*Notice of Correction—The middle initial of the second author in the byline on page 237 has been corrected to Jared M. Goetz.*

LESSONS LEARNED AT THE INTERFACE OF MEDICINE AND PSYCHIATRY

The Psychiatric Consultation Service at Massachusetts General Hospital (MGH) sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. Such consultations require the integration of medical and psychiatric knowledge. During their thrice-weekly rounds, Dr. Stern and other members of the Psychiatric Consultation Service discuss the diagnosis and management of conditions confronted. These discussions have given rise to rounds reports that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

Dr. Bhuvaneswar is a clinical fellow in psychiatry at Harvard Medical School (HMS) and a resident in psychiatry at Massachusetts General Hospital (MGH)/McLean Hospital. Mr. Goetz is a graduate of Brandeis University and a clinical research assistant in the MGH Posttraumatic Stress Disorder Laboratory. Dr. Stern is chief of the Psychiatric Consultation Service at MGH and a professor of psychiatry at HMS.

Corresponding author and reprints: Theodore A. Stern, M.D., MGH, 55 Fruit St., Warren 6, Boston, MA 02114 (e-mail: tstern@partners.org).

# Multiple Neurologic, Psychiatric, and Endocrine Complaints in a Young Woman: A Case Discussion and Review of the Clinical Features and Management of Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroke

**Chaya G. Bhuvaneswar, M.D.; Jared M. Goetz, B.A.; and Theodore A. Stern, M.D.**

Have you ever been perplexed as to how to explain a bevy of neurologic, psychiatric, and endocrine complaints, including weakness and fatigue, in a young adult? Have you wondered how extensive a workup to pursue when multiple physical complaints appear to lack a unifying etiology and are accompanied by psychiatric symptoms? Have you considered whether mitochondrial disorders could account for seemingly diverse signs and symptoms that may include a stroke before the age of 40 years? If you have, then the following case vignette and questions and answers should serve to highlight issues related to these matters.

## Case Vignette

Ms. A, a 28-year-old short, thin, and disheveled woman, presented to the psychiatric emergency department looking frightened and fatigued. Her presenting complaint was, "I just feel so tired." However, on interview she revealed that for the past several weeks, her ex-husband had been "watching her every move," that he "controls the TV networks," and that he had "done something" to her head to cause her to start going deaf. She admitted to having thoughts about hurting him.

Her history was notable for several episodes of depression, for sporadic headaches (that were relieved by use of nonsteroidal anti-inflammatory drugs), and a progressive decline in function (e.g., she had dropped out of college and become unemployed during the previous year). Her urine toxicology screening was negative and her vital signs were normal (except for a slightly increased respiratory rate).

When brought to a holding area, she stopped talking, looked terrified, and then had a generalized tonic-clonic seizure. After intramuscular lorazepam was administered, her convulsions ended, but she continued lateral tongue deviation and bilateral ptosis without diplopia.

She was transferred to the neurology service; neuroimaging revealed focal posterior cerebral lesions with T2 hyperintensities (that did not follow any vascular distribution) and symmetrical basal ganglia calcifications. On repeat imaging 2 weeks later, while her fatigue, extraocular muscle dysfunction, and psychiatric symptoms persisted, several of her central nervous system lesions (seen on the initial magnetic resonance imaging [MRI]) had disappeared.

## What Neurologic, Psychiatric, and Medical Complaints Are Consistent With a Diagnosis of a Mitochondrial Encephalopathy?

