Nail-Patella Syndrome

Contents

In 1820, Chatelain (1951) first observed the nail-patella syndrome in a patient with a triad of abnormal nails, elbows, and knees. The hereditary nature of the syndrome was first described by Pye-Smith in 1883 in the English literature. The presence of iliac horns was first noted by Kieser (1939) in 1939 and later by Fong (1946) in 1946. In 1948, Mino et al. described the tetrad of abnormal nails, elbows, knees, and iliac horns for which the name hereditary onycho-osteodysplasia was coined by Duncan and Souter in 1963.

Synonyms and Related Disorders

Hereditary onycho-osteodysplasia (Duncan and Souter 1963; Carbonara and Alpert 1964)

Genetics/Basic Defects

1. Genetic heterogeneity (Ghoumid et al. 2015)
2. An autosomal dominant disorder with complete penetrance (Lucas and Opitz 1966; Beals and Eckhardt 1969; Figueroa-Silva et al. 2016)
3. An autosomal recessive inheritance: reported in a Saudi Arab family with nail-patella syndrome (Al-Dawsari et al. 2015). Genetic analysis of the *LMX1B* gene detected a previously reported homozygous mutation (c.268C > TP. Leu90Phen) in exon 2 of the *LMX1B* gene in both of the affected sisters. Both of the parents were confirmed to be heterozygous for the same mutation
4. Case reports of donor insemination, embryo donation (Figueroa-Silva et al. 2016)
5. *LMX1B*
    1. The only gene known to be associated with nail-patella syndrome (NPS)
    2. A LIM-homeodomain transcription factor involved in normal patterning of the dorsoventral axis of the limb during development and early morphogenesis of the glomerular basement membrane (Bongers et al. 2002)
    3. Targeted disruption of *Lmx1b* results in skeletal defects, including hypoplastic nails, absent patellae, and a unique form of renal dysplasia (Chen et al. 1998)
    4. *LMX1B* gene maps to 9q in the same region as the NPS locus by fluorescence in situ hybridization. Three unrelated NPS patients carried *de novo* heterozygous mutations in this gene (Dreyer et al. 1998)

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6. A microdeletion of chromosome 9q33.3 encompassing the entire *LMX1B* gene have been reported in a Chinese family with nail-patella syndrome (Jiang et al. 2014)
7. Demonstration of association between the haplotype of the mutant allele and the variability in the nail score ($p = 0.024$) (Dunston et al. 2005a)
8. Genotype/phenotype correlations (Bongers et al. 2005a)
    1. Individuals with an *LMXB1* mutation located in the homeodomain showed significantly more frequent and higher values of proteinuria than subjects with mutations in the LIM domains
    2. No clear genotype-phenotype association was apparent for extrarenal manifestations (McIntosh et al. 1998)

Clinical Features

1. Inter- and intrafamilial phenotypic variabilities (Lee et al. 2009)
2. Classic clinical tetrad
    1. Onychodysplasia (Sweeney et al. 2003): the most constant feature of the syndrome (approximately 98% of cases)
        1. Variable
        2. Absent, hypoplastic, or dystrophic nails usually noted at birth
        3. Spoon-shaped nails (Koilonychia)
        4. Pitting, discoloration, thin/thick nails
        5. Often bilateral or symmetrically involved
        6. Longitudinally or horizontally ridged (grooved) nails
        7. Thin or less often thickened nails
        8. Triangular lunules (lunulae): a characteristic feature of the syndrome
        9. Most pronounced involvement in thumbnails, decreases in severity ulnarward
        10. Dysplasia of toenails usually less marked, often affecting little toenails, and less frequent than that of the fingernails
        11. Report of nail changes in the mother and son (Neri et al. 2015)
            1. Mother: missing ulnar half of the first fingernail, triangular lunula associated with pseudopterygium/fissure/furrow
            2. Son: anonychia of the first fingernail, koilonychia of the third fingernail, triangular lunula associated with pseudopterygium/fissure/furrow
    2. Knee dysplasia (approximately 74% of cases)
        1. Small, irregularly shaped, or absent patella that is prone to dislocate
        2. May be asymmetrically involved
        3. Hypoplastic patella often located laterally and superiorly, even though not actually dislocated
        4. May be associated with prominent medial femoral condyles, hypoplastic lateral femoral condyles, and prominent tibial tuberosities
        5. Appearance of flattened profile of knee joints
    3. Elbow dysplasia (approximately 70% of cases)
        1. May be asymmetrical
        2. The deformity is characterized by hypoplasia of the capitellum, commonly by secondary dysplasia and dislocation, usually posteriorly, of the radial head, associated with limitation of rotation (pronation and supination) of variable degree
        3. Triceps hypoplasia with antecubital pterygia, a frequent accompaniment of the syndrome, further limiting extension resulting in cubitus valgus
    4. "Iliac horns" (Cottereill and Jacobs 1961)
        1. Clinically palpable
        2. Generally symmetrical
        3. Known to develop a secondary center of ossification
        4. The iliac horns can be present at birth by X-ray examination
    5. To the classical clinical tetrad of involvement of the nails, knees, and elbows and

