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Case Report

Noonan Syndrome and Hyperexcitability and Attention Deficit (ADHD) and Autism Spectrum Disorder (ASD) Comorbidities. Clinical Study of One Case

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Abstract

In the present study we describe from the clinical point of view a case of Noonan Syndrome (NS) and two simultaneous comorbidities, the hyperexcitability and attention deficit (ADHD) and autism spectrum disorder (ASD). A five years old patient with short stature, hyperexcitability and attention deficit, stereotyped movement of hands expressing autism spectrum disorder, facial dysmorphism, featured by bulbous nose, elevated implantation of ears, arched brows, and palpebral ptosis, dental malformations and unique central incisive, cardiovascular disease as ductus arteriosus and tachycardia, skeletal malformations, such as pectus excavatum, gait disturbance, and neurological deficits as paresis of right lower limb and osteotendinous areflexia, cognitive deficit and language disorder. This heterogeneous clinical condition corresponds to the NS phenotype involved in the Ras/MAPK (mitogen-activated protein kinase) signal transduction pathway and also to the genes involved in ADHD and ASD.

Keywords: *Noonan Syndrome; Hyperexcitability; Attention Deficit; Autism*

Introduction

Noonan syndrome (NS) is a common, clinically and genetically heterogeneous condition characterized by distinctive facial features, short stature, chest deformity, congenital heart disease, and other comorbidities. Gene mutations identified in individuals with the NS phenotype are involved in the Ras/MAPK (mitogen-activated protein kinase) signal transduction pathway and currently explain ~61% of NS cases [1-4].

The RASopathies are a group of syndromes and rare diseases that have in common germline mutations in genes that encode components of the RAS/mitogen-activated protein kinase (MAPK) pathway and have been a focus of study to understand the role of this pathway in development and disease. These syndromes include Noonan syndrome (NS), NS with multiple lentigines (NSML), neurofibromatosis type 1 (NF1), Costello syndrome (CS), cardio-facio-cutaneous (CFC) syndrome, neurofibromatosis type 1-like syndrome (NFLS) and capillary malformation-arteriovenous malformation syndrome (CM-AVM). These disorders affect multiple systems, including the craniofacial complex [1-7]

Fetal autopsies with abnormal prenatal ultrasound findings and suspicion of Noonan syndrome showed signs of fetal hydrops and polyhydramnios, cystic hygroma, pleural and abdominal effusions, congenital heart and kidney defects, skeletal defects and facial dysmorphism [8].

In the present study we describe from the clinical point of view a case of Noonan Syndrome and two simultaneous comorbidities, the hyperexcitability and attention deficit (ADHD) and autism spectrum disorder (ASD).

Case Report

A five years-old girl patient was studied at the Clinical Neuroscience Institute Outpatient Clinic at the Clinical Home San Rafael in Maracaibo. Venezuela. She was previously examined from the psychological point of view at the Departments of Psychology of CETRO, San Rafael Home Clinic.

Results

Five years old patient with short stature, hyperexcitability and attention deficit, stereotyped movement of hands expressing autism spectrum disorder, facial dysmorphism, featured by bulbous nose, elevated implantation of ears, arched brows, and palpebral ptosis, dental malformations and unique central incisive, cardiovascular disease as ductus arteriosus and tachycardia, skeletal malformations, such as pectus excavatum, gait disturbance, and neurological deficits as paresis of right lower limb and osteotendinous areflexia, cognitive deficit and language disorder.

Figure 1: *Facial dysmorphism characterized by bulbous nose, elevated implantation of ears, and arched brows and palpebral ptosis.*

