Anderson-Fabry Disease: Extrarenal, Neurologic Manifestations

EDWIN H. KOLODNY* and GREGORY M. PASTORES*†
*Neurogenetics Program, Department of Neurology and † Pediatrics, New York University School of Medicine, New York, New York.

The advent of enzyme replacement therapy for Anderson-Fabry disease (AFD) adds impetus for the early detection of patients with this inherited multiorgan lipid storage disease. The resultant accumulation of neutral glycosphingolipids, especially globotriaosylceramide (Gb3), in various cell types promotes development of disease-related complications associated with renal, cardiovascular, and cerebrovascular involvement. In the central nervous system, diffuse storage occurs in the cerebral vasculature, with more localized involvement of central neurons together with the dorsal root and autonomic ganglia in the peripheral nervous system (1,2,3). Although the disease primarily manifests among hemizygous males, a significant proportion of heterozygous (carrier) females also develop symptoms albeit with a later age of onset (4,5,6). This article focuses on neurologic manifestations of AFD, which when present can lead the nephrologist to consider the disease.

Cerebrovascular Disease
Renal insufficiency and subsequent kidney failure represent the major source of morbidity for most symptomatic patients (detailed earlier in this supplement); however, significant complications may also develop as a consequence of cerebrovascular disease. The cerebrovascular manifestations, reported to affect the posterior circulation predominantly, consist of large-vessel ectasia and large-vessel and small-vessel occlusive disease (7). The reason for the mainly vertebrobasilar distribution is unclear. The repeated occurrence of cerebrovascular events within the vertebro-basilar territory may lead initially to a diagnosis of multiple sclerosis. However, allied features seen with AFD, such as angiokeratoma (telangiectatic skin lesions), corneal and lenticular opacity, and the presence of acroparesis and possibly a positive family history (consistent with X-linked inheritance), offer clues to the correct diagnosis.

The average age at the onset of cerebrovascular symptoms is 34 yr for men and 40 yr for women. In one longitudinal study of 50 patients, no patients younger than 26 yr had lesions on magnetic resonance imaging (MRI), whereas all patients older than 54 yr had cerebrovascular involvement, the disease burden increasing with age (8). In this study, only 37.5% of patients with cerebral lesions had neurologic symptoms. The presence of cerebrovascular disease indicates a poor prognosis with a high likelihood of recurrence or death for both hemizygotes (76%) and heterozygotes (55%). These observations suggest the need for surrogate markers, such as assessment of regional cerebral blood flow (CBF), which may help predict risk of stroke among these patients. Stratification on the basis of risk may lead to consideration of therapy at an earlier stage of disease for this patient group and the potential for stroke-risk reduction, although longitudinal studies will be required to clarify this issue.

Multiple explanations exist for the high incidence of cerebrovascular events in AFD. These include deposition of glycosphingolipid in the wall of the small arteries and arterioles and dolichoectasia of intracranial arteries due to lipid involvement of the vascular smooth muscle. Cardiogenic embolism resulting from myocardial ischemic disease, valvular heart disease and hypertrophic cardiomyopathy (detailed earlier in this supplement), and impairment in cerebrovascular reactivity due to autonomic dysfunction and increased platelet reactivity may also play contributory roles.

Additionally, affected individuals have been found to have a higher incidence of both venous and arterial intravascular thrombosis. A Japanese study, which examined 60 patients with AFD (45 hemizygotes and 15 heterozygotes), revealed that seven had experienced thrombotic accidents (9). Six of these thrombotic patients developed brain infarctions, including one man who had the complication of recurrent thrombophlebitis. The remaining woman showed central retinal artery occlusion and thrombophlebitis. A recent study, which involved 25 Fabry patients, revealed increased concentrations of soluble intercellular adhesion molecule-1, vascular cell adhesion molecule-1, P-selectin, and plasminogen activator inhibitor, and decreased thrombomodulin levels (10). These findings suggest increased levels of endothelial pro-thrombotic factors and leukocyte adhesion-molecule expression may play a significant part in the occurrence of the vascular events and represent added risk factors for stroke in AFD. The use of anticoagulants as a prophylaxis has been recommended (but not decisively) for patients with AFD at risk for strokes. Antihypertensive medications are instituted as needed.

