

Exceptional Case

Adult-onset renal failure in a family with Alagille syndrome with proteinuria and a novel *JAG1* mutation

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Abstract

Alagille syndrome (AGS) is an autosomal-dominant multi-organ disorder involving the liver, heart, eyes, face and skeleton. In addition, various renal abnormalities have also been reported in several cases. We describe a patient with a novel frameshift mutation in exon 12 of the *JAG1* gene who presented with chronic renal failure. In this family, five members of three generations had clinical features implicated in AGS. Three members had adult-onset renal dysfunction with proteinuria, and two of them required haemodialysis therapy. AGS should be considered in the differential diagnosis of proteinuric renal disease, even in adult patients.

Keywords: Alagille syndrome; notch signalling pathway; proteinuria

Background

Alagille syndrome (AGS; OMIM 118450) is an autosomal-dominant multi-organ disorder characterized by clinical features that include chronic cholestasis, cardiac abnormalities, butterfly vertebrae, posterior embryotoxon of the eye and a characteristic face. Forty-five to seventy-five percent of patients are diagnosed with cholestatic jaundice due to bile duct paucity during the first 3 months of life [1]. Renal abnormalities have been reported less frequently. AGS is caused by mutations in one of two genes: the *JAG1* gene, which encodes the Jagged1 ligand, and the *NOTCH2* gene, which encodes the Notch2 receptor. They play an important role in the Notch intercellular signalling pathway during embryonic development. Notch pathway activation is required for the progression of renal vesicles to comma- and S-shaped bodies and for determining the proximal tubule and podocyte fates [2].

We describe a Japanese patient with AGS with a novel *JAG1* mutation. There was a relevant family history involving five members across three generations with various phenotypes and levels of disease severity.

Case report

A 47-year-old man was admitted to our hospital for treatment of end-stage renal disease (ESRD). He was born at term with a weight of 2550 g. He was diagnosed

with pulmonary artery stenosis (PS) at the age of 14 years when he had an operation for atrial septal defect (ASD). He had occasionally presented with proteinuria and hypertension since high school. He underwent a liver biopsy at the age of 34 years due to a slightly elevated liver enzyme level. There was no bile duct paucity. He was later diagnosed with an alcoholic liver injury. At this time, renal dysfunction with serum creatinine level of 114.9 $\mu\text{mol/L}$ was noted for the first time. Subsequently, this patient stopped attending the hospital. Two months before admission, he came to our hospital with general malaise and leg oedema, and was diagnosed with chronic renal failure of unknown origin. After admission, we started him on haemodialysis. Physical examination disclosed a characteristic triangular face, a straight nose and a pointed chin (Figure 1). A pulmonary ejection systolic murmur was heard. Additional investigations showed creatinine clearance of 0.117 mL/s. The 24-h protein excretion level was 1 g without haematuria. Although serological markers for hepatitis virus were negative, elevated levels of liver enzymes (AST, 39 U/L; ALT, 38 U/L; γGTP , 672 U/L and ALP, 1886 U/L) were found. A computed tomography (CT) scan showed hypoplastic and malrotated kidneys (Figure 2) and a vascular abnormality, namely, persistent left superior vena cava. A cervical X-ray showed butterfly vertebrae (Figure 3). Molecular genetic testing of the patient revealed deletion of a cytosine in exon 12 of the *JAG1* gene (c. 1544delC, p. Thr515MetfsX49), which led to a shift in the reading frame starting at amino acid 515 and a subsequent early stop codon at position 564 (Figure 4).



Fig. 1. Characteristic face of the AGS case: note the triangular shape, straight nose and pointed chin.

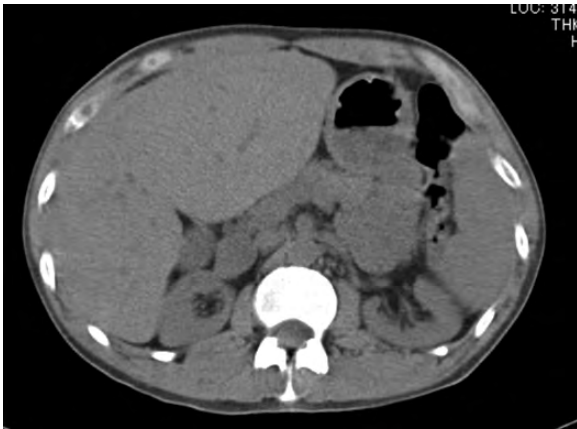


Fig. 2. CT scan showing a hypoplastic right kidney and a malrotated left kidney.

