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Lipid Storage Myopathy and Probable Late-Onset Multiple Acyl-CoA Dehydrogenase Deficiency: A Case Report

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Data Interpretation D
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Conflict of interest:

None declared

Patient: Male, 60-year-old
Final Diagnosis: Lipid storage myopathy
Symptoms: Proximal weakness for more than 1 year and elevated muscle enzymes and aminotransferase
Clinical Procedure: —
Specialty: Neurology

Objective: Unusual clinical course
Background: Late-onset multiple acyl-CoA dehydrogenase deficiency can mimic inflammatory myopathy. We report a probable *ETFDH*-related case to illustrate diagnostic reconsideration after corticosteroid nonresponse when biopsy and genetic findings do not establish a definitive etiology.
Case Report: A 60-year-old man presented with proximal weakness for more than 1 year and elevated muscle enzymes and aminotransferases. No sertraline or other selective serotonin reuptake inhibitor exposure was reported. Corticosteroid treatment produced no objective strength improvement. Biopsy showed marked lipid accumulation. Sanger sequencing confirmed *ETFDH* c.1227A>C (p.Leu409Phe), classified as pathogenic, and c.1732C>T (p.Arg578Trp), classified as a variant of uncertain significance. Metabolic testing and functional validation were not performed. Strength and aminotransferases improved during combined riboflavin and coenzyme Q10 treatment, but an intercurrent brainstem infarction confounded recovery. At 1 month, creatine kinase and lactate dehydrogenase were not rechecked.
Conclusions: The findings supported probable, not definitive, *ETFDH*-related late-onset disease. Lipid-storage pathology should prompt reconsideration of a treatable metabolic myopathy while acquired alternatives remain under consideration. Improvement during combined treatment was supportive but nonspecific and did not verify the diagnosis or isolate a riboflavin effect.

Keywords: Genetic Testing • Muscle Weakness • Peripheral Nervous System Diseases • Riboflavin

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Introduction

Late-onset multiple acyl-CoA dehydrogenase deficiency (MADD) is an inherited metabolic disorder affecting fatty acid, amino acid, and choline metabolism. Adult presentations are frequently associated with variants in the electron transfer flavoprotein dehydrogenase (*ETFDH*) gene [1,2]. Clinical manifestations are heterogeneous and include proximal weakness, exercise intolerance, myalgia, fatigue, and elevated creatine kinase (CK) [1,3]. The overlap with inflammatory myopathy can delay recognition and lead to unnecessary immunosuppression [4,5].

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) can increase with skeletal muscle injury as well as liver disease [6]. Sensory or sensorimotor neuropathy has also been reported in some adults with MADD [7,8]. Muscle biopsy can identify a lipid-storage pattern and direct further metabolic and genetic investigation when biochemical or molecular evidence is incomplete, but intramyofiber lipid accumulation alone does not establish *ETFDH*-related MADD [1,4,5].

Improvement with riboflavin has been described in *ETFDH*-associated lipid storage myopathy [9,10]. The present report is an incremental clinical illustration rather than a new phenotype: corticosteroid nonresponse prompted diagnostic

reframing, but coexisting hepatobiliary disease, diabetes, an intercurrent stroke, and a variant of uncertain significance limited etiologic and therapeutic attribution. Its value lies in recognizing a potentially treatable metabolic myopathy without equating supportive pathology or short-term improvement with definitive confirmation.

Case Report

A 60-year-old man presented with progressive proximal limb weakness and reduced exercise tolerance for more than 1 year. His medical history included type 2 diabetes mellitus and hypertension. The available medication history indicated no sertraline or other selective serotonin reuptake inhibitor (SSRI) use before symptom onset, and no prior statin or other known myotoxic medication exposure was reported. No similar illness was reported among relatives in his generation or preceding generations. His grandson had gait unsteadiness, but an etiologic diagnosis for that symptom was not available; this was not considered a confirmed family history of MADD.