Moore and colleagues recently reported increased resting regional cerebral blood flow (CBF) among patients with AFD in the absence of occlusive vasculopathy or cerebral hypoper-
fusion (11). Studies performed on skin biopsy specimens and archived brain tissue revealed enhanced nitrotyrosine staining in dermal and cerebral blood vessels, findings that are suggestive of a chronic alteration of the nitric oxide pathway in AFD (12). The relation between the increased risk of stroke in AFD and the elevated regional CBF is unclear. It is possible that the increased regional CBF contributes to endothelial dysfunction and vessel wall dilation, resulting in a procoagulant and abnormal flow state and the potential for an increased incidence of emboli or thrombosis. Interestingly, treatment with agalsidase-alfa (Replagal; Transkaryotic Therapies, Cambridge, MA) has been shown to lead to a reduction in the noted elevation in regional CBF (13). This observation raises the prospect of a reduction in the risk of stroke after the institution of enzyme therapy, although this hypothesis requires further investigation.

Changes in regional blood flow were also noted peripherally. Investigations involving 17 normotensive and normocholesterolemic hemizygous (male) patients (aged 21 to 49 yr) with AFD revealed increased forearm blood flow after the administration of acetylcholine (14). These observations buttress the hypothesis of increased endothelium-mediated vascular reactivity in AFD, which in this study was interpreted as reflecting altered functionality of non-nitric oxide endothelium-dependent vasodilatory pathways.

In contrast, studies of cerebral blood flow in the knockout mouse model for AFD revealed a trend to lower CBF globally and locally when compared with normal mice (15). Histologic mouse model for AFD revealed a trend to lower CBF globally reflecting altered functionality of non-nitric oxide endothelial reactivity in AFD, which in this study was interpreted as necessarily due to circulatory insufficiency. The significance of these observations for humans with AFD is not certain, but they imply caution in interpretation of the applicability of preclinical studies in mice to humans. Recent studies conducted among patients with AFD also revealed decreased regional cerebral glucose (rCGlu) metabolism, particularly in the deep white matter (16). The changes were exacerbated in regions corresponding to areas associated with high-signal intensity on MRI-fluid attenuation inversion recovery (FLAIR) studies. The findings were interpreted as indicative of chronic white matter ischemia and promoted as a rational for consideration of AFD as a model of leukoaraiosis (16).

Assessment of cortical and subcortical neuropathy in AFD, using MRI-spectroscopy, revealed a widespread pattern of neuronal involvement on the basis of reduction of cortical and subcortical N-acetacacetate (NAA) (17). The basis for the decrease in NAA levels is not known, but it could reflect either direct metabolic dysfunction of neurons secondary to α-galactosidase A deficiency and Gb₃ accumulation or to subclinical ischemia of various brain areas. The lack of signs of brain atrophy and absence of relevant signs of central nervous system involvement indicate that the decrease in NAA levels is probably not due to neuronal loss or degeneration. Interestingly, the changes were noted to extend to areas beyond the MRI-visible cerebrovascular abnormalities. Seven patients were also found to have discrete MRI abnormalities consisting of white matter hyper-intensities or basal ganglia infarcts (17). The functional significance of these changes is not certain, because neurologic examination performed on AFD patients do not often reveal focal deficits that correlate with the anatomical localization of the changes in white matter. Cognitive decline, epileptic seizures, or cortical atrophy do not occur in patients with AFD unless extensive ischemic damage is visible by MRI (18).

Acroparesthesias

Patients with AFD characteristically experience acroparesthesias (constant burning pain and tingling), especially in the toes and fingers, and episodic pain crises or bouts of extremely severe attacks of sharp neuropathic pain (19,20). Acroparesthesias can be debilitating, occur at an early age, and are encountered more often that problems associated with the stroke-like features discussed above. The pain complaints may be precipitated by changes in temperature, exercise, or stress and can be accompanied by fatigue, low-grade fever, and joint pains. A progressive peripheral neuropathy is usual, and thermal sensitivity is diminished.

