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CASE REPORT

Prenatal diagnosis of trisomy 21 and semilobar holoprosencephaly. Presentation of a rare association

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Abstract We present the first case reported in the Republic of Colombia of associated trisomy 21-holoprosencephaly, one of the few in the world literature. The patient was a male newborn, the son of a healthy primiparous 19 year old. An obstetric sonogram at 27 weeks gestation revealed the foetus with both cerebral ventricles dilated, semilobar holoprosencephaly and cleft lip and palate. The mother received a detailed ultrasound scan and amniocentesis for foetal cytogenetic study. A caesarean section was performed at 38 weeks. The newborn weighed 2200 g and was 46 cm long. The head circumference was 28 cm; thoracic girth, 28.5 cm; and abdominal girth, 27 cm. Apgar score was 6 at 1 min, 6 at 5 min and 9 at 10 min. Physically, the newborn had a full moon face, mongoloid obliquity of the palpebral fissure, nasal bone hypoplasia, micrognathia and cleft lip and palate. Simple and contrast computed axial tomography of the brain showed semilobar holoprosencephaly and cleft lip. At 25 h of life, the newborn expired from respiratory arrest.

Prenatal chromosome analysis presented a 47, XY, +21 G-band karyotype. Postnatal cytogenetic analysis, performed on umbilical cord blood using the fluorescent in situ hybridisation (FISH) technique with a locus specific identifier (LSI) 13/21 probe, showed the formula: nuc ish (D13ZX2), (D21ZX3) [30].

The cytogenetic aetiology of chromosome 21 and the holoprosencephaly gene are discussed, focusing on the fact that cytogenetic and gene alterations could function synergically and coincide in their expression with the postulate of the multiple-hit process.

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Genes SHH;
No disyunción;
Multiple-hit process

Diagnóstico prenatal de trisomía 21 y holoprosencefalia semilobar. Presentación de una asociación poco frecuente

Resumen Se presenta el primer caso reportado en la República de Colombia y otro de los pocos en la literatura médica mundial, de la asociación de trisomía 21 y holoprosencefalia. Paciente recién nacido, masculino, hijo de madre primípara sana de 19 años de edad. Con ultrasonido obstétrico realizado a las 27 semanas de gestación, se encontró feto con dilatación de ambos ventrículos cerebrales, holoprosencefalia semilobar, labio y paladar fisurados. A la madre se le realizó, ecografía de detalle y amniocentesis para estudio citogenético foetal. Se practicó cesárea a las 38 semanas, cuyo producto presentó peso de 2.200 g, talla de 46 cm, perímetro cefálico de 28 cm, perímetro torácico de 28,5 cm y perímetro abdominal de 27 cm. Puntuación de Apgar de 6 al primer minuto, 6 a los 5 min y 9 a los 10 min. Físicamente se observó cara de luna llena, oblicuidad mongoloide de las fisuras palpebrales, hipoplasia nasal, labio y paladar fisurados, micrognatia. La tomografía cerebral axial computarizada simple y con contraste mostró holoprosencefalia semilobar y labio fisurado. A las 25 h de vida, murió de paro respiratorio.

El cariotipo prenatal presentó fórmula cromosómica 47, XY, +21, por el método de bandas «G». El estudio citogenético posnatal, realizado con sangre de cordón umbilical y con el empleo de la técnica de FISH y la sonda LSI 13/21, mostró la fórmula: nuc ish (D13ZX2) (D21ZX3)[30].

Se discute la etiología citogenética del cromosoma 21 y la génica de la holoprosencefalia, pensando en el hecho de que alteraciones citogenéticas y génicas podrían trabajar de manera sinérgica y concordar en su expresión con el postulado del múltiple-*hit process*.

The diagnosis of an uncommon rare association

The diagnosis of this association confirmed using detailed ultrasound that makes it possible to visualise this central nervous system abnormality, with alteration in the early formation of the embryo prosencephalon; diagnosis is also confirmed by cytogenetic study, generally in amnioblasts, giving information as to the correct chromosome formula that the individual affected presents, but not about the degree of mental retardation or the capacity of learning. Because this syndrome is more frequent in young parents (due to the greater number of pregnancies presented in this age group), it would be of great interest to change the prenatal diagnosis protocol in the screening of young women at risk. Not only the routine genetic marker screening should be implemented, there should also be detailed ultrasounds between weeks 12 and 14 of gestation. This would make early detection of this type of association possible and allow for appropriate genetic counselling for the parents, in addition to better psychological preparation for receiving and handling children affected by these diseases.

Introduction

Given the characteristics of the clinical phenotype of the case that we report, it is a good idea to present relevant information on trisomy 21 and its rare association with semilobar holoprosencephaly. Trisomy 21 is one of the most common genetic disorders. It was described for the first time in 1866, by John Langdon Haydon Down, who also called it ''Mongolian idiocy''. Lejeune, in 1959, showed that this disorder was associated with an extra chromosome of the ''G'' group. Trisomy 21, or Down syndrome, is known to be phenotypically characterised by mental retardation and multiple malformations, within which cardiac anomalies and intestinal atresia are the most frequent. Other, less frequent malformations have been described, such as a flat occiput, brachycephaly, epicanthic folds, mongoloid palpebral fissures, Brushfield spots, strabismus and nystagmus, sunken nasal base, micrognathia, large fissured tongue, hypodontia, auricular hypoplasia with thickened helix, flat full-moon face with anterior–posterior flattening, short thick neck, excess nuchal fold tissue, diastasis of the rectus abdominis muscle, simian fold, fifth-finger clinodactyly and hypoplasia of the phalanges the same digit, ATD angle greater than 55°, radial loop on the ring finger, loop in the third interdigital space, radial loop in the hypothenar area, dysplastic pelvis with the iliac and acetabular angles lower than normal percentiles and cryptorchidism, and diastasis between the first and second knuckle. World prevalencia of Down syndrome is 1/800 births. However, the risk rises with the age of the mother, reaching 1/200 births when the mother is older than 35 years old.

This rare congenital malformation is the product of incomplete segmentation of the prosencephalon, Cohen (2006)[1] mentioned that holoprosencephaly is a failure in the division of the embryonic structures of the anterior brain midline, which also caused defects in the middle of the face. De Myer et al. (1963)[2] classified holoprosencephaly cases according to rising degree of severity as: lobar, semilobar and alobar. The most serious form is the alobar, in which the