

Case Report

Neonatal Hemochromatosis: Favorable Effect of Pharmacotherapy

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INTRODUCTION

Neonatal or Perinatal Hemochromatosis is an uncommon disorder, clinico-pathologically defined as a severe liver disease of intrauterine onset associated with extrahepatic siderosis that spares reticuloendothelial elements^[1]. This entity was initially recognized post-mortem during autopsies and was thought to be due to abnormal placental handling of the iron in the intrauterine period. During the past decade, more cases have been reported and evaluated in the neonatal period and early infancy due to the increase in awareness of this condition. It is a rare, and usually fatal, multi-system disease. The management of this condition remains a challenge to the perinatal team. Previously, the affected patients were treated with supportive measures while waiting for a liver transplant, but recently, pharmacotherapy with an antioxidant-chelation cocktail was tried with varying degrees of success. Generally, however, the outcome has not been satisfactory. We report a case of neonatal hemochromatosis which showed a very good response, both clinically and biochemically, to pharmacotherapy with antioxidants and desferrioxamine. This is the first case reported from this region of a Saudi patient residing in Kuwait.

CASE REPORT

The patient is a male Saudi infant born in a regional hospital (Al Jahra Hospital) in Kuwait on 11 May 1998. The baby is the first child of consanguineous parents (first cousins) who are healthy and normal. After uneventful first and second trimesters, intrauterine growth retardation of the fetus was noted from the 28th week of gestation, with a lag of about two weeks. The mother was booked for regular serial follow-ups and investigations were done to rule out common causes of intrauterine growth retardation. Antenatally, the mother did not have any medical illnesses. There was no history of perinatal loss in the family.

The mother went into spontaneous pre-term labor at 31 weeks of gestation. She delivered a 750 gram male child with symmetrical growth retardation. The delivery was normal with Apgar scores of 6 and 8 at 1 and 5 minutes, respectively. The baby had respiratory distress syndrome, was ventilated and received two doses of exogenous surfactant. At birth he was noted to be pale and icteric. Laboratory results revealed: hemoglobin-108 g/l (normal 145-325 g/l); Total bilirubin 89 $\mu\text{mol/l}$ [normal < 34 $\mu\text{mol/l}$ (Premature)]; direct bilirubin 12 $\mu\text{mol/l}$ (normal <3.42 $\mu\text{mol/L}$); Aspartate aminotransferase- 120 U/L (normal 15-55 U/L); Alanine amino transferase-60 U/L (normal 6-50 U/L); Alkaline phosphatase 234 U/L (normal 145-420 U/L); albumin 23 g/l (normal 18-30 g/l). Hemolytic disorders were ruled out as the cause of this early icterus and anemia. The baby was started on early photo-therapy as the bilirubin started to increase and was given packed cells for the anemia.

By the 5th day of age, significant bronzing of the skin was noted and the baby became dark gray in color, which was not explainable by the direct bilirubinemia alone (12% of the total bilirubin). Hence, serum iron profile, transferrin, percent saturation and ferritin were requested. The initial result showed a high normal serum iron -24.5 $\mu\text{mol/l}$ (normal 4 - 33 $\mu\text{mol/l}$), high percent saturation 77% (normal 50%), low transferrin -1.3 g/l (normal 2.18- 3.47 g/l), and a significantly elevated ferritin of 1485 $\mu\text{g/l}$ (normal 25- 200 $\mu\text{g/l}$) on the fifth day. The baby was further investigated for other causes of deranged liver functions, cholestasis-like intrauterine viral infections, biliary atresia, tyrosinemia, alpha one antitrypsin deficiency, bile acid disorders and galactosemia. None of these could be detected.

