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Research Letter

Deletion of macro domain containing 2(MACRO D2) associated with transient hydrops fetalis

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Dear Editor,

Macro Domain Containing 2 (MACRO D2) gene is a gene from macro family which is highly expressed in the ventriculer zone of the brain during embryonic development. Association between Autism spectrum disorders and MACRO D2 gene polymorphisms has been reported before [1]. Deletion in MACRO D2 gene has also been associated with Kabuki Syndrome which is a well described congential anomaly syndrome [2].

Here we report a case of prenatally diagnosed non-immune hydrops fetalis associated with deletion in the 20p12.1 region affecting MACRO D2 gene. 33 years old multiparous woman (gravida 3-para 2) was admitted with hydrops fetalis at 18 weeks of gestation. Ultrasound revealed subcutaneous edema, bilateral pleural effusion and accompanying ascites in fetal abdomen. The nuchal translucency measurement was 9,5 mm. On fetal echocardiography, structural or cardiac rhythm abnormality was not detected (Fig. 1).

The patient's blood type was A Rh (D) negative, indirect coombs test was negative. The Doppler indices of middle cerebral artery, namely peak systolic velocity, were in normal ranges, so fetal anemia was not suspected. TORCH antibody screening tests and parvovirus antibody tests were all negative. Amniocentesis was performed. G-banding karyotype using amniocentesis material revealed 46 XX karyotype. We have offered termination of pregnancy due to the widespread hydrops, but the family denied the termination of pregnancy.

At 32 weeks of gestation, she was admitted again for delivery planning. Ultrasound revealed a fetus at 32 weeks of gestation with increased amniotic fluid (AFI: 23 cm), however signs of hydrops were completely regressed. A repeat cesarean section was performed at the 39 weeks of gestation. A female infant weighing 3490 g and 48 cm in length was delivered with Apgar scores of 3, 6 and 7 at the 1st, 5th and 10 th min., respectively. At the newborn examination, low set ears, flattened nose bridge and Simian line at the left hand were observed (Figs. 2 and 3).

Oxygen therapy was introduced for three days with a diagnosis of transient tachypnea of the newborn. There were no pathological findings on the abdominal ultrasound. Patent ductus arteriosus (1.3 mm) was detected by echocardiography. The newborn was consulted with department of medical genetics for other possible genetic and metabolic disorders. Blood samples were taken for extended genetic evaluation and thereafter at the 8th day after delivery, the newborn was discharged from the hospital.

The infant was referred to the neonatology unit with coughing, irregular respiration, cyanosis, tachypnea and nasal flaring one month later. On the physical examination, the infant was acutely ill and severely dehydrated. There were costal and sternal retractions. Respiratory acidosis was detected and mechanical ventilation was necessitated. Antibiotic therapy was initiated for bronchopneumonia. At the 15th day in the critical care unit, the infant died due to sepsis and respiratory failure.

Postnatal genetic analysis from peripheral venous blood for CFTR mutation, SMN1-SMN2 deletion-duplication were all negative. In arrayCGH analysis we have detected 401 kb microdeletion including MACROD2 gene [arr cgh (hg 19) 20p12.1 (14,817,836–15,219,086)×1].

Non-immune hydrops fetalis (NIHF) is a complex disease with different types of etiology. In a meta-analysis, it has been reported that genetic disorders are the causes of NIHF in 13,4% of the patients

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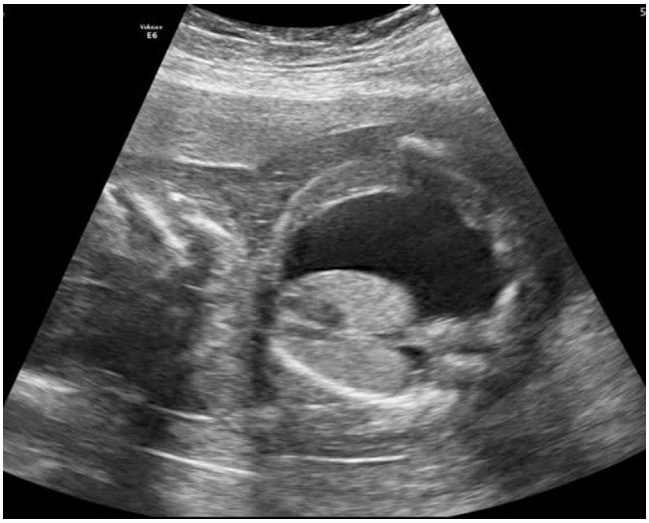

Fig. 1. Hydrops fetalis.

Fig. 2. Low set ears, flattened nose bridge.

Fig. 3. The newborn.

[3,4]. 45 X0, trisomy 21, trisomy 18 are the most common chromosomal disorders [5].

In our case we have found a deletion in the 20p12.1 which includes MACRO D2 gene. Previously, deletion in MACRO D2 has been reported in a single case of Kabuki syndrome [2]. Kabuki syndrome is a well defined congenital anomaly syndrome, characterized by growth and developmental delay, cardiac, renal and vertebral anomalies and distinct facial features [6]. Several mutations and deletions has been associated with Kabuki syndrome. The most common mutations are the frameshift mutations in the KMT2D (MLL2) gene [7]. For the clinical diagnosis of Kabuki syndrome, characteristic eye confirmation with long palpebral fissures and typical eyebrows has been suggested as minimal criteria.

Congenital Heart defects were observed in 80–90% of the infant series [7,8]. Growth retardation, epilepsy and musculoskeletal problems are the other common problems which may be associated with Kabuki syndrome.

Polyhydroamnios has been reported in up to a third of pregnancies affected by fetal Kabuki syndrome [6]. Non-immune hydrops fetalis associated with Kabuki Syndrome has been reported as two case reports [6]. However, the clinical diagnosis of Kabuki syndrome in the prenatal period and in the first months of the life is not possible, because the phenotype and characteristic facial features will be more evident during childhood [8,9].

In our case, we have only detected transient hydrops fetalis, there were no growth retardation and major structural malformations. On the newborn examination, we have detected low set ears, flattened nasal bridge and simian line at the left hand.

At the 18 weeks of gestation ultrasound revealed widespread hydrops fetalis. There were no major structural malformations. The conventional karyotyping was normal and there was no hydrops anymore at 32 weeks of gestation. But after birth, the baby was found to have some clinically important problems.

Deletion in MACRO D2 gene has thought us that the clinical problems may be associated with Kabuki syndrome.

In Conclusion, It seems rationale to offer arrayCGH analysis to the patients who has fetal hydrops fetalis in early pregnancy. Regression of hydrops does not guarantee the solution of the problem.

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