# The Psychiatric Manifestations of Mitochondrial Disorders: A Case and Review of the Literature

*Rebecca E. Anglin, MD, FRCP(C); Sarah L. Garside, MD, PhD, FRCP(C); Mark A. Tarnopolsky, MD, PhD, FRCP(C); Michael F. Mazurek, MD, FRCP(C); and Patricia I. Rosebush, MScN, MD, FRCP(C)*

**ABSTRACT**

***Objective:*** Mitochondrial disorders are caused by gene mutations in mitochondrial or nuclear DNA and affect energy-dependent organs such as the brain. Patients with psychiatric illness, particularly those with medical comorbidities, may have primary mitochondrial disorders. To date, this issue has received little attention in the literature, and mitochondrial disorders are likely underdiagnosed in psychiatric patients.

***Data Sources:*** This article describes a patient who presented with borderline personality disorder and treatment-resistant depression and was ultimately diagnosed with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) 3271. We also searched the literature for all case reports of patients with mitochondrial disorders who initially present with prominent psychiatric symptoms by using MEDLINE (from 1948–February 2011), Embase (from 1980–February 2011), PsycINFO (from 1806–February 2011), and the search terms *mitochondrial disorder*, *mitochondria*, *psychiatry*, *mental disorders*, *major depression*, *anxiety*, *schizophrenia*, and *psychosis*.

***Study Selection:*** Fifty cases of mitochondrial disorders with prominent psychiatric symptomatology were identified.

***Data Extraction:*** Information about the psychiatric presentation of the cases was extracted. This information was combined with our case, the most common psychiatric manifestations of mitochondrial disorders were identified, and the important diagnostic and treatment implications for patients with psychiatric illness were reviewed.

***Results:*** The most common psychiatric presentations in the cases of mitochondrial disorders included mood disorder, cognitive deterioration, psychosis, and anxiety. The most common diagnosis (52% of cases) was a MELAS mutation. Other genetic mitochondrial diagnoses included polymerase gamma mutations, Kearns-Sayre syndrome, mitochondrial DNA deletions, point mutations, twinkle mutations, and novel mutations.

***Conclusions:*** Patients with mitochondrial disorders can present with primary psychiatric symptomatology, including mood disorder, cognitive impairment, psychosis, and anxiety. Psychiatrists need to be aware of the clinical features that are indicative of a mitochondrial disorder, investigate patients with suggestive presentations, and be knowledgeable about the treatment implications of the diagnosis.

*J Clin Psychiatry 2012;73(4):506–512*

*© Copyright 2012 Physicians Postgraduate Press, Inc.*

***Submitted:*** *June 30, 2011; accepted September 6, 2011. (doi:10.4088/JCP.11r07237).*
***Corresponding author:*** *Rebecca E. Anglin, MD, FRCP(C), F413-1 Fontbonne Bldg, St Joseph's Healthcare, 50 Charlton Ave E, Hamilton, Ontario, L8N 4A6 (anglinr@mcmaster.ca).*

Mitochondria are considered the "power plants" of the cell and generate the majority of cellular energy in the form of adenosine triphosphate. The proteins required for mitochondrial function derive from 2 genetic sources. The majority of proteins required for mitochondrial function are encoded by nuclear DNA and transported into the mitochondria.[1] In addition, mitochondria contain their own 16.6 kilobase circular genome that is entirely maternally inherited and encodes for important mitochondrial proteins. As a result, gene mutations in mitochondrial or nuclear DNA that impair mitochondrial function and result in deficient energy production can give rise to clinical syndromes known as mitochondrial disorders.[2] Mitochondrial disorders typically present with multiple symptoms affecting highly energy-dependent tissues such as muscle and brain. It is not commonly recognized that psychiatric illness may be the presenting feature of a mitochondrial disorder. We present a case of a patient with borderline personality disorder and treatment-resistant depression who was diagnosed with mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) 3271 and discuss the diagnostic and treatment implications of the psychiatric manifestations of mitochondrial disorders.

## CASE PRESENTATION

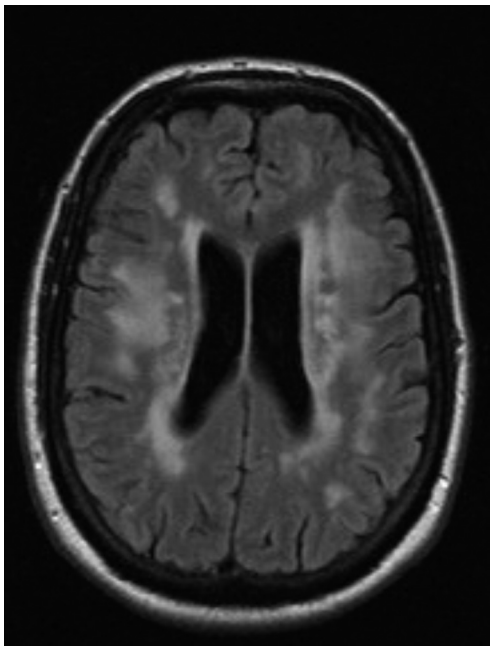
Ms A, a 45-year-old single woman, was a graduate student when she presented to treatment center with a 2-week history of low mood, disturbed sleep, anergia, suicidality, and auditory hallucinations. These symptoms developed in the context of the stress associated with placing her mother in a nursing home. She was diagnosed with psychotic depression and prescribed sertraline 300 mg/d, perphenazine 8 mg/d, and lorazepam 4 mg/d. Despite treatment with multiple psychotropics, her depressive symptoms persisted. Approximately 2 years later, while still on the same pharmacologic regimen, she expressed concern about a possible decline in her memory and general intellect. Cognitive testing revealed a full-scale IQ of 95. Over the next 3 years, she remained on the aforementioned medications but continued to experience cognitive decline, had to leave her academic program, and was supported by social assistance. At the end of this 3-year period, she was referred to us for evaluation.

