

Nail-Patella Syndrome Associated with Respiratory Chain Disorder

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Key Words

Mitochondria · Genetics · Muscle · Echocardiography

Abstract

Nail-patella syndrome (NPS) has not been described to be associated with a respiratory chain disorder (RCD) before. In a 42-year-old man with the typical phenotype of an NPS, weakness and wasting of the shoulder girdle muscles, muscle cramps, fatigability, hyperhidrosis, chest pain and creatine kinase elevation were observed. Echocardiography revealed left ventricular hypertrabeculation. Needle electromyography was myopathic, lactate stress testing was abnormal, muscle biopsy showed typical features of an RCD and mtDNA analysis revealed the A3243G MELAS mutation. In conclusion, this case demonstrates that NPS may be randomly associated with RCD. NPS patients should undergo detailed cardiovascular and neurological investigations, in order not to overlook a double trouble partially mimicking NPS.

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Introduction

Nail-patella syndrome (NPS), also termed hereditary osteo-onychodysplasia, Turner-Kieser syndrome or Fong's disease, is a congenital, pleiotropic and autosomal dominant connective-tissue disorder with complete penetrance, characterised by dysplastic or hypoplastic patellae and nails, posterior iliac horns, elbow deformities, muscle hypoplasia, nephropathy and occasionally other abnormalities [1, 2]. Recent evidence shows that NPS is the result of at least 25 mutations in the LIM homeodomain gene LMX1B [3, 4]. Though muscle wasting is a frequent finding in NPS, respiratory chain disorder (RCD) has not been reported in NPS so far.

Case Report

The patient is a 42-year-old man with bilaterally dysplastic patellae, subluxation of the radial head, hypoplastic triceps muscles, antebrachial pterygium, 'iliac horns' and hypoplastic deep-set nails, predominantly of the thumbs and the right digits 2–4, in whom NPS was diagnosed at birth (fig. 1). At the age of 18 years, proteinuria, microscopic haematuria and chronic renal failure were detected. Kidney biopsy revealed proliferation of mesangium cells, segmental thickening of the glomerular basement membrane in the axial part of the glomerulum with bundles of collagen fibrils and small subepithelial

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electron-dense deposits, proliferation of podocytes, multinuclear epithelial giant cells and proliferation in epithelial cells of Bowman's capsule. Being under regular observation, chronic renal failure did not require further intervention. At the age of 30 years, he underwent complete thyroidectomy because of a medullary C-cell carcinoma of the thyroid gland with affection of the local lymph nodes, followed by chemotherapy with cisplatin and mitoxantron. As a consequence, laevothyroxin substitution and therapy of secondary hypoparathyroidism were begun. Regular follow-ups did not reveal a relapse of the malignoma. At the age of 36 years, sulcus ulnaris syndrome with recurrent numbness of the right 4th and 5th fingers was diagnosed. Since the age of 37 years, hyperlipidaemia had been noted. Since July 1998 (age of 41 years), he had observed recurrent numbness of the left arm. Since December 1998, he had experienced recurrent anginal pain with elevated creatine kinase but normal myocardial fraction, being initially misinterpreted as myocardial infarction. Coronary angiography was normal, but echocardiography revealed reduced fractional shortening and abnormal left ventricular trabeculations. Since December 1998, he had also observed tinnitus, fatigability after strenuous exercise, muscle cramps and hyperhidrosis. NPS was also diagnosed in the patient's recently born daughter, but no clinical features of an RCD have been detected in this child so far. A further diagnostic work-up in his daughter was refused by the patient. No other family members were affected by either NPS or RCD.

On clinical neurological examination, there was diffuse wasting of the shoulder girdle, arm and intrinsic hand muscles, hypoplasia of the triceps brachii muscle, weakness of the shoulder muscles (MRC grade 5-) and elbow extensors (MRC grade 4-), antebrachial pterygium, contractures of the elbow joints and absent Achilles tendon reflexes (fig. 1). Blood chemistry revealed a creatine kinase level of 380 U/l (normal: <80 U/l), lactate dehydrogenase of 481 U/l (normal: 120-240 U/l), creatinine of 3.8 mg/dl (normal: 0.5-1.1 mg/dl), blood urea nitrogen of 89 mg/dl (normal: 10-50 mg/dl) and a creatinine clearance of 18 ml/min (normal: 95-163 ml/min). Electrocardiography showed left ventricular hypertrophy and negative T waves in I, aVL and V₂₋₆. Abdominal ultrasound showed bilateral, mild renal shrinkage.

