CASE REPORT

Sideroblastic anaemia and primary adrenal insufficiency due to a mitochondrial respiratory chain disorder in the absence of mtDNA deletion

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SUMMARY

A fatigued 8-year-old boy was found to have sideroblastic anaemia (haemoglobin 7.8 g/dL) which over time became transfusion dependent. Subtle neurological dysfunction, initially manifesting as mild spastic diplegia, was slowly progressive and ultimately led to wheelchair dependence. Elevated plasma lactate and urinary 3-methylglutaconate led to a muscle biopsy which confirmed partial complex IV deficiency. PCR in leucocytes and muscle was negative for mitochondrial DNA (mtDNA) deletions. Faltering growth prompted an insulin tolerance test which confirmed growth hormone sufficiency and adrenal insufficiency. Plasma renin was elevated and adrenal androgens were low, suggesting primary adrenal insufficiency. Glucocorticoid and mineralocorticoid replacement therapy was initiated. A renal tubular Fanconi syndrome and diabetes mellitus developed subsequently. Sideroblastic anaemia and primary adrenal insufficiency, both individually and collectively, are associated with mtDNA deletion; however, absence of the same does not exclude the possibility that sideroblastic anaemia and primary adrenal insufficiency are of mitochondrial origin.

BACKGROUND

Mitochondrial cytopathies are a heterogeneous group of disorders caused by mutations of nuclear or mitochondrial DNA (mtDNA) and may affect multiple organ systems. Some discrete clinical syndromes exist but there is also considerable phenotypic variability.

Sideroblastic anaemia (SA) is a recognised manifestation of mitochondrial dysfunction. The classic mitochondrial phenotype associated with SA is the Pearson marrow-pancreas syndrome (PMPS). PMPS occurs due to deletions of mtDNA,¹ and affected patients present in infancy, typically with failure to thrive, malabsorption and anaemia. Sporadic SA cases have been documented in other mitochondrial disorders including the Kearns-Sayre syndrome (KSS) and Wolfram syndrome.^{2–4}

Primary adrenal insufficiency of mitochondrial origin is rare (table 1),^{5–12} and the majority of patients harbour substantial mtDNA deletions.^{6–11} Occurrence of primary adrenal insufficiency and SA of mitochondrial origin in the same patient has been reported only once previously in a patient with PMPS.¹⁰

CASE PRESENTATION

An 8-year-old boy was referred for evaluation of fatigue. He was born at term weighing 4 kg to

non-consanguineous parents and attained normal early developmental milestones. Height and weight were on the 10th and 50th centiles, respectively. Preliminary examination was remarkable only for hepatomegaly extending 3.5 cm below the right costal margin.

Initial laboratory evaluation revealed normochromic normocytic anaemia (haemoglobin 7.8 g/dL (11.5–16), mean corpuscular volume (MCV) 85.8 fL (75–87) and mean corpuscular haemoglobin (MCH) 25.4 pg (25–35)) with marked anisocytosis (red-cell distribution width (RDW) 29% (11–14.5)). Hypochromia and teardrops were evident on a blood film. Leucopenia was also a feature (white cell count $2.9 \times 10^9/L$ (4.5–13.5), neutrophils $1.7 \times 10^9/L$ (2–7.5) and lymphocytes $0.8 \times 10^9/L$ (1.5–4)).

A bone marrow aspirate and biopsy revealed a hypercellular marrow with erythroid hyperplasia. An iron stain revealed that approximately 50% of erythroblasts were ringed sideroblasts. Marrow cytogenetics were normal including fluorescence in situ hybridisation studies of chromosomes 5q, 7 and 8 and flow cytometry did not detect a blast population. Serum copper and lead were normal, as were blood smears on the proband's parents and sister. Analysis of several genes responsible for hereditary SA (*ALAS2*, *ABC7*, *FECH* and *PUS1*) revealed no reported pathogenic variants.