There was a relevant family history (Table 1). His father had proteinuria from the age of 30 years. At the age of 45 years, he was referred to our hospital because of severe hypertension and leg oedema, and was diagnosed with chronic renal failure. Six months later, he commenced haemodialysis. At the age of 51 years, he died suddenly after dialysis. Autopsy revealed liver cirrhosis without bile duct paucity, ASD, PS and anomalous origin of renal arteries with pericapsular fibrosis of glomeruli, severe arteriosclerosis and advanced interstitial fibrosis (Figure 5). The younger brother of the patient was found to have proteinuria for the first time at the age of 36 years. Renal dysfunction progressed over several years.

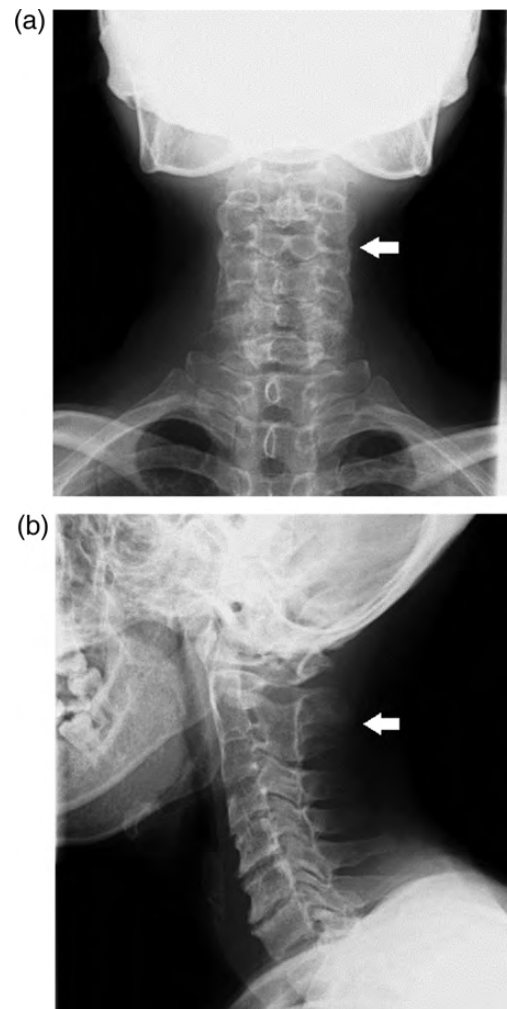


Fig. 3. Cervical X-ray showing butterfly vertebrae (a) and synostosis of vertebral arches (b) (arrows).

Discussion

AGS (OMIM 118450) is an autosomal-dominant disorder that involves abnormalities in multiple organ systems. The phenotypic findings are highly variable in severity in each patient. The diagnosis of AGS has been based on the finding of bile duct paucity associated with three to five major clinical features as follows: chronic cholestasis (75%), cardiac abnormalities (85%), butterfly vertebrae (87%), posterior embryotoxon of the eye (80%) and a characteristic face (95%) [1]. Renal abnormalities have been reported less frequently (44%) [3]. Previous case reports have described renal structural abnormalities such as renal agenesis or hypoplasia, renal cysts, renal artery stenosis and functional abnormalities such as renal tubular acidosis, proteinuria and recurrent urinary tract infection [4–7]. Pathological features have been reported, such as mesangioliipidosis, glomerulosclerosis and interstitial fibrosis [8, 9]. These renal abnormalities have a lot in common with those in congenital anomalies of the kidney and urinary tract (CAKUT).

The *JAG1* gene, which encodes the Jagged1 ligand, and the *NOTCH2* gene, which encodes the Notch2 receptor, have been implicated in AGS. They play an important

