Alagille syndrome with moyamoya disease

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Abstract

We report a 5 year old male child who presented with a history of progressive jaundice since infancy and generalized pruritus. He was also found to have typical triangular facies, posterior embryotoxon on both eyes, peripheral pulmonary stenosis and paucity of bile ducts in liver biopsy. Magnetic resonance angiography of brain showed typical features of moyamoya disease. The child was diagnosed as a case of Alagille syndrome. This particular syndrome with feature of moyamoya disease has been rarely reported.

Introduction

Alagille syndrome is an autosomal dominant disorder and its main defect is in the notch signaling pathway. It is a multisystem disorder with characteristic facies that affects various organ system like liver, heart, eyes, skeletal system, kidneys and vasculature. Alagille et al. first described the disease in 1969 and also described as Alagille–Watson syndrome, as well as arteriohepatic dysplasia.[1] The reported prevalence is 1:70,000.[2]

Alagille syndrome is traditionally diagnosed on the basis of interlobular bile ductular paucity in the liver histology with any three of five major features such as cholestatic liver disease, consistent cardiac disease, skeletal abnormalities (butterfly vertebrae), ocular abnormalities (posterior embryotoxon) and a characteristic alagille (triangular) facies. The most common cardiovascular anomaly is congenital hypoplasia of the pulmonary arteries, occurring in up to 92% of all patients.[3, 4] Other reported sites of vascular lesions in Alagille syndrome are renal artery, arch of the aorta, celiac artery, hepatic artery, superior mesenteric artery, subclavian artery and the coronary ostia.[5-9] There are occasional reports of cerebral vasculopathy in Alagille syndrome.[5] Central nervous system vascular lesions that have been described to be associated with Alagille syndrome are aneurysm of basilar and middle cerebral arteries, anomalies of internal carotid artery and moyamoya disease.[9-14] Association of Alagille syndrome and asymptomatic moyamoya disease is extremely uncommon and to the best of our knowledge, there is no such report of this association from Asia.

Case Report

A 5 year old male child of a non-consanguineous parents came to the Pediatric Gastroenterology Department with excessive pruritus since his 1 year of age. The boy was well up to one month of age. Then he developed jaundice which was progressive and intermittent pale-colored stool. At that time he was diagnosed as neonatal cholestasis due to Herpes simplex virus infection and was treated with parenteral acyclovir for 14 days. He apparently improved but lost to follow-up. At 1 year of age he started having generalized pruritus which was severe in intensity (disturbing sleep and daily activities) without any diurnal variations and improvement with topical calamine lotion and oral antihistamines. There is no history of sib death or family history of similar type of illness.

Examinations showed a severely underweight, moderately wasted and moderately stunted child. He had typical triangular facies with broad forehead, deep-set eyes, saddle nose and a pointed chin (Figure 1A). There were multiple, small, palpable, non-tender, blackish spot in different parts of the body and thick skin in palm and soles due to excessive itching. Abdominal examination showed 4 cm firm liver and cardiovascular system examination showed grade 3 ejection systolic murmur along the left sternal border in the 2nd intercostal space. The child was assessed in the Pediatric Neurology Department using Bayley scales of Infant and Toddler development and was found developmentally backward.

Investigations showed normal complete blood counts. Serum total bilirubin was 1.9 mg/dL (conjugated bilirubin 0.9 mg/dL), alanine

