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Abbreviations

NS: Noonan Syndrome; SNML: Noonan Syndrome with Multiple Lentigines; CHD: Congenital Heart Disease

Research Article

Characterization of Patients with Noonan Syndrome-Type Rasopathies by PTPN11 Variant

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Abstract

Introduction: RASopathies are a set of phenotypically overlapping syndromes caused by mutations in genes that play a role in the RAS/MAPK pathway involved in development through growth factors. The most common is Noonan Syndrome (NS) which is an autosomal dominant genetic disorder, of low prevalence and which in 50% of cases is associated with variants in the PTPN11 gene. Clinical manifestations are short stature, dysmorphic facial features, congenital heart defects, most commonly pulmonary valve stenosis, typical chest, and cryptorchidism.

Results: We describe 4 patients with RASopathy Noonan syndrome due to alteration in the PTPN11 gene: 3 males, and 1 female, with an average gestational age of 37.6 weeks, 2.9 kg of weight, and 45.5 cm of height at birth. 100% had: palpebral ptosis, winged neck, pectum carinatum, and short stature, 75% had heart diseases such as subaortic stenosis and ventricular septal defect, and 33% had hypoacusis and altered genitalia. The genetic variants found in the PTPN 11 gene, all heterozygous were: in the sporadic males: Exon 7 c.836 A>G. pTYR:279cys, and c.417G>C (p. Glu139Asp) and p.Asn 308 Ser , c..923A>G heterozygosis. The female with a variant in c.417G>C (p. Glu139Asp) whose mother has SN.

Analysis: We found the PTPN11 gene variant in all our patients with NS, 75% being sporadic and 25% familial. Although the diagnosis of Noonan syndrome is clinical, this variant according to the literature is found in 50% of patients, in almost 60% of familial cases, and in almost 40% sporadic. There is a phenotype-genotype correlation in these patients and it is suggested that they should be monitored for predisposition to malignancy.

Conclusions: It is essential to typify the clinical and genetic alteration in patients with RASopathies so that physicians involved in the care of these patients are familiar with the diagnosis, genetic variant, manifestations, and clinical follow-up, especially because of their predisposition to malignancy.

Introduction

RASopathies are a group of clinical syndromes caused by variants in the regulatory genes of the RAS/MAP Kinase signaling pathway (mainly gain-of-function), which is involved in the regulation of cell proliferation, cell survival, and differentiation [1,2]. Several phenotypically overlapping entities are classified within this group with the most frequent being Noonan syndrome (MIM ID#163950), Noonan syndrome with multiple lentigines, formerly known as LEOPARD (NSML) (OMIM ID#151100), Costello syndrome (OMIM ID# 218040), cardiofaciocutaneous syndrome (OMIM ID#155150), capillary malformation-arteriovenous malformation syndrome (CM-AVM) O (MIM ID#608354), Neurofibromatosis type 1 (OMIM ID#162200) and Legiu syndrome. This overlapping or overlapping clinical manifestation over time includes several affected systems such as characteristic facial dysmorphology; the presence of cardiovascular, cutaneous, musculoskeletal, and ocular alterations; neurocognitive problems; hypotonia, and a slightly elevated risk of tumor development. Affecting equally both sexes with a prevalence that varies in each condition, being Noonan the most common (1 in 2000 births), while Costello (1 in 300,000 births), CM-AVM, and CFC syndrome are less prevalent (1 in 810,000 births) [1,2]. Hence, due to the overlapping and variable expressivity, molecular study is necessary and important to make an accurate and timely diagnosis that will also allow monitoring of the risk of hematoncologic abnormalities such as bleeding and tumors in these patients. The Noonan Syndrome with Multiple Lentigines (SNML) due to its clinical characteristics was established as the LEOPARD mnemonic: multiple lentiginosis, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonary stenosis, genital abnormalities, growth retardation, and neurosenorial sorDera. The associated genetic alterations have been in the PTPN11 (90%), RAF1 (5%), and BRAF (5%) genes [2]. While cardiofaciocutaneous syndrome SCFC is characterized by the presence of craniofacial dysmorphia, neuromaturative delay, with alterations such as congenital heart disease, ectodermal and musculoskeletal disorders, it is due to de novo alterations in the BRAF (75%) and MEK1/MEK2 (25%) genes, and in < 1% alterations in the KRAS gene.

