

Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Strokelike Episodes: A Distinctive Clinical Syndrome

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We report on two patients who have a mitochondrial myopathy, encephalopathy, lactic acidosis, and recurrent cerebral insults that resemble strokes (MELAS). These two and nine other reported patients share the following features: ragged red fibers evident on muscle biopsy, normal early development, short stature, seizures, and hemiparesis, hemianopia, or cortical blindness. Lactic acidemia is a common finding. We believe that MELAS represents a distinctive syndrome and that it can be differentiated from two other clinical disorders that also are associated with mitochondrial myopathy and cerebral disease: Kearns-Sayre syndrome and the myoclonus epilepsy ragged red fiber syndrome. Existing information suggests that MELAS is transmitted by maternal inheritance. The ragged red fibers suggest an abnormality of the electron transport system, but the precise biochemical disorders in these three clinical syndromes remain to be elucidated.

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In the past five years we have evaluated three patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and a strokelike syndrome. One of these patients was reported on separately in abstract form [17]. We have identified eight other patients reported on in the medical literature who evidence similar clinical and histopathological features. The cardinal characteristics of these eleven patients include ragged red fibers in skeletal muscle, short stature, seizures, and hemiparesis, hemianopia, or cortical blindness. Ragged red fibers derive their name from the appearance of the degenerating granular fibers after they have been stained with the modified Gomori trichrome stain. The red staining represents proliferating mitochondrial elements. The presence of ragged red fibers suggests an abnormality of the electron transport system, because these findings are regularly seen in documented biochemical deficiencies that involve the respiratory chain [1, 6, 7, 20, 21, 27-29, 31, 33, 37, 40]. Ragged red fibers also have been seen in two other, similar clinical disorders: Kearns-Sayre syndrome [32] and a syndrome characterized by myoclonus epilepsy and ragged red fibers. Fukuhara [10] has proposed the acronym MERRF for the latter syndrome. The purpose of this report is to review the distinctive characteristics

of these three syndromes and to propose the acronym MELAS for this newly described entity.

Case Reports

Patient 1

A boy had a normal prenatal and perinatal history. Polydactyly was noted at birth. By 3 years of age delayed motor and language development were evident; school performance was significantly below grade level by first grade. Short stature was noted at 8 years and sensorineural hearing loss was documented at 14 years. His one sibling was unaffected, and the family history was normal. He was otherwise well until age 15½ years when he had two generalized tonic-clonic seizures that lasted 10 minutes, with residual left arm and hand weakness and sensory loss. These abnormalities partially resolved within four weeks. A computed tomographic (CT) scan demonstrated a small right frontoparietal lucency. At age 16 he was admitted to a hospital after the sudden onset of right hand weakness, hyperaggressive behavior, and confusion. There were expressive aphasia and right hemiparesis. Cerebrospinal fluid (CSF) was normal except for a protein concentration of 76 mg/dl. A CT scan showed bilateral non-enhancing parietal lucencies. Cerebral angiography with magnification views showed no abnormalities. The patient was treated with phenytoin and a two-week course of prednisone. The right hemiparesis resolved.

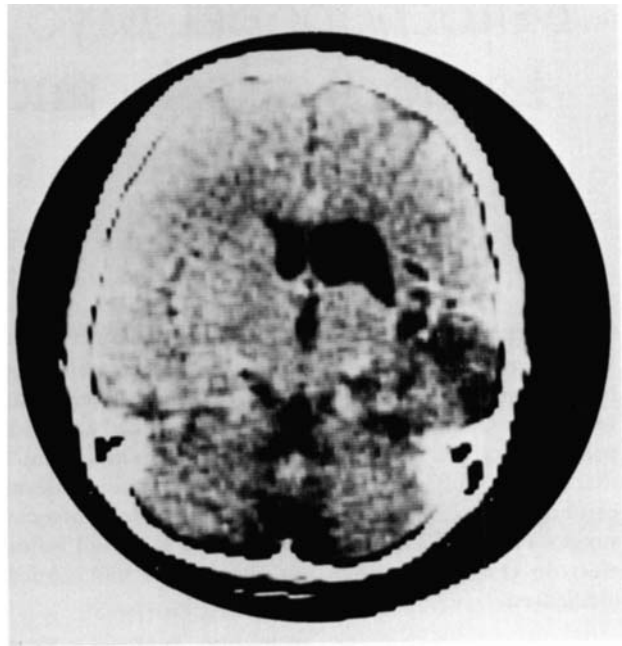
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A



