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Congenital Hypoplastic Anemia, Diabetes, and Severe Renal Tubular Dysfunction Associated with a Mitochondrial DNA Deletion

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ABSTRACT. Mitochondrial DNA (mtDNA) deletion is associated with a variety of clinical entities. In addition to progressive external ophthalmoplegia and Kearns-Sayre syndrome, mtDNA deletions have been demonstrated in Pearson's syndrome. We report an mtDNA deletion in an infant with a variant of Pearson's syndrome. Not only does she have congenital anemia, severe tubulopathy, and exocrine pancreas insufficiency, but she also has diabetes and cerebral atrophy. However, there are no signs of gut or liver involvement. Bone marrow improved while new tissues were involved, thus showing variability in progression of the disease. Decreased respiratory chain enzyme activities were demonstrated in muscle, and an mtDNA deletion was demonstrated in muscle, kidney, leukocytes, and fibroblasts. (*Pediatr Res* 30: 327–330, 1991)

Abbreviations

cyt c, cytochrome c
KSS, Kearns-Sayre syndrome
mtDNA, mitochondrial DNA
PCR, polymerase chain reaction

Mitochondrial dysfunction has been described in a heterogeneous group of clinical entities varying from benign ocular myopathy to fatal encephalomyopathy and multisystem disorders of organs with a high energy demand. Typically, "ragged-red-fibers" are found in modified Gomori-trichrome stained muscle biopsies and abnormal mitochondria in electron microscopy of affected tissues. Defects are demonstrated in several biochemical pathways of energy production, most frequently in the mitochondrial respiratory chain enzymes, which are encoded both by nuclear and mitochondrial genes. A large deletion of human mtDNA in patients with mitochondrial myopathies was first described by Holt *et al.* (1). This has led to new possibilities in diagnosing and classifying mitochondrial diseases. Deletions have been found in patients with progressive external ophthalmoplegia (2) and KSS (3, 4). In addition to these clinical entities, deletions have been reported in one patient with pancytopenia (5) and in Pearson's syndrome (6, 7). We now report a 2-yr-old child with severe renal tubular dysfunction, pancreatic insufficiency, diabetes, cerebral atrophy, and recovery from congenital hypoplastic anemia (a multisystem disease with an mtDNA deletion).

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CASE REPORT

This 28-mo-old girl is the first child of healthy, nonrelated parents. The pregnancy was uneventful except for a mild polyhydramnios. She was born after 38 wk of gestation with a weight of 2400 g and a macrocytic, normochromic anemia, a low reticulocyte count, and considerable aniso- and poikilocytosis. Her lowest Hb level was 56 g/L, reticulocytes 0.5%, leucocytes 4.6×10^9/L (11% granulocytes), and thrombocytes 73×10^9/L, respectively. The bone marrow was hypoplastic, but without signs of dyserythropoiesis or malignancy. Screening for intrauterine infections was negative. Ringed sideroblasts and vacuolization of myeloid precursors were seen in the bone marrow.

At 2 mo, oral prednisolone (2 mg/kg/d) was started. It was discontinued after 12 d when the child developed diabetes mellitus, which was treated with insulin for 3 wk. Anemia with reticulocytopenia, granulocytopenia, and thrombocytopenia persisted, and at 3.5 mo cyclosporin was started (10–30 mg/kg/d). Blood specific cyclosporin concentration was 115–290 μg/L (Cyclotrac; Ingstar, Stillwater, MO). Signs of bone marrow recovery were seen at 7.5 mo. At 10 mo, diabetes mellitus redeveloped and cyclosporin was discontinued.

Up to the age of 1.2 yr, her height was 3 SD below the mean, then her growth ceased. Her peak weight was 30% above the mean at 6 mo but decreased to 35% below the mean by 2 yr.

At 17 mo, polyuria (14 mL/kg/h) was noticed. There was a metabolic acidosis (arterial blood pH 7.15, base excess −19.4 mmol/L, standard bicarbonate 9.5 mmol/L, urine pH 5.0), hypophosphatemia (0.3 mmol/L), hypocalcemia (1.6 mmol/L), hypomagnesemia (0.5 mmol/L), hyponatremia (124 mmol/L), hypokalemia (2.5 mmol/L), glucosuria, and a generalized aminoaciduria with normal plasma amino acids. The polyuria was unresponsive to desmopressin. Alkali, phosphate, dihydrotachysterol, calcium, and magnesium supplementation were started.