### Personal and Psychiatric History

Ms A was born prematurely at 2 lb 11 oz, but she otherwise had a normal developmental history. Her siblings,

© COPYRIGHT 2012 PHYSICIANS POSTGRADUATE PRESS, INC. © COPYRIGHT 2012 PHYSICIANS POSTGRADUATE PRESS, INC.

**Figure 1. Cranial Magnetic Resonance Imaging at Presentation Showing Extensive Periventricular White Matter Abnormalities**



whom we interviewed, described her as shy, sensitive, and "always odd" as a child. She was an average student in school but had longstanding problems with math and right-left orientation, which was subsequently confirmed during cognitive testing.

At age 16 years, Ms A had an episode of "confusion" and "auditory hallucinations" for which she was hospitalized and treated with electroconvulsive therapy (ECT). Both she and her family felt that she worsened with this treatment, although she eventually recovered and completed high school. During her twenties she was employed full time but experienced intermittent depression and engaged in self-mutilating behaviors and substance abuse. She had 2 psychiatric admissions and was followed by an outpatient psychiatrist. At age 39, she entered graduate school as a mature student and completed her Master's degree. At age 41, she was accepted into a PhD program.

### Past Medical History

Although Ms A was born premature, there were few complications other than retinopathy of prematurity. As a child she was seen as "sickly" and "always tired" such that she could not swim, engage in sports, or ride a bicycle. She was frequently seen by her family doctor for fatigue and weakness and was treated with injections of immunoglobulins. She had a history of asthma. As an adult, she developed hypertension and type 2 diabetes mellitus and was diagnosed with left-sided carpal tunnel syndrome, which was successfully treated with surgery.

**Clinical Points**

- Patients with mitochondrial disorders may present with psychiatric symptoms.
- Many psychotropic medications can impair mitochondrial function or have side effects that may worsen medical conditions associated with mitochondrial disorders.
- Psychiatrists should take a detailed personal and family medical history in all patients, appropriately investigate patients with suggestive clinical presentations, and be aware of the treatment implications of the diagnosis of a mitochondrial disorder.

### Family History

Ms A's mother developed a dementia of unknown etiology at age 70 years, with rapid functional decline and death at age 75. Prior to our patient's birth, she had a history of 2 miscarriages, 1 stillbirth, 1 child who died in infancy, and a prolonged postpartum depression for which she was hospitalized and treated with ECT. Her father carried a diagnosis of bipolar affective disorder and had a history of prostate cancer and chronic obstructive pulmonary disease. He died in his seventies from "dementia." Of her 4 siblings, 1 of Ms A's sisters had an episode of depression, a second was being treated for panic disorder, and a third had problems with substance abuse. A maternal uncle had died prematurely in his sixties of a "circulation problem," and a second maternal uncle had a premature dementia in his sixties.

### Clinical Assessment and Mental Status Examination

Ms A presented as an alert, fully oriented, short, masculine-looking woman. In addition to her cognitive concerns, depressed mood, and suicidality, she described ongoing intermittent auditory hallucinations. Cognitive testing revealed impaired short-term memory and word fluency, a poor fund of general knowledge out of keeping with her academic achievements, and a full-scale IQ of 88. On the initial neurologic examination, she had markedly reduced arm swing on the left compared to the right. Reflexes were brisk with 2 to 3 beats of clonus at the ankle. Her plantar response was flexor bilaterally. A positive glabellar tap and bilateral palmomental reflexes were elicited. She had mild dysdiadochokinesia on her left side. The remainder of the neurologic examination was unremarkable.

### Investigations

Routine blood work was normal. Cranial magnetic resonance imaging (MRI) was grossly abnormal with extensive periventricular white matter abnormalities adjacent to the occipital horns of both lateral ventricles, consistent with demyelination (Figure 1). Subsequent investigations, including lumbar puncture (with testing for oligoclonal bands), cerebral angiography, electroencephalogram (EEG), and extensive serologic testing (folate, fasting homocysteine, thyroid stimulating hormone, antinuclear antibodies,

© Copyright 2012 Physicians Postgraduate Press, Inc.