B

Two months later, after a febrile illness, he experienced visual and auditory hallucinations with disorientation and slurred speech. At Babies Hospital physical examination showed short stature (164 cm) and small head circumference (52.75 cm), both at the 3rd percentile for age. There were abnormalities of speech with word substitutions, deletions, and anomia. Auditory acuity was diminished bilaterally; there was diffuse limb weakness and drift of the left arm. Tendon reflexes were present. There was no fundoscopic abnormality, ophthalmoplegia, tremor, or myoclonus. An electroencephalogram (EEG) showed diffuse slowing without paroxysmal features. Bilateral nonenhancing parietal lucencies were noted on CT scan. Arterial lactate concentration was 2.7 mM/L and CSF lactate was 4.0 mM/L (normal CSF and serum lactate ranges, 0.5 to 2.2 mM/L). Results of all other serum laboratory studies were normal. Biopsy of the quadriceps muscle showed ragged red fibers on modified Gomori trichrome staining. Activities of pyruvate carboxylase and pyruvate dehydrogenase enzyme complex were normal in cultured skin fibroblasts [4, 5].

Several months later the patient had an acute psychotic episode with hyperaggressive behavior and paranoid delusions. Examination showed dysdiadochokinesia of the left hand and mild drift of the left arm as the only abnormalities. All language abnormalities had resolved. CSF lactate concentration during the psychotic behavior was 4.9 mM/L, and arterial lactate level was 4.8 mM/L. Formal psychometric testing demonstrated a Verbal IQ of 57, with Performance and Full Scale IQs below 50. In the ensuing 18 months the patient had no recurrence of seizures, motor deficits, or acute personality disorder.

Patient 2

The second patient, also a boy, had an uneventful prenatal and perinatal history. Early growth and development were

Computed tomographic scans of the head (patient 2), showing multiple nonenhancing lucencies involving both occipital lobes, (A) the right parietal lobe and (B) the right basal ganglion.

normal. At age 6 years he experienced intermittent headaches and lethargy. By 9 years school performance deteriorated and short stature was noted. At 5 years his height was at the 50th percentile for age, but 4 years later it was at the 3rd percentile. At 9 years he was hospitalized with fever, vomiting, lethargy, and right hemiparesis. EEG showed left focal slowing. The right hemiparesis gradually resolved over four weeks. Two months later he complained of sudden blindness, which was followed by a generalized clonic seizure. The blindness improved, and a CT scan showed bioccipital lucencies. A regimen of phenobarbital was started. Four-vessel cerebral angiography demonstrated a right extracranial carotid occlusion. In the next twelve hours the patient gradually developed a left hemiparesis and left homonymous hemianopia. CT scanning showed lucencies in the right basal ganglia and both occipital lobes.

At age 13 years he was admitted to Babies Hospital for further evaluation. His one sibling was unaffected, and the family history was normal. He was short (128 cm; 3rd percentile for age), and head circumference (54 cm) was at the 50th percentile. Intellectually he functioned at a 6-year-old level and could recall only one of three objects at five minutes. He had a left homonymous hemianopia, diffuse limb weakness, and left hemiparesis. Tendon reflexes were present. There was no fundoscopic abnormality, ophthalmoplegia, tremor, or myoclonus. EEG showed diffuse slowing with right midtemporal and central epileptiform discharges. Bilateral occipital, right parietal, and right basal ganglia lucencies were evident on CT scan (Figure). The arterial lactate concentration was 4 mM/L, CSF lactate level 6.1 mM/L, and CSF protein concentration 53 mg/dl. Results of all other

