Nail-patella syndrome

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Abstract
Nail patella syndrome or hereditary osteo-onychodysplasia is an autosomal dominant disorder defined by the association of nail dysplasia, bone anomalies and renal disease. In addition to nail dysplasia, the patellas are hypoplastic or absent, the elbows are dysplastic and iliac horns are observed on X-rays. Renal symptoms are observed in 30 to 40% of cases, with proteinuria and microscopic hematuria. Progression to renal failure is observed in 1/3 of patients with renal involvement. The nail-patella syndrome gene, LMX1B, is a transcription factor belonging to the LIM homeodomain protein family playing an important role during development. It has been suggested that there may be two allelic mutations of the gene, one responsible for the nail-patella syndrome without nephropathy and one for the syndrome with nephropathy. The disease has been reported in patients worldwide.

Keywords
Nail-patella syndrome, dysplastic nails, hypoplastic patellae, *LMX1B*gene.

Disease name and synonyms

- Nail-patella syndrome, NPS
- Onychoosteodysplasia

Definition

NPS or osteo-onychodysplasia is an autosomal dominant disorder characterized by hypoplastic or absent patellae, dystrophic fingernails and toenails and dysplasia of the elbows and iliac horns [1-3]. Renal involvement is inconstant.

Incidence

The incidence has been estimated at 22 per million inhabitants' live births children. The disease has been reported in patients worldwide.

Clinical description

Extrarenal manifestations

Nail abnormalities are present in 80-90% of patients and are observed at birth [4]. The nails may be absent but more often are hypoplastic or dysplastic [5]. Abnormalities predominate on the fingernails, particularly the thumb and index finger, whereas the toenails are often normal. The lesions are bilateral and symmetrical and

include discoloration, longitudinal pterygium, splitting, and triangular lunulae [6].
Abnormalities of the knees and elbows are found in almost all patients [4]. The patellae may be absent or hypoplastic, often with fragmentation, causing lateral slippage during knee flexion [4,5,7,23]. Complications such as arthritis, arthrosis, and knee effusion, may cause knee pain. Common elbow symptoms are attributable to radial heads that are typically hypoplastic, leading to subluxation. The distal ends of the humerus are also hypoplastic and posterior processes limit extension, pronation and supination of the forearm.
Iliac horns, observed in 30-70% of the patients, are pathognomonic radiologic features of the disease. They consist of symmetrical bone spurs arising from the anterosuperior iliac crest [7]. They are asymptomatic and may be detected on physical examination. Other bone anomalies, affecting the feet and the ankles, may be seen and scoliosis has been described.

Renal manifestations
Renal symptoms are present in approximately one-half of NPS patients [8]. Females and males are equally affected. The degree of renal involvement varies from one family to another but also within single families. The most frequent symptoms are proteinuria, sometimes with a nephrotic syndrome, hematuria and hypertension [9,10]. Urine-concentrating ability may be impaired.
End-stage renal disease develops in approximately 30% of the patients [4] at a mean age of 33 ± 18 years [11]. The evolution of the renal disease is extremely variable, suggesting that non-genetic factors may be involved in the rapid deterioration of renal function observed in some patients. For example, superimposed nephritis has been described in this disorder including anti-glomerular basement membrane (GBM) antibody disease [12], membranous nephropathy [13], IgA nephropathy [4], and necrotizing vasculitis [14]. It is not known if these disorders occur with increased frequency in NPS.

Treatment
No specific therapy is available to treat NPS. The GBM lesions do not recur after renal transplantation and these patients do not produce anti-GBM antibodies, a finding that is occasionally seen in hereditary nephritis, another genetic disorder of collagen metabolism.

Etiology
The abnormal gene in NPS has been localized to the distal end of the long arm of chromosome 9. It is closely linked to the genes coding for the ABO blood groups [15] and for adenylate kinase [16]. The gene encoding a transcription factor of the LIM-homeodomain type, which plays an important role for limb development in vertebrates, named *LMX1B*, was mapped to the same location at 9q34. Several mutations in this gene have been identified independently in NPS patients [17,18]; these defects are thought to result in the loss of function of this protein.
It has been suggested that there may be two allelic mutations of the gene, one responsible for the NPS without nephropathy and one responsible for the NPS with nephropathy. It has been calculated that, for a parent with NPS with 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 % [11].
It was recently shown that *LMX1B* regulates the coordinated expression of type IV collagen alpha-3 and alpha-4 in the GBM and that its dysregulation in the GBM contributes to the nephropathy [19].

Diagnostic methods
Light microscopy of renal biopsies shows normal or nearly normal glomeruli in patients with normal renal function. In comparison, patients with severe proteinuria and/or impaired renal function may show GBM thickening and non-specific lesions of focal and segmental glomerulosclerosis. Immunofluorescence microscopy is negative or detects non-specific segmental deposits of IgM and C3 in the sclerotic areas.
Electron microscopy reveals the pathognomonic and constant lesions of the GBM [15,20], consisting of irregular and lucent rarefactions within the lamina densa, containing clusters of cross-banded collagen fibrils [14,20,21]. These abnormalities may also be found in the mesangial matrix, but the tubular basement membranes are not affected. The fibril clusters are clearly visualized by staining with uranyl acetate and phosphotungstic acid. They may be observed within segments of thickened GBM or along the entire GBM.
Immunohistochemical studies have shown an irregular mesangiocapillary localization of collagen type III and an abnormal distribution of collagen type VI. These findings are compatible with an abnormal composition of the basement membranes which could be responsible for the renal and extrarenal manifestations.
Although the collagen fibrils are a constant feature of NPS, they are also found in patients without clinical evidence of renal involvement [9]. Furthermore, there is no correlation between the

severity of the ultrastructural lesions and the clinical manifestations. Similar collagen accumulation in the GBM has recently been described in patients with a form of familial progressive glomerulopathy that is not associated with nail or bone involvement [14,22]. It is not known if this disorder is related to the NPS.

Antenatal diagnosis

At this time, prenatal diagnosis is not available.

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