© Copyright 2012 Physicians Postgraduate Press, Inc.

antineutrophil cytoplasmic antibody, perinuclear antineutrophil cytoplasmic antibody, rheumatoid factor, complement, cortisol, lactate, pyruvate, human immunodeficiency virus (HIV), very long chain fatty acids, aryl sulfatase activity, hexosaminidase, and galactocerebrosidase levels) were all normal. Her vitamin $B_{12}$ level was low at 127 pmol/L (normal range, 133–500). Ophthalmologic assessment including slit lamp examination revealed only left amblyopia and retinal changes due to prematurity. Subcortical auditory-evoked responses showed sensorineural hearing loss bilaterally. Visual-evoked responses showed delays of the P100 and N120 components from the left eye, consistent with demyelination. Mitochondrial genetic analysis for 2 mutations (MELAS 3271 and 3243) performed on blood samples at 2 separate laboratories were both negative. Muscle biopsies of the right deltoid and vastus lateralis showed a single ragged red fiber and increased lipid staining. These results were judged to be diagnostically inconclusive for a mitochondrial disorder.

### Course of Illness

Over the next 12 months, Ms A continued to experience depression and auditory hallucinations despite treatment with sertraline and perphenazine. She complained of ongoing memory impairment, periods of extreme fatigue, hand clumsiness (left greater than right), gait unsteadiness, paresthesias, dysphagia, word-finding problems, and intermittent urinary and fecal incontinence. She was unable to return to her studies or to work and became dependent on social assistance. Her neurologic examination fluctuated over time. She intermittently displayed ptosis, dysarthria, hand dystonia, dysmetria and dysdiadochokinesia, decreased strength and coordination, a positive Romberg sign, and impaired tandem gait. The majority of her findings were worse on the left side compared to the right. She continued to have very brisk reflexes and 2 to 3 beats of clonus, with a flexor plantar response on the right and an equivocal response on the left.

A second MRI, carried out 18 months following the first scan, revealed worsening of the white matter abnormalities. Repeat neurocognitive testing demonstrated no significant change in her overall IQ (IQ 90). A repeat muscle biopsy did not show any pathological abnormalities. Genetic analysis on fibroblasts subsequently demonstrated a MELAS 3271 mutation, a maternally inherited point mutation of the mitochondrial DNA.

### Follow-Up

Ms A continued to be depressed and experienced ongoing auditory hallucinations. Given her lack of response to psychotropic medications, these were tapered and discontinued. This intervention was followed, over a 1-year period, by significant improvement in her psychiatric symptoms and cognitive functioning to the point that she was able to return to work. Repeat neurocognitive testing 10 years after her original presentation showed significant improvement, and her IQ was measured at 99. At the time of this report, our patient has been working full time for 9 years. Serial MRI scans have been virtually unchanged from her second scan. For her mitochondrial disorder, she is currently treated with coenzyme Q10, α-lipoic acid, vitamin $B_2$, vitamin C, vitamin D, vitamin E, and creatine monohydrate.

## REVIEW

Our patient presented with a childhood history of fatigue and a long-standing history of psychiatric problems, including borderline personality disorder and treatment-resistant major depressive disorder with psychotic features (diagnosed using *DSM-IV-TR*[3] criteria by several psychiatrists). She was referred to our service for ongoing psychiatric symptoms and a subjective sense of cognitive dysfunction while on psychotropic medications. A cranial MRI revealed significant white matter pathology, which prompted extensive investigations and ultimately led to the diagnosis of a mitochondrial disorder.

Mitochondrial disorders have only recently been described, with the first pathogenic mutation identified in 1988.[4] Since that time, it has become apparent that they are much more common than previously appreciated, with an estimated prevalence of 12–16 cases per 100,000 persons.[5,6] While mitochondrial disorders have typically been named based on common phenotypes, such as MELAS, it is now recognized that patients with a particular gene mutation can present with a variety of phenotypes and that a particular phenotype can be associated with several different gene mutations.

Patients with mitochondrial disorders generally present with unexplained symptoms involving multiple organ systems, including fatigue, muscle weakness, migraines, diabetes, cardiac problems, constipation, hearing loss, recurrent miscarriages, strokes, and seizures.[2] The brain, as an intensely energy-dependent tissue, is particularly vulnerable to the effects of mitochondrial dysfunction. There has been considerable interest in the possibility that mitochondrial dysfunction may play a role in the pathophysiology of psychiatric illnesses such as bipolar disorder and schizophrenia.[7] To date, however, the psychiatric presentation of mitochondrial disorders has been underrecognized in the fields of mitochondrial medicine and psychiatry.

The prevalence of mitochondrial disorders in patients with psychiatric illness is not known, and genetic mitochondrial mutations have not been systematically investigated in sufficiently large samples of psychiatric patients. A single study[8] has assessed the rates of psychiatric comorbidity in adults with mitochondrial disorders and found that 70% of the 36 patients interviewed met criteria for a major mental illness. The literature on patients with mitochondrial disorders who initially present with prominent psychiatric symptoms is currently limited to case reports.

## DATA SOURCES AND STUDY SELECTION

A search of MEDLINE (from 1948 to February 2011), Embase (from 1980 to February 2011), PsycINFO (from

© Copyright 2012 Physicians Postgraduate Press, Inc.

© Copyright 2012 Physicians Postgraduate Press, Inc.

