A newborn with positive antiglobulin test whose mother took methyldopa in pregnancy

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Methyldopa is known to cause the production of autoantibodies against red blood cells (RBCs), leading to a positive direct antiglobulin test (DAT) and hemolytic anemia. In about 20% of patients taking methyldopa, IgG autoantibodies develop against RBCs. However, most of the patients do not have hemolysis. A small percentage of such DAT-positive patients, about 2% of those taking methyldopa, develop an autoimmune hemolytic anemia (AIHA). The fact that the DAT is positive in the newborn with unconjugated hyperbilirubinemia is considered as an isoimmune hemolytic disease caused by blood group incompatibility. In this article, a newborn with jaundice and positive DAT without hemolysis is reported. Her mother had the history of taking methyldopa in her pregnancy. Thus, when newborns are detected with positive DAT and jaundice, without blood group incompatibility, mothers should be questioned regarding drugs used in their pregnancy.

Key words: newborn, methyldopa, antiglobulin test.

Direct antiglobulin test (DAT) positivity in the newborn with unconjugated hyperbilirubinemia is considered as an isoimmune hemolytic disease caused by blood group incompatibility[1]. Methyldopa is known to cause the production of autoantibodies, including red blood cell (RBC) autoantibodies. Approximately 10-20% of patients who have taken methyldopa appear to produce IgG RBC autoantibodies, leading to a positive DAT. A small percentage of such DAT-positive patients, about 2% of those taking methyldopa, develop an autoimmune hemolytic anemia (AIHA)[2,3]. Methyldopa and IgG autoantibodies produced against RBC are transferred to the fetus via the placenta[4,5]. In this article, we report a newborn with unconjugated hyperbilirubinemia who had positive DAT. It is believed that IgG autoantibodies were developed against maternal methyldopa in this case and were transferred to the fetus via the placenta. However, the newborn had no signs of hemolysis.

Case Report

A female infant of 37 weeks gestational age was born by cesarean section to a 33-year-old mother. At birth, her weight was 2610 g (25-50th percentile), length 46 cm (25th percentile), and head circumference 34 cm (25-50th percentile). Her mother had taken methyldopa (250 mg twice daily) for hypertension during the period of pregnancy. Physical examination of the baby was normal except for jaundice, which occurred on the second day. The peak serum total bilirubin value was 18.7 mg/dl on the third day, and direct and indirect bilirubin values were 0.7 mg/dl and 18.0 mg/dl, respectively. Indirect bilirubin value was reduced to a normal level after a few days of phototherapy.

Laboratory findings included hemoglobin 16.2 g/dl, hematocrit 47%, platelet count 364000/mm^3, reticulocyte count 2%, TSH 7.22 μU/ml, and T_4 10.7 μg/dl. Peripheral RBC smear of the patient did not show nucleated RBCs, spherocytes or other fragmented cells. The baby's blood group type was A Rh (+), DAT +++, and her mother's blood group type was B Rh (+), indirect antiglobulin test (IAT) +, and DAT +++. DiaMed-ID Micro Typing System using gel centrifugation was utilized to determine the DAT of the baby and her mother. Furthermore, an autologous control was added to DAT. The levels of

glucose-6-phosphate dehydrogenase (G6PD) and lactate dehydrogenase, serum liver and renal functions, and electrolytes of the baby were normal. When we assessed for the non-D Rhesus blood group type, the baby's blood group type was C-, c+, E+, e-, M+, N-, S-, s+, Fy^a- Fy^b+, K-, k+, Jk^a+, Jk^b+, le^a+, le^b-, P+, while her mother's blood group type was C-, c+, E+, e+, M+, N+, S+, s+, Fy^a+, Fy^b+, K+, k+, Jk^a+, Jk^b+, le^a+, le^b+, P_1+. No irregular antibody was detected on screening. Klebsiella pneumoniae was detected on the culture from the urine collected by bladder catheterization (>100000 col). Thus, parenteral antibiotic treatment was initiated. Renal ultrasonography of the baby was normal. At the postnatal 9th week of life, while DAT of the baby was negative, DAT of the mother was positive.

Discussion

Methyldopa was the first drug to be proven to cause production of RBC autoantibodies in vivo[2]. In about 20% of patients taking methyldopa, IgG autoantibodies develop against red cells. However, most of the patients do not have hemolysis[6]. It was reported that a small percentage of DAT-positive patients, about 2% of those taking methyldopa, have developed an AIHA[2,3,7]. As reported previously, methyldopa can produce both a positive DAT and less commonly a positive IAT[8]. The positive test develops within three to six months after the onset of therapy[9]. In the present case, the mother of the patient had taken methyldopa (250 mg twice daily) for hypertension during the period of pregnancy. DAT of the present newborn and indirect and direct antiglobulin test of her mother were positive, although other signs of hemolysis such as anemia, reticulocytosis, RBC fragments, nucleated RBC, and spherocytes were not present in blood films of the mother and baby. It is still controversial why some patients taking methyldopa make RBC autoantibodies, and why most of these DAT-positive patients have no signs of decreased RBC survival. The most popular theory for the etiology of methyldopa-induced RBC autoantibodies has been based on the study by Kirtland et al.[10], who suggested that methyldopa inhibited suppressor-lymphocytes functions[7]. Kelton[6] observed that every patient taking methyldopa who had a positive DAT but no hemolysis had unimpaired Fc-dependent reticuloendothelial function.

It was reported that the autoantibodies due to use of drugs such as methyldopa may be able to react with the patient's own red cells and usually most other normal red cells in vitro without drug ingestion[11]. Methyldopa and IgG are transferred to the fetus via the placenta[4,5]. The production of autoantibodies to red cells in utero by the fetus is possible, though rare[12]. Erler et al.[12] reported a positive DAT in a newborn infant without evidence of maternal alloantibodies or autoantibodies. In the present study, the positive DAT after adding an autologous control indicates the presence of red cell IgG autoantibodies in the mother. This data suggests that the positive DAT of the newborn is caused by the maternal IgG autoantibodies crossing the fetus via the placenta.

As it is known, ingestion of methyldopa has been shown to cause positive direct and sometimes indirect antiglobulin tests in patients[11]; however, it has not been shown previously in the fetus or newborn. To our knowledge, this is the first report about a newborn with positive DAT whose mother had taken methyldopa in pregnancy. The positive DAT associated with methyldopa gradually diminishes over weeks or months[9]. At the postnatal 9th week of life, while DAT of the mother was positive, DAT of the patient was negative.

In conclusion, a neonate whose mother has taken methyldopa in pregnancy should be followed closely for positive antiglobulin test and hemolysis. In other words, if there is no blood group incompatibility in newborns with positive DAT, drugs used by the mother during pregnancy should be investigated.

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