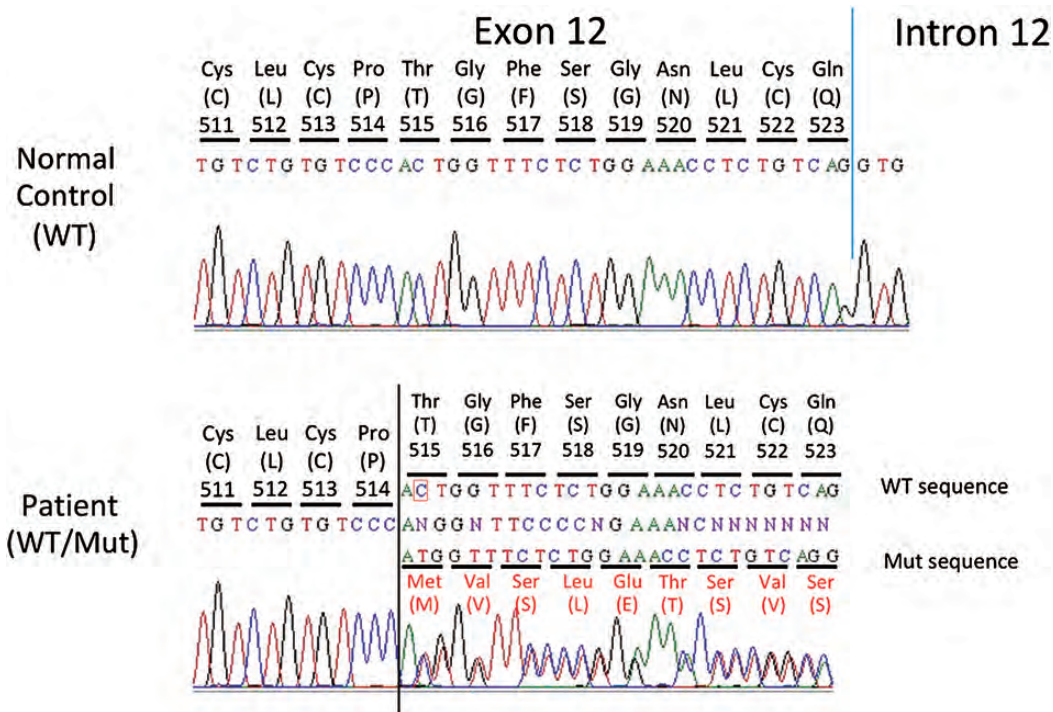


Fig. 4. In the mutation allele, one base deletion (1544delC) causes amino acid substitution of threonine to methionine at codon 515, and the following frameshift creates an aberrant amino acid sequence, with a stop codon at the 49th codon from the substitution (Thr515Met).

Table 1. Clinical features of our patient's family^a

	Patient	Father	Brother	Son	Nephew
Age (years)	47	51 (deceased)	45	4	12
Serum creatinine (μmol/L)	ESRD (HD)	ESRD (HD)	221	30.9	39.8
Proteinuria (g/day)	1.0	2.0	1.0–2.0	(–)	(–)
Liver					
Elevated enzymes	(+)	(+)	(+)	(+)	(+)
Bile duct paucity	(–)	(–)	NA	NA	(–)
Others	Alcoholic injury	Hepatitis B virus infection			Biliary atresia liver transplantation
Heart/vessels	ASD, PS PLSVC	ASD, PS Renal artery anomaly	ASD, PS	PS	PS
Face	(+)	NA	(–)	NA	NA
Skeleton	(+)	(–)	(+)	NA	NA
Eye	(–)	(–)	NA	NA	NA

^aESRD, end-stage renal disease; HD, haemodialysis; ASD, atrial septal defect; PS, pulmonary artery stenosis; PLSVC, persistent left superior vena cava; NA, not available.

role in the Notch intercellular signalling pathway during embryonic development. The Notch signalling pathway is an evolutionarily conserved cell–cell communication mechanism that influences cellular proliferation and differentiation. Notch pathway activation is also required for the progression of renal vesicles to comma- and S-shaped bodies and for determining the proximal tubule

and podocyte fates. The Jagged1 ligand is expressed on the cell surface and is composed of some extracellular domains, a transmembrane domain and a small intracellular region. In our patient, we found a novel frameshift mutation in exon 12 of the *JAG1* gene. It introduced an early stop codon, which led to truncation of the Jagged1 protein. As a result, haploinsufficiency of the Jagged1 ligand was induced. In AGS, total gene deletions (6%), protein-truncating mutations (insertions, deletions and nonsense mutations) (82%) and missense mutations (12%) have been found in the *JAG1* gene. These mutations are distributed in the part of the gene encoding the extracellular and transmembrane domains of the protein [10]. Because most mutations induce a loss of Jagged1 protein function, there is no correlation between the clinical manifestation of AGS and specific *JAG1* mutation types or the mutation site in the gene [11]. In AGS, mutations in *JAG1* were identified in 94% of individuals. Otherwise, mutations in *NOTCH2* were found in <1%, but individuals harbouring these mutations had a similar prevalence of renal abnormalities to *JAG1* patients [12].

