

Alagille's syndrome associated with cystic renal disease

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Abstract

Although renal abnormalities have been described in children with Alagille's syndrome, cystic kidney disease has not often been documented, and then usually only at necropsy. Three children with Alagille's syndrome are described, in two of whom a unilateral multicystic dysplastic kidney was detected by prenatal ultrasound; in the other, a solitary cortical cyst was found later in childhood. All have normal renal function, growth, and liver synthetic function but continue to have clinical and biochemical signs of cholestasis. These cases show that unilateral cystic kidney disease with or without renal dysplasia may be associated with Alagille's syndrome, that the clinical course is not necessarily unfavourable, and that Alagille's syndrome should be included in the differential diagnosis of cystic kidney disorders associated with cholestatic liver disease. Patients with Alagille's syndrome should be evaluated by renal ultrasound. (*Arch Dis Child* 1996; 74: 232-235)

Keywords: Alagille's syndrome, multicystic dysplastic kidney, ultrasound.

Alagille's syndrome, one of the most common causes of intrahepatic cholestasis of infancy, is a familial disorder characterised by five major features: abnormal facies, chronic cholestasis, butterfly vertebrae, peripheral pulmonary artery stenosis, and posterior embryotoxon of the eye.¹ Renal involvement, which is included among a number of other less common manifestations, has recently been reported more often.²⁻¹² Renal abnormalities comprise three main types: non-specific mild alterations in renal function,^{8 10 12} those possibly related to the hypercholesterolaemia that is associated with cholestasis, such as mesangiolipidosis,²⁻⁴ and those resulting from abnormalities in renal morphogenesis.^{2 4-12} We present three French Canadian children with Alagille's syndrome associated with cystic kidney disease, in two of whom the diagnosis was initially made by fetal ultrasound. These observations have

importance for the significance of multicystic kidneys detected prenatally and extends the differential diagnosis of hepatic disorders associated with cystic kidney disease.

Case 1

A 21 month male was admitted to hospital at 4 months of age for jaundice associated with acholic stools. Previously, he had been investigated for renal disease that presented with a multicystic right kidney detected by fetal ultrasound at 16 and 24 weeks' gestation and confirmed postnatally (fig 1). Evaluation in the neonatal period revealed a urinary tract infection with *Escherichia coli* that was treated. He was jaundiced in the first week of life but the jaundice resolved spontaneously. Results of investigations of his kidney disease are shown in table 1. At 4 months of age investigations for cholestasis revealed a total bilirubin of 139 mmol/l (normal <23 mmol/l) and direct bilirubin of 105 mmol/l (normal <19 mmol/l). The γ glutamyltranspeptidase (γ GT) was 40 \times normal and there was evidence of fat soluble vitamin deficiency. The diagnosis of Alagille's syndrome was suggested by the presence of four of the five major clinical features - cholestasis associated with the typical facies, peripheral pulmonary stenosis, and posterior embryotoxon. In addition, the patient's cry was high pitched, as previously described in this syndrome.² Liver biopsy revealed diffuse cholestasis, enlargement of the portal tracts with mild fibrosis, paucity of interlobular bile ducts, and a degeneration of the bile ducts with vacuolisation of the epithelium.

At 23 months of age, his course has been marked by normal growth (height 5th centile for age, weight 10th centile), variable cholestasis (currently: total bilirubin 136 mmol/l; direct bilirubin 74 mmol/l; γ GT 15 \times normal, and normal liver synthetic function). He receives supplemental fat soluble vitamins. Xanthomas were first observed at 14 months of age; serum cholesterol peaked at 17 months of age at 41 mmol/l (normal <4.3 mmol/l) and has since gradually declined to 15.9 mmol/l. Pruritus became clinically significant at 10 months of age and was treated with variable

Table 1 Investigations of renal disease in the three patients

	Patient 1	Patient 2	Patient 3
BUN	N	N	N
Creatinine	N	N	N
DMSA scan*	Non-functioning right kidney	Non-functioning left kidney	ND
Ultrasound	Multicystic, dysplastic right kidney	Multicystic, dysplastic left kidney	Right renal cortical cyst
CT scan	N	Atrophic left kidney	ND
VCUG**	Thick bladder wall, diverticulum	Vesicoureteral reflux, grade I	ND

*Dimercaptosuccinic acid, **voiding cystourethrogram. ND=not done; N=normal.

