

## Stroke-like episodes in familial mitochondrial encephalomyopathy: clinical and biochemical aspects

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**Summary.** Acute episodes of focal neurological dysfunction are a well-recognized complication of the mitochondrial encephalomyopathies. Because of rapid remission, biochemical tests and other diagnostic procedures are mostly performed after the acute phase. We report the case of a patient suffering from mitochondrial disease manifesting primarily with seizures, progressive deafness and dementia, who experienced multiple stroke-like episodes. Other members of the family with evidence of mitochondrial dysfunction are presented briefly. EEG and biochemical findings in the acute stage are correlated with clinical symptoms, showing characteristics distinct from the chronic illness. The possible involvement of dietary factors in the provocation of stroke-like episodes is discussed and regulation of glucose intake suggested as a strategy in the prevention of stroke-like episodes.

**Key words:** Lactic acidosis – Mitochondrial myopathy – Mitochondrial encephalopathy – Stroke-like episodes – Myoclonus epilepsy

### Introduction

Defects of mitochondrial metabolism have been recognized in numerous disorders affecting the nervous system as well as other organs [3]. Clinical syndromes observed in adults include the Kearns-Sayre syndrome [7] and the syndromes of myoclonus epilepsy with ragged-red fibres (MERRF) [6] as well as mitochondrial myopathy, encephalopathy, lactic acidemia and stroke-like episodes (MELAS) [11]. However, the underlying defects of mitochondrial metabolism are heterogeneous, and symptoms vary considerably [3, 12]. The pathogenetic mechanisms in acute “stroke-like” episodes are not yet clear. Various hypotheses such as cardiac embolism secondary to cardiomyopathy [1], anoxia secondary to cerebral mitochondrial dysfunction [8, 9] or capil-

lary occlusion caused by endothelial swelling [10] have been proposed.

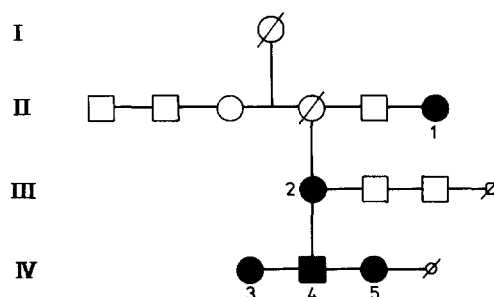
In this paper, the case of a patient with symptoms of both MERRF and MELAS is discussed in detail. No further family members had stroke-like episodes or myoclonus epilepsy, but hearing loss, mental and growth retardation, pigmentary retinopathy, lactic acidosis and diabetes mellitus were observed.

Figure 1 shows a pedigree of the family under study. Table 1 summarizes the clinical features of affected members. Patient 2 is discussed in detail.

### Case report

The female patient's birth and childhood were normal. Progressive deafness was noted when aged 23 years. During the same period a personality change with apathy, moodiness and restless sleep developed. Myoclonic jerks provokable by bright light were first observed at 30; tonic-clonic seizures brought her to neurological attention.

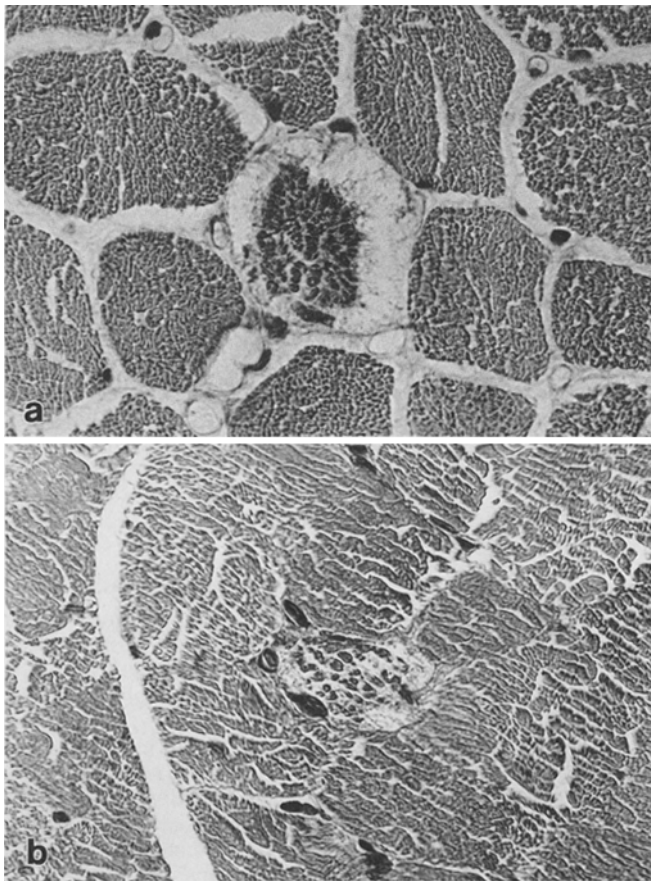
Evaluation in 1985 (at age 32) revealed mild intellectual impairment, severe sensorineural hearing loss and a discrete right-sided hemiparesis with generally sluggish reflexes. Electroencephalography (EEG) 5 days after the last tonic-clonic seizure showed discrete generalized slowing with left temporo-parietal accentuation and intermittent bursts of sharp waves. The cerebrospinal fluid (CSF) lactate was 6.17 mmol/l (normal: <1.9 mmol/l).



