Beyond the Liver: Alagille Syndrome's Silent Impact on Chronic Kidney Disease

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Abstract

Alagille syndrome (AS) is a multisystemic autosomal dominant disorder caused by mutations in *JAG1* or *NOTCH2,* with variable manifestations affecting the liver, heart, skeleton, eyes, kidneys, and other organs. While hepatic and cardiac features are classically emphasized, renal involvement is increasingly recognized but often underdiagnosed, particularly in adults with chronic kidney disease (CKD) of unknown etiology. We report the case of a 33-year-old Caucasian man who presented with stage 5 CKD of unknown origin and was on maintenance hemodialysis. His medical history included a childhood liver biopsy revealing bile duct paucity and abnormal liver enzymes. However, no definitive diagnosis had been previously established. The diagnosis of AS was only considered after his daughter was diagnosed with tetralogy of Fallot, prompting genetic screening. A heterozygous pathogenic variant in *JAG1* c.2230C>T p.(Arg744*) confirmed the diagnosis of AS. This case highlights the diagnostic challenges of AS in adult patients presenting with renal insufficiency as the predominant feature. Despite a syndromic phenotype and early liver abnormalities, the absence of a unifying diagnosis delayed recognition. Renal involvement in AS is diverse and may include renal dysplasia, tubular dysfunction, and vascular anomalies such as renal artery stenosis. A growing body of evidence supports the utility of genetic testing in unexplained CKD, particularly in syndromic young adults. In this case, a definitive diagnosis enabled genetic counseling and avoided further unnecessary investigations.

Keywords: Alagille Syndrome; Jagged-1 Protein; Kidney Failure, Chronic; Receptor, Notch2; Renal Replacement Therapy

INTRODUCTION

Alagille syndrome (AS) is a rare autosomal dominant disorder characterized by multisystemic involvement, affecting mainly the liver, heart, skeleton, eyes, and kidneys.[1-4] It is primarily caused by mutations in two genes involved in the Notch signaling pathway: *JAG1,* which encodes the ligand Jagged1 and accounts for over 90% of cases, and, less frequently, *NOTCH2,* which encodes the receptor *Notch 2*.[5,6] This signaling pathway plays a critical role in cell fate determination through direct ligand-receptor interactions. Mutations in *JAG1* and *NOTCH2* disrupt normal signaling and lead to the phenotypic features of AS.[7]

Early estimates of AS prevalence of 1 in 70 000 live births were biased due to the selection of patients primarily presenting with childhood cholestasis.[8] With improved molecular diagnostics and recognition of interindividual and interfamilial phenotypical variability,[9] a broader clinical spectrum and a wider age range at presentation have been documented, indicating that the condition is likely underdiagnosed.[10-12]

Historically, AS was recognized primarily through its hepatic manifestations, notably chronic cholestasis due to intrahepatic bile duct paucity, typically presenting within the first three months of life. However, hepatic involvement varies considerably: while some patients develop progressive liver disease requiring transplantation in childhood, others remain asymptomatic or present with only mild biochemical abnormalities that may go undetected.[11,13]

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Beyond the liver, cardiovascular anomalies are among the most commonly recognized features, typically involving right-sided lesions such as peripheral pulmonary artery stenosis or hypoplasia. More complex abnormalities, including tetralogy of Fallot, may also occur. Skeletal involvement, particularly butterfly vertebrae, and ophthalmologic anomalies such as posterior embryotoxon, are frequently observed. Distinctive craniofacial features, including a broad forehead, deep-set eyes with ocular hypertelorism, prominent ears, a triangular face, and a straight nose, are also characteristic.[14,15]
In addition to these classical features, increasing attention has been given to genitourinary manifestations, now recognized in up to 40% of patients. These may include renal artery stenosis, renal dysplasia, renal tubular acidosis, ureteropelvic or vesicoureteral urinary obstruction, and vesicoureteral reflux. Such abnormalities can contribute to the development and progression of CKD at various stages throughout life.[12,16-18]
Given the highly variable expressivity of AS, with atypical presentations and delayed diagnosis, renal manifestations may be under-recognized in adulthood. We report a case of a 33-year-old man on hemodialysis due to stage 5 CKD of unknown etiology, later diagnosed with AS following genetic evaluation.