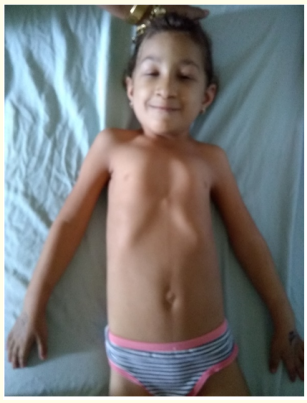

Figure 2: *Peptus excavatum.*

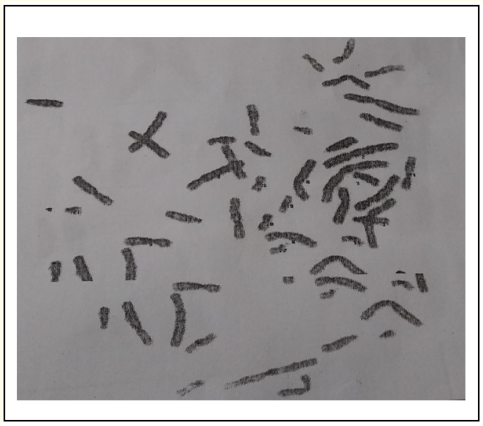

Figure 3: *Chromosomal karyotype 48 XX in all metaphases.*

Discussion

The present study provides the mutation and phenotypic spectrum of one patient with clinical diagnosis of Noonan Syndrome (NS). The patient exhibited the clinical symptoms and related cardiovascular, neurological, locomotor disturbances, cognitive deficit already described in Noonan Syndrome [1-10]. In addition, the patient exhibited the following comorbidities, hyperactivity and attention deficit (DHD), autism spectrum disorder (ASD), language impairment, suggesting multiple causative genes. We have applied the clinical diagnostic criteria published elsewhere [11,12]. Castejón., *et al*. 2018, 2019 in the study of comorbidities found in the present study, such as ADHD and ASD. Language impairment has been described in most patients with NS described thus far.

We have found autism spectrum disorder featured by stereotyped hand movements. According to Adviento., *et al*. [13] (2014), autism traits in the RASopathies share characteristics with autism traits in the general population and clinical ASD population and can shed light on idiopathic ASDs. Garg., *et al*. [14] (2017) also reported a high prevalence of ASD in Noonan and Cardiofaciocutaneous syndrome (CFC) and offered crucial evidence to support the importance of the Ras/MAPK pathway in the aetiology of ASD. We have above reported dental malformation and an unique frontal incisive. According to Cao., *et al*. [5] (2017), the dental phenotypes have not been analyzed in detail for each of the RASopathies.

Possible mechanisms of short stature in NS include growth hormone (GH) deficiency, neurosecretory dysfunction, and GH resistance [15].

This patient showed ductus arteriosus and tachycardia. As genotype-phenotype associations are being better understood, the mechanisms for development of cardiomyopathy are also becoming elucidated [16]. The RAS/MAPK signaling pathway, summarizes multiple molecular genetic approaches used during the last several decades to discover genes responsible for different RASopathies, and finally focuses on several major disease genes associated with Noonan syndrome and related disorders with regard to genomic locations, structure, mutations, and genotype-phenotype correlations [17].

Nine genes (PTPN11, SOS1, KRAS, NRAS, RAF1, BRAF, SHOC2, MEK1 and CBL) have been documented to underlie this disorder or clinically related phenotypes Affected genes encode for proteins participating in the RAS-mitogen-activated protein kinases (MAPK) signal transduction pathway, which is implicated in several developmental processes controlling morphology determination, organogenesis, synaptic plasticity and growth. In addition, several genes including RIT1, RRAS, RASA2, A2ML1, SOS2 and LZTR1, have been also shown

to be associated with RASopathies, further expanding the disease entity. Although further analysis will be needed, these findings will help to better elucidate an understanding of the pathogenesis of these disorders and will aid in the development of potential therapeutic approaches [18].

The patient herein examined showed cardiovascular disease as ductus arteriosus and tachycardia. According to Ezquieta., *et al*. [19] (2012) most patients (94%) with a positive genotype had known congenital heart disease, 79% pulmonary stenosis and 12% hypertrophic cardiomyopathy.

Cardiofaciocutaneous syndrome (CFC), a Noonan syndrome related disorder showed six different mutations in BRAF, as well as 2 MAP2K1 mutations. Short stature, developmental delay, language difficulties and ectodermal anomalies were more frequent in CFC patients when compared with other neuro-cardio-faciocutaneous syndromes [19].

