Syndrome of the month

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The Alagille syndrome (arteriohepatic dysplasia)

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Alagille *et al*[1 2] first drew attention to a group of children with hypoplastic intrahepatic bile ducts but patent extrahepatic ducts. Watson and Miller[3] and Alagille *et al*[4] reported two series of children with chronic cholestasis due to this cause, noting congenital heart disease, a characteristic facies, and minor skeletal abnormalities as associated findings with what was felt to be a distinct recognisable syndrome, which is known as the Alagille syndrome or arteriohepatic dysplasia. Subsequent case reports have drawn attention to the ocular involvement seen in persons with this disorder and its familial nature.[5–11]

Clinical features*

CARDIOVASCULAR FEATURES

The classical cardiovascular involvement in persons with the Alagille syndrome is peripheral pulmonary artery stenosis, which can occur either as a single isolated narrowing or at multiple sites. This finding is present in just under 90% of persons with the disease as definitively shown by cardiac catheterisation or post mortem examination, or inferred from Doppler echocardiography. In one-third of persons with the Alagille syndrome, peripheral pulmonary artery stenosis occurred along with a variety of other types of structural congenital heart disease, both intra- and extra-cardiac. The cardiovascular findings in just over 10% of persons with this syndrome did not involve the pulmonary artery tree.

HEPATOBILIARY FEATURES

Persistent neonatal jaundice is the most common presenting symptom of the hepatobiliary involvement seen in persons with the Alagille syndrome. Often jaundice may not develop until later in infancy. Other symptoms or signs of cholestasis such as pruritus, acholic stools, xanthomata, or hepatomegaly are also commonly present.

The typical liver histology seen in liver biopsies of persons with the Alagille syndrome is intrahepatic cholestasis in association with a relative paucity of the intrahepatic interlobular bile ducts. Normally there should be approximately one to two interlobular bile ducts per portal triad.[4 17] In persons with the Alagille syndrome in whom a liver biopsy was performed, 95% showed a relative paucity of interlobular bile ducts. A paucity of interlobular ducts is not specific to the Alagille syndrome and can be seen either in isolation or in association with other causes of intrahepatic cholestasis.[24]

The timing of the liver biopsy may be critical in showing the paucity of interlobular ducts. In a series of children clinically suspected to have the Alagille syndrome reported by Dahms *et al*,[17] the relative paucity of interlobular bile ducts was only apparent on repeat liver biopsies done in childhood or adolescence, normal numbers of intrahepatic bile ducts having been seen in the original liver biopsies done in infancy.

Portal inflammatory changes and bile duct proliferation reported in the liver biopsies of many patients are secondary or reactive changes and are features which are seen in cholestasis of any cause. These latter findings are usually present in liver biopsies performed in infancy but often have resolved in subsequent biopsies done in childhood or adolescence.[17]

The ultrastructural changes seen in electron microscopy studies of liver biopsy specimens in persons with the Alagille syndrome are distinctive, lacking the pericanalicular changes, canalicular plugging, and dilatation usually seen in association with other causes of long standing cholestasis. Conversely, while the presence of biliary material in intercellular spaces is an occasional finding in other causes of chronic cholestasis, it was a marked feature in the series of liver biopsies of persons with

*Based on information in the case reports reviewed in reference 11 and subsequent case reports in references 12 to 28 where the information is available.

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the Alagille syndrome reported by Valencia-Mayoral *et al.*[24]

It has been suggested that extrahepatic biliary duct involvement in persons suspected to have the Alagille syndrome may represent a separate entity and precludes the diagnosis of this syndrome.[29 30] However, extrahepatic biliary duct involvement has been shown in approximately one-fifth of persons with the other typical features of the disorder. Extrahepatic involvement may be missed, particularly if only percutaneous liver biopsy is performed.[11 18 23]

Raised serum bile acid levels have been reported in persons with the Alagille syndrome.[6–8 14 25] A reversed ratio of the trihydroxy to dihydroxy bile acids has been noted.[12] A defect in secretion of conjugated bile acids has been suggested as being a primary abnormality.[14 23]

FACIAL FEATURES

The characteristic facial features seen in persons with the Alagille syndrome are a prominent forehead, deep set eyes, a long nose with a flattened tip, and a prominent chin (figs 1, 2, and 3). These features are often difficult to distinguish in infancy (fig 1). The prevalence of these features in early reports was underestimated, but when specifically

