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Case Report

MADD-like pattern of acylcarnitines associated with sertraline use

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ABSTRACT

Multiple acyl-CoA dehydrogenase deficiency (MADD) is a primary mitochondrial dysfunction affecting mitochondrial fatty acid and protein metabolism, caused by biallelic pathogenic variants in ETFA, ETFB, or ETFDH genes. The heterogeneous phenotypes associated with MADD have been classified into three groups: neonatal onset with congenital anomalies (type 1), neonatal onset without congenital anomalies (type 2), and attenuated and/or later onset (type 3). Here, we present two cases with biochemical profiles mimicking late-onset MADD but negative genetic testing, associated with the use of sertraline, a commonly used antidepressant. Case 1 is a 22 yo woman diagnosed with depression and profound fatigue who was referred to the metabolic clinic because of carnitine deficiency and a plasma acylcarnitine profile with a MADD-like pattern. Case 2 is a 61 yo woman with a history of chronic fatigue who was admitted to the emergency department with difficulty swallowing, metabolic acidosis, and mild rhabdomyolysis. Plasma acylcarnitine profile showed a MADD-like pattern. The muscle biopsy revealed lipid droplet accumulation and proliferation of mitochondria with abnormal osmiophilic inclusions, and a biochemical assay of the respiratory chain showed a deficit in complex II activity. In both cases, urine organic acid profile was normal, and genetic tests did not detect variants in the genes involved in MADD. Sertraline was on their list of medications and considering its association with inhibition of mitochondrial function and rhabdomyolysis, the team recommended the discontinuation under medical supervision. In Case 1 after discontinuation, the plasma acylcarnitine test normalized, only to return abnormal when the patient resumed sertraline. In Case 2, after sertraline was discontinued rhabdomyolysis resolved, and the muscle biopsy and biochemical assay of the respiratory chain normalized. Although sertraline is considered a safe drug, these two cases suggest that the use of sertraline may be associated with a potentially reversible form of mitochondrial dysfunction mimicking MADD. Further studies are needed to confirm and estimate the risk of MADD-like presentations with the use of sertraline, as well as identifying additional contributing factors, including genetic factors. Metabolic physicians should consider sertraline use in the differential diagnosis of MADD, particularly when genetic testing is negative.

1. Introduction

Multiple acyl-CoA dehydrogenase deficiency (MADD), also called glutaric aciduria type 2, is a primary mitochondrial disorder that impairs adenosine triphosphate (ATP) biosynthesis, affects fatty acid and protein metabolism, causing excessive lipid accumulation in different organs and insufficient gluconeogenesis [1,2]. MADD is caused by biallelic pathogenic variants in *ETFA*, *ETFB*, or *ETFDH* genes encoding the electron transport flavoprotein (ETF) and ETF ubiquinone oxidoreductase (ETF:QO), which are involved in electron transfer in the mitochondrial respiratory chain [3]. The clinical presentation of MADD varies depending on the severity of the enzyme deficiency. The heterogeneous phenotypes associated with MADD have been classified into three groups: neonatal onset with congenital anomalies (type 1), neonatal onset without congenital anomalies (type 2), and attenuated and/or later onset (type 3) [1,4]. Treatment involves a diet restricted in

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fat and protein, fasting avoidance, and supplementation with riboflavin, with positive outcomes reported in most patients with MADD type 3 [4,5]. Biochemical diagnosis is based on the analysis of plasma acylcarnitines and urine organic acids. The characteristic acylcarnitine profile includes the elevation of several short-, medium- and long-chain acylcarnitine species, such as C4, C5, C6, C8, C10, C12, C14:1, C16, C18:1 (Fig. 1), and elevation of multiple organic acids in urine [5]. Diagnosis late-onset MADD is challenging due to the wide variability of the clinical presentation [4,6], which can resemble a general mitochondrial dysfunction. We present two cases with biochemical profiles mimicking late-onset MADD but negative genetic testing, associated with the use of sertraline, a commonly used antidepressant belonging to the class of selective serotonin reuptake inhibitors [7]. We propose that these cases represent an underappreciated, environmentally induced mitochondrial disorder, possibly related to an off-target impairment of mitochondrial function [8].

