Observation

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Later-Onset Fabry Disease

An Adult Variant Presenting With the Cramp-Fasciculation Syndrome

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Abstract

Background Classic Fabry disease, an X-linked recessive lysosomal storage disease due to the deficient activity of α-galactosidase A, typically presents in early childhood with acroparesthesias, angiokeratomas, hypohidrosis, and corneal dystrophy. The neuropathic pain presumably results from glycosphingolipid accumulation in the vascular endothelium and in small-caliber nerve fibers, and is treatable by enzyme replacement therapy. Later-onset variants with residual α-galactosidase A activity lack vascular endothelial involvement and classic symptoms, which lead to the development of cardiac and/or renal disease after the fourth decade of life.

Objective To expand the later-onset Fabry phenotype to include cramp-fasciculation syndrome without small-fiber neuropathy.

Methods A 34-year-old man who presented with chronic exercise-induced pain, fasciculations, and cramps of the feet and legs, and his similarly affected mother, were evaluated. Clinical, biochemical, and molecular studies were performed.

Results Clinical evaluation suggested the diagnosis of Fabry disease, which was confirmed by reduced plasma and leukocyte α-galactosidase A activities (8.8% and 13.4% of normal, respectively) due to a missense A143T mutation. His mother was heterozygous for the A143T mutation.

Conclusion The presentation of cramps and fasciculations without apparent small-fiber neuropathy expands the phenotype of later-onset Fabry disease.

Fabry disease is an X-linked recessive inborn error of glycosphingolipid catabolism resulting from deficient or absent activity of the lysosomal exoglycosidase α-galactosidase A (α-Gal A).[1] The enzymatic defect leads to the systemic accumulation of globotriaosylceramide (GL-3) and related glycosphingolipids in the plasma and in cellular lysosomes throughout the body.[2] Clinical onset in classically affected men occurs in childhood and is typically characterized by episodic painful burning sensations in the hands and feet (acroparesthesias), typical skin lesions (angiokeratomas), hypohidrosis, and corneal opacities. The acroparesthesias, which typically manifest at 4 to 9 years of age, presumably result from vascular ischemia within the microvessels of nerves and dorsal root ganglia and small-fiber sensory neuropathy (dorsal-C and A-δ sensory fibers predominately affected).[2-4] With advancing age, the progressive lysosomal GL-3 accumulation, particularly in the vascular endothelium, leads to renal failure and vascular disease of the heart and the brain, with premature demise in the fourth and fifth decades of life.[2,5,6] Later-onset variants, which have residual α-Gal A activity and lack the hallmarks of the classic phenotype (ie, angiokeratomas, acroparesthesias, hypohidrosis, and ocular abnormalities), typically develop renal and/or cardiac disease without neurologic symptoms in the sixth decade of life or later.[7-10]

The painful distal small-fiber neuropathy of Fabry disease may go undiagnosed by conventional nerve conduction studies and needle electromyography.[3,11] Modern techniques include the following: (1) quantitative whole sural nerve biopsy; (2) skin biopsy with examination of small-caliber unmyelinated terminal sensory nociceptor nerve fibers[12]; (3) quantitative sensory testing of small fibers; and (4) sudomotor testing with the potential ability to diagnose the small-fiber sensory neuropathy characteristics of this disease.[3,13] Identification of the typical glycosphingolipid accumulations may require electron microscopy. Consideration of α-Gal A enzymatic testing in otherwise cryptogenic small-fiber sensory neuropathies is important.

We describe a 34-year-old man who initially presented with idiopathic activity-induced cramps and fasciculations characteristic of cramp-fasciculation syndrome.[14] He had serial nerve skin biopsies without overt evidence of epidermal denervation. The diagnosis of Fabry disease was prompted by his mother's similar but less severe symptoms beginning at age 50 years. The patient's plasma and leukocyte α-Gal A activities were deficient and sequencing of his *α-Gal A* gene revealed the missense mutation A143T, a previously identified mutation in later-onset Fabry disease.[15-17] Here we extend the phenotype of later-onset Fabry disease to include the neurologic presentation of cramps and fasciculations without initial evidence of small-fiber neuropathy.