**Fig. 1.** Pedigree of the family under study. ○ Female, □ male, ●, ■ affected, ∅ deceased, ∅, ∅ miscarriage, 1–5 patient no. (Table 1)

**Table 1.** Clinical features. ○, Not observed; ○+, discrete; +, mild; ++, moderate; +++, severe; GR, growth retardation; LAC, lactic acidotic coma; DM, diabetes mellitus; ME, myoclonus epilepsy; A, ataxia

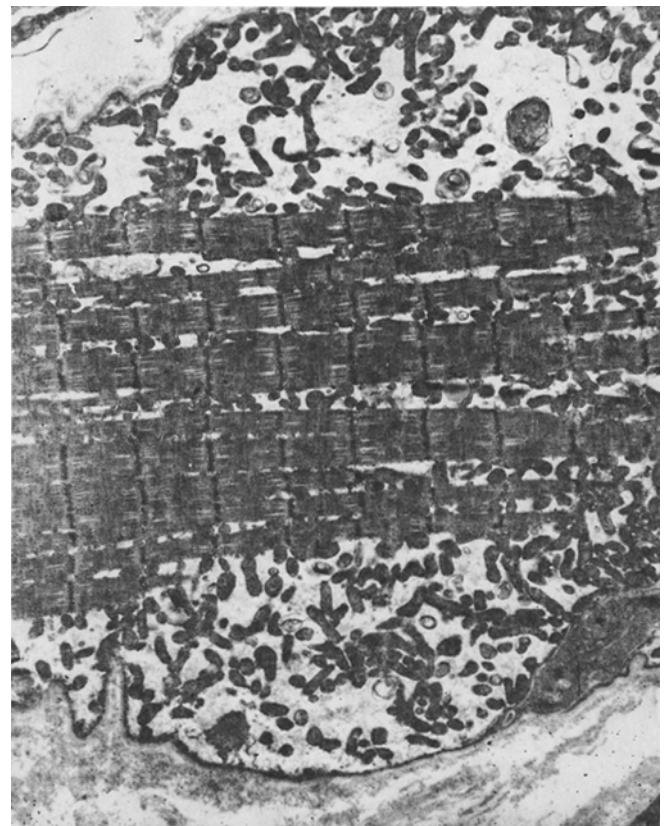
	Case no.				
	1	2	3	4	5
Age/sex	57/f	35/f	18/f	14/m	6/f
Lactic acidemia	+++	++	++	+	+++
Stroke-like episodes	○	+++	○	○	○
Dementia/retardation	○+	++	+	+	+
Myopathy	++	+	○	○	○
Pigmentary retinopathy	○	○	+	○	+
Deafness	++	+++	○	○+	○
Other	GR, DM, A	GR, DM, ME, A	GR	GR	GR, LAC, ME



**Fig. 2a, b.** Light microscopy findings of muscle biopsy with ragged-red fibres. **a** Red stained "ragged-red fibre" in trichrome stain (Goldner), paraffin section,  $\times 350$ . **b** Typical coarse granular aspect of a centrally situated so-called ragged-red fibre. H&E, frozen section,  $\times 420$

Computed tomography (CT) showed a large, contrast-enhancing left temporal hypodensity. Magnetic resonance imaging (MRI) confirmed the lesion and revealed multifocal signal changes with irregular enhancement after gadolinium-DTPA. Electrocardiograms (ECG), echocardiography and cerebral angiography were normal.

On follow-up the right-sided weakness had resolved and the background EEG pattern was normal, but bilateral irregular 3–5 Hz spike-wave and poly-spike-wave complexes were prominent. CT demonstrated progressive cerebral atrophy. The patient continued to have frequent myoclonic jerks and occasional tonic-clonic fits.