**Table 1. Summary From 50 Cases of the Psychiatric Presentation of Mitochondrial Disorders**

| Psychiatric Presentation | N[a] | Mutations (n) | References[b] |
|---|---|---|---|
| Major depressive disorder | 22 | POLG (7), MELAS (4), unknown (3), other (8) | 9,14,16,18,23,27,31,35,38,41–45,46,48,49 |
| With psychotic features | 14 | POLG (6), MELAS (1), unknown (3), other (4) | 9,14,16,18,35,38,41–44,48,49 |
| Bipolar disorder | 2 | KSS (1), ANT1 gene mutation (1) | 34,47 |
| Cognitive impairment | 19 | MELAS (11), POLG (2), KSS (1), other (5) | 10,11,13,17,18,20,24,26,29,32,34,36,37,39,40,43–45,49 |
| Psychotic disorder | 17 | MELAS (15), KSS (1), C3256T mutation (1) | 10–13,15,17,19,20,24,26,28,29,30,32,33,36,37,39,40 |
| Anxiety disorder | 6 | MELAS (6) | 22,23,27 |
| Frontal lobe syndrome | 4 | MELAS (3), twinkle mutation (1) | 17,21,30,35 |
| Personality change | 2 | MELAS (2) | 21,30 |
| Psychosomatic disorder | 1 | KSS (1) | 25 |

[a]The majority of patients had more than 1 diagnosis. [b]Some references included more than 1 case.
Abbreviations: KSS = Kearns-Sayre syndrome, MELAS = mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes, POLG = polymerase gamma mutation.

1806 to February 2011) using the search terms *mitochondrial disorder, mitochondria, psychiatry, mental disorders, major depression, anxiety, schizophrenia,* and *psychosis* revealed 50 reported cases of patients with mitochondrial disorders presenting with psychiatric symptoms (Table 1).[9–49] We also reviewed bibliographies of retrieved articles, relevant review articles, and book chapters and contacted corresponding authors for missing information.

## DATA EXTRACTION

Information about the psychiatric presentation of the cases was extracted. This information was combined with our case, and the most common psychiatric manifestations of mitochondrial disorders were identified, and the important diagnostic and treatment implications for patients with psychiatric illness were reviewed.

## RESULTS

The most common psychiatric presentations in the cases of mitochondrial disorders included mood disorder, cognitive deterioration, psychosis, and anxiety. The most common diagnosis (52% of cases) was a MELAS mutation. Other genetic mitochondrial diagnoses included polymerase gamma mutations, Kearns-Sayre syndrome, mitochondrial DNA deletions, point mutations, twinkle mutations, and novel mutations.

## DISCUSSION

Ms A's case and the other case reports of patients with mitochondrial disorders presenting with psychiatric symptoms raise several important questions that are of particular interest to psychiatrists.

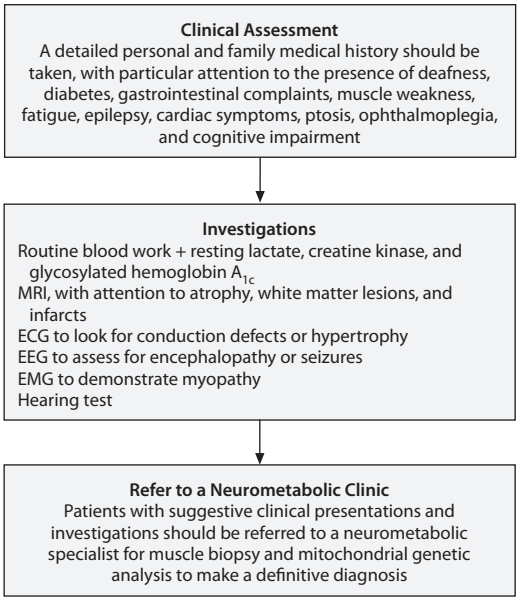
### What Features Should Alert a Psychiatrist to Consider a Mitochondrial Disorder?

Several features should prompt consideration of a mitochondrial disorder diagnosis:

1. *Abnormal neurologic investigations.* In the case of Ms A, the diagnosis was considered as a result of extensive white matter abnormalities on MRI, which is a common feature of mitochondrial disease. Generalized cerebral and cerebellar atrophy, focal lesions in the deep gray matter structures, basal ganglia calcification, and stroke-like lesions that do not follow vascular territories may also be seen on neuroimaging.[50] Other neurologic investigations that may be abnormal include EEG, electromyography (EMG), and visual- or auditory-evoked potentials.
2. *A past medical history of multiple medical problems affecting several organs*. In particular, involvement of energy-dependent organs, such as the brain (cognitive impairment, strokes, seizures, migraines), heart (cardiomyopathy, conduction abnormalities), and muscle (fatigue and atrophy), and the presence of other key features of mitochondrial disorders, such as short stature, diabetes mellitus, severe or chronic constipation, sensorineural hearing loss, recurrent miscarriages, ptosis, and ophthalmoplegia. Patients with mitochondrial disorders may present with unexplained neurologic symptoms or multiple unusual symptoms affecting different organ systems and therefore may be misdiagnosed as having conversion disorder or somatization disorder.
3. A *significant family medical history.* A history of classic mitochondrial symptoms, multiple medical problems, or unusual neurologic symptoms, particularly in maternal relatives, is suggestive of a mitochondrial disorder, reinforcing the importance of obtaining a thorough family medical history as part of a psychiatric assessment.
4. *Treatment resistance or worsening clinical status with psychotropic medications*. These clinical features are, in our opinion, important clues that should cause one to rethink the nature of the primary psychiatric diagnosis and, in the context of other suggestive features, consider an underlying mitochondrial disorder in the differential. Ms A had such a history, and her psychiatric symptoms improved dramatically after gradual tapering of her psychotropic medications and initiation of mitochondrial supplements.