Report of a case

A 34-year-old man presented with a 5-year history of progressively worsening activity-induced foot and leg cramps and fasciculations with pain. He was otherwise healthy and worked in the lawn and garden business where walking triggered the painful attacks. Initially he could obtain complete resolution of attacks by resting, but eventually the pain was present at all times and kept him from walking any distance such that he changed job responsibilities to reduce ambulation. He did not have skin hypersensitivity, loss of feeling, paresthesias, burning, or dysesthesias.

Previous evaluations, 2 and 4 years after onset of the attacks, included skin nerve biopsies at the proximal and distal thigh, calf, and distal leg including studies with the panaxonal antibody, protein gene product 9.5. The biopsy results were normal. He also had normal lower extremity nerve conductions, electromyography, magnetic resonance imaging (MRI) of the brain and whole spine, and a normal myelogram of the lumbar spine.

On neurologic examination at age 34 years, the patient had normal strength, reflex, and bedside sensation testing, including ability of his toes to distinguish between and feel light touch (cotton gauze), hot (40°C), cold (Minnesota thermal discs), and pin prick. There was no allodynia (pain on palpation) of the feet or legs. He had no cutaneous (angiokeratomas) or ocular manifestations (corneal opacities) of Fabry disease. When walking more than 25 yards or with 10 or more plantar flexion exercises, he had painful leg cramps with associated increased fasciculations. Calf fasciculations were present to some degree at all times, but became consistently worse by activity. The feet were not cold and dorsal pedal pulses were present and robust.

Nerve conduction studies showed a preserved medial plantar response of 7 μV, a normal sural sensory amplitude of 8 μV (16th percentile of normal age- and anthropomorphic-matched controls), and normal peroneal and tibial motor responses. The cramp fasciculation protocol failed to induce sustained contractions recorded at the abductor hallucis at 2, 5, and 10 Hz.[14] However, leg exercise could produce the typical electrophysiologic cramps and exaggerated fasciculations of that disorder. Autonomic reflex studies measuring adrenergic and cardiovagal responses to tilt-table testing and the Valsalva maneuver were normal. Postganglionic sudomotor function was normal by quantitative sudomotor axon reflex testing of the foot, distal and proximal leg, and forearm (1.40 [0.84-5.42] μL/cm^2, 2.94 [0.76-3.91] μL/cm^2, 3.36 [0.93-4.98] μL/cm^2, and 2.64 [0.70-5.39] μL/cm^2, respectively). Electrolytes for calcium, magnesium, sensitive thyrotropin-stimulating hormone, and voltage-gated potassium channel antibodies were all normal. His 24-hour urinary protein level was 32 mg per 24 hours (normal, 10-102 mg per 24 hours) with a protein/osmolality ratio of 0.03 (normal, <0.12). Magnetic resonance imaging of the brain and spinal cord was normal without evidence of small vessel ischemia.

The history, neurologic examination, and testing, including normal skin biopsies, suggested the diagnosis of a cramp-fasciculation–like syndrome. Carbamazepine, 300 mg twice daily, helped only modestly to prevent cramps and fasciculations and pain persisted. Because the medical history of the patient's mother in-

cluded activity-induced foot pains, the diagnosis of X-linked Fabry disease was considered. His mother had been evaluated 10 years earlier and gave us permission to review her medical records. Her symptoms began at age 58 years with progressive painful feet and legs, and the pain increased with walking and standing. She was a physician and thought that her pain symptoms were similar to those of her son. She had an acute central ischemic attack at age 37 years at the time she began oral contraceptive medication. The associated brainstem weaknesses resolved after 3 weeks.

