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CLINICAL CASE

Short stature and hypothyroidism in a child with Nail-Patella Syndrome. A case report

Talla baja e hipotiroidismo en un niño con Síndrome de Nail-Patella. Reporte de un caso clínico

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Abstract

Background: Nail-Patella syndrome (NPS) (OMIM: 161200) or hereditary onycho-osteodysplasia is an autosomal dominant disorder characterized by skeletal anomalies, nail dysplasia, renal and ocular abnormalities. The diagnosis is based on clinical and radiological findings and confirmed by the identification of a heterozygous pathogenic variant in the *LMX1B* gene. Management of these patients involves continuous follow-up and treatment of the orthopedical, ocular and renal problems that may occur. **Objective**: To describe a case of NPS with short stature and hypothyroidism, an association that has not been described in the literature. **Case report**: An eleven-year-old boy with a height of 130 cm (-2.01 Standard Deviations [SD]) was referred to the Endocrine Unit at the age of 2 years due to altered thyroid tests. At that time, dysplastic nails and disproportionate short stature were detected. Radiological abnormalities initially suggested a skeletal dysplasia. A primary hypothyroidism was confirmed, without anti-thyroid antibodies and with a normal thyroid ultrasound. Levothyroxine treatment was initiated. The diagnosis of NPS was confirmed by a genetic study with a single pathogenic variant in the *LMX1B* gene. His father presented a similar phenotype with normal stature. His bone age was equivalent to his chronological age. Laboratory screening for short stature and a GH stimulation test were normal. **Conclusion**: We present a child with proven NPS with short stature and hypothyroidism. We did not find publications that described this triple association. It can't be ruled out that there could be a relationship between NPS and the thyroid alterations found in this patient.

Keywords:
Hypothyroidism;
Short stature;
Nail-Patella Syndrome;
Nail dysplasia;
Patellar hypoplasia;
Hereditary onycho-osteodysplasia

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Introduction

The Nail-Patella syndrome (NPS) (OMIM: 161200) or hereditary onycho-osteodysplasia is an autosomal dominant disorder that affects ectodermal and mesodermal tissues[1], and it is characterized by skeletal anomalies, such as nail dysplasia, patellar aplasia/hypoplasia, iliac horns, anomalies of the elbow and renal and ocular disorders. The first description of NPS and its related characteristics were reported by Chatelain in 1820[2].

Nail disorders have an incidence rate of 98%[3], affecting mainly thumbs and index fingers in a symmetric and bilateral way. It can appear as dystrophy, hypoplasia or absence of nails. Nails show longitudinal or horizontal striations, sometimes discolored and split by a longitudinal fissure. A pathognomonic finding of NPS is an abnormal lunulae, which can be triangular or absent. Lunulae are more visible in thumbs, usually crescent-shaped and slightly paler than the rest of the nails.

Radiological study is essential in the diagnosis and shows characteristic findings of the disease. 74% of the patients have an asymmetric alteration in the knees, with small, absent or irregular patellas, which suffer from frequent subluxation. 70% of these patients also have compromise of the elbow joint, with limitations of the extension, pronation and supination, and cubitus valgus. The compromise can be asymmetric; the nursemaid's elbow is frequent and can be confirmed by a radiological study[4].

Iliac horns are conical bone protuberances, which grow in the central area of the iliac bone. They are present in 70% of the patients with NPS, they are asymptomatic and considered pathognomonic[3]. They are easily detected in radiographies and could even be visible in the prenatal ultrasound in the third quarter if the technician has experience[5].

Male and female are equally affected. This condition is an autosomal dominant disease[6] with complete penetrance and variable expression. 88% of people with NPS have an affected parent and 12% correspond to *de novo* mutation. Clinical manifestations are extremely inconsistent, both in frequency and severity, with inter- and intrafamilial variability. The prevalence of NPS has been estimated in 1/50,000[3], however, it could be higher since patients with mild phenotype are not diagnosed.

This syndrome is caused by heterozygous pathogenic variants in the *LMX1B* gene, located in the chromosome 9q33.3. This gene codifies for an indispensable transcription factor for the development of dorsal structures of limbs, morphogenesis, and fusion of podocytes and the glomerular basement membrane; it also participates in the development of the anterior chamber of the eye[6]. Regarding the central nervous system, the *LMX1B* gene is related to the development of dopaminergic and serotonergic neurons of the midbrain and posterior parietal cortex, and to spinal interneurons[7].