The diagnosis of a congenital myopathy is typically considered when a child, adolescent, or young adult presents with a combination of seizures, a change in

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muscle tone, muscle weakness, and developmental problems (including cognitive and psychiatric problems).[1] Types of congenital myopathies include nemaline myopathy (named for rod-like inclusions in muscle cells and also seen in patients with acquired immunodeficiency syndrome [AIDS]), central core disease, myotubular myopathy, and the mitochondrial myopathies, including MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke). Proximal muscle weakness and dystonia are associated with mitochondrial myopathies; presentations early in life are associated with a more severe disease course.[2]

Clinical history should establish whether there has been intermittent versus persistent weakness; an intermittent pattern is more consistently associated with mitochondrial disorders. When intermittent weakness arises, it may be useful to test early on for myoglobinuria. Myoglobinuria is defined as the presence of any myoglobin in the urine, causing it to turn pink in room air. Important causes include excessive, unaccustomed exercise; crush injuries; muscle infarction; prolonged tonic-clonic seizures; polymyositis; chronic hypokalemia; alcoholic binges; viral infections; hyperthermia; exposure to arthropod venom; rhabdomyolysis from any cause (including compartment syndrome and renal failure); use of drugs (e.g., risperidone and the statins); and other processes that destroy muscle (including failures of aerobic metabolism).[3] If myoglobinuria is present without any of the above causes, and weakness is the presenting symptom, mitochondrial disorders should be considered (and the standard battery of screening tests for these ordered). Since proximal limb weakness may be worse with exercise in mitochondrial disorders, forearm exercise is often useful as a provocation test. Intense exercise of any kind may also result in myoglobinuria if a mitochondrial defect is present, as may the stresses of illness, dehydration, starvation state, or surgery.[4]

Dystonias, or abnormal sustained postures, may also be presenting features of mitochondrial disorders such as MELAS (as with patients who have a 3243 mutation and present initially with muscle cramps, then develop proximal muscle weakness, exercise intolerance, ptosis, and sensorineural hearing loss).[5] The differential of congenital dystonia in young adults is broad and includes dopa-responsive dystonia (which is more common in females and often mistaken for juvenile-onset Parkinson's disease, but is more responsive to low-dose levodopa than is Parkinson's disease), myoclonic dystonia (with rapid jerks instead of sustained abnormal postures), idiopathic and focal torsion dystonia, cerebral palsy, Huntington's disease, Parkinson's disease, and psychogenic dystonia. Other associated features of each of these diagnoses, including birth history of children (e.g., anoxia leading to cerebral palsy), an autosomal dominant pattern (as in idiopathic dystonia and Huntington's disease), and psychiatric symptoms (e.g., *la belle indifference* in conversion disorder), may help rule out mitochondrial disorders.[2] The presentation may be of complex movement abnormalities, having an episodic course that combines disordered movement with confusional states. There may be combined features of Wilson's disease (including psychiatric manifestations such as psychosis and early dementia) and the hereditary ataxias (including spinocerebellar ataxia).[6]

In young adults who present with weakness, neuropathies, visual deficits (which can include optic neuritis and visual field defects), and a fluctuating course, MELAS and other disorders (such as multiple sclerosis, which cannot yet be diagnosed by a reliable genetic test or set of biomarkers) should be considered. Family history, neuroimaging, genetic testing, electromyography, and muscle biopsy each play an important role in ruling out multiple sclerosis. Internuclear ophthalmoplegia (from plaque involvement of the medial longitudinal fasciculus) and abnormal sensory-evoked potentials, which reflect demyelination in multiple sclerosis, are less likely to be found in MELAS. Oligoclonal bands of protein in cerebrospinal fluid as well as Lhermitte's sign (an electrical sensation running down the back when the neck is bent forward, reflecting dorsal column disease from multiple sclerosis, Behcet's syndrome, subacute combined degeneration, trauma, or tumor) are also less likely to be present in MELAS.[7] Other disorders that present with weakness share a broad differential diagnosis, including myasthenia gravis (with "head-drop" sign, positive edrophonium test, and easy fatigability), muscular dystrophy (including Duchenne's muscular dystrophy, which is distinguished by calf hypertrophy and a positive dystrophin test), myotonic dystrophy, myotonia congenital (distinguished by apparent muscle stiffness due to impaired relaxation), polymyositis, dermatomyositis (characterized by distinctive dermatologic findings, an association with thoracic malignancies, and a significantly elevated creatine kinase level), and inclusion body myositis (also characterized by proximal weakness, as are mitochondrial disorders, but with an onset after age 50 years and diagnosed by histologic findings).[8] Neurologic examination, clinical history, and relevant laboratory and histologic tests can assist in distinguishing these conditions from MELAS.

