

# A rare case of nephrotic syndrome: 'Nailed' the diagnosis

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## ABSTRACT

An 18-month-old female child presented to us with clinical features suggestive of nephrotic syndrome. Her physical examination and detailed family history highlighted the familial occurrence of abnormal nails, suggesting a diagnosis of the Nail-Patella syndrome. Nail-Patella syndrome is a rare cause of nephrotic syndrome in children. This case highlights the importance of a detailed history, including pedigree and a thorough examination of the patient.

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## Introduction

Ninety percent of the children with nephrotic syndrome have the idiopathic nephrotic syndrome.<sup>[1]</sup> The remaining 10% have secondary nephrotic syndrome.<sup>[1]</sup> Some rare genetic types of nephrotic syndrome include: The Finnish-type congenital nephrotic syndrome, Denys–Drash nephrotic syndrome, Alport syndrome, Galloway–Mowat syndrome, etc.<sup>[1]</sup>

## Case Details and Discussion

An 18-month old female child, first birth by order, born of a third degree consanguineous marriage, presented to our institute with a history of reduced urine output and gradually progressing swelling all over the body, since one month. There was no history suggestive of feeding difficulty, respiratory distress or jaundice. The perinatal history revealed a full-term, normal delivery, with the child weighing 2.5 kg. There was a history of 'stiff' elbows, with limited movements since birth, which the mother noticed during

the traditional massage. The child had gross global developmental delay. On examination, the child was stable hemodynamically. Her blood pressure was 90/60 mmHg. She weighed 6.5 kg (between the third and tenth percentile, as per the World Health Organization (WHO) growth chart), had a length of 69 cm (<the third percentile), and a head circumference of 41 cm (<3SD). She was pale, with anasarca and soft pitting pedal edema. On examination, her developmental age was of eight months; with a development quotient of 44%. The child had bilaterally limited movement of the elbow joint, although no pterygium or skin fold at the elbow was visible. We noticed that the child and the mother had strikingly abnormal nails. The child had anonychia of the thumb nails and hypoplasia and dysplasia of the other nails (bilaterally symmetrical), of the fingers as well as the toes [Figures 1 and 2]. The child also had absence of the skin creases on the dorsal aspect of the distal interphalangeal joints, appreciated better in the fingers. The mother had anonychia of both the thumb nails, with nail hypoplasia and dysplasia in the other eight fingers, sparing the toes [Figure 3]. The child also had absent patellae [Figure 4]. The mother's radiograms revealed normal patellae with bilateral symmetrical bony spikes arising from the anterior–superior iliac crests, known as iliac horns [Figure 5]. On enquiry the mother's father and her paternal grandfather also had similar hypoplastic and dysplastic nails [Figure 6]. However, they were not available for a detailed examination. The mother's grandfather had a history of early onset knee pain (since his early 40s) and gait difficulty. However, she denied any other family members having significant renal disease.

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**Figure 1:** Right hand of patient — note the abnormal nails (dystrophic nails with absent thumb nail) and absence of skin creases over the distal interphalangeal joints



**Figure 2:** Right foot of patient — note the abnormal nails and absence of skin creases over the distal interphalangeal joints



**Figure 3:** Both hands of the patient's mother — note the abnormal nails (dystrophic nails with absent thumb nail) and absence of skin creases over the distal interphalangeal joints



**Figure 4:** Radiograph of pelvis with both legs- note the absence of the patella bilaterally in the patient

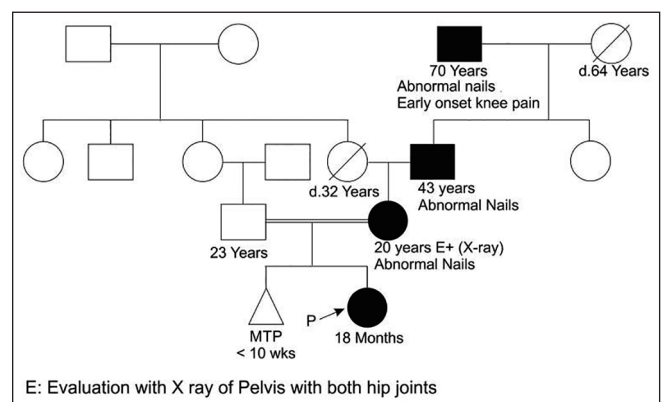


**Figure 5:** Radiograph of the pelvis, with both hips of the patient's mother showing bilateral iliac horns

### Question 1

Which are the disorders involving the nails?

