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Bone Deformities and Kidney Failure: Coincidence of *PHEX*-related Hypophosphatemic Rickets and m.3243A>G Mitochondrial Disease

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Abstract

X-linked hypophosphatemic rickets (XLH) and m.3243A>G mitochondrial disease share several clinical findings, including short stature, hearing impairment (HI), nephropathy, and hypertension. Here, we report on a case with the rare coincidence of these two genetic conditions. In early childhood, the patient presented with hypophosphatemia and bone deformities and was clinically diagnosed with XLH. This was genetically verified in adulthood with the identification of a de novo pathogenic deletion in phosphate-regulating endopeptidase homolog X-linked (*PHEX*). In addition, the patient developed HI and hypertension and when his mother was diagnosed with m.3243A>G, subsequent genetic testing confirmed the patient to carry the same variant. Over the next two decades, the patient developed progressive renal impairment however without nephrocalcinosis known to associate with XLH which could indicate an m.3243A>G-related kidney disease. Parallel with the progression of renal impairment, the patient developed hyperphosphatemia and secondary hyperparathyroidism. In conclusion, this case represents a complex clinical phenotype with the reversal of hypo- to hyperphosphatemia in XLH potentially mediated by the development of an m.3243A>G-associated nephropathy.

Keywords

m.3243A>G, *PHEX*, kidney disease, bone deformities, hypophosphataemic rickets

Statements and Declarations:

The authors have no relevant financial or non-financial interests to disclose.

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Background

X-linked hypophosphatemic rickets (XLH) and m.3243A>G mitochondrial disease represent two rare genetic diseases that exhibit individual phenotypes with some overlapping clinical findings. The XLH has a prevalence of 1.7–4.8 per 100,000 [1–3] and is caused by X-linked dominant inherited or de novo pathogenic genetic variants in phosphate-regulating endopeptidase homolog X-linked (*PHEX*) [MIM: 300550]. The kidney's ability to reabsorb phosphate is impaired which relates to overexpression of fibroblast growth factor 23 [4]. As a result, patients have low plasma (p)-phosphate and impaired bone mineralization with skeletal abnormalities, including bowed legs, growth failure, osteomalacia, bone pain and short stature [5].

The m.3243A>G, tRNA-leu(UUR) [MIM: 590050], the most common pathogenic mitochondrial variant, has a prevalence of 0.14–0.24% [6, 7]. Clinical presentations include mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), maternally inherited diabetes and deafness (MIDD), in addition to fatigue, ataxia, migraine, hypertrophic cardiomyopathy, short stature, and nephropathy [8]. Uniquely, pathogenic m.3243A>G co-exist with wildtype (normal) referred to as heteroplasmy. Levels of heteroplasmy vary between tissues and correlate positively with disease severity [9].

Case Presentation

The index patient, a 40-year-old man, was born after an uneventful pregnancy by cesarean section as the first child of Caucasian non-consanguineous parents. At the age of 2 years, he presented with bowed legs (Fig. 1a), elevated p-alkaline phosphatase (ALP) of 800–900 U/L (130–385 U/L), and low p-phosphate of 0.76 mmol/L (1.16–1.81 mmol/L) compatible with hypophosphatemic rickets. Treatment with oral phosphate mixture and alfacalcidol were initiated. At the age of 8 years, he underwent a bilateral correcting femoral osteotomy. At 11 years old he developed bilateral sensorineural hearing impairment (HI). The following year, he was diagnosed with hypertension in the presence of normal kidney function. Throughout childhood, he presented with growth retardation three standard deviations below normal reference intervals (Fig. 1b). Initial complaints of fatigue were reported at the age of 18 years (Table 1).

