Liver Transplantation in a Child With Severe Hypercholesterolaemia in Alagille Syndrome

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Abstract

***Introduction**: Liver transplantation is a curative treatment modality in children with end stage liver disease in Alagille syndrome. **Clinical Picture**: We report a 3-year-old child with this condition who had severe hypercholesterolaemia, pruritus and extensive xanthomatosis. **Treatment**: Liver transplantation was performed in this patient. **Outcome**: He recovered well with normalisation of his lipid profile. This procedure also resulted in resolution of the disfiguring xanthomatosis.*

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Key words: Alagille syndrome, Child, Hypercholesterolaemia, Liver transplant, Xanthoma

Introduction

Alagille syndrome (AS) or arteriohepatic dysplasia[1] is a genetic disorder transmitted in an autosomal dominant inheritance. The chromosomal abnormality has been identified to the short arm of chromosome 20.[2] Main features of this syndrome[3] are a characteristic triangular facies with cholestatic jaundice resulting from a paucity of intrahepatic bile ducts, cardiac, ocular and spinal defects.

The extent of hepatic dysfunction is largely dependent on the severity of bile duct hypoplasia, and many patients remain relatively well in the milder cases. Some patients, on the other extreme, have progressive disease culminating in cirrhosis and liver failure. Even before the end-stage disease, the quality of life may be affected from other complications[4] such as pruritis, hypercholesterolaemia, development of xanthomata, malnutrition and failure of growth.

Recent advances in paediatric liver transplantation[5] have led to improved survival in those with end-stage liver disease, as well as to an improved quality of life in younger children affected by this syndrome.[4,6] The indications for, and timing of, liver transplant in each child must be individualised in accordance with the benefits versus risks of a major surgery and potential graft rejection, and the need for life-long immunosuppression.

Case Report

A 3-year-old boy was diagnosed with AS shortly after birth when he presented with cholestatic jaundice. The liver biopsy confirmed bile duct hypoplasia. In addition, other features of AS were present, including the typical facies, posterior embryotoxon and a butterfly-shaped sixth thoracic vertebra. There was peripheral pulmonary stenosis, suggested by a systolic murmur and confirmed on echocardiogram.

When he was referred to our unit, his weight was just under the third centile. The liver involvement was evident from an abnormal liver function test with a conjugated bilirubin of 18 μmol/L (unconjugated bilirubin 5 μmol/L), alanine transaminase [ALT] 251 (10-70) U/L, aspartate transaminase [AST] 289 (10-50) U/L and glutanyl transaminase [GGT] 619 (20-90) U/L. However, the patient had developed progressive and extensive xanthomatosis from about 2 years of age. The xanthomata covered his trunk and limbs (Fig. 1), including the palms and soles (Fig. 2) This was accompanied with severe pruritis. Hypercholesterolaemia was clearly responsible for this, with the fasting lipid profile as follows: total cholesterol 41.51 mmol/L, triglycerides 2.86 mmol/L, high density lipoprotein (HDL)-C 0.74 mmol/L, low density lipoprotein (LDL)-C 39.48 mmol/L. Treatment with fibrates and

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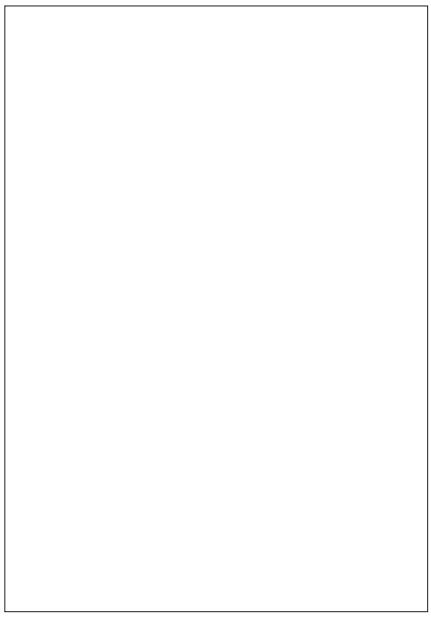

Fig. 1.

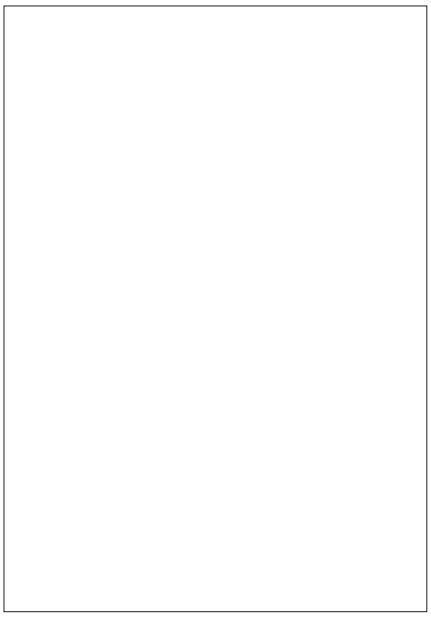

Fig. 2.

