

mast cell localization and disease progression (J. R. Gorospe, M. D. Tharp, J. Hinckley, et al, unpublished data). Thus, whereas the local release of bFGF from injured or exercised muscle may normally lead to local muscle healing and regeneration, the chronic release of bFGF by dystrophin-deficient muscle may result in the excess fibrosis and scarring associated with DMD.

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# Myo-Leukoencephalopathy in Twins: Study of 3243-Myopathy, Encephalopathy, Lactic Acidosis, and Strokelike Episodes Mitochondrial DNA Mutation

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Two dizygotic twins with myopathy and leukoencephalopathy are described. The female twin had an incomplete form of MELAS syndrome (myopathy, encephalopathy, lactic acidosis, and strokelike episodes) with severe myopathy, epileptic seizures without strokelike episodes. The male twin presented clinical features exclusively of myopathy and subclinical leukoencephalopathy. The MELAS mitochondrial DNA point mutation (MELAS-3243) was found by southern blot and polymerase chain reaction in muscle, skin fibroblasts, and blood of the female twin and was not detected in the skin fibroblasts nor in the blood of the mother, nor in any of the tissues tested in the male twin. The absence of mutation in male twin tissues raises questions about the pathogenetic significance of the mutation in this family.

Degoul F, Diry M, Pou-Serradell A, Lloreta J, Marsac C. Myo-leukoencephalopathy in twins: study of 3243-myopathy, encephalopathy, lactic acidosis, and strokelike episodes mitochondrial DNA mutation. *Ann Neurol* 1994;35:365–370

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Within the past 3 years, at least three specific point mutations (3243, 3271, 3250) have been described in the mitochondrial tRNA<sup>Leu(UR)</sup> gene associated with MELAS (myopathy, encephalopathy, lactic acidosis, and strokelike episodes) syndrome, a maternally inherited syndrome [1, 2] or with mitochondrial myopathy [3]. However, it has been demonstrated recently that in spite of being a high level of concordance between the clinical diagnosis of MELAS syndrome and the presence of the 3243 mutation, this mutation is also exhibited in patients with incomplete MELAS syndrome [4], in asymptomatic relatives of MELAS pa-

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tients [5], in patients with progressive external ophthalmoplegia (PEO) [6], and in others [7]. All these facts mean that MELAS 3243 mutation is not completely specific for MELAS patients, that some patients can present typical clinical features of MELAS syndrome without specific MELAS point mutation and that others, with clinical features other than those described in MELAS syndrome, can exhibit this mutation.

We present here 2 dizygotic twins, female and male patients, with childhood-onset myopathy and leukoencephalopathy discovered by neuroimaging studies. The leukoencephalopathy appeared with features apparently identical to those recently described in one family with adult-onset dystrophic myopathy and leukoencephalopathy [8]. In this study, we investigated the MELAS 3243 mutation in the female twin with recognized mitochondrial myopathy and epileptic seizures, in her brother with clinical and histopathological myopathy compatible with limb-girdle dystrophy, and in the asymptomatic mother.

## Patients Reports

### Clinical Data

The pedigree is shown in Figure 1. Five members were examined; 1 female patient (Patient II-2) had muscle weakness, fatigability, and epileptic seizures, and her male twin (Patient II-1) had only muscle weakness. The other members of the family did not present any neurological symptoms. Patients II-1 and II-2 were followed for 20 years for a predominantly proximal muscular deficit without an increase of muscle enzyme activity.

The details of the clinical features and laboratory examinations have been published. First, these cases have been published among a series of spinal muscular amyotrophy [9] according to their clinical and neurophysiological data [electromyographic (EMG) records and clinical deficit being myogenic proximally and neurogenic distally]. Twelve years later, they have been published as a clearly demonstrated mitochondrial disease (especially in the female) [10]. The clinical, histopathological data are summarized in the Table.

**PATIENT II-1.** A 32-year-old man started to complain of abnormal muscle weakness at the age of 7. At the beginning, he complained about distal paresis in his lower extremities. Some years later, weakness involved the proximal four limbs. Recently, neurological examination showed weakness of limb-girdle muscles with bilateral winging scapulae and distal paresis of lower extremities with lateral foot-drop and bilateral hypertrophic calves. He maintained walking capacity. Cognitive functions were normal. He worked as a printer. His daughter, 2 years old, is normal. Muscle biopsy examination showed only a predominance of type I fibers, 2% ragged red fibers (RRF), fiber splitting, and some fibers with internal nuclei.