Fatigue must be distinguished from asthenia (defined as a weary avoidance of physical activity in the context of depression and anxiety) and from such conditions as fibromyalgia and mitochondrial myopathy (in a young or middle-aged adult).[8] When MELAS or another mitochondrial disorder presents later in life, the course is more likely to be chronic and debilitating (though dramatic regressions of function may be seen under acute stress, such as a viral illness). Pathologic fatigue, unlike asthe-

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nia, can result from a mitochondrial defect or from a defect in glycolysis and lipid metabolism, and it is nearly always accompanied by abnormal laboratory studies.[9] Polymyalgia rheumatica, also on the differential diagnosis of mitochondrial disorders presenting with subacute or chronic fatigue, is nearly always accompanied by elevated erythrocyte sedimentation rate.[6] Fibromyalgia, in contrast, is associated with "pressure points" that define areas of discomfort and pain as well as with mood symptoms but is not linked with any abnormal laboratory findings.[10]

Family history (with a maternal line of inheritance of afflicted family members strongly suggestive of mitochondrial myopathy/encephalopathy) is important to the clinical diagnosis of MELAS. Maternal inheritance of mitochondrial DNA, while not absolute (with some exceedingly rare reports of paternal inheritance), has been reliable enough to be used in forensic medicine and in human rights investigations in the Balkans and Latin America. Mitochondrial DNA is thought to be informative and distinctive, as many mutations can be passed on from a mother to all of her children without any harmful effects. Only 1 surviving relative, linked to the missing person by a purely maternal relation, is required to make the identification. Since mitochondrial DNA is present in diverse tissues, it may also be more easily obtained than nuclear DNA (which requires bodily fluids, e.g., semen or blood, buccal mucosal cells, or hair).[11]

An array of seemingly unrelated and confusing symptoms (accounting for a "positive review of symptoms") may be consistent with MELAS and other related disorders, although malingering and confabulation must also be excluded through follow-up studies and a general assessment of distress and the progressive nature of disease effects.[12] In addition, maneuvers as part of the neurologic examination, e.g., Hoover's sign (measuring hip extension isometric force with contralateral hip flexion) and abductor's sign (using synergic movements of bilateral hip abductors) may be helpful in excluding nonorganic causes (e.g., the somatoform disorders).[13,14]

Evaluation of the brain, heart, liver, kidney, eyes, and ears should take priority when a presentation is confusing or if it could be explained by a mitochondrial disorder. Long-term regression of skills and function, as well as the occurrence of pediatric stroke or a stroke-like episode following a stress (e.g., a minor illness, surgery, pregnancy, or more rarely, drug toxicity, as reported with statins and valproate) are highly suggestive of the diagnosis.[15–17] Of note, myopathy and neuropathy may both be present; more commonly, one process is initially prominent, then the other is discovered on workup with an electromyogram or a muscle biopsy.

Initial laboratory studies should include general chemistries, toxicologic screening, thyroid function tests, a lipid panel, a fasting glucose test, an erythrocyte sedimentation rate, microbiology testing, and a complete blood count with differential to rule out underlying medical causes (including primary endocrine disorders and infectious encephalopathies such as herpes and systemic autoimmune disease) manifest by symptoms involving an occult multi-organ disease. An electroencephalogram (EEG), a noncontrast computed tomography, and a brain MRI scan should be conducted during the workup of new-onset seizures or stroke. Evaluation for stroke risk factors (e.g., hyperlipidemia or diabetes mellitus) should incorporate a more general history, a detailed family history, a neurologic examination, and a workup of any unexpected disease process that does not fit with the tempo of end-organ damage in diabetes mellitus (e.g., 15 years of untreated hyperglycemia before the development of nephrotic syndrome) before relatively rare diagnoses (e.g., diabetes mellitus as the result of MELAS versus idiopathic or obesity-related insulin resistance and diabetes mellitus) are excluded.