Figs. 1 & 2. Extensive xanthomata resulting from hypercholesterolaemia.

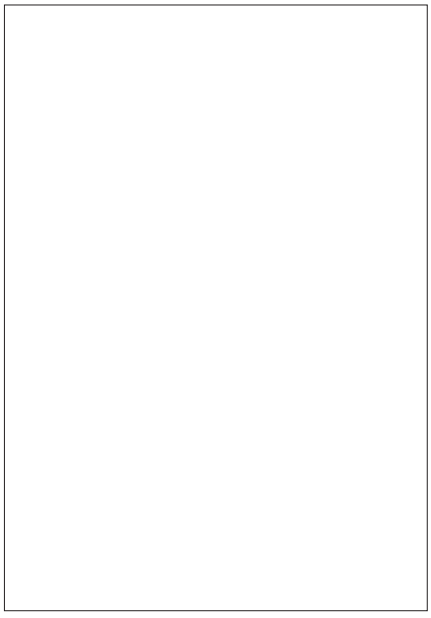

Fig. 1a.

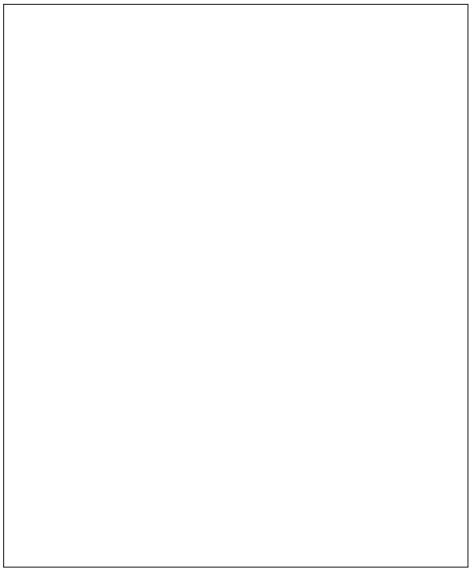

Fig. 2a.

Figs. 1a & 2a. Resolution of xanthomata in the same patient after liver transplant.

simvastatin for 6 months did not lower the levels satisfactorily to prevent progression of symptoms.

A cardiac catheterisation was performed with a view to coronary angiography and obtaining right heart haemodynamics. Narrowing of both branch pulmonary arteries was noted from the right ventriculogram (Fig. 3). The pressure within the distal pulmonary artery was 20/10 mmHg and a gradient of 30 mmHg obtained on pull-back of the catheter into the right ventricle. This was not considered a major risk factor to liver transplant. Coronary angiography demonstrated pristine vessels without evidence of atheromatosis.

A joint decision was made between the medical team and the child's family for him to undergo a living-related liver transplantation. The chief indications were the severe hypercholesterolaemia, the extensive and disfiguring xanthomatosis and the pruritus. The donor was his mother whose liver and lipid profile were normal.

The transplant was uncomplicated and the graft took well with clearance of the jaundice and normalisation of the

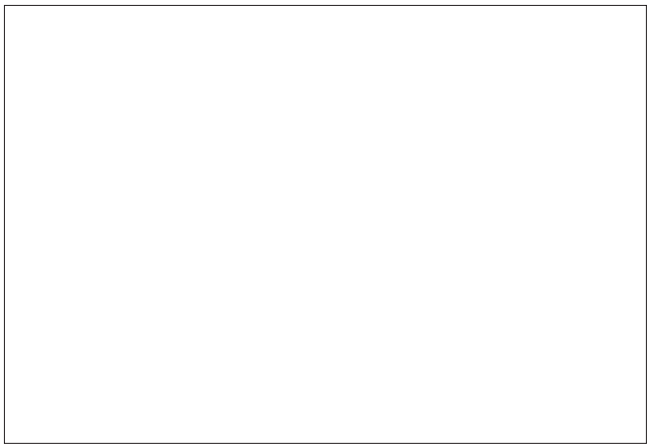

Fig. 3. Right ventriculogram demonstrating hypoplastic pulmonary artery in this patient with Alagille syndrome.

liver function (conjugated bilirubin 1 μmol/L, ALT 36 U/L, AST 56 U/L, GGT 168 U/L). What was more impressive to the family was the fact that the xanthomata began to shrink with time and the pruritis improved. Correction of the metabolic derangement was evident in the fasting lipid profile: total cholesterol 5.3 mmol/L, HDL-C 1.6 mmol/L, LDL-C 2.7 mmol/L and triglyceride 2.3 mmol/L.