© COPYRIGHT 2012 PHYSICIANS POSTGRADUATE PRESS, INC. © COPYRIGHT 2012 PHYSICIANS POSTGRADUATE PRESS, INC.

**Figure 2. How to Diagnose Mitochondrial Disorders**




Abbreviations: ECG = electrocardiogram, EEG = electroencephalogram, EMG = electromyography, MRI = magnetic resonance imaging.

## How Might Mitochondrial Disorders Give Rise to Psychiatric Symptoms?

It is likely that the white matter abnormalities associated with mitochondrial disorders play an important role in the development of psychiatric symptoms. White matter involvement is common in mitochondrial disorders, occurring in up to 90% of patients,[51] and may give rise to psychiatric symptoms by disrupting pathways that connect different parts of the brain involved in emotion, thought, and behavior. In addition, the brain is especially energy dependent, and any compromise in adenosine triphosphate production may lower the threshold and reduce the safety margin for the development of psychiatric disorders in those with other risk factors for mental illness. For example, Ms A had a history of psychiatric illness in both her mother and father and also had vitamin $B_{12}$ deficiency, which can present with neuropsychiatric symptomatology. Although she clearly inherited a mitochondrial mutation from her mother, it is possible she also inherited a genetic predisposition to psychiatric illness from her father, and the interaction of the two, combined with $B_{12}$ deficiency, resulted in the crossing of a threshold and her development of psychiatric illness.

Patients with mitochondrial disorders frequently experience profound fatigue, cognitive dysfunction, and illness throughout their lives, as was the case with Ms A. This can impair their ability to partake in many activities, lead to low self-esteem, and influence interpersonal relationships, culminating in an Axis II or perhaps Axis I disorder. Finally, patients with mitochondrial disorders often grow up with family members who are chronically unwell as a result of an underlying mitochondrial disorder. Such an environment has the potential to negatively affect early life experience and the ability to develop normal and secure attachments, which may in turn increase the risk of developing a psychiatric illness.

## How Does One Make the Diagnosis of a Mitochondrial Disorder?

Patients with suspected mitochondrial disorders should undergo a thorough clinical assessment, including a review of systems, past medical history, and family medical history (Figure 2). In particular, patients should be asked specifically about their maternal family medical history and any family history of neonatal or childhood deaths, recurrent miscarriages, deafness, diabetes, gastrointestinal complaints, epilepsy, cardiac symptoms, visual impairment, and developmental delay.[52]

Clinical investigations can support the diagnosis and may include (1) determination of creatine kinase, resting blood lactate, complete blood count, creatinine, urea, electrolytes, liver function tests, thyroid stimulating hormone, blood glucose, and glycated hemoglobin $A_{1c}$; (2) an electrocardiogram to determine the presence of cardiac conduction defects or hypertrophy; (3) EEG to assess for generalized slowing (suggestive of encephalopathy) or seizure activity; (4) EMG to demonstrate myopathy; (5) auditory testing to detect hearing loss; and (6) MRI and computerized tomography to look for characteristic abnormalities. Interested readers are referred to recent reviews,[53,54] which outline in more detail the investigations involved in diagnosing mitochondrial disorders.

Patients with classic clinical presentations or those with suggestive features and abnormal clinical investigations should be referred for further investigation. A muscle biopsy may be performed to measure mitochondrial enzyme activities and look for characteristic abnormalities including subsarcolemmal accumulations of mitochondria termed *ragged red fibers* and cytochrome oxidase negative fibers. As a result of variable distribution of mutant mitochondria within a tissue, it is possible to get different results on separate muscle biopsies, as occurred with Ms A. Molecular genetic testing can be performed to definitively identify pathogenic nuclear DNA or mitochondrial DNA mutations. Although testing can be performed on blood, saliva, cultured fibroblasts, or muscle, muscle specimens have the highest yield for detecting mitochondrial DNA mutations and are preferred. In Ms A's case, genetic testing on blood failed to detect any mutations, and analysis of fibroblasts was required to make the diagnosis.

## What Are the Treatment Implications of the Diagnosis?

Currently there is no curative treatment for mitochondrial disorders. Although there is mixed evidence from randomized controlled trials, supportive treatment with supplements, including creatine and coenzyme Q10 (ubiquinone), are generally initiated.[55–57] Identification and appropriate treatment of medical conditions associated with mitochondrial disorders, such as diabetes mellitus, seizures, constipation,

© Copyright 2012 Physicians Postgraduate Press, Inc. © Copyright 2012 Physicians Postgraduate Press, Inc.

cardiac conduction abnormalities, and ptosis, are important in the management of these patients.