In the less frequent Costello syndrome, a history of sucking disorders at birth, high birth weight, coarse fascicles, kinky hair, intellectual disability and the presence of peribuccal, perinasal and perianal papillomas, thick palmar and plantar deep folds (simulating cerebriform aspect), abnormally elastic and thick hyperpigmented skin with tendency to the formation of nuchal folds have been described. Hyperlaxity of the interphalangeal and metacarpophalangeal joints with ulnar deviation of the hands, humorous personality. The most frequent cardiac anomalies found in them are Tetralogy of Fallot, pulmonary stenosis, interatrial and interventricular communication. And more than 13% risk of developing malignancy. It is associated with heterozygous alterations in more than 80% of cases in the HRAS proto-oncogene [3]. Legius syndrome inicalmente called NF1-like; is characterized by the presence of brown-au-lait spots, axillary freckling, macrocephaly (27%), facial dysmorphism similar to NS and with an autosomal dominant inheritance whose associated genetic variant is the loss of function in the SPRED1 gene [4]. Noonan syndrome (NS) is an autosomal dominant genetic disorder, located on

chromosome 12q22. The first cases described date back to the end of the 19th century, however, it was not until 1963 that Noonan and Emke described it for the first time, reporting a total of 9 cases of children: six males and three females with malformations suggestive of Turner syndrome and associated pulmonary stenosis. And in 1968, Dr. Jacqueline Noonan described a series of 19 patients with the characteristic features of the disease [1,5]. NS is characterized by multisystemic involvement with high heterogeneity and variable clinical expression, the aim of this article is to characterize patients with Noonan Type Syndrome with the PTPN11 variant from a pediatric endocrinology practice.

Methodology

A cross-sectional, observational, and descriptive study was conducted, which included patients with the clinical diagnosis "Rasopathies" syndrome Noonan type of pediatric endocrinology consultation during the years 2016-2021 in a tertiary hospital in whom genetic confirmation was made and was found as a genetic variant alteration of the PTPN11 gene. Prior informed consent was signed by the legal representative of the patients, as well as authorization by the institutional medical ethics committee. A retrospective collection of the information recorded in the clinical history available at the Fundación Clínica Infantil Club Noel, Cali, Colombia, was performed.

Results

Case 1

Male patient, the second child of non-consanguineous parents. He attended endocrinology control at the age of 15 years due to short stature (-3DE). He was born at 40 weeks of gestation, with a birth weight of 2740 g (-3DE), and a length of 50 cm (p50). Personal history of delayed psychomotor development, congenital heart disease (surgically corrected coarctation of the aorta), iris involvement, surgically corrected cryptorchidism, and horseshoe kidney. Clinical examination revealed palpebral ptopsis, winged neck, pectum carinatum, and stunting (-3DE). Clinically Noonan syndrome was suspected due to personal history and a genetic exome was performed confirming NS.

Case 2

Male patient was the third child of non-consanguineous parents. He was born at 35 weeks of gestation with a weight of 2371 grams (-3DE), and a length of 45 cm (-3DE). She consulted pediatric endocrinology at the age of 2 years due to height delay. With a personal history of congenital heart disease (ventricular septal defect), inguinal hernia, swallowing disorder, hearing loss, and global developmental delay. Physical examination revealed a short patient, with palpebral ptopsis, winged neck, pectum carinatum. Finally, she was diagnosed clinically and genetically with NS.

