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Renal Anomalies in Alagille Syndrome: A Disease-Defining Feature

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Alagille syndrome (ALGS) is an autosomal dominant condition, primarily caused by mutations in *JAGGED1*. ALGS is defined by cholestatic liver disease, cardiac disease and involvement of the face, skeleton, and eyes with variable expression of these features. Renal involvement has been reported though not formally described. The objective of this study was to systematically characterize the renal involvement in ALGS. We performed a retrospective review of 466 *JAGGED1* mutation-positive ALGS patients. Charts were reviewed for serum biochemistries, renal ultrasounds or other imaging, urinalysis, and clinical reports from pediatric nephrologists. The clinical data were reviewed by two pediatric hepatologists and a pediatric nephrologist. Of 466 charts reviewed we found 187 yielded evaluable renal information. Of these, 73/187 were shown to have renal involvement, representing 39% of the study cohort. Renal dysplasia was the most common anomaly seen. Genotype analysis of the *JAGGED1* mutations in the patients with and without renal involvement did not reveal an association with mutation type. From the study we concluded that renal involvement has a prevalence of 39% in ALGS in our evaluable patients. Renal dysplasia is the most common renal anomaly. This finding correlates with the known role of the Notch pathway in glomerular development. Since renal disease of the type seen in ALGS can impair growth and impact liver transplantation, there is a clear need for a prospective study of renal involvement in ALGS and the development of guidelines for evaluation and management. These data also suggest that renal involvement be considered the sixth defining criterion for ALGS.

Key words: liver disease; renal disease; Alagille syndrome

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INTRODUCTION

Alagille syndrome (ALGS) is an autosomal dominant condition, primarily caused by mutations in *JAGGED1* (*JAG1*), which encodes a ligand in the Notch signaling pathway (NSP) [Li et al., 1997]. The majority of ALGS patients carry a disease-causing mutation in *JAG1* and a small number (2%) have a mutation in another member of the NSP, *NOTCH2* [McDaniell et al., 2006; Warthen et al., 2006]. Traditionally ALGS has been clinically defined by cholestatic liver disease in association with bile duct paucity on liver biopsy, cardiac disease (typically peripheral pulmonary artery stenosis), skeletal involvement (usually butterfly vertebrae), ophthalmologic anomalies (posterior embryotoxon), and characteristic facial features [Alagille et al., 1975]. Although a molecular diagnosis is possible on a commercial and research basis, the diagnosis of ALGS often remains largely based on clinical features due to the time required to

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obtain a genetic result. According to the criteria initially described by Alagille, the diagnosis was based on the presence of bile duct paucity in association with 3 of the 5 main criteria listed above [Alagille et al., 1975]. However, these criteria have some limitations. The association of butterfly vertebrae and cardiac anomalies can be seen in other conditions, namely chromosome 22q deletion [McDonald-McGinn et al., 1999]. In addition, posterior embryotoxon can be seen in 22% of the normal population [Rennie et al., 2005]. Furthermore, a liver biopsy is not always necessary for the management of cholestatic liver disease in ALGS and therefore it would be preferable to avoid the potential risk of a biopsy simply for diagnostic purposes. Thus, there is a need to clarify and update the disease-defining criteria for ALGS.

There are multiple case reports of renal structural and medical disease in ALGS [Chung-Park et al., 1982; Habib et al., 1987; Tolia et al., 1987; Pombo et al., 1995; Devriendt et al., 1996; Harendza et al., 2005; Hirai et al., 2005; Jacquet et al., 2007; Bourdeaut et al., 2008; Shrivastava et al., 2010]. Renal involvement has also been described in prior series of ALGS individuals though it has not been systematically characterized [Alagille et al., 1987; Hoffenberg et al., 1995; Emerick et al., 1999; Quiros-Tejeira et al., 1999]. These earlier studies of ALGS are outlined in Table I. The prevalence of renal anomalies in these reports ranged from 19% to 74%, however, these retrospective series described general clinical features of ALGS and were not focused on evaluating and characterizing renal involvement. It is not clear if a nephrologist was involved in the characterization of the renal involvement and definitions of the renal diagnoses were not provided. In addition a molecular diagnosis was not confirmed in all the described individuals. Molecular advances in *JAG1* sequencing have allowed the identification of milder affected ALGS individuals and of note, mutation-positive individuals with unusual and atypical features [Kamath et al., 2003]. This approach has widened our appreciation of the phenotype associated with *JAG1* mutations. Of note, the original report of ALGS associated with *NOTCH2* mutations suggested a renal phenotype in the first two families described [McDaniell et al., 2006]. However, this has not been substantiated in other individuals and overall *NOTCH2* is only implicated as the disease gene in a minority of ALGS cases. Therefore, *NOTCH2* mutation-positive cases were excluded from the following analysis. The objective of this study was to describe and characterize renal involvement in a large cohort of *JAG1* mutation-positive individuals.