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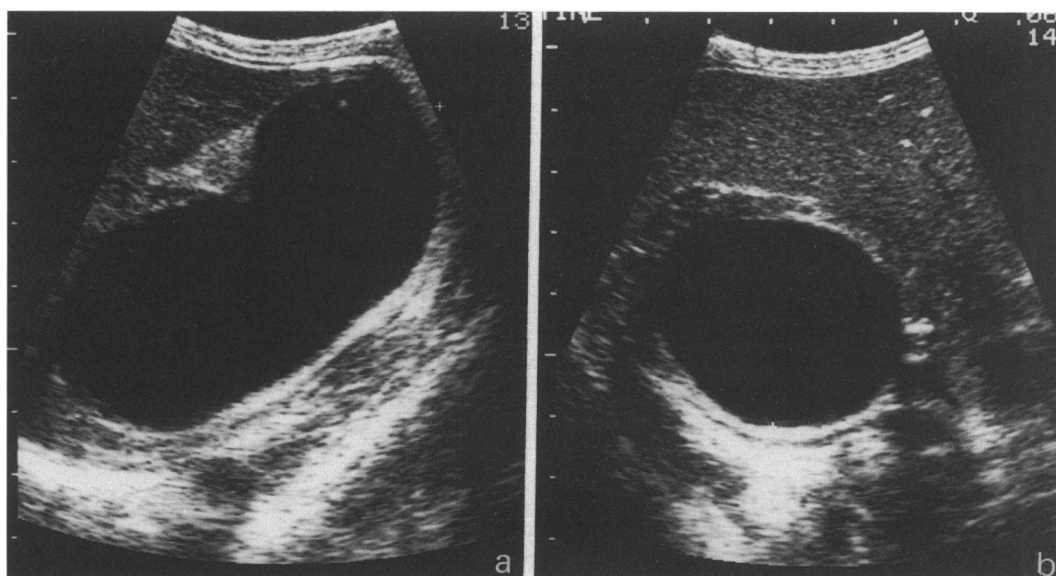


Figure 1 Patient 1 at 4 months of age. (A) Longitudinal scan of the right kidney. Macrocystic changes are obvious in a 76 mm kidney. The left kidney (not shown) was normal (66 mm in length in compensatory hypertrophy). (B) Transverse scan.

success with hydroxyzine, phenobarbitone, ursodeoxycholic acid, or rifampicin.

Case 2

A left multicystic dysplastic kidney was detected by prenatal ultrasound in this patient at 19 weeks (fig 2) and confirmed at 21 and 27 weeks' gestation. He was born at term with a birth weight of 3750 g. Jaundice was noted on the third day of life; the serum bilirubin concentration peaked on the fifth day (total bilirubin 208 mmol/l; direct 111 mmol/l). At six weeks of age he was admitted to hospital for investigation of his kidney disorder and persistent cholestasis. The renal findings are summarised in table 1. The diagnosis of Alagille's syndrome was established from the presence of chronic cholestasis, peripheral pulmonary stenosis, posterior embryotoxon, butterfly vertebrae, and typical facies. Follow up was notable only for biochemical signs of cholestasis (total bilirubin 23 mmol/l; direct bilirubin

19 mmol/l; γ GT 29 \times normal, cholesterol 6.9 mmol/l) without xanthomas, for which he has received supplemental fat soluble vitamins, and a mild pruritus that was successfully treated with ursodeoxycholic acid. His growth is normal (weight 10th centile for age, height 50th centile).