Case 3

Female patient, a product of the first gestation of non-consanguineous parents, who attended the endocrinology service at the age of 3 years 11 months due to short stature. She was born at 38 weeks of gestation with a birth weight of 3000 grams (p50), a length of 45 cm. Personal history of astigmatism and constipation, a mother with SN fascies. Physical examination revealed a short patient, with palpebral ptopsis, winged neck, pectum carinatum. Given the clinical and genetic study, SN was diagnosed.

Case 4

Male patient born to non-consanguineous parents, second gestation, healthy brother, birth weight 3600 grams (p50) size 42 cm (-1DE) Caesarean section for acute fetal distress, meconium with ASD type Ostium secundum spontaneous closure and also mild stenosis of the pulmonary branch. Pediatric endocrinology consultation 4 years 2 months for short stature and failure of medro, on examination palpebral ptosis, slight palpebral fissures elongated and inclined downward, ogival palate, Quelprud nodules in ears, in anteversion, slight pectum excavatum and spontaneous ecchymosis with normal coagulation times factor XII 102%, factor XI 100%. With late clinical expression and genetic confirmation of SN (Table 1).

Table 1: Late clinical expression and genetic confirmation of SN.

Case	Sex	Birth Size Cm	Birth Weight Grams	Age at Diagnosis	Weight at Diagnosis Kg	Height at Diagnosis Cm	Gene Variant: PTPN11 Heterozygous	Echocardiographic Findings	Systems Compromised
1	M	50	2.74	15 years and 2 months	36	148	Nucleotide substitution: c.836 A>G and Variant: pTYR:279cys	aorta coartment	Musculoskeletal, facial, ocular, cardiac, genitourinary, neurodevelopmental delay.
2	M	45	2.73	2 years and 1 month	8,8	77	Nucleótide: c.417G>C and Variant: p. Glu139Asp y	Ventricular Septal Defect (VSD)	Musculoskeletal, cardiac, auditory, neurodevelopmental delay.
3	F	45	3	3 years and 11 months	11,7	91	Nucleotide: c.417G>C and Variant: p. Glu139Asp	none	Musculoskeletal, gastrointestinal, ocular.
4	M	42	3.6	4 years and 2 months	14	102	Nucleotide c.923A>G and Variant: p. Asn308Ser	CIA, Pulmonary stenosis	Hearing, neurodevelopmental delay, cardiac facial musculoskeletal, genitourinary.

M: Masculine, F: Female

The 4 patients found had genetic confirmation of Noonan syndrome with a variant in the PTPN11 gene: 3 males, and 1 female, with averages of: 37.6 weeks gestational age, 2.9 kg of weight, and 45.5 cm of height at birth. The 100% had: palpebral ptosis, winged neck, pectum carinatum, and short stature, 75% had variable cardiopathies including pulmonary stenosis, ASD-IVC, and aortic coarctation, and 50% had hypoacusis and alteration of genitalia. The variants found in the PTPN 11 gene, all heterozygous were: in the sporadic males: Exon 7 c.836 A>G. (pTYR:279cys), and c.417G>C (p. Glu139Asp) and c.923A>G (p.Asn 308 Ser), and the female with a variant of c.417G>C (p.Glu139Asp) whose mother has SN.

Discussion

There are other variants in genes encoding proteins of the RAS-MAPKinases pathway, which lead to clinically overlapping conditions hence their collective designation of "RASopathies" (Table 2). Possible genotype-phenotype correlations [4].

Table 2: Genes encoding proteins of the RAS-MAPKinases.

GENE VIA RAS-MAPKinasas	Clinical Partnership
PTPN11	leukemia, pulmonary stenosis, ASD, minor association with hypertrophic cardiomyopathy, and coarctation of the aorta.
KRAS	Mental retardation, colorectal cancer risk
SOS1	short stature, ASD and less mental retardation
RAF1	Hypertrophic cardiomyopathy ,failure to growth
SHOC2	Growth hormone deficiency, behavioral alterations. Mitral valve dysplasia
CBL	Failure to thrive, cryptorchidism. The bicuspid aortic valve, mitral insufficiency, predisposition to juvenile myelomonocytic leukemia.