Nerve conduction studies and electromyography were carried out according to standardised procedures. Nerve conduction studies of the right median, ulnar and left peroneal nerves showed normal nerve conduction velocity, reduced amplitudes of the compound muscle action potentials without conduction block, Martin-Gruber anastomosis and a peroneus tertius. Conventional needle electromyography of the right brachial biceps and anterior tibial muscles showed fibrillations and high-frequency discharges at >4 of 20 sites, shortened mean motor unit action potential duration and reduced amplitude of the dense interference pattern at peak torque. Resting lactate was normal, but under a workload of 30 W for 15 min, serum lactate increased to 5.7 mmol/l (normal: <2.0 mmol/l) [5, 6]. Muscle biopsy from the left deltoid muscle, processed for frozen sections and electron microscopy according to standard procedures [7], showed mild myopathic features with increased fibre size variability and central nuclei. Trichrome stain demonstrated numerous ragged red fibres (fig. 2) which intensely reacted for NADH tetrazolium reductase and succinate dehydrogenase. Deficiency of cytochrome c oxidase was noted in ragged red and non-ragged red fibres. Electron microscopy showed accumulations of enlarged mitochondria between myofibrils and beneath the sarcolemma, occasionally harbouring paracrystalline inclusions (fig. 2). Single-strand conformation polymorphism and restriction fragment length polymorphism inves-



Fig. 1. Patient with NPS, showing antebrachial pterygium, missing patellae, hirsutism and wasting of the limb girdle and intrinsic hand muscles.

tigations of the muscle mtDNA revealed an A→G transition at nt 3243 with a heteroplasmy rate of 40% (MELAS, i.e. mitochondrial myopathy, lactacidosis and stroke-like episode mutation). Search for LMX1B point mutations was negative. Southern blot to look for LMX1B deletions is under way.

Discussion

NPS is an autosomal dominant disorder without evidence of a preferential transmission through the mother that largely affects the musculoskeletal system [8]. The characteristic phenotype is usually present at birth and

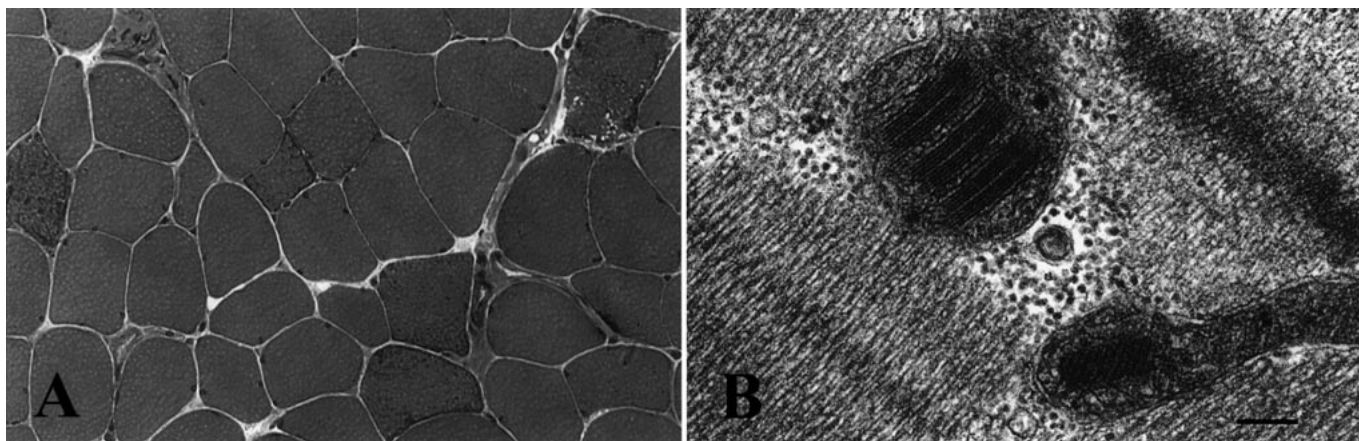


Fig. 2. A muscle biopsy from the left deltoid muscle shows numerous ragged red fibres with subsarcolemmal red granular deposits (Gomori trichrome, $\times 150$; **A**) and paracrystalline inclusions in enlarged mitochondria on electron microscopy (bar = 0.25 μm ; **B**).