Table 1. Characteristics of MELAS^a

Patient No.	Author	Additional Clinical Features	Additional Laboratory Features
1	Koenigsberger et al [17]	6-yr-old girl with periodic loss of consciousness, dementia, hearing loss, transient right hemiparesis; died at 9 yr	ECG showed flattened T waves; CK and LDH elevated; muscle carnitine decreased
2	Askanas et al [2] ^b	9-yr-old boy with deteriorating school performance, focal seizures, alternating hemiparesis, episodic vomiting	Basal ganglia calcification; slow sensory conduction velocities; blunted hGH response to insulin-induced hypoglycemia
3	Askanas et al [2] ^b	9-yr-old boy with episodic vomiting, focal seizures, alternating hemiparesis, single episode of blindness	...
4	Skoglund [35]	11-yr-old boy with left homonymous hemianopia following right-sided headache; alexia without agraphia	Basal ganglia calcifications; bilateral parieto-occipital lucencies; elevated SGOT and LDH
5	Hart et al [14]	18-yr-old woman with episodic vomiting, headache, left visual field cut and hemiparesis, cortical blindness, dementia	Alteration of cerebral cortex; microcystic liquefaction; basal ganglia mineralization noted postmortem
6	Hart et al [14]	16-yr-old brother of patient 5 with limited extraocular motility and progressive encephalopathy; no strokelike syndrome	...
7	Shapira et al [34]	16-yr-old girl with episodic vomiting and ataxia, left visual field cut and hemiparesis, deafness, myoclonic seizures, progressive encephalopathy	ECG showed flattened T waves; focal microcystic softening of cerebrum and basal ganglia mineralization noted postmortem
8	Shapira et al [34]	10-yr-old brother of patient 7 with episodic vomiting, right hemiparesis, blindness, myoclonic seizures, progressive encephalopathy	Elevated CK and LDH; postmortem findings similar to those of sister; muscle not examined
9	Gardner-Medwin et al [12]	12-yr-old boy with episodic vomiting, blindness, progressive encephalopathy, coma	Focal lucencies on CT scan
10	Patient 1 (present report)	16-yr-old boy with alternating hemiparesis, aphasia, decreased hearing, progressive encephalopathy	Bilateral parietal lucencies on CT scan
11	Patient 2 (present report)	13-yr-old boy with episodic vomiting, alternating hemiparesis, blindness, progressive encephalopathy	Bilateral occipital, right parietal, and basal ganglia lucencies

^aEleven patients with limb weakness, ragged red fibers, short stature, lactic acidemia, encephalopathy, seizures, and recurrent strokelike syndrome.

^bWe reexamined patients 2 and 3, reported previously by Askanas et al. CT scan of patient 2 at 10 years of age showed basal ganglia calcifications.

ECG = electrocardiogram; CK = creatine kinase; LDH = lactic dehydrogenase; hGH = human growth hormone; SGOT = serum glutamic-oxaloacetic transaminase; CT = computed tomographic.

blood and CSF studies were normal, and a biopsy of the quadriceps muscle showed ragged red fibers.

Methods and Results

Mitochondrial enzymes in skeletal muscle were analyzed in four patients with MELAS. The methods for the determination of cytochrome c oxidase [42], succinate-cytochrome c reductase [36], NADH-cytochrome c reductase [36], citrate synthetase [38], carnitine acetyl transferase [23], and carnitine palmitoyl transferase [23] have been previously described. Control muscle was obtained by diagnostic biopsy

from patients who were ultimately deemed free of neuromuscular disease. The results of the mitochondrial muscle enzymes are tabulated in Table 5.

