). In a recent study using this classification system, children with fractures resulting from “slight trauma” were more likely to exhibit signs of skeletal fragility, including a lower volumetric bone area, bone mineral density, and bone mineral content, than children without fractures (17). Thus, in a subset of our patients with multiple fractures, a consistently low trauma index is likely to reflect underlying deficits in bone structure/integrity that make these children more vulnerable to fracture occurrence.

Several patients, including patients 1 and 8, reported bilateral fractures in opposite lower extremity bones within the same year. This predominance of minimally traumatic, potentially symmetric fractures in weight-bearing long bones is suggestive of underlying osteomalacia (20). Osteomalacia is a condition of insufficient skeletal mineralization, which is caused by a deficiency in calcium and/or phosphorus. Children with AGS may be especially susceptible to this condition because they almost uniformly suffer from cholestasis, which impairs intestinal bile salt delivery and leads to malabsorption of calcium, vitamin D, and other fat-soluble vitamins. Indeed, bone fragility is a widely recognized complication of chronic cholestasis. Several groups have identified deficits in bone mineral density and accretion of bone mass in children with cholestatic liver diseases (21,22), however studies exploring fracture incidence are few. To date, only one study has documented fracture occurrence in children with a range of chronic liver diseases (10). In this study of 117 children undergoing liver transplantation, the fracture incidence was 16.2% overall, rising to 19% in patients with biliary atresia. Similar to our patient population, the majority of the fractures in this study occurred at an early age (median 13.5 months) and with minimal or no trauma. Interestingly, the only patient with AGS experienced 11 fractures, which exceeded the number reported for any other patient.

Our data suggest that patients with and without fractures had similar overall anthropometrical profiles. The two groups did not differ with respect to height, weight or BMI z-scores. While we were not able to determine malabsorption coefficients or vitamin/mineral levels at the time of fracture, these variables have been prospectively examined in AGS patients undergoing DEXA analysis. One study revealed that surrogate markers of cortical bone strength, including height-adjusted whole body bone area and bone mineral content z-scores, were significantly lower in children with AGS than in healthy controls. However, differences were not associated with steatorrhea or 25-OH vitamin D levels (16). Thus, skeletal fragility in this population may involve some element of osteopenia that is not entirely attributable to the malabsorptive consequences of cholestasis.

One potential mechanism of fracture vulnerability may involve dysregulation of the growth hormone axis (23). Previous work suggests that certain AGS patients suffer from growth hormone insensitivity. In response to recombinant growth hormone administration, these patients exhibited an anticipated elevation in circulating growth hormone, but they failed to develop a corresponding elevation in circulating IGF-1 (23). While this work focused on the effects of growth hormone on height acquisition, other studies documenting a critical role for growth hormone and IGF-1 in pediatric bone mass accretion suggest that disturbances in the growth hormone axis may contribute to fracture vulnerability (24).

Recent animal studies suggest that genetic predisposition should also be considered as a potential mechanism underlying fracture vulnerability in AGS. In the last year, two independent research teams have shown that mice with targeted mutations in Notch pathway components develop significant reductions in trabecular bone mass. Both groups provide strong *in vitro* evidence that trabecular volume loss is related to a Notch-mediated increase in osteoblast-dependent osteoclast activity (14,15). While defects in the vertebral skeleton (i.e., butterfly vertebrae) are a well-recognized consequence of *JAG1* mutation in AGS, genetically determined microstructural abnormalities that might contribute to fracture vulnerability have not been previously considered. In this study, patients with fractures were not more likely to have vertebral anomalies than patients without fractures. We also found no departure from published genetic mutation distributions in the overall Alagille population (25). However, our patient sample size was small, which rendered the study inadequately powered to determine specific genotype-phenotype relationships.

In summary, this study is the first to document fracture distribution and estimate fracture incidence in children with AGS. Our findings suggest that clinicians should maintain a high index of suspicion for atraumatic fractures in this population. Young patients, in particular, may have an increased risk of sustaining fractures in a unique anatomic distribution. Patients in our sample experienced a remarkably high number of femur fractures. Indeed, the calculated incidence rate of femur fractures was more than 50 times that cited in the general pediatric population. However, these calculations reflect only incidence estimations and may be limited by both small sample size and ascertainment bias introduced by our survey method. Larger studies are therefore needed to confirm these high incidence rates and to explore factors that may contribute to fracture vulnerability and yield this unusual distribution. In addition to the nutritional consequences of cholestasis, which may promote skeletal fragility in a variety of chronic liver diseases, the skeletal implications of genetic and hormonal disturbances warrant further exploration.

