Table 3. Clinical summary of MADD patients.

Patient	Age	Gender	Clinical feature	Serum CK (IU/L)	CoQ_{10} level (μg/g muscle)	Treatment	Clinical course
4	5 mo	F	Muscle weakness, hepatomegaly	55	NA	NA	NA
5	6 mo	M	Muscle weakness, hepatomegaly	2000-4000	NA	L-carnitine riboflavin	Normal development after treatment
6	11 mo	M	Vomiting, hypertrophic cardiomyopathy	128-618	24.1	L-carnitine	Died at 2 years of age due to pulmonary alveolar bleeding
7	13 y 4 mo	F	Progressive muscle weakness	127	32.3	L-carnitine riboflavin	No muscle weakness at present

NA, not available. Normal range: CK, 57-197 IU/L; CoQ10, 32.1 ± 6.8 (mean ± standard deviation).

FIGURE 4. Routine histochemical staining of patients with LSM. Ragged-red–like fibers are seen on modified Gomori trichrome staining **(A)** and numerous lipid droplets are seen with oil-red-O **(B)** in a PCD patient, but not in an MADD patient **(C, D)**. Rimmed vacuoles are seen in myofibers of patients with NLSDM **(E)**, in addition to the characteristic numerous lipid droplets predominantly in type 1 fibers **(F)**. Bar = 20 μm.

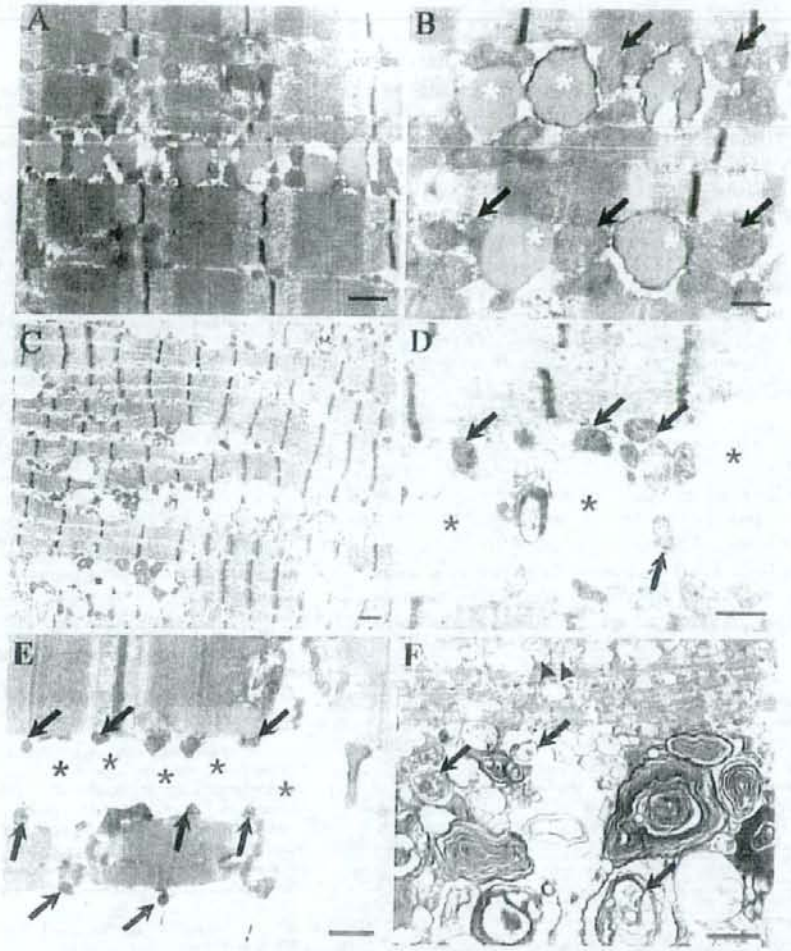

FIGURE 5. Electron microscopy findings. In a patient with PCD, markedly increased lipid droplets and increased numbers of mitochondria are seen **(A)**. On higher magnification, lipid droplets (asterisks) are seen next to mitochondria (arrows) **(B)**. In a patient with MADD, note the increase in the number of lipid droplets **(C)** and the proximity of these droplets (asterisks) with mitochondria (arrows) **(D)**, findings similar to those for PCD. In a patient with NLSDM, there is also a marked increase in the amount of lipid (asterisks) deposited within the myofibers; however, note that mitochondria appear pyknotic (arrows) **(E)**. In this patient, numerous autophagic vacuoles (arrows) in close proximity to lipid deposition (arrowheads) are also observed **(F)**. Bar 1 μm in **(A)**, **(C)**, and **(F)**. Bar 0.5 μm in **(B)**, **(D)**, and **(E)**.

are necessary to fully understand the mechanism of the disease.

CPT II deficiency has been reported to show increased lipid droplets in muscle.[5] However, in all patients whose samples were suitable for biochemical assays, normal enzymatic activity was seen. Furthermore, in our series, we had 7 patients with CPT II deficiency, but none showed lipid droplet accumulation on muscle pathology (data not shown) This suggests that lipid storage may not be a common pathological feature of CPT II deficiency, although analysis of a larger population of patients with CPT II deficiency would be needed to further support this contention.

In spite of an extensive genetic survey of known causative genes for LSM, we did not find mutations in 76% of the patients. One possible explanation for the absence of mutations in these patients is that

they may have secondary LSM, as intramuscular lipid content is known to be secondarily increased under a variety of conditions, including diabetes, renal disease, iatrogenic conditions, gastrointestinal disturbance, elevated plasma fatty acid levels, and high dietary fat intake.[18] The fact that 2 patients were taking antiepileptic drugs could be supportive of this notion. In the majority of patients without mutation, conditions associated with a secondary increase in muscle lipids were not seen. In addition, 2 patients had pathological features that differed from the rest of the patients in the form of lipid droplets almost exclusively in type 2 fibers, in contrast to the preference of lipid accumulation in type 1 fibers in all others, indicating the probability of a common pathomechanism, at least in these 2 cases.

Among the 28 patients without mutations in known causative genes, 5 had a positive family history and/or consanguinity (Table 1), suggesting that these individuals are likely to have primary genetic lipid disorders, rather than secondary LSM and the presence of additional yet-to-be-identified causative genes for LSM. Further analysis on biochemical analyses of accumulated metabolites and extended study of candidate genes involved in lipid metabolism will be helpful in the genetic diagnosis of LSM patients.

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