Discussion

These two patients had a mitochondrial myopathy, encephalopathy, lactic acidosis, and a strokelike syndrome (MELAS). These two and nine other patients [2, 12, 14, 17, 34, 35] met the following criteria: normal early development, short stature, seizures, and alternating hemiparesis, hemianopia, or cortical blindness (Table 1). All eleven children were normal at birth

Table 2. Characteristics of MERRF (Fukuhara Syndrome)^a

Patient No.	Author	Additional Clinical Features	Additional Laboratory Features
1	Holliday et al [15]	28-yr-old man with short stature, seizures, optic atrophy, deafness, dementia; died at 32 yrs	Elevated lactate
2	Holliday et al [15]	18-yr-old brother of patient 1 with short stature, seizures, optic atrophy, deafness, dementia	Elevated lactate
3	Riggs et al [31]	9-yr-old girl with short stature, tremor, encephalopathy; no limb weakness	Elevated CK; lactate normal
4	Riggs et al [31]	7-yr-old brother of patient 3 with short stature, seizures, tremor; no limb weakness	Elevated CK; lactate normal
5	Feit et al [8]	30-yr-old woman with tremor, progressive encephalopathy, possible neuropathy	Lactate value not reported

^aRepresentative patients with limb weakness, ragged red fibers, ataxia, and myoclonus. Sixteen patients are reported in the literature [8, 10, 15, 31]. Eleven cases were reviewed by Fukuhara [10]. We have added patients 1 through 5.

CK = creatine kinase.

and had normal early development, with symptoms of MELAS beginning between ages 3 and 11 years. All were short and had a seizure disorder. The seizures were focal or generalized; two patients had myoclonic seizures. All had either hemiparesis, hemianopia, or cortical blindness, except one [14] who had the other manifestations and is included in this group because his sister had the full syndrome. Nine developed hemiparesis or hemianopia, and six had episodes of cortical blindness [2, 12, 14, 17, 34, 35]. Nine patients became demented [2, 12, 14, 17, 34]. Episodic vomiting was prominent in seven patients [2, 12, 34, 35]. Three had neurosensory hearing loss [17, 34], and there were two pairs of affected siblings [14, 34]. Significant cerebellar dysfunction, interictal myoclonus, heart block, ophthalmoplegia, and retinal pigmentary changes were absent.

Fukuhara and associates [11] described a syndrome that was similar in some respects but differed in others. Fukuhara called the syndrome MERRF (myoclonus epilepsy and ragged red fibers) and cited eleven patients who met the following criteria: normal early development, myoclonus, and a cerebellar syndrome [10]. We have found five other patients reported in the literature [8, 15, 31] (Table 2). Like those with MELAS, these patients had normal early development with symptoms beginning between ages 5 and 42 years; eleven had seizures, eleven became demented, and six had hearing loss [8, 10, 15, 31]. Ten of the sixteen patients had affected family members [10, 15, 31]. Unlike those with MELAS, all had myoclonus and ataxia and none had hemiparesis, hemianopia, or cortical blindness. (We are making a distinction here between myoclonic epilepsy and myoclonus.) All patients with MERRF had interictal myoclonus, not seen in any MELAS patient. In contrast to the findings in those

with MELAS, intention tremor was prominent in twelve patients with MERRF [8, 10, 31] and deep sensation was impaired in six of the sixteen [10]. In eight, optic nerve atrophy was noted [10, 15]. One patient had a menstrual disorder secondary to hypothalamic dysfunction [9]. No patient had significant ophthalmoplegia, retinal pigmentary degeneration, or heart block.

Kearns-Sayre syndrome, a disease also associated with ragged red fibers, has been defined [32] as an acquired condition with onset before age 20, ophthalmoplegia, atypical pigmentary degeneration of the retina, and one of the following: heart block, CSF protein level greater than 100 mg/dl, or a cerebellar syndrome. Using these criteria Rowland and co-workers [32] identified seventy reported cases of Kearns-Sayre syndrome. Like those of MELAS and MERRF, nearly all cases were associated with growth failure, and neurosensory hearing loss was common. Unlike MELAS and MERRF, few cases were familial. Focal neurological signs, episodic vomiting, cortical blindness, and myoclonus were absent, and seizures occurred only in three patients with concomitant hypoparathyroidism.

