TREATMENT IN PSYCHIATRY

Psychiatric Implications of Mitochondrial Disorders

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CASE SCENARIO

A 51-year-old Caucasian female presents to your office with mood lability. She reports fatigue, anorexia, and intermittent gait instability. She suffers from word-finding difficulty and reports cognitive dulling.

Her medical history is significant for frequent vomiting as a child, ileitis at the age of 9, and polyarthritis and hearing loss since adolescence. She presents with a stunningly long diagnosis list that includes conversion disorder (1).

It is obvious that this is going to be a complicated case. The idea that her entire clinical picture could fit into one diagnosis appears unrealistic.

Mitochondrial diseases, a heterogeneous group of disorders, bring a lot of clarity to a confusing clinical picture. Decades of medical teaching and research have repeatedly highlighted mitochondria as "the energy factory" of the cell. Aside from oxidative phosphorylation and production of ATP, however, mitochondria play various other vital roles, such as maintaining the intracellular calcium homeostasis, regulating apoptosis, and supporting amino acid (such as neurotransmitters), lipid, and steroid metabolism.

PATHOPHYSIOLOGY

Mitochondrial dysfunction may result from maternally inherited or spontaneous (age- or malignancy-related) (2) mutations of the mitochondrial DNA, or from Mendelian mutations in the nuclear DNA encoding for mitochondrial proteins. "Hot spot" point mutations or deletions of the mitochondrial DNA lead to well-defined clinical syndromes such as MELAS [mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes], MERFF [myoclonic epilepsy with ragged red fibers], or CPEO [chronic progressive external ophthalmoplegia]. Other mutations cause more nonspecific clinical presentations, ranging from isolated myopathy or encephalomyopathy to multisystem disease (2). Organs with the highest energy requirement, such as the brain, skeletal and cardiac muscle, and kidneys, are the most commonly affected; however, symptoms in any organ or tissue can present itself at any age. Although symptoms range, some symptoms are more commonly seen than others (Table 1) (3). There is significant phenotypic variability, even among blood relatives, due to varying genotype, heteroplasmy rate (the mutant to normal mitochondria ratio within the cells), and threshold effect (the proportion of affected mitochondrial necessary to cause symptoms) of different tissues. Most patients are symptomatic at baseline with chronically elevated lactate levels. However, at times of increased energy demand, such as an infection, fever, heavy exercise, fasting, and temperature extremes, patients develop higher lactate levels and metabolic acidosis, resulting in worsening (or emergence) of symptoms, often combined with altered mental status (4). Longitudinal course of the illness shows a relapsing-remitting pattern, with incremental worsening and partial recovery (5).

Clinical experience shows that family history in these cases is positive for several medical and psychiatric disorders and, frequently, substance use disorders, giving the clinician the impression of a "cursed" family.

DIAGNOSIS

Based on the data available, overall prevalence is estimated to be 13.1/100,000 (6), making primary mitochondrial disorders the most common metabolic disorders. As a general rule, the involvement of three or more organ systems without a unifying diagnosis should raise suspicion for mitochondrial disease (7). Positive family history (especially if suggestive of maternal inheritance pattern), the presence of lactic acidosis, and white

TABLE 1. The Most Frequently Affected Organs and Symptoms of Mitochondrial Disorders[a]

Organ System	Symptoms
CNS	Developmental delay, mild cognitive dysfunction to mental retardation, seizures, cerebral palsy, migraines, strokes, dementia, myoclonus, dystonia, atypical white matter disease, areflexia, hypotonia, ataxia, neuropathic pain, psychiatric disturbances
Musculoskeletal	Weakness, cramps, myalgia
Renal	Proximal renal tubular wasting of electrolytes
Cardiovascular	Cardiac conduction defects, cardiomyopathy
Hepatic	Hepatic failure
Ophthalmic	Visual loss and blindness
Otologic	Hearing loss and deafness
Gastrointestinal	Reflux, constipation, pseudo-obstruction, exocrine pancreatic failure
Systemic	Failure to thrive

[a] For further details, see Brenner (reference 3).

matter changes on MRI are further red flags. Workup is best done at specialized centers and includes detecting an elevated lactate:pyruvate ratio, serum alanine levels, and serum acyl/free carnitine ratio, as well as elevated serum and urine organic acids. A myriad of additional tests (EMG, EKG, EEG, exercise testing, etc.) might be indicated, depending on the phenotype. Gold standard for diagnosis in the majority of cases is genetic testing from the skin or a muscle biopsy (postmitotic tissue), which is generally performed in specialized laboratories. Providers play a very important role in decreasing the time to diagnosis by referring patients for further testing in a timely manner. Challenging aspects of these cases are the atypical, multisystemic manifestation, the potentially incomplete phenotypic expression of the disease at the time when medical attention is sought, as well as the lack of reliable biomarkers for screening of these disorders (7).

PSYCHIATRIC INVOLVEMENT

Early case studies have documented the association between a variety of psychiatric disorders and mitochondrial dysfunction. A few systematic studies have been conducted and found high prevalence of psychiatric comorbidities, especially affective disorders, which were present in 42% (8) and 71% (54% major depressive disorder, 17% bipolar disorder) (9) of the cases in this patient population. Comorbid psychiatric diagnosis meant more hospital admissions (p=0.02), more medical conditions (p=0.01), and lower quality of life (p=0.01) (9). Cognitive deficits are also prevalent (10). Children present with developmental delays, learning difficulties (working in "spurts" and then "zoning out"), and, occasionally, hearing difficulties. It has been postulated that the CNS dysfunction is a result of impaired calcium homeostasis (11), altered synthesis and release of neurotransmitters (12), and altered receptor signaling and synaptic plasticity (13).

