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CASE REPORT

Neonatal haemochromatosis with reversible pituitary involvement

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Summary

Neonatal haemochromatosis is a rare alloimmune gestational disease with a high mortality. The hallmark of neonatal haemochromatosis is severe neonatal liver failure associated with extrahepatic siderosis. Thus far, no pituitary dysfunction has been reported to result from the tissue damage associated with extrahepatic siderosis. The present report describes a neonate with neonatal haemochromatosis and secondary hypothyroidism associated with pituitary iron deposition. Both the conditions were successfully treated by ABO-incompatible liver transplantation. Pituitary gland dysfunction is another possible extrahepatic manifestation of neonatal haemochromatosis, and it is reversible after liver transplantation.

Introduction

Neonatal haemochromatosis (NH), the most common cause of neonatal liver failure [1], is a rare alloimmune gestational disease with a high mortality [2]. NH is characterized by massive iron deposition in liver and other organs' parenchymal cells and histologically resembles hereditary haemochromatosis seen in adults [2]. The recurrence of NH in offspring of mother who had a previous child with this disease is preventable by infusions of high-dose immunoglobulin during pregnancy [1]. Conversely, severe NH diagnosed at birth often requires liver transplantation (LT) as salvage treatment, despite the encouraging results of immunomodulatory treatment (high-dose intravenous immunoglobulins) in combination with exchange transfusions [3–5].

Compatible, size-matched grafts are often difficult to find for neonates, and this is the main reason for high mortality at this age as compared to the entire paediatric population undergoing liver transplantation [5]. To reduce the wait time on the list and to improve the outcome of NH, the first size-matched organ may be accepted regardless of ABO group compatibility, especially in infants [6]. No pituitary dysfunction due to extrahepatic siderosis has been reported so far in NH. The present report describes the case of a newborn diagnosed with NH and hypopituitarism ascribed to iron deposition, successfully treated by ABO-incompatible LT.

Case report

A two-day-old child born at term from an uneventful pregnancy, with a body weight of 3.2 Kg, presented with jaundice, hypoglycaemia and marked coagulopathy, and was therefore diagnosed with neonatal liver failure. At that time, AST was 86 IU/l, ALT 35 IU/l, γGT 32 IU/l, total bilirubin 14.3 mg/dl, conjugated fraction 4.6 mg/dl, ammonia level 84 μmol/l, and ferritin 1339 ng/ml. International normalised ratio (INR) was 3.4, albumin 1.5 g/dl, thyroid-stimulating hormone 0.28 μUI/ml (normal values 1.7–9.9), free thyroxine 1.28 ng/dl (n.v. 2.3–7.1), and random cortisol 5.8 μg/dl (n.v. 5–25). The abdominal ultrasound showed a reduced liver size with heterogenous parenchyma and normal gallbladder. A complete diagnostic workup was carried out and ruled out tyrosinaemia type 1, galactosaemia, organic acidemias, Niemann–Pick type C disease, alpha-1-antitrypsin deficiency, mitochondrial and peroxisomal disorders. There was no serological evidence of hepatitis A, B and C, cytomegalovirus, Epstein–Barr virus, adenovirus, herpes simplex, rubella and varicella zoster virus infection. Screening for *Treponema pallidum* and toxoplasma was negative. NH was suspected and confirmed by the biopsy of the oral mucosa that showed the presence of iron deposition in the minor salivary glands (Fig. 1). Supportive treatment with vitamin E (25 IU/kg/day, orally), N-acetylcysteine (100 mg/kg/day, intravenously), desferoxamine (30 mg/kg/day, intravenously) and selenium (3 mg/kg/day, intravenously) together with intravenous immunoglobulins (1 g/Kg) and L-thyroxin was started. The clinical condition of the child progressively worsened with the appearance of poor feeding, lethargy and vomiting. The brain magnetic resonance study, performed to rule out the presence of intracranial haemorrhagic stroke, showed iron accumulation in the adenohypophysis (Fig. 2a). At 23 days of life, the patient underwent ABO-incompatible (A1 on O) liver transplantation with a left lateral segment from a deceased donor split graft. The donor was a four-year-old boy (body weight 15 Kg, height 100 cm); the graft weight was 87 g and the graft-recipient weight ratio 2.02. The immunosuppressive regimen consisted of steroids and tacrolimus (aimed at obtaining a trough level of 8–10 ng/ml). Because of the increased titre of anti-A antibodies, the child underwent a total of four blood exchanges intra-operatively, on day 0 (anti-A titre pre- and post-blood exchange 1:64 and 1:32, respectively), on day 1 (anti-A titre pre- and post-blood exchange 1:64 and 1:16, respectively) and on day 17 (anti-A titre pre- and post-blood exchange 1:32 and 1:16, respectively); rituximab was administered on day 1 (Fig. 3), with the sudden decrease in the lymphocyte count below 1% of the circulating white cells. Post-transplantation native liver pathology showed cirrhosis, diffuse parenchymal siderosis with the sparing of reticulo-endothelial structures confirming the diagnosis of NH. Following rituximab, the level of Ig was consistently low and therefore, the patient received intravenous Ig (400 mg/kg) every 27 days for 6 months. Thyroid function slowly normalized and L-thyroxine supplement was withheld at 6-week's follow-up. A follow-up brain magnetic resonance study performed 10 months after LT did not show any sign of iron deposition in the adenohypophysis (Fig. 2b). The subsequent 2-year follow-up was uneventful with normal graft, thyroid function and motor and cognitive development.

