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CASE REPORT

Noonan Syndrome

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Abstract

Noonan syndrome is a common genetic disorder of autosomal dominant origin. Genes related to signaling via RAS/MAPK were related to the etiology and clinical findings are prevalent cardiovascular abnormalities, short stature, developmental delay and facial dysmorphisms. The degree of occurrence of phenotypic findings may vary with the age of the patient and the types of gene mutations, which delays the diagnosis of the syndrome and prejudice the management of the phenotypic changes and quality of life. This article reports the case of a patient, male, six years old, in a regular monitoring with pediatric cardiologist diagnosed with Noonan syndrome to 1 year and 3 months.

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INTRODUCTION

Noonan syndrome (NS) was discovered in 1963 by pediatric cardiologist Jacqueline Noonan[1-4]. It is hereditary, with dominant autosomes and with similar distribution in both sexes[3,5-7]. Despite the fact that it is inherited, 60% of cases are sporadic[8].

The *PTPN11*, *SOS1*, *RAF1, KRAS,* and *SHOC2* genes have been associated with the etiology of the syndrome and are responsible for the RAS/MAPK signaling pathwayK[2,5,6,9-12]. There are cases in which the mutation occurs after conception (de novo mutation), as will be presented in the report[13].

It is considered one of the most frequent Mendelian syndromes and is also underdiagnosed in our field[1,3]. Incidence ranges from 1:1000 to 1:2500 live births[1,2,4,5,7,9,10,14,15]. It is closely associated with severe heart defects, being one of the most prevalent causes of these defects, second only to Down syndrome[6]. Previously described characteristics associated with the syndrome include typical facial features, a webbed neck, *pectus carinatum,* short stature, pulmonary stenosis, hypertrophic cardiomyopathy, dermatological, ophthalmic, and renal disorders, lymphatic dysplasia, deficiency in coagulation factors, and cryptorchidism[1,4-6,8-10,12-14].

This article aims to provide information on the existence of the syndrome and its phenotypic characteristics, thus enabling early diagnosis and treatment of complications.

CASE REPORT

The six-year-old male "pardo" patient is referred to as S.S.B.H. He was conceived via *in vitro* fertilization by healthy parents. He is regularly monitored by a pediatric cardiologist due to pulmonary stenosis diagnosed at birth. His mother reported that, during the prenatal period, she took prenatal multivitamins, used only symptom-relief medications, and did not ingest alcohol or drugs.

At six months of pregnancy, the mother of the patient was hospitalized in Belo Horizonte due to the onset of labor. Cesarean section was performed at 34 weeks. At birth, the patient's weight was 2150 g, his length was 42 cm, his head circumference was 32 cm, and the Apgar score was 6-8.

The newborn developed severe dyspnea, was transferred to the ICU, received a pulmonary surfactant, and underwent phototherapy. In the ICU, he was diagnosed with pulmonary stenosis, which was confirmed by two Doppler echocardiograms. He remained in the neonatal unit for eight days and was then discharged. The newborn screening test, the red reflex test and pulse oximetry presented no abnormalities.

In the first months of life, the patient exhibited phenotypic changes such as ptosis, hyperemic and swollen feet and hands, and hemangiomas on the face and cheeks. In addion, the patient exhibited low-set ears with thickened lobes, a short neck, and an upper lip with a deep groove line (Figure 1). Respiratory crises characterized by coryza and dyspnea were common, which led the mother to consult with several doctors, but no diagnosis was made.



Figure 1. Low-set yars and thickened lobes, a short neck and upper lip with a deep groove line.

Due to pulmonary stenosis, the mother consulted three cardiologists, but the possibility of Noonan syndrome was never addressed. The diagnosis was eventually made by a geneticist at a year and three months of life after a pediatrician referred the patient because of his phenotypic abnormalities. The patient underwent a valvuloplasty for stenosis correction and is monitored by a cardiologist every three months.

DISCUSSION

NS has phenotypic overlap with other syndromes, including neurofibromatosis type 1, Turner syndrome, Leopard syndrome, Costello syndrome, Legius syndrome and Cardiofaciocutaneous (CFC) syndrome[1,10,12]. The diagnosis is therefore hindered by the variety of clinical symptoms and the syndrome is therefore underdiagnosed[1]. Clinical characteristics, which are grouped according to the criteria developed by Van der Burgt (Table 1), aid professionals in determining which patients are candidates for genetic testing for a confirmation of the diagnosis[5,8].

The most common congenital anomaly is a heart defect[5,6]. Thus, it is recommended that all patients undergo cardiac evaluation by a specialist at the time of diagnosis as well as a chest X-ray, ECG, and echocardiogram[15]. Patient follow up should be individualized based on the specific disorders present. Patients without heart disease in their initial assessments should be re-assessed every five years[15].

