Short report

Endocrine involvement in mitochondrial encephalomyopathy with partial cytochrome c oxidase deficiency

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SUMMARY A 19-year-old man born with thyroprivic hypothyroidism, due to congenital developmental defect, manifested hypogonadism, stunted growth, chronic progressive external ophthalmoplegia (CPEO), diffuse muscle weakness and wasting, right bundle branch block, cerebral atrophy. Muscle biopsy showed mitochondrial abnormalities. Biochemical investigations on muscle disclosed partial (50%) cytochrome c oxidase deficiency, 58% decrease of cytochrome aa₃, and 41% decrease of cytochrome b. Enzyme-linked immunosorbent assay showed decrease of the immunologically active enzyme protein.

Cytochrome c oxidase deficiency has been reported in several mitochondrial encephalomyopathies and has very heterogeneous clinical manifestations. Among them chronic progressive external ophthalmoplegia (CPEO) is the most frequent. Endocrine involvement has not been reported in partial cytochrome c oxidase deficiency, but has been described in some cases of CPEO with mitochondrial alterations not biochemically investigated (see refs: 2, 12).

We describe a 19 year old patient with endocrine involvement as the first sign of mitochondrial encephalomyopathy. Biochemical investigations and ELISA on muscle homogenate disclosed partial cytochrome c oxidase deficiency.

Case report

The patient was born of non consanguineous parents with negative family history for neuromuscular diseases. At age 2 months thyroprivic hypothyroidism due to congenital development defect was found and the patient was treated with replacement therapy. In spite of normalised thyroid hormone values, he had delayed developmental milestones, began to walk at 30 months and was never able to cope with playmates. At age 12 years primary hypogonadism was found with decreased testosterone increment (0.8 ng/ml with normal values 3–9 ng/ml) both before and after administration of human chorionic gonadotropin (HCG). Bone age was 7 years, height was 131 cm (<3rd centile) and weight was 22 kg (<3rd centile). In spite of adequate endocrinological treatment, the patient continued to show retarded growth. At 17½ years bilateral ptosis of the eyelids was observed.

The patient was referred to us when aged 19 years. Height was 156 cm (<3rd centile), weight 28 kg (<3rd centile). Examination showed scoliosis, external ophthalmoplegia, diffuse wasting and weakness affecting proximal more than distal muscle groups. There was no ataxia or sensory loss and no retinopathy. Intellectual function was normal. Endocrinological tests during replacement therapy showed normal values of thyroid stimulating hormone, triiodothyronine, tetraiodothyronine, free triiodothyronine, free tetraiodothyronine, testosterone, follicle stimulating hormone, and growth hormones. ECG disclosed right bundle branch block. Echocardiography and electromyography were normal. Cerebral CT demonstrated dilatation of anterior cisternae of the brain stem, cisterna magna, fronto-parietal subarachnoid spaces. Serum creatine kinase was 211 U/l (normal <170). Lactic acidemia was 24-54 mg/dl (normal 3–12). Piruvic acidemia was 0.92 mg/dl (normal 0.3–0.7). Electromyography showed low amplitude polyphasic motor unit action potentials and normal motor and sensory conduction velocity. The patient refused to undergo lumbar puncture.
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Fig. (a) Gomori trichrome; (b) cytochrome c oxidase. Serial sections showing two "ragged red" fibres devoid of cytochrome c oxidase activity. × 512 (bar = 20 μm). (c) Thin section demonstrating abnormal mitochondria with paracrystalline inclusions both subsarcolemmal and among myofibrils. × 40,000 (bar = 0.25 μm).
Material and methods

Triceps brachii muscle biopsy was performed under local anaesthesia and the specimen was processed for light and electron microscopy. Specimens were immediately frozen, stored in liquid nitrogen and described spectrophotometric assays were used to measure succinate cytochrome c reductase, DPNH cytochrome c reductase, succinate dehydrogenase, NADH dehydrogenase, citrate synthase and cytochrome oxidase activities.