On clinical examination, she had diffusely brisk reflexes including the jaw-jerk response without plantar extensor response or other pathologic signs. She had foot hypersensitivity, without sensory loss, and otherwise had normal clinical examination findings. Nerve conduction tests and electromyographic studies were normal and MRIs of her brain and spine revealed T2 hyperintensities in the periventricular regions and at the ninth thoracic level. She was given the diagnosis of possible multiple sclerosis and was seen in the pain clinic where analgesics were advised for her foot pains. Twelve years later, she reported worsening foot pain including cramping and fasciculations that were less severe than her son's symptoms. She has not developed other neurologic or medical symptoms at age 66 years.

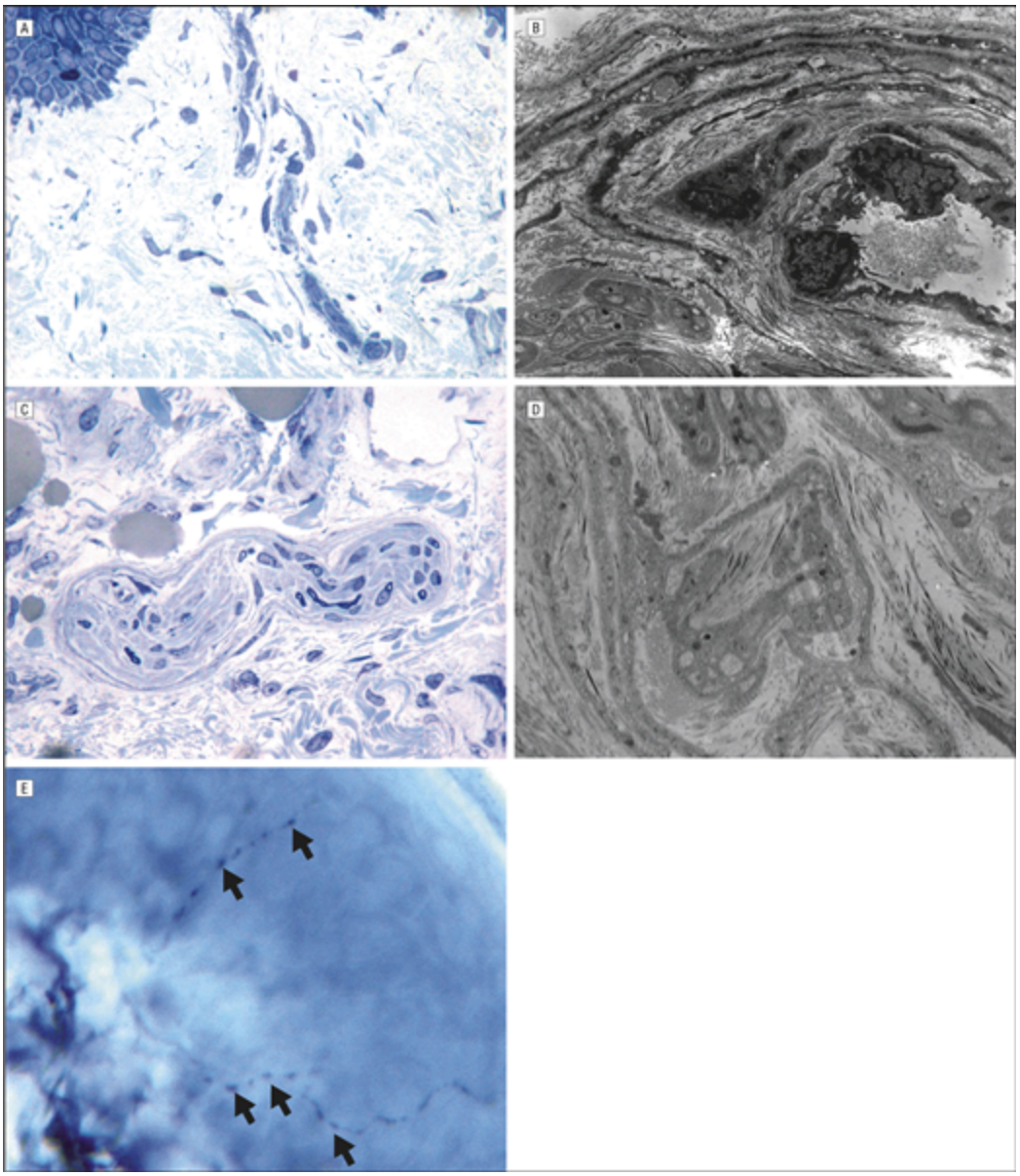
The patient's α-Gal A activity was markedly decreased in plasma (1.9 U/mL; normal mean ± SD, 21.6 ± 6.4 U/mL) and isolated leukocytes (9.3 U/mg; normal mean ± SD, 69.4 ± 32.9 U/mg). Subsequent sequencing of the patient's *α-Gal A* gene revealed a missense mutation due to a guanine-to-adenine substitution in codon 143, predicting the replacement of an alanine by a threonine residue (designated A143T). His mother was heterozygous for the A143T mutation, while his asymptomatic 38-year-old sister did not inherit the mutation.