The patient had been on follow-up for 2 years since his transplant. He remained well and his weight had increased considerably to beyond the 25th centile. He was anicteric and there was striking cosmetic improvement with resolution of the xanthomata (Figs. 1a and 2a).

Discussion

AS is an autosomal dominant condition with a high mutation rate, wide variability in expression and incomplete penetrance. Recent work has identified the genetic abnormality to chromosome 20p12. The incidence is estimated at 1 in 70,000 live births.[7] Several large series of patients with AS have been published.[3,8] In a recent review by Emerick and co-workers,[8] paucity of interlobular bile ducts leading to cholestatic jaundice was found in 85% of patients who had liver biospy, a characteristic facies present in 96%, cardiac murmur in 97%, ocular involvement (posterior embryotoxon) in 78% and butterfly-shaped vertebrae in 51%. The facial features include a prominent forehead, deep set eyes, hypertelorism, saddle nose and a pointed chin producing a triangular appearance.[9] Renal disease and intracranial pathology were also described in 40% and 14% of the patients respectively.

There is a wide spectrum in the degree of hepatic dysfunction.[10,11] Many patients have mild involvement requiring supportive medical care. The degree of liver involvement may vary with time. Improvement or progressive deterioration has been described. On the more extreme end are those with severe cholestasis culminating in liver cirrhosis. It has been estimated that about 12%[12] to 21%[8] develop cirrhosis and require liver transplantation.

The most commonly associated structural cardiac defect is peripheral pulmonary stenosis. The severity of this complication is directly related to the degree of obstruction. While not usually a contraindication for liver transplant, cardiovascular complications may be an incremental risk factor for the success of the transplant.[4,6,8]

Hypercholesterolaemia and xanthoma formation[13] are also associated with this condition. In a study reported by Dupont et al,[14] high serum cholesterol of between 15 to 20 mmol/L was reported in children with AS, and in another series of 12 patients by Cordona et al[4] who underwent liver transplantation, the serum cholesterol ranged from 3.5 to 29 mmol/L.

The indications for and timing of liver transplant in AS are important considerations of those looking after children with this condition. Major indications for liver transplant[6] include progressive and severe liver dysfunction leading to cirrhosis, portal hypertension, ascites and hypersplenism. It has also been carried out for failure to thrive, hypercholesterolaemia, xanthomatosis and pruritus where the quality of life is much improved after the transplant.[6,13] The timing of the transplant would be greatly dependent on the intensity of the problem and the degree to which the child's growth and life are affected by the complications. With increased experience in paediatric liver transplant and advances in immunosuppressive therapy, it is now possible to carry out a transplant with good results in a young child before school-going age. In our centre which carries out liver transplantation in Singapore, a total of 28 patients have been transplanted, of whom 24 have done well.

In the above patient, the main concerns relate to the severe hypercholesterolaemia, intense pruritus and disfiguring exanthomata. Liver transplantation has been reported to be a therapeutic option in the management of familial hypercholesterolaemia, particularly before the onset of cardiovascular complications.[15-17] Why coronary artery disease is not more prevalent despite the abnormal lipid profile in AS makes for an interesting study. Davit-Spraul et al[18] pointed out that perhaps the inhibitory effect of ApoE-rich HDL particles on platelet aggregation may be protective. It has been suggested that cells in these patients may have a membrane defect in the transfer of cholesterol (LDL receptor defect) leading to its excessive synthesis.[14] The cholesterol level in this patient was the highest we have encountered in our own series of patients with AS. The extensive xanthomatosis was disfiguring and causing the patient and his family a great deal of distress, constituting major indications for liver transplantation. The transplant

was curative from these aspects, and the intense pruritus causing significant discomfort to the patient resolved. His growth also improved and the quality of life, despite the continuing need for follow up and immunosuppressive medication, was enhanced.

Conclusion

The spectrum of involvement in AS is extremely variable. This applies to the various features of AS, whether from the hepatic, cardiovascular or other standpoints. While the milder cases require minimal medical treatment, the severe cases may end up in cirrhosis or present with other complications such as metabolic disturbance. The role of liver transplantation in addressing these problems is highlighted in this report.

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