Three years later, his mother presented clinical symptoms suggestive of the MELAS syndrome and genetic testing identified the m.3243A>G variant. The patient was subsequently diagnosed with the same mitochondrial genetic variant with high levels of heteroplasmy in muscle, blood, urine, and buccal mucosa 90%, 57%, 83%, and 65%, respectively. A skeletal muscle biopsy demonstrated cytochrome oxidase-negative fibers with ragged red fibers. Additional genetic screening identified a deletion in *PHEX*: NC_000023.11(NM_000444.6):c.(1079+1_1080-1)_1302+1_1303-1)del; p.?, including exon 10 and 11. A similar variant has previously been reported and thereby genetically verifying the diagnosis XLH [10]. During the next 10 years, compliance to treatment including ingestion of phosphate supplements and follow-up with clinical and laboratory monitoring was poor. At the age of 32 years, he resumed outpatient visits and both XLH and m.3243A>Gassociated diseases showed significant progression. In addition, he developed frequent migraines and musculoskeletal pain from his lower back and trunk, symptoms that may relate to both XLH and m.3243A>G, respectively. The biochemistry showed low p-phosphate (Fig. 2a), hypocalcemia, (Fig. 2b) and p-25-hydroxy-vitamin D below the detection limit while p-ALP was elevated (292 U/L) (35–105 U/L). Phosphate mixture, alfacalcidol and antihypertensive treatment were reintroduced, however, shortly after he discontinued phosphate treatment due to the development of side effects in particular diarrhea. Otherwise, regular measurements of p-25-

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hydroxy-vitamin D remained above 50 mmol/L (Fig. 2c). Oral magnesium and calcium supplements were introduced as he presented with hypocalcemia (Fig. 2b) and mild hypomagnesemia (Fig. 2d). Concurrently at the age 32 of years, he was diagnosed with hyperparathyroidism [p-parathyroid hormone (PTH) 40.3 pmol/L (2–8.5 pmol/L)], kidney disease [p-creatinine 121 µmol/l (60–105 µmol/l)], and hypertrophic cardiomyopathy initially classified as moderate hypertrophy with normal ejection fraction (EF).

At age 34 years he developed hypercalcemia (Fig. 2.b) and treatment with calcium and magnesium was discontinued subsequently. The same year, he developed proteinuria [1.34 g/day (< 0.15 g/day)] and estimated glomerular filtration rate/1.73 m2 was 62 mL/min (> 60 ml/min), with a subsequent increase in p-creatinine (Fig. 2e). Abdominal ultrasound and CT scan showed small kidneys—longitudinal length of 7.4 and 9.0 cm, respectively—with narrow cortices, compatible with chronic kidney disease. At age 35 years, the left ventricular hypertrophia had progressed (two cm) with EF 40–50%. Periods with increasing bone pain, muscle stiffness, and cramps were reported from the age of 36 years. Bone scintigraphy showed dextro-convex lumbar scoliosis (Fig. 1c), while Dual-Energy X-ray absorptiometry displayed osteopenia in the hip with a reduction in *T*-score in the left hip of 0.6 to − 1.4 standard deviations since age 21 years. There was a short final statural height of 155 cm and bowed legs (Fig. 1d).

As the kidney disease progressed with the development of acidosis and hyperkalemia, the p-phosphate level normalized and p-PTH increased (Fig. 2a, e, f). Parathyroid scintigraphy did not identify adenomas.

Diabetes is a frequent finding in m.3243A>G; however, at age 39 years HbA1C remained within the normal range.

Discussion

Individually, XLH and m.3243A>G associate with the risk for the development of kidney disease; however, the coincidence of these conditions has to the best of our knowledge not previously been reported.

Our patient developed severe nephropathy. Treatment of XLH with phosphate and vitamin D supplements may increase the risk for the development of nephrocalcinosis [11] and although end-stage renal disease is a rare complication, chronic kidney disease is reported in approximately 9% of XLH [12, 13]. P-phosphate levels remained low until he developed impaired renal function (Fig. 2a, e). The apparent normalization of phosphate levels may therefore represent a pseudo-normalization secondary to impaired kidney function. Proteinuria and kidney disease are reported in patients with m.3243A>G [14], and kidney biopsy typically reveals focal segmental glomerulosclerosis [15]. Additionally, the hypomagnesemia and hypophosphatemia observed in this patient (Fig. 2a, d) may also relate to m.3243A>G [16], although the mechanisms are currently unknown. Collectively, renal impairment without signs of XLH-associated macroscopic nephrocalcinosis could suggest the kidney dysfunction primarily results from m.3243A>G disease in combination with hypertension for almost three decades.

