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Case Report

Autoimmune Hemolytic Anemia-Possible Association with Meningococcal-ACWY Vaccine?

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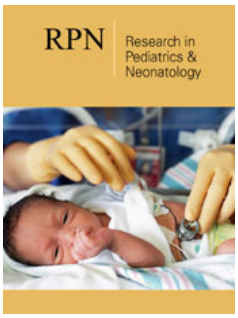

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Abstract

Autoimmune hemolytic anemia is an uncommon manifestation in the pediatric age and is frequently associated with a previous viral or bacterial infection. The authors report a clinical case of warm autoimmune hemolytic anemia following vaccination with meningococcal-ACWY vaccine (Nimenrix®). The clinical presentation was mild and resolved without directed treatment. To our knowledge there are no published reports of this adverse reaction and it is not mentioned in the vaccine's EPAR. This report aims to alert clinicians for this adverse event following meningococcal-ACWY vaccine. Patients should be instructed about the alarm signs and symptoms.

Keywords: Coluria; Acholia; Jaundice; Peripheral blood; Hyperbilirubinemia; Bilirubin predominance; Varicella Zoster; Epstein Barr Virus

Introduction

Autoimmune hemolytic anemia (AIHA) is relatively uncommon in children (incidence of 0,8-1,25/100000 cases) and is caused by the presence of autoantibodies that bind to the patient's erythrocytes and induce complement activation, leading to premature red cell destruction and consequent anemia [1-3]. AIHA can be classified in primary, with no underlying condition, post-infectious or secondary [2]. The mechanism underlying the production of autoantibodies is still unclear [4]. In the pediatric age, there is frequently a recognizable association with a previous viral or bacterial infection. Vaccination has been also reported as a trigger of acute AIHA [4]. The authors report one case of AIHA associated with meningococcal ACWY vaccine (Nimenrix®).

Case Report

A 6-year-old girl was admitted in the pediatric emergency department with jaundice since the previous day. A detailed clinical history excluded other associated symptoms, including coluria, acholia, fever or other constitutional manifestations. Aside from jaundice, the physical examination was normal. Ten days before she had been inoculated with the meningococcal vaccine against the serogroups A, C, W, Y (Nimenrix®). There was no recent history of infectious intercurrence, drug intake or travelling. Also, the country was under confinement measures due to the COVID-19 pandemic. The blood workup showed a normocytic normochromic anemia with hemoglobulin of 11.4g/dL, with 51960/uL reticulocyte count and normal white blood cell count (6090/µL) and plaque count (259000/µL). On peripheral blood smear there was a mild anisocytosis, anis chromia and polychromatophilia, with no other abnormal cells. Biochemical evaluation revealed an unconjugated hyperbilirubinemia (total bilirubin of 7.5mg/dL, with 96% indirect bilirubin predominance), serum LDH of 482U/L with haptoglobin <10mg/dL. Liver and kidney function were normal, c-reactive protein and erythrocyte sedimentation rate were negative. Urinalysis showed no evidence of coluria or other alterations. Direct antiglobulin test was strongly positive (3/4) for IgG (2/4) and C3d (3/4). Coagulation screen blood test was normal.

The diagnosis of AIAH was established and she was admitted in the Paediatric Department for clinical and analytical surveillance. Given the good clinical impression and mild anemia with no hemodynamic repercussions, no immediate directed treatment was started. The investigation proceeded in order to identify possible underlying disorders. Immune-

hematological investigation with complement (C3, C4, CH50), immunoglobulin class quantification, antinuclear antibodies, antiphospholipid antibodies, anti-transglutaminase antibodies, thyroid function and anti-thyroid antibodies was normal. Abdominal ultrasound showed no alterations. Urine culture, rapid streptococcal detection test, PCR for sars-cov-2 as well as serologic tests for cytomegalovirus, Epstein Barr virus, varicella zoster, herpes simplex, HIV, hepatitis B and C, syphilis, parvovirus and mycoplasma were negative. Serial analytic re-evaluations showed increasing reticulocytotic (192384/uL) and initial hemoglobin drop (minimum value of 10.1g/dL five days after admission) with gradual improvement. A gradual normalization of LDH and haptoglobin was also objectified. The jaundice resolved completely and bilirubin normalized after ten days. No other symptoms appeared. She kept follow-up in Pediatric Consultation, and to the present date (seven months after) she had no clinical or analytical relapse.

