Abstract  We report a rare presentation of mitochondrial disorder in a child with recurrent carpopedal spasms due to hypocalcemia and hypomagnesemia, secondary to renal proximal tubulopathy and possible hypoparathyroidism. At least two mutant mitochondrial DNA species were identified, and abnormal mitochondria were found in the muscle and renal biopsy specimens. The case illustrates the spectrum and diversity of mitochondrial presentations, arising because of heteroplasmy of mutations and the type of organs affected.

Keywords  Mitochondrial disorder · Proximal renal tubular dysfunction · Hypoparathyroidism

Introduction

Mitochondrial disorders arise from genetic defects of oxidative phosphorylation, which affect different organs and tissues. Since oxidative phosphorylation is fundamental for energy production in all tissues, the presentation of mitochondrial disorders is extremely variable. Although classically manifesting in tissues requiring high energy, such as neuronal and muscle tissues, more than half of pediatric patients with mitochondrial disorders reportedly present with non-neuromuscular symptoms [1], and may be misdiagnosed.

Case report

Our patient is the only child of non-consanguineous parents. Poor growth was noted from 3 years of age, and at 5 years of age he presented with recurrent episodes of carpopedal spasms. On examination, he had failure to thrive (height 94 cm, –4 SD; weight 11.2 kg, –3.5 SD) (mid parental height 168 cm, +0.5 SD above mean), with no evidence of rickets or malabsorption. Neuro-developmental assessment was normal.

Initial blood investigations revealed persistent hypomagnesemia (0.45–0.51 mmol/l, normal 0.7–0.91 mmol/l) and hypocalcemia (ionic calcium 0.78–1.06 mmol/l, normal 1.15–1.35 mmol/l). There was increased urinary fractional excretion of magnesium (6.1%) (normal <5%) and an increased urinary calcium/creatinine ratio (0.9 mmol/mmol, normal <0.7). Serum phosphate was normal at 1.38 mmol/l (0.85–1.45), as was the tubular phosphate reabsorption (TRP 92%, normal >85%) and TmP/GFR (1.44 mmol/l, normal 1.08–2.24). There was evidence of renal proximal tubulopathy with glycosuria, generalized aminoaciduria, and significant potassium loss (urinary potassium 40 mmol/l) with mild hypokalemia (2.9–3.2 mmol/l, normal 3.5–5.0 mmol/l). Fractional excretion of potassium was increased at 24.3% (normal 14.5±8.9%). Renal ultrasonography revealed no structural abnormalities. The intact serum parathyroid hormone (PTH) was persistently low (1.5–7.1 pg/ml, normal 10–65 pg/ml) despite correction of magnesium levels by supplementation, indicating the presence of primary hypoparathyroidism.

A high anion gap metabolic acidosis was present, secondary to lactic acidosis (arterial lactate 3.4–5.4 mmol/l, normal <2.2 mmol/l), which suggested the presence of a mitochondrial disorder. Serum carbonate was 15 mmol/l (22–28 mmol/l). The cerebrospinal fluid lactate was 4.7 mmol/l, with a corresponding arterial lactate of 3.7 mmol/l. The arterial lactate/pyruvate ratio was 16.6, which was within normal limits (normal range 10–25). The urine demonstrated peaks of lactic acid, pyruvic acid, 2-hydroxybutyric acid, and a small peak of 4-hydroxyphenyllactic acid.

The blood counts, including hemoglobin levels and white cell counts, were consistently normal, and the bone marrow aspirate demonstrated normal cellularity of erythroid, myeloid, and platelet precursors, with no evidence of ringed sideroblasts or abnormal vacuolated precursor cells. The clinical history and examination of stool for fat globules did not indicate the presence of pancreatic insufficiency. Blood folate, iron, liver function test, and alkaline phosphatase were normal.