Evaluation of warm and cold perception thresholds (i.e., small nerve fiber function) in two male patients (15 and 17 yr old) with AFD and their heterozygote mother revealed development of intense burning pain and numbness during and after cold stimulation (21). It was hypothesized that glycolipid accumulation in cutaneous and vasa nervorum vessels as well as small nerve axons led to a perturbation of skin and small fiber perfusion during cold-induced vasoconstriction. Ultrastructural examination of intradermal nerve fibers in AFD revealed signs of lipid accumulation and small unmyelinated nerve fiber degeneration (22,23). Many axons were swollen, and their internal organelles were lost. In several damaged axons, dense inclusions, probably lipid, were observed. No lipid inclusions were found in Schwann cells, which may indicate that they use different metabolic processes or are impervious to Gb₃. It is hypothesized that Schwann cells and myelin sheaths act as a metabolic barrier protecting the larger myelinated fibers. Lack this barrier, the smaller unmyelinated fibers are more susceptible to lipid infiltration. This view may explain the small fiber neuropathy in AFD. Lipid accumulation in cells of the dorsal root (sensory) ganglia is also likely involved in the causation of pain.

In a separate study, testing of constant current perception threshold (CPT) was performed on 16 patients with AFD (eight hemizygous men and eight heterozygous women) in one family to assist subjective complaints of pain and paresthesias (24). The investigators noted testing of CPT in the low frequencies (5 and 250 Hz) was significantly more sensitive than assessments at a higher frequency (2 kHz) and studies of nerve conduction in detecting sensory neuropathy among patients with AFD. However, there was no correlation between CPT
testing and clinical symptom scores, duration of disease, creatinine clearance values (as a measure of renal status), or residual α-galactosidase A enzyme activities. In this study as with other studies of the natural history of AFD, hemizygous patients clinically demonstrated more severe symptom scores, poorer renal function, and higher prevalence of hypohidrosis and corpora angiopteromas than did heterozygous patients (24).

Examination of the cutaneous innervation density among patients with AFD and normal results on studies of nerve conduction and large fiber quantitation (by sural nerve biopsy) showed severe loss of intraepidermal innervation at the ankle (25). Fiber loss was also noted at the distal thigh, although the changes were proportionately less severe. All of the patients examined in this study had preserved renal function. These results confirm the exclusive involvement of small myelinated and unmyelinated fibers, and the possible utility of skin biopsy in detection and quantitation of such damage. Comparison of cutaneous innervation density with quantitation of sural nerve biopsy specimens demonstrated that skin biopsy specimens were comparatively sensitive in detecting the presence of neuropathy (25). As the diagnosis of AFD can be confirmed on the basis of determination of enzyme activity in a blood sample, the practical usefulness of obtaining a skin biopsy is not certain. It is also not known whether the histologic changes indicative of small myelinated and unmyelinated nerve fibers are reversible with enzyme therapy. Long-term follow up of patients on therapy should provide additional information on the usefulness of cutaneous nerve testing in the monitoring of patients with AFD.

The differential diagnoses often considered for the unusual symptom of burning, painful hands include urticaria, C1 esterase deficiency, acute intermittent porphyria, erythromelalgia, reflex sympathetic dystrophy, peripheral neuritis, and underlying psychologic causes (26). As noted above, the search for the presence of other systemic signs often found in patients with AFD should help avoid confusion with these other clinical entities.

Phenytoin, carbamazepine, and/or gabapentin have been administered for symptomatic treatment of painful crises and acrocyanosis. Hydration and acetaminophen may be given in case of fever or exposure to a warm environment. Patients are often advised to avoid intense physical exertion or exposure to circum- stances that may provoke pain attacks. The clinical trial with enzyme therapy using agalsidase alfa (Replagal) demonstrated significantly reduced the frequency and severity of neuropathic pain in treated patients when compared with placebo (27).

