Inherited Metabolic Disorders and Stroke Part 1

Fabry Disease and Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis, and Stroklike Episodes

Fernando D. Testai, MD, PhD; Philip B. Gorelick, MD, MPH

Inherited metabolic disorders are single-gene genetic diseases associated with multiorgan damage. Some of these conditions increase the risk of stroke through a variety of mechanisms, and there is evidence that early recognition and initiation of appropriate treatment may improve prognosis. In this 2-part review we provide an update of the genetics, stroke pathophysiology, clinical manifestations, diagnosis, and treatment of metabolic disorders associated with stroke. In part 1, we concentrate on Fabry disease and mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes. In part 2 we will review homocystinuria, organic acidurias, and urea cycle disorders.

FABRY DISEASE

Genetics

Fabry disease is an X-linked sphingolipidosis caused by deficiency of α-galactosidase A (α-gal). The defect of this lysosomal enzyme leads to a failure in the metabolism of glycosphingolipids containing α-D-galactosyl moieties, particularly globothriacosylceramide (Figure 1), which accumulate in the lysosomes of most organ cells. More than 400 mutations of the α-GAL gene have been identified, most being missense or nonsense nucleotide substitutions. As de novo mutations are documented, the absence of a family history of disease does not rule out the diagnosis of FD. The incidence of FD is estimated to be 1 in 117,000 live births and 1 in 40,000 men.

Epidemiology

In a German study, 721 adult patients aged 18 to 55 years with cryptogenic stroke (289 women and 432 men) were screened for FD. A biologically significant mutation of α-GAL was found in 4.9% of men and 2.4% of women. Based on these findings, it was estimated that FD is responsible for 1.2% of cryptogenic strokes in patients younger than 55 years.

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Table 1. Inherited Metabolic Disorders Associated With Increased Risk of Stroke

<table>
<thead>
<tr>
<th>Disorders</th>
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<tr>
<td>Sphingolipidoses</td>
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<td>Fabry disease</td>
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<td>Mitochondrial diseases</td>
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<td>MELAS</td>
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<td>Hereditary connective tissue disorders</td>
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<td>Homocystinuria</td>
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<td>Organic acidurias</td>
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<td>Branched-chain organic acidurias</td>
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<td>Isovaleric aciduria</td>
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<td>Methylmalonic aciduria</td>
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<td>Propionic aciduria</td>
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<td>Glutaric aciduria</td>
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<td>Type I</td>
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<tr>
<td>Type II</td>
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<tr>
<td>Urea cycle</td>
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<tr>
<td>Carbamoyl phosphate synthetase I deficiency</td>
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<tr>
<td>Ornithine transcarbamylase deficiency</td>
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<td>Citrullinemia</td>
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Abbreviation: MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes

According to the FD outcome database (n = 366), women with FD are more likely to experience stroke (27%) than men (12%). In this study, the mean age at onset of stroke was 28.8 years in men and 43.4 years in women. Stroke in patients with FD may occur in the absence of other clinical manifestations and more commonly affects the posterior circulation.

Stroke Pathophysiology

A number of pathophysiologic factors have been linked to stroke in FD. The prevalence of traditional stroke risk factors such as cardiac valvular disease, left ventricular hypertrophy, cardiac arrhythmia, and hypertension may be higher in patients with FD with a history of stroke than in those without a history of stroke. In addition, progressive accumulation of globo- triaosylceramide in endothelial and vascular smooth muscle cells causes progressive stenosis and occlusion of small arterial vessels. Furthermore, the large vessels dilate, resulting in dolicho- ectatic changes and flow stagnation, increasing the risk of artery-to-artery embolism and vessel thrombosis. These changes occur more frequently in the posterior circulation, and increased basilar artery diameter has been shown to be a sensitive indicator of FD. It has been suggested that the vertebrobasilar system may have an intrinsic susceptibility to oxidative stress that has been linked to impairment of cerebral vasoreactivity and persistent vasodilation. Also, hyperreactivity to acetazolamide infusion and hyporeactivity to ascorbate have been observed in FD, suggesting a lack of autoregulation.

In animal models of FD, accelerated atherosclerosis and enhanced thrombosis suggest the presence of an underlying prothrombotic state. In patients with FD there may be premature atherosclerosis and elevated homocysteine levels. Serologic evidence of endothelial and leukocyte activation and high prevalence of autoantibodies (eg, extractable nuclear antigens, double-stranded DNA, lupus anticoagulant, anticyclophilin, and antiphosphatidylserine antibodies) have been described in small series. In patients with FD, polymorphic forms of proteins involved in inflammation, vascular wall pathophysiology, and the coagulation cascade (eg, interleukin 6, endothelial nitric oxide synthase, Factor V Leiden, and protein Z) have been associated with characteristic cerebral lesions.