At admission, he was alert, with normal higher cortical and cranial nerve function. Muscle bulk and tone were preserved. The clinical account documented proximal-predominant limb

Table 1. Clinical events and serial biochemical findings.

Analyte	Reference range	Admission	Before discharge	1-month follow-up
CK	50-310	672	177	Not rechecked
LDH	15-220	920	653	Not rechecked
ALT	5-50	150	101	21
AST	0-40	99	31	25
GGT	7-50	61	153	Not reported

Clinical events

Time point	Observation
Before admission	Proximal weakness and reduced exercise tolerance for more than 1 year
During admission	Methylprednisolone 1000 mg/day intravenously for 3 days, then tapered; no objective strength improvement. Acute left brainstem infarction; exact onset date unavailable
Hospital day 18	Enteric-coated aspirin 100 mg orally once daily and atorvastatin 20 mg orally nightly started 2 days after corticosteroid discontinuation
Hospital day 22	Riboflavin 60 mg/day orally and coenzyme Q10 5 mg intravenously once daily, after corticosteroid withdrawal
At 1 month	Reported MRC grade 5/5; independent in daily activities

Biochemical values and reference ranges are in U/L. CK/LDH were not rechecked at 1 month. GGT “Not reported” does not imply normality. No dates or values were imputed. Initial strength records differ: clinical account 4/5; undated genetic referral 5-/5. No serial change was inferred. Stroke recovery confounds the follow-up strength assessment. CK, creatine kinase; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; MRC, Medical Research Council.

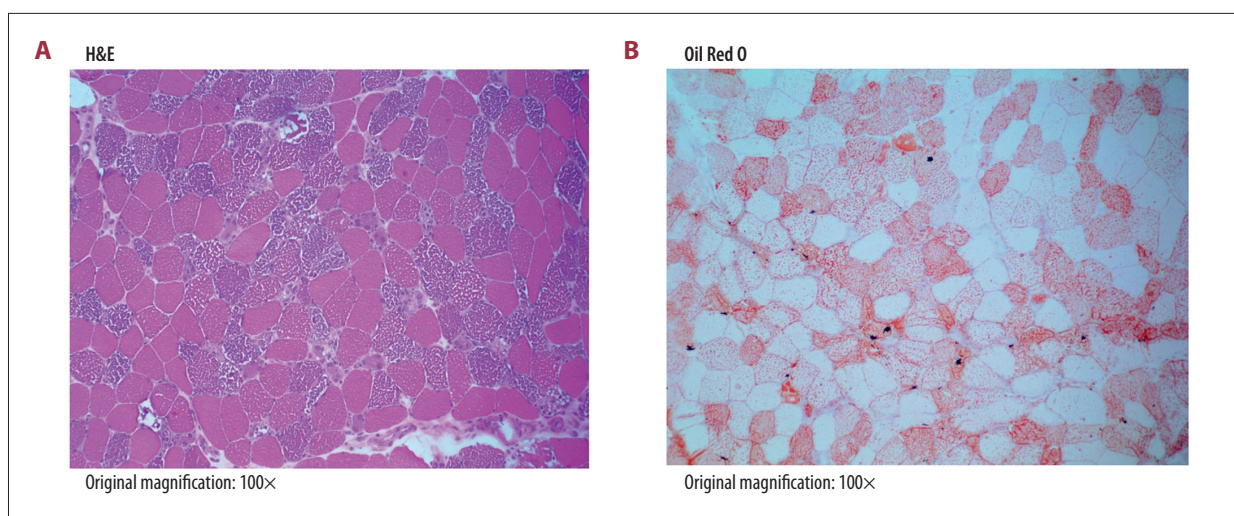


Figure 1. Source-derived muscle histology. (A) Hematoxylin and eosin staining shows variable myofiber caliber and vacuolation. (B) Oil Red O staining shows lipid accumulation. The report from Zhongda Hospital, Southeast University, states an original magnification of 100 ×. Tissue pixels and colors were preserved; only labels and margins were added. No scale calibration was available. Biopsy followed corticosteroid exposure, and the written report did not explicitly document absence of inflammation.

weakness at Medical Research Council (MRC) grade 4/5 and reduced tendon reflexes. Bedside superficial and deep sensory testing showed no clear deficit, and pathological reflexes were absent bilaterally. Finger-to-nose testing was normal and the Romberg test was negative.