Case 3

This 14 year old patient was initially discovered to have a solitary cortical cyst of the right kidney on routine follow up ultrasound at 11 years of age (table 1). He was first admitted to hospital at Hôpital Sainte Justine at 21 months of age for pruritus and biochemical changes consistent with cholestasis. He had presented elsewhere with cholestasis on the fourth day of life that had not subsequently been extensively investigated. The presence of cholestasis, typical facies, peripheral pulmonary stenosis, and posterior embryotoxon suggested the diagnosis of Alagille's syndrome;

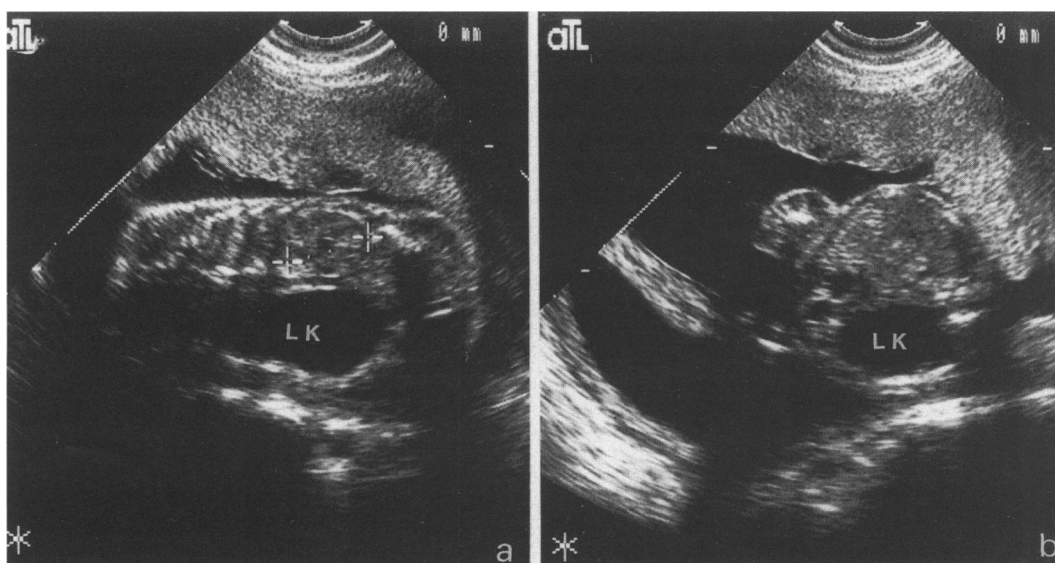


Figure 2 Antenatal ultrasound of patient 2 at 19 weeks' gestation. (A) Longitudinal scan. Normal right kidney (in between calipers); multicystic dysplasia of left kidney (LK). (B) Transverse scan.

his mother was also observed to have the typical facies of Alagille's syndrome, pruritus, and characteristic voice, but she refused further investigation. A liver biopsy at 21 months of age revealed a paucity of bile ducts without fibrosis or histological signs of cholestasis. The evolution of this patient's illness was characterised by almost complete remission of the cholestasis (total bilirubin 5 mmol/l, direct bilirubin 0 mmol/l, γ GT 3 \times normal, cholesterol 4.1 mmol/l). He receives rifampicin for mild pruritus and fat soluble vitamin supplementation, and is growing normally (weight 75th centile for age, height 50th centile).

Discussion

Renal involvement was not a prominent feature of early reports of Alagille's syndrome.¹ Since then, a variety of non-specific findings has been described, including azotaemia, urine concentration defects, and nephrolithiasis. Mesangiolipidosis is common and while it most probably relates to the hypercholesterolaemia that is associated with chronic cholestasis,²⁻⁴ Alagille and coworkers did not find a correlation with the serum lipid levels.² In addition, a variety of abnormalities in renal morphogenesis has been described, which include small kidneys,^{6 10 12} congenital single kidney,^{5 10} microcystic tubular dilatation with interstitial fibrosis,^{4 9-11} and renal cysts.^{2 4 5 7 9 11} The association of cystic kidney disease with Alagille's syndrome has been reported infrequently (table 2), possibly because of the poor definition of cysts using older ultrasound equipment and the difficulty in identifying early lesions by ultrasound. Medullary cystic kidney disease was found at necropsy in two patients with a partial form of Alagille's syndrome,⁵ in one dying of sepsis following liver transplantation at three years of age,⁴ and in another who died at two months of age in renal failure.¹¹ All other documented cases of cystic kidney disease have been described at necropsy, prompting some investigators to question whether this finding may suggest a poor prognosis in Alagille's syndrome.^{5 6} However, none of our three patients has shown signs of deteriorating renal function, while showing the full spectrum of possible evolution of their cholestasis. This implies that cystic kidney disease may not of itself indicate a poor prognosis, but rather the type (simple cyst versus nephronophthisis) and extent (unilateral versus bilateral) of renal involvement that governs the patient's prognosis.