The diagnosis of a mitochondrial disorder has particularly important treatment implications for patients with psychiatric illness, as certain psychotropic medications can interfere with mitochondrial function.[58] For example, antipsychotic medications (both typical and atypical) have been shown to inhibit complex I of the respiratory chain and therefore may worsen symptoms,[59] and valproic acid can cause a secondary impairment of mitochondrial function through the induction of carnitine deficiency.[60]

Many psychotropic medications also have side effects that may contribute to or worsen medical conditions associated with mitochondrial disorders. Some atypical antipsychotics can induce a metabolic syndrome and thereby compound the risk of developing diabetes. Medications with prominent anticholinergic properties may worsen both cognitive dysfunction and constipation. Selective serotonin reuptake inhibitors may exacerbate migraine headaches, and tricyclic medications may worsen cardiac conduction abnormalities. Many psychotropic agents lower the seizure threshold, increasing the likelihood of seizures and status epilepticus, which is a leading cause of death in patients with mitochondrial disease.[61]

It has been our experience that many patients improve from a psychiatric standpoint when psychotropic medications are carefully withdrawn, as was the case for Ms A. In patients with mitochondrial disorders, it is especially important to minimize polypharmacy, use psychotropic medications judiciously, and initiate nonpharmacologic interventions whenever possible.

## CONCLUSIONS

Since the identification of the first pathogenic mitochondrial mutation in 1988,[3] the field of mitochondrial medicine has developed at a rapid pace. Unfortunately, many clinicians are still not familiar with the clinical features of mitochondrial disorders, and psychiatrists may not be aware that patients with mitochondrial disorders can present with psychiatric symptoms. Making the diagnosis of a mitochondrial disorder has important treatment implications, as many psychotropic medications impair mitochondrial function or have side effects that may worsen medical conditions associated with mitochondrial disorders. Therefore, it is important that psychiatrists maintain a high level of suspicion for mitochondrial disorders in their patients and appropriately investigate patients with suggestive clinical presentations.

***Drug names:*** lorazepam (Ativan and others), sertraline (Zoloft and others), valproic acid (Depakene, Stavzor, and others).

***Author affiliations:*** Departments of Psychiatry and Behavioural Neurosciences (Drs Anglin, Garside, and Rosebush), Pediatrics (Dr Tarnopolsky), and Neurology (Dr Mazurek), McMaster University, Hamilton, Ontario, Canada.

***Potential conflicts of interest:*** **Dr Tarnopolsky** has served on the advisory board of Transgenomics. **Drs Anglin**, **Garside**, **Mazurek**, and **Rosebush** do not have any potential conflicts of interest pertaining to this article.

***Funding/support:*** Funding for this project was provided by Physicians Services Inc, and Dr Anglin is supported by an Ontario Mental Health Foundation Research Training Fellowship.

***Acknowledgments:*** We would like to thank all the patients who contributed to our understanding of the psychiatric presentation of mitochondrial disorders. In addition, we would like to acknowledge the contributions of Mr Andy McDonald, who has worked tirelessly to increase awareness about mitochondrial disorders and the associated psychiatric symptoms and has supported the authors' work by holding charity fundraisers in the community to raise money for mitochondrial research. Mr McDonald does not have an academic affiliation or any conflict of interest.

## REFERENCES

1. Calvo SE, Mootha VK. The mitochondrial proteome and human disease. *Annu Rev Genomics Hum Genet*. 2010;11(1):25–44.
2. DiMauro S, Schon EA. Mitochondrial respiratory-chain diseases. *N Engl J Med*. 2003;348(26):2656–2668.
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
4. Wallace DC, Singh G, Lott MT, et al. Mitochondrial DNA mutation associated with Leber's hereditary optic neuropathy. *Science*. 1988; 242(4884):1427–1430.
5. Chinnery PF, Johnson MA, Wardell TM, et al. The epidemiology of pathogenic mitochondrial DNA mutations. *Ann Neurol*. 2000;48(2): 188–193.
6. Schaefer AM, McFarland R, Blakely EL, et al. Prevalence of mitochondrial DNA disease in adults. *Ann Neurol*. 2008;63(1):35–39.
7. Clay HB, Sillivan S, Konradi C. Mitochondrial dysfunction and pathology in bipolar disorder and schizophrenia. *Int J Dev Neurosci*. 2011;29(3):311–324.
8. Fattal O, Link J, Quinn K, et al. Psychiatric comorbidity in 36 adults with mitochondrial cytopathies. *CNS Spectr*. 2007;12(6):429–438.
9. Ahn MS, Sims KB, Frazier JA. Risperidone-induced psychosis and depression in a child with a mitochondrial disorder. *J Child Adolesc Psychopharmacol*. 2005;15(3):520–525.
10. Amemiya S, Hamamoto M, Goto Y, et al. Psychosis and progressing dementia: presenting features of a mitochondriopathy. *Neurology*. 2000; 55(4):600–601.
11. Apostolova LG, White M, Moore SA, et al. Deep white matter pathologic features in watershed regions: a novel pattern of central nervous system involvement in MELAS. *Arch Neurol*. 2005;62(7):1154–1156.
12. Ban S, Mori N, Saito K, et al. An autopsy case of mitochondrial encephalomyopathy (MELAS) with special reference to extra-neuromuscular abnormalities. *Acta Pathol Jpn*. 1992;42(11):818–825.
13. Clark JM, Marks MP, Adalsteinsson E, et al. MELAS: Clinical and pathologic correlations with MRI, xenon/CT, and MR spectroscopy. *Neurology*. 1996;46(1):223–227.
14. Campos Y, García A, Eiris J, et al. Mitochondrial myopathy, cardiomyopathy and psychiatric illness in a Spanish family harbouring the mtDNA 3303C > T mutation. *J Inherit Metab Dis*. 2001;24(6): 685–687.
15. Desnuelle C, Pellissier JF, Serratrice G, et al. [Kearns-Sayre syndrome: mitochondrial encephalomyopathy caused by deficiency of the respiratory chain]. *Rev Neurol (Paris)*. 1989;145(12):842–850.
16. Gardner A, Pagani M, Wibom R, et al. Alterations of rCBF and mitochondrial dysfunction in major depressive disorder: a case report. *Acta Psychiatr Scand*. 2003;107(3):233–239.
17. Inagaki T, Ishino H, Seno H, et al. Psychiatric symptoms in a patient with diabetes mellitus associated with point mutation in mitochondrial DNA. *Biol Psychiatry*. 1997;42(11):1067–1069.
18. Jaksch M, Lochmuller H, Schmitt F, et al. A mutation in mt tRNALeu(UUR) causing a neuropsychiatric syndrome with depression and cataract. *Neurology*. 2001;57(10):1930–1931.
19. Kaido M, Fujimura H, Soga F, et al. Alzheimer-type pathology in a patient with mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS). *Acta Neuropathol*. 1996;92(3): 312–318.
20. Kiejna A, DiMauro S, Adamowski T, et al. Psychiatric symptoms in a patient with the clinical features of MELAS. *Med Sci Monit*. 2002; 8(7):CS66–CS72.
21. Köller H, Kornischka J, Neuen-Jacob E, et al. Persistent organic

