Passive Transfer of Hepatitis B Antibodies through Intravenous Immunoglobulin in a Neonate

Transferência Passiva de Anticorpos Hepatite B através de Imunoglobulina Endovenosa num Recém-nascido

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ABSTRACT

Passive transfer of antibodies secondary to intravenous immunoglobulin infusion is a rare but important side effect that can lead to the wrong diagnosis and therapeutic decisions. It has never been reported in a newborn. A male newborn, vaccinated against hepatitis B and diagnosed with dilated cardiomyopathy, presented positive hepatitis B core antibodies at 12 days of life. Exclusion of hepatitis B infection was mandatory as it would be a contraindication to heart transplant. Passive transfer of antibodies was confirmed at 44 days of age, after seroreversion of hepatitis B core antibodies. Passive transfer of antibodies after intravenous immunoglobulin infusion can lead to a misleading diagnosis if not recognized. In our patient it could have been especially harmful had it prevented heart transplant. Screening for hepatitis B should be performed at least 1 month after intravenous immunoglobulin infusion.
Keywords: Cardiomyopathy, Dilated; Hepatitis B Antibodies; Immunoglobulins, Intravenous/adverse effects; Infant, Newborn

RESUMO

A transferência passiva de anticorpos secundária à infusão de imunoglobulina endovenosa é um efeito secundário raro, mas importante, que pode levar a um diagnóstico e decisões terapêuticas erradas. Nunca foi descrito num recém-nascido. Um recém-nascido do sexo masculino, vacinado contra a hepatite B e diagnosticado com miocardiopatia dilatada, apresentou anticorpos *anti-core* do vírus da hepatite B aos 12 dias de vida. A exclusão da infecção por hepatite B foi obrigatória, pois seria uma contra-indicação ao transplante cardíaco. A transferência de anticorpos através de imunoglobulina endovenosa foi confirmada aos 44 dias de idade, após sero-reversão dos níveis de anticorpos *anti-core* do vírus da hepatite B. A transferência passiva de anticorpos após a infusão de imunoglobulina endovenosa pode levar a um diagnóstico errado se não for reconhecida. Neste doente poderia ter sido especialmente prejudicial caso tivesse impedido o transplante de coração. O rastreio para hepatite B deve ser realizado pelo menos um mês após a infusão.
Palavras-chave: Anticorpos Anti-Hepatite B; Cardiomiopatia Dilatada; Imunoglobulinas Intravenosas/efeitos adversos; Recém-Nascido

INTRODUCTION

As intravenous immunoglobulin (IVIG) increases its clinical application it becomes increasingly important for attending physicians to be alert to the risk of passive transfer of antibodies, especially in patients whose seropositivity may lead to unnecessary therapies or even prevent essential treatments. Even though this phenomenon has already been described in literature,[1–4] it remains little known. We report a case of a neonate with dilated cardiomyopathy who presented positive hepatitis B core antibodies after administration of IVIG.

CASE REPORT

Male infant, six months old at the time of this report, with no relevant family history. Pregnancy was uneventful, except for an obstetric ultrasonography with left ventricular hyperechogenic focus at the 31st week, which disappeared at the 36th week. No fetal echocardiogram was performed. Maternal serologic screening for human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV) and toxoplasmosis was negative, and she was immune to rubella and cytomegalovirus. Delivery occurred at term and had no complications. He received anti-hepatitis B vaccine according to the national vaccination schedule. In the first hour of life the newborn developed respiratory distress with hypoxemia and was transferred to the Neonatal Intensive Care Unit where he received supplemental oxygen therapy. Blood work showed negative infection parameters and the blood culture was negative. Early metabolic screening was normal. A echocardiography screening suggested congenital heart disease. Subsequent evaluation by Pediatric Cardiology on the second day of life was inconclusive. The newborn was clinically stable until the fifth day of life when he presented severe symptoms of congestive heart failure and required invasive ventilation. At eight days of life, the echocardiogram showed dilated cardiomyopathy. He was started on diuretics (furosemide), aldosterone receptor antagonist (spironolactone), digitalis (digoxin), beta-blocker (carvedilol) and calcium channel sensitizer (levosimendan) infusion. Since one of the most common causes for dilated cardiomyopathy are viral infections, he received an IVIG infusion (Octagam® 5%), 2 g/kg for 24 hours, at 11 days of life. Etiological studies showed normal carnitine and acylcarnitine levels [total carnitine 72.9 µM [reference range (RV) 39.9 – 55.3], free carnitine 48.6 µM (RV 29 – 42) and acylcarnitine 24.3 µM (RV 8.9 – 15.1)], carbohydrate-deficient transferrin < 20.9 mg/L (RV 28,1 – 76), normal urinary organic acid chromatography and normal quantitative determination of plasma amino acids with mild hypoaminoacidemia, excluding metabolic disease. Thyroid function was