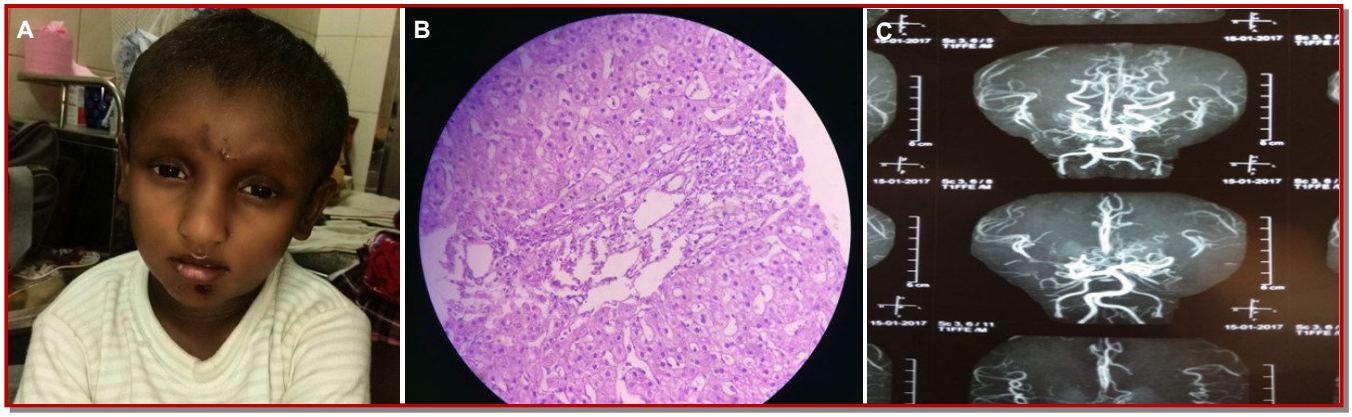

Figure 1: (A) Boy showing typical triangular facies with broad forehead, deep-set eyes, saddle nose and a pointed chin; (B) Liver histopathology showing normal lobular hepatic architecture including normal appearing hepatocyte cords. Portal areas contain mildly dilated hepatic artery and portal vein. No bile ductule was seen. The portal areas contained moderate number of chronic inflammatory cells and showed periportal fibrosis; (C) MRA of the brain showing multiple enlarged deep collateral vessels which is giving "puff on smoke" appearance while both ICAs show diffuse narrowing along with occlusion of supraclenoid part of both ICAs. MCAs and ACAs appear normal. Distal basilar artery appears normal

transaminase 147 U/L, alkaline phosphatase 806 U/L and GGT 868 U/L, INR 1.01, serum cholesterol level was 211 mg/dL. Renal functions and ultrasonography of whole abdomen were normal. X-ray spine showed spina bifida occulta. Echocardiography showed both right and left pulmonary artery stenosis, with mild aortic valve stenosis and mild coarctation of aorta. Slit lamp examination of eyes showed posterior embryotoxon on both eyes. Hepatic histopathological examination revealed paucity of interlobular bile ducts (out of eight portal tracts examined, none had bile duct) (Figure 1B). Magnetic resonance angiography of brain showed "puff of smoke" appearance which is typical features of moyamoya disease (Figure 1C). The child was diagnosed as a case of Alagille syndrome and started on ursodexycholic acid, cholestyramine (240 mg/kg/day) and fat-soluble vitamin supplementation. Pruritus was relieved partially with these treatment.

Discussion

In a study of 92 cases of Alagille syndrome, Emerick et al. described of interlobular bile ductular paucity in 85%, cholestatic jaundice in 96%, cardiac anomalies in 97%, characteristic triangular facies in 96% cases, vertebral defects (butterfly vertebra) in 51% and posterior embryotoxon in the eye in 78%.[3] Though we could not do mutation analysis due to lack of facilities in our country but our case had four of five major features of Alagille syndrome and they were characteristic triangular facies, pulmonary artery stenosis, posterior embryotoxon and bile ductular paucity. Pruritus is the major symptom and some of the cases respond to bile acid binding agents like cholestyramine (12-15 g/day). Our patient also showed some response to cholestyramine and his pruritus improved partially. External/internal partial biliary diversion (PBD) helps in ameliorating pruritus in the majority of cases who do not respond to medical therapy. A proportion of cases of Alagille syndrome require liver transplantation mainly for intractable pruritus. The long-term prognosis of Alagille syndrome is variable and depends on the severity of congenital heart disease, progression of liver disease to cirrhosis, development of intracranial bleeding and renal abnormalities.[4]

In a large retrospective chart review of 268 cases of Alagille syndrome, moyamoya disease was documented only in 1 patient.[5] To the best of our knowledge, this association has been reported only in a few cases. Most of the reported cases presented with cerebrovascular events. Among them two cases came with right-sided weakness and remaining two cases reported with left hemispheric stroke.[5, 9, 14] It seems that this association is rare but exact magnitude is not known as routine brain imaging to find out this association is not practiced regularly. As we were aware of this association, magnetic resonance angiography of brain was done despite the child was asymptomatic and to our surprise the child had features of moyamoya disease. In Bangladesh, a few cases on symptomatic moyamoya disease in children have been reported but our patient having associated Alagille syndrome.[15]

Moyamoya disease is progressive intracranial arterial occlusive described as definite moyamoya (when changes on both side) and probable moyamoya (if changes are restricted to one side).[8] The disease has a worldwide prevalence though initially seen in the Japanese population. Most of the children with moyamoya usually presents with cerebral ischemia though adults come with

hemorrhagic stroke. Moyamoya in Japanese means "hazy puff of smoke" appearance and angiography shows abnormal networking of collateral vessels arising from base of brain and basal ganglia.[16] The etiology of moyamoya disease is still unknown. There may be increased opportunity to identify asymptomatic moyamoya disease with the availability of magnetic resonance imaging technique. According to a nation-wide questionnaire study which was conducted in 1994, Yamada et al. (2005) has done a retrospective analysis of prognosis in 33 asymptomatic moyamoya patients and described 4 (12%) patients experienced transient ischemic attack and only 2 (6%) patients died of hemorrhagic stroke.[17] Among 10 asymptomatic patients of moyamoya disease, Nanba et al. (2003) found only 1 patient (10%) developed ischemic stroke due to disease progression over a four year study period.[18] A prospective, nation-wide, multicenter observational study (asymptomatic moyamoya registry, Japan) has started to look for the epidemiology, pathophysiology, and prognosis in asymptomatic moyamoya disease.

