Do you know this syndrome?*

Você conhece esta síndrome?

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CASE REPORT

A 10 year-old female patient presented with keratosis pilaris and characteristic facial anomalies. The prenatal history did not indicate any particular risk factors, the patient being born by normal delivery, without incidents and presenting with a good physical condition at the moment of birth (APGAR scores 9 and 10).

Physical examination showed signs of hypertelorism, down-slanting palpebral fissures, low set posteriorly rotated ears, palpebral ptosis, short neck, micrognathism and short stature (Figures 1 and 2). The mother reported some degree of learning disability and the need for special educational support in school.

The echocardiography demonstrated dilatation of the pulmonary artery and mitral regurgitation (although the patient did not have clinical symptoms). The jaw/ skull panoramic radiograph presented with bad dental occlusion.

The karyotype was 46 XX.

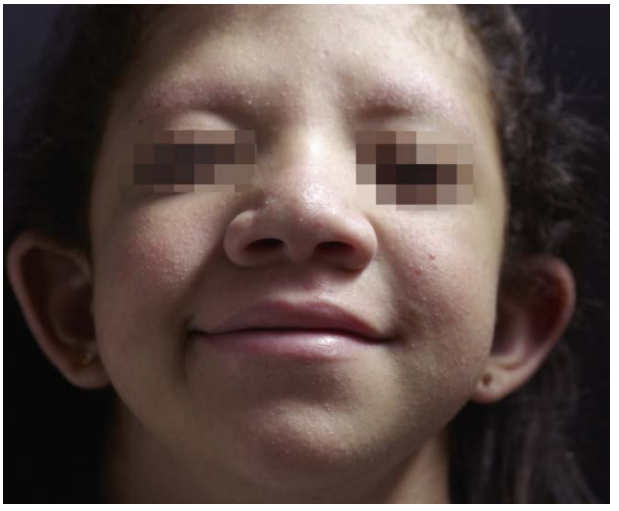

FIGURE 1: Syndromic facies and keratosis pilaris

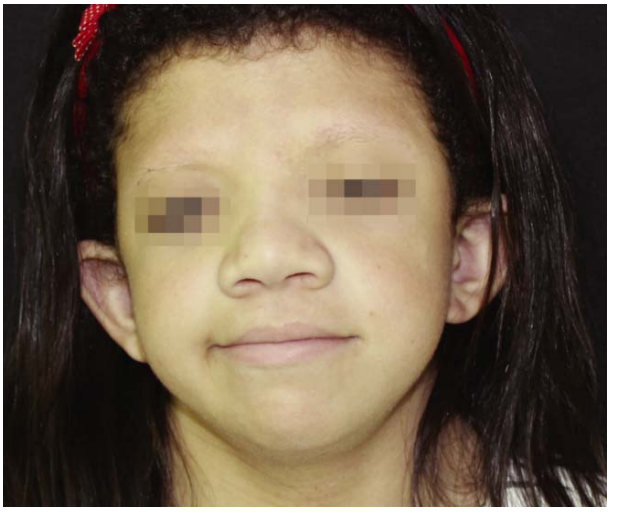

FIGURE 2: Hypertelorism, downward slanting palpebral fissures, micrognathia, ptosis and short neck

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DISCUSSION

The patient presented keratosis pilaris and a syndromic face, similar to Turner's phenotype. However her karyotype was normal (46 XX). These clinical features, then lead us to further investigate her condition.

Keratosis pilaris (KP) is a common skin disorder of childhood that often improves with age. Less common variants of this dermatosis include keratosis pilaris atrophicans, and atrophodermia vermiculata. KP has been reported as a feature of Noonan syndrome (NS).[1,2] This condition is characterized by congenital heart defects, characteristic facial anomalies and wide phenotypic variation.[3-6]

Noonan syndrome (NS) is the eponymous name for the disorder described in 1963 by two pediatric cardiologists, Noonan & Ehmke, at a conference and later published by Noonan alone. They based their description of this novel syndrome on observations made over nine patients with pulmonary valve stenosis, low-set ears, webbed neck, chest deformities, and a distinctive dysmorphic facial appearance with hypertelorism and ptosis. Opitz suggested that this disorder should be called Noonan Syndrome, a terminology that was subsequently adopted.[3]

NS may occur in a pattern consistent with autosomal dominant inheritance with almost complete penetrance.[3-6] In recent years, germline mutations in the components of RAS-MAPK (mitogen activated protein kinase) pathway have been shown to be involved in the pathogenesis of NS. Mutations in *PTPN11, KRAS, SOS1, NRAS, RAF1, BRAF, SHCO2, CBL e MEK1* can explain 60-75% of NS molecular cause.[7,8] Each affected gene could be implicated in several developmental processes controlling morphology determination, organogenesis, synaptic plasticity and growth[8]. Genotype-phenotype correlations have been documented previously (Romano et al, 2010;Tataglia et al, 2011) (Chart 1).[7,8]

