

Renal abnormalities in a family with Alagille syndrome

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INTRODUCTION

Alagille syndrome is largely unknown to the general internist because the diagnosis is usually made by a paediatrician. Nevertheless, it is important to be aware of this syndrome because it sometimes manifests later in life with a great variability in clinical presentation and important consequences for the individual patient. We therefore discuss this syndrome using a patient with the usual characteristics of this syndrome.

KEYWORDS

Alagille syndrome, renal failure, dysmorphic features

CASE

A 38-year old woman was referred to our outpatient clinic because of hypertension. She felt otherwise well. On physical examination she had a peculiar face with a prominent forehead, straight nose and a pointed chin. Her blood pressure was 180/70 mmHg, with a regular pulse rate of 80 beats/min. She had a systolic ejection murmur, crescendo-decrescendo, grade II/VI at the left upper sternal border.

Her previous medical history revealed a heart operation because of pulmonary artery stenosis, and jaundice during her childhood. She had also had four miscarriages in the past. The diagnosis of Alagille syndrome was established. Two sisters and two brothers had already been diagnosed with Alagille syndrome.

Initial biochemistry results were normal with an isolated high gamma-glytamyl transpeptidase of 172 U/l. Ultrasound examination of the kidneys showed that she only had one kidney on the left side. Further analysis with a digital subtraction angiography showed a shrunken kidney

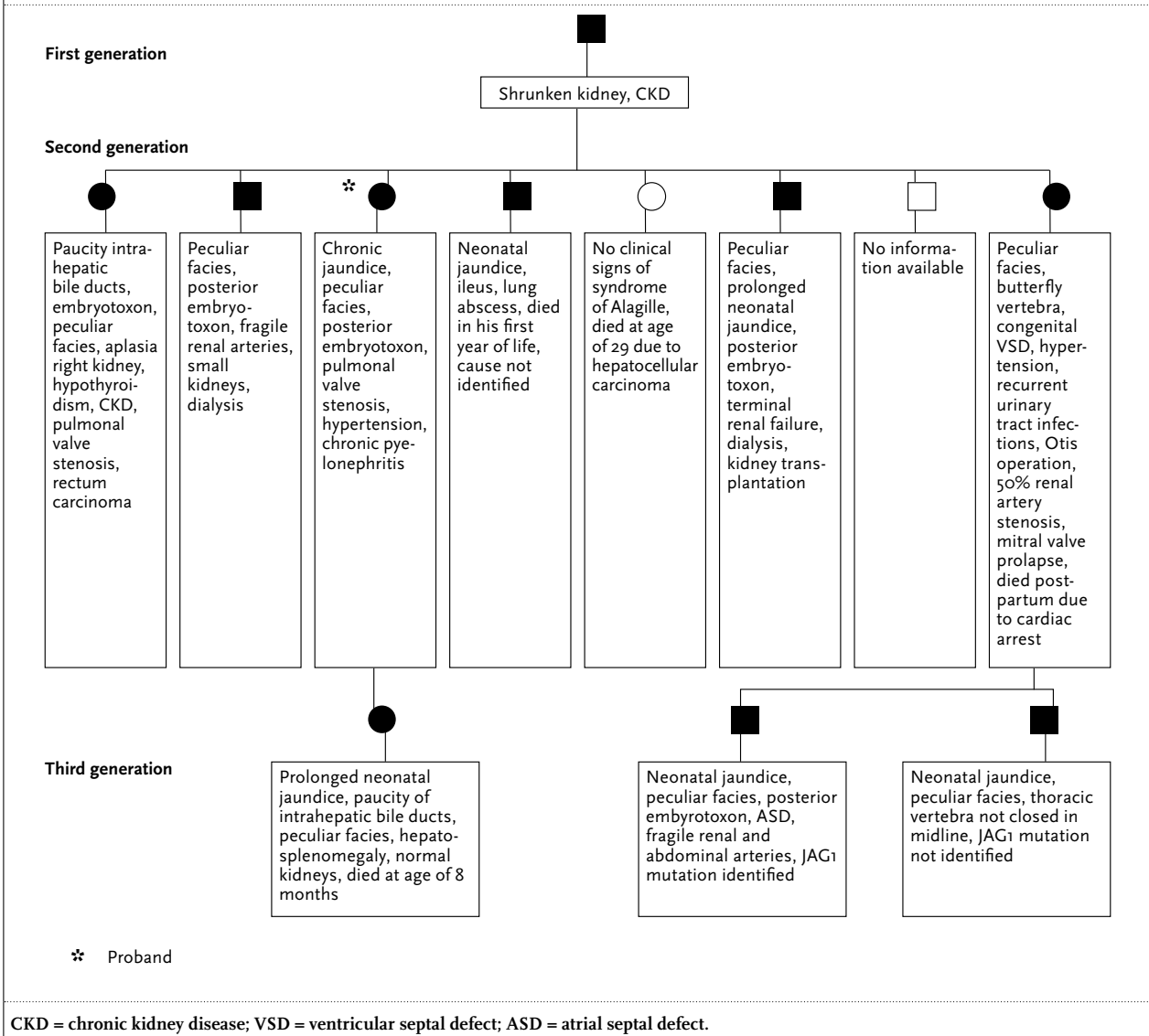
on the right side and evidence of a hypoplastic left renal artery and abdominal aorta with 50% concentric narrowing. Ophthalmological examination confirmed a posterior embryotoxon. She was treated for her hypertension with a calcium channel blocker and follow-up was organised at our outpatient clinic. After 13 years she underwent a successful living kidney donor transplantation because of terminal renal insufficiency due to slowly progressive kidney failure.