presence of iliac horns, kidney disease, and glaucoma had been added as recognized parts of the syndrome (McIntosh et al. 2005)

3. Other skeletal abnormalities
    1. Talipes equinovarus, talipes calcaneovalgus deformities, and flat feet
    2. Mild short stature
    3. Adults with nail-patella syndrome have a bone mineral density (BMD) that is 8–20% lower than controls, which is associated with an increase in the prevalence of fractures and scoliosis (Towers et al. 2005)
4. Associated nephropathy (Darlington and Hawkins 1967; Eisenberg et al. 1972; Bennett et al. 1973) (30–50% of cases) (renal failure in approximately 5% of cases)
    1. Proteinuria
        1. Usually the first sign of renal involvement
        2. With or without hematuria
        3. May present at any age from birth onward
        4. May be intermittent
        5. May remit spontaneously, remain asymmetric, progress to nephritic syndrome, and occasionally to renal failure
        6. May be exacerbated during pregnancy
    2. Relatively benign although fatality at a young age from this complication has been described (Leahy 1966)
    3. Progression to chronic glomerulonephritis leading rarely to renal failure
        1. May occur rapidly
        2. May occur after many years of asymptomatic proteinuria
5. Eye involvement
    1. Primary open-angle glaucoma
    2. Ocular hypertension
    3. Iris pigmentary changes: frequent observation of a zone of darker pigmentation shaped like a cloverleaf or flower around the central part of the iris (Lester's sign)
6. Gastrointestinal involvement (about one third of cases)
    1. Constipation
    2. Irritable bowel syndrome
7. Neurologic and vasomotor symptoms are also part of the NPS phenotype (Sweeney et al. 2003)
    1. Neurological involvement
        1. Intermittent numbness, tingling, and burning sensations in the hands and feet in some cases
        2. Epilepsy (6% of cases)
        3. Neurologic symptoms: considered particularly interesting in light of the role of Lmx1b in neuronal migration in the mouse and in the developing brain (Dunston et al. 2005b)
    2. Vasomotor problems in some cases
        1. Poor peripheral circulation, presenting as very cold hands and feet even in warm weather
        2. Raynaud's phenomenon
8. Dental problems
    1. Weak, crumbling teeth
    2. Thin dental enamel
9. Differential diagnoses (Bongers et al. 2005b; Sweeney et al. 2014)
    1. Small patella syndrome (ischiopatellar dysplasia, coxo-podo-patellar syndrome, Scott-Taor syndrome) (Bongers et al. 2004)
        1. Similarities: small or absent patellae, recurrent patella dislocations, pelvic anomalies
        2. Differences, defective ossification at the ischiopubic junction, ischial hypoplasia, infra-acetabular "axe-cut" notch, no nail changes, no elbow changes, no renal involvement, no ocular involvement
    2. Patella aplasia-hypoplasia
        1. Familial occurrence (Bernhang and Levine 1973; Braun 1978)
        2. A family segregating PTLAS mapping to 17q21-q22 (Mangino et al. 1999)
        3. Similarities: isolated aplasia or hypoplasia of the patella
        4. Differences: no nail changes, no elbow changes, no renal involvement, no ocular involvement
    3. Familial recurrent dislocation of the patella (Carter and Sweetnam 1960; Miller 1978; Borochowitz et al. 1988)