Admission testing showed CK 672 U/L, lactate dehydrogenase (LDH) 920 U/L, ALT 150 U/L, AST 99 U/L, and gamma-glutamyl transferase (GGT) 61 U/L. Reference ranges and subsequent measurements are provided in **Table 1**. Folate, vitamin B12, thyroid function, hepatitis markers, autoimmune serology, and myositis-specific antibodies showed no clinically significant abnormalities. Abdominal ultrasonography was reported to show changes consistent with schistosomal hepatic fibrosis, chronic cholecystitis, and multiple gallbladder polyps. These findings were considered in the interpretation of the aminotransferase abnormalities; they were not treated as a normal hepatobiliary examination.

Nerve conduction studies showed reduced sensory nerve action potential amplitudes and slowed conduction in both median and ulnar nerves, with reduced peroneal motor conduction velocity. The findings suggested sensory-predominant sensorimotor peripheral nerve involvement. Repetitive nerve stimulation showed no significant decrement. Numerical nerve conduction measurements were not available in the material assembled for this report.

Inflammatory myopathy was initially suspected. Intravenous methylprednisolone 1000 mg/day was administered for 3 days, followed by tapering. No objective strength improvement was

documented, and exercise tolerance and walking distance declined. Scattered erythematous papules developed during tapering and improved with symptomatic antiallergic treatment. The eruption lacked typical dermatomyositis features.

During hospitalization, acute weakness of the right upper and lower limbs and facial sensory symptoms developed. Examination showed leftward deviation of the angle of the mouth, flattening of the right nasolabial fold, rightward tongue deviation, proximal and distal right arm strength of MRC grades 3/5 and 4/5, respectively, right leg strength of 4+/5, and a right pyramidal sign. The National Institutes of Health Stroke Scale score was 4. Brain magnetic resonance imaging with diffusion-weighted imaging showed an acute left brainstem infarction. On hospital day 18, 2 days after corticosteroid discontinuation, enteric-coated aspirin 100 mg once daily and atorvastatin 20 mg nightly were started orally. Symptoms gradually improved.

Muscle biopsy, obtained after corticosteroid exposure, was evaluated at Zhongda Hospital, Southeast University. The report described variation in myofiber caliber (30-90 micrometers), degeneration, necrosis, regeneration, and vacuolation, particularly in type I fibers, with abundant intramyofiber lipid accumulation (**Figure 1**). Ancillary stains showed focal reductions in oxidative enzyme activity and no abnormal sarcolemmal expression of the tested dystrophin, sarcoglycan, or dysferlin proteins. The pathology impression was possible lipid storage disease requiring clinical correlation. The original written report did not explicitly state that inflammatory infiltrates were absent; absence of inflammation was therefore not used to exclude inflammatory myopathy.