Calcium homeostasis is tightly regulated by the kidneys, parathyroid glands, intestines, and bone and more factors may contribute to the dysregulation observed in this patient. First, chronic kidney disease with phosphate retention and lower levels of active vitamin D cause hypocalcemia with stimulation of PTH secretion. This is in accordance with the biochemical findings at the age of 32 years supported by a positive association between levels of p-PTH and p-creatinine (Fig. 2e, f). Second, XLH is not associated with hypocalcemia and treatment with active vitamin D is administered to increase intestinal absorption of phosphate, while phosphate supplement replaces renal loss. Reintroducing alfacalcidol and calcium treatment normalized the serum calcium levels in the patient despite the kidney function further declining and the development of secondary hyperparathyroidism (Fig. 2f). Third, hyperparathyroidism

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is described in up to 80% of XLH patients which appears to be related to treatment with phosphate supplements [13]. Fourth, mitochondria contribute to the regulation of intracellular calcium homeostasis and in addition, a fraction of m.3243A>G patients develop basal ganglia calcification indicating an underlying calcium imbalance [17, 18]. Together, the mitochondrial dysfunction may contribute to the altered calcium levels observed in the patient. In the present case, progressive renal impairment is likely a driving force of hyperparathyroidism.

In adulthood, the patient's skeletal symptoms progressed with elevated p-ALP, a biomarker of osteomalacia [19] and a decline in hip bone mineral density. Patients with XLH often complain of joint pains [5], especially during treatment interruptions [12]. Subjects with XLH are generally not reported to have bone loss and here the decreased bone density is most likely explained by hyperparathyroidism. Moreover, the short stature may result from the combination of m.3243A>G-associated low height [8] and bowed legs related to XLH [5]. Taken together, XLH-induced osteomalacia, secondary hyperparathyroidism, and low compliance to treatments could all contribute to the skeletal symptoms.

In conclusion, the coincidence of two rare genetic diseases XLH and m.3243A>G demonstrated the complex clinical phenotype with osteomalacia, impaired calcium metabolism, and hypophosphatemia inverted to hyperphosphatemia related to the progression of a likely m.3243A>Gassociated nephropathy.

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Authors' contributions

Data collection and analysis were performed by Simone Rask Nielsen. The first draft of the manuscript was written by Simone Rask Nielsen and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent for publication

The patient gave written informed consent for the publication of this article.

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Table 1 Timeline table with the age of onset of symptoms and if the symptom is related to X-linked hypophosphatemic rickets (XLH) or m.3243A>G where + or - indicates if the symptom is related to or not, respectively.

Diagnosis or symptom	**Age (years)**	**XLH**	**m.3243A>G**
Hypophosphatemia and bowed legs	2	+	-
Growth retardation	2	+	+
Femoral deformities corrected with bilateral osteotomy	8	+	-
Bilateral sensorineural hearing impairment[a]	11	+	+
Hypertension[a]	12	+	+
Fatigue	18	+	+
Migraines	21	+	+
Hyperparathyroidism	32	+	-
Hypertrophic cardiomyopathy	32	-	+
Kidney disease[b]	32	-	+

a Hearing impairment and hypertension are observed in patients with XLH as well as with m.3243A>G mitochondrial disease [8, 20–22]
b Kidney disease does not associate directly with XLH but is more likely secondary to its treatment [11]

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Figure Captions

Fig. 1 a) Patient at age 2 years illustrative of bowed legs. **b** Growth chart of the patient's height from age two to age 20 years, and x's illustrate the patient's height. The black-curved line is the mean (M) for Danish boys aged 0–20 years [23], and additional curved lines display 1, 2, and 3 standard deviations (SD) above and below the mean, respectively. **c** Bone scintigraphy at age 36 years illustrative of scoliosis, lower limb bone deformities, and suggestive of bone degeneration. **d** Patient at age 39 years illustrative of lower limb bone deformities

Fig. 2 Horizontal lines indicate normal adult reference intervals (> 20 years). Association between: **a** plasma (p)-phosphate and age (the few elevated values of p-phosphate indicate a recent intake of phosphate supplements prior to blood sampling). **b** p-calcium and age. **c** p-25-hydroxy-vitamin D and age. **d** p-magnesium and age. **e** p-creatinine and age. **f** p-parathyroid hormone and age