CASE REPORT

A 33-year-old Caucasian man was referred to the emergency department due to high blood pressure (200/100 mmHg), asthenia and renal failure, with a serum creatinine level of 6.9 mg/dL on blood analysis performed 22 days earlier.
The patient's medical history was notable for elevated liver enzymes from the age of 13, resulting in two liver biopsies at the age of 15 and 21. The first biopsy was unremarkable, whereas the second demonstrated bile duct paucity in the portal tracts, assessed with immunohistochemistry. Despite these findings, no definitive diagnosis was made, and the patient was lost to follow-up. His medical history also included a knee bone tumor diagnosed at the age of 18, treated surgically with bone grafting, and considered in remission. The histopathological diagnosis remains unknown, as it is not recalled by the patient and prior medical records are unavailable. Additional history is significant for multiple traumatic bone fractures, recurrent gout arthritis, and tobacco use. There was no family history of CKD. His 4-year-old daughter had undergone corrective surgery for tetralogy of Fallot.
During the emergency department evaluation, the patient reported a recent diagnosis of arterial hypertension, established three months prior, for which he had been started on bisoprolol. His attending physician requested laboratory tests, which revealed anemia (hemoglobin 9.4 g/dL), elevated serum creatinine (6.9 mg/dL), and hyperuricemia (9.6 mg/dL). Electrocardiography showed sinus rhythm without criteria for left ventricular hypertrophy. Abdominal computed tomography demonstrated normal liver size but with globular morphology consistent with chronic liver disease, dilated splenic and portal veins, and kidneys at the lower limit of normal size (right: 9 cm; left: 10 cm) with lobulated contours suggestive of CKD. At the emergency department, the patient appeared pale and had high blood pressure (177/77 mmHg), with a heart rate of 82 bpm. Cardiac and pulmonary auscultation was normal, and there was no peripheral edema.
Initial laboratory workup (Table 1) revealed severe azotemia, anemia and elevated parathyroid hormone level of 954.8 pg/mL. The patient also presented with elevated liver enzymes, including AST 98 U/L, ALT 142 U/L, alkaline phosphatase 192 U/L, and gamma-glutamyl transferase 421 U/L. Total bilirubin was within normal limits. Arterial blood gas analysis showed hyperchloremic metabolic acidosis (pH 7.25, pO2 113 mmHg, pCO2 23 mmHg, SO2 98%, bicarbonate 10 mmol/L, sodium 139 mEq/L, potassium 5.6 mEq/L, chloride 117 mEq/L, anion gap of 12). Urinalysis revealed density 1.010, pH 5.5, proteinuria 1.5 g/L and hematuria 25/uL (normal range <15). No further quantitative proteinuria assessment was available.
Renal ultrasound showed bilaterally reduced kidney size (7 cm bipolar length), increased parenchymal echogenicity, and reduced corticomedullary differentiation (Fig. 1).

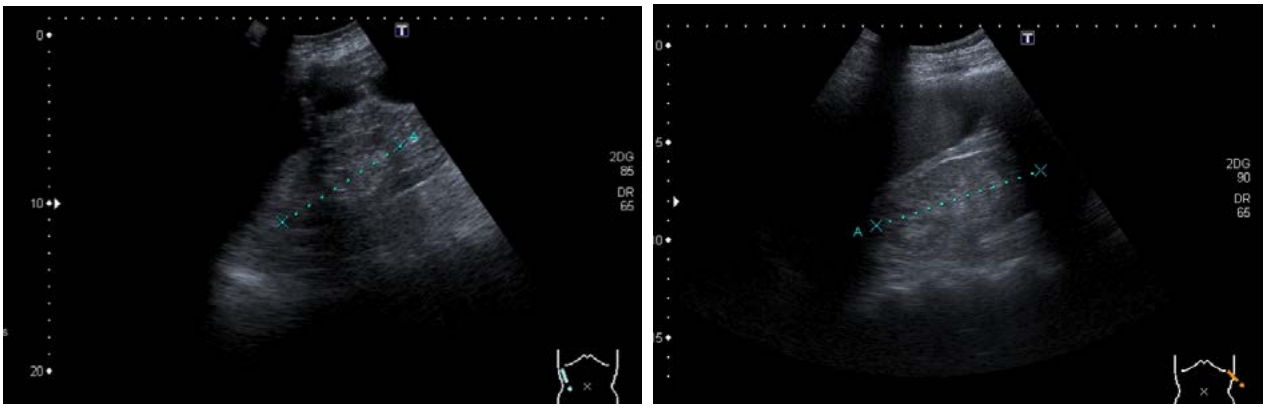

Figure 1. Kidney ultrasound showing bilaterally reduced kidney size, increased parenchymal echogenicity, and loss of corticomedullary differentiation.