On admission to our institution at 20 mo, she was hypotonic with delayed motor development, but without ataxia. She had lost her ability to walk but was able to sit and stand unsupported. The tendon reflexes as well as cranial nerve functions were normal. Her hearing was normal and she could speak a few words. Although easily fatigued, she was mentally alert. Electroencephalography showed mild general background slowing, and a cranial computed tomography scan showed marked cerebral atrophy. There were no signs of polyneuropathy on electroneuromyography and the ophthalmologic examination was normal. Blood lactate was 4.5 mmol/L (normal value < 1.6 mmol/L) and pyruvate was 100 μmol/L (normal value < 68 μmol/L) (lactate:pyruvate 44). Cerebrospinal fluid lactate was 6.6 mmol/

L (normal value < 2.7 mmol/L) and cerebrospinal fluid protein concentration was 465 mg/L (normal value < 400 mg/L).

There was a macrocytic, normochromic anemia with a positive erythrocyte i-antigen. Reticulocytes were 1.4–4.0% and fetal Hb 16%, and thrombocytes and leucocytes were normal. The bone marrow was normocellular with a striking vacuolization of nonerythroid precursors.

Liver function tests, ultrasound examination of the liver, chest x-ray and echocardiography were normal. However, the levels of C-peptide and pancreatic amylase in the serum were immeasurable, and stool fat excretion was increased.

The kidneys were enlarged, with increased echodensity on ultrasound examination. Blood pressure was 97–158/60–103 mm Hg, serum creatinine, 34–64 μmol/L, and glomerular filtration rate, 37 mL/min/1.73 m^2. The urinary volume was 11–16 mL/kg/h, with proteinuria, glucosuria, and generalized aminoaciduria but no hematuria. Fractional excretion of sodium and phosphate increased to 0.03 and 1.5, respectively. Urinary phosphate excretion and phosphate clearance were high (64 μmol/min/1.73 m^2 and 103 mL/min/1.73 m^2, respectively). Blood standard bicarbonate was 9–17 mmol/L with a urinary pH of 5.0–8.5.

Potassium, calcium, magnesium, phosphate, bicarbonate (30 mmol/kg/d), dihydrotachysterol, and carnitine supplementation normalized her respective serum concentrations except serum bicarbonate (10–16 mmol/L). Insulin and pancreatic enzyme supplementation were used. After exclusion of more common causes of severe renal tubular dysfunction, a respiratory chain defect was suspected.

At 34 mo, the patient remains an outpatient with nearly normal blood count (Hb 116 g/L, fetal-Hb 4.6%, mean corpuscular volume 95 fL, and thrombocytes 434 × 10^9/L), normal electrolytes, serum bicarbonate 10–18 mmol/L, blood lactate 2.6 mmol/L, and pyruvate 148 μmol/L, an immeasurable level of serum C-peptide, normal serum phosphate, and generalized aminoaciduria. Treatment with indomethacin (3 mg/kg/d) reduced her diuresis from 12 mL/kg/h to 5–6 mL/kg/h and normalized her serum phosphate transiently. Presumably because of her malnutrition and hypoproteinemia, this resulted in edema. The medication had to be discontinued because of intestinal bleeding. Subsequently, her urinary volume has normalized. She has not grown and has severe muscle wasting, but is mentally alert. Renal transplantation was discussed but rejected because of her poor general condition and the multisystemic nature of her disease. Her renal dysfunction has not progressed recently.

MATERIALS AND METHODS

A kidney biopsy specimen was fixed for light and electron microscopy in phosphate-buffered 10% formalin and phosphate-buffered 2.5% glutaraldehyde, respectively. The paraffin-embedded sample was stained with hematoxylin-eosin, modified Masson-Trichrome, van Gieson, and periodic acid-Schiff. For electron microscopy, the sample was postfixed with 1% osmium tetroxide and stained with uranyl acetate and lead citrate. For immunofluorescence, the sample was frozen in liquid nitrogen, cut at 7 μm, and stained by antibodies against immunoglobulins, complement factor 3, complement factor 1q, and fibrin.