Discussion

Hemolytic anemia (HA) occurs by an increase destruction of red blood cells (RBC) and affects a significant proportion of the pediatric population. Our patient presented with all the characteristic laboratory findings of HA, including unconjugated hyperbilirubinemia, elevated lactate dehydrogenase, decreased haptoglobin and subsequent reticulocytotic. The hemolysis mechanism can be extravascular or intravascular. Extravascular hemolysis is mediated by the reticuloendothelial system and occurs by phagocytosis of erythrocytes, followed by sequestration and removal. The heme group released from free hemoglobin is converted to bilirubin. These patients can present with jaundice (resulting from unconjugated hyperbilirubinemia), and splenomegaly (due to RBCs sequestration). In intravascular hemolysis, there is direct RBC membrane destruction due to shear stress, toxins, or complement-mediated lysis, and in this cases patients may describe dark urine (due to hemoglobinuria) [5]. In the reported case the clinical findings were suggestive of an extravascular mechanism.

Autoimmune hemolytic anemia occurs when autoantibodies are produced against antigens on the patient's own erythrocytes [6]. The antiglobulin test (DAT) is the primary method to document antibody-mediated hemolysis and helps to confirm the diagnosis of AIHA [5,6]. A positive DAT must follow the identification of the type of immunoglobulin. AIHA is classified in "warm" or "cold" based on the thermal reactivity of the autoantibodies. Most commonly the patients with AIHA are diagnosed with warm agglutinins, which are almost always IgG but sometimes involve complement. Cold agglutinin disease is caused by IgM autoantibodies, that trigger complement deposition, resulting in complement-mediated intravascular hemolysis or immune-mediated extravascular clearance [3,5]. This patient presented with a warm AIHA, with characteristic positive IgG antibodies and C3d.

Most cases of AIHA are secondary to diseases that may stimulate the production of autoantibodies, such as infections, autoimmune diseases, malignancies and certain drug exposures [1,5]. In the reported case, the short time lag between vaccination and onset of symptoms strongly suggests a causal relationship. Furthermore, major alternative explanations for the occurrence of AIHA were not found. A report of this adverse reaction was submitted to Portugal's national drug and health products authority (Infarmed), and was scored by specialized professionals as "Probable". There have been some clinical reports of vaccine induced AIHA, particularly with diphtheria-tetanus-pertussis (DTP), polio and Influenza vaccines [1,4,6,7]. To our knowledge there are no previous reports referring to meningococcal-ACWY vaccination. It is well described the phenomenon of vaccination-induced autoantibodies in cases of autoimmune thrombocytopenia; however, the underlying mechanism for this event is still largely unknown [4]. It was hypothesized that antibodies to vaccine components could cross-react with RBC surface antigens, or vaccine antigens could bind to the red blood cell and induce complement activation [8].

In this case the hemolysis was mild and self-limited, with no need for specific treatment, but some cases can be severe and demand immediate intervention. Evolution to chronicity is also a concern. Steroids are the first-choice treatment in all cases of warm-type AIHA. In more severe cases, intravenous immunoglobulins may be indicated as adjunctive therapy, and if severe anemia and hemodynamic instability are present, red blood cells transfusion should be performed [2]. This report intents to alert clinicians for this possible adverse reaction. The authors would like to emphasize that vaccines are safe, rigorously tested and play a crucial role in the prevention of many life-threatening diseases. Its global impact in the mortality and morbidity is unquestionable. As any medicine, serious side effects are possible but very rare, and the benefits far outweigh the risks.

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