

Severe Hemolytic Disease of the Newborn Caused by Anti-M Antibodies

Eduardo Alfredo Duro, MD, MPH; Liliana Desalvo, MD;
Sandra Kuret

Facultad de Medicina, Universidad de Buenos Aires

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Anti-M's are naturally occurring antibodies described by Wolff and Johnsson in 1933. They have been rarely associated as cause of diseases with different degrees of severity as intrauterine deaths or hemolytic disease of the newborn HDN^[1,2]. The detection of anti-M in antenatal screening is a rare finding^[3]. High titers of IgG and IgM anti-M are responsible for neonatal red cell aplasia and HDN. The MNSs blood group system is considered to be clinically insignificant as it only reacts at temperatures below 37 °C and appears to be more common in infants than in adults. MN antibodies do not usually cause severe hyperbilirubinemia.

A review of seven cases of patients with auto anti-M antibodies reported a varied degree of symptoms^[4]. In a study carried out to detect the prevalence of alloantibodies among 3,577 multigravida women in India, only one was anti-M positive by column agglutination technology^[5].

HDN is a condition in which infant's red cells are destroyed by the action of maternal antibodies derived by placental transfer formed due to previous transfusion or by the entry of fetal red cells into the maternal circulation.

A 36-hrs-old full term female neonate, born vaginally at 40 weeks with an Apgar score of 9/10 was found to have mild jaundice with a transcutaneous bilirubin measurement of 15mg/dl. The neonate's red cells and mother's red cells were typed O RhD positive. Direct Coomb's test in the patient was negative using a conventional tube technique; conventional phototherapy was started.

Laboratory tests showed that infant's blood hemoglobin and serum total bilirubin concentrations were 11.0 g/dl and 31.9 mg/dl respectively, and the peripheral blood smear demonstrated numerous nucleated RBCs, schistocytes, prominent spherocytes and polychromasia. Serological TORCH screening was

negative. Intensive phototherapy and IV fluids were started. On physical examination, the infant was slightly irritable but did not appear sick. A complete blood count showed a hematocrit level of 33%, the leukocyte count was 15,900/mm³ with a differential cell count of 2% band forms, 52% segmented forms, 4% eosinophils, 30% lymphocytes and 4% monocytes and a reticulocyte count of 1.9%.

Following institution of intensive phototherapy, an exchange transfusion was performed. Pre exchange transfusion laboratory analysis showed: indirect bilirubin 29.3 mg%; direct bilirubin 3.0 mg%. New studies were ordered including type and cross match for another exchange transfusion. Ultrasound scan of the liver did not suggest biliary atresia or other obstructive liver disease as cause of the jaundice. The introduction of gel technology showed positive direct Coomb's test in the newborn baby.

The patient was exchange transfused twice before maternal anti-M was detected. She was then exchange transfused with M-negative packed red blood cells and after that her condition stabilized and was transferred to a third level hospital.

The patient's blood group was O RhD positive, M positive and her mother's blood group O RhD positive, M negative. Neonatal direct Coomb's test was positive only in column technology in the form of the gel technology. Maternal serum samples showed anti-M immunoglobulins.

Anti-M's are the second most common non-Rh antibodies, after anti-Kell, to cause HDN. Prescribing the appropriate blood group takes an important role in patient's outcome. The level of bilirubin before exchange transfusion is the only important factor which sometimes causes the necessity of second or third exchange.

The use of gel techniques may be the gold standard in the investigation of infants with severe hyperbilirubinemia and HDN in the first week of life. We think the direct Coomb's test by gel technique is better than the conventional technique based on the fact that it is simple, reliable, involves less technical error and requires a small amount of blood sample. The grading system is clear-cut, especially compared with the conventional technique which requires examination under a microscope. We think it should be included in the screening of infants with

* Corresponding Author; Address: Farias 30 (B1662AYB) Muñiz.
Provincia de Buenos Aires, Republica Argentina
E-mail: eduro@unimoron.edu.ar

hyperbilirubinemia, especially in cases of suspected rare blood groups causing HDN.

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A Novel Missense Mutation in *BRAF* Caused Cardio-Facio-Cutaneous Syndrome

Filiz Hazan¹, PhD; Emin Karaca¹, PhD; Sultan Aydin Koker², MD; Huseyin Anil Korkmaz², MD; Timur Mese³, MD; Huseyin Onay¹, MD; Ferda Ozkinay¹, PhD

1. Department of Medical Genetics, Dr. Behcet Uz Children's Hospital, Izmir, Turkey
2. Department of Pediatrics, Dr. Behcet Uz Children's Hospital, Izmir, Turkey
3. Department of Pediatric Cardiology, Dr. Behcet Uz Children's Hospital, Izmir, Turkey

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To the Editor

Cardiofaciocutaneous syndrome (CFC) is a multiple congenital anomaly syndrome characterized by craniofacial features, cardiac defects, ectodermal anomalies and neurocognitive delay^[1]. CFC is caused by mutations in *BRAF*, *MEK1*, *MEK2*, *KRAS* genes encoding proteins of the RAS/MAPK signaling pathway. In more than 70% of CFC patients, *BRAF* mutations are detected^[2].

We present here a 10-year-old boy who was referred to the department of Medical Genetics for dysmorphological evaluation because of severe developmental delay, short stature and dysmorphic features. He was the third child of healthy, non-consanguineous Turkish parents. His parents and two siblings were healthy. He was born at term after an uneventful pregnancy. His birth weight was 3000 g (10-25th centile), height 50 cm (50th centile). His developmental milestones were globally delayed.

At the age of 10, his height was 87.5 cm (<3rd centile), his weight 15300 g (10-25 centile) and head circumference 49,5 cm (<3rd centile). Physical examination revealed coarse facial appearance, low-set ears, sparse eyebrows, bilateral ptosis, down-slanted palpebral fissures, epicanthal folds, bulbous nose, prominent philtrum, high-arched palate, thick lower lip, pectus excavatum, clinodactyly of fifth fingers (Fig. 1a). His hair was curly. Two cafe-au-lait spots were also noted. A hypertrophic cardiomyopathy was detected by echocardiography. On neurological examination, he had severe mental retardation (IQ below 50) with poor social interaction at the age of 10. Myopia was detected on ophthalmical examination. Fundus examination and visual evoked potentials were normal. Laboratory tests were normal. Magnetic resonance imaging showed cortical atrophy of the brain. Abdominal ultrasonography, X-ray of vertebral column and extremities were normal. A hearing test was normal. His karyotype was 46 XY.

On the basis of the observed facial dysmorphisms, hypertrophic cardiomyopathy and mental retardation, he was diagnosed as CFC. Genomic DNA from blood lymphocytes of the patient was isolated. Seven coding exons (6, 11-16) in *BRAF* were amplified by polymerase chain reaction. The polymerase chain reaction products were gel-purified and sequenced on an ABI PRISM 310 automated DNA sequencer (Applied Biosystems). A novel, missense heterozygous c.1442C>A mutation in exon 12 was identified in the proband. This mutation was not detected in both parents (Fig. 1b).

The cardio-facio-cutaneous syndrome (CFC) was first reported by Reynolds et al in 1986^[3]. Overlapping phenotypes of patients with CFC, Costello Syndrome (CS) and Noonan Syndrome (NS) have been recognized^[4]. Digilio et al

* Corresponding Author; Address: Department of Medical Genetics, Dr. Behcet Uz Children's Hospital, Izmir, Turkey
E-mail: filizhazan@hotmail.com