Diagnosis of 22q11.2 Deletion Syndrome in a Child With Congenital Heart Disease and Facial Dimorphism: A Case Report

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Abstract- 22q11.2 deletion syndrome is caused by a deletion in chromosome 22q11.2 and has more than 180 distinct phenotypes; however, no finding is pathognomonic or even mandatory. This syndrome can be diagnosed by fluorescence in situ hybridization. Thus, we report herein a patient from Manaus, Brazil, who has congenital heart disease and facial dimorphism with the presence of 22q11.2 deletion in the N25 region. Male patient, a 1-year-old son of non-consanguineous parents and without a family history of genetic disease. The patient was hospitalized in the cardiac intensive care unit of the Francisca Mendes University Hospital for surgery. The patient was diagnosed with interventricular communication, low atrial implantation, hypertelorism, and macroglossia. The FISH result revealed the presence of a proximal deletion in the N25 region (22q11.2) in only one of the pairs in chromosome 22. This finding revealed a diagnosis of 22q11.2 deletion syndrome, in other words, a hemizygotes deletion with haploinsufficiency of the CLTCL1 gene in this region. However, it is valid to say that the CLTCL1 gene is related to the clinical picture of the patient reported in this study. Cytogenetic analysis was essential for the etiological diagnosis and revealed 22q11.2 deletion in the N25 region, which resulted in 22q11.2 deletion syndrome. The importance of diagnosing this syndrome lies in the best therapeutic conduct, thus allowing a better quality of life for the patient and adequate genetic counseling. Other cytogenetic studies are essential in order to elucidate the size of the deletion and low copy repeats involved in this deletion.

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Introduction

The 22q11.2 deletion syndrome corresponds to the group of genetic conditions that result from a deletion in chromosome 22q11.2 and is considered one of the most frequent microdeletions in humans (1,2). The term 22q11.2 deletion syndrome etiologically unifies the Digeorge (SDG), Velocardiofacial (VCF), conotruncal anomaly face, Sedlačková, Cayler, Shprintzen, and CATCH22 (conotruncal heart defect, abnormal face, deficient T cells, cleft, and hypocalcemia, resulting from an abnormality on chromosome 22) syndromes (3). This syndrome has more than 180 distinct phenotypes, which are both physical and behavioral. Facial dimorphisms, palatal anomalies, immunodeficiency, hypocalcemia, thymic hypoplasia, language/learning/development changes, intellectual disability, and congenital heart disease can be highlighted as the most frequent clinical signs (1,2,4,5). However, none of these are pathognomonic or even mandatory, and, as a result, this can end up hindering clinical diagnosis.

As for the diagnosis of this syndrome, affected individuals present a deletion in chromosome 22q11.2. This is detected by the technique of fluorescence in situ hybridization (FISH), which is considered the gold standard for this diagnosis. Within this context, we report a case of a patient from Manaus, Brazil with congenital heart disease and facial dimorphism with the presence of

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22q11.2 deletion in the N25 region, resulting in 22q11.2 deletion syndrome. In addition, this report highlights the importance of cytogenomic analyses for the diagnosis of this syndrome, as well as better clinical follow-up, which in unison allow for more adequate patient follow-up and genetic counseling.

Case Report

Male patient, 1-year-old, who was hospitalized in the cardiac intensive care unit (ICU) Francisca Mendes University Hospital of the city of Manaus, Brazil, while awaiting cardiac surgery. The patient was diagnosed with interventricular communication, low atrial implantation, hypertelorism and macroglossia.

Son of non-consanguineous parents and no family history of genetic disease. The informed consent form was completed and duly signed by the parents/legal guardians of the patient. Cytogenomic analysis using fluorescence in situ hybridization (FISH) technique with DIGEORGE/VCFS probes in the N25 region (22q11.2, spectrum red) and N85A3 (22q13.3, spectrum green) was performed in this study. The patient presented the presence of deletion in the N25 region (22q11.2) (Figure 1). Currently, the patient is being followed up with a multi-professional approach, in order to provide a better quality of life.