**PATIENT II-2.** A 32-year-old woman had normal motor milestones and intellectual development until the age of 6 years. Then she experienced exercise-induced walking difficulties due to a foot-drop. At the age of 11, she had the first generalized myoclonic seizure. Afterward, walking difficul-

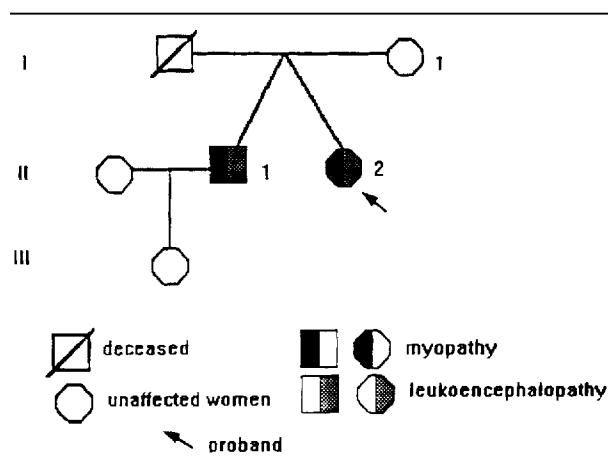


Fig 1. Pedigree of the family. Circles = female; squares = male. Open symbols are nonaffected subjects; dashed symbols are subjects clinically affected; a slash in the symbol indicates death.

ties were due to a proximal and a distal muscular weakness. At the age of 28 years, she became wheelchair dependent. The epileptic symptoms improved with time. The neurological examination showed a very severe and diffuse weakness in all proximal and distal muscles. Blood lactate acid level was elevated at rest and further abnormally increased during exercise. Muscle biopsy (deltoid) revealed many RRF.

### Radiological Studies in Brain

Leukoencephalopathy without ventricular enlargement was present in both twins. It was defined as confluent, not well-demarcated areas of high-signal intensity on long repetition time (TR 2,500 msec), long echo time (TE 60 seconds), spin echo magnetic resonance images (MRIs) (0.6 T) corresponding with areas of low attenuation on the computed tomogram (CT) (Fig 2). No progression of white matter abnormalities in both patients was observed on CT and MRI images during the past 4 years.

## Methods and Results

### Ultrastructural Study of Muscle

Muscle tissue (deltoid muscle) from Patient II-1 was fixed in glutaraldehyde and osmium tetroxide and embedded in polar-bed resin. Sections of two blocks were examined by an electron microscope, Philips 301. Most of the muscle fibers contained one or several large subsarcolemmal aggregates of mitochondria (Fig 3), usually protruding in the muscle surface. Mitochondria showed no structural abnormalities except for an increase in electron density of cristae. No intramitochondrial crystalline inclusions were found. Muscle tissue from Patient II-2 processed with the same method showed intense proliferation of the size and number of mitochondria located in the subsarcolemmal and intermyofibrillar spaces [10].