TABLE I. Prevalence of Renal Anomalies in Other Alagille Syndrome Series

Refs.	Renal anomaly (%)	Renal patient frequency
Alagille et al. (1987)	73.9	17/23
Hoffenberg et al. (1995)	19	5/26
Emerick et al. (1999)	40	28/69
Quiros-Tejeira et al. (1999)	50	15/30
Current study	39	73/187

MATERIALS AND METHODS

A retrospective review of the ALGS Database at the Children's Hospital of Philadelphia was performed. This database represents clinical and genetic information about individuals with ALGS recruited from various institutions under an Institutional Review Board-approved protocol of consent. At the time of review there were 466 *JAG1* mutation-positive individuals in the database. Clinical information was obtained from direct examination of patient charts and every attempt was made to obtain additional information relevant to this study by contacting individuals' primary physicians. The clinical data were reviewed by two pediatric hepatologists and a pediatric nephrologist. Charts were reviewed for renal data such as serum biochemistries, renal ultrasounds or other imaging, urinalysis, and clinical reports from pediatric nephrologists. A renal ultrasound and serum biochemistry were considered the minimum data for a chart to be included in the analysis. In general, renal dysplasia is defined by unilateral or bilateral disorganization of renal architecture, with or without the presence of renal cysts, ectopic tissue, and impaired function. For the purposes of this study, renal dysplasia was defined by increased echogenicity on ultrasound, with or without renal cysts and reduced size. Hyperchloremic metabolic acidosis was defined by serum bicarbonate $\leq$18 mEq/L and serum chloride greater than the upper limit of normal. Renal insufficiency was classified according to National Kidney Foundation guidelines [Levey et al., 2003]. For patients $<$18 years of age with documented renal involvement and adequate information, glomerular filtration rate (GFR) was estimated using the Schwartz equation [Schwartz et al., 1976]. For adult patients, GFR was estimated using the modified MDRD equation [Levey et al., 1999]. Any individual with evidence of renal insufficiency or disease following liver transplantation was excluded from the analysis due to the potential nephrotoxicity of immune suppressants.

RESULTS

Of 466 *JAG1* mutation-positive individuals, 329 (70.6%) were probands and 137 (29.4%) were relatives of the probands. All individuals met classic clinical criteria for ALGS except for seven patients, who had subtle or atypical features, but all carried typical *JAG1* mutations.

From the 466 charts reviewed, 187 yielded evaluable renal information. Of these, 73/187 were shown to have a renal anomaly or disease, representing 39% of the study cohort. Of the 73 patients with renal anomalies, 65 were probands and 8 were family members. Eighty-two anomalies were described in these 73 ALGS patients (Table II). Eight individuals fulfilled criteria for renal involvement in two categories of renal disease and 1 ALGS individual met criteria for three categories. The majority of diagnoses were made based on biochemical and imaging data. Four renal biopsies were performed in the cohort. Two biopsies revealed renal lipidosis and 1 demonstrated focal segmental glomerulosclerosis. A fourth patient was included in our study cohort on the basis of renal dysplasia and a biopsy was performed 10 years after liver transplantation, at which time the biopsy confirmed the presence of cyclosporine toxicity and IgA nephropathy.

TABLE II. Distribution of Renal Anomalies in Alagille Syndrome Study Cohort

Categories of renal anomalies	Number of patients w/each renal anomaly
Dysplasia	43 (58.9%)
Generalized	28
Focal	8
With vesicoureteric reflux	5
With renal insufficiency	2
Renal tubular acidosis	7 (9.5%)
Vesicoureteric reflux	6 (8.2%)
With hydronephrosis	1
Obstruction	6 (8.2%)
Uretero-pelvic junction	2
With hydronephrosis	4
Chronic renal failure	4 (5.4%)
End-stage renal disease	3 (4.1%)
Requiring kidney transplant	1
Acute kidney injury	2 (2.7%)
Renal lipidosis	2 (2.7%)
Renal artery stenosis (bilateral)	2 (2.7%)
Focal segmental glomerulosclerosis	2 (2.7%)
Duplex collecting system	2 (2.7%)
Other	3 (4.1%)

The *JAG1* mutations seen in the 187 ALGS individuals with evaluable renal information are shown in Table III. The distribution of mutations was similar to other reported series. In addition, there were no differences in types of mutations between the groups with and without renal anomalies. Thus, there was no evidence of *JAG1* genotype–phenotype correlations.