**What Is MELAS?**

MELAS constitutes one of several mitochondrial encephalopathies that result from point mutations in mitochondrial DNA.[18] Although MELAS is thought to be the most common mitochondrial encephalopathy, the precise prevalence within the United States has yet to be determined. No ethnic or gender predilection has been shown. The minimal childhood prevalence has been estimated as 1 in 5000 by United States researchers.[2] Worldwide, the most common point mutation is the mitochondrial DNA 3243 A→G mutation, present in up to 80% of persons with the disease, although other substitutions have also been detected.[19] Among white populations, the prevalence of MELAS may be as high as 18.4 per 100,000, as in a large Finnish pediatric cohort.[20] Other studies in Australia (occurring in 236/100,000), England (occurring in 9.2/100,000 adults and in 16.5/100,000 children), and Taiwan (where mitochondrial point mutations are thought to be associated with up to 2% of the MIC9D gene mutation known to be a highly prevalent genetic polymorphism for Asians) have established that mitochondrial disorders are common genetic diseases, whether or not they are detected.[21–23]

One of the obstacles to the detection of MELAS and other mitochondrial disorders is their protean symptoms. Disease severity may vary between affected individuals within a given maternal line (the primary mode of transmission for mitochondrial diseases), while childhood and adulthood manifestations may vary over a given individual's life. This diversity of the MELAS phenotype results from genetic heteroplasmy or the presence of the point mutation in some, but not all, mitochondrial genomes.[24] Not all somatic cells affected will bear enough

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of a genetic "load" to manifest the disease.[25] There is a *forme fruste* phenomenon (i.e., an incomplete form of the disease initially); a patient's only symptom may be headaches in childhood, but as the pathologic mutations accumulate in various tissues over time, stroke-like episodes and dementia may arise in young adulthood. In addition, the detection of the disease, which relies initially on clinical history (as detailed here), may be more challenging because of the possibility of autosomal (rather than solely maternal) inheritance due to the encoding of mitochondrial proteins by nuclear DNA.[25] Indeed, in infants and children, defects in nuclear DNA (that in turn affect mitochondrial function) account for the majority of mitochondrial disorders.[2]

The cardinal clinical features of MELAS are stroke before age 40 years (including pediatric stroke, which greatly raises the index of suspicion) and a progressive functional decline (including cognitive deficits with or without other psychiatric symptoms). Organ systems most often affected include the brain, eyes (retina), skeletal muscle, heart, liver, and kidneys given the high-energy demand and large presence of mitochondria in these organs. In general, dysfunction in 3 or more organ systems accompanied by a decline in function raises the suspicion of a mitochondrial disorder.[2]

In the brain, stroke-like episodes are thought to result from dysfunction of oxidative phosphorylation within the brain parenchyma or from a decrease in oxygen availability and a decrease in free nitric oxide (that results in microvascular damage, presumably from free radicals and glutamate) that is initially caused by disrupted nitric oxide synthesis from impaired binding with cytochrome C and other proteins of the respiratory chain.[20] There is also a "neuronal hyperexcitability" hypothesis that links seizure activity to the development of stroke-like episodes; the stroke is thought to be a nonischemic event mediated by epileptic depolarization, energy imbalance, and, ultimately, cortical lesions with vasogenic edema, focal periodic epileptiform discharges, focal hyperperfusion, and cortical laminar necrosis (with occipital lobe hypoperfusion more common in the chronic stage).[26] Since these events typically fail to follow a vascular distribution, clinical deficits that result (which are commonly transient, though occasionally permanent) are not pathognomonic. Of note, however, is the clinical tempo, which may give a clue to diagnosis: there may be a slowly progressive spread of the stroke-like lesions from temporal to parietal or occipital cortex in the weeks after the initial onset of focal neurologic symptoms.[27]

