An unusual cause of hypertension and renal failure: a case series of a family with Alagille syndrome

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Abstract

Alagille Syndrome (OMIM 118450) is a multisystem developmental disorder inherited in an autosomal dominant pattern with variable expression. It commonly manifests in children with early cholestatic jaundice due to paucity of interlobular biliary ducts. Renal involvement is less common but can take various forms including renovascular disease, renal agenesis or hypoplasia, cystic renal disease, mesangiolipidosis, tubulointerstitial nephritis and renal tubular acidosis. We describe a family of Alagille syndrome with JAG 1 mutation running through at least two generations, affecting four members with variable

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phenotypic expressions and disease severity. Alagille syndrome should be considered in the differential diagnosis of adults with renovascular disease and children with agenesis/dysgenesis of kidney and reflux nephropathy even in the absence of hepatic disease. Renal transplant can be successful in these patients although living related donation may not be appropriate given the high penetrance and variable expression of this condition. This syndrome may cause symptomatic bradyarrhythmias as described in our series.

**Keywords:** Alagille syndrome; renal failure; hypertension; renal transplant; haemodialysis

**Introduction**

Alagille Syndrome (OMIM 118450) is a multisystem developmental disorder inherited in an autosomal dominant pattern with variable expression. It commonly manifests in children with early cholestatic jaundice due to paucity of interlobular biliary ducts [1]. Renal involvement is less common. Genetic studies have identified mutations (in 60–75%) or deletions (in 3–7%) in the JAG 1 gene located on chromosome 20p12 in typical cases of Alagille syndrome [2–5]. Recently, NOTCH 2 and HEY 2 mutations have also been implicated [6,7]. However, genotype–phenotype correlations have not been clarified yet [4,8].

We describe a family of Alagille syndrome with JAG 1 mutation running through at least two generations, affecting four members with variable phenotypic expressions and disease severity (Figure 1).

**Case 1**

A 62-year-old male was referred with refractory hypertension and chronic kidney disease. He was noted to have an asymptomatic murmur in childhood. He was diagnosed with hypertension at the age of 42 years. Following the diagnosis of Alagille syndrome in his son, he underwent genetic studies which confirmed that he too had the same mutation in the JAG 1 gene (heterozygous for a frameshift mutation—2874_2875delTG in exon 23 of JAG1 gene) consistent with a diagnosis of Alagille syndrome.

He had dysmorphic facies (Figure 2) and posterior embryotoxon. His blood pressure at presentation was 200/90 mmHg. He had a pulmonary ejection systolic murmur. There was no evidence of peripheral vascular disease.

Creatinine at presentation was 154 μmol/l [estimated glomerular filtration rate (eGFR) 42 ml/min/1.72 m²] with urea of 9.8 mmol/l. His liver functions were normal. Urine dipstick showed no haematuria or proteinuria. Ultrasound scan revealed small asymmetric kidneys (right kidney 9.4 cm and left kidney 8.3 cm) and a hepatic angioma. Computed tomography (CT) angiogram showed significant arterial stenosis involving left renal, right subclavian and coeliac arteries (Figures 3 and 4). Echocardiogram did not show any valvular lesion. His blood pressure is currently 130/80 mmHg on four anti-hypertensive agents. His renal function has remained stable over the last 6 years, and his creatinine is currently 130
μmol/L (eGFR 51 ml/min/1.72 m²). His liver function tests have remained normal.

Two years after his initial presentation, he required a permanent pacemaker for symptomatic sinus pauses.

Case 2 (case 1’s brother)

He was diagnosed with an asymptomatic heart murmur in childhood. He was referred at 50 years of age with severe systolic hypertension and renal impairment. He had dysmorphic facies, right-sided cataract and left retinal pigmentary changes. There was no clinical evidence of peripheral vascular disease. He had a loud ejection systolic murmur in the pulmonary area.

Creatinine at presentation was 144 μmol/L (eGFR 48 ml/min/1.72 m²). He had normal liver functions. He had a 24-hour protein excretion of 900 mg with no haematuria. Ultrasound of the renal tract showed small kidneys, with thin cortices suggestive of parenchymal renal disease. CT renal angiogram revealed 50% ostial stenosis in the right renal artery. He had significant stenoses of external carotid arteries, coeliac axis and superior mesenteric artery. Echocardiogram showed left ventricular hypertrophy with mild mitral regurgitation. He has had two separate admissions for symptomatic bradycardia and a 24-hour tape showed sinus bradycardia with first-degree atrioventricular block and several sinus pauses, the longest being 2.6 sec-
Case 1's son. He was unfortunately lost to follow-up until his brother (case 1) presented to us 9 years later. The diagnosis of Alagille syndrome was made in retrospect.

His systolic hypertension has been difficult to control despite introduction of six antihypertensive medications including an angiotensin-converting enzyme inhibitor. His renal function has gradually deteriorated with a creatinine of 265 μmol/L (eGFR 23 ml/min/1.72 m²) 14 years later. His liver function tests remain normal.