Reply: Disorders limited to the nails include — Anonychia,



**Figure 6:** Pedigree chart for the patient's family showing the autosomal dominant inheritance pattern

Racket nails, Koilonychia, Congenital pitting, Ridging, Micronychia, Polyonychia, Hereditary clubbing, and Periodic shedding; while nail changes are also seen in disorders of multiorgan systems like — Hidrotic congenital ectodermal dysplasia, Anhidrotic congenital ectodermal dysplasia,

Pachyonychia congenita, Chondroectodermal dysplasia, Coffin–Sirris syndrome, Tuberous sclerosis, Epidermolysis bullosa, Nail–Patella–Elbow syndrome, Wilson’s disease, and Iso–Kikuchi syndrome.<sup>[2,3]</sup>

### **Case Details (Continued)**

Investigations of the child revealed nephrotic range proteinuria (72 mg/kg/day), hematuria (20–30 RBC/high power field), severe hypoalbuminemia (1.5 gm/dl), raised serum triglycerides (859 mg/dl), deranged prothrombin time (42.2 seconds, control 13.3 seconds, INR 4.70), deranged activated partial thromboplastin time (>120 seconds, control 30.3 seconds), and a decreased C3 level. The child had normal blood urea nitrogen, serum creatinine, alanine and aspartate transaminases, serum bilirubin and thyroid function tests, and C4 levels. Ultrasonography of the abdomen revealed gross ascites. Computed tomography of the brain revealed prominent ventricles and no evidence of intracranial bleed. The child’s blood tested negative for HIV, HBsAg, and HCV.

### **Question 2**

*What are the causes of nephrotic syndrome in early childhood?*

Reply: A European review of 89 children, who presented with nephrotic syndrome in the first year of life, showed that 85% of the nephrotic syndrome in infancy is due to mutation in one of the four genes (NPHS1, NPHS2, WT1, LAMB2).<sup>[4]</sup> Nephrotic syndrome in infancy can also be secondary to infections like syphilis, cytomegalovirus, toxoplasmosis, Hepatitis B or syndromes like Nail–Patella syndrome and Lowe syndrome.<sup>[1]</sup>

### **Case Details (Continued)**

Based on the clinical and biochemical profile of the patient, along with the confirmed family history, a final diagnosis of Nail–Patella syndrome (NPS) presenting as nephrotic syndrome was made. However, we could not test the child for the LMX1B mutation due to financial restraints and unwillingness of the parents.

### **Question 3**

*How common is the Nail–Patella syndrome with renal involvement in the pediatric age group?*

Reply: The estimated incidence of NPS is 22 per million.<sup>[5,6]</sup> Only one-third of the affected individuals have renal disease. Of these, <15% of them develop end-stage renal disease (ESRD).<sup>[5,6]</sup> Although NPS is often listed among the causes of congenital and infantile nephrotic syndrome, precise information on individual patients is scarce.<sup>[5,6]</sup> Ours is one of the very rare cases, with NPS presenting as a nephrotic syndrome in the pediatric age group.

### **Question 4**

*How is the Nail–Patella syndrome inherited?*

Reply: It is an autosomal dominant disease involving several organs including the skeleton, the eyes, the ears, and the kidneys.<sup>[6]</sup> In 1998, Dreyer *et al.* demonstrated that mutations

of the *LMX1B* gene associated with limb, eye, and renal development, are responsible for NPS.<sup>[7]</sup>

### **Question 5**

*What abnormalities of the nails are noted in the Nail–Patella syndrome?*

Reply: This uncommon condition is of special interest because it involves abnormalities of the ectodermal and mesodermal structures.<sup>[8]</sup> Nail abnormalities are present in 80 to 90% of the patients and may be absent, hypoplastic or dysplastic.<sup>[9]</sup> The nails may be grossly defective, but the nail bed is always present. Finger nails are more commonly involved than the toes. The nails are only one-third to half of the normal size and never reach the free edge of the finger.<sup>[8]</sup> The thumbnails are most affected and the remaining nails, if involved, are progressively less damaged, from the index to the little finger.<sup>[8]</sup> The lesions are bilateral and symmetrical and include discoloration, longitudinal pterygium, splitting, and triangular lunulae.<sup>[10]</sup> Of importance is the fact that the absence of skin creases on the dorsal aspects of the distal interphalangeal joints is a more specific sign of this disorder; and may be present in these patients even in the absence of nail changes.<sup>[11]</sup> Thus, it may be worthwhile to carefully check the nails and fingers in every child presenting with nephrotic syndrome.<sup>[11]</sup>

### **Question 6**

*What are the renal manifestations of the Nail–Patella syndrome?*

Reply: The clinical spectrum of NPS can be varied; with nephropathy and ESRD representing the worst end of the spectrum.<sup>[6]</sup> NPS is known to cause congenital (onset in the first three months of life) and infantile (onset from three months to one year of life) nephrotic syndrome.<sup>[6]</sup> The presentation includes proteinuria, sometimes with the nephrotic syndrome, hematuria, and hypertension.<sup>[6]</sup> Renal manifestations in NPS are highly variable and unpredictable. They vary between families and also within single families. This suggests the existence of genetic or environmental modifiers.<sup>[6]</sup>

Histologically, the renal biopsy of patients with NPS and those having proteinuria, sometimes shows non-specific changes, resembling focal segmental glomerulosclerosis (FSGS), consisting of immune complexes of IgM and C3.<sup>[12]</sup> This could result in the consumption of C3, and thus the low C3 levels seen in our patient. We could not prove this, as we did not do a renal biopsy in our patient.