Patients might seek mental health treatment at the time when no physical signs of the illness are manifested (9). Psychiatrists, therefore, play a pivotal role in ensuring that the patient gets on the right trajectory. Thorough and detailed history taking, appropriate referrals, longitudinal follow-up, and ongoing interdisciplinary collaboration are all essential in the adequate management of these cases.

TREATMENT

General

Currently, there is no "cure" for these disorders. Realistic goals of the treatment are to alleviate symptoms and slow the progression of the disease. The majority of patients benefit from the empiric '"mitochondrial cocktail," which is the combination of vitamins and supplements aimed at slowing the progression of the disease and preserving mitochondrial function. "Cocktail" ingredients are creatine (increases ATP production), L-carnitine (transports molecules facilitating the metabolism of lipids to ATP), coenzyme Q_{10} (part of the energy transport chain), and B, C, and E vitamins, folic acid, and beta-carotenes (14) that mitigate the effect of enhanced oxidative stress. Interestingly, benefits of the interventions may take a few months to be noticeable or may never get noticed. However, they still may be effective in delaying the progression of the disease (14). According to a recent meta-analysis, only creatine has been shown to significantly benefit patients; however, the authors concluded that well-controlled trials are "essential building blocks in the continuing search" for better treatments (15). Newer agents are currently tested to potentially bypass the electron transport chain, alter mitochondrial dynamics, or shift the heteroplasmy rate. Cytoplasmic mitochondrial transfer is being considered as a therapeutic approach to mitochondrial DNA-related diseases. Dubbed a "three parent in vitro fertilization," this is a process that involves transfer of a third donor's cytoplasm and healthy mitochondria. Despite some success stories and the fact that it has been approved in the United Kingdom, studies in the United States await federal funding. Preimplantation genetic diagnosis may be able to provide carriers of mitochondrial DNA mutations the opportunity to conceive healthy offspring (16) in the future.

Psychiatry

Given that the etiology of psychiatric symptoms secondary to mitochondrial disorders somewhat differs from primary psychiatric disorders, it is no surprise that the symptoms show an atypical course. Furthermore, they may be resistant to or even exacerbated by usual psychopharmacologic treatment (17). Antipsychotics and antidepressants—selective serotonin reuptake inhibitors,

KEY POINTS/CLINICAL PEARLS

- Characteristics of cases with high suspicion for mitochondrial disease are the involvement of three or more organ systems without a unifying diagnosis, positive family history (especially if suggestive of maternal inheritance pattern), and the presence of lactic acidosis and white matter changes on MRI.
- These disorders might present with atypical, therapy-resistant psychiatric symptoms as first manifestation of the disease; therefore, psychiatrists play a pivotal role in timely referral to specialized centers. Clinicians should be aware of disease characteristics and obtain a comprehensive family history and medical review of systems.
- The importance of identifying these disorders cannot be overemphasized because of the implications for treatment. Commonplace psychotropics, including typical and atypical antipsychotics, selective serotonin reuptake inhibitors, and antiepileptics, interfere with important mitochondrial functions and may worsen symptoms. The medications can also have side effects that contribute to and worsen comorbid medical conditions. Frequently, it is the discontinuation of psychotropics and the use of a cocktail of mitochondrial supplements that improves symptoms.

mirtazapine, trazodone—inhibit several mitochondrial enzyme complexes (17). Antiepileptics inhibit overall mitochondrial function (18). It has been hypothesized that mitochondrial toxicity may contribute to side effects of psychotropic medications in a much wider population of patients (17). Patients with mitochondrial disorders show an increased susceptibility to side effects. Anticholinergic compounds can worsen cognitive decline and arrhythmia. Atypical antipsychotic drugs can aggravate metabolic syndrome in these patients, many of whom are already at risk for diabetes. It is therefore essential to weigh risks versus benefits when choosing medications. Experience shows that psychiatric symptoms might improve with the mitochondrial cocktail alone, which should be considered before progressing to psychopharmacologic interventions. Unfortunately, patients frequently end up on psychotropic polypharmacy, with questionable or no benefit.

PREVENTING EPISODES

General preventive measures—such as minimizing exposure to alcohol, tobacco, and chemicals, avoiding extreme temperature and sleep deprivation, proper management of infection, fever, and dehydration—are important in the prevention of medical and psychiatric relapses in patients with mitochondrial diseases. On a general note, special considerations are required for anesthesia, surgery, and immunizations for these patients. Modification of diet is also important. An anaplerotic diet, which consists of 4–6 complex carbohydrate/protein meals a day, has been shown to be beneficial (19). Fasting should be avoided at all costs, including prolonged overnight fasting (patients are educated to take a bedtime snack). Self-monitoring (20) is essential in order to address relapses in a timely manner. Healthy lifestyle discussions and patient education can go a long way with this patient population, and there are several websites (mitoaction.org; mitochondrialdiseases.org) to help providers and patients find reliable information.

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The author thanks Professors Maria Judit Molnar (Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Hungary) for her clinical supervision and help with this article, and Professor Salvatore DiMauro (Neurological Institute of New York, Columbia University) for reviewing this article. The author also thanks Dr. Rajarshi Bhadra for help with submission of this article.

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