The patient was referred to the International Center for Fabry Disease at the Mount Sinai School of Medicine, New York, NY, for further evaluation. He continued to complain of the cramping pain and fasciculations without hypohidrosis. On examination, he had no angiokeratomas and his corneas and lenses were clear by slitlamp microscopy. Blood cell counts and serum chemistry findings were normal including electrolytes, liver function tests, and lipid profiles. His serum creatinine level was 0.9 mg/dL and creatinine clearance was 163 mL/min per 1.72 mm^3. Urine analysis revealed 100 mg/dL per 24 hours and trace blood. His electrocardiogram was normal and an echocardiogram had borderline normal left ventricular function, normal size, and normal diastolic compliance. He had mildly decreased right ventricular function with mild right ventricular dilatation, but no evidence for right ventricular hypertrophy. Pulmonary function tests, results from an audiogram, and results from a brain MRI were normal. An MRI of the kidney revealed slightly obliterated corticomedullary differentiation bilaterally.

A repeat skin biopsy revealed none of the typical lysosomal inclusions in the vascular endothelial or smooth muscle cells or in nerves or perineural cells (**Figure 1**), which were consistent with the findings of his skin biopsies obtained at age 30 years to determine the etiology of his pain. Additionally, recent skin biopsies from the left proximal thigh and distal leg, stained with protein gene product 9.5 to examine