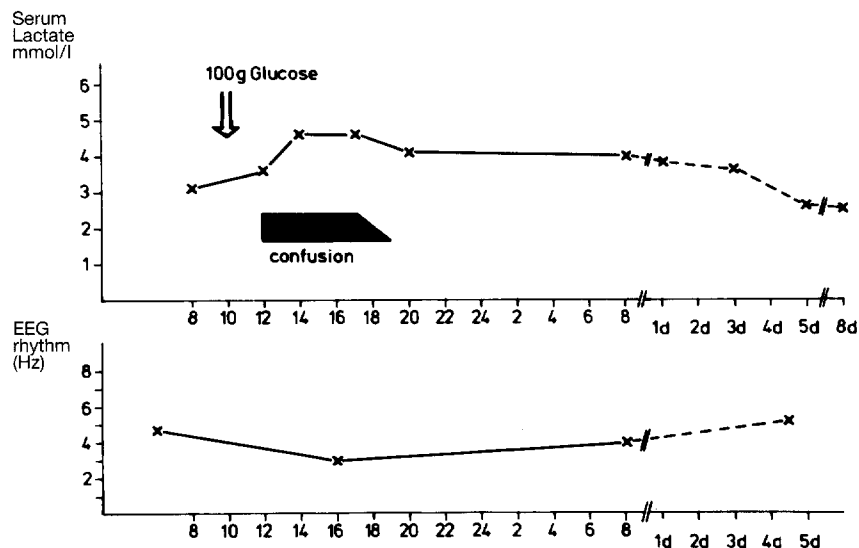
**Fig. 3.** Electron microscopic aspect of an atrophic muscle fibre with subsarcolemmal accumulation of normally sized mitochondria and a few admixed membrane whorls.  $\times 16000$

In December 1987 she suffered acute confusion and loss of vision. Gait was now ataxic, but a visual disturbance was not demonstrable on admission. Pigmentary retinopathy was absent. The EEG showed a background rhythm of 4–6 Hz without signs of myoclonic epilepsy. CSF lactate was again increased (6.1 mmol/l). Confusion remitted spontaneously in 48 h, leaving deafness, mild ataxia and moderate intellectual impairment. A repeat EEG after discharge was without generalized slowing; the poly-spike-wave pattern had returned. Seizures were controlled with sodium valproate.

Electromyography demonstrated discrete myopathic changes. A biopsy specimen from the left deltoid muscle showed approximately 5% ragged-red fibres (Fig. 2) and increased lipid storage on oil-red staining. NADH-tetrazolium reductase revealed only occasional small dark fibres and a few type 1 fibres with ballooned un-

**Table 2.** Respiratory chain activity and muscle carnitine concentrations

	Case no. (as in Fig. 1)				Controls
	2	3	4	5	
NADH dehydrogenase	71.0	54	78	65	48.0 ± 9.4 units/g muscle
NADH-cytochrome <i>c</i> reductase	5.33	7.3	12	13	3.2 ± 1.53 units/g muscle
Succinate dehydrogenase	1.93	2.6	3.6	3.5	2.4 ± 1.1 units/g muscle
Succinate-cytochrome <i>c</i> reductase	1.91	3.3	4.5	3.7	1.64 ± 0.62 units/g muscle
Cytochrome <i>c</i> oxidase	4.7	2.5	3.4	1.8	2.8 ± 1.0 units/g muscle
Muscle carnitine (total)	16.1	12.73	17.7	17.7	20.0 ± 7.6 nmol/mg protein
Muscle carnitine (free)	12.1	8.64	16.9	14.2	17.4 ± 7.0 nmol/mg protein

**Fig. 4.** Effect of glucose tolerance test: 100 g oral glucose after a fasting lactate value of 3.1 mmol/l led to clinical deterioration approximately 2 h later. This lasted 6 h accompanied by an increase of serum lactate levels and slowing of the EEG pattern. Reversal of symptoms was paralleled by EEG acceleration and decrease in lactate

stained areas below an intensely stained subsarcolemmal rim. Acid phosphatase activity was seen in some fibres, indicating a degenerative process. Accumulations of mitochondria without paracrystalline inclusions were seen on electron microscopy (Fig. 3). A standard bicycle exertion test showed an excessive increase in lactate (8.8 mmol/l after 15 min at 30 W) despite suboptimal cooperation. Serum lactate was at rest constantly elevated (2.5–4.0 mmol/l; normal: < 2.2 mmol/l). Biochemical evaluation of the respiratory chain by spectrophotometric methods [14] failed to identify a specific enzyme defect (a cytochrome *c* oxidase defect has since been demonstrated in her daughter, case 5). Table 2 shows the evaluation of respiratory chain enzyme activity in four members of the family. Serum and muscle carnitine concentrations were normal.

In January 1989 the patient suffered acute confusion and cortical blindness. The next day, a left hemianopia remained; she had dystonic posturing of the left hand. CSF lactate was 5.81 mmol/l; serum lactate 2 days after admission was 2.9 mmol/l. MRI demonstrated an extensive area of pathological signal in the right occipital region. Transcranial Doppler ultrasound (TCD) was normal, as was repeat ECG. The symptoms resolved in several days.