Noonan syndrome is a rare pathology, whose true prevalence is unknown, it occurs in both sexes and its characteristics and presentation vary with age, some authors have stated that the average age at the time of diagnosis is puberty, contrary to our patients, three of them were diagnosed at an early age [1,6]. Four types of genetic variations have been described most frequently associated with SN, of which 50% are associated with the PTPN11 gene, between 3 to 17% with the RAF1 gene, about 10% with the SOS1 gene, less than 5% with the KRAS gene, and less frequently with the NRAS gene (< 1%), BRAF (< 1%), SHOC2 (< 1%), MEK1 (< 1%) and CBL (< 1%). In the remaining 20-30 %, the causal variants have not been identified. De novo variations account for 60 % of cases with SN [2]. The variant in PTPN11 produces hyperactivation of the protein-encoding gene, a cytoplasmic tyrosine phosphatase SHP2. This protein is involved in the intracellular signaling pathway RASMAPK, which is involved in the control of cell growth, differentiation, migration, and apoptosis. It is a key molecule in the cellular response of growth factors, hormones, cytokines, and cell adhesion molecules, and is also important in semilunar valvulogenesis [6]. Noonan syndrome is characterized by a wide variety of clinical manifestations that may vary in presentation and severity in each affected individual. Clinical manifestations have been detected from birth as facial dysmorphia with hypotonia, feeding problems, and severe vomiting, and help the diagnosis, however, in most cases are born without frank manifestations. And it is diagnosed at late ages [7,8].

Some of the common clinical manifestations of Noonan syndrome are:

Facial alterations

Characteristic facial features such as a broad forehead, ocular hypertelorism, arched eyebrows, low-set and posteriorly rotated ears, thickened helix, a full and high peaked upper lip with a depressed nasal bridge, inverted triangle fascicles, nose with depressed root and bulbous tip, long and deep philtrum, neck with excess nuchal skin in newborns.

Ophthalmic alterations

Refractive, strabismus, nystagmus, and amblyopia; also, alterations in the anterior segment such as prominent corneal nerve, cataracts, and stromal corneal dystrophy. Extraocular manifestations, such as hypertelorism, ptosis, downward slanting palpebral fissures and epicanthal folds, anomalies of the anterior segment, and hypoplasia of the optic nerve have been reported [8].

Growth disturbance

Short stature, with slow growth in childhood and adolescence. Some authors report that females usually reach a height between 1.50 cm and 1.55 cm and males between 1.60 cm and 1.68 cm, however, this varies according to nationality. Recently, a higher prevalence of short stature has been found in individuals who are positive for the PTPN11 gene variant than in those who are negative [9,10].

Cardiac disorders

Congenital heart defects occur in two-thirds of the population, such as pulmonary stenosis (50%), hypertrophic cardiomyopathy (20-30%), atrial septal defect (10%), asymmetric septal hypertrophy (10%), ventricular septal defect (5%), and patent ductus arteriosus (3%) [11].

Musculoskeletal alterations

These are present in 90% of patients, such as pectus excavatum (chest deformity), scoliosis, pectum carinatum, clubfoot, joint hypermobility, and limb deformities (cubitus valgus, clinodactyly, brachydactyly, curvature of the fifth toe). More than half of the population has hyperextensible joints and hypotonia [12].

Renal alterations

Renal problems occur in 10% of individuals and are usually of little relevance, it has been reported the presence of Renal ectopia and structural anomalies: frequently a single kidney, dilatation of the renal pelvis, and duplication of the collecting system.

Alteration of genitalia

Cryptorchidism is present in 80% of males, delayed puberty, and hormonal problems such as hypogonadism.

Gastrointestinal disturbances

Gastroesophageal reflux and constipation. Feeding difficulties in 75% of neonates, with some studies reporting immaturity in swallowing and delayed gastrointestinal motility [4,6].

Ocular problems

Visual problems such as myopia, astigmatism, strabismus, and amblyopia are present in 70% of the patients.