Seizures in MELAS may be of any type (including myoclonic jerks and generalized tonic-clonic seizures); one report documented how a woman with adult-onset epilepsy carried diagnoses of lipothymic episodes, migraine, idiopathic photosensitive generalized epilepsy, partial occipital epilepsy, and progressive myoclonic epilepsy for 11 years until genetic testing detected a 3243 mutation.[28] Other neurologic manifestations include developmental delays, migraine-like headaches, stroke-like episodes, ataxia, dystonia, parkinsonism, visual impairment, sensorineural deafness, and spinal muscular atrophy. Magnesium deficiency and vascular dysfunction have been implicated in MELAS-related migraine, which is often difficult to distinguish from subthreshold seizure activity or from evolving stroke (prompting preemptive inpatient monitoring in some cases in which the patient has been known to progress to stroke after initial headaches).[27] Mitochondrial deafness, seen in MELAS and in other mitochondrial disorders (e.g., Kearns-Sayre syndrome; neuropathy, ataxia, and retinitis pigmentosa; and mitochondrial encephalopathy with ragged red fibers), can take several possible forms—from progressive, otherwise unexplained sensorineural hearing loss in up to 25% of MELAS patients, to gradual deafness associated with diabetes mellitus (either from cranial nerve involvement or from the maternally inherited diabetes and deafness mitochondrial syndrome causing both), to acute bilateral hearing loss secondary to seizure and stroke-like events that persist after other neurologic deficits have resolved.[29,30] Visual impairment (classically associated with mitochondrial disorders like progressive extraocular ophthalmoplegia and Leber's optic neuropathy) can be caused by progressive degeneration with the 3243 (A-G) mutation or with the 3271 (T-C) mutation, which may cause impaired saccadic movements from cerebellar dysfunction.[31,32] A complex pathophysiology is involved, making optic neuritis (with a somewhat characteristic finding of hemianopsia), cortical blindness, and fluctuating visual acuity all possible presentations in MELAS.[32] The cognitive deficits (in addition to other psychiatric complications, as described here) may include visuospatial deficits and impaired executive function (detected by abnormal neuropsychological testing).[33] If there is childhood onset, mental retardation and developmental delay may be noted (preceding the first stroke and therefore not attributable to stroke deficits), often accompanied by short stature and failure to thrive and thereby facilitating earlier genetic diagnosis and provision of family support.[34]

Other neurologic manifestations include peripheral neuropathies. Leigh syndrome (a subacute necrotizing encephalopathy and the most common childhood-onset mitochondrial disorder) may be manifest by ataxia in adulthood and "floppy baby" status in infancy before severe cortical deficits develop.[35] Lactic acidosis may not be a feature of this presentation.[2]

Myopathy is a prominent feature absent from other neurologic illnesses (e.g., polymyositis and dermatomyositis, which have elevated creatine kinase levels that are

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not expected in MELAS). Lactic acidosis, the result of impaired pyruvate lactate breakdown, causes decreased exercise tolerance, proximal limb myopathy, pathologic fatigue, and impaired extraocular movements (though usually without diplopia because the deficit is in muscle rather than the oculomotor nerve).[3] Fatigue, may be a function of limb myopathy, pulmonary disease (e.g., pulmonary hypertension), or, more commonly, from conduction defects (e.g., Wolff-Parkinson-White syndrome). Long QT and hypertrophic cardiomyopathy may also arise in MELAS in either childhood or late adulthood.[36,37]

Other affected organ systems in MELAS involve liver dysfunction, renal disease (most commonly nephrotic syndrome from focal segmental glomerulonephritis), and, more rarely, gastrointestinal disturbances (ranging from mild constipation to gastroparesis, either independently or secondary to diabetes mellitus or pancreatitis). Endocrine dysfunction as a result of MELAS can also include hypothalamic hypogonadism, hypoparathyroidism, and adrenal insufficiency. Thus, the nausea and vomiting that commonly precede either seizure or stroke-like activity in MELAS should be considered in light of endocrine disease.[2] Primary endocrine myopathies should also be considered in the differential diagnosis of MELAS; hypo- or hyperthyroidism, hyper- or hypoparathyroidism, hypoadrenalism, hypopituitarism, and acromegaly may all cause myopathy and weakness, which are often reversible by treatment of the primary endocrine disorder (when this is not an endocrine manifestation of MELAS).[6]