Brain imaging manifestations are common in FD and may provide evidence of stroke pathophysiology. For example, brain magnetic resonance imaging (MRI) may show progression of white-matter lesions. On positron emission tomography these areas may be associated with increased regional cerebral blood flow and decreased regional glucose metabolism. These findings may represent an underlying metabolic insufficiency due to impaired arterial autoregulation, cellular dysfunction, or occlusive microangiopathy with luxury perfusion. Elevated regional cerebral blood flow might increase white-matter interstitial pressure which, together with a metabolic vulnerability, leads to demyelination, gliosis, and increased white-matter water content as evidenced on MRI. By using diffusion tensor MRI, diffuse abnormalities have been observed in patients with FD, indicating microstructural abnormalities even when these areas appear normal on conventional MRI.

Clinical Manifestations

Patients with FD may present in childhood with painful crises (eg, acroparesthesias), fever, hypohidrosis/anhidrosis, and exercise intolerance. Depending on the residual enzyme activity and severity of the disease, symptoms may go unrecognized for years. Other common clinical manifestations are summarized in Table 2. Owing to skewed organ-specific X chromosome inactivation (nonrandom lyonization), women may have atypical organ-specific presentations, making diagnosis more challenging. Such manifestations in women may include those of skin, cardiac, renal, or cerebrovascular abnormalities.

Abbreviation: MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes

Figure 1. Metabolism of glycosphingolipids. SAP-B indicates saposin-B.
Diagnosis

The laboratory diagnosis of FD is made by direct measurement of α-gal activity in leukocytes or plasma. However, this assay may not identify heterozygotes. Therefore, in women, gene sequencing and genetic linkage studies may be necessary.

Treatment

The goal of treatment for patients with FD with stroke is to prevent new ischemic events and halt progression of underlying disease. Enzyme replacement therapy with α-gal was approved by the US Food and Drug Administration in 2003. In a double-blind study of patients with FD, a significant reduction in the amount of vascular endothelial globosotriaosylceramide deposits of the kidney, heart, skin, and liver was observed after a 20-week α-gal infusion period of 1 mg/kg biweekly (P<.001).10 It also may slow the progression of renal disease, reverse hypertrophic cardiomyopathy and elevated regional cerebral blood flow, and improve autonomic function, neuropathic pain, and perspiration.17

The effect of enzyme replacement therapy on stroke prevention remains promising but uncertain. In a series of 43 patients with FD, enzyme replacement did not significantly alter the progression of neurological deterioration, especially among those who had preexisting cerebrovascular disease.18 Possible reasons for failure include intrinsic resistance of brain pathology to enzyme replacement, failure of α-gal to adequately reach the brain, and irreversible vascular damage owing to late initiation of treatment. In relation to stroke prevention, questions remain regarding proper dosage and long-term benefits of enzyme replacement therapy that have not yet been fully clarified. Early treatment with enzyme replacement therapy, however, should be considered. Based on the existing evidence, an expert panel has recommended that enzyme replacement therapy be initiated in all patients with FD as soon as clinical signs and symptoms of disease are observed. This recommendation includes treatment of carriers with significant signs or symptoms.19 In addition, the use of antithrombotic agents (ie, antiplatelet agents or anticoagulants in appropriate circumstances) and control of vascular risk factors according to currently recommended stroke-prevention guidelines is indicated. Finally, the American Heart Association statement for management of stroke in infants and children recommends enzyme replacement therapy for patients with FD (class I, level of evidence B rating).20 Recombinant α-gal is available in the United States in 5-mg and 35-mg vials with a direct cost of US $643 and US $4503, respectively. The usual dosage is 1 mg/kg biweekly. The manufacturer offers a support mechanism to assist patients with reimbursement from health insurers as well as a charitable access program (www.genzyme.com).

Pharmacologic chaperones may provide a new treatment opportunity for FD. By facilitating mutant protein folding, they improve trafficking and prevent endoplasmic reticulum–associated degradation. 1-Deoxygalactonojirimycin is a potent inhibitor of α-gal with chaperone-like properties. This compound corrected α-gal trafficking and increased residual enzyme activity in FD animal models and in cultured cells from patients with FD.21,22

MITOCHONDRIAL MYOPATHY, ENCEPHALOPATHY, LACTIC ACIDOSIS, AND STROKELIKE EPISODES

Genetics

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes is a progressive disorder caused by mitochondrial dysfunction. Almost 80% of patients with MELAS have a mitochondrial DNA (mtDNA) A-to-G transition at nucleotide 3243 of the transfer RNA of leucine. However, other mtDNA and nuclear DNA mutations have been described.23 The mtDNA mutations are maternally transmitted in a non-Mendelian manner. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes has no ethnic predilection and is one of the most common maternally inherited mitochondrial disorders. The prevalence of the most common MELAS mutation is estimated to be 7.59 per 100 000 persons in Northeast England, 16.3 per 100 000 in Northern Finland, and 236 per 100 000 in Australia.24

