CHARGE syndrome and CHD7 gene mutation

Síndrome de CHARGE y mutación en el gen CHD7

Dear Editor:

The CHARGE syndrome groups together multiple congenital anomalies and owes its name to Guyot,[1] who formed and acronym with the most characteristic features: coloboma, cardiac alterations, atresia of choanas, delayed psychomotor development and/or growth, alteration in the genitalia and alteration in the ears.[1] Its incidence is less than 1 in 10,000 live neonates[2,3] and it is thought to be under-diagnosed due to the existence of incomplete forms.[2] Most of them are sporadic (due to *de novo* mutations) but familial cases have been described, generally with mothers less affected and offspring with greater severity, so it has been suggested that its transmission may be autosomal dominant.[3,4] It has recently been associated with mutations in the CHD7 gene *(chromodomain helicase DNA-binding protein),* located in chromosomal region 8q12.1.[3-5] This case report presents a patient suffering from CHARGE syndrome confirmed by a genetic study.

A male neonate following vaginal delivery at 39+5 weeks of gestational age, Apgar 4/9, weight at birth 3.910 kg, length 50 cm and cephalic perimeter 34 cm. Parents are healthy and not consanguineous; no history of miscarriages. Laryngeal stridor from birth. Dysmorphic phenotype with rear implanted dysplastic external ears, a long philtrum and a fine upper lip. Hypoplastic genitalia. Atresia of the left choana. Dysfunction of the auditory route with brainstem auditory potentials. *Ostium secundum* type interauricular communication and interventricular communication, which both closed spontaneously. Retinal coloboma in the right eye. From the age of 6 months, bouts of apnoea, lost gaze and perioral cyanosis with widespread hypotonia lasting less than 1 minute. At 15 months, examination revealed micropenis; weight, height and cephalic perimeter below the third percentile. At 15 months, gestural language with scant bisyllabic references; at 18 months, he used 4-5 words. Crawling began at 16 months and autonomous gait at 19 months. At 3 years of age, concern arose over a non-brilliant, somewhat disperse contact, use of meaningless jargon and a certain motor clumsiness. Magnetic resonance of the brain at 22 months was normal. A molecular study for the analysis of small deletions/insertions and point mutations in the encoding region and the splicing sites of the CHD7 gene revealed two changes in heterozygosis: at exon 21, transition from an adenine to a guanine (c.4787A>G), a mutation at the protein level producing a change of asparragin to glycin at position 1596 (p.Asp1596Gly), and a second alteration (c.4614T>C) that does not produce any change of amino acid in the protein.

It is very common to find patients without all the malformations contained in the acronym, i.e. catalogued as "partial", "atypical" or "incomplete" CHARGE. Major diagnostic criteria: coloboma, atresia of choanas, facial alterations, alterations in the outer ear and alterations in the middle or inner ear. Minor criteria: cardiac defects, delayed psychomotor and/or growth development, genitourinary anomalies, delayed onset of puberty and the presence of a typical phenotype. Atypical CHARGE syndrome is defined by 3 major criteria or 2 major plus 2 minor criteria; partial or incomplete CHARGE by 2 major plus 1 minor criteria; and atypical CHARGE by 2 major criteria in isolation, or 1 major and 3 minor criteria.[6] A mutation in the CHD7 gene is identified in 2/3 cases;[3-5] in the other cases it is believed to be potentially due to genetic heterogeneity, mutations in introns on the CHD7 gene, deletions in exons (lost in sequencing) or mutations in region 3' or 5'.[3,5] CHD7 belongs to a family of proteins that participate in the organization of chromatin, participating in multiple development pathways in the foetal stage,[3] a datum that explains the great disparity of anomalies present in this syndrome. The identification of mutations allows the establishment of a definitive diagnosis,[7,8] and this, together with a better understanding of the syndrome, have entailed an increase in the number of diagnoses in the last decade.

References

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