### DNA Preparation and Southern Blot Analysis

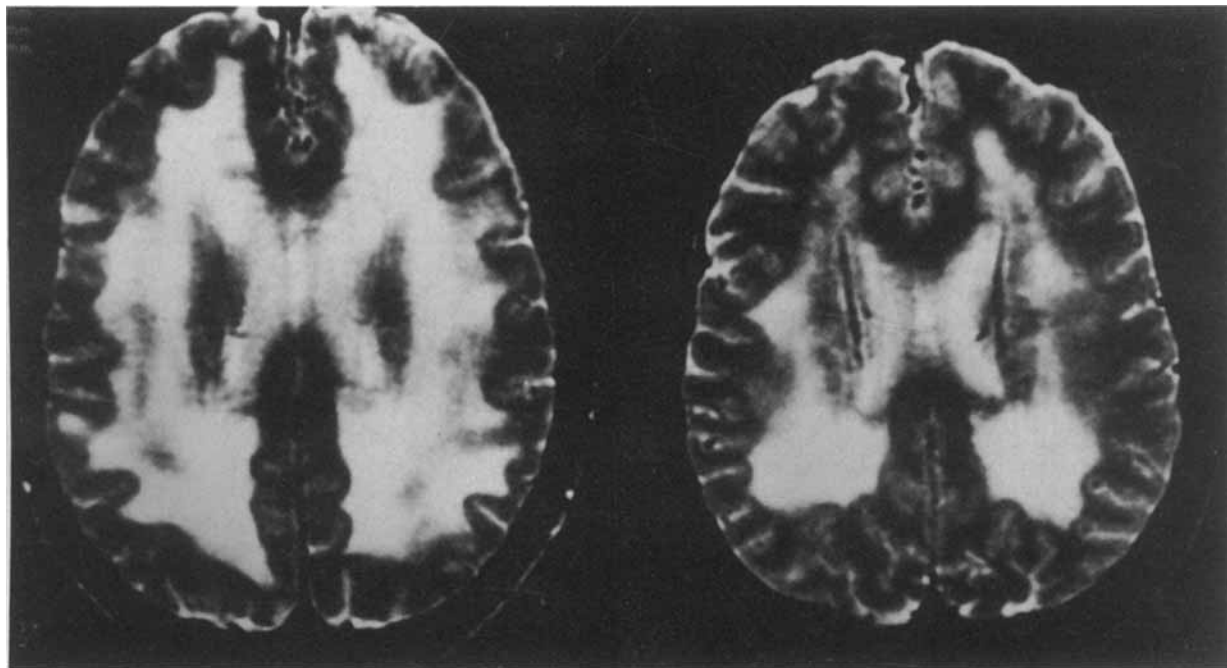
Total DNA was extracted after digestion of muscle, blood, and fibroblast cell pellets by proteinase K followed by phenol, phenol/chloroform extractions, and southern blot analysis was realized as described previously [11]. Total DNA (1 µg) was loaded after restriction with *Apa* I enzyme on a 1.2%

Clinical and Histopathological Data

	Patients	
	II-1	II-2
Sex	M	F
Age (yr)	32	32
Symptoms		
Early fatigability	-	+
Muscle weakness	++	++++
Respiratory distress	-	+
Epileptic seizures	-	++
Serum lactate level		
At rest	-	↑
After exercise	-	↑
Muscle biopsy		
Variability in fiber size	++	+
Splitting fibers	+	-
Central nuclei	++	+
Ragged red fibers	+	+++
Fiber type predominance	Type I	-
Fiber type deficiency	2B	-
Mitochondrial subsarcolemmal accumulation	++	+++
Radiological studies in brain		
CT, low attenuation on the white matter	+++	++
MRI, high signal intensity on white matter	+++	++
Progressivity of leukoencephalopathy	-	-

CT = computed tomography; MRI = magnetic resonance imaging.

Fig 2. Magnetic resonance imaging of Patients II-1 (A) and II-2 (B) showing increased signal intensity of the supratentorial white matter.



agarose gel. After transfer, filter was hybridized with a probe encompassing nt 3007 to 4508. The probe used was a purified polymerase chain reaction (PCR) product obtained after amplification with primers ND1For and ND1Rev and was radiolabeled by random priming. Oligonucleotides used are as follows: ND1For: 5'CCCGATGGTGCAGCCGC3' (3007-3023) and ND1Rev: 5'GATGGTAGAGTAGATGACGG3' (4508-4489).

The heteroplasmic point mutation at position 3243 according to Anderson's sequence can be detected by southern blot because of the creation of the new restriction site for enzyme *Apa* I. In normal mtDNA, the probe recognizes fragment restrictions 3822 and 2965; in mutant DNA, the 2965 fragment was cleaved in two smaller, 1781 and 1184 bp. The ratio of mutant DNA to wild-type was obtained by scanning nonsaturated exposures of fragments 2965 to 1184, after correction by the size of these two fragments, with an image analyzer (Starwise, version 4.11, 1991, Instar, Paris, France). By this technique (Fig 4A), we were able to point out the A-G transition in the blood cells and skin fibroblasts in culture from the girl twin. This mutation was also detected in the muscle biopsy in the laboratory of Pr S. DiMauro. Mutated molecules were not detectable in the muscle (not shown), the blood, or in skin fibroblasts in culture (not shown) from the male twin, or in the fibroblasts (not shown) or blood from the mother. By Southern blot, we could quantify the proportion of mutated DNA in total mtDNA. In female twin, the percentage varied from 40% in muscle to 25% in blood and 40% in skin fibroblasts.

To detect the MELAS mutation more sensitively, we performed PCR amplification of fragment encompassing nt 3243.