2. Cases

Case 1 is a 26-year-old woman diagnosed with depression, profound fatigue, psychogenic non-epileptic seizures, subclinical hypothyroidism, and heart palpitations. She was referred to the metabolic clinic because of carnitine deficiency and a plasma acylcarnitine profile showing elevations of medium- and long-chain acylcarnitine species with a MADD-like pattern (Fig. 2). Urine organic acid, urine acylglycine, and plasma amino acids profiles were normal (data not shown). Serum levels of creatine kinase were also normal. A gene panel including *ETFA, ETFB, and ETFDH* genes was nondiagnostic, showing single heterozygous variants of uncertain significance in genes associated with autosomal recessive conditions, though no variants were detected in genes associated with MADD (see supplemental file).

The patient was treated with riboflavin and carnitine supplementation and was encouraged to avoid fasting and increase caloric intake when ill. After four weeks of this treatment, repeat biochemical testing showed normalization of plasma carnitine levels, but an unchanged acylcarnitine profile, still showing a MADD-like pattern (Fig. 3A). Because of the nondiagnostic genetic testing and persistence of the abnormal biochemical profile despite riboflavin supplementation, the team investigated alternative causes of mitochondrial dysfunction including medications. Rare reports suggested possible cytotoxic effects of some antidepressant medications including sertraline, which was hypothesized to induce mitochondrial dysfunction through an effect on the electron transport chain [8,9]. Because at the time the patient was taking sertraline, the team recommended temporary discontinuation for three months, under medical supervision, to evaluate whether discontinuation modified the biochemical findings and clinical status. Three months after discontinuing sertraline, while still on carnitine and riboflavin supplementation, the patient reported mild improvement in fatigue. The plasma acylcarnitine profile normalized when off the medication. After resuming sertraline and still on both supplements, however, the MADD-like pattern reappeared (Fig. 3).

Case 2 is a 61-year-old woman who presented with chronic fatigue, exercise intolerance, proximal muscle weakness, and some leg spasticity. After several months, the patient was admitted to the emergency department with syncope, trismus, difficulty swallowing, metabolic acidosis and mild serum creatine kinase elevation (500 U/L; reference range: 26–192 U/L) which quickly increased to 2800 U/L (Fig. 5C). Biochemical tests were performed to exclude a possible metabolic disorder. Plasma acylcarnitine profile showed a MADD-like pattern (Fig. 4), whereas urine organic acids were normal (data not shown). A muscle biopsy was performed to further investigate this mild rhabdomyolysis and revealed lipid droplet accumulation and proliferation of mitochondria with abnormal osmiophilic inclusions (Fig. 5A, B). A biochemical assay of the respiratory chain was performed and showed an isolated deficit in complex II activity (data not shown). On chart review she was found to be taking sertraline, known to be associated with an increased risk for creatine kinase elevation [9,10]. Milder forms of the symptoms described were noted shortly after the patient began using sertraline. Moreover, the admission to the emergency department occurred after an increase of sertraline dosage to 100 mg\day. After sertraline discontinuation, serum levels of creatine kinase rapidly decreased. Twenty-four hours later, the team also initiated the nutritional interventions, including riboflavin supplementation and protein and fat restriction. The creatine kinase levels continued to decrease to 500 U/L (Fig. 5C) and normalized after several days. All symptoms also improved. A rhabdomyolysis genetic sequencing panel, including *ETFA, ETFB, and ETFDH* genes identified several heterozygous VUS in genes associated with autosomal recessive conditions (see supplementary data); however, no variants were detected in genes associated with MADD and Complex II deficiency. Respiratory chain assay (data not shown) and muscle biopsy (see supplementary data) were repeated two years after sertraline discontinuation while the patient was still on