Oxygen consumption of isolated muscle mitochondria was measured polarographically (8, 9). The activities of respiratory chain enzymes [rotenone-sensitive NADH coenzyme Q reductase (10), rotenone-sensitive NADH cyt c reductase (11), antimycin A-sensitive succinate cyt c reductase (12), cyanide sensitive ferrocytochrome c oxidase (13) and citrate synthase (14)] were assayed spectrophotometrically from a sonicated mitochondrial preparation, as previously described (10–14). As controls, we used diagnostic muscle biopsies showing no morphologic abnormalities from patients who were eventually considered unaffected by muscle diseases.

A culture of fibroblasts was established from a skin biopsy. Cells were harvested for the isolation of total DNA after six passages.

Total DNA was prepared from 40 mg of a muscle biopsy sample, from leukocytes and cultured fibroblasts as previously described (15). After the histologic analysis, the remaining kidney needle biopsy sample was incubated in proteinase K and directly subjected to PCR. Primers and conditions will be described ahead. Ten micrograms of DNA were digested with restriction enzyme *Pvu*II, electrophoresed through 0.6% agarose gel, and transferred to nylon filters (Hybond-N, Amersham, Buckinghamshire, UK), according to Southern (16). Hybridization was carried out with the probe (total mouse mtDNA, courtesy of Dr. Per Sunnerhagen, University of Gothenburg, Sweden) labeled with ^{32}P to a sp act of 10^9 dpm/μg using primer extension reaction (17) (Random primer DNA labeling kit; Boehringer Mannheim, Germany) followed by overnight exposure to Kodak X-Omat AR film a −70°C. Further analysis was carried out by hybridizing the filters with short cloned fragments of human mtDNA provided by Dr. Nils-Göran Larsson (University of Gothenburg, Sweden). The probes covered the regions of mtDNA map positions (18) 8.287 to 8.587 (K10) and 8.729 to 10.254 (K12). After the approximate localization of the deletion, specific oligonucleotide primers were synthesized to flank the suspected deletion breakpoints so that they contained the restriction sites of restriction endonucleases *Xba*I (map location 8.289) and *Taq*I (map location 14.967). PCR was carried out with 100 ng of template DNA and two units of Taq-polymerase (Perkin-Elmer Cetus, Norwalk, CT), using 25 cycles of 94°C for 1 min, 55°C for 2 min, and 72°C for 2 min on an automated thermal cycler (Perkin-Elmer Cetus).

RESULTS

The renal biopsy showed tubular dilation in conjunction with degenerative changes in the tubular epithelium but not immunofluorescence for immunoglobulins, complement factor 3, complement factor 1q, or fibrin. Electron microscopy revealed enlarged mitochondria (Fig. 1).

Biochemical analysis of muscle mitochondria showed a general respiratory chain defect (Table 1). Oxygen consumption was decreased with all tested substrates, suggesting cyt c oxidase deficiency. No respiratory control was observed. Of the respiratory chain enzymes, complex I was most severely affected (25–37% of control values), and the others were 50–70% of control.

Genomic Southern blot analyses demonstrated two different populations of mtDNA in muscle, leukocytes, and fibroblasts (Fig. 2). The hybridizing band of 16.5 kb corresponded to the normal-sized mtDNA and that of approximately 10.5 kb corresponded to the deleted population of mtDNA. In muscle, the

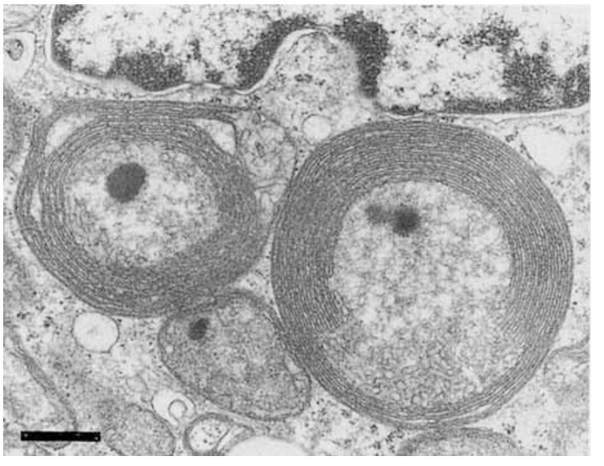

Fig. 1. Electron microscopy. Giant mitochondria in proximal tubules of the kidney biopsy. Magnification ×15 000, bar = 500 nm.