The baby had hypoalbuminemia, transient hypoglycemia in the first 48 hrs, and biochemical evidence of hemochromatosis (hyperferritinemia, high iron, decreased transferrin, increased

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saturation, and increased alpha-feto protein). The baby developed progressive cholestasis, with worsening liver functions and persistent hyperferritinemia as shown in Figs. 1 and 2. A liver biopsy was done at six weeks of age when the clinical condition was more stable. The biopsy showed Grade 2 hemosiderosis in hepatocytes of zone 1 with normal lobular pattern, normal number of bile ducts, no inflammation in portal tracts and marked cholestasis of the lobules, predominantly in zone 3. A repeat liver biopsy at eight weeks revealed, on electron microscopy, changes secondary to cholestasis, normal glycogen content, normal mitochondria, normal endoplasmic reticulum and peroxisomes. CT scan of the liver revealed increased density (> 65 Hf units) which is compatible with iron load. Lip biopsy could not be done due to the very small size of the baby.

The baby was extubated at 35 days of age, and was managed with supportive measures. The course was subsequently complicated by biochemical evidence of hypoparathyroidism at eight weeks of age and hypothyroidism at 20 weeks of postnatal age. Appropriate treatment was started. Arrangements were made for a liver transplant abroad. As the patient did not show any spontaneous resolution of cholestasis or hyperferritinemia and was not thriving, antioxidant treatment was started at the age of 18 weeks with Vitamin E parenterally (25 units/kg), ursodeoxycholic acid (600 mg/m²) orally, N-acetyl cysteine (170 mg/kg/day orally 4 hourly for 21 doses). Intravenous desferrioxamine was also given at a dose of 30 mg/kg daily and continued until the ferritin level came down to 500 μ g/l. There was a fall in ferritin level from 2627 μ g/l pre treatment to 1453 μ g/l at 2 weeks, to 877 μ g/l at 4 weeks, and 255 μ g/l at 6 weeks after the starting of the above regimen (Fig. 1). There was also a concurrent fall in bilirubin levels from 308 μ mol/l total and 198 μ mol/l of direct (pre-treatment) levels to 217 μ mol/l of total and 128 μ mol/l of direct at 2 weeks post-treatment. At 4 weeks, the levels fell to 143 μ mol/l of total and 82 μ mol/l of direct, and to 85 μ mol/l of total and 49 μ mol/l of direct bilirubin at 6 weeks (Fig. 2).

After 6 weeks, the baby started to gain weight and became more alert and active. The liver functions and ferritin levels subsequently improved and were maintained in the normal ranges for the next three months. The baby was discharged at nine months of age in good condition. He was recognizing and interacting with his parents, smiling, following objects, had head control, and started to roll over. One month after discharge, the baby was admitted with massive aspiration and died in the pediatric intensive care unit.

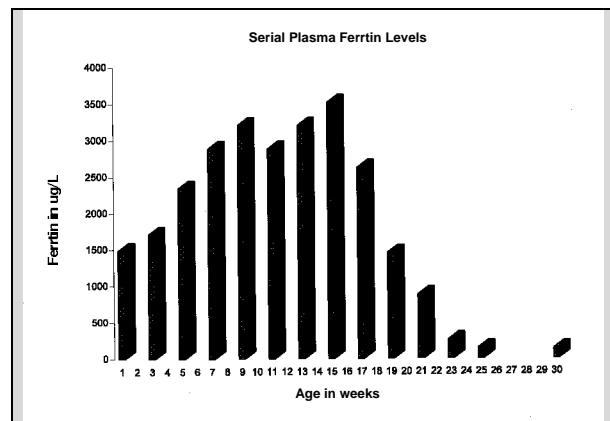


Fig. 1: Showing the Ferritin levels in ug/L before and after starting treatment at 18 weeks of age.

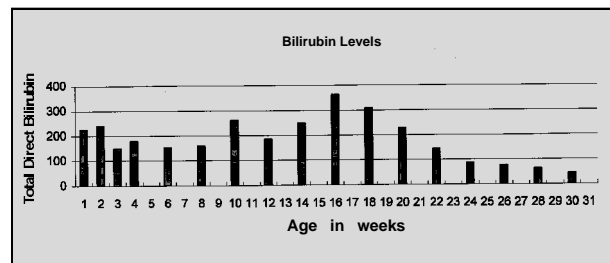


Fig. 2: Showing the serial total and direct serum bilirubin levels. The top darker portion showing direct bilirubin component.