Polymerase Chain Reaction Analysis

Total DNA (0.1 µg) was amplified in a mixture containing 200 µM of each dNTP with 1 µl of [ $\alpha$  -  $^{32}$ P]dCTP (3,000

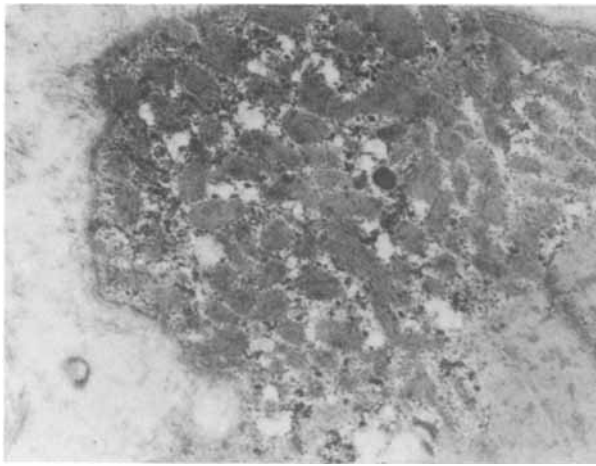


Fig 3. Electron micrograph of deltoid muscle biopsy of Patient II-1. There is intense proliferation of muscle mitochondria located in the subsarcolemmal and intermyofibrillar spaces ( $\times 7,000$  before 39% reduction).

Ci/mmol), 30 pmol of each primer, 2.5 units of TamTaq polymerase (Promega) by 35 cycles of 1 min denaturation at 90°C, 1 min of annealing at 55°C, and 1 min of extension at 70°C. The primers used to detect MELAS mutation were as follows: primer A: 5'AGGACAAGAGAAATAAGGCC3' (3130–3149) and primer B: 5'AAGAGCGATGGTGA-GAGCTA3' (3555–3536).

The amplified fragment (425 bp) was digested overnight with *Apa* I and the digestion products were analyzed on a 6% polyacrylamide gel and detected by autoradiography.

In this way, we confirmed the presence of the heteroplasmic mutation in the two tested tissues (fibroblasts and blood) from Patient II-2 and could not detect any mutated molecule in Patient II-1 nor in the mother's tissues (Fig 4B).

### Discussion

These dizygotic twins are affected by a similar pathology, myopathy, and leukoencephalopathy, but with different clinical expressions. The female patient (Patient II-2) suffered from a rapidly progressive and severe myopathy of mitochondrial origin (lactic acidosis, RRF, ultrastructural abnormalities, epileptic seizures, presence of MELAS mutation 3243), while the male patient (Patient II-1) suffered from slowly progressive and well-tolerated myopathy compatible with muscular dystrophy (but with normal creatine kinase enzymatic activity [97 IU]).

In our Patient II-2, the MELAS 3243 point mutation was found in muscle, blood, and fibroblast tissues with a low percentage of mutated molecules, particularly in muscle (40% mutated mtDNA). In typical MELAS syndromes, >60% of mutated muscle mtDNA has usually been described [5]. Because of the lack of strokelike episodes, this patient could be considered to have an "incomplete" form of MELAS, or an oligo-symptomatic form, a group very difficult to classify. In

