Case Report

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Disproportionate Short Stature in Nail Patella Syndrome: Clinical, Radiological, and Genetic Insights

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Abstract

This case report presents an 11-year-old male with disproportionate short stature as a rare manifestation of Nail Patella Syndrome (NPS). NPS is an autosomal dominant disorder caused by mutations in the LMX1B gene and is typically characterized by nail dysplasia, skeletal anomalies, and renal complications. The patient exhibited classical features of NPS, including dysmorphic traits, nail abnormalities, and radiological evidence of patellar aplasia and iliac horns. Genetic analysis identified a p.Arg221Ter pathogenic variant in LMX1B, confirming the diagnosis. Importantly, comprehensive evaluations excluded endocrine, renal, and systemic causes for short stature, suggesting it as a direct, albeit uncommon, feature of NPS. This case underscores the importance of genetic testing in diagnosing atypical presentations and highlights the need for tailored management, including regular monitoring for renal and ophthalmological complications. By documenting short stature in NPS, this report expands its clinical spectrum, contributing valuable insights to the understanding of this complex condition.**Keywords:** Chronic pancreatitis, complication, ductal rupture

Keywords: Childhood anomalies, nail-patella syndrome, short stature

Introduction

Nail Patella Syndrome (NPS), also known as hereditary osteoonychodysplasia or Turner-Kieser syndrome, is a rare genetic condition with an incidence ranging from 4.5 to 22 per million people (1,2). It is inherited in an autosomal dominant manner, affecting both genders equally. The causative mutations are found in the LIM homeobox transcription factor 1-beta (LMX1B) gene, located on chromosome 9q33.3 (3-5). This gene encodes a transcription factor that is essential for the development of dorsal limb structures, podocyte morphogenesis and fusion with the glomerular basement membrane, and the formation of the anterior chamber of the eye (6). The LMX1B gene is also involved in the development of dopaminergic and serotonergic neurons in the midbrain and posterior parietal cortex, as well as spinal interneurons in the central nervous system (7).

Clinical manifestations of NPS include short stature, particularly rhizomelic shortening, and less frequently, hydrocephalus, true megalencephaly, midface hypoplasia, trident hand configuration, and joint hyperextension (8,9). NPS was first described in 1820 by Chatelain (10) and later insights into its familial and hereditary nature were provided by Pye-Smith in 1883 and Little in 1897 (11). The clinical definition of NPS is based on a tetrad of features: nail dysplasia, hypoplastic or absent patella, radial head dislocation, and iliac horns with bony prominences on the iliac bones (1,2).

Nail abnormalities affect approximately 98% of NPS patients, primarily involving the thumbs and index fingers symmetrically. These abnormalities include dystrophy, hypoplasia, or nail absence, often accompanied by longitudinal or horizontal stripes that may change color and be separated by longitudinal cracks. An abnormal lunula, which may be triangular or absent, is a pathognomonic feature of NPS, most noticeable on the thumbs [12]. Soft tissue complications include renal dysplasia, muscle weakness, hearing loss, shaky gait, and winging of the scapula. Renal involvement is seen in 30-50% of NPS cases and significantly affects prognosis. Proteinuria, with or without hematuria, is common and may progress to end-stage renal disease over time (13,14).

While the classical features of NPS are well-documented, disproportionate short stature remains an uncommon and underexplored manifestation. Although reports linking NPS

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to short stature are scarce in the literature, we present a rare case of disproportionate short stature in a patient with Nail Patella Syndrome. NPS is frequently associated with renal anomalies; however, this case is notable for contributing to the limited knowledge of its association with growth abnormalities. By reviewing this presentation in the context of short stature and dysmorphic features, this report aims to enhance understanding of the broader phenotypic spectrum of NPS and its implications for clinical management.

Case Report

A patient with short stature, monitored in our outpatient clinic from the age of 9 to 11 years, was evaluated. His birth weight was 3600 grams, with no reported postpartum complications. On physical examination, the patient's height was 130 cm (<3rd percentile), body weight was 40.9 kg (25th–50th percentile), and he was at Tanner stage 2. Dysmorphic features were observed (Figure-1a). The patient's maternal height was 148.2 cm, paternal height was 158 cm, and mid-parental height was calculated at 159.75 cm. His parents, who are cousins, had no known medical conditions or dysmorphic features.