Other facial and dermatologic features

Skin moles, short neck, thick or redundant skin on the nape of the neck, and coffee-with-milk spots on the skin.

Neurological, cognitive, and behavioral alterations

They may present cognitive and learning problems, CNS alterations, and multiple neurological problems. Most individuals have normal intelligence, however, about 30% have mild to moderate retardation, which can lead to learning and coordination problems, mild intellectual disability, autism spectrum disorder, and attention deficit hyperactivity disorder [13]. Motor development is often delayed by hypotonia and joint laxity. Common nervous system malformations are hydrocephalus and Arnold- Chiari malformation [14].

Audiological alterations

They usually present deafness. It can be sensorineural, conductive, or mixed and of any severity, including severe-profound sensorineural hearing loss [15].

Hematologic

Coagulation problems are commonly observed, due to factor deficiency (factor VII), thrombocytopenia, or qualitative and quantitative platelet defects. Ecchymosis and bleeding, are more characteristic in those with PTPN11 variants. Hemorrhagic diathesis was moderate in 39% of patients and severe in 18% in a small series [16].

Oral and dental

SN patients present deep and arched palate (55%-100%), occlusion alterations (50%-67%), temporomandibular joint problems (72%), and micrognathia (33%- 43%) [17].

Other facial and dermatologic features

Skin moles, xerosis, lentigines, short neck, thick or redundant skin on the nape of the neck, and café-au-lait spots on the skin, other patients present lymphedema [18]. A study in Argentina of 96 patients with NS showed 100% facial dysmorphia, 51% had short stature, 76% of patients had heart disease with pulmonary stenosis being the most relevant, 61% had short stature, the percentage of global neurodevelopmental delay was 59%, being the most frequent mutation in PTPN11 [2]. This finding correlates with our patients. PTPN11 mutations are more likely to be found in individuals with pulmonary stenosis, short stature, spontaneous ecchymosis with factor VIII deficiency, pectus deformity, cryptorchidism, and a typical face. Unlike our patient, the most significant finding is short stature and pectus deformity, and only one of them presented cryptorchidism, and one with spontaneous ecchymosis with no hematologic alteration even found. The clinical spectrum of NS may differ slightly depending on the causative genes, and "Noonan-like" forms (NS-like disorder with juvenile myelomonocytic leukemia and NS-like disorder with loose anagen hair) have also been described. The risk of malignancy in SN appears increased compared to the general population. Much of the increased risk in childhood is attributed to the high frequency of myelocytic leukemia. Increased risks of brain tumors, acute lymphoblastic leukemias, and neuroblastomas have also been described [15].

Diagnosis

The diagnosis of NS is made from the clinical features described above but can be difficult due to the high variability of clinical presentation, there are no laboratory tests that indicate the diagnosis, so genetic testing is required, allowing the genotype-phenotype correlation. Many patients for diagnosis require molecular tests found even in the approach of other associated pathologies such as whole genome sequencing, performed from studies of Congenital Heart Disease (CHD), short stature, and neurodevelopmental delay. Even in the prenatal period, several studies detect on ultrasound nuchal thickening together with cystic hygroma, polyhydramnios, hydrops, renal anomalies, lymphatic sacs, hydrothorax, or cardiac anomalies that could raise suspicion of the diagnosis [19]. The clinical diagnosis is based on the presence of prenatal features, feeding difficulties, relative macrocephaly and short stature, and clinical features that vary with age. The criteria used are those of Dr. Vander Burgt (Table 3), where the most distinctive diagnosis is facial dimorphism, associated with one or two major or minor signs [20].

Table 3: Modified criteria for the Vand Der Burgt

Clinical Manifestations	Minor Criteria	Major Criteria
Facial	Suggestive face	Typical face
Cardiac	any other defect	Pulmonary stenosis
Height	Size less than P10	Size less than P3
Thorax	Wide thorax	Pectum carinatum / excavatum
Family History	Suggestive first-degree relative	First-degree relative with NS
Others	One (mental retardation, cryptorchidism, lymphatic dysplasia)	Having all of the following: mental retardation, cryptorchidism, lymphatic dysplasia
SN diagnoses: typical face + 1 major or 2 minor criteria, suggestive face + 2 major criteria or 3 minor signs.		