The diagnosis is based on clinical and radiological findings and it is confirmed with the identification of a heterozygous pathogenic variant in the *LMX1B* gene. The management of these patients implies a continuous follow-up and control of orthopedic, ocular (primary open-angle glaucoma and ocular hypertension) and renal (proteinuria with or without hematuria, nephrotic syndrome, chronic renal failure), complications that may occur.

The objective of this study is to describe an NPS case with short stature and hypothyroidism, an association that has not been described in the literature.

Clinical Case

Male adolescent, who was initially referred to the Endocrinology Unit at the age of two due to abnormal thyroid blood tests: TSH 7.46 mUI/ml (reference value, RV 0.7-5.7 mUI/ml), T4L 1.33 ng/dl (RV 0.8-2.1 ng/dl). At that time, it was possible to observe dysplastic nails (figure 1) and disproportionate short stature (size 2.6 ft-82.2 cm/-2.29 Standard Deviation [SD] according to the growth curve of Centers for Disease Control and Prevention and National Center for

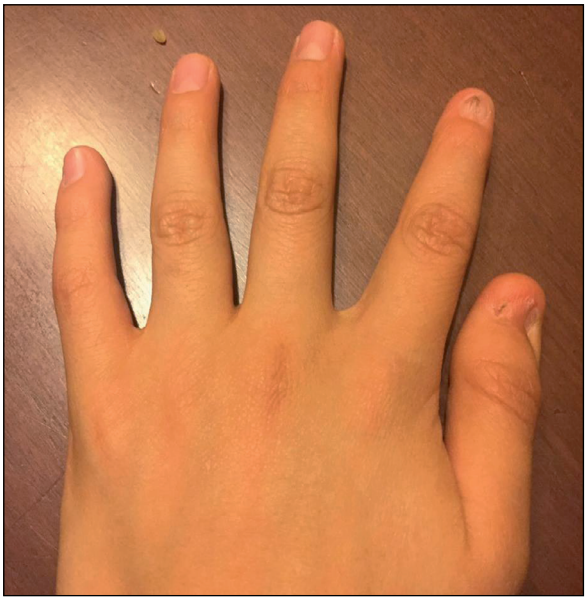

Figure 1. The patient presented triangular lunules and hypoplastic nails. The thumb and index finger were separated into two halves by a longitudinal ridge of skin. Nail changes are the most constant feature of NPS[3].

Health Statistics [CDC/NCHS]; segment relation upper/lower of 1.6) (figure 2).

Only son of parents without consanguinity or isonymy. There were no thyroid disorder or short stature history. His mid-parental height was 5.5 ft - 1.70 cm (-0.3 SD) (father height: 5.5 ft-167.8 cm and mother height: 5.2 ft-159.3 cm). The requested radiological study related to short stature showed signs of skeletal dysplasia. Thyroid tests were performed several times (TSH 13.32 mUL/ml, T4L 1.46 ng/dl), which confirmed the diagnosis of hypothyroidism, with negative anti-thyroid antibodies and normal thyroid ultrasound. The patient was asymptomatic at all times; the treatment started with levothyroxine 75 ug/day, which was later adjusted to 62.5 ug/day. His bone age was equivalent to his chronological age. Laboratory screening for short stature as well as a GH stimulation test with clonidine were normal.

The patient was referred to a geneticist and to a pediatric traumatologist and kept sporadic controls in our Endocrinology Unit. Short stature was observed in almost all of its evaluations, growing just below the 3rd percentile of the growth curve.

During his school years he had a knee sprain, showing small and unstable patellas, genu varum, hyperextension of proximal interphalangeal joints and distal interphalangeal joint flexion.