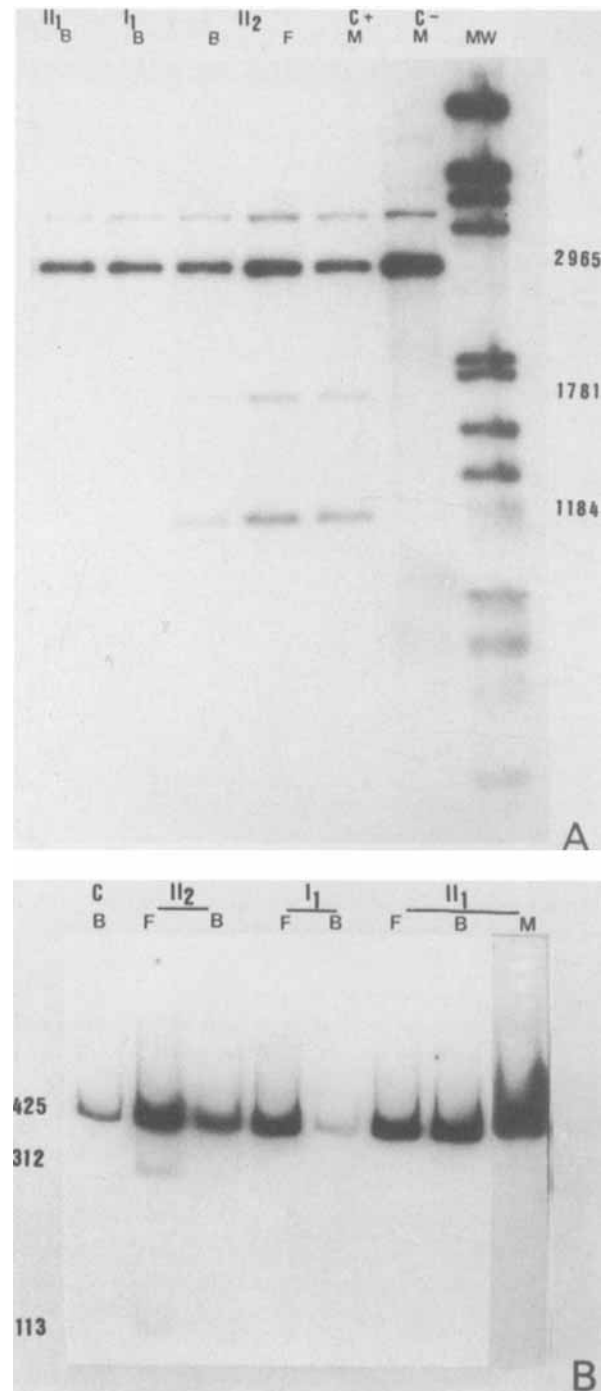


Fig 4. (A) Southern blot analysis of MELAS (myopathy, encephalopathy, lactic acidosis, and strokelike episodes) mutation. B = blood; F = fibroblasts; M = muscle; C+ = other patient with MELAS mutation; C- = control subject; MW = molecular weight. (B) *Apa* I digestion of the polymerase chain reaction (PCR) amplified mtDNA. PCR product (425 bp) was cleaved in two smaller fragments (312 and 113 bp) in mutated mtDNA. B = blood; F = fibroblasts; M = muscle; C = control subject.

this group Ciafaloni and co-workers [5] have found that the proportion of mutated mtDNA in muscle was lower than this usually described in typical MELAS syndrome.

In Patient II-1, the MELAS 3243 point mutation was not detected even by PCR amplification in all tested tissues. This fact could be related to the non-mitochondrial features of his myopathy, i.e., clinically and histologically it was quite similar to limb-girdle dystrophy. But a mitochondrial pathology is suggested because of the clear predominance of type I fibers and the abnormal subsarcolemmal accumulation of mitochondria. The absence of detection of MELAS mutation in this male twin's tissues could be also correlated with the benign symptomatology and the lack of clinical central nervous system symptoms. Similar differences on the distribution of the mutant mtDNA in dizygotic twins with MERRF syndrome (one clinically affected, the other asymptomatic) also have been mentioned previously [12].

Leukoencephalopathy, without clinical manifestations, could correspond, in our patients, with either a demyelination or a dysmyelination due to developmental disturbances, although the lack of progression of leukoencephalopathy on successive MRI and CT scans suggest a dysmyelinating condition. Similar familial leukoencephalopathy has been recently associated with autosomal recessive inheritance [8]. In our family, we cannot exclude the possibility that the male patient presented just this autosomal recessive disorder of leukoencephalopathy with muscular dystrophy and that the girl patient had a mitochondrial encephalomyopathy associated with the 3243 mutation. This A-G transition could represent a de novo mutation or a maternally inherited mutation present in only some tissues of the mother. This mutation is generalized in patients with MELAS [13], but the proportion of mutated molecules in the blood cells is lower than in the muscle. We did not find any mutated molecules in blood and fibroblast culture of the mother. We cannot exclude the presence of a few mutated molecules in her muscle, but to our knowledge only one case without mutation in the blood and with mutation in the muscle has been described [8].

Other studies demonstrate that this mutation was found in all progeny of heteroplasmic females but was not retrieved in the blood along all the maternal lineage [14]. These results show that this mutation could appear between two generations by replication mistakes and/or by amplification of traces of mutated mitochondrial genomes. A recent work emphasizes the fact that the MELAS 3243 mutation found in PEO and atypical MELAS patients could play a pathological role according to the tissue adaptability [15]. Therefore, the MELAS 3243 mutation may not be disease causing in our dizygotic twins.

