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SPECIAL ARTICLE

Neonatal hemochromatosis: Another entity that is no longer orphan. Advances in the diagnosis and management of the main cause of neonatal acute liver failure☆

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Abstract Neonatal hemochromatosis is the most common cause of acute liver failure in the neonatal period. It is associated with high morbidity and mortality due to iron overload in hepatic and extrahepatic tissues. New evidence has emerged during the last few years as regards its alloimmune aetiology, which have had an important repercussion on the diagnosis, treatment and prognosis of these patients. Treatment with immunoglobulins and exchange transfusions has radically changed the prognosis without liver transplant. Another great success has been the preventive use of immunoglobulin in pregnant women with a past history of neonatal hemochromatosis, thus decreasing the rate of disease recurrence up to 70%.

This new paradigm has led to an entity with a poor prognosis becoming a curable disease if diagnosed and treated early. Nevertheless, a large widespread ignorance of the disease persists, with medical implications that result in significant health problems, due to the delayed referral of these patients to specialised centres.
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PALABRAS CLAVE
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Hemocromatosis neonatal: otra entidad que deja de ser huérfana. Avances en el diagnóstico y manejo de la principal causa de fallo hepático agudo neonatal

Resumen La hemocromatosis neonatal es la causa más frecuente de fallo hepático agudo en el periodo neonatal. Asocia una elevada morbimortalidad dado el daño hepático secundario a acúmulo de hierro. En los últimos años, las nuevas evidencias acerca de su etiopatogenia aloinmune han repercutido sobre el diagnóstico, el tratamiento y el pronóstico de estos pacientes. El tratamiento con gammaglobulinas y exsanguinotransfusión ha cambiado radicalmente el pronóstico libre de trasplante. Otro gran éxito ha sido el uso preventivo de gammaglobulina en las gestantes con antecedentes de hemocromatosis neonatal, disminuyendo así la tasa de recurrencia de la enfermedad de hasta un 70%.

Este nuevo paradigma ha convertido a una entidad con un pobre pronóstico en una patología con posibilidad de curación si se diagnostica y trata precozmente. A pesar de ello, sigue habiendo un gran desconocimiento generalizado de la enfermedad, con implicaciones médicas que derivan en un importante problema sanitario, ya que estos pacientes se derivan de forma tardía a los centros especializados.
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Neonatal haemochromatosis is the most frequent cause of acute hepatic failure in the neonatal period.[1] It is characterised by severe liver damage accompanied by iron overload in both the liver and other tissues.[2–4]

Its actual pathophysiology remained unknown from the time it was first described until very recently, although the literature emphasised its similarities with hereditary haemochromatosis in adults, by which a supposed primary disorder of iron metabolism would lead to the deposition of iron in the liver, which in turn would cause irreversible liver damage. These cases of fatal liver failure developed in the early hours of life, and there was a surprising rate of recurrence in successive pregnancies. In most cases, the diagnosis was made post mortem, so the possibility of attempting an effective treatment was not even contemplated.[5,6]

This framework has changed radically in recent years. The evidence that is currently available suggests that an insult to the liver during the foetal period causes a disorder in iron homeostasis, resulting in the buildup of iron in hepatic and extrahepatic tissues.[3]

Understanding the pathophysiology of haemochromatosis requires knowing the role of two proteins: placental ferroportin and foetal hepcidin. The first one regulates the transfer of iron from mother to foetus. On the other hand, hepcidin, a protein synthesised by the liver, has an inhibitory effect on ferroportin. An insult to the liver in the foetal period would lead to changes in the synthesis of hepcidin, secondarily causing a defect in ferroportin inhibition followed by iron overload. Thus, the buildup of iron would be the consequence and not the cause of the disease.

Since the recurrence pattern of neonatal haemochromatosis is similar to that of diseases such as erythroblastosis fetalis or alloimmune thrombocytopaenia, it has been proposed that it has an alloimmune aetiology. The transplacental transfer of maternal immune globulins against a foetal hepatocyte antigen would lead to subacute liver damage[2,7] and, secondarily, to the defect in hepcidin synthesis. This would explain the impairment in iron homeostasis and the hepatic and extrahepatic siderosis.[4] As happens in all alloimmune diseases, once the mother has become sensitised, maternal IgG will be transferred across the placenta in subsequent pregnancies, leading to a high recurrence rate (>90%).[2,8]

This new understanding has led to a new definition of this entity: gestational alloimmune liver disease (GALD), a name that is used synonymously with neonatal haemochromatosis. While the alloimmune aetiology is not the only cause of neonatal haemochromatosis, it may account for up to 95% of the cases of this disease.[7]