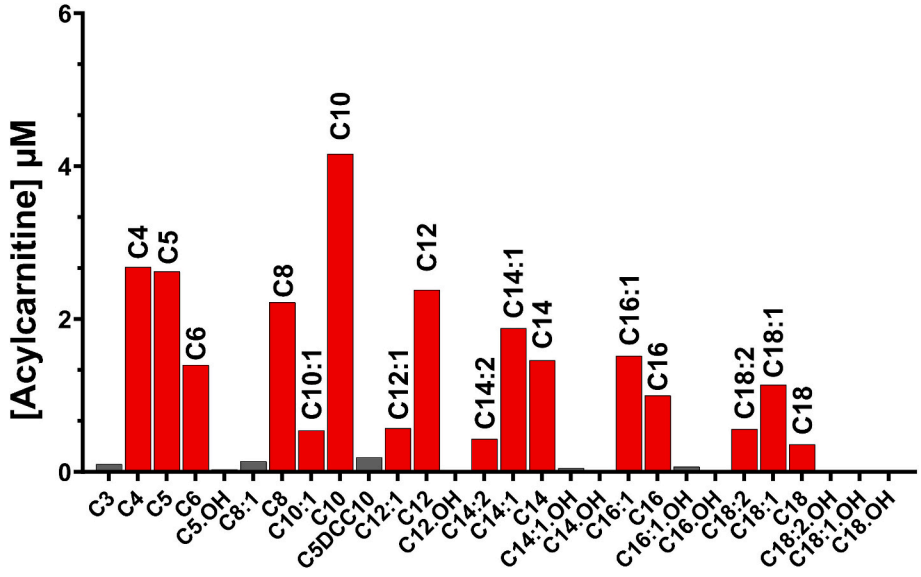
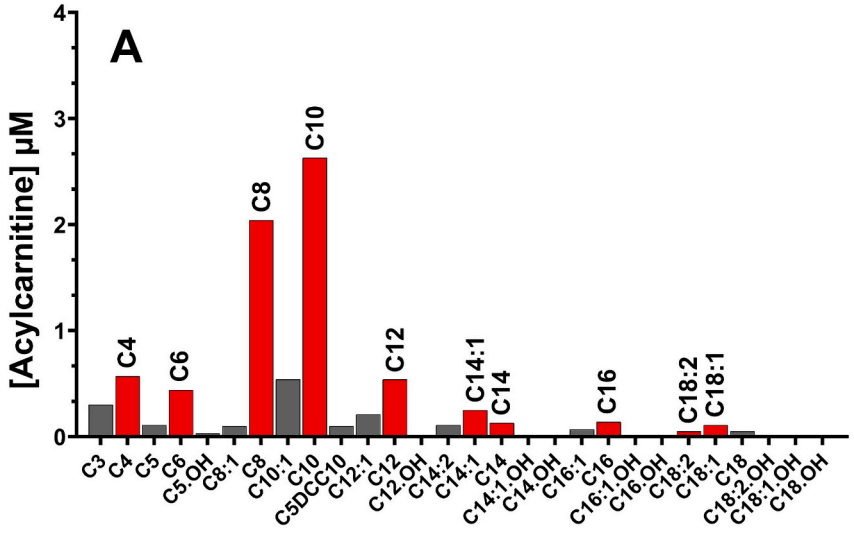


Fig. 1. Typical MADD plasma acylcarnitine profile showing elevated short-, medium-, and long-chain acylcarnitine species. Red bars indicate concentrations above the normal range.



B

Carnitine Free µmol/L	17	Ref. Range 25-60
Carnitine Total µmol/L	24	Ref. Range 34-86

Fig. 2. Case 1 plasma acylcarnitine profile with MADD-like pattern (A) and plasma levels of free and total carnitine (B). A. Red bars indicate concentrations above the normal range. Grey bars indicate concentrations in the normal range. B. Reference intervals based on age of the patient.