## How Can the Diagnosis of a Mitochondrial Disorder Like MELAS Be Confirmed?

Confirmatory laboratory studies include an elevated serum lactic acid level (often without a systematic metabolic or "anion gap" acidosis). Lactic acid alone is not diagnostic, since several disorders (like Leigh syndrome) may have normal levels, and other conditions (e.g., use of a tourniquet to collect the sample, anaerobic exercise preceding the study, hypoxia, hypotension, renal failure, shock, cerebral ischemia, and thiamine deficiency) may also elevate serum lactic acid measurements.[3] If the serum lactic acid level is normal, cerebrospinal fluid lactate may still be elevated, particularly if neurologic signs and symptoms are present. A lactic acid:pyruvic acid ratio is also likely to be elevated (although a normal ratio does not exclude a mitochondrial disorder). Plasma alanine may also reflect decreased pyruvate.[2] An oxygen desaturation test (with forearm exercise) has also been proposed to increase the sensitivity of lactic acid screening.[38] Other metabolic tests that are part of the battery for mitochondrial disorders include blood creatine kinase, plasma carnitine, and serum amino acids, with urine metabolic testing (considered less useful, apart from the determination of myoglobinuria and glucosuria/24-hour proteinuria for diagnosis of renal disease and diabetes mellitus, which may be comorbidities) (Table 1).[18,20] Levels of creatine kinase, while not expected to be as elevated in MELAS as in polymyositis or dermatomyositis, may be elevated before and after stroke-like episodes.[6]

**Table 1. Common Tests to Diagnose Mitochondrial Disorders[a]**

| Test |
|---|
| **Physical examination:** short stature, neurologic examination (ataxia, abnormal mental status examination, focal deficits, extraocular muscle weakness, hemianopsia, and hemiplegia) |
| **Laboratory:** serum and cerebrospinal fluid lactate, cerebrospinal fluid protein (elevated), serum alanine and amino acids and carnitine and creatine kinase, muscle biopsy and histology (abnormal mitochondria) |
| **Neuroimaging:** computed tomography, magnetic resonance imaging (including diffusion-weighted and proton magnetic resonance imaging), and near-infrared spectroscopy |
| **Other:** extensive clinical family history with detailed information about any maternally inherited disorders or decline in function |

[a]Based on DiMauro.[18]

Once the clinical presentation and initial screening laboratory tests suggest a mitochondrial disorder, the differential diagnosis is still quite broad. Many diseases have been identified via use of electron microscopy (developed in the 1960s for histologic studies), the complete sequencing of the mitochondrial genome (sequenced in 1981), and the discovery (in 1972) of ragged red fibers (abnormally proliferating muscle fibers to compensate for oxidative defects).[25] The disorders include chronic progressive external ophthalmoplegia (CPEO) (found in over half of all mitochondrial disorders, with varying degrees of weakness of extraocular muscles and ptosis without diplopia), Kearns-Sayre syndrome (a constellation of CPEO with onset before age 20 years, complete heart block as the most common cause of death, cerebellar ataxia, and pigmentary retinopathy), and autosomal recessive cardiomyopathy and ophthalmoplegia (with onset between age 8–10 years, exercise intolerance, fatigue, dilated cardiomyopathy, highly elevated creatine kinase levels, and death often in adolescence without cardiac pacemaker or transplant). Two other mitochondrial myopathies (which may share clinically overlapping features with MELAS) include myoclonic epilepsy with ragged red fibers or myoclonus epilepsy with ragged red fibers (with variable onset, myoclonic epilepsy, cerebellar ataxia, progressive muscle weakness, a seizure disorder [often the presenting symptom], and a slowly progressive limb-girdle muscle weakness).[25] Myopathy with ragged red fibers may also be seen among HIV-infected patients receiving zidovudine, and it may coexist with polymyositis; the symptoms are similar to those of a mitochondrial disorder and result from toxic effects of zidovudine on muscle.[6]