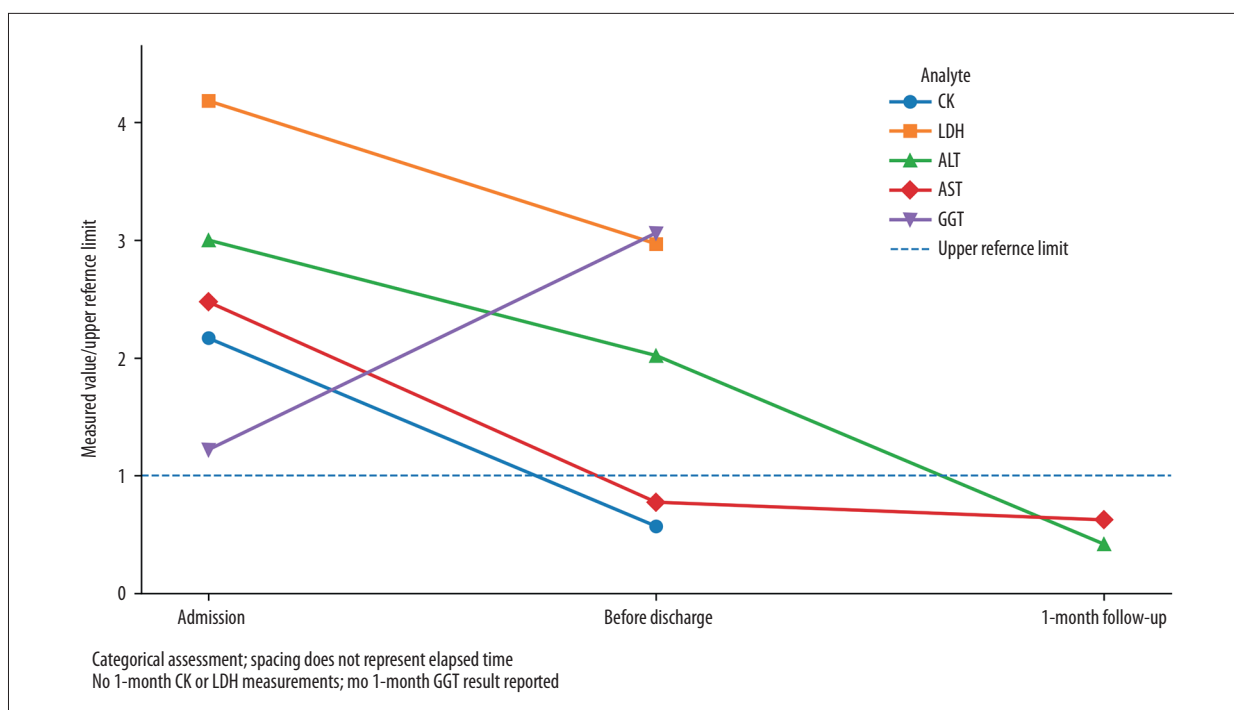


Figure 2. Biochemical course. Values are displayed as multiples of analyte-specific upper reference limits (ULN); the dashed line is 1x ULN. Raw values and abbreviations are in Table 1. Positions are categorical assessments, not elapsed time; lines are visual guides. CK and LDH were not rechecked at 1 month, and GGT was not reported; no values were imputed. The graph does not establish tissue source or treatment causality.

Following corticosteroid discontinuation, oral riboflavin 60 mg/day and coenzyme Q10 5 mg once daily by intravenous infusion were started on hospital day 22. Strength and exercise tolerance subsequently improved. Before discharge, CK was within its reference range and LDH had decreased but remained elevated; GGT had increased to 153 U/L. At 1-month follow-up, reported limb strength was MRC grade 5/5 and the patient was independent in daily activities. ALT and AST were within their reference ranges, but CK and LDH were not rechecked, and no follow-up GGT result was available (Table 1, Figure 2).

Guangzhou Oumeng Weiyi Medical Laboratory performed exome-capture sequencing of DNA from EDTA-anticoagulated blood (collected on March 31, 2023) on an Illumina platform, with phenotype-directed analysis for lipid storage myopathy and alignment to hg19. Mean sequencing depth was 179.6x; 96.72% of target regions had at least 20x coverage, and Q30 exceeded 90%. The relevant transcript was NM_004453.4. The sequencing instrument model and capture-kit name were not specified in the available laboratory report.