1. Similarities: familial tendency toward patella dislocation (autosomal dominant inheritance)
2. Differences: absence of other NPS features

4. Meier-Gorlin syndrome (ear-patella-short stature syndrome) (Shalev and Hall 2003; Bicknell et al. 2011)
   1. Caused by homozygous or compound heterozygous mutation in the ORC1 gene on chromosome 1p32
   2. Similarities: Absent patellae, dislocation of the radial head
   3. Differences: microtia, markedly short stature, delayed bone age, characteristic facial appearance, autosomal recessive inheritance
5. Genitopatellar syndrome (Cormier-Daire et al. 2000; Sankararaman et al. 2012) (please see the chapter on "► Genitopatellar Syndrome")
   1. Similarities: absent patellae, renal anomalies, flexion deformities of the knees and hips, club foot
   2. Differences: hypoplasia of the ischia and iliac bones, genital anomalies, facial dysmorphism, microcephaly, intellectual disability, structural (multicystic kidneys or hydronephrosis) rather than functional abnormalities, renal manifestations
6. DOOR syndrome (deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures syndrome) (Cantwell 1975; Nevin et al. 1982; James et al. 2007)
   1. Caused by homozygous or compound heterozygous mutation in the *TBC1D24* gene on chromosome 16p13 (Campeau et al. 2014)
   2. Similarities: absent or poorly formed nails
   3. Differences: long thumbs and big toes, often with triphalangy, other fingers and toes short as the result of an absent or hypoplastic distal phalanx, bilateral ptosis, short broad nose with a broad nasal tip and large nostrils, structural renal tract abnormalities, cataracts, optic atrophy, Dandy-Walker malformation, seizures, autosomal recessive inheritance
7. Trisomy 8 mosaicism (Jones 1997) (please see the chapter on "► Trisomy 8 Mosaicism Syndrome")
   1. Similarities: absent or hypoplastic patellae, limited elbow supination, abnormal nails
   2. Differences: significant learning difficulties, variable facial dysmorphism, camptodactyly, and progressive joint restriction, usually of the fingers and toes
8. Coffin-Siris syndrome (Vergano and Deardorff 2014)
   1. Caused by heterozygous mutation in the *ARID1B* gene on chromosome 6q25 (Wieczorek et al. 2013)
   2. Similarities: absence or hypoplasia of the nails and patellae, elbow dislocation
   3. Differences: nail hypoplasia, usually affecting the little finger nails, facial dysmorphism
9. RAPADILINO syndrome (Kääriäinen et al. 1989)
   1. The acronym RAPADILINO stands for the characteristic main features: RAdial and PAtellar aplasia or hypoplasia, cleft or highly arched PAlate, infantile DIarrhea and DIslocated joints, LIttle size and LImb malformation, and long slender NOse and NOrmal intelligence
   2. Caused by homozygous or compound heterozygous mutation in the DNA helicase gene *RECQL4* on chromosome 8q24 (Siitonen et al. 2009)
   3. Similarities: absent or hypoplastic patellae, dislocated joints
   4. Differences: cleft palate, facial dysmorphism, short stature, radial defects, including absent or hypoplastic thumbs and radii, autosomal recessive inheritance
10. Senior syndrome (Brachymorphism-onychodysplasia-dysphalangism syndrome) (Senior 1971; Verloes et al. 1993)
    1. Similarities: small nails