The patient was admitted for further evaluation. Viral serologies for hepatitis B (HBV) and C (HCV), as well as HBV DNA and HCV RNA, were negative. Autoimmune and monoclonal gammopathy panels were unremarkable. Ceruloplasmin and alpha-1-antitrypsin levels were within normal limits. Upper gastrointestinal endoscopy was normal, with the absence of esophageal varices. Abdominal ultrasound with portal vein Doppler ruled out portal hypertension. Based on these findings, a renal biopsy was deferred. The patient was diagnosed with stage 5 CKD of unknown etiology, initiated maintenance hemodialysis, and subsequently discharged.

One year later, a thoracoabdominal and pelvic computed tomography (CT) angiography excluded vasculopathy of the aorta, renal and iliac arteries. Retrospective review of imaging revealed the presence of a *butterfly* vertebra at the thoracic level, which had not been described in the original radiology report (Fig. 2). Family history became relevant when his daughter with tetralogy of Fallot performed a genetic test, which identified a pathogenic variant in the *JAG1* gene. This gene was analyzed for sequence variants in the coding regions and flanking consensus splice sites by polymerase chain reaction (PCR) followed by direct bidirectional sequencing.[19] Screening for large genomic rearrangements was also performed using multiplex ligation-dependent probe amplification (MLPA).[20] Genetic testing revealed a heterozygous pathogenic variant c.2230C>T p.(Arg744*), in the *JAG1* gene. Cascade genetic testing confirmed the presence of the familial variant in the father, which, in combination with bile duct paucity, a vertebral anomaly, and kidney disease, established a diagnosis of AS.

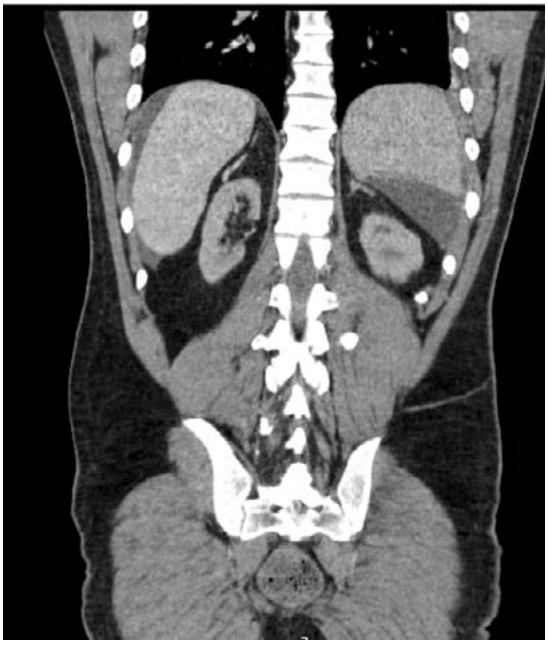

Figure 2. Thoracic computed tomography reveals a butterfly vertebra at the thoracic level (arrow), representing a congenital vertebral fusion anomaly and a characteristic skeletal feature of Alagille syndrome.

DISCUSSION

We present the case of a 33-year-old man with stage 5 CKD undergoing maintenance hemodialysis, in whom the etiology of renal disease was initially unknown. A late diagnosis of AS was established based on the presence of syndromic CKD, histological demonstration of bile duct paucity, mild cholestatic liver abnormalities, a butterfly vertebra, and a family history notable for tetralogy of Fallot in his daughter, whose genetic testing revealed a heterozygous pathogenic variant c.2230C>T p.(Arg744*), in the *JAG1* gene.