Sanger sequencing confirmed heterozygous *ETFDH* c.1227A>C (p.Leu409Phe; A/C) and c.1732C>T (p.Arg578Trp; C/T). The issuing laboratory classified the former as pathogenic and the latter as a variant of uncertain significance (VUS); these are the reported

classifications, not a new classification performed for this article. The laboratory-reported evidence labels were PM2_P+PM3_VS+PP3_M for c.1227A>C and PM2_P+PM3_P+PP3_M for c.1732C>T. Targeted family testing found c.1227A>C in the heterozygous state and the reference C/C genotype at c.1732 in the daughter, son, and grandson (Figure 3). This pattern was consistent with a likely trans configuration in the proband, but did not establish the pathogenicity of p.Arg578Trp or the cause of the grandson's gait unsteadiness.

The proband result pages were issued on April 25, 2023, and the family-validation report on July 4, 2023. These later laboratory records are presented as etiologic evidence and are not assumed to have been available when treatment began. Plasma acylcarnitine profiling, urinary organic acid analysis, electron transfer flavoprotein-ubiquinone oxidoreductase (ETF-QO) activity testing, RNA analysis, and variant-specific functional studies were not performed. The overall assessment remained probable *ETFDH*-related late-onset MADD rather than a definitive biochemical or biallelic molecular diagnosis.

Discussion

Three clinical lessons emerge from this case: reconsidering a metabolic myopathy after an unhelpful empirical corticosteroid