Differential diagnoses include a number of conditions with phenotypes strikingly similar to NS. First there is Turner syndrome (45, X0), a well-known chromosomal abnormality occurring on girls. Then there is a group of distinct syndromes with partially overlapping phenotypes in which causative mutations are found in genes of RAS-MAPK pathway. These include Cardio-Facio-cutaneous syndrome, Costello syndrome, Neurofibromatosis type 1, generalized woolly hair and LEOPARD syndrome.[4,9]

CHART 1: Most frequently used medications and potential interactions with systemic antifungals*

Gene	Cardiovascular Features	Growth Features	Developmental Features	Skin/Hair Features	Other Features
PTPN11	Pulmonary valve stenosis	Overrepresentation of short stature	Little or no cognitive delays	-----	-----
PTPN11	Underrepresentation of hypertrofic cardiomyopathy	Lower IGF-1 levels	-----	-----	-----
KRAS	-----	-----	More severe cognitive delay	Cardiofaciocutaneous syndrome-like skin and hair findings	-----
SOS1	-----	Lower prevalence of short stature	Lower prevalence of cognitive delays	Cardiofaciocutaneous syndrome-like skin and hair findings	-----
RAF1	Overrepresentation of hypertrofic cardiomyopathy	-----	-----	-----	-----
SHOC2	Overrepresentation of mitral valve prolapse and septal defects	Higher prevalence GH deficiency	Distinctive hyperactive behaviour	Easily pluckable, sparse, thin, slow growing hair. Darkly pigmented skin eczema icthiosis.	Hypernasal speech
*NRAS**	-----	-----	-----	-----	-----

***KRAS, SOS1, RAF1, SHOC2, NRAS*:** genes of the mitogen-activated protein kinase pathway
***PTPN11*:** protein tyrosine phosphatase non-receptor type 11 gene
***IGF-1*:** insulin-like growth factor; GH: growth hormone.
* Too few cases precludes adequate analysis
Adapted from Romano *et al.*

The diagnosis is based on a clinical score system proposed by van der Burgt.[2] A dysmorphic face is mandatory, associated to another major criteria or two minor criteria. The major criteria are: pulmonary valve stenosis, hypertrophic myocardiopathy, short stature (below third percentile), *pectus carinatum* and/or *pectus excavatum*, and a first-degree relative with diagnosis of Noonan syndrome. The minor criteria are: other cardiac defects, short stature (below tenth percentile), other thoracic abnormalities, first-degree relative suggestive of Noonan syndrome and other findings (bad dental occlusion, micrognathism, mental retardation, developmental delay, deafness).[3,8,10] Our patient presented with the typical facies and also cardiac defects (pulmonary dilatation and mitral regurgitation), dental malocclusion, micrognathism, short stature, and a degree of learning disability. So, this patient had diagnostic criteria for Noonan syndrome. The genetic abnormalities were not investigated in this case.

Treatment for patients with NS is symptomatic and directed at the specific associated anomalies or clinical findings.[6] ❑

Abstract Noonan Syndrome is one of the most common genetic syndromes and also an important differential diagnosis in children presenting with syndromic facies similar to Turner's syndrome phenotype. This syndrome is characterized by facial dysmorphism, congenital heart defects, short stature and also a wide phenotypic variation. This article discusses the case of a 10 year-old patient with Noonan syndrome that presented typical facies, cardiac defects (pulmonary dilatation and mitral regurgitation), dental malocclusion, micrognatism, short stature and a certain degree of learning disability.
Keywords: Genetics; Heart defects, Congenital; Noonan syndrome; Stature by age; Turner syndrome

Resumo Síndrome de Noonan é uma das mais frequentes síndromes genéticas e importante diagnóstico diferencial em crianças com fácies sindrômica similar ao fenótipo da síndrome de Turner. É caracterizada por dismorfismo facial, defeitos cardíacos congênitos, baixa estatura e uma ampla variação fenotípica. Esse artigo apresenta um caso de uma paciente de 10 anos de idade com síndrome de Noonan que apresentava fácies tiípica além de defeitos cardíacos (dilatação de artéria pulmonar e insufiência mitral), má oclusão dentária, micrognatismo, baixa estatura e dificuldade de aprendizado.
Palavras-chave: Cardiopatias congênitas; Estatura-Idade; Genética; Síndrome de Noonan; Síndrome de Turner

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