Laboratory and Hormonal Investigations

Laboratory screening included a growth hormone stimulation test using L-Dopa and clonidine, which showed normal results. Specifically, theL-Dopa stimulation was 9 ng/mL, clonidine stimulation was 13 ng/mL, thyroid-stimulating hormone (TSH) was 1.2 mIU/L, and free T4 was 1.3 ng/dL. These values were within normal reference ranges, indicating no growth hormone deficiency, normal thyroid function, and no evidence of hypothyroidism.

Clinical Examination and Radiological Findings

The patient exhibited frail upper limbs with straight, grooved fingernails, predominantly affecting the 1st and 2nd metacarpals (Figure-1b). Similar abnormalities were observed in the toenails (Figure-1c). Both elbows showed a full range of motion, with no crepitation and unrestricted pronation and supination. A careful assessment of the lower extremities revealed equal leg lengths and squareness of the knees, with no signs of ligament laxity. The feet were noted to be in a valgus position.

Radiographs of the knees revealed complete absence of the patella on both sides, along with moderately hypoplastic lateral femoral condyles (Figure-2a). Pathognomonic posterior iliac horns, characteristic of Nail Patella Syndrome (NPS), were evident (Figure-2b).

Genetic Analysis

Given the patient's dysmorphic features, short stature, and abnormal radiographic findings, genetic analysis was pursued. Sanger sequencing identified a pathogenic variant in the LMX1B gene: NM_002316.3(LMX1B):c.661C>T (p.Arg221Ter), associated with dbSNP identifier rs121909487. This mutation is known to cause phenotypic features such as nail dysplasia, swan-neck toes, and patellar dysplasia, consistent with the clinical presentation.The same mutation was not observed in parental analysis. Along with clinical examination of the parents, who do not display any features characteristic of NPS, suggests the mutation is likely de novo.

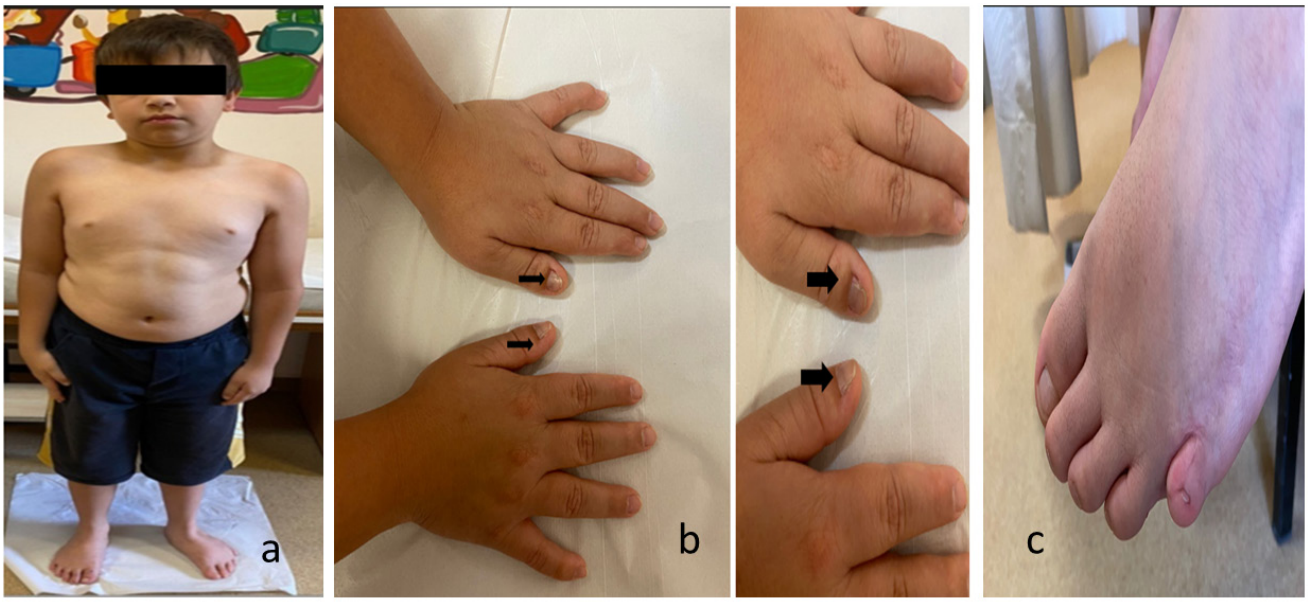

Figure 1. Characteristics of Nail-Patella Syndrome with Short Stature: a; Dysmorphic features observed during physical examination. b; Clinical image illustrating subtle discoloration and dystrophy of nails, with mild ridges primarily evident in the thumbs, index, and middle fingers on both sides. c; Presentation of dystrophic toenails associated with Nail-Patella Syndrome.