DISCUSSION

This patient has four characteristic hallmarks of Alagille syndrome: peculiar facies, posterior embryotoxon, chronic cholestasis and pulmonary valve stenosis. Patients with Alagille syndrome have five main features, four of which were demonstrated by our patient. The usual fifth feature is the existence of vertebral arch defects. Her family history revealed four siblings diagnosed with Alagille syndrome. The unusual findings in this family are agenesis of the kidney, kidney dysfunction and renal artery stenosis. One brother also underwent successful kidney transplantation due to terminal renal failure. The complete history of the proband and her family is summarised in *figure 1*.¹

In 1969, Daniel Alagille, a French paediatric liver specialist, described a new and distinct form of cholestasis in infancy in association with cardiac abnormalities, vertebral malformations and a peculiar facies. We now know that Alagille syndrome is a genetic syndrome due to a mutation of the *JAG1* gene on chromosome 20p12 that encodes Jagged 1, which has an important role in cell fate determination. Mutations in the *JAG1* gene are associated with developmental problems in especially the cardiovascular and bile duct system, but also in other organ systems.²

Figure 1. This figure shows three generations of the family of the proband (*). The relevant medical history of each family member is described shortly



Alagille syndrome is diagnosed almost exclusively in children in the setting of predominant liver manifestations. It remains a 'paediatric diagnosis' largely unknown to practitioners who deal with adult patients. Although the diagnosis is made on clinical grounds, genetic testing is possible. There is an autosomal dominant inheritance with a high variability of expression and a high rate of new mutations, approximately 35%. In approximately 70% of the patients a *JAG1* mutation can be identified. The inability to identify a mutation in the remaining 30% is thought to be because of technical limitations in testing this fairly large gene.^{3,4} We would like to conclude that renovascular and renal problems are not uncommon in Alagille syndrome as a review of the literature and the family history of our patient demonstrated. We believe that Alagille syndrome is probably underdiagnosed in adult patients, especially in the absence of severe hepatic disease and/or a positive familial

history. Because of the high frequency of new mutations and differences in the clinical features in affected families, it is important to look for renovascular abnormalities in a patient with Alagille syndrome.

REFERENCES

- Schonck M, Hoorntje S, van Hooff J. Renal transplantation in Alagille syndrome. *Nephrol Dial Transplant.* 1998;13(1):197-9.
- Jacquet A, Guiochon-Mantel A, Noël LH, et al. Alagille syndrome in adult patients: It is never too late. *Am J Kidney Dis.* 2007;49(5):795-9.
- Kamath BM, Spinner NB, Emerick KM, et al. Vascular anomalies in Alagille syndrome: a significant cause of morbidity and mortality. *Circulation.* 2004;109(11):1354-8.
- Warthen DM, Moore EC, Kamath BM et al. Jagged1 (*JAG1*) mutations in Alagille syndrome: increasing the mutation detection rate. *Hum Mutat.* 2006;27(5):436-43.