The neuropathological characteristics of MELAS, MERRF, and Kearns-Sayre syndrome are somewhat similar in that spongy degeneration of the brain has been described in all three syndromes. Three patients with MELAS were studied postmortem (see Table 1). One had a spongy state of the brain with cerebral cortical microcystic liquefaction [14]. Two siblings showed focal encephalomalacia of the cerebral cortical mantle [34]. Our patients and two others [12, 35] had focal lucencies on CT scan. Five patients with MELAS had basal ganglia calcifications evident on CT scan or postmortem, without clinical hypoparathyroidism [2, 14, 34]. No spinal cord findings have been reported.

Table 3. Cases with Characteristics of Both MELAS and MERRF^a

Patient No.	Author	Clinical Features	Laboratory Features
1	Kuriyama et al [18]	14-yr-old boy with short stature, episodic vomiting, myoclonic epilepsy, ataxia, deafness, macular degeneration	Multiple "infarcts" of cerebrum and cerebellum; basal ganglia calcification
2	Fukuhara [10]	13-yr-old girl with episodic vomiting, seizures, myoclonus, deafness, Babinski's signs; no ataxia	Elevated CK; right occipital lucency on first CT scan; cerebellar atrophy and basal ganglia calcification on second scan; ECG showed ST depression
3	Holliday et al [15]	26-yr-old woman with short stature, seizures, visual field cut and hemiparesis, episodic headaches, myoclonus, optic atrophy, deafness, ataxia; asymptomatic half-sister with elevated lactate	...

^aAll patients had ragged red fibers and lactic acidemia.

CK = creatine kinase; CT = computed tomographic; ECG = electrocardiogram.

Three patients with MERRF were studied postmortem [10]. Two had a spongy state of the cerebral hemispheres. One of these had spongy degeneration of the subcortical white matter of the cerebellum as well. The third patient was difficult to assess because of antecedent head trauma. All three had degeneration of neurons with glial proliferation in the dentate nuclei and superior cerebellar peduncles. Notably, all three patients had degeneration in the posterior columns and anterior and posterior spinocerebellar tracts of the spinal cord. Thirteen postmortem reports of Kearns-Sayre syndrome revealed a spongy state of the brain [32]. On CT scan four patients with Kearns-Sayre syndrome had lucencies and two showed calcifications in the presence of hypoparathyroidism [32]. The neuropathological findings of these syndromes overlap, but microcystic liquefaction or focal softening and basal ganglia calcification are most prominent in MELAS. Spinal cord degeneration involving posterior columns and spinocerebellar tracts has been seen only in MERRF.

Three patients with ragged red fibers had features of both MELAS and MERRF [10, 15, 18]. For example, Kuriyama and associates [18] (Table 3) presented a patient with short stature, episodic vomiting, myoclonic epilepsy, and cerebellar syndrome. The patient had no strokelike episodes. Postmortem examination revealed basal ganglia calcifications and multiple cerebral "infarcts" that were not in the distribution of a specific arterial blood supply. Presumably, the areas of "infarction" were due to some mechanism other than vascular occlusion. The short stature, episodic vomiting, and basal ganglia calcifications were similar to those in patients with MELAS, but the cerebellar syndrome was like that in MERRF. The patient of Kuriyama and co-workers had myoclonic epilepsy but not continuous myoclonus. Fukuhara [10] (see Table 3) presented a patient with episodic vomiting and myoclonus, as in

MERRF, but without ataxia. CT scan showed right occipital lucency and basal ganglia calcifications similar to those in a number of patients with MELAS. Finally, one of three patients reported by Holliday and colleagues [15] (see Table 3) had intermittent headache, myoclonus, seizures, dementia, and ataxia, as in MERRF, but also had postictal hemiparesis, as in MELAS. These cases illustrate the problem of making clear distinctions between the two syndromes.