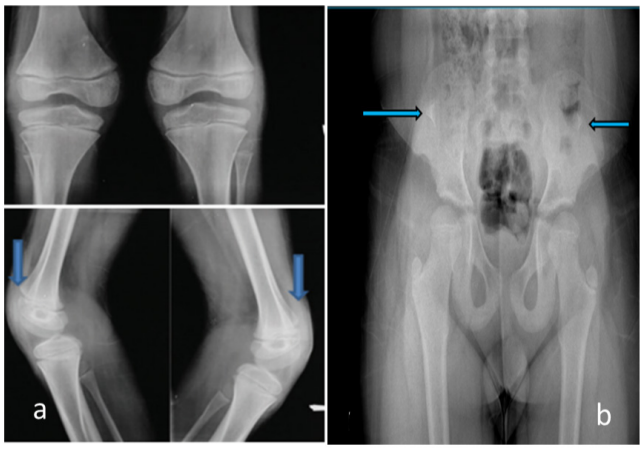

Figure 2. Radiographic Features of Nail-Patella Syndrome with Short Stature: a; X-ray depicting the absence of patellae. B; Pelvic X-ray revealing the presence of bilateral iliac horns.

Follow-up and Diagnosis Confirmation

At the final evaluation at age 11, the patient's height remained 130 cm, corresponding to -2.01 SD. NPS was diagnosed based on the identified genetic mutation, as well as the clinical and radiological findings. Kidney and ophthalmological screenings were performed to assess any potential complications. No evidence of renal disease, such as proteinuria or hematuria, was found, and renal ultrasound results were normal. Ophthalmological examination also revealed no abnormalities.

Discussion

Documented cases of Nail Patella Syndrome (NPS) associated with short stature are scarce, with limited literature specifically addressing this rare manifestation. This case report enhances the existing knowledge by identifying disproportionate short stature as an uncommon feature of NPS, underscoring the critical role of genetic testing, and offering a comprehensive clinical, radiological, and diagnostic profile to guide future research and clinical management.

The patient demonstrated disproportionate short stature, a rare feature in Nail Patella Syndrome (NPS). A previous case series reported two pediatric patients with NPS presenting for short stature evaluation, underscoring that while this association is uncommon, it is documented in the literature (15). Clinical manifestations of NPS are highly variable, and although short stature is not a defining characteristic, it has been observed in some cases alongside classical NPS features. For example, a study described a family with multiple affected members exhibiting varying degrees of short stature in conjunction with the typical symptoms of NPS [16,17]. In certain cases, endocrine factors such as hypothyroidism have been implicated as contributing factors to growth impairment in children with NPS [12].The role of genetic variations in the LMX1B gene has also been highlighted, as exemplified by Alvarez Martin et al., who identified a c.728G>C (p.Trp243Ser) mutation in a patient presenting with short stature (16). Similarly, Lindelöf H et al. reported an inversion of the LMX1B gene in a Swedish family, all members of whom exhibited varying degrees of short stature, further expanding the genetic spectrum associated with this phenotype (17). Recently, Jang J et al. reported a deletion variant in the LMX1B gene, specifically NM_001174147.2(LMX1B):c.641_887-556delinsGG, p.(Lys214Argfs*11), associated with Nail Patella Syndrome (NPS); however, short stature was not identified as a typical characteristic in their findings (18).