In view of the possibility of a mitochondrial disease, a muscle biopsy was performed. Light microscopy of the muscle biopsy demonstrated ragged red fibers. Electron microscopy revealed muscle fibers with an increase of sub-sarcomemmal aggregates of mitochondria, demonstrating variation in size and abnormal

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Mitochondrial tubulopathy: the many faces of mitochondrial disorders

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cristae formation (Fig. 1a). Renal biopsy showed proximal tubular changes with small cells and nuclear crowding, and focal interstitial fibrosis. Electron microscopy revealed marked hyperplasia and crowding of the mitochondria, with hypertrophied, irregular mitochondria in the proximal tubular epithelial cells (Fig. 1b) and abnormal cristae formation (Fig. 1c).

To screen for potential mitochondrial mutations, total DNA was extracted from peripheral blood leukocytes, analyzed uncut, and following restriction endonuclease digestion with (1) BamHI and (2) BamHI and EcoRV. Southern blot analysis of the patient's sample compared with normal control revealed the presence of three mitochondrial DNA (mtDNA) species: the wild type mtDNA [16.6 kilobases (kb)], the mutant mtDNA with insertion-rearrangement (about 22 kb), and a deleted species (6 kb).

Discussion

We report a case of mitochondrial deletion-duplication syndrome with the first presentation of renal proximal tubulopathy and possible primary hypoparathyroidism, with lactic acidemia typical of a mitochondrial disorder. Our patient’s presentation was atypical, as it was predominantly renal tubular dysfunction and electrolyte imbalance. The pathological process was confirmed by histopathology and electron microscopy of muscle and renal tissues. Interestingly, genetic analysis of the peripheral blood demonstrated mitochondrial deletions and insertion-rearrangements.

However, it is important to note that the patient manifested growth retardation from 3 years of age, which is a frequent but non-specific early sign of a mitochondrial disorder. Common features of mitochondrialopathies were not present, such as ptosis, external ophthalmoplegia, night blindness, cardiac conduction defects, or cardiomyopathy. The lactate/pyruvate ratio was not elevated, and this may be due to normal mitochondrial activities of unaffected tissues, which normalize the ratio.

The commonest renal manifestation in mitochondrial disorder is proximal tubulopathy or Fanconi syndrome [2, 3, 4, 5, 6]. ATP drives the Na+-, K+-ATPase pump, which generates an electrical gradient across the proximal tubular epithelium and maintains a low sodium concentration in the tubular cell. This gradient drives the proximal tubule activities, as well as other cotransporter activities, such as sugar, phosphate, and amino acid reabsorption, and thus this process, which is highly dependent on energy, is most susceptible to mitochondrial dysfunction. Other reported renal diseases are focal segmental glomerulosclerosis and tubulointerstitial nephropathy. However, prominent extra-renal symptoms were almost always present in these reported cases, and it is extremely unusual to present with dominant renal manifestations.

Mitochondrial disorders represent a continuum of clinical entities, in which mtDNA mutations may cause a spectrum of diseases depending on the organs affected. It is becoming increasingly clear that mtDNA mutations can cause a strikingly diverse spectrum of diseases, and a high index of suspicion and astute awareness of the diversity of mitochondrial disorders are essential in order to consider the diagnosis.

While large-scale mtDNA deletions and rearrangements have been described in Kearns Sayre syndrome, progressive external ophthalmoplegia, and Pearson syndrome, [7, 8], our patient did not have clinical features of these conditions, which are defined by symptomatology without direct correlation to genotype. The phenotypic hallmarks of Kearns Sayre syndrome include external ophthalmoplegia, pigmentary retinopathy, and cardiac conduction block, while Pearson syndrome is generally defined by sideroblastic anemia and pancreatic insufficiency. As our patient lacked obvious neurological, marrow, and pancreatic exocrine dysfunction, it is thus inappropriate to classify our patient with as any of these classical mitochondrial syndromes, which are defined by symptomatology.

Known mtDNA mutations include deletions, insertion-rearrangements, and point mutations. Genotype-phenotype correlation is not always clear. A classical mitochondrial disorder syndrome (such as Pearson syndrome) may have several associated genotypes, and vice versa [9]. The reason for the poor genotype-phenotype correlation in mitochondrial disorders lies in the degree...