Reduced-minus-oxidised spectra of cytochromes were recorded at room temperature as previously reported. The immunological analysis was carried out by enzyme-linked immunosorbent assay (ELISA) using an antiserum against purified cytochrome c oxidase.

Results

Light microscopic examination showed the typical picture of a mitochondrial myopathy (fig a, b): 10% muscle fibres were ragged red. The same fibres stained more intensely with the reactions for NADH-tetrazolium reductase, lactate dehydrogenase, succinate dehydrogenase, and several of them showed increased staining with periodic acid Schiff and Oil Red O stains. In 20% fibres histochemical staining showed absence of cytochrome c oxidase activity. Electron microscopy demonstrated abnormal mitochondria with paracrystalline inclusions both under the sarcolemma and within muscle fibres (fig c). There was also a slight increase of free glycogen and lipids. Biochemical studies showed 50% decrease of cytochrome c oxidase activity in muscle homogenate (27.95 nmol/min/mg protein; controls = 55.9, SD 10.2), and normal values of other mitochondrial enzymes. A parallel decrease of immunologically reactive enzyme protein was demonstrated by ELISA of muscle homogenates (50 mg/ml protein) from control and patient muscle, with progressive dilutions of purified antihuman cytochrome c oxidase immunoglobulin G. The spectra of reduced-minus-oxidised cytochromes of isolated muscle mitochondria showed 58% decrease of cytochrome aa, (273.8 pmol/mg mitochondrial protein; controls = 652-83, SD 104) and 41% decrease of cytochrome b (385.3 pmol/mg mitochondrial protein; controls = 653, SD 42).

Discussion

In the reported case, the association of CPEO, diffuse muscle weakness and wasting, ECG alterations, CT brain abnormalities, stunted growth and endocrine disturbances could suggest the diagnosis of Kearns-Sayre syndrome, but the absence of retinitis pigmentosa does not agree with this. The mitochondrial dysfunction proved by lactic acidosis and by the results of morphological, histochemical and biochemical investigations of muscle biopsy indicates that our patient may be included in the group of so called "mitochondrial encephalomyopathies". In these syndromes endocrinopathies have already been reported as additional features, more frequently in the form of diabetes and hypoparathyroidism whereas hypothyroidism and hypogonadism are less common. Thyroprvic hypothyroidism, as in our patient, is quite unusual and probably represents another sign of the multisystem involvement in mitochondrial encephalomyopathies.

In our patient histochemical, biochemical and immunological investigations showed partial cytochrome c oxidase deficiency. Cytochrome c oxidase deficiency has been reported in infancy, more frequently with fatal outcome, less commonly with a benign course. In all these cases the enzyme activity is almost completely absent in the newborn period when severe generalised weakness is present. Cases of partial deficiency of cytochrome c oxidase have also been reported, usually with juvenile or adult onset and slow progression of the disease. The significance of these partial defects is debatable: in fact single muscle fibres devoid of histochemical activity of cytochrome c oxidase are relatively common in mitochondrial myopathies (personal observation) and have also been reported in patients with defects of the respiratory chain other than complex IV. These findings suggest that partial defect of activity of the enzyme may be secondary, as stressed by the progressive decline of the enzyme activity in a case and by the low levels of the enzyme found in patients with complex I defects. As we did not perform polarographic studies we cannot exclude complex I deficiency, but biochemical determinations of mitochondrial enzymes activity did not suggest this defect. On the other hand the parallel deficiency of the immunologically active protein, observed in our case and already reported, is difficult to interpret as secondary.

The partial decrease of cytochrome aa and b, demonstrated in isolated muscle mitochondria, does not establish a more accurate correspondence between the biochemical defect and the clinical picture. In fact the other reported cases with partial deficiency of cytochrome aa, and b presented clinical features different from our case and very heterogeneous.

Our report confirms the multisystemic involvement in mitochondrial encephalomyopathies and stresses that endocrinopathy may be an unusual onset of these diseases.

References

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