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Case Reports

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16p11.2 Delection Syndrome and complex congenital cardiopathy

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Introduction

The 16p11.2 delection are recurrently associated with characteristic clinical variables including language development delay, learning difficulties and/or intellectual disability, socialization difficulties with or without autism spectrum disorder, and minor dysmorphic facial features (without a constant pattern) (1,2,3). However, the main characteristic of the patient in our case is complex congenital heart disease related with " novo"delection in cytoband 16p11.2 of chromosome 16 with genomic coordinates chr16:28,824,594-29,031, 200.

CLINICAL CASE

A 20-year-old male, of non-consanguineous parents and without a family history of interest, who was assessed in the union for a polymalformative syndrome characterized by mild mental retardation, complex congenital heart disease (dextrocardia and dextroapex, absence of inferior vena cava, ventricular inversion, atresia pulmonary with interventricular communication and ascending aortic dilation), and altered basal glycemia. Also mild hypercalcemia, subclinical hypothyroidism, vitamin D deficiency and left cerebral cortical dysplasia. Derived from congenital heart disease, there is chronic heart failure and polyglobulia secondary to chronic hypoxia due to the right-left short circuit. No dysmorphic features, language disorders, social disability, psychiatric disorders or obesity. At birth palatal fissure and cleft lip that were intervened during childhood, as well as heart disease. Initially, bilateral systemic-pulmonary fistula was performed and, at 5 years, in a second time, and after the fistula was removed, it was intervened to make anastomosis of the vena cava superior to the right pulmonary branches (Kawashima procedure).

Phenotypically, it also showed alterations of the midline, mild generalized hypotonia, unstable gait, flat feet and functional limitations, mainly in activities performed by lower limbs. On physical examination, the patient was eupneic and cyanotic at rest, with good oxygen saturation but with dyspnea (NYHA II). No palpitations, syncope, jugular engorgement, visceromegaly or edema. Cardiac auscultation showed rhythmic tones, with a breath of light grade aortic insufficiency. Palpable pulses in lower limbs. EKG showed a sinus rhythm and in blood analytics only one polyglobuly maintained over time stood out.

Given this polyformative phenotype, a karyotype was performed and a study of subtelomeric probes was reported as normal. An Array-CGH arr [hg19] study was then carried out with a depth level of 95%, which detected a probably pathogenic deletion in the cytoband 16p11.2, chr16 genomic coordinates: 28,824,594-29,031,200. The variation in the number of copies (CNV), of approximately 210 kilobases, contained 9 genes, among which is the SH2B1 gene (* 608937). Alterations in this gene are associated with obesity, due to its relationship with the signaling pathway of leptin and insulin, which generates a high risk of generating severe obesity of early onset and, in some cases, developmental delay.

DISCUSSION

Proximal 16p11.2 microdeletion syndrome is a chromosomal abnormality characterized by a delay in development (delay in fine and gross motor skills and coordination) and language (specifically at the beginning and in the development of expressive language -apraxia of child speech-), mild intellectual disability, social disability with or without autism spectrum disorders (ASD), mild and inconstant dysmorphic features and predisposition to obesity. Other less frequent additional features include hypotonia, abnormalities in the EEG, another psychiatric illness other than ASD and minor cardiac abnormalities. The presentation is extremely variable and in some cases they can also be associated with a normal phenotype. The differential diagnosis should be made with psychiatric disorders (mainly ASD) and dysmorphic features. (4)

The diagnosis is based on clinical manifestations that lead to chromosomal analysis (including fluorescent in situ hybridization (FISH), MLPA, comparative microarray based genomic hybridization (aCGH) and quantitative polymerase chain reaction (qPCR)). These mutations almost always appear de novo, but, in a small number of cases, they can be inherited from autosomal dominant parents affected. In cases of family history, genetic counseling is advisable, but the result of this cannot really predict the clinical phenotype accurately (5).The prognosis depends on the severity of the clinical manifestations (1,2).

Although there have been no specific descriptions of heart disease in the clinical descriptions of this deletion, they do appear in a large group of patients with valvulopathies (bicuspid aortic valve with or without stenosis, tricuspid regurgitation or other cardiac abnormalities (endocardial fibroelastosis bradycardia, syncopes) (3,4,7)

Only the DECIPHER database describes a patient (297117) with a de novo deletion covering a greater area affected by congenital heart disease (coarctation of the aorta and ventricular septal defect (5) and intellectual disability . Because, despite the deletion associated with a pathogenic phenotype, it does not fully explain the test phenotype and is assigned a probably pathogenic value. So even if there are mild heart diseases related to this syndrome, no case has been described with complex congenital heart disease and the mutation that the patient presents. Recently, different variants of the 16p11.2 deletion with VACTERL phenotype have been described, which consists of the combination of vertebral, anal, cardiac, tracheoesophageal, renal and limb abnormalities; as well as with prolapse of the syndromic or non-syndromic mitral valve. (8,9)

The analysis of chromosomal microarrays will allow us to detect some of these conditions associated with developmental delay, autism and / or multiple congenital anomalies that would not be detected with a karyotype.

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