Fasting lactate was elevated at 3.8 mmol/L. Neurological examination identified upper motor neuron signs in the lower limbs bilaterally; however, cerebellar signs were negative. MRI of the brain demonstrated volume loss with slight prominence of the cerebellar folia. Urine organic acids revealed elevated 3-methylglutaconate and 3-methylglutarate. The lactate:pyruvate ratio was elevated (30:1). Muscle biopsy revealed a structurally normal muscle and biochemical assay of respiratory chain components resulted in a diagnosis of partial complex IV deficiency. He subsequently commenced a high-fat diet and coenzyme Q with a resultant improvement in energy. Analysis of mtDNA in leucocytes and muscle utilising PCR did not reveal a deletion. Carnitine, vitamin A, thiamine, pyridoxine, folate and uridine were supplemented without improvement in his anaemia. Haemoglobin levels fell to 4.4 g/dL, leading to occasional and then regular three-weekly red cell transfusions. With repeated transfusions, ferritin rose to 1700 µg/L, necessitating iron chelation.

Peak growth hormone and cortisol to insulin-induced hypoglycaemia were 30.9 mU/L (normal

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Table 1 Previous reports of patients with primary adrenal insufficiency in the context of a mitochondrial disorder

Reference	Age	Diagnosis	Mutation	Respiratory chain	GC deficiency	MC deficiency	Associated features
5	Neo	Unspecified	Nil	Complex I and IV deficiency	++	—	Lipid storage myopathy and cataracts
6	4	Unspecified	7.4 kb deletion mtDNA	Normal	++	++	Sensorineural deafness, ataxia, short stature, hypoparathyroidism
7	5	Unspecified	7 kb deletion mtDNA	Complex I and IV deficiency	++	++	Multiple endocrinopathies
8	5	KSS	4.9 kb deletion mtDNA	—	++	—	Chronic mucocutaneous candidiasis
9	5	KSS	9 kb deletion mtDNA	Not reported	++	++	Hypoparathyroidism, myopathy, renal tubulopathy
10	4	PMPs	5.1 kb deletion mtDNA		++	++	Sideroblastic anaemia, leucopenia, thrombocytopaenia
11	3	Unspecified	7.3 kb deletion mtDNA	Not reported	++	++	Congenital glaucoma, chronic pancreatitis, myopathy
12	5	MELAS	m.8344A>G mutation in tRNA	NA	++	—	Seizures

GC, glucocorticoid; KSS, Kearns-Sayre syndrome; MC, mineralocorticoid; MELAS, mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes; mtDNA, mitochondrial DNA; NA, not applicable; PMPs, Pearson marrow-pancreas syndrome.

>20) and 447 nmol/L (normal >500), respectively, at age 13 years. Thyroid function was normal. Repeat peak cortisol was 384 nmol/L following adrenocorticotrophic hormone (ACTH) stimulation. Plasma renin activity was elevated to 15 ng/mL/h, and adrenal androgens were below the lower limit of assay detection. A urinary steroid profile was qualitatively normal, as was an abdominal ultrasound. Hydrocortisone 5 mg twice daily and fludrocortisone 100 µg daily were initiated. Adrenal autoantibodies to 21-hydroxylase were negative and very-long-chain fatty acids were normal.

The patient has recently developed a renal tubular Fanconi syndrome including glycosuria, hypokalaemia, hypophosphataemia with low maximal tubular reabsorption of phosphate and a generalised aminoaciduria. In addition, he was incidentally noted to have hyperglycaemia during an admission for percutaneous endoscopic gastrostomy insertion. Glycated haemoglobin was elevated to 62 mmol/mol (7.8%) despite rapid red cell turnover. Pancreatic autoantibodies were negative (glutamic acid decarboxylase, anti-insulin, anti-islet antigen 2 and pancreatic islet cell antibodies). He is maintained on twice daily insulin detemir with satisfactory glycaemic control with fructosamine 161 µmol/L (205–285).