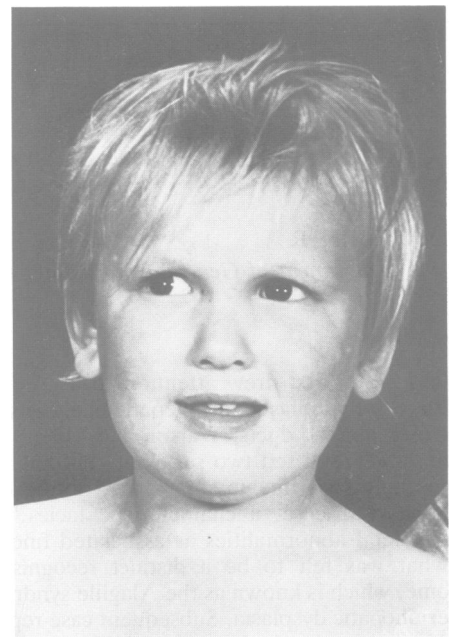

FIG 2 *Facies of a child with the Alagille syndrome.*

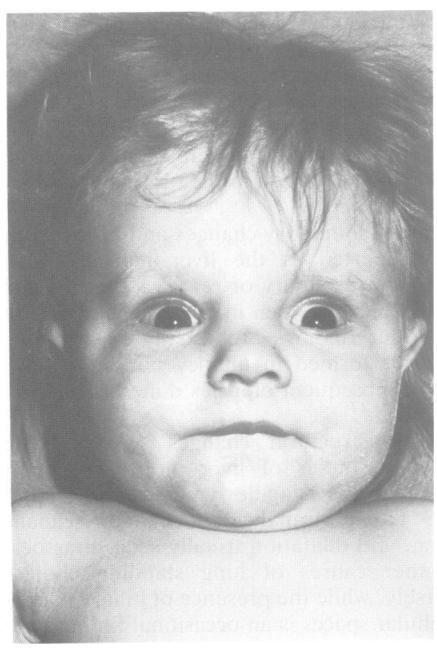

FIG 1 *Facies of an infant with the Alagille syndrome.*

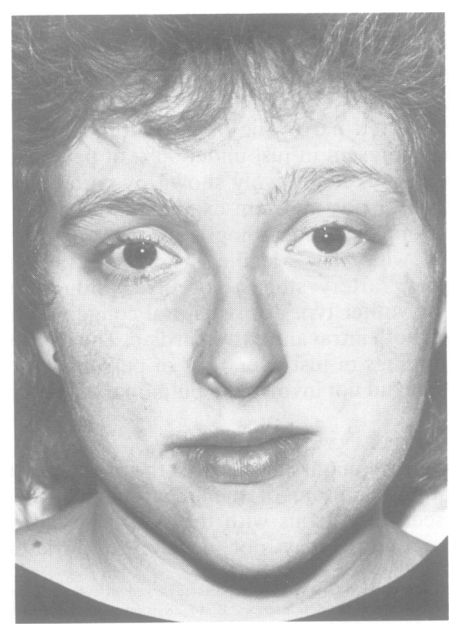

FIG 3 *Facies of an adult (mother of child in fig 1) with the Alagille syndrome.*

looked for are present in approximately 90% of those affected.

Sokol *et al*[31] have suggested that the facial features seen in persons with the Alagille syndrome may not be primary dysmorphic features but secondary to long standing cholestasis. The presence of the typical facial features in persons with minimal liver disease and the reports of first degree relatives of persons with the Alagille syndrome who have the typical facial features as their only evidence of involvement (figs 3 and 4) is against this.[16 22]

FIG 4 *Facies of mother and her two daughters with the Alagille syndrome.*

OCULAR FEATURES

The eye findings commonly seen in persons with the Alagille syndrome include the anterior chamber anomalies posterior embryotoxon, an abnormal prominence of Schwalbe's line (the line formed by the junction of Descemet's membrane with the uvea at the anterior chamber angle) (fig 5), and Axenfeldt's anomaly (iris strands), as well as retinal involvement which can include chorioretinal atrophy and pigmentary clumping.[32] The latter is not associated with symptoms of retinal degeneration and ERGs, where performed, have been normal. Other ocular features reported in affected persons include convergent or divergent squint, ectopic pupil, choroidal folds, anomalous optic discs or vessels or both, and refractive errors.[13 32] One or more of the major eye findings have been present in just under two-thirds of affected persons when specifically examined for.

