Pediatric Dimensions

Case Report ISSN: 2397-950X

A case of neonatal alloimmune neutropenia in premature infants with response to intravenous immunoglobulins

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Abstract

Neonatal alloimmune neutropenia (NAN) results from neutrophil destruction by transplacental maternal neutrophil-specific immunoglobulin G (IgG) antibodies directed against the antigen inherited from the father. Few such cases have been described in the literature, although it is probably not as uncommon as once thought, since its benign evolution in most patients. There are still doubts about which treatment is the most appropriate. We present the case of a new born who did not respond to granulocyte colony-stimulating factor (G-CSF), however, after treatment with intravenous immunoglobulins (IVIG) the patient responded in a few hours to the administration of IVIG.

Introduction

Neutropenia is defined as a decrease in the absolute number of circulating neutrophils. This value is age dependent. In neonates, neutropenia is present at <1000 neutrophils/µl and severe neutropenia at <500 neutrophils/µl.

Neonatal alloimmune neutropenia (NAN) occurs when the mother produces antibodies to an antigen of foetal neutrophils, which is inherited from the father and non-existent in the maternal neutrophils. These maternal alloantibodies are transfused into the foetus, destroying its circulating neutrophils and causing neutropenia. The antigens most frequently involved in this process are NA1 and NA2 [1].

Case study

The neonate was delivered prematurely, with a gestational age of 33 weeks and birth weight of 1914g. Mother with 31 years, blood group O+. This was her second child; the first had died at 25 days of age, in Bolivia, due to a respiratory pathology of unspecified origin. Gestation without infectious risk factors. The O'Sullivan's test results and blood pressure were normal. Caesarean birth due to breech presentation. The Apgar score was 4/7. At birth, grade 2 hyaline membrane disease was observed, requiring endotracheal intubation, and two doses of surfactant were administered. On admission, analysis revealed neutropenia of 80 neutrophils/µl and leukopenia of 8110 cells/µl. The red blood cell and platelet counts were normal. After lumbar puncture revealed no pathological findings, an empirical antibiotic regimen was started, with cefotaxime and gentamicin. The neutropenia persisted, and so treatment was initiated with granulocyte-colony stimulating factor at 10 µg/kg/day (SC). After 4 days, as no response had been achieved, treatment with i.v. gamma-globulin at a dose of 400 mg/kg/day was indicated. Three doses were given. The patient presented a response at 24-48 hours after administration of the first dose of gamma-globulin, with neutrophil levels rising to 2040 neutrophils/µl at 24 hours and to 13500 neutrophils/µl at 48 hours. There was no elevation of procalcitonin, and the cultures were negative.

Neutrophil typing, performed to study antibodies in the maternal blood in the neonate, and in the mother and father, detected anti-HLA class I antibodies and antineutrophil specific HNA2.

Discussion

To diagnose NAN, other causes of neonatal neutropenia must first be excluded, the most frequent of which are maternal hypertension, sepsis, foeto-foetal transfusion, alloimmunisation and haemolytic disease. The initial study includes a blood count in the parents and, if this is normal, the typing of neutrophils and maternal antibodies [1]. If neutropenia persists, a bone marrow study, seeking normal cellularity, should usually be performed. In the case presented, the parents' blood count was normal, and the diagnosis was confirmed by the study of maternal antibodies. Therefore, it was not considered necessary to perform a bone marrow study or other tests.

Once the diagnosis is confirmed, treatment is recommended for patients with severe neutropenia (< 500 neutrophils/µl) or persistent neutropenia (> 5-7 days) [1]. In recent years, granulocyte-colony stimulating factor (G-CSF) has been used, with favourable results. This drug increases the production of neutrophils and delays their apoptosis, in addition to regulating the expression of antigens expressed by neutrophils, making them less vulnerable to circulating antibodies. The normal dose is 5-10 µg/kg/day [2]. In most cases, the effect begins in the first 24-48 hours, and at least 3-6 doses are required.

In our case, there was no response to the administration of G-CSF. However, numerous articles have been published supporting its use, including some in which premature patients are treated, as is our case

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Key words: *neonatal alloimmune neutropaenia, immunoglobulin, granulocyte colony-stimulating factor*

Received: March 18, 2019; **Accepted:** March 23, 2019; **Published:** March 29, 2019

[3]. One study describes the failure of treatment with G-CSF, as well as the appearance of thrombocytopaenia [4,5].

Another widely used treatment is intravenous immunoglobulin. This works by mobilising neutrophils from the bone marrow into the bloodstream. The most commonly used dose is 400 mg/kg/day [6]. Some studies report this treatment to be effective in neonates with NAN [6]. In the case presented, the patient responded immediately to the administration of immunoglobulin iv., an outcome similar to that reported in a previous article, in which antibodies to antigen 1c were detected [7]. Most studies consider that immunoglobulin iv., should be reserved for second-line treatment [6,7]. In general, steroids have not been shown to be effective in children, although some studies have detected raised neutrophil levels in 75% of patients treated with corticosteroids [6]. Granulocyte transfusions can be effective in acute cases, although no clear benefit has yet been established [5].

In the clinical case presented, neutropenia was resolved in the first 15 days of life. As in the present case, NAN is usually self-limiting, although it may take up to 6 months to disappear, depending on maternal antibody levels [6].

Conflict of interests

The authors declare that they have no conflicts of interest.

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