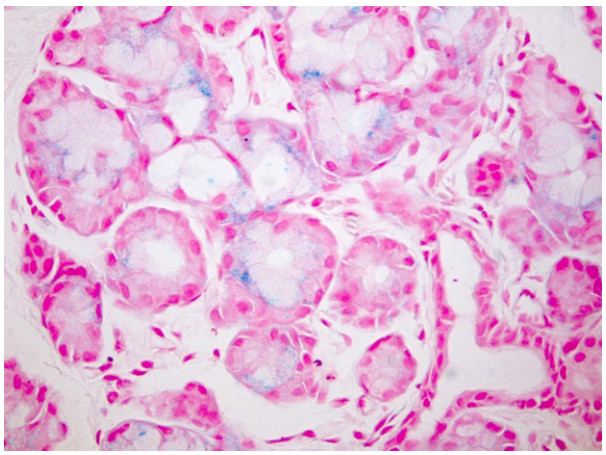

Figure 1 Prussian blue stain showing iron deposition in the mucous acinar cells of a labial minor salivary gland lobule. By courtesy of Dr Annamaria Buccoliero, University of Florence.

Discussion

The present report describes a neonate diagnosed with NH and hypothyroidism associated with iron deposition in the adenohypophysis, successfully treated with liver transplantation.

Neonatal haemochromatosis is the most common cause of neonatal liver failure and has a poor prognosis [1,2,7]. The treatment with antioxidant and iron-chelating agents is often ineffective [5]. Despite the encouraging preliminary results reported with the use of exchange transfusion and intravenous Ig [7], LT is still the treatment of choice for severe NH refractory to medical treatment [2–4,7]. Indeed, the child described in the present report arrived to the transplantation centre with an INR >4 and encephalopathy. He had already received two doses of iv immunoglobulins and was judged too haemodynamically unstable to undergo exchange transfusion. Normalization of INR in NH patients managed conservatively takes, on average, 4–6 weeks according to previous reports [7], and as a suitable organ became available for this baby, the pros and the cons