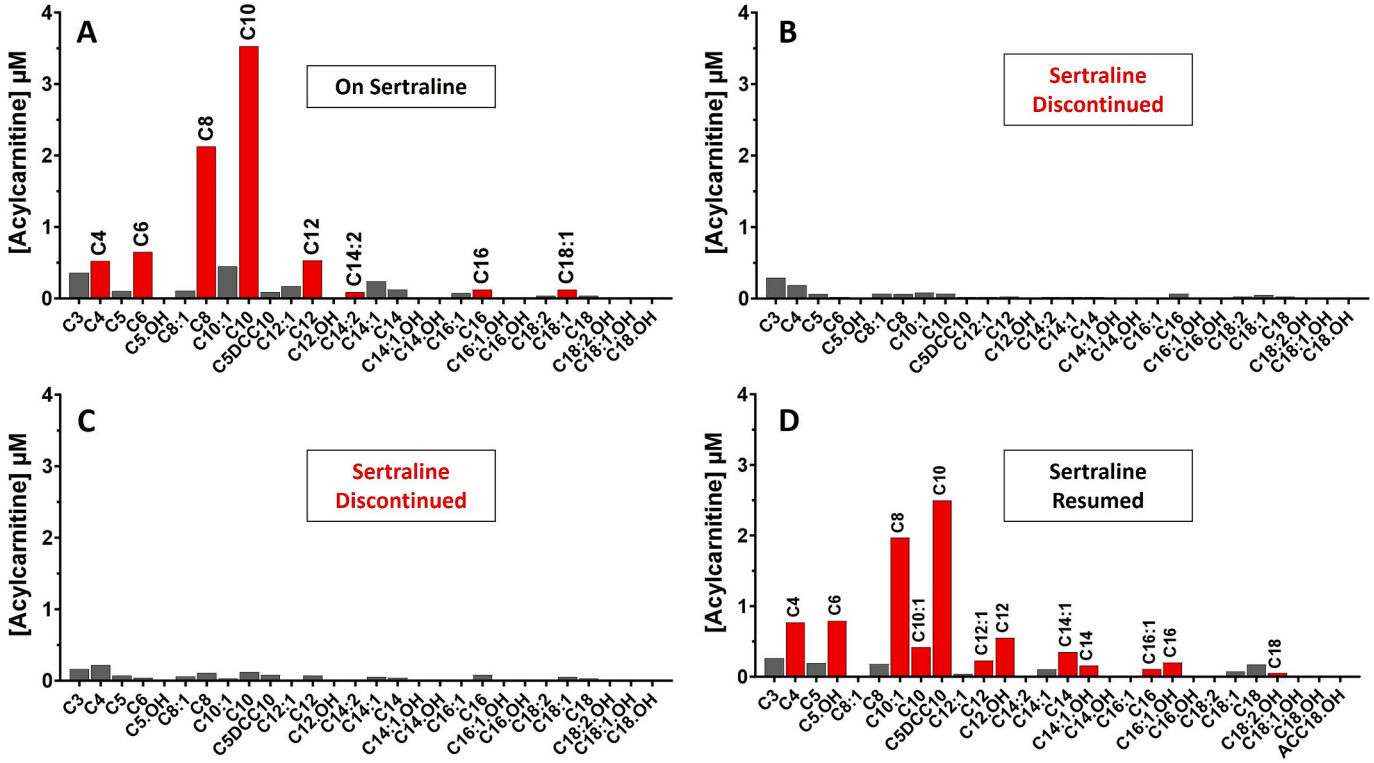


Fig. 3. Plasma acylcarnitine profiles on (A, D) and off sertraline medication (B, C). Sample D was collected after sertraline therapy was resumed. Red bars indicate concentrations above the normal range. Grey bars indicate concentrations in the normal range.

riboflavin supplementation, and both were normalized.

A. Light microscopy of muscle biopsy resin section showing lipid droplet accumulation in most fibers (arrow), with scattered fibers showing marked accumulation of dark-staining material (asterisk). B. Electron microscopy of individual dark-staining muscle fibers showing abundant lipid droplets (asterisk) and abnormally-shaped mitochondria with osmiophilic inclusions (arrows) (B). C. Serum creatine kinase levels on sertraline and after sertraline discontinuation. Day 1–6 (day of admission).