Normal laboratory and hormonal profiles along with no evidence of proteinuria, hematuria, renal abnormalities, or ophthalmological issues was found during comprehensive screenings.These results indicate that the patient's short stature is unlikely due to systemic conditions such as growth hormone deficiency, thyroid dysfunction, or renal complications, which are common contributors to growth impairment. Additionally, the absence of proteinuria, hematuria, renal abnormalities, and ophthalmological issues suggests that the patient does not exhibit some of the more typical complications associated with Nail Patella Syndrome (NPS). This reinforces the conclusion that the disproportionate short stature observed in this case is a rare and isolated manifestation of NPS rather than a secondary effect of other systemic abnormalities.

Despite full genetic penetrance in familial contexts, Nail Patella Syndrome (NPS) exhibits a variable degree of clinical manifestation. The syndrome lacks specific diagnostic criteria; however, it is often diagnosed based on a combination of clinical and imaging findings (18-22). In cases where clinical evaluation is inconclusive, genetic testing provides a valuable diagnostic tool (23). LMX1B, a member of the LIM-homeodomain family of transcription factors, plays a critical role in establishing ventral-dorsal body patterning during embryonic development (13).

NPS warrants careful attention due to its association with complications carrying significant morbidity and mortality, particularly chronic renal failure, with a reported incidence of 5%, and glaucoma. Renal involvement, characterized by hematuria and proteinuria that can progress to the nephrotic range during childhood or adolescence, occurs in approximately 40% of cases (23). Annual urine testing, including microalbuminuria/creatinine ratio assessment, and regular blood pressure monitoring are recommended. Ophthalmological complications affect 35% of NPS patients (6), with primary open-angle glaucoma, normal-tension glaucoma, ocular hypertension, and isolated glaucomatous optic disc lesions more frequently manifesting at a younger age compared to the general population. Annual ophthalmological evaluations are therefore advised (24). In the present case, renal and ophthalmological evaluations revealed no abnormalities.

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NPS is a condition that must not be overlooked due to its association with complications of significant morbidity, including chronic renal failure and glaucoma. Renal involvement, evident in 40% of cases, underscores the need for vigilant monitoring. Nail dysplasia and patellar aplasia or hypoplasia are hallmark features of NPS (21). Thumb anomalies are particularly severe; in this case, the patient exhibited longitudinal protrusions. While toenail involvement is less common, the presence of triangular lunulae is considered pathognomonic (21). In this case, toenails were not involved. Nail dysplasias in NPS can include horizontal or longitudinal protrusions, pitting, or longitudinal clefts. Patellar anomalies, such as absence, hypoplasia, or abnormal formation, are frequently associated with recurrent patellar subluxation, indicative of knee involvement. Elbow abnormalities, including restricted joint movement, capitellum hypoplasia, and radial head subluxation, can occur, often asymmetrically (25). Iliac horns, bony projections from the middle of the outer iliac fossa, are pathognomonic for NPS and present in over 80% of cases (22,26). Radiographs in this patient revealed complete absence of the patella bilaterally and moderately hypoplastic lateral femoral condyles (Figure-1b).

NPS manifestations extend to sensorineural hearing loss, gastrointestinal involvement, and neurological or vasomotor dysfunction. Skeletal deformities such as pes planus, pes equinovarus, pectus excavatum, and scoliosis have also been reported (27). Short stature in NPS patients is inconsistently described in the literature (23-27). While individuals with NPS are, on average, shorter than the general population, this difference is not statistically significant. A study of 89 British patients reported a mean final height of 170.9 cm (-0.77 SD) in males and 158.5 cm (-0.71 SD) in females[6,23–25,28,29]. Notably, only a few reports, including two Tunisian sisters with short stature (-4.0 SD) and a Spanish case of short stature associated with hypothyroidism, link short stature to NPS (12). In this case, the patient harbored a p.Arg221Ter pathogenic variant, a mutation previously described in the literature (28). The patient presented with disproportionate short stature (-2.01 SD) alongside nail and finger anomalies but demonstrated normal hormonal and bone age assessments.

Conclusion

This case highlights disproportionate short stature as a rare feature of Nail Patella Syndrome (NPS), expanding its clinical spectrum. The identification of the *LMX1B* pathogenic variant (p.Arg221Ter) underscores the role of genetic testing in diagnosing atypical presentations. The absence of systemic abnormalities suggests short stature may be a direct feature of NPS rather than a secondary complication. This report emphasizes the importance of comprehensive evaluations and monitoring to improve management and outcomes for individuals with NPS.

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