Autonomic Dysfunction

Disturbances in the autonomic nervous system are typically seen in AFD, and they include abnormalities of tears and saliva formation, cerebrovascular reactivity, cardiac rhythm, gastrointestinal motility and pain perception. Peripheral edema is another manifestation but may also reflect cardiac or renal dysfunction. Autonomic centers throughout the neuro-axis show a predilection for lipid storage including the supra-optic and paraventricular nuclei, the parahippocampal gyrus, the vagal nuclei, Onuf’s nucleus, and the ganglion cells of the myenteric plexuses. The reasons for this proclivity to involve the cells and nuclei of the autonomic nervous system remain unknown.

Postprandial pain, nausea, and diarrhea are common complaints in AFD, prompting the patient to eat frequent small meals (28,29). Accumulation of lipid in the autonomic ganglia of the intestine results in impaired mobility and loss of the haustral markings in the large intestine. Outpouchings in the lax smooth muscle develop, and diverticulae may rupture with consequent peritonitis. Esophageal vascular ectasias may be a cause of hematemesis. Investigations of the basis for gastrointestinal symptoms in seven patients with AFD revealed abnormally decreased gastric emptying (30). Six of seven symptomatic patients treated with metoclopramide reported clinical improvement. In two of four patients with follow-up studies, symptomatic relief was associated improvement in gastric emptying.

Jejunal diverticulosis with perforation and abscess formation as a complication of AFD has been reported (31). Light microscopy studies disclosed glycolipid deposition in the neurons and nerve fibers of the intestinal nerve plexuses and smooth muscle. Silver stains of the myenteric plexus in the involved segment of the bowel showed enlarged, granular argyrophobic neurons and a marked decrease in the number of argyrophilic neurons, with those remaining being enlarged and distorted by the cytoplasmic glycolipid accumulation. These abnormalities of the myenteric plexus suggest that jejunal diverticulosis may be the result of a variety of disorders of the smooth muscle or myenteric plexus, or both.

Sweating is reduced (hypohidrosis) or absent (anhidrosis) among patients with AFD due to lipid accumulation in the eccrine cells and possibly also to autonomic nervous system dysfunction (32). This may partly explain the increased likelihood in warm weather of painful crises as well as nausea, dyspnea, and headache. The production of tears and saliva is also reduced.

Ophthalmologic and Acoustic Vestibular Involvement

Tortuosity of conjunctival and retinal vessels, especially veins, occurs in the absence of hypertension. Whorl-like feather corneal opacities and anterior, capsular or subcapsular and posterior lenticular deposits may be detected on a slit lamp examination (32). One or more of these are seen in almost all men and in 70 to 90% of heterozygous women. Vision is usually unaffected by these alterations, but retinal complications, hypertension, and uremia may occur later in the illness. Unilateral central retinal artery occlusion has also been reported.

Many patients develop nerve deafness, often asymmetrically (32). The loss is progressive and predominantly in the high tone range. This is believed to be due to lipid storage within nerve cells of the cochlea, but sudden loss of hearing could arise due to occlusion of the branch of the basilar artery to the cochlea. Peripheral vestibular abnormalities have also been described.

Neuropsychiatric Considerations

Recurring pain and exercise intolerance limit the activity of the symptomatic patients with AFD to a sedentary life-style. With increasing disability and awareness of shortened life span in general (and of older relatives with the disease), the unpredictability and difficulty of controlling the pain and gastroin-
testinal distress and the disfiguring effects of the angiokeratomas, patients are at risk for chronic depression. Some patients become sullen, withdrawn, and fatalistic, believing that there is little that medical science can do to help. Alcoholism and suicide have been reported among patients with AFD. The neuropathic pain may lead to dependence on narcotics. Late in the disease, mild dementia can appear secondary to diffuse leukomalacia, multiple strokes or possibly to lipid storage in hippocampal and frontal lobe neurons.

In summary, neurologic (and other extrarenal) manifestations serve as an important cause of morbidity among patients with AFD and may also provide clues to the nephrologist regarding the diagnosis. Importantly, these manifestations are not expected to improve after dialysis or renal transplantation; therefore, enzyme therapy should be considered even after the development of ESRD.

References