3. Discussion

Multiple acyl-CoA dehydrogenase deficiency (MADD) is an autosomal recessive disorder associated with impaired mitochondrial electron transfer chain function and affecting fatty acid oxidation and protein metabolism. The phenotypes associated with MADD have been classified into three groups: neonatal onset with congenital anomalies (type 1), neonatal onset without anomalies (type 2), and late onset (type 3). The late-onset form is highly variable and can present with fatigue, exercise intolerance, muscle weakness, and lipid storage in myofibers. This presentation resembles that of other neuromuscular disorders,

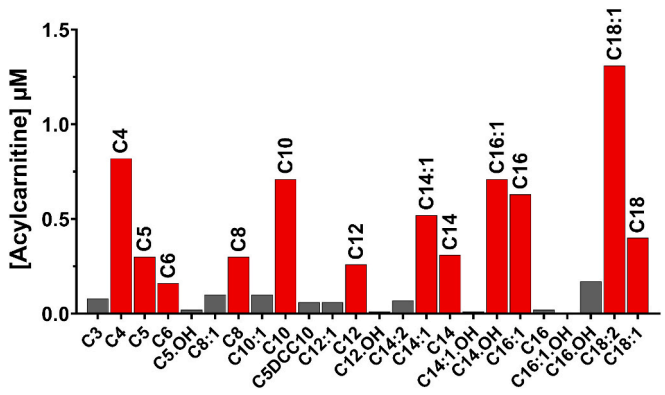


Fig. 4. Case 2 plasma acylcarnitine profile with MADD-like pattern. Red bars indicate concentrations above the normal range. Grey bars indicate concentrations in the normal range.

resulting in a challenging diagnostic situation [4,6]. In addition to genetic factors, mitochondrial function can be impaired by environmental factors, including drugs, resulting in varying degrees of metabolic dysfunction [10].

In the two cases presented here, the clinical presentation and biochemical data suggested late-onset MADD. Specifically, Case 1 presented with carnitine deficiency, abnormal plasma acylcarnitine profile, and marked fatigue. Case 2 presented with an abnormal plasma acylcarnitine profile, chronic fatigue, and elevation of creatine kinase. However, unlike most genetic forms of MADD, urine organic acid profile and urine acylglycine were normal. Some individuals with genetic forms of MADD show no significant abnormalities in biochemical testing, in particular in urine organic acids [4]. However, the lack of response to riboflavin supplementation in Case 1 and the absence of variants in the ETFA, ETFB, and ETFDH genes in both Cases raised doubts about the diagnosis of late-onset MADD. Moreover, although plasma levels of riboflavin were not assessed, the absence of variants in the *SLC52A1–3* and *FLAD* genes excluded genetic disorders affecting riboflavin transport and metabolism, whose symptoms resemble MADD [11].

Alternative diagnostic possibilities included the potential impact of depression [10] and antidepressant medication on mitochondrial function. Studies have suggested that some cases of depressive disorders may be linked to metabolic dysfunction, resulting in abnormal acylcarnitine profiles [12], and further hypothesized that the effectiveness of some antidepressant drugs could be mediated in part by the modulation of mitochondrial function [13,14]. However, other studies have suggested that antidepressant drugs may cause mitochondrial dysfunction [15]. Regarding sertraline, which both patients were taking, limited experimental evidence indicates that it could inhibit mitochondrial function through an effect on the electron transport chain [8,9], and cause rhabdomyolysis [16,17]. In case 1, a causative role for sertraline is suggested by the biochemical normalization when the patient was off sertraline and by the recurrence of the MADD-like acylcarnitine pattern after it was restarted (Fig. 3). In Case 2, the muscle biopsy showed lipid droplet accumulation in most fibers and mixed proliferation of mitochondria, whereas the mitochondrial function test showed reduced activity of complex 2. Because of the known correlation between sertraline and rhabdomyolysis, the antidepressant drug was discontinued, with rhabdomyolysis resolving two days after discontinuation (Fig. 5C). Repeat testing after two years of discontinuing sertraline while the patient was still on riboflavin supplementation showed normal function of mitochondrial complexes (data not shown) and normal muscle biopsy (see supplementary data).