Neuroimaging plays an important role in the workup of MELAS. Findings (e.g., generalized brain atrophy and basal ganglia calcifications) may be found in both

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Kearns-Sayre syndrome and MELAS; these calcifications may also be associated with Leigh syndrome (a necrotizing encephalopathy) and are often symmetric.[34] The signal changes associated with stroke-like episodes may be fleeting as well, with initial lesions often noted in the posterior cerebral hemisphere.[20] The abnormalities seen on imaging and on the EEG help distinguish MELAS from other seizure disorders with psychiatric manifestations, e.g., temporal lobe epilepsy, although epileptogenic lesions in temporal lobe epilepsy, particularly in the mesiotemporal lobe, may appear similar to the bitemporal lesions in MELAS.[39] Diffusion-weighted MRI scans may also be helpful in distinguishing the stroke-like episode from MELAS from an ischemic event: in mitochondrial disease, an increased diffusion coefficient is expected, while in an acute ischemic stroke, a decreased diffusion coefficient may be seen.[2]

Positron emission tomography scanning may also be useful; some studies have shown decreased glucose intake in the occipital and temporal lobes. Regional cerebral blood flow may be decreased just before a seizure or be associated with a stroke-like episode.[40,41] Single photon emission computerized tomography (SPECT) imaging will likely have an increasingly important role in diagnosis of MELAS, with the ability to detect the lactate:creatine ratio in the brain or muscle when cerebrospinal fluid or serum levels are normal, but the clinical presentation is suggestive of disease.[20] Studies over the past decade have raised the possibility that proton magnetic resonance spectroscopy may be more sensitive for diagnosis than a regular MRI scan.[42] SPECT studies can confirm MELAS using a tracer, *N*-isopropyl-p-[123-I]-iodoamphetamine, as well as follow the progression of the disease with decreased accumulation of the tracer in the parieto-occipital region following stroke-like episodes even in the presence of normal cerebral blood flow.[43]

A skeletal muscle biopsy is of value in the diagnostic workup; it confirms MELAS through abnormal complex I in the respiratory chain enzymes within muscles and through the visualization of abnormal muscle fibers, and it distinguishes the syndrome from other progressive neurologic diseases. Muscle biopsy may also be of particular value when other screening tests are normal but the clinical picture is highly suggestive of MELAS.[20,44,45]

## What Are the Psychiatric and Neuropsychiatric Aspects of MELAS?

The neuropsychiatric aspects of MELAS are diverse. Some preliminary investigations have found potential genetic overlap between point mutations of mitochondrial disorders and abnormalities seen in atypical psychosis and bipolar disorder.[46,47] In a review by Fattal and colleagues,[48] over 50% of patients in a MELAS case series met DSM-IV criteria for major depressive disorder (with a significant percentage developing depression with psychotic features), with anxiety, other affective disorders, and suicidal ideation also present at rates greater than 15%. There did not appear to be an increased risk of substance disorders despite a significant finding of disability among adults with the syndrome (over 50% of 89 subjects). On average, subjects were more likely to develop psychiatric symptoms after seizures and stroke-like episodes occurred (on average, 7–10 years after being diagnosed with MELAS), raising the possibility of psychiatric morbidity secondary to functional and perceived disability—although other case reports suggest that psychiatric manifestations, including mood disorder, may be the initial manifestation of MELAS.[49,50] Indeed, in a case series of 19 MELAS patients (among whom physical fatigue, muscle weakness, and hearing loss were the most common presenting neurologic symptoms), psychiatric illness (primarily mood disorder with or without psychotic features) preceded these presentations in nearly all cases by several years.[50]

