Reye syndrome and liver transplantation

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Reye syndrome is a rare, but severe and often fatal disease. The etiology of the classical Reye syndrome is unknown, but it is typically preceded by a viral infection with a free interval of three to five days. The main physiopathological hypothesis is a mitochondrial metabolism insult causing acute liver failure and encephalopathy. Survivors present serious neurological sequelae. The treatment of Reye syndrome is usually medical with intensive care management. Herein, we present the clinical case of a six-month-old baby diagnosed with Reye syndrome with a fulminant hepatitis, who was successfully liver transplanted with an auxiliary partial orthotopic liver transplantation.

Key words: Reye syndrome, fulminant hepatitis, auxiliary partial orthotopic liver transplantation, pediatric liver transplantation, aspirin.

Reye syndrome (RS) was first described in 1963 by Reye et al.[1] from the Royal Alexandra Hospital for Children in Sydney, NSW, Australia. RS is rare, affects predominantly children, and occurs as a 'two-phase illness' after a free interval of three to five days following a viral infection with moderate fever[2]. The clinical manifestations are profuse vomiting and severe encephalopathy with convulsions; jaundice is usually absent, but a mild hepatomegaly can be found. The biological findings are disturbed liver functions associated with hypoglycemia and hyperammonemia[3]. Liver needle biopsies can reveal fatty liver degeneration with no inflammation, which is suggestive of RS but not pathognomonic. The prognosis is poor, with death occurring in 40%. The survivors commonly present neurocognitive sequelae[4]. The exact etiology of RS remains unknown; however, the hypothesis of an immunologic mitochondrial insult resulting from a viral infection has been advanced[2]. Salicylate administration in viral syndrome was pointed to as contributing to the development of RS. The incidence of RS decreased in the eighties with the warnings of salicylate use in viral disease. Debate continues regarding the relationship between aspirin and RS[5].

We report the clinical case of a six-month-old infant diagnosed with RS following the administration of aspirin in the context of an upper airway viral infection. An auxiliary partial orthotopic liver transplantation (APOLT) was performed in order to alleviate the acute liver dysfunction.

Case Report

The baby was born at term following an uneventful pregnancy. The Apgar score was 10; the newborn jaundice was treated with phototherapy. At the age of six months, the baby presented a moderate hyperthermia with anorexia, diarrhea and cough. A few hours later, the corporeal temperature increased, and the baby presented vomiting with clonic movements of upper and lower limbs. The baby appeared tired and pale, and was sweating. He was taken under the care of the emergency team and transferred to a pediatric reanimation unit. The clinical state required intubation and mechanical ventilation. A hepatomegaly was noted; however, the spleen was not palpable. A severe hypoglycemia (0.17 g/L) was compensated by perfusing glucosate solution 30%. The status epilepticus was controlled with diazepam injection. The parents reported the

administration of an adapted dose of aspirin 12 hours prior to the onset of the symptoms.

The biological investigations revealed an acute liver dysfunction with an important cytolysis in 24 hours. Aspartate aminotransferase (AST) increased from 402 IU/L to 17 530 IU/L and alanine aminotransferase (ALT) from 75 IU/L to 11 270 IU/L. The hemostasis was perturbed with a prothrombin time of 19% and a factor V at 18%. The ammonemia increased moderately to 80 pmol/L. The analysis of the cerebrospinal fluid gave no clue for a meningoencephalitis. The serologies of hepatotropic virus were negative (Epstein-Barr virus [EBV], cytomegalovirus [CMV], hepatitis A virus (HAV), HBV, HCV, herpes simplex virus [HSV], varicella zoster virus [VZV], human immunodeficiency virus [HIV]). The ratio of acetoacetate/beta hydroxybutyrate was normal. Results of the investigation of galactosemia were negative, and chromatography analysis provided no evidence of urea cycle disturbance or fatty acid oxidation disorders. The transfontanellar echography did not show any signs of hemorrhage but an aspect compatible with cerebral edema. The liver Doppler-echography confirmed the hepatomegaly, but there was no biliary tract dilation; the portal vein and the hepatic artery flows were normal. The electroencephalogram showed signs of a delta coma.

The diagnosis of a fulminant hepatitis due to RS was posed. The situation was discussed between pediatricians and the local liver transplant team, and it was decided that an emergency liver transplantation was required. The transplant surgeons performed an APOLT, which was realized 40 hours after registration on the waiting list. There were no complications associated with the surgery, which consisted –according to Couinaud's classification- of a right hepatectomy (the left lobe was preserved). The donor right lobe was implanted.