Hyams and colleagues, in observing that their patient did not have dysplastic changes in either kidney, suggested that the findings in Alagille's syndrome differed from other conditions with cystic renal lesions associated with biliary tract abnormalities such as Meckel's syndrome, Jeune's syndrome, and Zellweger's syndrome.⁹ Two of our patients presented prenatally with a unilateral multicystic dysplastic kidney, suggesting that dysplastic kidneys may also occur in this syndrome. Indeed, concentric layering of mesenchymal cells around bile ducts in early Alagille's syndrome was suggested to be superficially reminiscent of changes observed in dysplastic kidneys.¹³ Desmet hypothesised that a defect in epithelial-mesenchymal inductive interactions in early gestation may explain the coexistence of biliary and renal cystic abnormalities in a variety of inherited malformation syndromes associated with fibrocystic cholangiopathy and abnormal remodelling of the primitive ductal plate.¹⁴ In some, progression of the disease leads to ductal degeneration and involution. He suggested that because intrahepatic paucity of interlobular bile ducts is not associated with renal lesions, the cause and mechanism of bile duct destruction is probably different from those disorders associated with congenital hepatic fibrosis. Our observations, together with other reports of abnormalities in renal morphogenesis with Alagille's syndrome, suggest that a defect in epithelial-mesenchymal induction may also be responsible for the constellation of abnormalities in this disorder. The lack of reports of ductal plate malformation does not necessarily exclude Alagille's syndrome from Desmet's hypothesis. Rather this may merely reflect a slower, less aggressive hepatic disease process that allows more complete ductal plate remodelling to occur, while in other organs more severe disturbances arise in early development, giving the typical postnatal pattern of malformations of Alagille's syndrome. The cause of such failures of induction is likely to be multifactorial and may include differences in the expression of genes regulating inductive interactions. Such differences may account for the variability of clinical expression of inherited disorders with biliary and renal manifestations.

In conclusion, Alagille's syndrome belongs in the spectrum of disorders associated with cystic renal disease and thus expands the differential diagnosis of multicystic kidney detected by prenatal ultrasound. Cystic dysplastic kidneys may be included in the

Table 2 Review of published cases of cystic renal abnormalities in Alagille's syndrome

Reference	Features*	Renal findings	Status
2	5/5	'Polycystic kidneys'	Died
4	5/5	1-5 mm Corticomedullary cysts; microcystic tubular dilatation; interstitial fibrosis	Died
5	4/5	Single 2 cm subcapsular cyst	Died
5	1/5	Medullary cystic disease (nephronophthisis)	Died
7	1/5	Medullary cystic disease (nephronophthisis)	
7	3/5	'Cystic kidney disease'	Died
9	3/5	'Cystic kidney disease'	Died
9	3/5	Severe tubulointerstitial nephropathy with microcystic tubular dilatation	Died
10	3/5	Bilateral focal tubular dilatation; interstitial fibrosis	Alive
11	3/5	Subcortical cysts; interstitial fibrosis; nephronophthisis)	Died

*Number of major characteristics of Alagille's syndrome.

spectrum of abnormalities of renal morphogenesis associated with Alagille's syndrome. Cystic renal lesions are not always associated with a poor prognosis. We support the recommendation that all patients with Alagille's syndrome be evaluated by renal ultrasound in order to determine the prevalence of cystic renal disease.

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