Apart from mood and psychotic symptoms attributable to mitochondrial disease, depression secondary to medical illness, and depression secondary to progressive functional disability, predictable psychiatric manifestations of MELAS are lacking. Some of the comorbidities, such as diabetes mellitus, may in turn be associated with psychiatric symptoms.[51] Visual hallucinations may accompany seizures and stroke-like episodes.[52] In rare cases, persistent, eccentric personality changes may accompany an increasing tempo of seizures and stroke-like episodes, making the differential problematic.[53] Maternal inheritance of migraine headaches associated with mood and anxiety disorders, when present along with cardinal neurologic and cardiovascular manifestations, may also raise the suspicion for MELAS.[18]

## How Can Mitochondrial Disorders Be Treated or Managed?

At a minimum, supportive therapy is indicated, including dietary antioxidants, exercise as tolerated, weight management (to reduce the risk of early diabetes when possible), and the avoidance of oxidative stresses (by avoiding cigarette smoking). Medical procedures that may be required for cardiomyopathy and sensorineural hearing loss include heart and cochlear transplantation, respectively.[54,55]

Apart from these general supportive and preventive measures, however, consensus guidelines for treatment and management of MELAS have yet to be developed, reflecting continued uncertainty about the underlying pathophysiology of the syndrome. Models have considered decreased aminoacylation of mitochondrial tRNA (causing impaired mitochondrial protein synthesis), altered calcium homeostasis, and imbalances in nitric oxide metabolism.[56]

According to Scaglia and Northrop,[56] empirical treatment has been guided by numerous case reports. Various

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pharmacologic treatments have been tried; these include dichloroacetate (which reduces lactic acid, though this has also been implicated in toxic neuropathy),[57] L-arginine,[58] anticonvulsants,[59] edaravone,[60] coenzyme Q10,[61] sumatriptan,[62] corticosteroids,[63] creatine monohydrate,[64] idebenone,[65] riboflavin,[66] nicotinamide,[67] vitamins $B_1$ and $B_2$,[68] and carnitine.[69] Some possible therapeutic effects of coenzyme Q10, L-arginine, and corticosteroids have been shown. Combination therapy of coenzyme Q10 with alpha lipoic acid appears to reduce serum lactate levels by targeting reactive oxygen species (free radicals), although normalization of these does not indicate disease remission.[69,70] Double-blind trials have not yet demonstrated any long-term benefit for coenzyme Q10. In contrast, several prospective studies have shown improved endothelial function and a possible preventive benefit for long-term L-arginine therapy.[58] Corticosteroids have been used for symptom exacerbation, although they do not alter disease course; their use may have been initially suggested by the vasogenic edema present in imaging during stroke-like episodes (resolving within days).[62]

Common treatment strategies for MELAS combine antiepileptic agents, the electron acceptors, and cofactors described previously (thiamine, riboflavin, nicotinamide, coenzyme Q10, and alpha lipoic acid) as well as cytochrome C, vitamin K, vitamin C, carnitine, arginine, and the experimental neural growth factor, humanin (which has been tried in other diseases involving neurodegeneration, e.g., Alzheimer's disease).[56]

Many patients take a "mitochondrial cocktail" available over the counter at most health food stores, usually containing coenzyme Q10, carnitine, creatine, and vitamin E.[71] Safety considerations factor into the choice of an antiepileptic medication, with some data suggesting that valproate, benzodiazepines, and phenobarbital may all interfere with mitochondrial respiration.[56] There may be some preference for phenytoin, carbamazepine, gabapentin, lamotrigine, and zonisamide in MELAS, although individualized anticonvulsant regimens must be clarified by a consulting neurologist and preferably by an epileptologist. Genetic counseling (for patients wishing to have children) and psychiatric care (for manifestations of MELAS and management of difficult questions of prognosis) are also recommended.

Although current treatment options are limited, gene therapies using vectors (e.g., restriction endonucleases), novel strategies, and other investigational drugs can offer promise for the future.[72]

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