Although initial case reports suggested that posterior embryotoxon might be a pathognomonic finding for the Alagille syndrome, it occurs in approximately 15% of the normal population. Therefore it can be an incidental finding in children with other causes of cholestasis.[13 32 33]

While posterior embryotoxon can be apparent on naked eye examination, slit lamp examination or gonioscopy may be necessary to show or exclude its presence.[8 13]

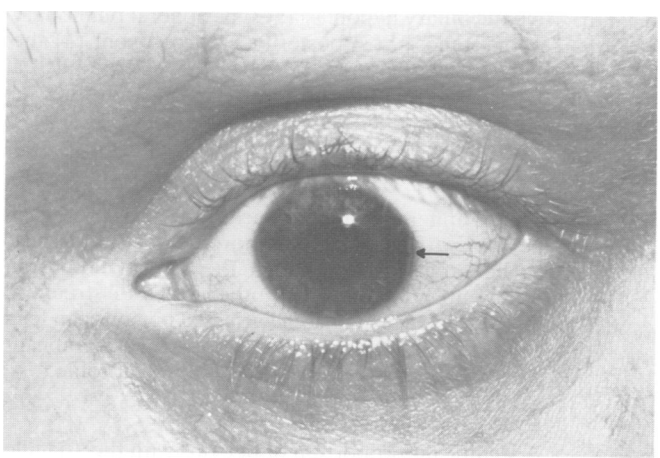

FIG 5 *Close up of the eye of the person in fig 3 showing posterior embryotoxon (arrow).*

SKELETAL FEATURES

A variety of skeletal abnormalities have been described in persons with the Alagille syndrome (table 1), the most common skeletal finding being butterfly vertebrae. The other skeletal findings may be under-reported because they will only be found if a skeletal survey is obtained. One or more of the skeletal features listed have been present in just over half of persons with the syndrome.

A delayed bone age, osteoporosis, or osteopenia,[5 17 28] along with vitamin D resistant rickets[12] have been reported in affected persons. The latter findings may be the result of a deficiency of lipid soluble vitamins, a consequence of significant, long standing hepatic disease.

GENERAL/OCCASIONAL FEATURES

The number of males and females with the Alagille syndrome is approximately equal. Growth retardation has been noted in just under half and developmental delay/mental retardation in approximately one-fifth of affected persons. A variety of different structural and parenchymal renal abnormalities have been reported in nearly 10% of persons with the Alagille syndrome (table 2).

Other occasional features which may or may not be part of the syndrome include deafness,[16] delayed puberty[4 17] or hypogonadism,[4] and primary hypothyroidism.[7]

Differential diagnosis

The main differential diagnoses of the Alagille syndrome are disorders with cholestasis which present in the neonatal or infant period. Most of these disorders have other distinguishing features, either physical or biochemical, which helps to differentiate them (table 3). If one considers a child presenting with peripheral pulmonary artery stenosis, while this can occur in congenital rubella, the associated features and serology should allow one to differentiate between them easily.

TABLE 1 *Skeletal findings in persons with the Alagille syndrome.*

Skeletal findings	*References*
Vertebral	
Abnormal vertebral body shape	6 9 10
Fused vertebral bodies	3 22
Butterfly vertebrae	3 4 8–10 11 13 15 17 22 23 25
Hemivertebrae	5 6
Pointed anterior process to C1	8 9
Lack of normal increase in interpedicular distance from L1 to L5	8 9 11 17–19
Spina bifida occulta	6 15 22 27
Hand/wrist	
Shortened distal phalanges	8 9 11 13
Shortened ulna	8 11

TABLE 2 *Renal findings reported in persons with the Alagille syndrome.*

Renal findings	*References*
Structural abnormalities	
Hypoplastic kidneys	7
With renal artery stenosis	16
Unilateral absence	16 25
Reduplicated ureters and renal pelves	34
Parenchymal abnormalities	
Tubulointerstitial nephropathy	16 21
Membranous glomerular lipid deposits with renal failure	17
Proliferative glomerulonephritis with transient renal tubular acidosis	12
Cystic disease of the kidney (two sibs)	5
Renal stones	27
With impaired renal function	7

TABLE 3 *Differential diagnosis of the Alagille syndrome.*

Ductal abnormalities
Extrahepatic
Biliary atresia/stenosis
Choledochal cysts
Cystic fibrosis
Intrahepatic
Isolated (non-syndromic)
Familial/syndromal
α_1 antitrypsin deficiency*
Benign recurrent cholestasis*
Byler's disease*
Cystic fibrosis (bile plugs)
Familial progressive cholestasis*
Inspissated bile syndrome
Lethal AR disorder with increased concentrations of trihydroxycoprostanic acid
Lymphoedema with recurrent cholestasis
Zellweger's (cerebrohepatorenal) syndrome
Cholestatic element with parenchymal hepatocellular disorders (for example, infections or metabolic disorders such as galactosaemia)

*Disorders in which a paucity of intrahepatic ducts can occur.

While the criteria for a syndrome diagnosis are often contentious, it would seem that three or more of the following features would allow one to make the diagnosis of the Alagille syndrome: (1) intrahepatic biliary hypoplasia; (2) peripheral pulmonary artery stenosis; (3) posterior embryotoxon; (4) the typical facial features; (5) butterfly vertebrae; (6) a first degree relative with the Alagille syndrome.