Each of these cardiovascular abnormalities is associated with a particular type of gene mutation, and the mutation on the PTPN11 gene is responsible for pulmonary valve stenosis with dysplastic leaflets, the most prevalent deformity in Noonan Syndrome[5,11].

Table 1. Clinical characteristics grouped by the criteria developed by Van der Burgt.

Characteristics	Criteria	
	Major	Minor
Facial	Typical	Suggestive
Cardiac	Pulmonary valve stenosis, hypertrophic cardiomyopathy	Others
Height	< 3rd percentile	< 10th percentile
Thoracic	*Pectus carinatum* and/or *pectus excavatum*	Extended
Family History	Immediate family member with a diagnosis of NS	Immediate family member with a possible NS diagnosis
Other: Mental retardation Cryptorchidism Lymphatic dysplasia	All three	Any

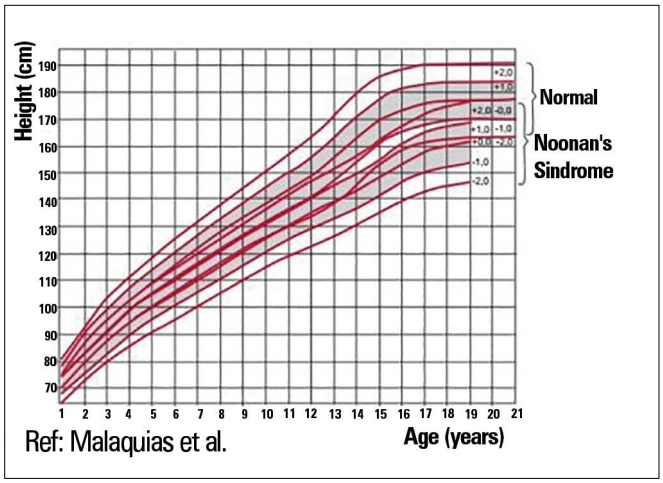
Diagnosis of Noonan Syndrome SN:
Typical face + another major criterion or two minor criteria.
Face sugestiva + dois outros critérios maiores ou três menores.
Suggestive face + two other major criteria or three minor criteria.
Adapted from Malaquias et al.(2008).

This disorder is the most common semiological finding and is highly associated with the outcome of death. Possible surgical interventions are percutaneous balloon valvuloplasty, transannular patch (TAP), pulmonary valvotomy (PV), and pulmonary valve replacement (PVR), which are indicated by the specialist according to the degree of valve involvement[6].

In addition to this anomaly, patients with NS may also have other heart defects such as hypertrophic cardiomyopathy. The initial treatment for this anomaly is the use of beta-blockers or amiodarone in cases of arrhythmia[8]. In cases of major congestive heart failure, or exercise-induced systemic hypotension, the treatment may include myomectomy and septal ablation[6].

Thoracic deformities and short stature are statistically significant in these patients (58% and 76% respectively)[5]. Children with the syndrome are often referred to endocrinologists because of their short stature and delayed onset of puberty. Therefore, when making a differential diagnosis of short stature, the Noonan syndrome should be considered because it has important implications for hormone therapy[9]. During childhood, growth is parallel to the reference curve (Graphic 1) with an average height standard deviation score of -3 and with a one-to-two year delay in bone age[1].

As the children age, their phenotypic characteristics begin to change. Noteworthy features in newborns include macrocephalia, a broad and high forehead, hypertelorism, ocular prominence, a high palate, epicanthal folds, and ptosis. The ears are oval shaped and low-set, with posterior rotation and thickened lobes. The upper lip tends to have a deep



Graphic 1. Growth chart showing height by age for normal children and for children with Noonan syndrome.

groove line, and the neck is typically short with excess skin. The patient often has a short nose, and a low posterior hairline. In childhood and adolescence, the phenotypic characteristics are more attenuated[15].

The variety of phenotypic presentations, the attenuation of these features with age, and the phenotypic overlap with other disorders are elements that complicate the diagnosis of Noonan syndrome. However, it is essential to determine the correct diagnosis, because the prognosis and management of each case differs accordingly and influence patients' survival and quality of life[11].

CONCLUSION

Noonan syndrome is a genetically heterogeneous disease characterized by congenital heart defects, distinct facial changes, short stature, and other manifestations. We emphasize the need to obtain an early and correct diagnosis to improve the quality of life of patients with the syndrome. If they receive proper treatment for the identified disorders and receive multidisciplinary care, most children can have a life without major limitations.

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