affects 22 of 10⁶ live births [9]. Life expectancy is normal and there is no impaired fertility [10]. Characteristic features of NPS comprise the tetrad of (1) hypoplastic or dysplastic finger and toe nails (radial > ulnar), (2) absent or hypoplastic patellae, (3) hypoplasia and subluxation of the radial head and (4) hypertrophy of the posterior part of the iliac bone ('iliac horns'). Non-obligatory abnormalities comprise pigmentary abnormalities of the iris, chronic renal failure, dysplasia of the scapuloperoneal cingulum, talipes equinovarus, pes planus, valgus of the femoral collum, short stature, polydaktylia, hyperostosis frontalis, small sella turcica, impaired hearing, spina bifida, hyperlordosis, scoliosis, muscle hypoplasia, waddling gait and scapular winging [11]. An increased rate of malignancies in patients with NPS has not been previously reported. In a single case, NPS was associated with colon carcinoma [9].

RCDs are characterised by impaired oxidative metabolism due to mutations in mtDNA- or nDNA-located genes that encode for subunits of respiratory chain enzymes, tRNAs and rRNAs [12]. Mitochondriopathies are often multisystemic and heterogeneous with affection of the central and peripheral nervous system, skeletal muscle, eyes, ears, heart, intestines, kidneys, endocrinium, bone marrow, cartilage and integument alone or in combination. The A3243G mutation has been reported to be associated with chronic progressive external ophthalmoplegia, MELAS syndrome, myopathy with painful stiffness, myopathy with dystonia, diabetes mellitus and deafness, and mitochondrial encephalomyopathy [13]. Abnormalities that were attributable to an RCD in our patient

were tinnitus, anginal chest pain, left ventricular abnormal trabeculation, heart failure, hyperhidrosis, renal failure, polyneuropathy, abnormal lactate stress test and myopathy with fatigability, muscle cramps and an abnormally high level of plasma creatine kinase [12]. Cardiac involvement is a frequent finding in RCD, usually manifesting as anginal chest pain, heart failure, electrocardiographic abnormalities, myocardial thickening and abnormal left ventricular trabeculation [14, 15]. The pathogenesis of anginal chest pain in our patient could not be definitively determined, but it is speculated that chest pain was due to contractions of the intercostal muscles or the diaphragm. Whether polyneuropathy in our patient was secondary to renal failure or a primary manifestation of RCD also remains speculative.

Whether the association between NPS and RCD in our patient is a mere random coincidence, or whether there is a causal relationship between these two entities, remains speculative. Assuming the patient had an LMX1B deletion, then the MELAS mutation is another example of a genetic 'double trouble' and its pathogenic significance is doubtful, particularly in view of the low rate of heteroplasmy. Heteroplasmy (mutated versus wild-type mtDNA) does not typically express disease. There is lower tissue-specific segregation in any given patient. If there is no LMX1B deletion, a possible pathogenic contribution of the MELAS mutation can be considered, although it is rather unlikely that a mitochondrial mutation may contribute to the pathogenesis of NPS. Arguments for an accidental association are that no RCDs have previously been reported in NPS, that a second, unrelated NPS patient

without any neuromuscular symptoms and signs, but not yet finished investigation, does not seem to have an RCD and that skeletal abnormalities are rare in RCDs. Moreover, the function of the LMX1B gene seems to be associated with early development in a spatially and temporally restricted manner for the specification of limb fate which is not a preferential target of RCDs. Arguments in favour of a causal relationship are that NPS is often associated with wasted or hypoplastic muscles, short stature, hypacusis, renal failure, hyperlordosis, scoliosis and gait disturbance, abnormalities which can also be found in RCDs [16]. Whether NPS or the RCD were responsible for the development of renal dysfunction and whether carcinoma

of the thyroid gland or chemotherapy had a role in the pathogenesis of the RCD in our patient remain speculative. Limitations of this study are that screening for LMX1B mutations is under way, that biochemical investigations were not carried out, that single-fibre PCR was not performed and that the relatives refused screening for the A3243G mutation. In conclusion, this case demonstrates that NPS may be randomly associated with an RCD, manifesting as tinnitus, myopathy, polyneuropathy, cardiomyopathy and renal failure. NPS patients should undergo detailed cardiological and neurological investigations in order not to overlook a double trouble, partially mimicking NPS.

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