Natural history, management, and treatment

CARDIAC

The peripheral pulmonary artery stenosis present in persons with the Alagille syndrome does not appear to be progressive although the information from follow up is limited. The other types of structural heart disease seen in some affected persons can lead to cardiac failure and contribute to a significant proportion of the mortality in the syndrome.

HEPATOBILIARY

A significant proportion of persons with the Alagille

syndrome continue to have either symptoms of liver involvement (jaundice or pruritus or both) or abnormal liver function tests (raised plasma bilirubin, bile acid, or lipid levels), although there is a natural tendency for bile pigment excretion to improve with time.[6 8 11] Phenobarbitone or bile acid binding agents such as cholestyramine can be used to increase bile acid excretion and have been reported to relieve pruritus and reduce the size of xanthomata.[12 34]

Biliary tract surgery has been carried out in a number of persons with the Alagille syndrome, often because extrahepatic biliary tract obstruction was originally suspected.[23] Surgery would appear to be of potential value only in those persons in whom there is definite evidence of extrahepatic involvement.

Approximately one-quarter of persons with the Alagille syndrome have been shown to have periportal fibrotic changes in their liver biopsies. The lack of long term follow up on most persons with this disorder does not allow one to know whether these changes are progressive or not. However, Shulman *et al*[22] reported a child dying from cirrhosis with portal hypertension at five years of age and Gorelick *et al*[18] recorded a young adult dying of hepatic failure at 18 years of age. Interestingly, there are two reports of primary hepatocellular cancer developing in persons with the Alagille syndrome, one in a three year old,[26] the other in a 36 year old.[27]

These latter complications may be a consequence of long standing cholestasis. Berman *et al*[15] reported pseudoxanthomatous transformation and copper accumulation in the liver biopsies in some affected persons, both characteristic signs of chronic cholestasis, the latter thought to reflect mild hepatocellular damage. Dupont *et al*[35] suggested that defective lipid absorption due to intrahepatic cholestasis could lead to a deficiency of essential fatty acids which could result in abnormal eicosanoid synthesis which might cause further hepatic damage. Against this hypothesis is the fact that the reports of hepatocellular cancer in persons with the Alagille syndrome occurred in the absence of evidence of cirrhosis, which is usually present when hepatocellular carcinoma has been reported as a complication of other causes of chronic cholestasis.[27]

In the only recorded instance of a pregnancy in a woman with the Alagille syndrome there was a worsening of pruritus and hyperbilirubinaemia in the third trimester.[19]

MORTALITY

Approximately 10% of the persons reported have died, about one-third from cardiac disease, one-third from hepatic involvement, and the remainder from a variety of causes such as infection and renal failure. The mortality from cardiac involvement occurred primarily in neonates and infants and was associated with surgery for structural congenital heart disease. The mortality from hepatic involvement was usually the result of complications of portal drainage procedures, often performed because the cholestasis had been thought to be extrahepatic in origin.

This mortality figure is probably too high to use in counselling since published reports probably represent the 'tip of the iceberg'.

Aetiological factors

The initial reports of the Alagille syndrome suggested a possible viral aetiology because of similarities with the abnormalities seen in congenital rubella.[5 17] However, the numerous reports of multiple affected sibs or persons with features of the syndrome in two generations,[1–7 11 13 16 17 24 28] a report of a probable three generation family,[22] and one report suggestive of one or more features of the syndrome in persons in four generations,[16] along with several instances of male to male transmission,[6 7 16] are all consistent with an autosomal dominant gene exhibiting reduced penetrance and variable expressivity.

The report of a child with mild peripheral pulmonic stenosis, and intrahepatic biliary hypoplasia along with some of the other associated features seen in persons with the Alagille syndrome, in whom a deletion of the short arm of chromosome 20 was found, might suggest that a mutation in gene(s) or genetic material in that region of chromosome 20 could be responsible for the phenotype seen in this disorder.[36] Byrne *et al*[36] suggested that this finding might account for the familial reports of this disorder and suggested that detailed prometaphase cytogenetic studies of chromosome 20 should be carried out in a number of persons with the Alagille syndrome to see whether this is a consistent finding or not.

Developmental basis

A unifying hypothesis for the various features seen in persons with the Alagille syndrome is not apparent at present, apart from suggesting that they are pleiotropic manifestations of an autosomal dominant gene showing reduced penetrance and variable expressivity. While the cardiovascular, skeletal, and anterior chamber eye findings are primary developmental abnormalities, other features are likely to be a consequence of a primary developmental abnormality as yet unrecognised. The information from

sequential liver biopsies in persons with the syndrome suggests that the paucity of bile ducts is more likely to be due to atrophy or destruction rather than a primary abnormality of development. It has been suggested that a primary hepatocellular defect or abnormality in bile formation may lead to the liver features seen in persons with the Alagille syndrome.[8 23 24]

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