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THE MAIN CONGENITAL HEART DISEASES IN PATIENTS WITH DOWN SYNDROME: AN UPDATE

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Abstract: Down syndrome (DS) results from trisomy 21 (T21) and is the most common chromosomal syndrome. Its prevalence varies between populations, but is increased in pregnant women over 42 years of age, certain ethnicities and in consanguineous parents. In the population with DS, congenital heart disease (CHD) is associated with approximately 50% of patients, being the main responsible for early death in these patients. Therefore, the objective is to understand the most common congenital heart defects in Down Syndrome. This is an integrative review of the literature, based on the VHL, PubMed/MEDLINE and Scielo databases, carried out in November 2022. The descriptors "Heart Defects, congenital" AND "Down syndrome" were applied, with the descriptor NOT review. Articles were selected from 2017 to 2022, with full text available, filtered by human limits and that responded to the proposed objective. After applying the method, 14 articles remained, which were read and analyzed. Two studies identified DS as the syndrome most commonly associated with the diagnosis of congenital heart disease. The type of CHD chosen as the most common was the common atrioventricular canal (CAVC), highlighting the atrioventricular septal defect (AVSD) and ventricular septal defect (VSD). The survival of DS patients with congenital heart disease depends on several factors. The hypotheses explain that defects in the endocardial cushion in a certain number of DS patients are mainly due to altered methylation profiles of genes involved in cardiac morphogenesis and a complex architecture of alleles and complex genetic and epigenetic interactions. Therefore, the correlation between DS and congenital heart disease is heterogeneous in its incidence and types of CHD, a relevant factor in public policy programming. More recent genetic and epigenetic studies point the way to unraveling the existing gaps, but new studies are needed.

Keywords: Congenital Heart Diseases. Down's syndrome. Genetics. Epigenetics.

INTRODUCTION

Down syndrome (DS) results from trisomy of chromosome 21 (T21), generated by the existence of an additional copy of chromosome 21 in the human chromosome set, being the most common chromosomal syndrome. For the most part, the additional presence of the aforementioned chromosome is made possible as a result of anomalous chromosomal segregation during the process of reduction division, which culminates in the disproportionate formation of gametes. A small proportion of DS patients manifest a condition known as "trisomy 21 mosaic", which originates in the primordial projects of cell division in the zygote. Furthermore, the syndrome can also be caused by translocation, a change in which a fragment of chromosome 21 attaches to another non-homologous chromosome (YAQOOB et al., 2019). The prevalence of DS varies between populations, as maternal age over 42 years, ethnicity and parental consanguinity increase the likelihood of this chromosomal abnormality, which is highlighted by the presence of intellectual disability, developmental delays, distinctive facial features, congenital malformations and hypotonia in early childhood (TAURA et al., 2021).

In the population with DS, congenital heart disease (CHD) is associated with approximately 50% of patients, translating into abnormalities of the heart and large cardiac vessels present since birth. Among the most frequently observed cardiac anomalies are interatrioventricular septal defect (AVSD), which appears in approximately 45% of cases, and interventricular septal defect (VSD), responsible for approximately 20-30% of occurrences. The surgical approach to treating congenital heart damage in such patients often implies a high risk of postoperative complications and mortality, as patients are susceptible to infections (SANTOS et al., 2019).

Furthermore, acquired heart diseases can also occur, either spontaneously, or due to the high occurrence of hematological malignancies and the use of cardiotoxic therapies. With the advancement of medicine, the survival rate of T21 patients is constantly growing, however, heart disease is among the main causes of early death in these patients, attracting the attention of the scientific community.

Although heart disease is a high predictor of mortality in this group, the overall survival of patients with DS has improved in recent years. Among the forms of treatment, heart transplantation becomes an alternative, as children with DS have a high risk of developing heart anomalies. Currently there are no concrete conclusions that contraindicate transplantation, but studies have shown that as DS leads to several extra-cardiac comorbidities, such manifestations can affect post-transplant recovery, such as pulmonary hypertension, immunological dysfunction, obesity, risk of acute leukemia and autoimmune disorders (GODOWN et al., 2022).

GOAL

To know the most common congenital heart defects in Down Syndrome.

METHOD

This is an integrative review of the literature, based on the research bases Virtual Health Library (VHL), Pubmed/MEDLINE and Scientific Electronic Library Online (Scielo), carried out during the month of November 2022. The descriptors applied were " Heart Defects, congenital" AND "down syndrome", in addition, the descriptor NOT

review was added. There was a delimitation in articles from 2017 to 2022, with full text available, with the human limit being selected. Furthermore, inclusion and exclusion criteria were used during the searches, reading titles, abstracts and in full, determining the articles that responded to the objective to integrate the present study.