Clinical Manifestations

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes is characterized by normal early development followed by stroke-like episodes (typically before the age of 40 years), mitochondrial encephalomyopathy, and lactic acidosis. Frequently encountered clinical manifestations of MELAS are summarized in Table 3.
Strokelike events are usually associated with migraine headaches and seizures. The spreading nature of strokelike lesions noted on brain MRI has raised the question of a neuronal hyperexcitability mechanism similar to that seen in status migrainosus and status epilepticus. It has been hypothesized that endothelial mitochondrial failure affects the blood-brain barrier and causes a shift in extracellular ion homeostasis, leading to neuronal hyperexcitability and cerebral hyperperfusion. Neuronal hyperexcitability may then initiate epileptic discharges and migraine headaches, which propagate to other brain areas, increasing the energy requirements of metabolically-vulnerable neurons with resultant cell death.29

**Diagnosis**

The diagnosis of MELAS may be challenging, as the tissue-specific content of mutated mtDNA, and thus the residual mitochondrial activity and clinical presentation, varies among members of the same family. Different factors account for this observation. Because each mitochondrion contains multiple mtDNA copies and each cell has multiple mitochondria, the proportion of normal and mutated mtDNA may vary among cells (heteroplasmy) and organs. Furthermore, each tissue has its own intrinsic threshold, being metabolically active tissues particularly susceptible to the deleterious effect of dysfunctional mitochondria.

A high index of clinical suspicion is a key factor in the diagnosis of MELAS, which is supported by laboratory results and confirmed by biopsy and genetic studies. Patients have increased lactate and pyruvate levels in serum and cerebrospinal fluid, and elevated lactate/pyruvate ratio. Lactic acidosis usually does not lead to systemic metabolic acidosis but can cause significant brain impairment. Some individuals have levels of serum lactate in the reference range and elevated cerebrospinal fluid lactate. Elevated brain lactate may be observed on proton magnetic resonance spectroscopy.30

Diagnosis of MELAS can be confirmed by skeletal muscle biopsy. The modified Gomori trichrome stain may reveal typical ragged-red fibers, which usually stain positive with cytochrome oxidase. A distinctive histological finding in MELAS is the presence of strongly positive succinate dehydrogenase staining of affected skeletal muscle fibers and blood vessels. As succinate dehydrogenase is the only mitochondrial complex that is entirely encoded by nuclear DNA, the strong staining denotes mitochondrial dysfunction with compensatory proliferation. The increased number of mitochondria, some with morphological abnormalities evidenced by the presence of paracrystalline inclusions, can be demonstrated by electron microscopy. Individual mitochondrial respiratory chain enzyme activities can be measured in skeletal muscle, and mitochondrial DNA mutation analysis can be performed on blood, skeletal muscle, hair follicles, urinary sediment, and buccal mucosa.

Brain biopsy shows nonspecific findings resembling ischemic infarction such as neuronal eosinophilia, reactive astrocytosis, inflammatory infiltration, and edema. Angiogenesis is seen in the acute/subacute state and cystic changes in the chronic phase.31

### Table 3. Clinical Manifestations of MELAS

<table>
<thead>
<tr>
<th>Location</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Exercise intolerance, Short stature</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Strokelike episodes, Seizures, Encephalopathy and/or dementia, Headache (usually migrainous), Elevated CSF protein</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>Myopathy, Peripheral neuropathy</td>
</tr>
<tr>
<td>Ear</td>
<td>Hearing loss</td>
</tr>
<tr>
<td>Eye</td>
<td>Optic nerve atrophy, Pigmentary retinopathy, Ophthalmoplegia</td>
</tr>
<tr>
<td>Heart</td>
<td>Dilated cardiomyopathy, Left ventricular hypertrophy, Conduction block, Preexcitation syndrome</td>
</tr>
<tr>
<td>Kidney</td>
<td>Nephropathy</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Dysmotility</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Diabetes mellitus</td>
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</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes.

**Stroke Pathophysiology**

The etiology of strokelike episodes in MELAS has not been completely explained. Patients may present with neurological deficits that correlate with MRI diffusion-weighted images that show hyperintense cortical multifocal laminar lesions. The apparent diffusion coefficient suggests the presence of vasogenic edema. These lesions may not follow a defined arterial territory distribution, have a predilection for the posterior areas of the brain, and may spread progressively to other brain areas.25

