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LETTER TO THE EDITOR

Sertraline use in mitochondrial cytopathy-associated depression: A case report

Mehri Durak, Burcin Ozlem Ates

Gulhane Training and Research Hospital, Department of Child and Adolescent Psychiatry, Ankara, Turkiye

Dear Editor,

Mitochondrial cytopathies are a heterogeneous group of inherited metabolic disorders caused by defects in mitochondrial DNA or nuclear genes encoding mitochondrial proteins, leading to impaired oxidative phosphorylation and multisystem involvement (1). These disorders are increasingly recognized as contributors to neuropsychiatric conditions, including major depressive disorder. Indeed, the lifetime prevalence of depression has been reported to reach approximately 50% in adult patients with primary mitochondrial cytopathies (2). To date, reliable epidemiological data specific to adolescents with mitochondrial cytopathy are lacking. Moreover, evidence-based guidance for managing such psychiatric comorbidities remains scarce. Here, we report the case of a 16-year-old boy with a diagnosed mitochondrial cytopathy and co-occurring moderate intellectual disability. Written informed consent was obtained from the patient and his parents for publication of this case. Over the course of one year, he developed a persistent depressive syndrome characterized by low mood, anhedonia, social withdrawal, irritability, decreased verbal communication, loss of interest in recreational activities, and sleep disturbance, as reported primarily by his caregivers. Importantly, no psychotic features, such as hallucinations, delusions, or thought disorganization, were observed at any point during evaluation or follow-up, thereby ruling out a prodromal psychotic phase. Given his neurodevelopmental profile, self-report measures were not feasible. Instead, the evaluation relied on the parent-rated Revised Child Anxiety and Depression Scale (RCADS-P) depression subscale and clinician-administered Clinical Global Impression scales (CGI-Severity and CGI-Improvement) (3-6).

Prior to initiating treatment, a comprehensive medical work-up was conducted to rule out other potential contributors to depression—including thyroid dysfunction, anemia, infection, and metabolic disturbances—all of which were within normal limits on laboratory screening. There was no evidence of substance use or exposure to other medications. Establishing this baseline also allowed for monitoring of tolerability: importantly, no clinically significant laboratory abnormalities emerged during therapy. No mitochondrial disease-specific biomarkers (such as serum lactate or pyruvate) were systematically monitored during psychiatric follow-up. Treatment was initiated with low-dose sertraline at 12.5 mg/day and titrated to 25 mg/day after two weeks. Between months 2 and 5 (weeks 8–20), the patient experienced a mild and transient partial re-emergence of symptoms—chiefly anhedonia, irritability, and social withdrawal—with occasional early-morning awakening. Appetite and psychomotor activity remained unchanged. There were no psychotic features and no global clinical deterioration; school

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Correspondence: Mehri Durak, Gulhane Training and Research Hospital, Department of Child and Adolescent Psychiatry, Ankara, Turkiye
E-mail: dr.mehridurak@gmail.com

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attendance remained regular, although participation in social and recreational activities transiently declined. Adherence was confirmed through caregiver-reported pill counts (≥95% of doses taken) and pharmacy refill records. No medical or etiological trigger was identified: there were no intercurrent infections or changes in medications or supplements, and repeat laboratory tests at month 5 (complete blood count, comprehensive metabolic panel, thyroid function tests) were within reference ranges. In addition, throughout the two-year follow-up period, the patient underwent periodic electrocardiogram (ECG) evaluations, all of which were normal. Weight and body mass index (BMI) were monitored regularly and remained stable without clinically significant changes. Sleep patterns, as reported by caregivers, were not adversely affected during treatment. The sertraline dose was subsequently increased to 50 mg/day at month 5, after which symptoms resolved within two weeks and remained stable thereafter.

At baseline, the patient's RCADS-P Major Depression Subscale score was in the severe clinical range, with a CGI-S score of 6. Symptoms improved to the moderate range by week 4 and to the mild range by week 6, corresponding to a CGI-S score of 3 and a CGI-I score of 2 (much improved). A transient worsening occurred at month 5 (moderate range; CGI-S score of 4). Thereafter, progressive recovery was observed, with scores reaching the remission range (RCADS-P score of 10; CGI-S score of 2) at the two-year evaluation, while the CGI-I was consistently rated as 1 (very much improved). Functionally, the patient's school attendance, which had been irregular prior to treatment, normalized. He demonstrated increased classroom engagement and renewed participation in social and recreational activities, reflecting sustained improvement in daily functioning alongside symptom reduction.

Sertraline was selected as the initial antidepressant in this case due to its well-established safety and tolerability profile in adolescents, as well as its pharmacological properties. Its low inhibition of CYP2D6 and minimal pharmacokinetic interaction risk allow for safer combination with other medications (7). Its relatively low sedative potential is advantageous for patients already experiencing fatigue and low energy. Furthermore, its putative antioxidant effects, which may mitigate oxidative stress associated with mitochondrial cytopathy (8, 9), provide an additional therapeutic rationale. Nevertheless, some reports have raised concerns regarding potential adverse effects of selective serotonin reuptake inhibitors (SSRIs) in the context of mitochondrial cytopathies. Recent studies suggest that SSRIs may impair mitochondrial function (10), and sertraline-associated lipid storage myopathy with mitochondrial respiratory chain deficiencies has also been documented (11). These findings underscore the importance of cautious monitoring when prescribing SSRIs to patients with mitochondrial disorders. Taken together, these considerations suggest that sertraline represents a rational and safe treatment option for depression associated with mitochondrial cytopathy. However, larger clinical studies are needed to confirm its superiority over other SSRIs.

Our report adds to the limited literature on the management of depression in the context of mitochondrial disease. Previous case reports indicate that standard antidepressants can be used in this population. For example, an adolescent with MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) demonstrated clinical recovery from a depressive episode following escitalopram therapy, and an adult with MELAS showed a similarly positive response to the serotonin–norepinephrine reuptake inhibitor (SNRI) duloxetine (12, 13). These observations support the feasibility of using SSRIs and SNRIs in patients with mitochondrial disorders. To the best of our knowledge, this is the first report of an adolescent with mitochondrial cytopathy and comorbid depression who was successfully treated with sertraline for more than one year. We acknowledge the inherent limitations of literature searches and recognize that other relevant reports may exist but were not identified. Nevertheless, the present case is distinctive in that it combines adolescent age, the coexistence of mitochondrial cytopathy and depression, and a two-year follow-up demonstrating sustained remission, thereby contributing a unique perspective to the literature.

Optimal management of psychiatric comorbidities in rare metabolic conditions requires an individualized and collaborative approach. In our case, close coordination among psychiatry, neurology, and metabolic specialists was essential. We emphasize slow titration, regular monitoring of psychiatric status and somatic health, and active caregiver engagement as key elements of care. Importantly, there are currently no definitive treatment guidelines for depression associated with mitochondrial disease; management is largely informed by case reports and clinical judgment (12-14). Existing therapies for mitochondrial disorders remain primarily supportive, focusing on symptomatic relief (e.g., coenzyme Q10 and vitamin

supplementation) rather than disease modification (15). Although this single-case observation has inherent limitations, it illustrates that an SSRI, when selected thoughtfully and monitored carefully, can lead to significant and sustained improvement in a patient with mitochondrial dysfunction. Systematic research and controlled trials are needed to establish safe, evidence-based treatment strategies for psychiatric manifestations in mitochondrial disease.

Informed Consent: Written informed consent was obtained from the patient's legal guardian for publication of this case.

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