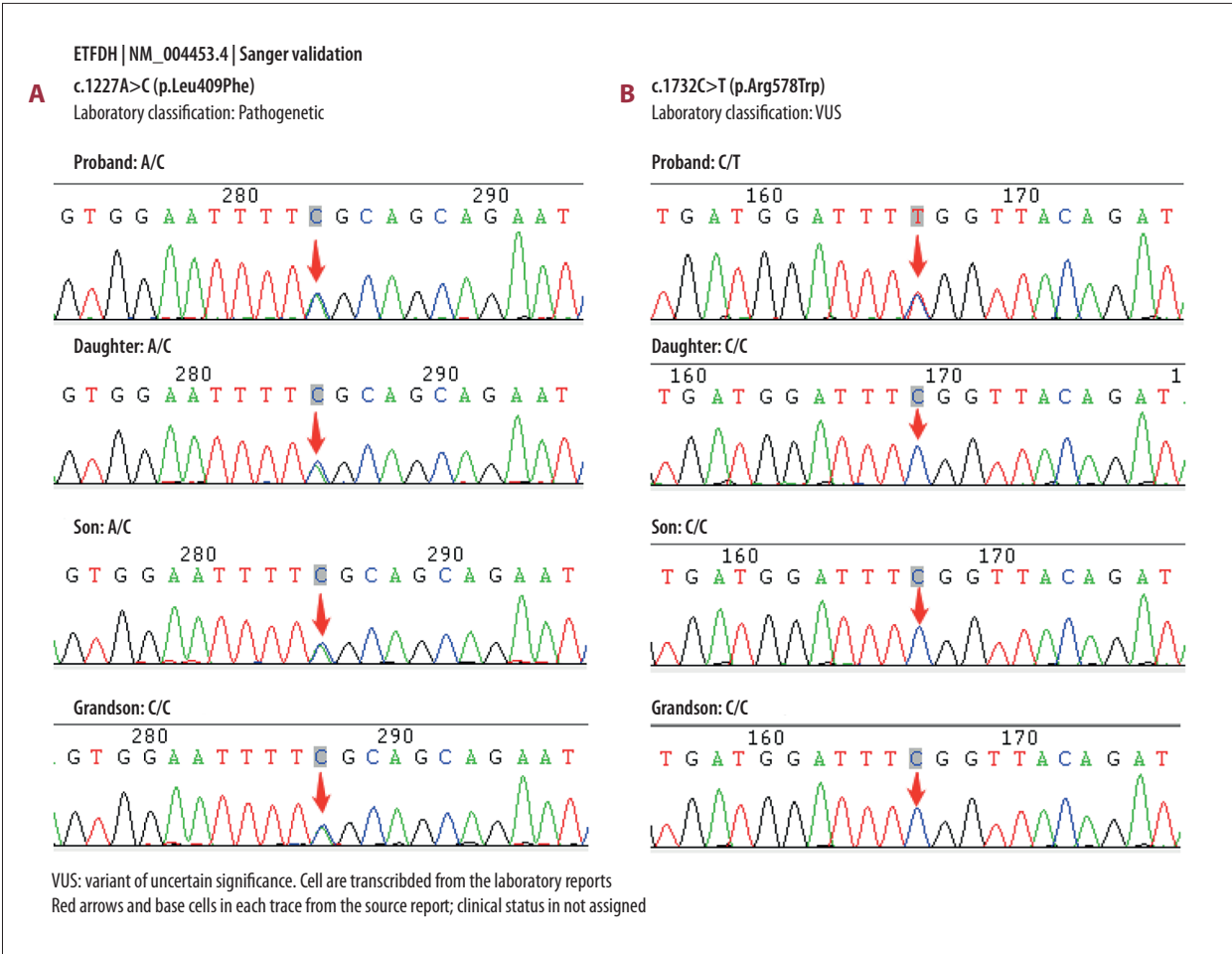


Figure 3. Source-derived Sanger results for *ETFDH* NM_004453.4. (A) c.1227A>C (p.Leu409Phe), laboratory-classified pathogenic. (B) c.1732C>T (p.Arg578Trp), laboratory-classified variant of uncertain significance (VUS). Proband genotypes were A/C and C/T; the daughter, son, and grandson were A/C and C/C, respectively. The traces were taken from the proband report (page 7) and the family-validation report (pages 1-2). Identifying headers were removed; source traces, arrows, and base calls were retained, with uniform integer pixel duplication for layout. Source strand orientation, including possible reverse-complement display, was retained. Genotypes neither establish VUS pathogenicity nor assign clinical status; the grandson's gait unsteadiness remained unexplained.

course, avoiding a single-source explanation for aminotransferase elevation, and separating a lipid-storage phenotype from a confirmed molecular etiology. Corticosteroid nonresponse is a reason to review the diagnosis, not an exclusion test for inflammatory myopathy. The biopsy redirected investigation because of its lipid-storage pattern, rather than because an absence of inflammation had been established [1,4,5].

The presentation overlaps with previously reported inflammatory-myopathy mimics. Zheng et al described an older adult with weakness, lipid-storage pathology, an abnormal acylcarnitine profile, and improvement with riboflavin [4]. Chen et al reported patients whose muscle-enzyme levels improved with glucocorticoids while muscle symptoms changed little before riboflavin treatment [2]. Tang et al and Wen et al integrated

clinical, pathological, metabolic, and genetic findings in their series [5,10]. Our patient shared proximal weakness and lipid accumulation, but lacked characteristic metabolic testing and complete molecular confirmation. Diabetes, hepatobiliary abnormalities, an intercurrent infarction, and short follow-up further limited interpretation; these differences, rather than a novel phenotype, define the report's contribution.

Skeletal muscle injury can contribute to elevated ALT and AST [6]. In this patient, CK elevation and lipid-storage pathology made such a contribution plausible, but ultrasonography showed hepatic and biliary abnormalities and GGT increased from 61 to 153 U/L before discharge. The biochemical pattern therefore could not be attributed predominantly to muscle. ALT and AST normalization at 1 month did not resolve

this uncertainty because CK and LDH were not rechecked and no follow-up GGT result was available. The relative muscular and hepatobiliary contributions remained undetermined (Table 1, Figure 2).