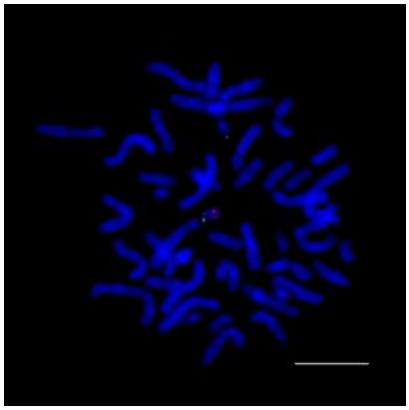

Figure 1. Karyotyping by FISH of the patient from Manaus with congenital heart disease. Patient with 46, XY, presence of deletion in the N25 region (22q11.2, red signal) and absence of deletion in the N85A3 region (green signal). The chromosomes were counterstained with DAPI. Scale bar equal to 20 μm

Discussion

Chromosome 22 has a genomic organization that consists of highly repetitive regions in low copy repeats (LCRs), which, due to the large homology between its sequences, act as a substrate for non-allelic, inter or intracromosomal homologous recombination, and favors the emergence of chromosomal anomalies (6,7). Most of these anomalies occur mainly in the 22q11.2 region (6,8-10).

In the 22q11.2 region, there are several genes, including TBX1 (T-box transcription factor 1), TUPLE 1/Hira (Hir histone cell cycle regulation defective), and CLTCL1 (Clathrin Heavy Chain Like 1) (6,10,11). These genes are associated with 22q11.2 deletion syndrome as a result of 22q11.2 deletion. The diagnosis of 22q11.2 deletion syndrome can be performed using the FISH technique with the use of commercial probes for the TBX1 (recognizes the TBX1 gene), TUPLE1 (recognizes the TUPLE1 gene), and N25 (recognizes the CLTCL1 gene) regions to detect proximal 22q11.2 deletion. It is important to note that alternatives to the FISH technique have also been used to identify 22q11.2 deletions in the chromosomal region (proximal, central, and distal 22q11.2 deletions), the size of the deletions (1.5 to 3 megabase deletions), and the LCRs involved (eight groups of LCR22s, A-H) (9,10).

In this study, the patient presented proximal deletion in the N25 region (22q11.2) in only one of the pair in chromosome 22, which resulted in 22q11.2 deletion syndrome. The N25 region possesses the CLTCL1 gene (Clathrin Heavy Chain Like 1), which is responsible for carrying out important functions in protein-coding. In addition, this deletion denotes a hemizygotes deletion and causes the loss of a gene copy and, as such, the existing copy is not able to express its genes at a sufficient level due to haploinsufficiency of the gene in this region (12,13). The haploinsufficiency of several genes seems to contribute to the phenotype of a syndrome/disease. However, the haploinsufficiency of a single gene allocated in the critical region of deletion has been considered as the main cause of the phenotype of an individual (14). In view of this, it is fair to say that the CLTCL1 gene is related to the occurrence of heart disease and facial dimorphism in the patient reported in this study

Reported a patient with heart defects suggestive of 22q11.2 deletion syndrome and evidence of a hemizygotes deletion in the TUPLE Region 1 (22q11.2) using FISH (15). Analyzed 39 patients with congenital heart disease using FISH and identified that 22 of these had a deletion in the TUPLE 1 Region (22q11.2) (16). In the Amazonas state, there have only been two studies with immunodeficient and congenital heart disease patients with suspected 22q11.2 deletion syndrome who were analyzed using FISH, and none of them presented 22q11.2 deletion (17,18). These authors suggest that even

with a negative result, this does not exclude the presence of 22q11.2 deletion in the region since some patients may present deletions in the TBX1 and N25 regions (detected by FISH) as well as atypical deletions. As such, it is necessary to perform complementary cytogenetic analyses for both these patients and others with distinct phenotypic characteristics that are associated with this syndrome.

In conclusion, cytogenetic analysis was essential for the etiological diagnosis, in which 22q11.2 deletion was revealed in the N25 region that resulted in 22q11.2 deletion syndrome in a patient with congenital heart disease and facial dimorphism. Thus, the importance of early diagnosis of this syndrome lies in the best therapeutic conduct, which allows a better quality of life for the patient and adequate genetic counseling. Complementary cytogenetic studies are necessary to identify the size of the deletions and the LCRs involved in this deletion.

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