Modified the Van Der Burgt I (2007) Noonan syndrome. Orphanet J Rare Dis 2(1): 1-6.

While confirmation of the disease is made with molecular confirmation and even molecular panels of "Noonan Syndrome" or "Rasopathy", which includes many or all of the genes known to be mutated in NS, are offered. As with any extended-spectrum test, there is the possibility of identifying variants of uncertain significance. Testing should be performed in a setting where genetic counseling is available [12]. There are some syndromes that have similarities to NS in terms of genetic alterations and manifestations. The most common differential diagnoses are Noonan/neurofibromatosis type 1, Leopard Syndrome, and Cardio-Facio-Cutaneous Syndrome. Especially important because of the association with the risk of malignancy in the future to establish follow-up. The treatment is multidisciplinary, treating all comorbidities, the use of growth hormone in patients with stunted growth, surgical management in the indicated pathologies, early approach in patients with ophthalmic alterations, neurodevelopmental disorder, and also genetic counseling informing the patient's family of diagnosis, implications and prognosis, risk of developing and transmitting it and the most appropriate options to treat the possible risks [21]. In long-term management, emphasis is placed on studies to manage molecules that seek to reduce the activity of the RAS-MAPK pathway, which have reported favorable responses in their research phases, such as 3-hydroxy-3-methylglutaryl coenzyme A inhibitors (statins) because they reduce the farnesylation of RAS and its localization in the plasma membrane, with emphasis on improving growth, Inhibition of the PI3/AKT/mTOR pathway with rapamycin and trametinib in cardiomyopathies has shown some hope for their possible uses [22,23].

Use of Growth Hormone

Although its use was approved by the US Food and Drug Administration in 2007, the European Medicines Agency (https://mri.cts-mrp.eu/ Human/ Product/ Details/14639), and the Spanish Agency of Medicines and Health Products (AEMPS) https://cima.aemps.es/ cima/ dochtml/ft /62977/FT_62977.html), it is reported that in published studies the recommended initial dose is 33 g/kg/d (if the response is not appropriate, it can be increased to a maximum of 66 g/kg/d). Published studies report that the recommended initial dose is 33 g/kg/d (if the response is not appropriate, it can be increased up to a maximum of 66 g/kg/d). If good growth is not achieved during the first 2 years, re-evaluate its use and consider the possibility of discontinuing it. Some studies have reported little response in patients with variants of PTPN11 while others show the opposite, so it has been suggested that treatment with rhGH in patients with NS should be individualized, being very relevant to the monitoring of the presence of hypertrophic cardiomyopathy, which without being exactly a contraindication according to authors, should have much closer monitoring, as well as the presence of scoliosis that could worsen during treatment; The presence of genetic variants with a higher oncologic risk should be discussed very well with the family and the patient, and in the case of initiating treatment, the patient should be very strictly monitored and always be vigilant with regard to carbohydrate metabolism and IGF1 levels [4]. Most patients with NS are usually functional and can perform a variety of roles in the community. Mortality in patients with NS is usually secondary to cardiac disease that may be related to surgical intervention, circulatory collapse, or possible arrhythmia. Reliable information on long-term morbidity and mortality is lacking.

Conclusion

In this series of cases it was determined that mutations in the PTPN11 genes are still the most frequent, not all patients have pulmonary stenosis as a cardiac manifestation, and multiple systems are involved, the approach is clinical rather than genetic but the latter is important to establish follow-up and counseling, require multiple evaluations and regular care for their identified problems and multidisciplinary management. It is essential that health personnel are involved in the care of these patients, and are familiar with their manifestations and clinical follow-up, especially because of the predisposition to malignancy.

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