In younger patients with kidney disease, the diagnostic workup often focuses on excluding glomerular diseases using serological biomarkers and imaging studies, while kidney biopsy is frequently avoided in advanced disease because of an increased hemorrhagic risk and limited diagnostic yield.[21,22] Consequently, a substantial proportion of patients requiring kidney replacement therapy (KRT) have an unknown disease etiology or are frequently misdiagnosed as hypertensive CKD.[23] In our patient, delayed diagnosis of AS likely resulted from under-recognition of multisystemic manifestations over decades, culminating in stage 5 CKD. Notably, the presence of liver abnormalities since childhood suggests that earlier recognition may have been possible, highlighting challenges in care continuity and diagnostic integration. This highlights the value of a multidisciplinary approach and structured transition programs from pediatric to adult care, particularly in young patients with unexplained CKD, as it can uncover syndromic causes that may be otherwise overlooked due to incomplete phenotype or absent family history.[24-26]

Although adult presentations of AS have been previously described, genotype–phenotype correlations remain limited, particularly regarding the severity and progression of renal involvement. In this context, the present case contributes to the growing recognition of kidney-dominant presentations associated with *JAG1* variants.

Although renal involvement is increasingly recognized in AS, detailed phenotypic characterization in adult patients remains limited. In the present case, the renal phenotype could not be fully characterized due to the advanced stage of CKD at presentation and the retrospective nature of data collection. Available findings, including bilaterally small echogenic kidneys, mild proteinuria, and absence of a defined glomerular syndrome, are more suggestive of a chronic parenchymal process than of a primary glomerular disease.

Renal involvement was not originally recognized as a core feature of AS in the initial descriptions by Daniel Alagille.[3] However, later studies have identified genitourinary abnormalities in up to 40% of patients,[17] occasionally in the absence of hepatic manifestations.[27] This has led to the proposal for renal involvement to be incorporated into the diagnostic criteria, alongside the classical hepatic, cardiovascular, skeletal, ocular, and facial features.[17]

The spectrum of renal manifestations in AS is likely multifactorial. A significant mechanism is vasculopathy, which extends beyond pulmonary involvement to affect the aorta and its branches, including the renal artery.[16] Renal artery stenosis has been reported, and vasculopathy has been linked to increased mortality in AS, particularly when it affects cerebral vessels and may impact transplant risk and outcomes.[2,16]

Beyond vasculopathy, structural kidney abnormalities are also common, including renal dysplasia, tubular acidosis, vesicoureteral reflux, and renal cysts.[17] In our case, arterial blood gas analysis revealed a non-anion gap hyperchloremic metabolic acidosis, which may suggest a tubular component, such as renal tubular acidosis, a recognized feature of AS. However, further evaluation, including urine pH and urine anion gap, was not available, precluding a definitive diagnosis.

Limited histopathological information exists, primarily from pediatric populations, with a prominent finding of glomerular mesangiolipidosis.[28] Currently, no population-based studies have evaluated the prevalence of kidney failure in AS.

Genetically, AS is primarily caused by mutations in *JAG1*, though *NOTCH2* mutations are found in a small subset of patients.[6,29] Both genes encode transmembrane proteins (Jagged1 and Notch2, respectively), that interact within the evolutionarily conserved Notch signaling pathway. This pathway plays a critical role in the development of the liver, kidney, vasculature, and other organs. In renal development, Notch signaling contributes to epithelial specification, nephron patterning, and vascular formation.[9, 30-32]

In our case, genetic testing revealed a heterozygous pathogenic variant c.2230C>T p.(Arg744*), in the *JAG1* gene. This variant consists of a cytosine-to-thymine substitution at nucleotide position 2230, resulting in the replacement of an arginine residue with a premature stop codon at position 744. This and other truncating variants in *JAG1* have been consistently reported in patients with AS, supporting haploinsufficiency as the underlying disease mechanism.[33] Despite being previously classified as pathogenic, current evidence does not support a genotype-renal phenotype correlation between *JAG1* c.2230C>T p.(Arg744*) variant and severe adult-onset renal disease. Negative family history does not exclude AS, as 50%-70% of *JAG1* mutations arise *de novo*.[34,35]

Unlike *JAG1*, most *NOTCH2* pathogenic mutations in AS are missense variants, suggesting the gene may be intolerant to loss-of-function mutations.[17] Initially, *NOTCH2* mutations were hypothesized to be associated with a higher frequency of renal involvement, although subsequent data have not consistently supported this observation.[6,17] Interestingly, *NOTCH2* is also implicated in Hajdu-Cheeney syndrome, another disorder with renal manifestations, however, in this context, mutations occur in the final exon and result in gain-of-function rather than loss-of-function.[12]

The observed phenotypic variability among individuals with the same mutation suggests that modifier genes or environmental factors may influence disease severity. While their role in kidney disease remains unclear, some insights have emerged regarding hepatic manifestations.[36]

Regarding bone tumors, and given the lack of histological data and outcome, any association remains speculative. Recurrent fractures may reflect underlying bone fragility, as skeletal involvement in AS is typically structural (e.g., vertebral anomalies). Hyperuricemia and gout are more plausibly secondary to CKD.