Given the nail alterations, swan neck fingers and patellar dysplasia, at the age of seven, the diagnosis of NPS was suggested and three years later it was possible to confirm it with a molecular study. A nonsense pathogenic variant of the *LMX1B* gene was found: c.661C > T; p.Arg221Ter. His father had a similar phenotype (figure 3), with normal stature and thyroid function, however, there is no genetic confirmation in

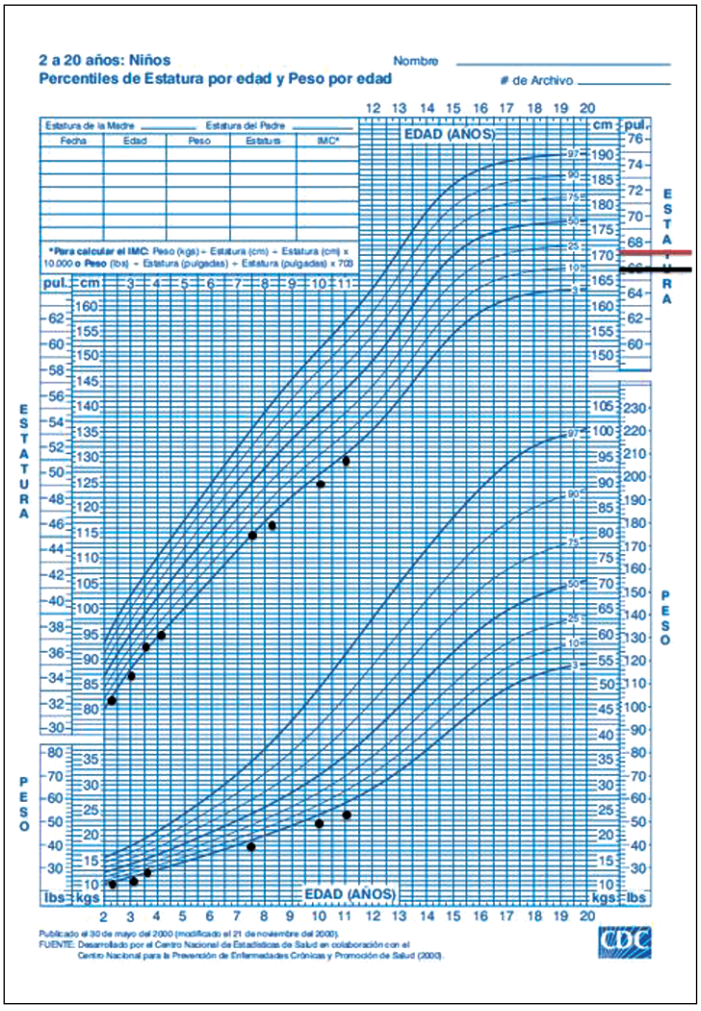

Figure 2. Growth chart (height-for-age and weight-for-age) of the patient from 2 to 11 years of age. One may see a parallel curve slightly below the third percentile, and below its target height (father's and mother's heights indicated in black and red respectively).

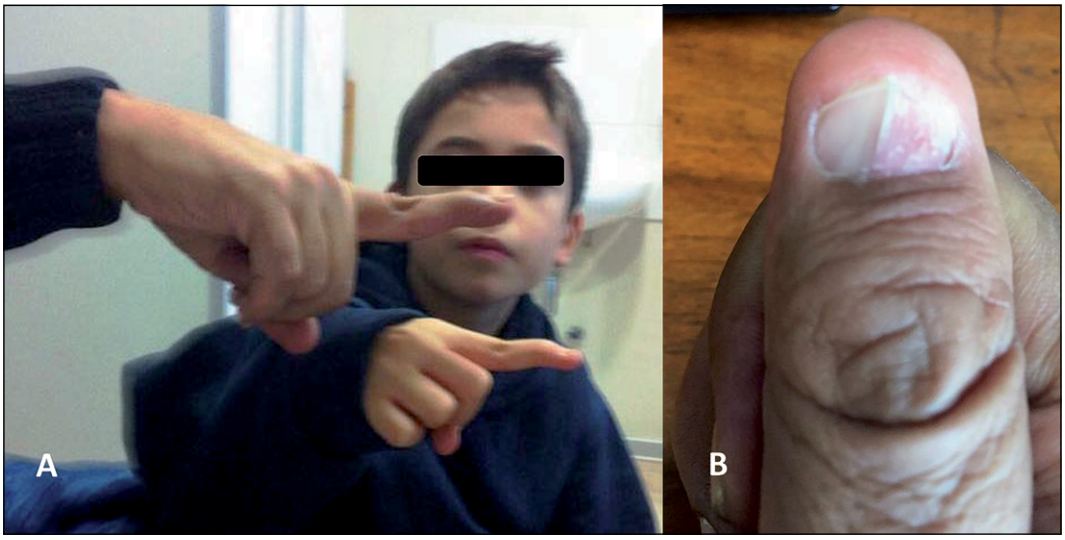

Figure 3. A) Both father and son had hyperextension of the proximal interphalangeal joints and flexion of the distal interphalangeal joints, resulting in "swan-necking". **B)** Nail dysplasia of the thumb in the father.

