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HYPERTROPHIC

CARDIOMYOPATHY IN NOONAN SYNDROME

MIOCARDIOPATÍA HIPERTRÓFICA EN EL SÍNDROME DE NOONAN

Carlos Gustavo López Barrionuevo[1]
E-mail: ua.carlosglopezb@uniandes.edu.ec
ORCID: https://orcid.org/0000-0003-1102-4350
Marlon Andrés García Santamaría[1]
E-mail: ma.marlonags31@uniandes.edu.ec
ORCID: https://orcid.org/0000-0002-2331-733X
Ana Belén Pérez Proaño[1]
E-mail: ma.anabpp80@uniandes.edu.ec
ORCID: https://orcid.org/0000-0001-6420-0843
Juan Alberto Viteri Rodríguez[1]
E-mail: ua.juanviteri@uniandes.edu.ec
ORCID: https://orcid.org/0000-0002-2463-7036
Salah Hasan Saleh Al-Subhi[2]
E-mail: salahcuba@hotmail.com
ORCID: https://orcid.org/0000-0002-6255-7491
[1] Universidad Regional Autónoma de Los Andes. Ecuador.
[2] The Combined Security Group. Fahaheel Mekka St, Alanoud Complex. Kuwait.

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ABSTRACT

Noonan syndrome is a rare genetic disorder. It has an autosomal dominant and heterogeneous pattern, with gain-of-function mutations in the genes of the RAS-MAPK signaling pathway. Cardiovascular diseases such as hypertrophic cardiomyopathy are associated with the mutation of RIT1, which causes an alteration in important proteins in the RAS signaling pathway. Patients with Noonan syndrome are more likely to have heart failure than other children with hypertrophic cardiomyopathy. An early diagnosis increases their survival by 70%. Being congestive heart failure, the main cause of death. Depending on the genetic mutation, differences will be seen in cardiovascular involvement. Patients with mutations in PTPN11 or SOS1 will have a lower prevalence of having hypertrophic cardiomyopathy than those with mutations in RAF1 or RIT1, who are very prone to developing hypertrophic cardiomyopathy in 85%. RIT1 mutations may also generate pulmonary valve stenosis. Genotype studies are being carried out to find out how signal transduction is altered, as well as possible treatments.

Keywords: Noonan, cardiopathy, mutations.

RESUMEN

El síndrome de Noonan es un trastorno genético poco común. Tiene un patrón autosómico dominante y heterogéneo, con mutaciones de ganancia de función en los genes de la vía de señalización RAS-MAPK. Las enfermedades cardiovasculares como la miocardiopatía hipertrófica se asocian a la mutación de RIT1, que provoca una alteración de proteínas importantes en la vía de señalización RAS. Los pacientes con síndrome de Noonan tienen más probabilidades de tener insuficiencia cardíaca que otros niños con miocardiopatía hipertrófica. Un diagnóstico precoz aumenta su supervivencia en un 70%. Siendo insuficiencia cardíaca congestiva, la principal causa de muerte. Dependiendo de la mutación genética, se observarán diferencias en la afectación cardiovascular. Los pacientes con mutaciones en PTPN11 o SOS1 tendrán una menor prevalencia de padecer miocardiopatía hipertrófica que aquellos con mutaciones en RAF1 o RIT1, que son muy propensos a desarrollar miocardiopatía hipertrófica en un 85%. Las mutaciones de RIT1 también pueden generar estenosis de la válvula pulmonar. Se están realizando estudios de genotipo para conocer cómo se altera la transducción de señales, así como posibles tratamientos.

Palabras clave: Noonan, cardiopatía, mutaciones.

INTRODUCTION

Noonan Syndrome is a rare, non-chromosomal genetic disorder. It has an autosomal dominant pattern, and it occurs in 1 out of every 1000 live newborns, with gain-of-function mutations in the genes of the RAS-MAPK signaling pathway. It is the second most common syndromic cause of congenital cardiopathy, in which there are several cardiovascular phenotypes, the most common are: pulmonary stenosis (60%), hypertrophic cardiomyopathy (20%), and secundum atrial septal defect (6 to 10%). There are also reports of stenosis, mitral valve abnormalities, aortic coarctation, and coronary artery abnormalities. Cardiomyopathy can be mild or severe with onset in the prenatal period through childhood.