DIFFERENTIAL DIAGNOSIS

The final step in haeme synthesis requires the incorporation of ferrous (Fe^{2+}) iron into protoporphyrin IX by ferrochelatase. Inability to incorporate iron may be a result of the failure of the mitochondrial respiratory chain to reduce Fe^{3+} to Fe^{2+} . Accordingly, heteroplasmic mutations in mtDNA affecting cytochrome c oxidase (complex IV) have been reported to cause SA in two adults.¹³ Two copper molecules are essential for normal function of complex IV. Haematological manifestations of copper deficiency include SA and leucopenia as in our case;¹⁴ however, serum copper was normal.

We outruled other potential hereditary causes of SA. X linked SA (XLSA) universally causes a microcytic anaemia and the *ALAS2* gene is expressed only in erythroid cells.¹⁵ In XLSA with ataxia due to *ABC7* mutations, cerebellar hypoplasia with ataxia is usually the dominant sign. It often presents in infancy with significantly delayed motor milestones.^{16 17} This patient had long tract signs and prominence of the cerebellar folia but no cerebellar signs.¹⁶ The anaemia may be microcytic or

normocytic but is typically mild and does not require transfusion.¹⁸ In MLASA (Mitochondrial myopathy, Lactic Acidosis, Sideroblastic Anaemia) due to *PUS1* mutations, macrocytosis is typical and leucopenia is not a characteristic.^{19 20}

PMPs is the combination of bone marrow failure, SA, lactic acidosis and failure to thrive with chronic diarrhoea due to exocrine pancreatic insufficiency, although pancreatic insufficiency may be absent. Macrocytosis is usual and marrow precursors have characteristic vacuolisation. No large mtDNA deletion was identified in our patient, however. Hypoadosteronism has been described in one patient with PMPs, and recently the first case of primary adrenal insufficiency has been documented.^{10 21}

DISCUSSION

Despite no mutation being detected in mtDNA, SA, adrenal insufficiency, diabetes mellitus and renal tubulopathy were part of a mitochondrial disorder in this case.

Adrenal insufficiency in our patient was not due to autoimmunity, adrenoleucodystrophy, congenital adrenal hyperplasia, familial glucocorticoid deficiency or other identifiable causes. Primary adrenal insufficiency is a rare feature of mitochondrial dysfunction and virtually all reported cases have large mtDNA deletions (table 1). In fact, combined glucocorticoid and mineralocorticoid deficiency has not been described previously in mitochondrial disease in the absence of mtDNA deletion. Three steps in adrenal steroid biosynthesis occur on the inner mitochondrial membrane: the conversion of deoxycorticosterone and deoxycortisol to corticosterone and cortisol, respectively, by CYP11B1 and the conversion of the former to aldosterone by aldosterone synthase (CYP11B2) in addition to the rate-limiting step, the conversion of cholesterol to pregnenolone by cytochrome P450SCC. Also, in this case, as previously, there was no evidence of lipid adrenal hyperplasia, suggesting that the trophic effects of ACTH are also affected by mitochondrial dysfunction.⁵

Diabetes mellitus is also a known complication of mitochondrial disease, often associated with sensorineural deafness due to a single point mutation in mtDNA (maternally inherited diabetes and deafness).²² A number of cases have been described in association with other mtDNA deletions in the Pearson syndrome, KSS and Wolfram syndrome.^{10 23 24}

Learning points

- ▶ Primary adrenal insufficiency and sideroblastic anaemia are recognised manifestations of mitochondrial dysfunction.
- ▶ Individually, they are usually associated with a large deletion in mitochondrial DNA and have only been reported to occur together once previously.
- ▶ Sideroblastic anaemia and primary adrenal insufficiency can be a manifestation of mitochondrial dysfunction in the absence of mtDNA deletion as in this case.

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Contributors MJO wrote the manuscript draft and approved the submitted version. MC, AAM and NPM edited the draft to reflect their subspecialty expertise and approved the final version.

Competing interests None.

Patient consent Obtained.

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