Table 1. *Enzyme activities in isolated muscle mitochondria*

	Patient	Controls*
Polarographic activities†		
RCR	1.0	3.5 ± 1.8 (26)
Pyruvate + malate	11.9	60 ± 24 (21)
Succinate + rotenone	12.5	65 ± 24 (26)
Ascorbate + TMPD	122.6	338 ± 140 (27)
Spectrophotometric activities‡		
Citrate synthase	504.2	836 ± 270 (31)
NADH:DB reductase	32.1	86 ± 27 (21)
NADH:cyt c reductase	76.2	299 ± 93 (23)
Succinate:cyt c reductase	108.9	225 ± 69 (27)
Cyto c oxidase		
50 μM ferrocyt c	574.6	1149 ± 286 (31)
100 μM ferrocyt c	1061.7	1547 ± 479 (36)

* Control values are mean ± SD; number of controls in parentheses.

† Polarographic activities correspond to oxygen consumption (nmol O/min/mg mitochondrial protein). RCR, respiratory control ratio: TMPD, tetramethyl-*p*-phenylenediamine.

‡ Spectrophotometric activities correspond to cyto c reduced or oxidized, *n*-decyl coenzyme Q (DB) reduced and citrate formed, expressed as nmol/min mg mitochondrial protein.

deleted population corresponded to 80% of total mtDNA estimated from densitometry of autoradiography, in leukocytes 75%, and in fibroblasts 35%, respectively. In the further hybridizations, the deletion population hybridized with the probe K10, but not with K12, indicating the upstream deletion breakpoint to be between the map positions 8.300 and 8.800. The PCR reaction product of 1.070 kb localized the other breakpoint between 13.900 and 14.300, corresponding to a deletion of approximately 5.7 kb. Because of the small size of the kidney biopsy available, PCR reaction with overall described primers was used, and the deletion was confirmed to exist also in kidney. The deleted region contained genes encoding subunit 6 of ATPase, subunit 3 of cyt c oxidase, and subunits 3, 4, 4L, and 5 of NADH-dehydrogenase complex, as well as five transfer RNA genes.

DISCUSSION

The infant described here presents a mtDNA deletion with a progressive clinical involvement, first affecting bone marrow, then pancreas, cerebrum, and kidneys. With this combination of organs involved, she most likely belongs to the group of Pearson's marrow-pancreas syndrome, which has recently been included in the mitochondrial disorders because of demonstrating mutations in mtDNA (6, 7).

In contrast to reported cases of Pearson's syndrome, our patient does not have any signs of liver or gut involvement. Furthermore, she shows spontaneous bone marrow recovery from congenital hypoplastic anemia. Her predominant symptom is severe renal tubular dysfunction, which has previously been associated with other mitochondrial disorders like Leigh syndrome (19), mitochondrial myopathy (20–22), KSS (23, 24), and also Pearson's syndrome (7). Although her tubular dysfunction has not recently progressed, it is presumably the main reason for her poor general condition. Exocrine pancreatic insufficiency is a well-known symptom of Pearson's syndrome. However, none of the previously reported patients had diabetes mellitus like our patient has. Nor does she have any clinical symptoms of encephalopathy, despite the severe cerebral atrophy seen in her computed tomography scan. Such neuroradiologic changes have not previously been reported in Pearson's syndrome.

Heteroplasmy of mtDNA was demonstrated in muscle, leukocytes, and cultured skin fibroblasts, with the deleted population corresponding to 80, 75, and 35% of total mtDNA, respectively. The mapping of the deletion showed it to be slightly larger than the previously reported 5.0-kb "common deletion" of the same region (25). The deletion was confirmed to exist also in kidney by PCR. The activities of respiratory chain enzymes in muscle mitochondria were generally decreased, corresponding to the mutation in mtDNA, which encodes several subunits of respiratory chain enzymes. Enlarged mitochondria were demonstrated in the renal tubular cells.