Twenty-five percent of patients die of heart failure in the first year of life. Electrocardiograms usually reflect wide QRS complexes with a predominantly negative pattern in the left precordial leads and left axis deviation with giant Q waves (Maheshwari et al., 2002).

In a study, survival of children with Noonan syndrome and familial or idiopathic hypertrophic cardiomyopathy was compared with information obtained from the United States pediatric cardiomyopathy registry database. (Hickey et al., 2011).

The data of 74 children with Noonan Syndrome and hypertrophic cardiomyopathy were compared. 792 children with idiopathic or familial cardiomyopathy were also analyzed. Children with Noonan Syndrome were diagnosed with hypertrophic cardiomyopathy before 6 months of age in 51%, while children with hypertrophic cardiomyopathy in 28% were diagnosed at that age, but were more likely to develop congestive heart failure in 24% versus 9% in children with Noonan Syndrome (Tartaglia et al., 2002), .

Survival of children with Noonan syndrome is higher than the group with other hypertrophic cardiomyopathies, but survival did not differ after adjustment for congestive heart failure and the age at the time of diagnosis (Lee et al., 2014), (Mar Cornelio et al., 2021). One-year survival in 78% was related to a diagnosis of hypertrophic cardiomyopathy before 6 months of age, while children with familial hypertrophic cardiomyopathy had a 31% of survival rate (Wilkinson et al., 2012).

Eight genes of the RAS-MAPK signaling pathway cause Noonan Syndrome (PTPN11, SOS1, KRAS, NRAS, RAF1, CBL, SHOC2, and BRAF). It is related to the chromosomal band 12q24.1 and PTPN11, which encodes the protein SHP2, which has essential functions in the signal translation pathways that control cardiac lunate valvulogenesis. Studies suggest that 50% of cases are caused by meaningless and gain-of-function mutations in the PTPN11 gene (Dhandapany et al., 2014), (Leyva-Vázquez et al., 2020).

Myocardial histology in cardiomyopathy associated with Noonan syndrome has different characteristics from sarcomeric hypertrophic cardiomyopathy caused by mutations that alter sarcomeric proteins. Cardiac hypertrophy associated with Noonan syndrome occurs early in life. It is usually diagnosed at six months of age, much earlier than other forms of pediatric hypertrophic cardiomyopathies that usually appear by the age of 8 (Marin et al., 2011), (Cornelio et al., 2019).

Patients with Noonan syndrome are more likely to have heart failure than other children with hypertrophic cardiomyopathy (24% vs 9%). This is added to a significant obstruction of the left ventricular outflow with a gradient of 32 mmHg. An early diagnosis increases survival by 70%, the main cause of death being congestive heart failure (Digilio & Marino, 2001), (Teruel et al., 2018), (Al-Subhi et al., 2020), (LEYVA et al., 2018).

Depending on the genetic mutation, differences will be seen in cardiovascular involvement. Patients with mutations in PTPN11 or SOS1 will be less likely to have hypertrophic cardiomyopathy than those with mutations in RAF1 or RIT1, who are very prone to developing hypertrophic cardiomyopathy in 85%. RIT1 mutations may also generate pulmonary valve stenosis.

Cardiomyopathies resulting from mutations that alter the RAS-mediated protein kinase pathway provide a target for molecular therapies. Hypertrophic cardiomyopathy appears due to increased activation of AKT through mTOR, mTOR (rapamycin) inhibitors are used as immunosuppressants to prevent post-transplant rejection and coronary restenosis after stent placement. Side effects include an increased risk of cancer or diabetes (Burch et al., 1993), (Fonseca et al., 2020).