The liver biopsy of the explanted piece revealed large necrosed areas (60%) with no inflammatory reaction or microvesicular steatosis. Mitosis of hepatocytes was observed; therefore, it was possible to expect a regenerative phenomenon. The aspect was compatible with a fulminant hepatitis.

Postoperatively, a quadruple inductive immunosuppressive protocol was established with azathioprine, cyclosporine, thymoglobulin, and corticosteroids, followed by a double long-term therapy with cyclosporine and corticosteroids. The hepatic liver function evolved favorably. The liver echographic follow-ups showed no abnormalities. Liver needle biopsies were performed on the auxiliary graft and on the native liver on the 10th and 21st days postoperatively. Three weeks after the transplantation, the native liver showed complete hepatic regeneration. A hepatobiliary scintigraphy one month after the transplantation showed a normal native and graft liver function.

The baby was free from respiratory assistance one month after the transplantation. However, the neurological evolution presented major impairment. A cerebral magnetic resonance imaging showed parieto-occipital ischemic lesions. Visual neurophysiologic explorations demonstrated an alteration of the central visual tracts. The baby had motor defect and developed a severe epilepsy. Intensive sensorial stimulation and motor kinesitherapy were proposed in order to limit the sequelae. Ten months after the APOLT, the immunosuppressive therapy was progressively stopped, leading to the liver graft involution.

Today, the child is 14 years old, and is still followed for severe epilepsy and delayed psychomotor development. His liver function is normal and echographic exploration showed a complete regression of the auxiliary liver graft.

Discussion

Reye syndrome should be precisely defined. The syndrome was first described as a 'clinicopathological entity of unknown etiology'. The anamnesis notes a biphasic evolution with an antecedent of a classical viral infection after a free interval of a few days prior to the beginning of the signs[4]. The clinical presentation is uncontrollable emesis, convulsion and coma. Biological data show hypoglycemia, increased transaminase but not bilirubin levels, hyperammonemia, and a prolonged prothrombin time. The liver histologic analysis reveals a suggestive fatty infiltration with microvesicular steatosis[3,6]. Meningoencephalitis and fulminant hepatitis should be explored in the differential diagnosis. Physicians have to be aware of the Reye-like syndrome due to inherent disorders of mitochondrial metabolism such as medium-chain acyl coenzyme A

dehydrogenase deficiency[7]. Other metabolic defects responsible for Reye-like syndrome or predisposing to RS are identified. Reye-like syndrome seems to be triggered by infective agents. Any child suspected of presenting a RS should undergo investigations for inborn errors of metabolism. Biochemical techniques available in the early eighties helped to detect these metabolic abnormalities[2]. Parallel to this, aspirin intake was supposed to be involved in RS. A large worldwide warning, more intensive in the United States and the United Kingdom, was broadcast in the eighties regarding the administration of aspirin in children even if the dose was adapted[8]. Pediatricians recommend parents to avoid the use of salicylates in the febrile state, and curiously, the incidence of the disease decreased. We should be aware that RS was also observed in the absence of aspirin intake; thus, the debate on this issue continues, and we could assume that a lack of understanding of the physiopathology of the disease led to a misdiagnosis and confusion between RS and Reye-like syndrome[5].

The syndrome is associated with a high mortality rate and the treatment is symptomatic: intensive care management with correction of metabolic imbalances, control of convulsions, and monitoring of intracranial hypertension due to cerebral edema[9].

In 1996, the Strasbourg transplant team successfully performed an APOLT in the context of a RS[10-14]. No case of RS treated with liver transplantation is reported in the literature. Moreover, pediatric liver transplantation for a small baby (<10 kg) is a true challenge due to the small vessel caliber and the small volume of the abdominal cavity. The decision of an auxiliary liver transplantation was indicated in this case. The RS was confirmed, and the differential diagnoses were explored. In a situation of an acute liver failure, we could expect a regeneration of the native liver; thus, the left lobe of the liver was preserved and the right lobe was resected, and its function was supplied by a right lobe graft, implanted orthotopically[15].

When the native liver regeneration was confirmed with biopsies, the decision of to decrease immunosuppressive treatment was taken. The graft involuted sponta-neously, and the secondary effects of a prolonged immu-nosuppressive treatment, such as infections, lymphomas and delayed development, could be avoided.

Reye syndrome raises controversies in the understanding of its physiopathology, and its prognosis is severe. In our experience, auxiliary liver transplantation was shown to be successful in a RS situation in a small baby.

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