However, treatment protocol for the asymptomatic patient with moyamoya disease is still controversial. Japanese Moyamoya disease Research Committee recommends lifestyle modification with risk factor management. Due to increased chance of hemorrhagic stroke, antiplatelet agents are not practiced for asymptomatic patient. Revascularization can be done who has cerebral hemodynamic abnormality. To predict ischemic and hemorrhagic stroke and for long-term follow-up regular MRA or MRI examinations can be done.[18]

Conclusion

We are reporting a case of Alagille syndrome with asymptomatic moyamoya disease detected on routine brain imaging. Magnitude of this association and the role of preventive measures need further evaluation in larger studies.

Conflict of interest

There is no conflict of interest.

References

1. Alagille D, Habib EC, Thomassin N. L'atresie des voies biliaires intrahepatiques avec voies biliaires extrahepatiques permeables chez l'enfant. Paris, Editions Medicales Flammarion, 1969, pp 301-18.
2. Danks DM, Campbell PE, Jack I, Rogers J, Smith AL. Studies of the aetiology of neonatal hepatitis and biliary atresia. Arch Dis Child. 1977; 52: 360-67.
3. Emerick KM, Rand EB, Goldmuntz E, Krantz ID, Spinner NB, Piccoli DA. Features of Alagille syndrome in 92 patients: Frequency and relation to prognosis. Hepatology 1999; 29: 822-29.
4. Hadchouel M. Alagille syndrome. Indian J Pediatr. 2002; 69: 815-18.
5. Kamath B, Spinner NB, Emerick KM, Piccoli DA, Krantz ID. Vascular anomalies in Alagille syndrome: A significant cause of morbidity and mortality. Circulation 2004; 109: 1354-58.
6. La Brecque DR, Mitros FA, Nathan RJ. Four generations of arteriohepatic dysplasia. Hepatology 1982; 2: 467-74.
7. Nishikawa A, Mori H, Takahashi M, Ojima A, Shimokawa K, Furuta T. Alagille syndrome: A case with a hamartomatous nodule of the liver. Acta Pathol Jpn. 1987; 37: 1319-26.
8. Quek SC, Tan L, Quek ST, Yip W, Aw M, Quak SH. Abdominal coarctation and Alagille syndrome. Pediatrics 2000; 106: E9.
9. Rachmel A, Zeharia A, Neuman-Levin M, Weitz R, Shamir R, Dinari G et al. Alagille syndrome associated with moyamoya disease. Am J Med Genet. 1989; 33: 89–91.
10. Connor SE, Hewes D, Ball C, Jarosz JM. Alagille syndrome associated with angiographic moyamoya. Childs Nerv Syst. 2002; 18: 186-90.
11. Moreau S, Bourdon N, Jokic M. Alagille syndrome with cavernous carotid artery aneurysm. Int J Pediatr Otorhinolaryngol. 1999; 50: 139-43.
12. Hoffenberg EJ, Narkewicz MR, Sondheimer JM. Outcome of syndromic paucity of interlobular bile ducts (Alagille syndrome) with onset of cholestasis in infancy. J Pediatr. 1995; 127: 220-24.
13. Watson GH, Miller V. Arteriohepatic dysplasia: Familial pulmonary arterial stenosis with neonatal liver disease. Arch Dis Child. 1973; 48: 459-66.
14. Woolfenden AR, Albers GW, Steinberg GK, et al. Moyamoya syndrome in children with Alagille syndrome: Additional evidence of a vasculopathy. Pediatrics 1999; 103: 505-08.
15. Akhter S, Riaaz R, Jahan R, Rahman SA. Moyamoya disease of a child. Bangabandhu Sheikh Mujib Med Univ J. 2017; 10: 101-04.
16. Suzuki J, Takaku A. Cerebrovascular "moyamoya" disease: Disease showing abnormal net-like vessels in base of brain. Arch Neurol. 1969; 20: 288–99.
17. Yamada M, Fujii K, Fukui M. Clinical features and outcomes in patients with asymptomatic moyamoya disease: From the results of nation-wide questionnaire survey. No Shinkei Geka. 2005; 33: 337–42.
18. Nanba R, Kuroda S, Takeda M, Shichinohe H, Nakayama N, Ishikawa T, et al. Clinical features and outcomes of 10 asymptomatic adult patients with moyamoya disease. No Shinkei Geka. 2003; 31: 1291–95.