DEVELOPMENT

Cohort studies published in the National Center of Biotechnology Information (NCBI) in the period 2015 to 2020 were reviewed. Search terms were ***Noonan Syndrome*** and ***hypertrophic cardiomyopathies***. In inclusion criteria, cohort studies of patients diagnosed with Noonan Syndrome who underwent two-dimensional echocardiography and Doppler studies were used to establish the degree of hypertrophic cardiomyopathy. The exclusion criteria were articles before 2015 and those related to clinical characteristics of the Noonan syndrome as postnatal reduced growth, facial dimorphism, and cognitive deficit.

An average of the data provided by these studies related to heart diseases observed in Noonan Syndrome was carried out to identify the prevalence of hypertrophic cardiomyopathy in heart diseases associated with Noonan Syndrome. Then the number of reports of each of the hypertrophic cardiomyopathies was identified by imaging studies to observe the incidence of each one(Palacios et al., 2021).

Finally, the mortality rate in patients with classic cardiomyopathies was compared to that of patients with Noonan Syndrome to observe the susceptibility of this group. An analysis of patients with this pathology in Ecuador was made, but there are only reports of cases with limited information.

Five cohort studies were found where it was evidenced that hypertrophic cardiomyopathy is one of the most important heart problems in Noonan Syndrome with an incidence of 8.8%, being the fourth cause of heart disease in this group of patients.

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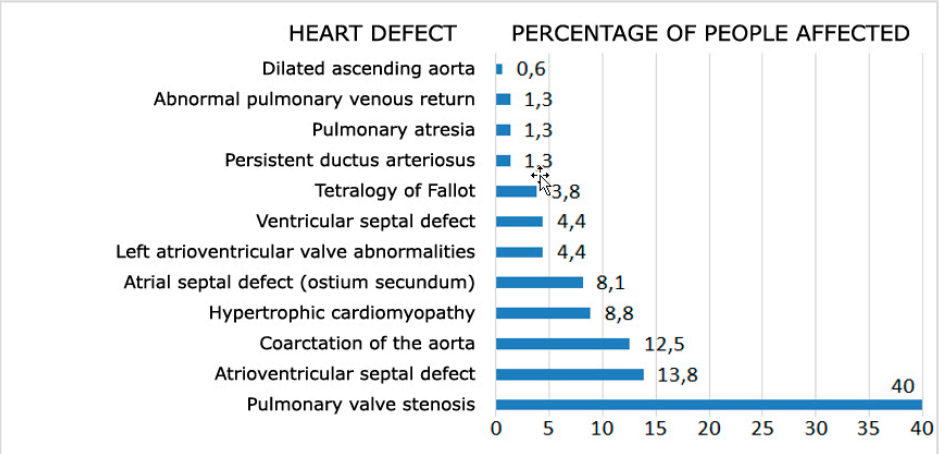

Figure 1. Cardiac clinical characteristics of Noonan Syndrome.

Source:(Briggs et al., 2020).

The typical morphology of hypertrophic cardiomyopathy in Noonan Syndrome is the anterior septal (41%) followed by pulmonary stenosis (35%). Most of them were mild or moderate with a heart defect on the right side and hemodynamic effects in the left ventricle.

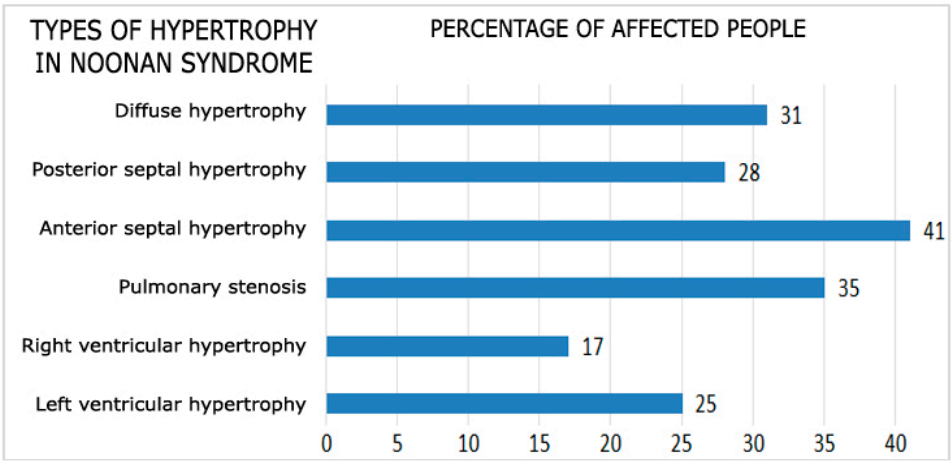

Figure 2 Ventricular hypertrophy in Noonan Syndrome.