Ten other patients previously referred to as having "Hackett-Tarlow syndrome" [10] or "juvenile mitochondrial myopathy" [32] have lactic acidemia and mitochondrial myopathy, often with growth failure [13, 19, 20, 22, 24-26, 28, 39, 41]. This is a heterogeneous group of patients, not easily categorized. One patient [25] probably had an incomplete form of Kearns-Sayre syndrome, and another [19] principally had ophthalmoplegia. Limb weakness was the dominant feature in four patients [20, 24, 28, 41]. The syndrome in five patients in this group resembles but does not meet the criteria for MELAS [13, 22, 26, 39] (Table 4). All had short stature, two had epilepsy [13, 22], two had episodic vomiting [13, 39], and four had hearing loss [13, 22, 26]. Monnens and colleagues [26] described a patient without encephalopathy or seizures who had sudden blindness reminiscent of MELAS. Some of these patients may have been in the early stages of MELAS. For instance, Hart and co-workers [14] reported two siblings, one with complete MELAS (see Table 1). The other had only seizures and encephalopathy and would not have met the criteria for MELAS if not for the affected sibling. The transition to MELAS was documented in another family that was first reported as evidencing fascioscapular myopathy with abnormal mitochondria [16]; lactic acidosis was noted later [3], and, finally, one sibling developed encephalopathy. It is difficult, therefore, to consider "Hackett-Tarlow" a distinct syndrome.

Table 4. Cases with Characteristics Resembling MELAS^a

Patient No.	Author	Clinical Features	Laboratory Features
1	Tarlow et al [39]	6-yr-old girl with episodic vomiting	...
2	Hackett et al [13]	20-yr-old woman with deafness, epilepsy, retarded sexual maturation	...
3	Hackett et al [13]	11-yr-old sister of patient 2 with deafness, episodic vomiting; severe metabolic acidosis before death	...
4	Markesbery [22]	27-yr-old man with seizures, deafness, neurogenic bladder	Elevated CSF protein; basal ganglia calcification
5	Monnens et al [26]	Female with deafness, acute visual loss; cousin with mitochondrial myopathy	Elevated CK; partial deficiencies of PDH and cytochrome c oxidase

^aAll patients had limb weakness, short stature, ragged red fibers, and lactic acidemia.

CSF = cerebrospinal fluid; CK = creatine kinase; PDH = pyruvate dehydrogenase.

Table 5. Mitochondrial Enzymes of Muscle in Four Patients with MELAS and Controls

Patient No. ^a	Cytochrome c Oxidase ^b	Succinate Cytochrome c Reductase ^b	NADH Cytochrome c Reductase ^b	Citrate Synthetase ^c	Carnitine Acetyl Transferase ^d	Carnitine Palmitoyl Transferase ^d
1	1.23	0.52	3.46	10.29	8.37	...
2	2.60	0.82	2.51	14.71	5.66	13.14
3	1.67	0.86	2.96	14.56	8.72	13.81
11	3.24	0.39	5.40	17.27	6.04	...
Control ^e	2.50 ± 0.50 (35)	1.08 ± 0.41 (26)	3.38 ± 1.33 (31)	8.81 ± 0.54 (28)	1.84 ± 0.54 (28)	7.45 ± 1.44 (58)
Range	1.76–3.74	0.42–1.89	1.82–6.22	4.12–16.50	1.05–2.90	4.62–10.49

^aPatients numbered as they appear in Table 1.

^bμmol oxidized or reduced per minute per gram.

^cμmol formed per minute per gram.

^dnmol formed per minute per gram.

^eControl values ± SD with number of controls in parentheses.

The cause of these syndromes is uncertain. All are associated with ragged red fibers, and most include elevated blood lactate concentrations. Presumably there is an underlying biochemical defect in mitochondria. There may be multiple biochemical defects or varied clinical expression of a single defect. The prominence of central nervous system manifestations suggests that nervous system mitochondria are affected. There has been no reported study of brain mitochondria, however.