2. Differences: characteristic facial appearance, short stature, mild intellectual impairment

Diagnostic Investigations

1. Diagnosis based on clinical and radiographic findings
2. Laboratory studies
    1. Urinalysis: proteinuria, hematuria
    2. Plasma urea, BUN, creatinine concentrations
3. Radiologic features
    1. The characteristic "NPS knee" consists of a combination of easily recognizable malformations (Tigchelaar et al. 2016)
        1. A small or absent patella and a number of malformations of the femoral condyles, encompassing shortening of the lateral femoral condyle, a prominent anterior surface of the lateral femoral condyle and a flat anterior surface of the medial femoral condyle
        2. At least one of these malformations is observed in all patients with NPS and at least three of them are observed in the majority of cases
    2. Elbow involvement
        1. Dysplasia of the radial head
        2. Hypoplasia of the lateral epicondyle and capitellum
        3. Prominence of the medial epicondyle
        4. Dislocation of the radial head, usually posteriorly
    3. Iliac horns
        1. Bilateral, conical, bony processes that project posteriorly and laterally from the central part of the iliac bones of the pelvis
        2. Present in about 70% of cases
        3. Considered pathognomonic of the syndrome (Goshen et al. 2000)
        4. Pelvic X-ray
            1. Usually necessary for detection of iliac horns, but large horns may be palpable clinically
            2. Iliac horns: may be observed at birth
            3. An epiphysis at the apex of iliac horns: may be present in children
    4. MRI
        1. For possible bone/soft tissue abnormalities
        2. For a subluxated or dislocated patella (Konrads et al. 2016)
    5. Ultrastructural (electron microscopic) abnormalities (Morita et al. 1973): the most specific histologic changes seen in nail-patella syndrome
        1. Collagen fibril deposition within the basement membrane and the mesangial matrix
        2. Irregular thickening of the glomerular basement membrane with electron-lucent areas giving a mottled "moth-eaten" appearance
        3. The skin revealed epidermal basement membrane thickening and redundancy in addition to significant perivascular basal lamina reduplication by electron microscopy (Burkhart et al. 1980)
    6. Renal histopathology (Browning et al. 1988)
        1. Characteristic changes in the glomeruli at age 27 months
        2. Strong immunofluorescent staining, particularly for IgM, raised the possibility of superimposed immune complex disease
    7. Molecular genetic testing: *LMX1B* gene mutation analysis available clinically

Genetic Counseling

1. Recurrence risk
    1. Patient's sib
        1. An affected parent: a 50% risk
        2. Clinically unaffected parents
            1. A low risk in a case of de novo mutation in the proband
            2. An increased risk if germline mosaicism exists in a parent (not been reported)
    2. Patient's offspring
        1. A 50% risk
        2. Affected person has a risk of about 1 in 4 of having a child with nail-patella syndrome nephropathy and a risk of about 1 in 10 of having a child in whom renal failure will develop (Looij et al. 1988)

2. Prenatal diagnosis
    1. Use of ultrasound in 3rd trimester diagnosis of NPS (Feingold et al. 1998)
    2. Use of five DNA markers flanking the LMX1B locus demonstrated that a fetus was affected (McIntosh et al. 1999). The pregnancy was terminated at 15 weeks
    3. Demonstration of the disease-causing mutation previously identified in the proband on fetal DNA obtained from amniocentesis or CVS
    4. Preimplantation genetic diagnosis (PGD) may be an option for some families in which the LMX1B pathogenic variant has been identified (Sweeney et al. 2014)
3. Management
    1. Patella dysplasia: most patients asymptomatic, rarely require surgical treatment
    2. Physiotherapy for orthopedic complaints
    3. Surgical treatment
        1. Bilateral elbow soft tissue release
        2. Bilateral radial head excisions
        3. Foot and ankle reconstructive procedures for equinus, pes cavus, calcaneovalgus, congenital vertical talus, and clubfoot deformities
        4. Knee extensor realignments and foot posteromedial releases had overall good results. Knee flexion contractures required full posterior capsular releases. Elbow reconstructive procedures were rarely indicated (Guidera et al. 1991)
        5. Occurrence of secondary patella dislocation is common in NPS. The most likely cause is a medial patellofemoral ligament (MPFL) tear and corrective surgery should be aimed at reconstructing the ligament. Reconstruction using gracilis tendon is a safe and effective method and can be used in NPS cases caused by an MPFL tear (Gong et al. 2016)
        6. Subluxated or dislocated patella (Konrads et al. 2016): early surgical treatment via resection of the trochlear septum and soft tissue balancing of the patella. When the septum displaces the patella and prevents physiological articulation of the patella with the trochlea femoris, early septum resection is likely to be important for a good functional outcome and proper development of the patellofemoral joint during growth
    4. Screening for proteinuria
    5. Screening for glaucoma
    6. Course of pregnancy: complicated by further deterioration of renal function with superimposed pre-eclampsia resulting in early delivery. Such pregnancies should be regarded as high risk and managed jointly with the renal physician in a tertiary care center to ensure an optimal outcome to the mother and baby (Chua et al. 2002)