© COPYRIGHT 2012 PHYSICIANS POSTGRADUATE PRESS, INC.  © COPYRIGHT 2012 PHYSICIANS POSTGRADUATE PRESS, INC.

personality change as rare psychiatric manifestation of MELAS syndrome. *J Neurol*. 2003;250(12):1501–1502.
22. Lacey CJ, Salzberg MR, Roberts H, et al. Psychiatric comorbidity and impact on health service utilization in a community sample of patients with epilepsy. *Epilepsia*. 2009;50(8):1991–1994.
23. Miyaoka H, Suzuki Y, Taniyama M, et al. Mental disorders in diabetic patients with mitochondrial transfer RNA(Leu) (UUR) mutation at position 3243. *Biol Psychiatry*. 1997;42(6):524–526.
24. Mizukami K, Sasaki M, Suzuki T, et al. Central nervous system changes in mitochondrial encephalomyopathy: light and electron microscopic study. *Acta Neuropathol*. 1992;83(4):449–452.
25. Nørby S, Lestienne P, Nelson I, et al. Juvenile Kearns-Sayre syndrome initially misdiagnosed as a psychosomatic disorder. *J Med Genet*. 1994; 31(1):45–50.
26. Odawara M, Isaka M, Tada K, et al. Diabetes mellitus associated with mitochondrial myopathy and schizophrenia: a possible link between diabetes mellitus and schizophrenia. *Diabet Med*. 1997;14(6):503.
27. Onishi H, Kawanishi C, Iwasawa T, et al. Depressive disorder due to mitochondrial transfer RNALeu(UUR) mutation. *Biol Psychiatry*. 1997; 41(11):1137–1139.
28. Prayson RA, Wang N. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes (MELAS) syndrome: an autopsy report. *Arch Pathol Lab Med*. 1998;122(11):978–981.
29. Saijo T, Naito E, Ito M, et al. Therapeutic effect of sodium dichloroacetate on visual and auditory hallucinations in a patient with MELAS. *Neuropediatrics*. 1991;22(3):166–167.
30. Sartor H, Loose R, Tucha O, et al. MELAS: a neuropsychological and radiological follow-up study. Mitochondrial encephalomyopathy, lactic acidosis and stroke. *Acta Neurol Scand*. 2002;106(5):309–313.
31. Shanske AL, Shanske S, Silvestri G, et al. MELAS point mutation with unusual clinical presentation. *Neuromuscul Disord*. 1993;3(3):191–193.
32. Shinkai T, Nakashima M, Ohmori O, et al. Coenzyme Q10 improves psychiatric symptoms in adult-onset mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes: a case report. *Aust N Z J Psychiatry*. 2000;34(6):1034–1035.
33. Spellberg B, Carroll RM, Robinson E, et al. mtDNA disease in the primary care setting. *Arch Intern Med*. 2001;161(20):2497–2500.
34. Stewart JB, Naylor GJ. Manic-depressive psychosis in a patient with mitochondrial myopathy—a case report. *Med Sci Res*. 1990;18:265–266.
35. Suomalainen A, Majander A, Haltia M, et al. Multiple deletions of mitochondrial DNA in several tissues of a patient with severe retarded depression and familial progressive external ophthalmoplegia. *J Clin Invest*. 1992;90(1):61–66.
36. Suzuki T, Koizumi J, Shiraishi H, et al. Psychiatric disturbance in mitochondrial encephalomyopathy. *J Neurol Neurosurg Psychiatry*. 1989;52(7):920–922.
37. Suzuki T, Koizumi J, Shiraishi H, et al. Mitochondrial encephalomyopathy (MELAS) with mental disorder: CT, MRI and SPECT findings. *Neuroradiology*. 1990;32(1):74–76.
38. Sweeney MG, Bundey S, Brockington M, et al. Mitochondrial myopathy associated with sudden death in young adults and a novel mutation in the mitochondrial DNA leucine transfer RNA(UUR) gene. *Q J Med*. 1993;86(11):709–713.
39. Thomeer EC, Verhoeven WM, van de Vlasakker CJ, et al. Psychiatric symptoms in MELAS; a case report. *J Neurol Neurosurg Psychiatry*. 1998; 64(5):692–693.
40. Yamazaki M, Igarashi H, Hamamoto M, et al. [A case of mitochondrial encephalomyopathy with schizophrenic psychosis, dementia and neuroleptic malignant syndrome]. *Rinsho Shinkeigaku*. 1991;31(11): 1219–1223.