We diagnosed our patient with AGS by the presence of cardiac abnormalities, butterfly vertebrae, a characteristic face and a *JAG1* mutation. We checked the specimen of a liver biopsy, but could not identify bile duct paucity. In this Japanese family, although we only performed molecular genetic testing in the patient, five members also had clinical features implicated in AGS. In particular, PS and mild-to-severe liver dysfunction were found in all members. However, we could not find bile duct paucity in three family members. On the other hand, three members had adult-onset renal dysfunction, and two of these required haemodialysis therapy. These family members showed similar patterns of proteinuria of 1–2 g/day, and their renal dysfunction progressed gradually

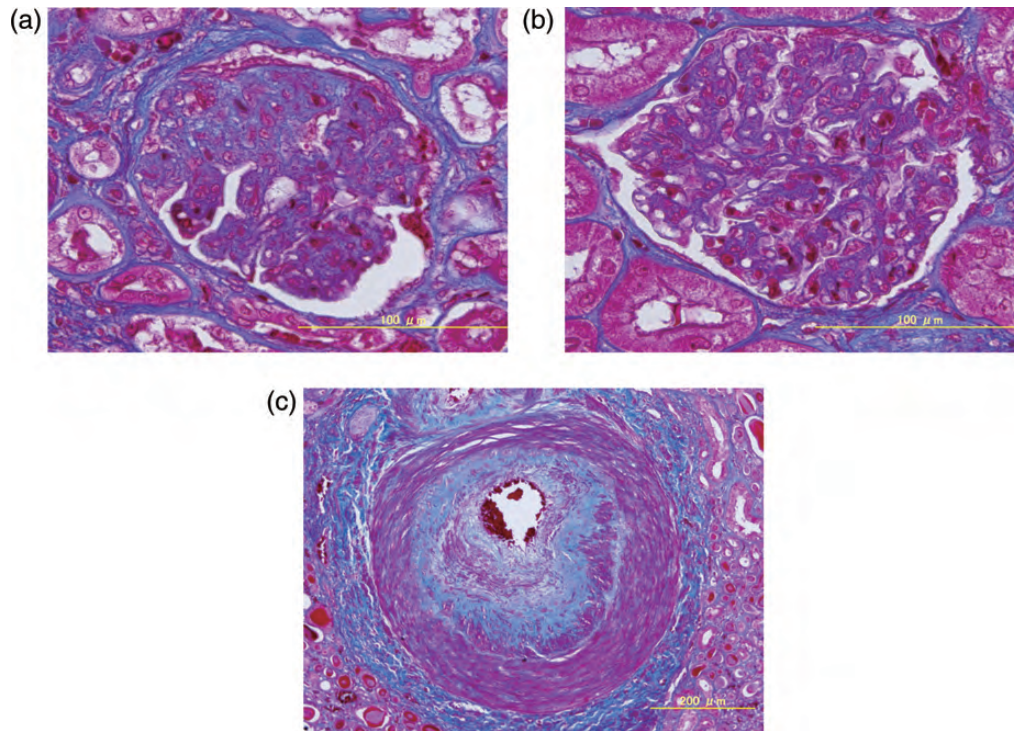


Fig. 5. Father's renal specimen at autopsy. (a) Pericapsular fibrosis and segmental sclerosis of glomeruli were found (Azan $\times 400$). (b) Some residual glomeruli showed glomerulomegaly (Azan $\times 400$). (c) Severe fibrous intimal thickening of arteries was found (Azan $\times 100$).

over several years. In our patient we found hypoplastic and malrotated kidneys, such as found in CAKUT. It is well known that some hereditary multi-organ disorder syndromes are complicated with CAKUT. In these diseases, congenital deficiency in nephron mass resulting from the intrinsic abnormal development of the kidney leads to compensatory glomerular hypertrophy or hyperfiltration. As a result, proteinuria and hypertension cause deterioration of renal function, even in the absence of severe structural anomalies of the kidney and urinary tract [13]. We speculated that proteinuria and hypertension that developed by the same mechanism cause end-stage renal failure in this family. A renal specimen from the father's autopsy suggests that glomerular hypertension and nephrosclerosis were the main factors behind his renal failure.

AGS exhibits high expressivity for each of the affected systems, ranging from no apparent clinical involvement to severe disease leading to transplantation or death. Renal disease caused by AGS is probably underdiagnosed in adult patients. Typical clinical and biological manifestations of renal pathology in AGS include proteinuria, renal insufficiency, acidosis and secondary hypertension due to renal artery stenosis. AGS should be considered in the differential diagnosis of these renal diseases with other clinical features or family history. It has been proposed that aggressive treatment of hypertension and proteinuria with the use of ACE inhibitors or angiotensin II receptor blockers slows down the rate of deterioration of renal function in adults with CAKUT [14]. Similarly, we may prevent end-stage renal failure in AGS by the control of hypertension and proteinuria.

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Conflict of interest statement. None declared.

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