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normal at the 10th and 34th days of life. He had no nutritional deficiencies. An extensive panel of viral serologies was requested for exclusion of a viral cause (coxsackie, adenovirus, echovirus, influenza A and B virus, parvovirus B-19, herpes virus 6, Epstein-Barr virus, cytomegalovirus, HIV 1 and 2, HCV), which was all-negative. Serology for HBV was repeated at the 12th day of life, one day after administration of IVIG, due to insufficient volume of the previous blood sample taken at the eighth day of life. He had positive anti-HBs and anti-HBc antibodies. Complete serology was performed the day after for confirmation: there were again positive anti-HBs and anti-HBc antibodies, negative HBs antigen, absence of IgM class anti-HBc antibodies, HBe antigen and anti-HBe antibodies. At 44 days of age, anti-HBc antibodies were negative (Table 1) and anti-HBs antibodies were positive, as expected in an infant with immunity to HBV infection after vaccination. The echocardiogram at two months of life showed severe left ventricular dilation with depressed systolic function and he was placed on the heart transplant waiting list. He was successfully transplanted at three months of age.

Table 1 – Results from hepatitis B virus research

	23/01/2017 (8 days of life)	26/01/2017 (12 days of life – 1 day post IVIg)	09/03/2017 (44 days of life – 33 day post IVIg)
Antigen HBs	Insufficient Sample	Negative (0.45)	Negative (0.62)
Antibody anti-HBc	Negative (2.07)	Positive (0.03)	Negative (1.48)
Antibody anti-HBs		Positive (> 1000)	Positive (202)
Antibody anti-HBc IgM class		Negative (0.08)	
Antigen HBe		Negative (0.10)	
Antibody anti-HBe		Negative (1.20)	

DISCUSSION

We present a case of a newborn in whom administration of IVIG interfered in the serology result for hepatitis B. This is a rare event and has never been described at such an early age and in this particular setting. Its recognition was key as he was a patient who could need cardiac transplantation and immunosuppressive therapy, with the consequent risk of viral reactivation. This reactivation can occur even in persons who are anti-HBs positive, although with a lower risk. As an example, in a prospective study evaluating the risk of HBV reactivation in 150 antigen HBs negative and anti-HBc positive patients undergoing chemotherapy with a rituximab-containing regimen for lymphoma, HBV reactivation occurred in nine of the 116 patients (8%) who were positive for anti-HBs at baseline and eight of the 35 (23%) who were negative for anti-HBs.[5]

Dilated cardiomyopathy (DCM) is defined by dilation and systolic dysfunction of the left ventricle (LV) or both ventricles not explained by abnormal ventricular filling conditions (e.g., arterial hypertension, valvular disease) or coronary disease.[6] Its etiology includes idiopathic DCM, familial DCM, viral, autoimmune or toxic myocarditis and metabolic disease. The most common cause of acquired DCM is viral myocarditis. Therapy in the neonatal period is extrapolated from children and adult data.[7] One of the possible treatments of viral myocarditis DCM is intravenous immunoglobulin infusion.[8] Treatment of DCM with refractory heart failure is cardiac transplantation.[9]

Arnold *et al* described an abnormally high rate of anti-HBc seropositive patients during a rituximab clinical trial.[1] The authors concluded that 10 out of the 11 seropositive patients had received IVIG therapy in the previous four weeks and found that seven of these patients reverted to seronegative after repeated testing. The patients were screened for HBV infection due to the risk of hepatitis B reactivation after immunosuppressive therapy. The authors stated that, in order to avoid misleading results, anti-HBc antibodies should only be evaluated either before or three months after the administration of IVIG. In our case, hepatitis B core antibodies were negative one month after IVIG infusion. We conducted a brief review of the literature which showed two more clinical cases[2,3] and a prospective study[4] that also reported this phenomenon.