DISCUSSION

Neonatal hemochromatosis is a rare disease, which presents as a multisystem involvement and is often fatal. The affected babies may be stillborn, preterm or manifest intrauterine growth retardation. Oligohydramnios, placental edema or rarely polyhydramnios have been associated with these pregnancies^[2]. The clinical illness is usually present at birth or within the first few hours of life. It appears as a chronic liver disease of intrauterine onset, characterized by deranged liver functions, cholestasis, hypoalbuminemia, hypoglycaemia, hyperferritinemia and increased alpha-fetoprotein. The pathogenesis is not clear and two hypotheses have been proposed. One is a disturbed iron uptake at the placental level with the resulting iron overload causing fetal liver injury. The other postulate is a primary intrauterine liver insult leading to impaired hepatic protein synthesis and reduced iron binding capacity and iron overload^[2].

In the 1980s, this condition was usually an autopsy diagnosis but in the past decade, due to increased awareness of this entity, more cases have been recognized and reported in the first few weeks of life. Since it is a highly recurrent condition in families, the diagnosis would be made earlier when a previous sib had died with the same problem. In this first-born baby, the diagnosis was, however, facilitated by a high index of suspicion in a child with intrauterine growth retardation, deranged liver functions and a significant bronzing of the

skin, which led to investigations for neonatal hemochromatosis.

The natural course of this disease has been unsatisfactory with only two cases in the available literature reported with spontaneous improvement and survival^[3,4]. This child did not show any spontaneous improvement in liver functions or ferritin levels until 18 weeks of age when pharmacotherapy was started. Initially, patients were treated with only non-specific supportive measures while waiting for an orthotopic liver transplant. Since 1993, the supportive management has been modified to include desferrioxamine and an antioxidant cocktail which consisted of d-alpha tocopheryl polyethylene glycol succinate 25 iu/kg per day orally; oral N acetyl cysteine 170 mg/kg every 4 hrs for 21 doses; prostaglandin E1 0.4 µg/kg/hr IV infusion for a maximum of 2 weeks; and selenium 3 µg/kg/day IV together with desferrioxamine 30 µg/kg/day IV until the ferritin comes down to 500 µg/l. The above regime was used in this patient except for prostaglandin, when early attempts for a liver transplant failed. After initiating this treatment, there was a significant fall in the ferritin level and improvement in the liver functions. In addition, the post treatment MRI showed no evidence of iron overload in the liver or other abdominal organs. This improvement was sustained for the next three months.

There have been reports of varying degrees of success with the pharmacotherapy. In a series of 14 reported cases, eight were started on pharmacotherapy of which only one, who underwent liver transplant, survived^[3], this cocktail of drugs has been used in different centers with varying results^[5,6]. This patient showed very good biochemical response and significant clinical response. The initial hesitation in starting the pharmacotherapy was due to the poor response reported in the previous studies, but was finally attempted when no other alternative was available. More case reports and studies will be needed to establish the effectiveness of pharmacotherapy.

Orthotopic liver transplant has given encouraging results though there are problems in getting the donors and in the technique because of

the small size of these infants^[3,7]. A few instances of recurrence of hemochromatosis in the transplanted liver have been reported. Advances in transplantation, such as living-related donors, reduced graft size, and hepatocyte infusions, may facilitate definitive therapy and better prognosis in future.

Due to the high recurrence risk in siblings, a perinatal team approach is warranted in the management of these cases with antenatal diagnosis (antenatal MRI and duplex Doppler sonography, cord blood ferritin levels)^[8,9] appropriate timing of delivery, and early postnatal diagnosis. Early diagnosis of liver failure helps to institute specific management and a better prognosis in this condition with otherwise poor outcome^[10].

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