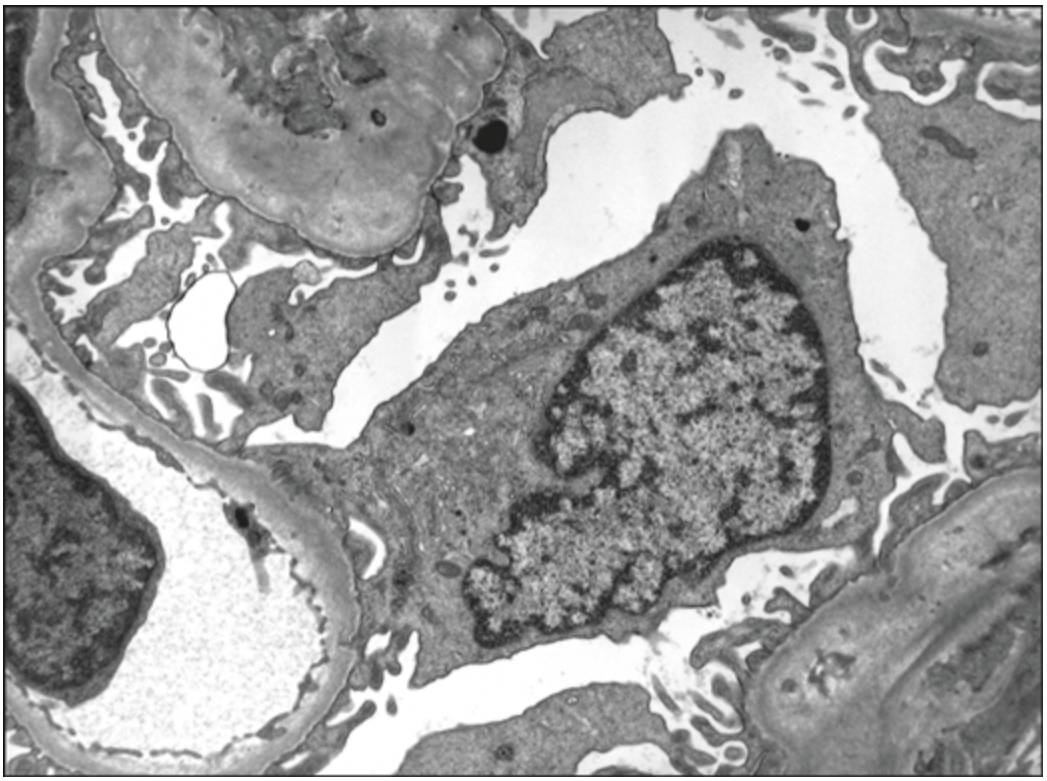
small-fiber nerve density, showed no detectable fiber loss, increased fiber tortuosity, or nerve fiber swellings suggestive of early nerve fiber degeneration (**Figure 1**). A percutaneous renal biopsy with 5 glomeruli showed podocytes with a few large vacuoles, but was otherwise histologically unremarkable except for a few thin-segment tubules, mainly in the outer medulla, containing osmophilic lamellar bodies. On electron microscopic examination, occasional endothelial cells containing small lysosomes with lamellar structures were seen, but no typical Fabry inclusions were observed in podocytes (**Figure 2**). Granular electron-dense deposits with neutral lipidlike material were found in a few proximal tubular cells. Typical Fabry inclusions as well as granular electron-dense deposits with neutral lipidlike material were noted in a few collecting ducts and distal tubules (**Figure 3**). The interstitial capillaries were unremarkable and immunopathologic study results were negative. Ultrastructural examination of his urinary sediment revealed cells containing some electron-dense lysosomes with the typical lamellar-type inclusions.

Figure 1.



Skin biopsy. A, Thick section showing superficial dermal capillary free of inclusions in endothelial cells (methylene blue/azure II, original magnification × 40). B, Electron micrograph showing endothelial cells and pericytes free of inclusions (original magnification × 3000). C, Thick section showing the absence of inclusions in the perineurium of a peripheral nerve in mid-dermis (methylene blue/azure II, original magnification × 40). D, Electron micrograph of a peripheral nerve in dermis showing the absence of inclusions in the perineurium (original magnification × 3000). E, Section stained with protein gene product 9.5 showing normal density with tortuosity and nerve fiber swellings (arrows) (original magnification × 40).

Figure 2.



Electron micrograph of a glomerular capillary with endothelial cell and podocyte containing a few osmophilic inclusions (original magnification × 6000).

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Figure 3.

Electron micrograph of a distal tubular segment containing osmophilic inclusions admixed with vacuoles consistent with neutral lipid. Interstitial cell (right) with a few osmophilic inclusions (original magnification × 4000).

Electron micrograph of a distal tubular segment containing osmophilic inclusions admixed with vacuoles consistent with neutral lipid. Interstitial cell (right) with a few osmophilic inclusions (original magnification × 4000).