The patient was readmitted on 2 February 1989 after sudden onset of right-sided weakness. There was a spastic right hemiparesis; the EEG showed severe generalized slowing (1–4 Hz background pattern). Serum lactate was 4.9 mmol/l. The next day, the hemiparesis had resolved, but serum lactate was still 4.4 mmol/l. At home again, she suffered several generalized tonic-clonic seizures; serum lactate reached 10.18 mmol/l. The EEG again showed severe generalized slowing but no poly-spike-wave pattern. Seizures ceased on the day of admission and the serum lactate 24 h later had returned to 2.2 mmol/l. Follow-up EEG revealed moderate slowing (5–6 Hz), the poly-spike-wave pattern

returned. A connection between increased glucose intake and clinical deterioration was suspected (see below), and dietary treatment commenced. No further stroke-like episodes have occurred since.

Clinical course, EEG changes and serum lactate levels suggested a metabolic influence outside the hospital no longer in effect during hospitalization. The patient's husband was questioned as to recent dietary habits. Having been informed of her defect in energy metabolism, he had supplemented her diet with dextrose and honey, amounting to approximately 200 g additional glucose/day.

The correlation between glucose challenge, metabolic upset and acute clinical deterioration was again suggested by a glucose tolerance test performed because of elevated serum glucose levels (Fig. 4). Serum lactate levels reached 4.6 mmol/l and were still over 4.0 mmol/l 10 h after glucose loading (blood glucose 126 mg/dl).

Clinical deterioration with confusion, restlessness, hyperaggressive behaviour and impaired vision was noted, remitting after 10 h. Average preprandial values of less than 3 mmol/l were regained. Marked generalized slowing (3 Hz) improved to a background EEG rhythm of 5–6 Hz. Repeated pre- and postprandial serum lactate studies on a standard 2000 kcal diet at rest and after clinical stabilization showed almost normal early morning values with a slight postprandial rise in lactate.

## Discussion

The patient belongs to a family suffering from a mitochondrial disease with considerable clinical variety.

Maternal inheritance must be considered, but a dominant pattern with incomplete penetrance cannot be ruled out. All affected members share mental and growth retardation, and all have elevated rest and exertion serum lactate. Our patient was the only one to have had stroke-like episodes at the time of this study. The diabetes mellitus of patients 1 and 2 needs further study. Investigation ruled out an autoimmune type I diabetes, and a connection with mitochondrial disease is suspected.

Other authors have observed an increased incidence of diabetes in mitochondrial disease [15].

Slow deterioration was punctuated by focal episodes with good remission. The EEG pattern of poly-spike-wave complexes in the interval changed to generalized slowing during stroke-like episodes. After several episodes, however, moderate slowing remained. Acute deterioration was accompanied by excessive lactate levels.

A chronic disorder of cerebral metabolism was recently demonstrated in mitochondrial disease by positron emission tomography [5]. A relationship between stroke-like episodes and cerebral embolism [1] appears unlikely, as ECG, cerebral angiography, EEG and TCD were normal. Our observations suggest a direct metabolic cause of acute CNS dysfunction [8]. The EEG pattern of severe generalized slowing also suggests generalized dysfunction more than embolic cerebrovascular occlusion. Serum lactate was excessively elevated during the acute phase of stroke-like episodes and rapidly decreased after hospitalization, remaining moderately elevated. Both generalized EEG slowing and excessive serum lactate were seen without preceding fits (e.g. the admissions December 1987, January 1989 and 2 February 1989).

Acute metabolic crises with sudden clinical deterioration and EEG changes appear to have been induced by a carbohydrate-supplemented diet, as has been observed in pyruvate dehydrogenase deficiency [2]. Other authors have reported exercise or fasting inducing acute symptoms [3]. We suggest an overload of metabolites preceding the defect in energy metabolism as a pathogenetic mechanism superimposed on chronic deficiency of end-product. Lactic acidemia seems to be an indicator of metabolic insufficiency and may be caused by glucose challenge. Elevated blood lactate in the bicycle exertion test is unlikely to have a major influence on the cerebral lactate concentration. As lactate crosses the blood-brain barrier slowly, alterations of venous and CSF lactate concentrations are not parallel [13]. Glucose, however, would influence both cerebral and peripheral metabolism. Co-existing diabetes mellitus would increase serum glucose elevation on dietary challenge, thus facilitating metabolic decompensation.

Therapeutic strategies can also include dietary measures [4] regulating carbohydrate supply as an adjunct to enzyme substitution [16] to prevent acute "stroke-like" events. No further stroke-like episodes have occurred in our patient since a diet with decreased carbo-

hydrate and increased percentage of fat was instituted 18 months ago, and her general condition remains stable, although MRI shows slightly progressive cerebral atrophy.

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