Renal dysplasia, as identified by increased echogenicity of the kidneys, reflecting increased fibrous tissue, was the most common anomaly seen (Table II). An ultrasound diagnosis of renal dysplasia was made in 59% of the cohort with renal involvement. In the majority of individuals this was a diffuse process, however in a few it was focal and in a minority it was associated with vesico-ureteric reflux or renal insufficiency. Renal tubular acidosis (RTA) was the next common anomaly seen in 9.5% of ALGS individuals with renal involvement. This was defined by documentation of hyperchloremic metabolic acidosis on serum biochemistries in the absence of diarrhea or other gastrointestinal losses.

Vesicoureteric reflux and urinary obstruction were equally prevalent in this ALGS renal cohort at 8.2%. Obstruction to urinary flow occurred in 2/6 individuals at the uretero-pelvic junction and in 4/6 at the vesico-ureteric junction. In 4/6 ALGS individuals there was also evidence of hydronephrosis in association with the obstruction, but in the absence of reflux. A range of other renal conditions was identified in a small number of ALGS patients and are listed in Table II.

Of the 73 patients with a documented renal anomaly or disease, data were available to estimate GFR in 39 at one point in time. GFR was estimated to be <90 ml/min/1.73/m^2 in 11/22 patients (50%) >2 years of age. Chronic kidney disease (CKD) was classified as Stage 2 (GFR 60–89.9 ml/min/1.73/m^2) in 7 patients, Stage 3 (GFR 30–59.9 ml/min/1.73/m^2) in 3 patients, and Stage 5 (GFR <15 ml/min/1.73/m^2) in 1 patient with end-stage renal disease who later underwent renal transplantation. The most common renal diagnoses in this group were CKD and generalized dysplasia, each in 3 patients. Other diagnoses included dysplasia with VUR, RTA with medullary sponge or acute kidney injury, and FSGS, each seen in 1 patient. Due to the developmental changes in renal function during infancy, for patients <2 years of age, we compared estimated GFR to the age-appropriate normal range as reported by Hellerstein [1993]. Of the 17 patients $<$age 2, 4 (24%) had an estimated GFR below the expected range for age. Three of these children had a diagnosis of generalized dysplasia, and 1 had dysplasia with VUR. Two additional ALGS individuals underwent kidney transplant only following liver transplantation and were excluded from the cohort due to the confounding effects of nephrotoxic immune suppressants.

DISCUSSION

This is the largest retrospective cohort study of the kidneys in *JAG1* mutation positive ALGS to date, and demonstrates a 39% prevalence of a renal anomaly or disease. Eighty-two renal anomalies were identified in 73 individuals from an evaluable cohort of 187. The most common renal involvement was renal dysplasia (58.9%), RTA (9.5%), vesico-ureteric reflux (8.2%), and urinary obstruction (8.2%).

Interestingly, abnormal GFR was relatively common in our cohort of patients with known renal involvement. Of 39 patients with sufficient data available to estimate GFR at some point in time, 24% of patients <2 years and 50% of patients >2 years had an estimated GFR below the normal range. This is the first series that focuses on characterization of the renal phenotype associated with *JAG1* mutations.