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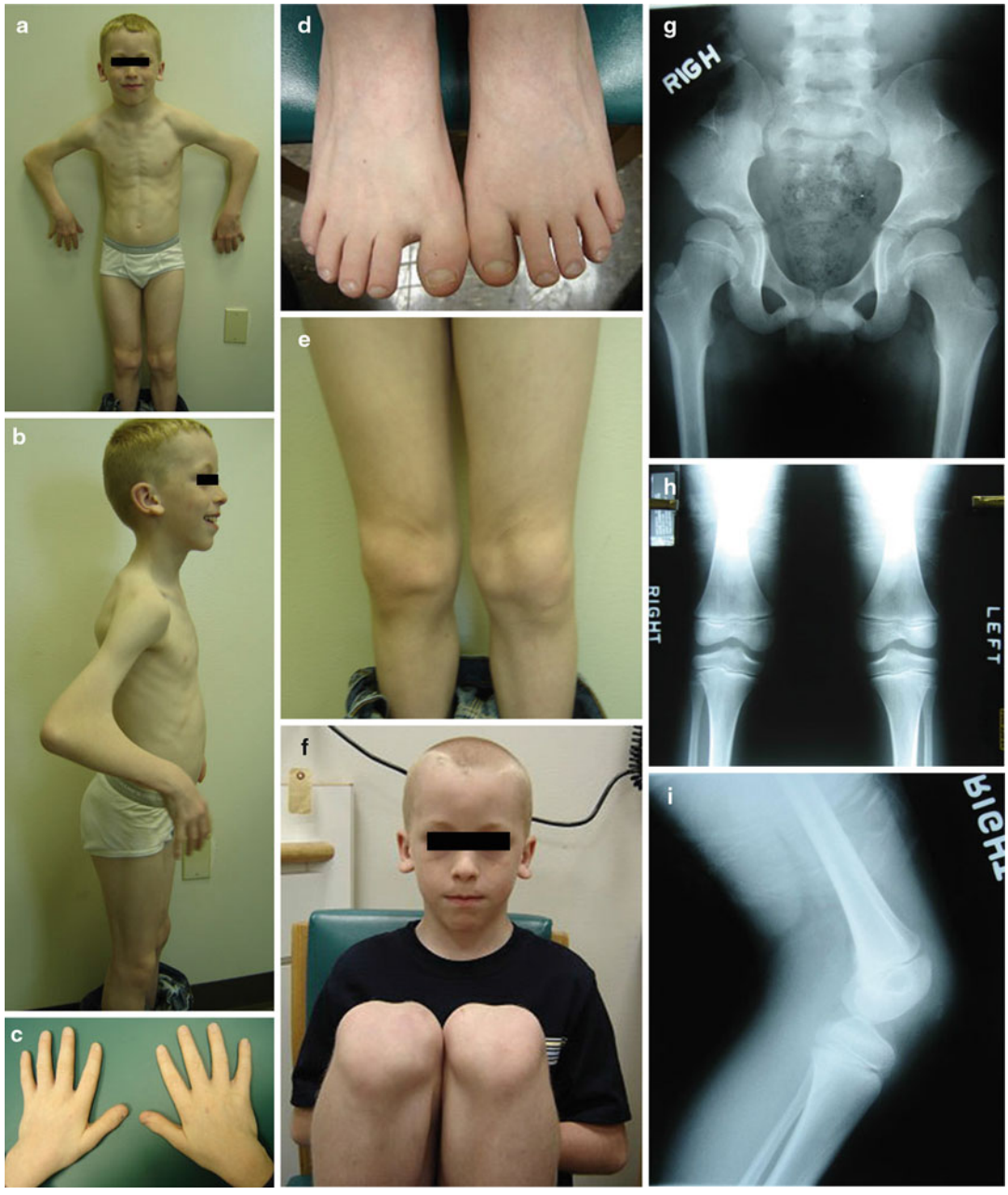

Fig. 1 (**a**–**i**) A 10-year-old boy (**a**, **b**) has classic nail-patellar syndrome. Note webbings of the neck and the elbows causing marked elbow contractures, abnormal muscle distribution of the upper extremities, nail hypoplasia (**c**, **d**), and absent patella (**e**, **f**). The radiographs show "iliac horn" sign of the pelvis (**g**) and patella agenesis (**h**, **i**)