Several biochemical abnormalities have been associated with ragged red fibers [27], including decreased function of cytochrome c oxidase [7], cytochrome b and aa₃ [40], cytochrome b [28, 37], NADH-CoQ reductase complex [20, 29] or ATPase [33], and loose coupling of oxidative phosphorylation [1, 6, 21]. A deficiency of succinate–cytochrome c reductase was found in two siblings with MERRF [31] (see Table 2). Monnens and colleagues [26] (see Table 4) described a patient who had a syndrome resembling MELAS and also had partial deficiencies of cytochrome c oxidase and pyruvate dehydrogenase. We have studied muscle tissue obtained from four patients with MELAS (patients 1, 2, 3, and 11, Table 1). Enzyme activities re-

lated to the respiratory chain, as shown in Table 5, are either normal or partially decreased (cytochrome c oxidase in patients 1 and 3 and succinate–cytochrome c reductase in patient 11). In contrast, citrate synthetase and carnitine acetyl transferase, two enzymes located in the mitochondrial matrix, and carnitine palmitoyl transferase, an enzyme located on the inner mitochondrial membrane, tend to be increased. Although the significance of a partial decrease in respiratory chain enzyme activities in some patients remains uncertain, the general increase in the other enzymes probably reflects the increased number of mitochondria, as shown by morphological study. Thus, no consistent biochemical abnormality has been found in any of these syndromes.

We believe that MELAS is a distinctive syndrome manifested by mitochondrial myopathy, encephalopathy, lactic acidosis, and recurrent strokelike episodes. MELAS, like MERRF, may be familial. Genetic factors, however, are difficult to elucidate, because only two pairs of siblings with MELAS have been reported [14, 34]. The patient with encephalopathy in the family with fascioscapular myopathy was not reported on in detail. Each pair of siblings may have had a partially

Table 6. Principal Clinical Features of Kearns-Sayre Syndrome, MERRF, and MELAS

Feature	Kearns-Sayre Syndrome	MERRF	MELAS
No. of cases	70	16	11
Ophthalmoplegia	70 ^a	0	0
Retinal degeneration	70 ^a	0	0
Cerebellar syndrome	56	16 ^a	0
Dementia	34	11	9
Myoclonus	0	16 ^a	0
Seizures	3	11	11 ^a
Short stature	47	6	11 ^a
Hearing loss	43	6	3
Impaired deep sensation (if described)	...	6	0
Cortical blindness, hemiparesis, or hemianopia	0	0	10 ^b
Optic atrophy	...	8	1
Positive family history	2	10	4

^aFeature present in all reported cases.

^bFeature absent only in patient 6, Table 1; this boy's sister had the full syndrome.

affected mother. One mother had neurosensory hearing loss and diabetes mellitus, and the other had night blindness and ST segment depression on the electrocardiogram. These observations raise the possibility that MELAS is transmitted by non-Mendelian maternal inheritance. Mitochondrial DNA is maternally derived and codes for several subunits contained within the respiratory chain [7]. It is tempting to speculate that the relatively low level of respiratory chain enzyme activity noted in Table 5 is the consequence of a generalized defect involving mitochondrial protein synthesis. Wiseman and Attardi [43], in fact, reported a decrease in cytochrome c oxidase and rutamycin-sensitive ATPase in a simian virus 40 transformed human cell line. Studies are in progress to determine whether the genetic aberration presumably associated with MELAS involves mitochondrial DNA.

The course of MELAS is variably progressive, punctuated by acute cerebral insults. It can be differentiated from MERRF and Kearns-Sayre syndrome as summarized in Table 6. Postmortem studies show focal encephalomalacia, and CT scans show cerebral lucencies or "infarcts," but the focal lucencies may not always correspond to a vascular distribution. Our second patient developed a left hemiparesis immediately after an arteriogram that showed right carotid occlusion. The occlusion may have been a complication of arteriography. Alternately, one could propose that the mitochondrial disturbance involves the endothelium of brain capillaries, contributing to the vascular compromise. It is known that the cerebral microvasculature is rich in

mitochondria [30]. The finding of ragged red fibers is the hallmark of these various syndromes. Further separation must await elucidation of the inherited biochemical abnormalities.

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