RESULT AND DISCUSSION

After applying the method, 14 articles remained, which were read and analyzed. Two studies identified DS as the syndrome most commonly associated with the diagnosis of congenital heart disease (NAMUYONGA et al., 2020; ZUECHNER et al., 2019). In research focused on DS, the type of CHD chosen as the most common was the common atrioventricular canal (CAVC), mainly the atrioventricular septal defect (AVSD), followed by ventricular septal defect (VSD), and, despite the frequency of CAVC decreasing in some regions due to advances in prenatal care, this is not the reality for all families (CHINAWA; CHINAWA, 2021; DOBOSZ; MULTANOWSKI, 2019). Other research has shown ventricular septal defect (VSD) as the most common, followed by patent ductus arteriosus (PDA) (NAMUYONGA et al., 2020; ZUECHNER et al., 2019) or atrial septal defect (ASD), (TASFAYE; TADELE, 2022). A study from Saudi Arabia had DSA as the most common and VSD as the second most common (TAURA et al., 2021).

The survival of DS patients with congenital heart disease depends on several factors. According to the study, adequate medical intervention associated with a specialized multidisciplinary approach are essential in maintaining the health of people with DS (YAQOOB et al., 2019). Advances in studies help with early diagnosis, but research has not yet found a significant statistical relationship between sex and the onset of congenital heart disease (TAURA et al., 2021). However, the majority of cardiac injuries were predominantly in females, except for VSD, which was more common in males (YAQOOB et al., 2019). Furthermore, the results show a strong correlation between CAVC and patients with DS, demonstrating that heart disease is present in more than 40% of children born with T21 (ZHANG et al., 2021).

The hypotheses explain that defects in the endocardial cushion in a certain number of DS patients are mainly due to altered methylation profiles of genes involved in cardiac morphogenesis and a complex architecture of alleles with cumulative effects and varied genetic and epigenetic interactions, including polymorphisms that determine the variety of DS phenotypes (DOBOSZ; MULTANOWSKI, 2019). The interaction of multiple factors, including polymorphisms in the functional pathways of VEGFA (Vascular Endothelial Growth Factor A) may contribute to the development of congenital heart disease in patients with DS (BALISTRERI et al., 2020). The development of a mature and healthy heart (with its four divided chambers) depends on the adequate differentiation of endothelial cells that will form the endocardial cushion and, thus, on the growth and remodeling of this mass of cells, which contribute to the formation of atrioventricular valves and of the interatrial, interventricular and atrioventricular septa (DOBOSZ et al., 2019). Recent studies have detected hypermethylation of the NGR1 gene promoter and reduced activity of three other connected genes (ERBB3, SHC3 and SHC4) in the DNA of these patients. These genes are responsible for the formation of endocardial cushions, thus causing valve malformations, which are the basis of the main CHDs (DOBOSZ; MULTANOWSKI, 2019). Variations in the number of gene copies are potentially related to the formation

of the CAVC and single ventricle (ZHANG et al., 2021).

It must be noted that Congenital Heart Diseases are significant causes of Pulmonary Arterial Hypertension, especially those characterized by significant shunts from left to right, in order to worsen the health status of these patients with T21. Regarding surgical interventions, CAVC repair and VSD closure are the most common initial operations (PETERSON et al., 2021). Biventricular repair procedures in patients with DS had a favorable early prognosis associated with intensive management of pulmonary hypertension (HOASHI et al., 2018). DS must not be a contraindication for heart transplantation due to this factor alone (GODOWN et al., 2022). Over the years there has been a significant reduction in complications and in-hospital mortality after surgery even with an increase in the number of patients operated on (SANTOS et al., 2019). SD associated with congenital heart disease is related to the response to bacterial sepsis treatment, with a double chance of death from sepsis (TASFAYE; TADELE, 2022).

CONCLUSION

The correlation between DS and congenital heart disease, although factual, is heterogeneous in its incidence and types of CHD. The articles analyzed brought advances in the understanding of the different manifestations, which are extremely important given the prevalence and severity of the conditions. Furthermore, the varied frameworks are a relevant factor in the programming of public policies and in the propaedeutic approach, understanding them influences the course and outcome of the pathology. More recent genetic and epigenetic studies show progress in unraveling existing gaps, in order to improve the tracking, diagnosis and treatment of these patients, in each of their specificities. New studies that reconcile such results with the reality of underdeveloped countries, a greater population and experimental approach, are necessary to ensure the effectiveness of this process, which directly impacts their future survival.

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