Different hypotheses have been proposed to explain these findings. According to the mitochondrial angiopathy hypothesis, lesions are ischemic in nature and are caused by cerebral small-vessel mitochondrial and vascular dysfunction.26 However, perfusion MRI, positron emission tomography, and single-photon emission computed tomography studies of patients with MELAS have shown evidence of hyperemia, and MRI studies usually do not show cytotoxic edema typically seen in brain ischemia.27 Alternatively, a mitochondrial-mediated cytopathic mechanism has been proposed. The transfer RNA of leucine mtDNA mutation decreases protein synthesis and causes oxidative phosphorylation failure, leading ultimately to adenosine triphosphate depletion and energy failure. Sano et al28 have provided support for this hypothesis by showing decreased cerebral metabolic rate for oxygen and decreased cerebral oxygen/glucose metabolic ratio. These results are consistent with preserved cerebral perfusion and failure of oxidative phosphorylation.28 In addition, combining the results obtained using MRI, MR spectroscopy, and MR perfusion imaging, Ito et al27 showed that strokelike episodes are related to vasogenic edema, hyperperfusion, and neuronal loss implicating cytopathic toxicity secondary to energy imbalance.

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A variety of approaches have been proposed to treat patients with MELAS. A limitation, however, is that large-scale clinical trials investigating the risks and benefits of such therapies are lacking. Most available information originates from small case series, anecdotal observations, or hypothesized benefits based on the mechanism of action of a specific treatment of interest. The main goal is to improve adenosine triphosphate production and electron transfer.

Coenzyme Q10 and its synthetic analog, idebenone, have antioxidant properties and have been used to improve the transfer of electrons in the mitochondrial respiratory chain in patients with mitochondrial diseases (Figure 2). Small trials and case reports indicate that coenzyme Q10 used alone or in combination with creatine and lipoic acid decreases the level of lactic acid. Long-term clinical improvement associated with the use of coenzyme Q10, however, remains to be proven. Because coenzyme Q10 does not cross the blood-brain barrier, a theoretical concern is that a direct beneficial effect in the brain is unlikely to occur, except in areas where the blood-brain barrier may be disrupted.

Idebenone has the theoretical advantage of crossing the blood-brain barrier, and case reports suggest that this drug improves mitochondrial metabolism in the brain and decreases the frequency of stroke-like episodes in patients with MELAS. The drug is not available, however, in the United States.

By inhibiting the pyruvate-dehydrogenase complex kinase, dichloroacetate activates the pyruvate dehydrogenase complex and increases the consumption of pyruvate (Figure 3). In MELAS, dichloroacetate has been shown to decrease the level of lactic acid. However, a randomized placebo-controlled trial using dichloroacetate in patients with MELAS did not show treatment benefits and was terminated early owing to frequent peripheral nerve toxicity.

L-arginine (L-arg) is a substrate of nitric oxide synthase and a precursor of the endogenous vasodilator nitric oxide. The L-arg level decreases in the acute phase of stroke-like episodes, and it has been hypothesized that these events are caused by impaired vasodilation due to nitric oxide deficiency. Based on this observation, L-arg was used in patients with MELAS in an attempt to preserve normal vascular tone. In an open-label study, the infusion of L-arg (0.5 g/kg per dose) shortly after the onset of stroke-like episodes improved functional cerebral hemodynamics, as measured by 99mTc-ECD single-photon emission computed tomography, and most of the associated clinical manifestations. In another study, 24 patients with MELAS were treated with an intravenous infusion of L-arg (0.5 g/kg per dose) within 30 minutes of onset of a stroke-like episode. Patients showed a significant improvement in all stroke-like symptoms as well as normalization of lactate and pyruvate concentrations within 24 hours of the infusion. Six of these patients were subsequently supplemented with oral L-arg during the interictal phase (0.15-0.3 g/kg per dose). In this group, a significant decrease in the frequency and severity of subsequent events was observed after the initiation of oral L-arg treatment. Although additional studies are necessary, these results suggest a possible role for L-arg in the treatment of stroke-like episodes in MELAS.

Owing to mitochondrial failure, patients with MELAS may experience secondary long-chain fatty-acid β-oxidation deficiency (Figure 3). Furthermore, patients with renal involvement may experience, at least theoretically, loss of carnitine. Therefore, oral carnitine supplementation has been used in these patients to enhance β-oxidation. Scaglia and Northrop provide a thoughtful review of these and other less-studied vitamins and antioxidants proposed in the management of this condition. The long-term effect of these compounds in MELAS has not been studied.
Clinical Outcome

Although the clinical presentation and progression of MELAS syndrome may be variable, overall, patients tend to have poor outcome. There may be progressive dementia and neurological deterioration related to stroke-like episodes and recurrent seizures. In a cohort of 33 patients with MELAS and the 3243 mtDNA mutation, progressive sensorineural hearing loss, left ventricular hypertrophy, and disability were noted during a 3-year follow-up period. Furthermore, in a pediatric cohort, younger age at onset of symptoms has been shown to be an independent predictor of death.

Our review of inherited metabolic disorders and stroke continues as a separate manuscript, Part 2, which addresses homocystinuria, organic acidurias, and urea cycle disorders.

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