Case 3 (case 2's daughter)

The diagnosis in this case was made in retrospect following the clinical presentation of her paternal uncle.

She was separated in childhood from her father. She developed neonatal urinary tract infections, and a micturating cystogram showed right-sided reflux while the left kidney was not visualized.

She appears to have been lost to follow-up until the age of 12 years when she presented with hypertension, breathlessness, renal impairment (creatinine 200 μmol/L—eGFR 30 ml/min/1.72 m²) and a loud systolic murmur over the precordium. She had dysmorphic facies, and her weight remained below the third centile for her age. She had normal liver function tests. An echocardiogram and cardiac catheterization study ruled out valvular stenosis and her murmur was thought to be secondary to a peripheral pulmonary stenosis.

Her renal function progressively deteriorated, and she commenced haemodialysis at the age of 16 when her creatinine was 640 μmol/L (eGFR 8 ml/min/1.72 m²).

She had three renal transplants between the ages of 17 and 20 years. The first two transplants failed due to acute cellular rejection after nine and thirteen months, respectively. The third renal transplant failed after 7 years due to chronic allograft nephropathy, and she subsequently went back on haemodialysis. The acute rejection in the first two transplants was thought to be secondary to non-compliance with medication. There was no documentation of any difficulty with vascular anastomoses during the three renal transplant procedures.

She however was subsequently found to have had multiple arterial stenoses including an 80% stenosis of distal left common iliac and proximal external iliac arteries. Her left subclavian artery was stented for symptomatic stenosis, and she was subsequently found to have had multiple arterial stenoses including an 80% stenosis of distal left common iliac and proximal external iliac arteries. Her left subclavian artery was stented for symptomatic stenosis. She had recurrent problems with vascular access and haemodialysis on account of widespread arterial stenoses.

She died at the age of 32 from metastatic gynaecological malignancy. Diagnosis of Alagille syndrome was not made in her case until her paternal uncle (case 1) presented to us 6 years later.

Case 4

Case 1's son. He presented with cholestatic jaundice in childhood. He subsequently developed hepatic cirrhosis with portal hypertension. There was no evidence of significant renal involvement. Genetic studies confirmed a mutation in the JAG 1 gene in keeping with a diagnosis of Alagille syndrome. He died at the age of 20 years from a variceal bleed.

Case 5

Case 1’s daughter. Phenotypically normal and genetic studies did not reveal any mutation.

Case 6

Case 1 and 2’s father. We do not have much information on him as he lived separately and died in his 40s in a road traffic accident.

Case 7

Case 1 and 2’s mother. We do not know much about her medical history apart from the fact that she died at 65 years from carcinoma of the breast.

Discussion

Alagille syndrome is a developmental disorder due to mutation in the genes involved in notch signalling pathway. JAG 1, NOTCH 2 and HEY 2 mutations have been described with JAG 1 mutations accounting for most of these [2–7]. JAG 1 gene encodes for a ligand (jagged 1) that interacts with Notch group of transmembrane proteins on neighbouring cells to generate notch signalling pathways that are crucial in cell differentiation in embryonic life [9,10]. Fameshif, missense, nonsense mutations (60–70%) and deletions (3–7%) have been described in almost all of the 26 exons of JAG 1 gene resulting in haploinsufficiency for Jagged 1 protein [11].

Notch is a signalling pathway between membrane-bound receptors and ligands expressed on adjacent cells. Binding of ligands induces a proteolytic cleavage of the Notch receptor, releasing its intracellular domain (ICD). This truncated form of Notch then translocates to the nucleus where it forms an active transcriptional complex with the DNA-binding protein CSL [also known as CBFI, Su(H), Lag-1 and RBP-J] and the co-activator Mastermind-like (MAML) [12]. Mammals express four Notch receptors (Notch 1–4) and five ligands [Jagged (JAG) 1 and JAG 2 and Dll (Delta-like) 1, Dll3, and Dll4]. Two Notch ligands, Jag1 and Dll4, are prominently expressed in the vasculature. Disruption of each of these genes in mice results in embryonic lethality associated with cardiovascular defects, suggesting that both play essential, non-redundant functions [12–15].

Endothelial-specific deletion of JAG 1 results in embryonic lethality and cardiovascular defects, similar to the gross defects reported for the complete Jag1 knockout. Expression of vascular smooth muscle markers is severely diminished in the endothelial-specific JAG 1 mutant embryos [16].

Diminished JAG 1 expression on endothelial cells results in abnormal smooth muscle development, which may be responsible for the pulmonary artery stenosis that is a frequent finding in Alagille syndrome patients. It has been shown that inhibition of Notch in neural crest cells (which act as smooth muscle precursors in the pulmonary artery) results in pulmonary artery stenosis and other con-
genital heart defects similar to those seen in Alagille syndrome [17].

