Novel LMNA Mutation in Atypical Werner Syndrome Presenting With Ischemic Disease

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Background and Purpose—Laminopathies arise through mutations in genes encoding Lamin A/C (LMNA) or associated proteins. They cause 4 different groups of disorders with diverse severity and often overlapping features: diseases of striated muscle (leading to muscular or cardiac involvement), peripheral neuropathy, lipodystrophy syndromes, and accelerated aging disorders.

Summary of Case—We report on a familial case of atypical Werner syndrome (a progeroid syndrome with Werner syndrome phenotype but without typical RECQL2 mutation) presenting with acute ischemic cerebral disease or peripheral artery disease associated with diffuse atherosclerosis, attributable to transmission of a novel LMNA mutation.

Conclusions—in young patients with ischemic events and a positive family history, other progeroid features have to be searched and LMNA testing has to be considered, allowing for genetic counseling and presymptomatic testing of at-risk relatives. (Stroke. 2009;40:000-000.)

Key Words: lamin ■ laminopathies ■ progeroid ■ Werner syndrome ■ ischemic

A 31-year-old man without medical history or vascular risk factors presented with acute onset right hemiplegia and aphasia. Werner syndrome (WS) with the following signs was previously diagnosed in his father: beaked nose, cataract, scleroderma-like skin changes, hair loss, generalized lipoatrophy, mild axonal sensorimotor polyneuropathy, severe coronary, and peripheral artery disease (with claudication as presenting symptom in absence of vascular risk factors). At that time, genetic analysis for WS was not performed but his DNA was available for molecular analysis. At age 52, he died after acute myocardial infarction.

Careful clinical examination of our patient revealed the same bird-like face appearance as his father (Figure 1A, B), scleroderma-like skin changes (Figure 1C, D), mild Dupuytren disease (Figure 1E), and lipoatrophy with low body weight (50 kg for 1.83 m).

Brain CT showed an acute left middle cerebral artery infarction and extensive thalamic calcifications (Figure 2A,B). CT angiography revealed internal carotid artery calcifications with a high-grade stenosis on the left side and a right-sided occlusion (Figure 2C, D). Blood count, C-reactive protein, renal and liver function tests, cardiac enzymes, antinuclear factor, lupus anticoagulant, anticardiolipin antibodies, serology for HIV, syphilis, and hepatitis B and C were normal, as well as levels of lactic acid, triglycerides, and cholesterol. Urine toxicological screening was negative for cocaine, heroin, amphetamines, and cannabis. ECG showed an old inferior myocardial infarction.

No arrhythmic events were observed on 24-hour Holter ECG. Transthoracic and transesophageal echocardiography revealed inferior hypokinesia, aortic valve calcifications (Figure 2E) associated with grade II insufficiency, and mild aortic atheromatosis, in absence of patent foramen ovale and atrial septum aneurysm. Coronary arteriography showed a (probably preexisting) right coronary artery occlusion. Lower limb duplex scanning showed mild atheromatosis, and osteodensitometry revealed marked generalized osteoporosis. Ophthalmological examination showed no cataract, and electromyography and nerve conduction studies were normal. The 24-hour urinary hyaluronic acid content was normal.

Acetylsalicylic acid 75 mg once daily, atorvastatin 80 mg once daily, and alendronate 10 mg once weekly were started. Left carotid endarterectomy was performed 2 months later.

A dominantly inherited disease was suspected because of the shared clinical features of our patient and his father. WS is a segmental progeroid syndrome, most frequently caused by an autosomal recessive RECQL2 mutation. The patient carried wild-type RECQL2 coding regions.