In summary, the clinical presentation, biochemical profile, negative genetic testing, and improvement after sertraline discontinuation suggest that the use of sertraline may be associated with a potentially reversible form of mitochondrial dysfunction mimicking MADD. This association was also recently reported by Sunebo et al. [18], who presented seven patients without identified disease-causing mutations, all on sertraline treatment, with some of the reported symptoms such as fatigue, myalgia, myopathy, and proximal muscle weakness in common with the two cases presented here, however, the relatively common occurrences of a dropped head syndrome or sensory disturbances observed by Sunebo et al. were not observed in the two cases presented here.

Our data report the association between sertraline use and MADD-like presentation, which has also been observed by other research groups [18,19]. However, the limiting factors of this work, such as the lack of more comprehensive molecular testing, the retrospective aspect,

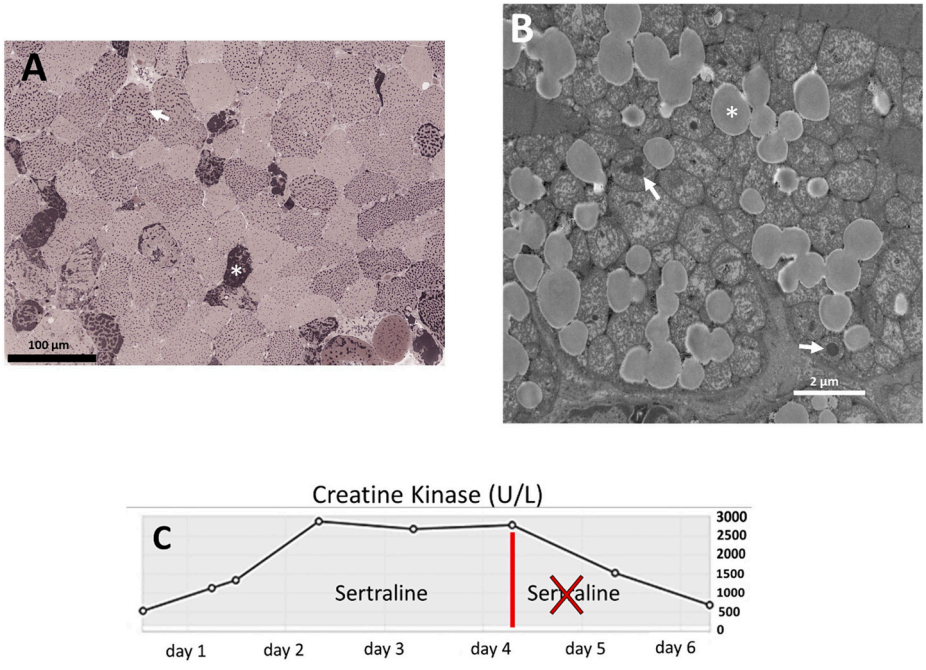


Fig. 5. Case 2 muscle biopsy results (A, B) and serum creatine kinase levels (C).

and the lack of consistency in the data available for the two cases, make further studies necessary to identify additional contributing factors, including genetic factors to confirm and estimate the risk of MADD-like presentations with the use of sertraline. It is possible that presentations such as those described here are more common than previously thought, as the biochemical testing (acylcarnitine profile, urine organic acids) required to identify MADD-like changes may not be commonly used in individuals on sertraline who have non-specific symptoms such as fatigue and exercise intolerance. Metabolic physicians should consider sertraline use in the differential diagnosis of MADD, particularly when genetic testing is negative.

CRediT authorship contribution statement

Filippo Ingoglia: Writing – original draft, Investigation, Data curation, Conceptualization. **Mohsen Tanfous:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Benjamin Ellezam:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Katherine J. Anderson:** Writing – review & editing, Investigation, Conceptualization. **Marzia Pasquali:** Writing – review & editing, Data curation, Conceptualization. **Lorenzo D. Botto:** Writing – review & editing, Investigation, Conceptualization.

Declaration of competing interest

None.

Data availability

The data that has been used is confidential.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2024.101142.

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