41. Grover S, Padhy SK, Das CP, et al. Mania as a first presentation in mitochondrial myopathy. *Psychiatry Clin Neurosci*. 2006;60(6):774–775.
42. Hopkins SE, Somoza A, Gilbert DL. Rare autosomal dominant POLG1 mutation in a family with metabolic strokes, posterior column spinal degeneration, and multi-endocrine disease. *J Child Neurol*. 2010;25(6): 752–756.
43. Koene S, Kozicz TL, Rodenburg RJ, et al. Major depression in adolescent children consecutively diagnosed with mitochondrial disorder. *J Affect Disord*. 2009;114(1–3):327–332.
44. Komulainen T, Hinttala R, Kärppä M, et al. POLG1 p.R722H mutation associated with multiple mtDNA deletions and a neurological phenotype. *BMC Neurol*. 2010;10(1):29.
45. Mancuso M, Ricci G, Choub A, et al. Autosomal dominant psychiatric disorders and mitochondrial DNA multiple deletions: report of a family. *J Affect Disord*. 2008;106(1–2):173–177.
46. Rantamäki M, Krahe R, Paetau A, et al. Adult-onset autosomal recessive ataxia with thalamic lesions in a Finnish family. *Neurology*. 2001;57(6): 1043–1049.
47. Siciliano G, Tessa A, Petrini S, et al. Autosomal dominant external ophthalmoplegia and bipolar affective disorder associated with a mutation in the ANT1 gene. *Neuromuscul Disord*. 2003;13(2):162–165.
48. Verhoeven WM, Egger JI, Kremer BP, et al. Recurrent major depression, ataxia, and cardiomyopathy: association with a novel POLG mutation? *Neuropsychiatr Dis Treat*. 2011;7:293–296.
49. Young TM, Blakely EL, Swalwell H, et al. Mitochondrial transfer RNA(Phe) mutation associated with a progressive neurodegenerative disorder characterized by psychiatric disturbance, dementia, and akinesia-rigidity. *Arch Neurol*. 2010;67(11):1399–1402.
50. Friedman SD, Shaw DW, Ishak G, et al. The use of neuroimaging in the diagnosis of mitochondrial disease. *Dev Disabil Res Rev*. 2010;16(2): 129–135.
51. Barragán-Campos HM, Vallée JN, Lô D, et al. Brain magnetic resonance imaging findings in patients with mitochondrial cytopathies. *Arch Neurol*. 2005;62(5):737–742.
52. McFarland R, Turnbull DM. Batteries not included: diagnosis and management of mitochondrial disease. *J Intern Med*. 2009;265(2): 210–228.
53. Tarnopolsky MA, Raha S. Mitochondrial myopathies: diagnosis, exercise intolerance, and treatment options. *Med Sci Sports Exerc*. 2005;37(12): 2086–2093.
54. van Adel BA, Tarnopolsky MA. Metabolic myopathies: update 2009. *J Clin Neuromuscul Dis*. 2009;10(3):97–121.
55. Tarnopolsky MA. The mitochondrial cocktail: rationale for combined nutraceutical therapy in mitochondrial cytopathies. *Adv Drug Deliv Rev*. 2008;60(13–14):1561–1567.
56. Rodriguez MC, MacDonald JR, Mahoney DJ, et al. Beneficial effects of creatine, CoQ10, and lipoic acid in mitochondrial disorders. *Muscle Nerve*. 2007;35(2):235–242.
57. Glover EI, Martin J, Maher A, et al. A randomized trial of coenzyme Q10 in mitochondrial disorders. *Muscle Nerve*. 2010;42(5):739–748.
58. Anglin RE, Rosebush PI, Mazurek MF. Treating psychiatric illness in patients with mitochondrial disorders [letter]. *Psychosomatics*. 2010; 51(2):179.
59. Burkhardt C, Kelly JP, Lim YH, et al. Neuroleptic medications inhibit complex I of the electron transport chain. *Ann Neurol*. 1993;33(5): 512–517.
60. Ponchaut S, Veitch K. Valproate and mitochondria. *Biochem Pharmacol*. 1993;46(2):199–204.
61. Klopstock T, Jaksch M, Gasser T. Age and cause of death in mitochondrial diseases. *Neurology*. 1999;53(4):855–857.

*Editor's Note:* We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

© Copyright 2012 Physicians Postgraduate Press, Inc. © Copyright 2012 Physicians Postgraduate Press, Inc.