The NSP is an evolutionarily conserved intercellular signaling mechanism [Gridley, 2003]. *JAG1*, the disease gene in ALGS, is one of the ligands in the NSP. A minority of individuals with ALGS have

TABLE III. Distribution of *JAGGED1* Mutations in Alagille Syndrome Patients With and Without Renal Disease

	JAG1 mutation type and frequency						
Phenotypic categories	Nonsense	Missense	Deletion	Insertion	Insertion/deletion	Splice site alteration	Translocation
Renal anomaly (n = 73)	16 (21.9%)	10 (13.7%)	23 (31.5%)	11 (15.1%)	2 (2.7%)	11 (15.1%)	0
No renal anomaly (n = 114)	28 (24.6%)	15 (13.2%)	33 (28.9%)	17 (14.9%)	0	20 (17.5%)	1 (0.9%)

mutations in *NOTCH2*, which is one of the receptors in the pathway [McDaniell et al., 2006]. There is evidence that the NSP is fundamental for kidney development [McCright, 2003; Reidy and Rosenblum, 2009]. Specifically mice heterozygous for both the Notch2 and Jag1 mutations have hypoplastic kidneys and abnormal glomeruli [McCright et al., 2001]. Recent data also suggest that Notch signaling is important for nephron segmentation and differentiation of the proximal nephron structures [Cheng et al., 2007; Surendran et al., 2010]. Therefore, it is not a surprise that structural renal disease is such a prevalent finding in ALGS. Interestingly, recent data also suggest that the NSP may have a role in renal regeneration following acute renal failure and thus may also play a role in the response to kidney injury [Gupta et al., 2010]. The lack of *JAG1* genotype–phenotype correlation (Table III) is consistent with other key clinical features of ALGS (hepatic and cardiac disease). The variation in renal involvement suggests a role for genetic modifiers of which there are many potential candidates in the NSP.

The primary limitation of this study is the retrospective nature. Although each *JAG1* positive subject had a minimum of serum biochemistry and a renal ultrasound for inclusion in the study, these individuals did not undergo a systematic renal evaluation. Since some of the records in the database are historic, there may have been missing recent data. It is likely that the prevalence estimated in this study is actually an underestimate, and a targeted and systematic evaluation of renal involvement in an ALGS cohort may demonstrate a higher prevalence. Another potential limitation is that evaluable renal data was only available on 187 individuals from a total cohort of 466. A screen of other phenotypic features of ALGS did not reveal significant differences between the study and total cohorts. Therefore, we surmise that the study cohort is representative of the whole cohort, suggesting that the results are generalizable to all ALGS individuals. The preliminary data shown in this retrospective study clearly demonstrate the need for a prospective study of renal anomalies and disease in ALGS. It would be valuable to identify a prevalence of structural renal disease but also to evaluate medical disease on an ongoing basis in a systematic fashion to determine if there is the new onset of medical renal disease with age.

Despite these limitations these data still provide important information. Firstly from a diagnostic standpoint, a prevalence of 39% provides a rationale for considering renal involvement a disease-defining criterion in ALGS. Although hepatic disease is generally reported as occurring with a high prevalence, typically >90% in large series, these data were drawn from studies of patients presenting with liver disease [Emerick et al., 1999]. When mutation-positive *JAG1* relatives (i.e., not probands) are studied it is clear that the prevalence of disease associated with a *JAG1* mutation is actually lower, only 31% for cholestatic liver disease [Kamath et al., 2003]. Therefore, a prevalence of 39% of renal involvement in association with *JAG1* mutations is comparable to the other disease defining criteria.

These data are also of importance to the clinician managing ALGS patients. Poor growth is a common and multifactorial problem in ALGS. Some of these factors are difficult to manage such as profound cholestasis and structural heart disease. Certain of the renal problems described in this cohort, such as RTA may also contribute to poor growth. RTA is easily treatable and thus it is important to actively seek out this diagnosis in poorly growing ALGS children. The high rate of GFR abnormalities in our patient cohort, especially in the patients over 2 years of age, highlights the importance of ongoing care by a pediatric nephrologist in ALGS patients with documented renal involvement. Furthermore, approximately 15–20% of ALGS individuals undergo liver transplantation [Kamath et al., 2010]. It is apparent that ALGS is a risk factor for chronic renal insufficiency in pediatric liver recipients implying that these children have an increased susceptibility to the nephrotoxic effects of immune suppressants [Harambat et al., 2008]. The data from the current study support increased vigilance for nephrotoxicity in ALGS patients and the usefulness of renal-sparing immune suppressant protocols in this setting.

CONCLUSION

Renal involvement in *JAG1* mutation-positive ALGS is common and has a prevalence of at least 39% in our evaluable patients. The most common renal anomalies are renal dysplasia, RTA, vesicoureteric reflux, and urinary obstruction. A targeted renal evaluation consisting of serum biochemistry, renal ultrasound, and urinalysis should be considered standard of care in ALGS. We also suggest that typical renal involvement is a sixth defining criteria for ALGS.

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