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Table 1

Study patient characteristics

	Fracture Group	No Fracture Group	Total Patients
N (%)	12 (28.6%)	30 (71.4%)	42 (100%)
Age (yrs) at questionnaire	11.7 + 5.9	10.5 + 7.4	10.9 + 7.0
	(3.9 to 20.6)	(1.4 to 32.7)	(1.4 to 32.7)
Male, n (%)	7 (58.3%)	16 (53.3%)	23 (54.8%)
Medical History of:			
Liver Disease	12 (100%)	29 (96.7%)	41 (97.6%)
Cardiac Disease	11 (91.7%)	26 (86.7%)	37 (88.1%)
Kidney Disease	3 (25.0%)	4 (13.3%)	7 (16.7%)
Vertebral Anomaly	8 (66.7%)	14 (46.7%)	22 (52.4%)
Surgical History of:			
Biliary Diversion	3 (25.0%)	6 (20.0%)	9 (21.4%)
Liver Transplant	3 (25.0%)	5 (16.7%)	8 (19.0%)
BD or LT	6 (50.0%)	10 (33.3%)	16 (38.1%)
Anthropometrics:			
Height z-score	-2.1 + 1.7	-1.5 + 1.7	-1.7 + 1.7
BMI z-score	-0.8 + 1.4	-0.4 + 1.0	-0.5 + 1.1

* No statistically significant differences were found between the Fracture and No Fracture groups with regard to the demographic, historical and anthropometric parameters outlined above.

Table 2

Fracture locations and associated mechanisms of injury

Patient	Gender	Age at Quest	Location	Age at Fracture	Recur	MLC	Mechanism
1	F	13yrs	Femur	3 yrs	N	SLT	Fell while standing on beach
			Femur	3 yrs	N	NT	No mechanism identified (began limping)
			Finger	4 yrs	N		Unknown
2	M	20 yrs	Tibia	3 yrs	N	SLT	Slipped & fell from standing
3	F	3 yrs	Fibula	20 yrs	N	SLT	Wrestling
			Tib/Fib	2 yrs	N	SLT	Stepped on a remote control
4	F	13 yrs	Femur	5 yrs	N	SLT	Fell from standing with preceding pain
			Forearm	7 yrs	N	MT	Fell while rollerskating
5	M	20 yrs	Metacarp	5 yrs	N	MT	Fell on outstretched hand
6	F	15 yrs	Femur	3 yrs	N	SLT	Fell to ground while seated on toilet
			Tib/Fib	3 yrs	N		Unknown
			Femur	4 yrs	N	SLT	Fell from standing
			Femur	4 yrs	N	SLT	Fell from standing
			Tibia	5 yrs	N	MT	Jumped off of swing
			Arm	9 yrs	N	SLT	Fell off of curb
			Tib/Fib	11 yrs	N	SLT	Fell from standing
7	M	21 yrs	Femur	6 yrs	N	SLT	Jump off one foot high platform
8	M	5 yrs	Tibia	3 yrs	N	SLT	Brother stepped on while pt. crawling
			Tibia	4 yrs	N	NT	No known trauma
			Tibia	5 yrs	Y	NT	No known trauma
9	M	11 yrs	Tib/Fib	4 yrs	N	SVT	Boat trailer fell on leg
10	M	9 yrs	Femur	7 yrs	N	SLT	Trip - Fell from standing
			Forearm	8 yrs	N	SLT	Trip - Fell from standing
11	F	5 yrs	Foot	4 yrs	N	SLT	2 year old brother stepped on foot
12	F	5 yrs	Tib/Fib	1 yr	N	SLT	Fell from standing
			Humerus	9 mos	N	NT	Brother picked patient up

Patient	Gender	Age at Quest	Location	Age at Fracture	Recur	MLC	Mechanism
			F arm	1 yr	N	NT	Someone picked patient up

Key: Age at Quest = Age at time of questionnaire; Recur = Fracture represents a recurrence with Y = yes and N = no; MLC = Estimated Modified Landin Category (17) with NT = No Trauma, SLT = Slight Trauma, MT = Moderate Trauma, and SVT = Severe Trauma