Our patient, a newborn with no identifiable cause for infection since his mother was hepatitis B seronegative and had no significant changes in liver markers, had a likely exogenous source of hepatitis B core antibodies, confirmed by their seroreversion at 44 days of age. Hepatitis B surface antibodies were and remained positive, as expected after successful vaccination.

Information provided by the manufacturer of the drug used, Octagam® 5%,[10] states that it is composed of ≥ 96% human IgG and prepared by fractionating fresh frozen plasma donated by the general population. Each preparation is made from a plasma pool of not less than 3500 donations. General measures to avoid transmission of infectious agents through the product include selection of donors, screening of individual donations and pooling of plasma for specific markers of infection, and inclusion of steps for inactivation and viral clearance. Viral inactivation of the product is carried out using the solvent/detergent method with a mixture of octoxynol (triton X-100) and TnBP (tri n-butyl phosphate) and a specific treatment with pH 4. The final product is tested for HBs antigen and HIV 1/2 antibodies. It is known that the infectious risk with immunoglobulin administration is extremely low.[11] The requirements for donor screening and infectious disease testing are generally stringent and the manufacturing process normally includes 1 to 2 steps of viral inactivation.[10] The manufacturer's information further states that, with the administration of IVIG, various antibodies may be passively transferred to the patient's blood, which may lead to positive serological tests. The half-life of the drug is 36 to 40 days, which agrees with the evolution of the patient's serology (Table 1).

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

INFORMED CONSENT

Obtained.

CONFLICTS OF INTEREST

All authors report no conflict of interest.

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Retalho Livre Anterolateral da Coxa para Tratamento de Quelóide Esternal

Use of Anterolateral Thigh Free Flap in the Treatment of a Sternal Keloid

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RESUMO

As cicatrizes hipertróficas e quelóides representam distúrbios cicatriciais hiperproliferativos que podem ter um impacto significativo na vida dos doentes. Os autores apresentam o caso de um doente de 53 anos, com uma cicatriz quelóide na região esternal após exérese de quisto sebáceo e múltiplas sessões de infiltração de corticóide, com um agravamento marcado da lesão. O doente foi submetido a exérese do quelóide e reconstrução do defeito com retalho livre fasciocutâneo anterolateral da coxa (*anterolateral thigh flap* — ALT). O pós-operatório imediato e tardio decorreu sem intercorrências, sem sinais de recidiva. O tratamento de quelóides esternais passa, inevitavelmente, por diminuir a tensão na região operada, de forma a evitar a recidiva e eventual agravamento da lesão. O tratamento deste tipo de cicatrizes é complexo, tornando-se um verdadeiro desafio para o cirurgião plástico. No caso clínico apresentado, dadas as dimensões e localização da cicatriz, a sua excisão provocou um defeito extenso, sendo necessária a transferência microcirúrgica de tecidos para cobertura completa, minimizando a tensão na região esternal.

Palavras-chave: Coxa; Esterno; Procedimentos Cirúrgicos Reconstrutivos; Quelóide; Retalhos de Tecido Biológico/transplantação

ABSTRACT

Hypertrophic and keloid scars represent hyperproliferative disorders that can have a significant impact on patients' lives. The authors present the case of a 53-years-old male with a sternal keloid after excision of a sebaceous cyst and multiple sessions of steroid infiltration, with worsening of the lesion. The patient underwent complete excision of the scar and reconstruction with an anterolateral thigh flap — ALT. The postoperative period was uneventful, with no signs of relapse. Keloid scar treatment in sternal area implies a reconstruction with no tension, in order to avoid relapse. Treatment of this type of scars is complex and a challenge to the plastic surgeon.

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