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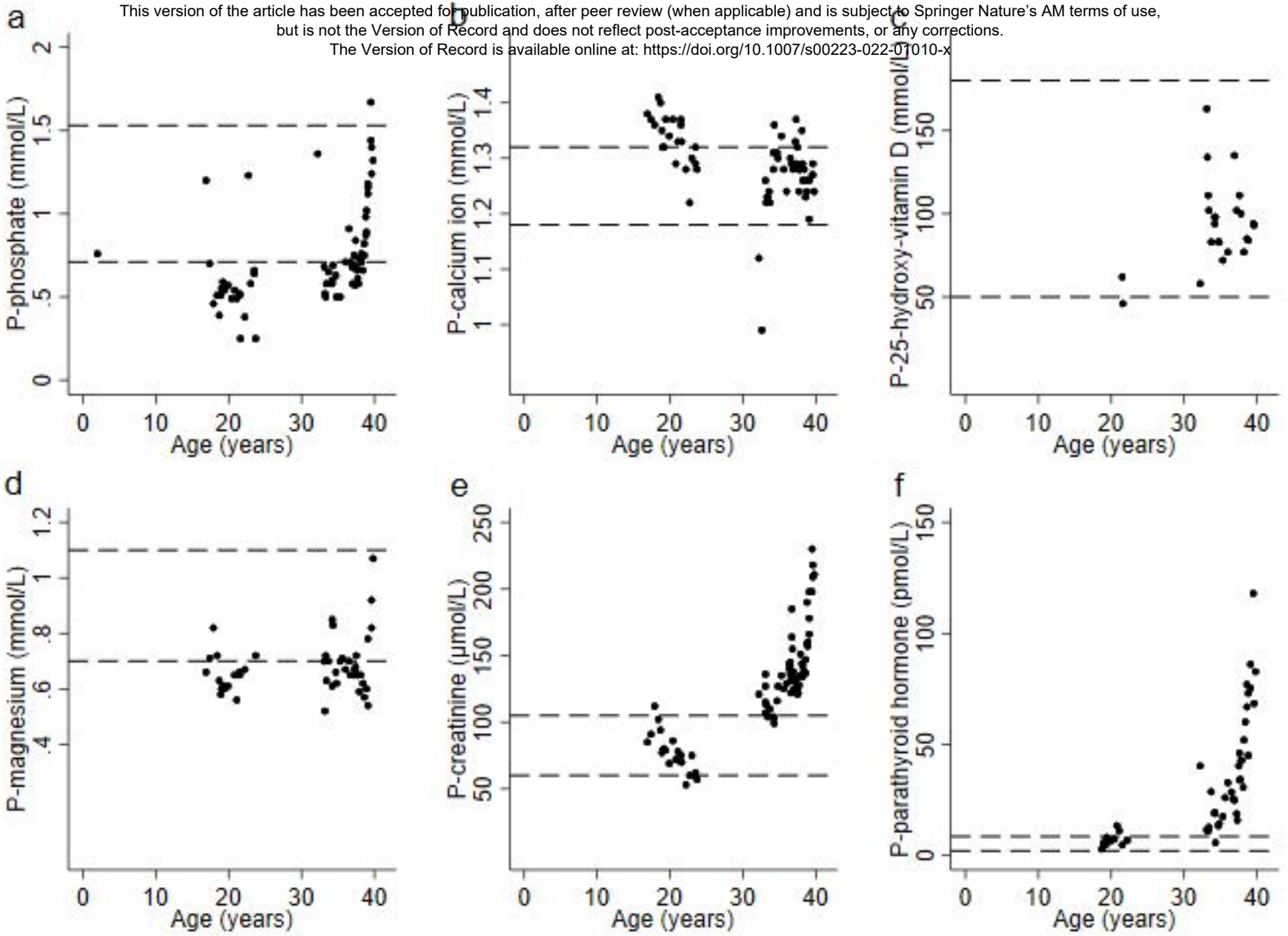

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