Conclusion

The Noonan Syndrome (NS) of a five years old girl showed two simultaneous comorbidities, the hyperexcitability and attention deficit (ADHD) and autism spectrum disorder (ASD). The patient exhibited short stature, hyperexcitability and attention deficit, stereotyped movement of hands expressing autism spectrum disorder, facial dysmorphism, featured by bulbous nose, elevated implantation of ears, arched brows, and palpebral ptosis, dental malformations and unique central incisive, cardiovascular disease as ductus arteriosus and tachycardia, skeletal malformations, such as pectus excavatum, gait disturbance, and neurological deficits as paresis of right lower limb and osteotendinous areflexia, cognitive deficit and language disorder. This heterogeneous clinical condition corresponds to the NS phenotype involved in the Ras/MAPK (mitogen-activated protein kinase) signal transduction pathway and also to the genes involved in ADHD and ASD.

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Bibliography

1. Zenker M. "Genetic and pathogenetic aspects of Noonan syndrome and related disorders". *Hormone Research* 72.2 (2009): 57-63.
2. Jorge AA., *et al*. "Noonan syndrome: clinical features, diagnosis, and management guidelines". *Pediatrics* 126.4 (2010): 746-759.
3. Romano AA., *et al*. "Noonan syndrome: clinical features, diagnosis, and management guidelines". *Pediatrics* 126.4 (2010): 746-759.
4. Tartaglia M., *et al*. "Noonan syndrome and clinically related disorders". *Best Practice and Research: Clinical Endocrinology and Metabolism* 25.1 (2011): 161-179.
5. Cao HT., *et al*. "New insight of craniofacial and oral findings of the RASopathies". *Zhonghua Kou Qiang Yi Xue Za Zhi* 53.12 (2018): 858-861.
6. Breilyn MS and Mehta L. "Clinical manifestations of noonan syndrome and related disorders". *Pediatric Endocrinology Reviews* 16.2 (2019): 428-434.
7. Jaouadi H., *et al*. "A severe clinical phenotype of Noonan syndrome with neonatal hypertrophic cardiomyopathy in the second case worldwide with RAF1 S259Y neomutation". *Genetics Research* 101 (2019): e6.

8. Tatiana S., *et al*. "Noonan syndrome from a fetopathologist perspective". *Československá Patologie* 55.1 (2019): 48-52.

9. Cao H., *et al*. "A review of craniofacial and dental findings of the RASopathies". *Orthodontics and Craniofacial Research* 20.1 (2017): 32-38.

10. Koh AL., *et al*. "The spectrum of genetic variants and phenotypic features of Southeast Asian patients with Noonan syndrome". *Molecular Genetics and Genomic Medicine* 7.4 (2019): e00581.

11. Castejón OJ., *et al*. "Maternal Stress, Pregnancy diseases and child hyperactivity and attention deficit". *Biomedical Journal of Scientific and Technical Research (BJSTR)* 12.2 (2018): 002228.

12. Castejón OJ., *et al*. "Subgroups of Attention Deficit Disorder (ADHD). A preliminary clinical descriptive study". *Biomedical Journal of Scientific and Technical Research (BJSTR)* 17.5 (2019): 003070.

13. Adviento B., *et al*. "Autism traits in the RASopathies". *Journal of Medical Genetics* 51.1 (2014): 10-20.

14. Garg S., *et al*. "Autism spectrum disorder and other neurobehavioural comorbidities in rare disorders of the Ras/MAPK pathway". *Developmental Medicine and Child Neurology* 59.5 (2017): 544-549.

15. Seo GH and Yoo HW. "Growth hormone therapy in patients with Noonan syndrome". *Annals of Pediatric Endocrinology and Metabolism* 23.4 (2018): 176-181.

16. Karnik R and Geiger M. "Cardiac Manifestations of Noonan Syndrome". *Pediatric Endocrinology Reviews* 16.2 (2019): 471-476.

17. Liao J and Mehta L. "Molecular Genetics of Noonan Syndrome and RASopathies". *Pediatric Endocrinology Reviews* 16.2 (2019): 435-446.

18. Aoki Y., *et al*. "Recent advances in RASopathies". *Journal of Human Genetics* 61.1 (2016): 33-39.

19. Ezquieta B., *et al*. "Alterations in RAS-MAPK genes in 200 Spanish patients with Noonan and other neuro-cardio-facio-cutaneous syndromes. Genotype and cardiopathy". *Revista Española de Cardiología* 65.5 (2012): 447-455.

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