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Atypical WS (ie, patients with WS carrying wild-type RECQL2 sequences) attributable to dominant LMNA mutations has recently been ascribed to the continuously expanding phenotypic spectrum of laminopathies. LMNA coding sequence and intronic boundaries were directly sequenced in the patient and subsequently in his father. LMNA genomic screening in the patient evidenced a novel missense transversion in exon 5: c.898G>A, predicted to cause the change of Aspartate 300 into Asparagine at the protein level (p.Asp300Asn, p.D300N). The transmission of the mutation from the affected father could be tested and confirmed on a DNA sample that had been conserved (Figure 3). The mutation was absent from 200 control chromosomes, as well as from the updated LMNA variation databases (http://www.umd.be and http://www.dmd.nl/lmna_seqvar.html). To exclude an impact of the mutation on splicing, LMNA transcripts issued from the patient’s lymphoblastoid cell line were retro-transcribed, amplified, and sequenced. The c.898G>A mutation was identified in Lamin A/C transcripts as well. No aberrant splicing was evidenced. A similar height of the wild-type and mutated peaks at position c.898 suggested a balanced allelic expression in the white cell lineage. All the heterozygous polymorphisms identified at the DNA level were retrieved as well. The patient’s sister, his only sibling, was clinically unaffected and carried wild-type LMNA sequences. Except in the patient’s father, progeroid features were absent in other family members.

**Discussion**

Progeroid syndromes constitute a group of rare disorders characterized by clinical features, which segmentally mimic physiological aging at an early age. WS is attributable to autosomal recessive mutations in the RECQL2 DNA helicase gene, involved in DNA repair and telomere maintenance processes. Similarly, other progeroid syndromes (eg, Cockayne syndrome, Rothmund-Thomson syndrome, Bloom syn-
Signs | Cardinal WS Signs | Other WS Signs | Common HGPS Signs | Patient | Father
--- | --- | --- | --- | --- | ---
Cataract | + | | | | +
Scleroderma | + | | + | + | +
Craniofacial abnormalities (bird-like facies) | + | | + | + | +
Short stature | + | | | + | +
Parental consanguinity | | | | + | +
Premature graying/alopecia | + | | | + | +
24-hour urinary hyaluronic acid | | + | | | +
Diabetes mellitus type 2 | | + | | + | +
Hypogonadism | | + | + | + | +
Osteopenia | | + | + | + | +
Soft tissue calcifications | | | | | +
Premature atherosclerosis | + | + | + | + | +
Mesenchymal neoplasm | + | | | | +
Voice changes | + | | + | + | +
Flat feet | | + | | + | +
Lipoatrophy | + | + | | + | +
Neuropathy | + | + | | + | +
Joint contractures | | + | | + | +
Abnormal dentition | | + | | + | +

In recent years, a novel group of progeroid syndromes involving mutations in different genes also encoding DNA repair proteins, WS, has an estimated incidence of 1 in 1 million births (its incidence is higher in Japan).

In contrast to tendinous and subcutaneous calcifications, ectopic brain calcifications have never been described in LMNA-associated progeroid syndromes. Basal ganglia calcifications have been reported in Cockayne syndrome, a non-LMNA-associated progeroid syndrome, and occur in many, otherwise normal, elderly persons. Therefore, the calcifications in our patient can be interpreted as an additional progeroid feature, although it is not clear why preferentially the thalamus was involved.

Premature atherosclerosis has been described in several laminopathies. In familial partial lipodystrophy, atherosclerosis seems to be related to characteristic proatherogenic metabolic disturbances such as dyslipidemia, hypertension, insulin resistance, and diabetes. Ischemic disease has never been reported in atypical Werner syndrome. Atherosclerosis in HGPS seems to be related to the same mechanisms by which mutant LMNA produces accelerated aging in other tissues, such as replicative senescence, telomere shortening, decreased capacity to propagate in subculture, and decreased repair capacity. Another proposed mechanism for atherosclerosis in HGPS is hyperhyaluronic acidemia and aciduria, which are suggested to cause vascular calcification.

As reported in earlier described patients with LMNA-associated atypical WS, in our patient several cardinal signs of WS lacked and additional progeroid features (osteoporosis, Dupuytren disease, thalamus calcifications, and severe atherosclerosis) were seen. Therefore, atypical WS seems to be not a specific diagnosis but rather a multisystem phenotype with progeroid features associated with Lamin A/C dysfunction. Differences in clinical features between our patient and
his father confirm earlier reported intrafamilial phenotypic variability in LMNA-associated disorders.

Because ischemic disease can be the presenting feature of a laminopathy, other progeroid features have to be searched and LMNA testing has to be considered in young patients with ischemic events and a positive family history, allowing for genetic counseling and presymptomatic testing of at-risk relatives.

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Disclosure
None.

References
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