Comment

This case is instructive because it expands the spectrum of later-onset Fabry disease to include otherwise idiopathic, painful, activity-induced cramps and fasciculations without overt small-fiber neuropathy. The patient's skin biopsy specimens did not have histologic evidence of GL-3 accumulation, in contrast to the findings of damaged and decreased small cutaneous fibers in the skin biopsies from classically affected men with preserved renal function.[18] His heterozygous mother developed similar but milder symptoms in her fifth decade of life. His mother had an episode of cerebral ischemia at age 37 years, which was originally interpreted from MRIs of brain and spine as possible multiple sclerosis. Her history initially suggested the diagnosis of Fabry disease because heterozygotes for the classic Fabry disease may present with neurologic involvement including fibromyalgia and abnormal brain MRIs resembling multiple sclerosis.[2]

Previously, reports of the A143T missense mutation have been limited to older patients in hemodialysis clinics who did not have the early manifestations of the classic phenotype.[15-17] Our patient had minimal glomerular changes seen only by electron microscopy with normal kidney function including a normal urinary protein-albumin ratio. Thus, it is likely that patients with the A143T genotype will develop renal and other Fabry disease manifestations with age. To date, the patients have not begun enzyme replacement therapy, so its effects on cramps, fasciculations, and renal involvement remain unknown.

Activity-induced cramps and fasciculations are nonspecific manifestations of lower motor neuron hyperexcitability. There are many symptomatic etiologies, including electrolyte derangement, root compression, potassium channel antibodies, and motor neuron disease. These possibilities were evaluated and excluded in this patient. How this mutation is producing pain, cramps, and fasciculations remains unclear, but the X-linked recessive pattern with a less severe phenotype in his heterozygous mother and absent symptoms in his mutation-negative sister support the α-Gal A deficiency as causative. No skin or renal microvascular GL-3 accumulations were observed, sudomotor function was normal, and kidney function was preserved. Therefore, it is likely that the cramps and fasciculations are due to alternations in the proximal nerve segments. Proximal glycosphingolipid deposits in the spinal ganglia have been reported in classically affected patients who had no distal nerve fibers loss.[19] These findings were also observed at autopsies of affected men who had minimal or no distal fiber loss.[3] Therefore, it is possible that glycosphingolipid deposits along the motor neuron or portions of the motor axons occurred in our patient.

The presence of cramps and fasciculation without identifiable small-fiber neuropathy[12] may be the first presenting symptom of later-onset Fabry disease, which can be readily diagnosed in men by determining the plasma or leukocyte α-Gal A activity, and confirmed by mutation analysis. Identification of patients with Fabry disease is important because enzyme replacement therapy is now available.[20-22]

Article Information

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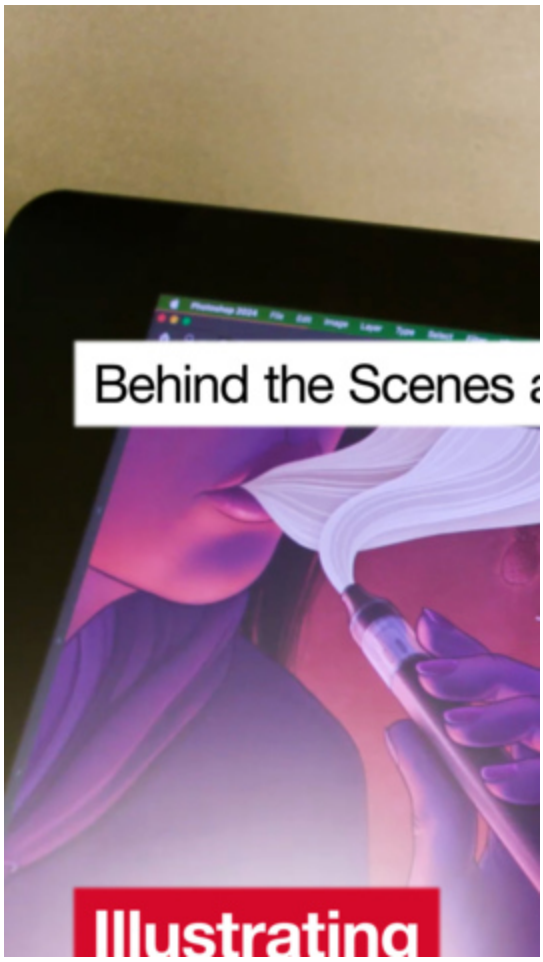

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