From a clinical standpoint, since the damage occurs in the foetal period, haemochromatosis usually presents along with intrauterine growth restriction, preterm birth, hydropsy, hepatomegaly, ascites and/or foetal death in the second or third trimester. The classical postnatal presentation is characterised by liver failure with hypoglycaemia and severe coagulopathy in the first hours or days of life. The main blood test findings are moderate hypertransaminasaemia (~100 IUI/L), hyperammonaemia (>95 μmol/L), hypoalbuminaemia, elevated α-foetoprotein (concentrations between 100 000 and 300 000 ng/mL), hyperbilirubinaemia (>30 mg/dL), hyperferritinaemia (800–10 000 ng/mL) and a transferring saturation greater than 95–100%. Fifteen percent of the patients develop thrombocytopaenia with less than $50\,000 \times 10^9$ cells/L. Some authors have described an association between haemochromatosis and patent ductus venosus, although the cause for this association remains unknown.[2]

Neonatal haemochromatosis is not diagnosed based on liver siderosis, as this finding is nonspecific and may be present in any neonatal liver disease, but on the evidence of iron overload in extrahepatic tissues. The presence of any amount of iron in the salivary glands (oral mucosa biopsy) is always diagnostic as long as the sample contains minor salivary glands as opposed to labial mucosa.[9]

An alternative method to detect extrahepatic iron overload is T2-weighted magnetic resonance imaging, in which the most frequently affected organs are the pancreas, the heart and the adrenal glands. It is also unknown why these organs are affected while others are not.[10]

Neonatal haemochromatosis requires urgent treatment, as otherwise its progression is fast, irreversible and fatal. Fortunately, early treatment came along with the alloimmune disease hypothesis. Thus, the iron chelation and antioxidant cocktail that was used traditionally has given way to a new therapeutic approach in these patients, with better outcomes. The new approach consists on double-volume exchange transfusion and early administration of immunoglobulin at 1 g/kg of body weight.[2,11] Taking into account its risk–benefit ratio, there is currently sufficient evidence to recommend this treatment whenever there is clinical suspicion of neonatal haemochromatosis, even before the diagnosis is confirmed. The transplant-free survival rate since the introduction of immunoglobulin therapy may have increased from 17% to 75% according to a recent study.[11] However, there are still no uniform treatment standards widely approved by scientific associations for the postnatal management of this disease. Many questions remain unanswered, such as: (a) the best time to start treatment; (b) the number of doses of immunoglobulin and the intervals at which they should be administered; (c) the exact time after which it should be considered that the patient has not responded to treatment and should be added to the transplant list; and (d) the usefulness of chelation therapy in cases with a non-alloimmune aetiology.

The potential usefulness of immunoglobulin therapy and administration of the chelation–oxidation cocktail ought to be considered in the few cases with a non-alloimmune aetiology. If treatment fails to revert liver failure, a transplant must be considered, even at very early ages. This is an extremely serious disease, and given the urgency of its diagnosis and treatment, it requires transfer of the patient to a tertiary care hospital capable of managing all the potential complications of liver failure.

A very important aspect is that prophylactic immunoglobulin therapy during pregnancy seems to have considerably decreased recurrence. In recent years, prenatal treatment protocols have been developed and established.[2,8] Thus, to prevent the disease from recurring, a 1 g/kg dose of immunoglobulin is administered at weeks 14, 16 and 18 of gestation, and then weekly until week 35. At that point, the induction of labour is recommended, as the risk of antibody transfer to the foetus is highest in the third trimester. This regimen appears to have a 100% success rate.[12]

The scientific turnaround in the past decade has resulted in a framework shift, whereby a condition with a poor prognosis that was destined to failure is now a disease for which there is hope and a possible cure. For it to be so, it is important to remain constantly aware of this entity so the patient can be diagnosed and given specific treatment early on. In the newborn, the liver has a high degree of plasticity and cirrhosis may even be reversible, which is why early diagnosis and treatment are key.

There are still important questions that need answering, chief of which is the identity of the foetal antigen that is targeted by maternal IgG. Its discovery could lead to the development of even more specific diagnostic and therapeutic methods, and possibly to a universal prenatal screening test similar to the indirect Coombs test. Until then, obstetricians as well as neonatologists need to remain very alert and be aware of this entity, with the former watching for a history of recurrence, and the latter suspecting neonatal haemochromatosis in all cases of liver failure until it can be ruled out.

In short, while haemochromatosis remains a healthcare challenge, we can declare that it has ceased to be an orphan disease that cannot be treated. The widespread ignorance of this disease has medical consequences that result in a significant health problem, as patients that receive early treatment can be cured, and patients that do not are destined to liver failure, which will be irreversible in many cases.

Conflict of interests

The authors have no conflicts of interest to declare.

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