The clinical correlation of JAG1 mutation is best illustrated in a study of 200 subjects who fulfilled the diagnostic criteria for Alagille syndrome [18]. Seventy-seven percent of the study group had mutation in the JAG1 gene. Individuals with JAG1 mutation had a significantly higher frequency of branch pulmonary arterial anomalies, bilateral branch pulmonary arterial anomalies and diffuse stenosis/hypoplasia of the pulmonary arteries than those with Alagille syndrome without the mutation. Within the cohort of subjects with a JAG1 mutation, there was no correlation between the type and location of the JAG1 mutation and the presence or type of cardiovascular anomaly. The variable phenotypic expression of a JAG1 mutation in the cardiovascular system suggests that additional epigenetic factors influence the final cardiac phenotype.

The diagnosis of Alagille syndrome in adults who present with chronic kidney disease can be difficult as illustrated in our case series. A high degree of clinical suspicion and a good family history is helpful (see Algorithm).

Prevalence of Alagille syndrome has been reported as 1 in 100 000 live births when probands were ascertained based on finding of neonatal liver disease [19].

In a summary of various studies looking in to clinical features of Alagille syndrome, the frequency of involvement of various organs was as follows: liver (95%), cardiovascular (92%), facies (91%), eye (78%), vertebra (70%) and renal (38%) [20].

Organ-specific manifestations of Alagille syndrome include the following:

1. Hepatic: Majority of symptomatic patients present with hepatic disease of varying severity in their infancy. Many progress to cirrhosis and liver failure with 15% requiring liver transplantation [21].

2. Cardiac: More than 90% of patients with Alagille syndrome have cardiac malformations, the commonest being peripheral pulmonary stenosis. Tetralogy of Fallot occurs in 7–10% but ventricular septal defects, atrial septal defects, patent ductus arteriosus, aortic stenosis and coarctation of aorta are also seen less frequently [1,18,22,23].

3. Ocular: Most of the ocular anomalies in patients with Alagille syndrome are related to the anterior chamber (posterior embryotoxon being the commonest) or retinal pigmentary changes [1,22].

4. Vascular: Stenoses of aortic, coeliac, superior mesenteric, subclavian and cerebral arteries are common although any artery may be involved. Sixteen percent of patients with Alagille syndrome have documented intracranial haemorrhage and strokes [25,26].

5. Skeletal involvement: Butterfly vertebra is the commonest skeletal abnormality in patients with Alagille syndrome (70%). Other skeletal anomalies include narrowing of interpeduncular spaces in the lumbar spine (50%), pointed anterior process of C1, spina bifida occulta, vertebral fusion, hemivertebrae, fused ribs and short fingers [20].

(6) Facies: Characteristic facies of Alagille syndrome is a triangular face composed of broad forehead, deep set eyes with hypertelorism, straight or saddle nose with bulbous tip [1,20,27].

(7) Renal: Renal anomalies have been reported in 23–74% of patients in studies where this was examined [1,20,28]. Renal involvement can take various forms including renovascular disease, renal agenesis or hypoplasia, cystic renal disease, mesangiolipidosis, tubulointerstitial nephritis and renal tubular acidosis [27,29–35].

Being primarily a paediatric disease affecting the liver, adult case reports of renal failure requiring renal replacement therapy including renal transplantation are limited [34]. Although renovascular disease and hypertension are the more likely mechanisms for renal injury, abnormal nephrogenesis due to JAG1 haploinsufficiency is also implicated. JAG1 expression has been seen in ureteric buds along with glomerular and tubular structures during all phases of renal embryogenesis [10].

Despite the association of various cardiac abnormalities with this syndrome, to the best of our knowledge, conduc- tion abnormality in the form of symptomatic bradycardia has not been described.

We report a family of Alagille syndrome with four affected members through two successive generations. Despite sharing the same mutation in the JAG1 gene (heterozygous for a frameshift mutation—2874_2875delTG in exon 23 of JAG1 gene) liver and renal disease seemed to manifest independent of each other. Only one of them had clinically significant hepatic disease. The other three had varying severity of renal disease with one requiring long-term renal replacement therapy. The aetiology of renal failure was renovascular disease in two patients and agenesis of one kidney with reflux nephropathy affecting the remnant kidney in the third patient. All three cases with renal disease had vascular abnormalities at more than one site and murmurs consistent with pulmonary artery stenosis.

The two adults with renovascular disease suffered from symptomatic sinus bradyarrhythmias, of whom one required a permanent pacemaker.

The patient who required renal replacement had three successful renal transplants. The first two failed within a year due to rejection possibly due to poor compliance. The third transplant lasted for >7 years and failed as a result of chronic allograft nephropathy.

**Conclusions**

Alagille syndrome should be considered in the differential diagnosis of adults with renovascular disease and children with agenesis/dysgenesis of kidney and reflux nephropathy even in the absence of hepatic disease. A family history of cardiovascular abnormalities, dysmorphic facies, liver and renal disease helps with the diagnosis.

Vascular access for haemodialysis may be difficult in these patients on account of vascular stenoses. Renal transplant can be successful in these patients although living related donation may not be appropriate given the high penetrance and variable expression of this condition. This
syndrome may cause symptomatic bradyarrhythmias as described in our series.

Conflict of interest statement. None declared.

References


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