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## Alagille Syndrome Associated With Moyamoya Disease

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**A 22-month-old girl with the typical manifestations of Alagille syndrome presented with acute right hemiparesis. Cerebral angiographic studies demonstrated the presence of complete occlusion of both internal carotid arteries with the formation of a collateral network of vessels compatible with the diagnosis of Moyamoya disease. This rare association has not been reported previously.**

**KEY WORDS:** hemiplegia, intrahepatic cholestasis, arterio hepatic dysplasia, cerebral artery diseases

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### INTRODUCTION

Arteriohepatic dysplasia or Alagille syndrome is a syndrome of intrahepatic cholestasis caused by paucity of interlobular bile ducts and cardiovascular and other morphologic anomalies. The syndrome is an autosomal dominant trait with variable penetrance and expressivity [Alagille et al., 1975; Watson and Miller, 1973].

The major abnormalities seen in this syndrome include chronic cholestasis, characteristic face, cardiovascular abnormalities, (mainly peripheral pulmonic stenosis), vertebral arch defects, and posterior embryo-toxon. Less frequently associated anomalies are growth retardation, glomerular changes in the form of mesangioliipidosis, mental retardation, and other skeletal abnormalities [Alagille et al., 1987]. Rarely have kidney abnormalities such as infantile polycystic kidney [Greenwood et al., 1976], nephronophthisis [Hyams, 1983], single kidney [Oestreich et al., 1983], and arterial hypertension caused by renal artery stenosis [Labrecque et al., 1982] been reported in this syndrome. Alagille has suggested that a mild form of the syndrome occurs when only three or

four of the five major abnormalities are present [Alagille et al., 1987].

We describe a child with Alagille syndrome who developed acute hemiparesis because of occlusion of both internal carotid arteries at the level of their terminal bifurcation, with the formation of a telangiectatic network of vessels, which had the distinct radiologic appearance of Moyamoya disease. This rare association has not been described previously.

### CLINICAL REPORT

A 22-month-old girl was admitted with a sudden onset of right hemiparesis. She was the second child of unrelated parents of Sephardic Jewish origin, born after uncomplicated gestation and delivery.

She was diagnosed as having Alagille syndrome on the basis of prolonged neonatal cholestatic jaundice with patent extrahepatic bile ducts, characteristic face, vertebral arch anomalies, peripheral pulmonic stenosis, and patent ductus arteriosus. Infectious and metabolic causes were excluded by appropriate tests. She continued to have mild cholestasis and was treated with cholestyramine and vitamin supplementation. The patient's mother and sister have facial characteristics compatible with Alagille syndrome. Her sister was diagnosed as having peripheral pulmonic stenosis, and the mother has an undiagnosed systolic murmur; however, neither has signs of hepatic dysfunction.

On her present admission the girl appeared well nourished and alert. She was afebrile, and her vital signs were normal. She had moderate right hemiparesis, with mild right facial weakness. The function of other cranial nerves was intact, deep tendon reflexes were symmetrically absent, and there was a bilateral flexor plantar response. All peripheral arterial pulses were palpable, and no murmurs or bruits were found over the carotid arteries or the skull. Her head circumference was 45 cm (below the 3rd centile).

Results of laboratory examinations, including complete blood count, erythrocyte sedimentation rate, urinalysis, coagulation studies, serum glucose, electrolytes, calcium, magnesium, phosphorus, and albumin levels were normal. Serum alanin aminotransferase was 154 i.u. (2.57  $\mu$ kat/L), alkaline phosphatase was 753 i.u. (12.6

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$\mu\text{kat/L}$ ), cholesterol was 424 mg% (10.96 mmol/L), and triglycerides were 68 mg% (0.77 mmol/L). Total and conjugated serum bilirubin were 1.5 mg% (25  $\mu\text{mol/L}$ ) and 0.9 mg % (15  $\mu\text{mol/L}$ ), respectively. Vitamin E level was 1.3  $\mu\text{g/ml}$  (3.0  $\mu\text{mol/L}$ ). The electroencephalogram demonstrated slow wave activity over the entire left hemisphere.

Cranial computerized tomography demonstrated a low-density area with small calcified foci in the left frontal



Fig. 1. Localized area of brain atrophy is demonstrated by CT scan (coronal section). A low-density area with calcifications is seen (arrow). The white square shows dilatation of the left lateral ventricle.

lobe. Mild dilatation of the left lateral ventricle and widening of the sulci were also noted. The findings were compatible with an old hemorrhage (Fig. 1). Transfemoral cerebral arteriography demonstrated complete bilateral occlusion of the internal carotid arteries at the level of the carotid syphon. A network of tiny collaterals extending from the external carotid circulation was demonstrated at the level of the ophthalmic arteries, the basal ganglia, and dural branches, with retrograde filling of the anterior cerebral arteries and part of the middle cerebral branches. The vertebral and basilar arteries had a normal appearance (Fig. 2). These angiographic changes were compatible with the diagnosis of "Moyamoya" disease. The girl's neurologic status improved gradually with intensive physiotherapy. Four months after the initial episode she had only very mild weakness of her right limbs. Encephalo-myosynangiosis as a palliative surgical procedure was considered, but the parents did not give consent for this procedure.