Another less probable possibility would be another

mutation associated with the clinical expression of the disease that leads to a phenotype analogous to the muscular dystrophy with leukoencephalopathy. This mutation would probably be nuclear because no mutation was found in the mitochondrial genome associated with MELAS mutation [16]. Our findings suggest that a possible relationship may exist between mitochondrial myopathy and other types of myopathies with leukoencephalopathy and point out the necessity to look for other abnormal genes or point mutations in nuclear DNA. The absence of MELAS mutation in one of two twins clinically affected raises questions about the pathogenetic significance of this mutation.

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## Mitochondrial Myopathy with Progressive Decrease in Mitochondrial tRNA<sup>Leu(UUR)</sup> Mutant Genomes

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A female patient with mitochondrial myopathy had a mitochondrial DNA mutation at nucleotide pair 3243, commonly seen in patients with mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), but unlike MELAS patients, she had no central nervous system symptoms. Muscle weakness, which was most severe when she was 7 years old, improved gradually with age. Comparison of two muscle biopsies obtained at an interval of 12.5 years (7 and 20 years of age, respectively), revealed that the number of ragged-red fibers was markedly decreased and histochemical cytochrome *c* oxidase activity increased in parallel with the decrease in population of mutant genomes.

Kawakami Y, Sakuta R, Hashimoto K, Fujino O, Fujita T, Hida M, Horai S, Goto Y, Nonaka I. Mitochondrial myopathy with progressive decrease in mitochondrial tRNA<sup>Leu(UUR)</sup> mutant genomes. *Ann Neurol* 1993;35:370-373

Since the first description of mitochondrial myopathy by Luft and colleagues [1] in 1962, many mitochon-

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drial disorders have been described in which almost 40% of patients have the following three major clinical forms: chronic progressive external ophthalmoplegia (CPEO) including Kearns-Sayre syndrome (KSS); mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS); and myoclonus epilepsy associated with ragged-red fibers (MERRF) [2]. Each disorder has disease-specific mtDNA abnormalities including large-scale deletions in CPEO and KSS, point mutations at nucleotide pairs (nt) 3243 and 3271 in MELAS and 8344 in MERRF. We present a female patient who had an A-to-G substitution at nt 3243 in mtDNA (3243 mutation), commonly seen in patients with MELAS [3] but with the unusual feature of improvement in her muscle weakness. While the 3243 mutation is thought to induce various clinical expressions from none to typical MELAS phenotype, this is the first report describing a patient who had reversible muscle weakness and pathology associated with a change in the mutant genome population.

### Clinical Summary

A Japanese girl first noticed muscle weakness and fatigue at 6 years 8 months of age. There was no family history of neuromuscular disorders. Her mother and brother were in good health with no muscle weakness or fatigability.

She had normal developmental milestones. She was first seen in our clinic at the age of 7 years 4 months when she had marked difficulty in climbing stairs. On examination, she was a slender girl, 113 cm in height (-1.61 SD) and 16.6 kg in weight (-1.75 SD). She was intelligent and had never experienced stroke-like episodes. She had marked proximal muscle weakness in the lower extremities and moderate weakness in the upper extremities. She could not climb stairs without help and utilized the Gowers' maneuver to arise from the prone position. She had no facial weakness and no external ophthalmoplegia. Deep-tendon reflexes were hypoactive, but she had no pathological reflexes. Except for diffuse muscle atrophy, she had no other neurological abnormalities.

On laboratory examination, routine hematological and blood chemical studies were normal except for the following: creatine kinase, 281 U/L (normal, 18-95 U/L); lactate dehydrogenase (LDH), 1,250 IU/L (normal, 50-400 IU/L); lactate, 25.7 mg/dl (normal, 3.3-14.9 mg/dl); and pyruvate, 1.42 mg/dl (normal, 0.30-0.94 mg/dl). Cerebrospinal fluid lactate was 25.3 mg/dl and pyruvate 0.76 mg/dl. Electromyography (EMG) showed a myopathic pattern. The sensory and motor nerve conduction velocities were normal.

She had no learning difficulty and graduated from high school with average grades. Her muscle weakness gradually improved. In high school she climbed stairs with minimal difficulty and could run as well as her friends. Serum lactate levels fluctuated reaching a maximum level of 67.3 mg/dl at 10 years of age. At 17 years of age, she began to lose body weight progressively despite adequate food intake. She lost 6 kg over 3 years and this was accompanied by excessive perspiration. At age 20 years, she was 156 cm in height and 28.5 kg in weight. She worked in a department store as a clerk without excessive fatigability. She commuted to the store by city bus with only mild difficulty in climbing up the steps.