### **Question 7**

*What are the other manifestations of the Nail–Patella syndrome?*

Reply: NPS is a clinical tetrad of abnormalities of the nails, knees, elbows, and the presence of iliac horns.<sup>[13]</sup> The patella may be absent, hypoplastic or fragmented.<sup>[7,8,13,14]</sup> Complications such as arthritis, arthrosis, and knee effusion, may lead to knee pain and thus cause gait difficulties.<sup>[7,13,14]</sup> Iliac horns, observed in 30–70% of the patients, consist of symmetrical bone formations arising from the anterosuperior iliac crests, and are pathognomonic radiological features of the disease. These iliac horns may be asymptomatic.<sup>[7,14]</sup>



The elbow joint abnormalities include hypoplasia and subluxation of the radial heads and hypoplasia of the distal end of the humerus.<sup>[7,13,14]</sup> This results in limitations of extension, pronation, and supination of the forearm in these patients.<sup>[1,14]</sup> Other associated features include hyperextension of the joints, skin laxity, hyperhidrosis, and open angle glaucoma.<sup>[6,10,14]</sup>

### Case Details (Continued)

The patient received intravenous fluids, antibiotics, albumin infusion, fresh frozen plasma, prednisolone (2 mg/kg/day), frusemide, with spironolactone (1 mg/kg/day) and enalapril (0.1 mg/kg/day). On day five of the ward stay the child developed generalized tonic clonic seizures lasting for ten minutes, which subsided with injectable midazolam (0.05 mg/kg). This was followed by prolonged apnea and worsening of the Glasgow Coma Scale (score 4), mandating intubation and mechanical ventilation. Renal biopsy could not be performed because of the hemodynamic instability of the child. After nine days of mechanical ventilation the child succumbed to pulmonary hemorrhage, secondary to a deranged coagulation profile (due to septicemia). The mother was advised to follow-up in the Genetic Clinic for antenatal genetic counseling during the next pregnancy.

### Question 8

*How do you treat a child with the Nail–Patella syndrome, along with the nephrotic syndrome?*

Reply: Most of the genetic nephropathies with end-stage renal disease have a poor prognosis. Other than renal transplantation, the treatment options are bleak.<sup>[6]</sup> Combined use of the angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has shown some success in slowing the progression in proteinuric nephropathies.<sup>[6]</sup>

However, in our case, we had given prednisolone (empirically). Steroids are best avoided in children with NPS and the nephrotic syndrome. The already high susceptibility for infections in these children can be exaggerated with steroids. Besides, there is no literature that supports the use of steroids in the nephrotic syndrome due to NPS.

### Question 9

*What is the genetic counseling required in a couple having a child affected with the Nail–Patella syndrome?*

Reply: Eighty-eight percent of the individuals diagnosed with NPS have an affected parent, while 12% have a *de novo* mutation.<sup>[13]</sup> On account of autosomal dominant inheritance, there is a 50% chance in every pregnancy that the child born will be affected with NPS.<sup>[13,15]</sup> Chorion villous sampling and amniocentesis can aid prenatal diagnosis if the disease causing mutation has been identified in the family.<sup>[13,15]</sup> NPS is a fully penetrant and highly variable disease.<sup>[13]</sup> Thus, such a testing can determine whether the fetus has inherited the LMX1B disease causing mutation, but it cannot predict the appearance or the severity of the clinical manifestations.<sup>[13]</sup> Talipes equinovarus or large iliac horns may be detected on fetal ultrasound examination in the third trimester.<sup>[13]</sup> It has been calculated that,

for a parent with NPS, whose family has nephropathy, the risk of having a child with nephropathy is 24% and the risk of having a child who will progress to end-stage renal disease is 7%.<sup>[15]</sup>

### Conclusions

The Nail–Patella syndrome is a rare genetic cause of nephrotic syndrome in young children. A careful examination of the nails and a radiological assessment when indicated, can give a clue to the diagnosis. It is advantageous to confirm the diagnosis by renal biopsy and a specific mutation study. Genetic counseling should be carried out for families with affected members.

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