Table 1. Frequency of Characteristics in NPS

Feature	Frequency	Patient's features
Nail changes (absent, hypoplastic or dystrophic nails; triangular lunules)	98%	(+)
Knee involvement (small, irregularly shaped or absent patellae; recurrent subluxation; prominent medial femoral condyles, hypoplastic lateral femoral condyles)	74%	(+)
Elbow involvement (radial head dysplasia, radial head subluxation; lateral epicondyle hypoplasia and prominence of the medial epicondyle; cubitus valgus)	70%	(-)
Iliac horns	70%	(-)
Renal involvement (proteinuria, with or without hematuria, nephrotic syndrome, end-stage renal disease)	40%	(-)
Ophthalmological findings (Primary open-angle and normal-tension glaucoma, ocular hypertension)	35%	(-)

him. In his last evaluation, the patient was 11 years old and was 4.2 ft-130 cm (-2.01 SD). An ophthalmological and renal function study was performed on the patient, both results were normal.

Discussion

The NPS is a pathology that must not be dismissed, since it is associated with other complications with high morbidity and mortality, such as chronic renal failure (with an incidence rate of 5%) and glaucoma. Renal involvement is characterized by hematuria and proteinuria that can reach the nephrotic-range during childhood or adolescence, and it is observed in 40% of these patients[5]; the recommendation is to control it with a urine test, an annual microalbuminuria/creatinuria ratio and blood pressure measurement[3]. Regarding ophthalmologic alterations, they are presented in 35% of patients with NPS[6]. They are more likely to present primary open-angle glaucoma, normal tension glaucoma, eye hypertension and isolated glaucoma lesion in the optic disk, at younger ages than the general population[8]. Therefore, it is recommended to perform an annual ophthalmological assessment soon after the child is able to contribute to the test[3]. The patient does not present renal or ocular alterations yet. Table 1 shows a summary of the NPS characteristics and its associated frequencies.

Regarding the short stature, it has been described as an inconstant feature in patients with NPS[2,9]. Overall, patients with NPS are shorter than the average population, but this difference is not significant. The final average height described in the revision of 89 British patients are 5.6 ft-170.9 cm for males (-0.77 SD) and 5.2 ft-158.5 cm for females (-0.71 SD)[4]. There are similar syndromes in the differential diagnosis, such as Meier-Gorlin syndrome, RAPADILINO syndrome, which differ due to the presence of microtia, a characteristic facies and bone age retardation in the first syndrome, and for a palatine fissure, facial dysmorphia and radial ray defects in the second one[10]. There is only one report in which the short stature (-4.0 SD) was associated with NPS in two sisters from Tunisia, however, they did not have a molecular confirmation and the segment description of the physical examination was not reported[11].

Thyroid structure alterations have not been described in this syndrome yet. The case of a young adult woman with NPS and autoimmune thyrotoxicosis was published[12], but there are no cases of NPS associated with hypothyroidism. It has been confirmed that the product of the *LMX1B* gene interacts with a CLIM protein (LIM –domain-binding protein), which acts as a transcriptional activator associated to LIM homeoproteins and expresses itself in the thyroid tissue[13].

The patient had a p.Arg221Ter pathogenic variant, which has been previously described in the literature[14]. He also had short stature (-2.01 SD) associated with non-autoimmune hypothyroidism, the rest of the hormonal test was normal and there was no bone age delay. Although it can affect, it is highly unlikely that hypothyroidism would be a cause of his short stature.

The fact that the product of the *LMX1B* gene normally interacts with proteins expressed in the thyroid tissue, may suggest that NPS could be associated with thyroid alterations. Assuming that both father and son, who share a similar phenotype, present the same pathogenic variable, the absence of hypothyroidism and short stature in the son could be explained by the variability of clinical symptoms reported by this syndrome, even within the same family.

Conclusions

The patient had NPS, confirmed by a molecular study, associated with short stature and hypothyroi-

dism. We did not find publications of patients with NPS and these other two pathologies. Future studies are required to establish a casual association of this genetic variant in thyroid formation and functioning.

Ethical responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

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Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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