Peripheral neuropathy has been reported in adult MADD [7,8], but the present sensory-predominant abnormalities were not specific. Diabetes was a competing explanation, bedside sensory testing showed no clear deficit, and numerical electrophysiological data were unavailable. The neuropathy was therefore retained as a complicating observation rather than attributed to MADD. Likewise, gait unsteadiness in the grandson could not be assigned to MADD or to his single detected *ETFDH* variant.

The genetic findings supported investigation of *ETFDH*-related disease without confirming it. Although family segregation was consistent with likely trans configuration, phasing and variant pathogenicity are separate questions. Under the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) guidelines, a VUS should not be treated as proof of disease or used to direct clinical decisions [11]. The laboratory-reported c.1732C>T classification was retained; no functional validation or independent reclassification was undertaken. In the absence of characteristic metabolic testing, the combination of one pathogenic variant and one VUS did not establish a definitive biallelic molecular diagnosis.

Acquired lipid storage myopathy is an important alternative. Recent clinical and pathological studies described sertraline-associated lipid storage myopathy or MADD-like presentations, including improvement during riboflavin treatment [12,13]. A subsequent nationwide study further supported the relevance of this association [14]. The patient's reported absence of sertraline or other SSRI exposure provided no exposure-based support for this specific explanation, but did not establish a hereditary etiology or exclude other acquired causes. The direct evidence cited concerns sertraline and should not be generalized to a proven class effect of all SSRIs.

Other relevant categories include primary carnitine deficiency, neutral lipid storage disorders, other fatty acid oxidation or mitochondrial disorders, and endocrine or other drug-associated myopathies [1,3,13]. Thyroid testing was unremarkable and no pre-onset statin exposure was reported, but the available workup did not systematically exclude every alternative. Lipid accumulation and preserved staining for selected muscle proteins are not sufficient to resolve that broader differential.

Improvement during riboflavin-based therapy remained supportive but nonspecific. Prior reports document clinical improvement with riboflavin in *ETFDH*-associated disease [3,10], but the effect in this patient could not be isolated from coenzyme

Q10, corticosteroid withdrawal, or recovery after the brainstem infarction. The infarction was considered an intercurrent vascular event in a patient with hypertension and diabetes; no causal link to MADD or the corticosteroid course was established. Post-stroke recovery and concurrent secondary-prevention treatment further complicated attribution of the subsequent course. Atorvastatin was started after the year-long weakness and admission enzyme abnormalities had already been documented; its contribution to later biochemical findings could not be determined. Short-term improvement was not used as an independent verification of MADD or proof of riboflavin efficacy.

The principal limitations were absent metabolic and functional confirmation, biopsy after corticosteroid exposure, incomplete electrophysiological detail, coexisting hepatic and biliary disease, and 1-month clinical follow-up without repeat CK or LDH. The 4/5 strength entry in the clinical account and the undated 5-/5 entry in the genetic referral could not be reconciled into a reliable serial examination. The genetic report cover stated that the results were for research reference and not for clinical diagnosis, whereas the result pages described them as clinical-reference findings requiring correlation with symptoms and other investigations. Its findings were therefore treated as supportive laboratory evidence rather than independent clinical molecular confirmation. These limitations restrict etiologic certainty and treatment attribution.

Conclusions

This remains a probable, not definitive, *ETFDH*-related late-onset MADD case. Lipid-storage pathology and supportive genetic findings warranted reconsideration of a treatable metabolic myopathy, but 1 pathogenic variant plus a VUS and short-term improvement did not establish its etiology. No sertraline or other SSRI exposure was reported; that negative history did not replace biochemical or molecular confirmation. The transferable lesson is to reconsider the diagnosis while retaining acquired alternatives and uncertainty, rather than infer disease confirmation or treatment efficacy from improvement during combined therapy.

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Patient Consent for Publication

Written informed consent for publication of the clinical information and accompanying images was obtained from the patient. The signed consent form is retained by the authors and is available on request.

Ethics Approval

The requirement for ethics committee approval was waived for this anonymized single case report in accordance with institutional policy.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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