### DISCUSSION

Moyamoya is a Japanese term that means "something hazy like a puff of cigarette smoke drifting in the air." It is applied to a peculiar angiographic picture consisting of abnormal net-like vessels at the base of the brain [Suzuki and Kodama, 1983]. There is usually bilateral stenosis or occlusion of the internal carotid artery at the level of its bifurcation, together with abnormalities of the anterior and middle cerebral arteries. In its more common, congenital form, the abnormality has been related to an arterial dysplastic process often associated with other systemic vascular anomalies such as renal artery stenosis, neurofibromatosis [Tomsick et al., 1976], and Down syndrome [Schrager et al., 1977]. An acquired form of the disease has been described in adults with sickle cell anemia [Stockman et al., 1972], tuberculous meningitis

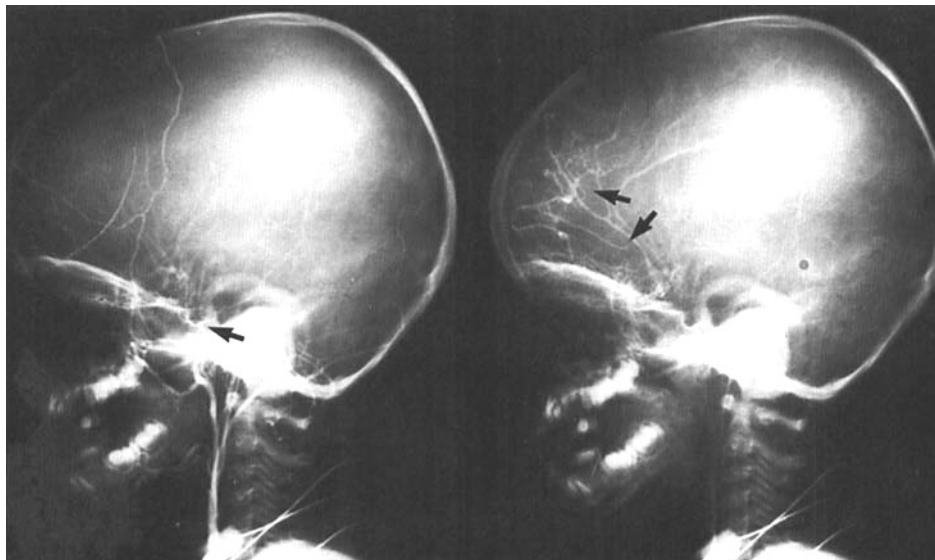


Fig. 2. Rt carotid angiography. **Left:** Early phase. Note the site of occlusion of the internal carotid artery (arrow). **Right:** Late phase. Collateral circulation in the form of a telangiectatic network of communication vessels between the extracranial arteries and the intracranial circulation is demonstrated (arrows).

[Mathew et al., 1970], connective tissue abnormalities [Richman et al., 1977], in association with Fanconi's anemia [Cohen et al., 1980], and following brain irradiation [Rajakulasingam et al., 1979].

The main cardiovascular anomalies in Alagille syndrome are well defined and consist of peripheral pulmonic stenosis, patent ductus arteriosus, ventricular septal defect, and atrial septal defect [Greenwood et al., 1976]. In a recent review of 80 patients [Alagille et al., 1987], cerebral vascular complication was mentioned as the cause of death of a 3-year-old patient, but no further details are given. Common carotid artery anomalies were found in two of seven autopsies in another series [Watson and Miller, 1973], but anomalies of cerebral arteries such as those found in our patient have not been described previously in this syndrome.

Low serum levels of vitamin E because of chronic cholestasis have been considered to be a cause for thrombocytosis and hypercoagulability state. However, our patient's thrombocytes were normal, and there were no signs of hypercoagulability. Moreover, recent review of vitamin E deficiency did not support previous concepts of its role in the development of vascular occlusion [Bieri et al., 1983].

Recently, evidence was presented for a vascular basis for neural and nonneural malformations, which were not previously related to vascular anomalies [Hoyme et al., 1981; Stevenson et al., 1987]. Thus, it is conceivable that the hepatic lesion in Alagille syndrome is also related to some early developmental vascular compromise, which might also cause vascular malformation at other sites, such as the heart, the great vessels, and the cerebral arteries. However, the rarity of this association prevents any substantiation of this hypothesis at the present time.

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