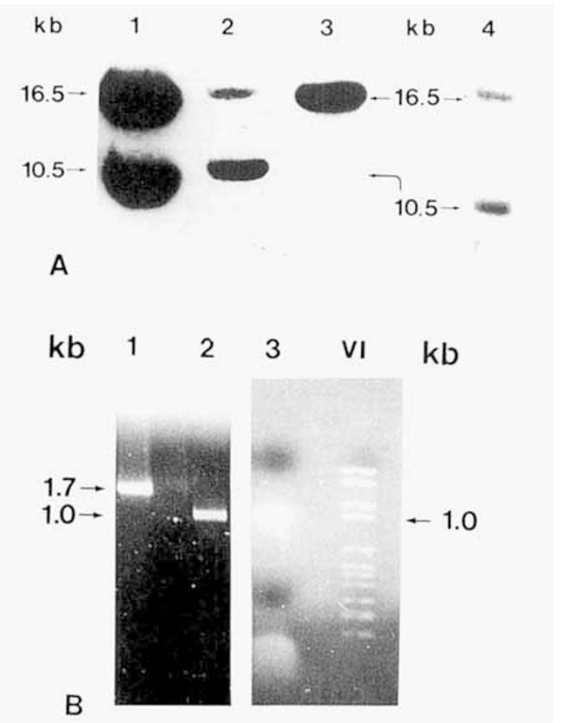

Fig. 2. *A*, Southern analysis. *Lane 1*, the patient, fibroblast DNA. *Lane 2*, the patient, muscle DNA. *Lane 3*, control, healthy person, muscle DNA. *Lane 4*, the patient, blood DNA. Using mtDNA as probe, two hybridizing bands were seen in the *lanes 1*, *2*, and *4*. Note a band at 10.5 kb corresponding to the more rapidly migrating mtDNA population due to a deletion of 5.7 kb. The sizes were calculated on the basis of bacteriophage lambda digested with *Hin*dIII as a marker. *B*, The size of the mtDNA deletion of the patient as well as its presence in her kidney tissue was confirmed using PCR. The distance of the primers Xba8.2 and Taq14.9 (see text) was 6.7 kb, which was too far to be amplified from the wild type mtDNA population. In the case of a deletion between primers, the small fragment was amplified efficiently and the size of the deletion was counted from the resulting fragment. In the PCR, the following fragments were detected. *Lane 1*, a control patient with progressive external ophthalmoplegia showing a "common deletion" of 5.0 kb that results in a fragment of 1.7 kb. *Lane 2*, muscle mtDNA of our patient; *lane 3*, Kidney mtDNA of our patient, a fragment of 1.0 kb corresponding to a deletion of 5.7 kb. The molecular weight marker VI (Boehringer Mannheim) was pBR328 DNA cut with *Bg*II and *Hin*dI (fragment sizes 2.167, 1.766, 1.230, 1.033, 653 bp, *etc.*).

The clinical presentation of mtDNA deletion has mostly been progressive external ophthalmoplegia. KSS, and, in a few cases, Pearson's syndrome. Each of these three entities appears with a distinct clinical picture and age of onset independent of the site of the deletion. However, the recent knowledge of these disorders indicates considerable overlapping between these groups, and even progression from one to another (26, 27). Phenotypic variability has been explained by differential tissue distribution of mutant mtDNA molecules during cell divisions in early embryonic development (28). The percentage of mutated mtDNA and tissue dependence on aerobic energy production together determine whether the tissue is clinically affected or not. The usual progression of the disease is gradual worsening of the symptoms and involvement of new tissues, which may be due to more rapid replication of deleted mtDNA molecules, leading to an increased percentage (26). The patient reported here demonstrates a variant of clinical expression and progression with

gradual bone marrow recovery and simultaneous involvement of new tissues. It would have been interesting to study this recovery phenomenon on the molecular level. Nevertheless, her bone marrow disease is similar to cases recently reported by Larsson *et al.* (26) and McShane *et al.* (27), who recovered from sideroblastic anemia and later developed KSS. It remains to be seen whether our patient also develops typical symptoms of KSS. Therefore, not only genotype and phenotype but also progression show variability in mitochondrial diseases.

Diagnosis of the heterogeneous group of mitochondrial disorders requires not only careful analyses of histopathology and biochemistry, but also recently developed molecular genetic approaches. A large mtDNA deletion is reasonably simple to analyze from small tissue samples. Such an analysis could well be initiated with even a slight suspicion of mitochondrial disease, which apparently is an expanding group of highly diverse diseases. Our patient originally came to our institution for evaluation of kidney transplantation because of her severe tubular dysfunction. The multisystemic symptoms from bone marrow, pancreas, and cerebrum led us to suspect a mitochondrial origin for her disease, and an mtDNA deletion was demonstrated.

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