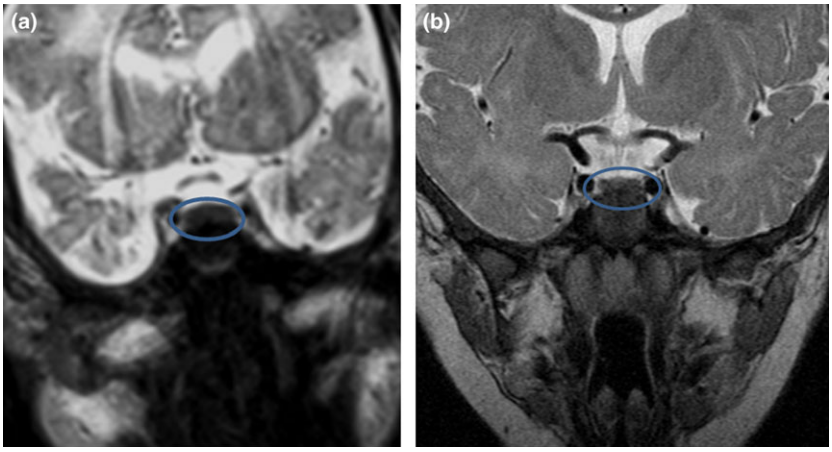

Figure 2 (a) Coronal T2 weighed magnetic resonance of the sellar region at 20 days of age (before liver transplantation), showing diffuse slight hypo-intensity of the adenohypophysis due to iron deposition. (b) Ten months later, after liver transplantation, follow-up MRI shows normalization of pituitary signal intensity.

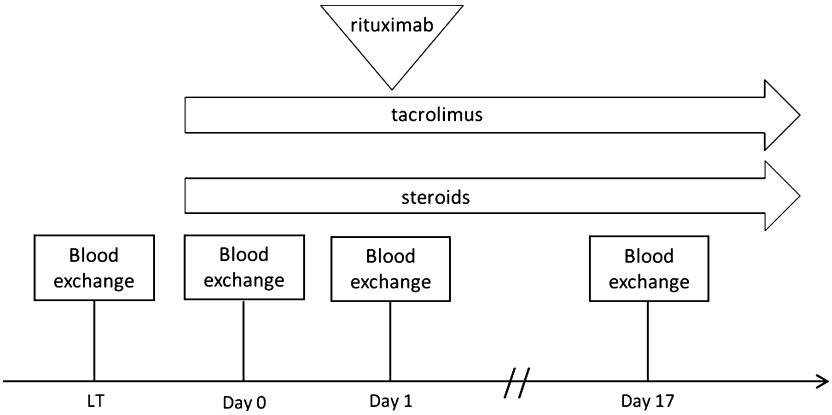

Figure 3 Protocol adopted in the perioperative phase. LT: ABO-incompatible liver transplant.

of the transplant were evaluated and it was decided not to miss the chance. LT in neonates is challenging because of the scarcity of size-matched organs and the high incidence of post-transplant complications [8–11]. In small infants in whom a left lateral segment is often large for size, liver transplantation using either mono-segment II or III is a technically challenging, effective option. To reduce the wait time on the list, nonanatomical resection and transplantation of segments II and III have been performed [12] and ABO-incompatible grafts have been used successfully [6,13,14]. In the neonate described in the present report, an ABO-incompatible LT together with exchange transfusions and the use of rituximab resulted in good control of humoral immunity and favourable outcome. The use of exchange transfusion or plasmapheresis to reduce the risk of humoral rejection in children undergoing ABO-incompatible LT is controversial, and positive results have been reported using standard immunosuppressive protocols [15,16]. The use of rituximab can reduce the risk of antibodies-mediated rejection as well as have an impact on graft survival in neonates, as already demonstrated in adults [17]. Thus far, no pituitary dysfunction has been reported in neonates with NH [2,7]. In the present report, iron deposition in the adenohypophysis was demonstrated by MR study and it was accompanied by secondary hypothyroidism due to low levels of thyroid-stimulating hormone. Random cortisol level was borderline low as well, suggesting pituitary dysfunction. Dynamic endocrine tests to confirm this hypothesis could not be performed due to the poor clinical condition of the child. The causal association between siderosis of the adenohypophysis and thyroid dysfunction was supported by the slow normalization of thyroid function after transplantation together with the disappearance of iron at the follow-up brain MR.

In conclusion, the present report describes a neonate with severe NH and NH-associated hypopituitarism suc-

cessfully treated with ABO-incompatible LT. As previously hypothesized, ABO-incompatible LT is a feasible therapeutic option in neonatal liver failure. Hypopituitarism due to iron deposition can be associated with NH and can be reversed by successful LT.

Authorship

GI: wrote the paper. RB: collected the data. IP, CA, MB, MZ, AL and MR: analysed and interpreted clinically the data. MC and LD: designed and critically revised the article.

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