Source: (Hemmati et al., 2019).

The survival of children with Noonan syndrome is higher than the group with other hypertrophic cardiomyopathies. One-year survival in 78% was related to a diagnosis of hypertrophic cardiomyopathy before 6 months of age, while children with familial hypertrophic cardiomyopathy had a 31% of survival rate.

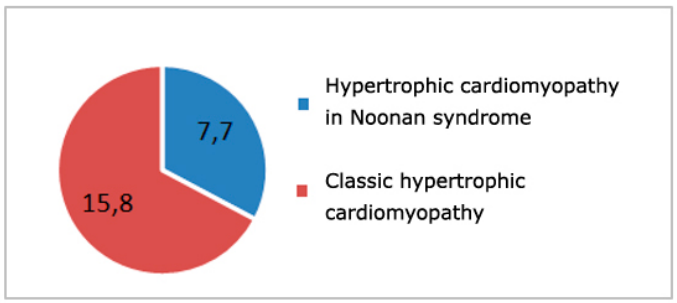

Figure 3 Mortality in classical cardiomyopathy and Noonan syndrome.

Source: (Yamamoto et al., 2020).

Noonan Syndrome is a rare, non-chromosomal genetic disorder. It has an autosomal dominant pattern, it occurs in 1 out of every 1000 live newborns, with gain-of-function mutations in the genes of the RAS-MAPK signaling pathway. It is the second most common syndromic cause of congenital heart disease (Hemmati et al., 2019).

The mortality rate in children with Noonan syndrome associated with heart disease is lower than in children with other causes of hypertrophic cardiomyopathy. The mortality of patients with Noonan syndrome is associated with age and the prevalence of congestive heart failure. A recent report noted that the survival of 30 Noonan Syndrome patients with hypertrophic cardiomyopathy was similar to that of 120 patients without Noonan Syndrome in the first decade after diagnosis. (Briggs et al., 2020), (Carralero et al., 2020).

However, the details about the clinic of these patients are limited and it is required to make a comparison. The early mortality in Noonan Syndrome is particularly striking: 26% at 3 years and there were no deaths after the diagnosis of hypertrophic cardiomyopathy at 2.5 years (Myers et al., 2014).

A history of hypertrophic cardiomyopathy was not associated with increased mortality. Congestive heart failure, on the other hand, is an important risk factor for mortality in children with hypertrophic cardiomyopathy due to Noonan Syndrome (Gómez et al., 2019).

Furthermore, when familial hypertrophic cardiomyopathy was present in children diagnosed with hypertrophic cardiomyopathy in the first 6 months of life, mortality was 69% in the first year after diagnosis. Severe hypertrophy leads to pulmonary edema and decreased cardiac output. A neonate with Noonan Syndrome having symptoms of congestive heart failure requires close monitoring and consideration of early inclusion for heart transplantation may be justified given the one-year mortality rate of 69% (Yamamoto et al., 2020).

The relationship of specific genotypes with clinical outcomes in children with Noonan syndrome and hypertrophic cardiomyopathy has not yet been described. More studies should be done as this could help to find a molecular treatment aimed at these patients, especially for children suffering from Noonan Syndrome with congestive heart failure due to its high mortality rate.

CONCLUSIONS

Children with Noonan syndrome develop hypertrophic cardiomyopathy at a younger age and more often with congestive heart failure than children with familial or idiopathic cardiomyopathy. The risk of death is highest in the first 6 months of life, particularly if familial hypertrophic cardiomyopathy is present.

Neonates with Noonan Syndrome cardiomyopathy should be evaluated because the phenotype may be more difficult to recognize. The finding of the mutation in hypertrophic cardiomyopathy could allow us to understand the disease with its molecular pathophysiology to find possible treatments in the future.

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