In addition to renal involvement, AS is associated with an increased risk of systemic vascular abnormalities, including intracranial aneurysms. Although neurovascular screening was not performed in this patient, this represents an important consideration in the long-term management of individuals with AS.

In conclusion, this case underscores the importance of recognizing AS as a potential cause of CKD, even in the absence of prominent hepatic involvement or a family history of renal disease. The variable phenotypic expression of AS may delay diagnosis, particularly in adults. While current treatments are limited to supportive care, establishing a genetic diagnosis has several advantages: 1) avoidance of unnecessary and invasive diagnostic procedures; 2) informed transplant planning, with no intrinsic risk of recurrence of the primary developmental nephropathy in the renal allograft; 3) genetic counseling for at-risk families. Timely genetic evaluation should be considered in cases of CKD of unknown etiology, particularly when extrarenal features suggest a syndromic disorder, to avoid delays in diagnosis.

Table 1. Patient blood tests in hospital admission

Laboratory parameter (units)	Result (normal range)
Hemoglobin (g/dL)	8.7 (13.0 – 18.0)
White blood cell count (x10^9/L)	7.15 (4.0 – 11.0)
Platelet count (x10^9/L)	150 (150 – 400)
Serum creatinine (mg/dL)	7.1 (0.8 – 1.3)
Serum urea (mg/dL)	350 (10 – 50)
Albumin (g/L)	43.7 (35 – 41)
Sodium (mEq/L)	138 (135 – 147)
Potassium (mEq/L)	4.6 (3.5 – 5.1)
Chloride (mEq/L)	111 (101 – 109)
Total calcium (mEq/L)	4.5 (4.05 – 5.2)
Phosphorus (mg/dL)	6.0 (2.7 – 4.5)
Aspartate aminotransferase (U/L)	98 (10 – 37)
Alanine aminotransferase (U/L)	142 (10 – 37)
γ-glutamyltransferase (U/L)	421 (10 – 49)
Alkaline phosphatase (U/L)	192 (30 – 120)
Total bilirubin (mg/dL)	0.31 (<1.20)
Parathyroid hormone (pg/mL)	954.8 (14 – 65)

Table 2. Red flags for Alagille syndrome in adult CKD

Domain	Clinical features ("red flag")	Relevance for AS diagnosis
Facial phenotype	Typical facies (broad forehead, deep-set eyes, hypertelorism, straight nose with bulbous tip, pointed chin)	Suggests syndromic etiology; often subtle and overlooked in adults
Hepatic involvement	Childhood cholestasis, elevated liver enzymes, or bile duct paucity on biopsy	May be mild or forgotten; key historical clue even without current liver disease
Cardiac anomalies	Congenital heart disease (e.g., peripheral pulmonary stenosis, tetralogy of Fallot) in patient or first-degree relatives	Strongly supports diagnosis; may be the trigger for genetic testing
Skeletal abnormalities	Butterfly vertebrae or other vertebral anomalies	Frequently incidental findings; should raise suspicion when combined with CKD
Renal presentation	CKD of unknown etiology, especially in young adults	Common but under-recognized manifestation of AS
Tubular dysfunction	Hyperchloremic metabolic acidosis disproportionate to CKD stage, suspected renal tubular acidosis	Suggests tubular involvement, a known feature of AS
Urinary findings	Mild proteinuria, hematuria, or nonspecific urinary abnormalities	Often non-glomerular pattern; may not fit classic nephropathies
Vascular involvement	Renal artery stenosis or systemic vasculopathy	May contribute to hypertension and CKD progression
Family history	Negative or positive; presence of congenital anomalies in relatives	Negative history does not exclude AS (frequent *de novo* mutations)

Ethical Disclosures

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All authors contributed to the conception and design, data acquisition, analysis and interpretation of data, article drafting, and critical revision.

All authors approved the final version of the manuscript for publication and assume responsibility for all aspects of the work, ensuring the accuracy and integrity of the data presented.

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