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 lipatrophy, 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.
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.\textsuperscript{3} $LMNA$ 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$\rightarrow$H11022A, 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$\rightarrow$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-
The LMNA gene encodes through alternative splicing 2 major nuclear proteins: Lamins A and C. Mature Lamin A is physiologically obtained through a series of posttranslational processing steps performed on the C-terminal region of a precursor, Prelamin A. Most typical HGPS cases are attributable to a heterozygous, recurrent, de novo Lamin A-specific mutation leading to the production of a truncated precursor, progerin, which cannot undergo complete maturation and accumulates in the cells’ nuclei. Most restrictive dermopathy cases and some mandibulocutaneous dysplasia forms result from secondary accumulation of normal-length Prelamin A forms, which remain aberrantly farnesylated. The toxic intranuclear accumulation of abnormal precursor protein is believed to be a key element leading to these severe phenotypes.

However, several heterozygous LMNA point mutations (p.A57P, p.R133L, and p.L140R) associated with atypical WS (a less severe progeroid phenotype) were located in the globular head and the central helical rod domain of Lamin, far away from the C-terminal region implicated in the posttranslational processing.

The dominant familial mutation we report (c.898G>A, p.Asp300Asn, p.D300N) has not been described previously. However, another missense mutation (c.899A>G) leading to a different amino acid substitution at the same position (p.Asp300Gly; p.D300G) has been reported once, in 6 individuals over 4 generations affected with cardio cutaneous progeria with clinical manifestations more closely recalling a typical WS phenotype. The p.D300N mutation we describe seems to be associated with a more subtle WS-like phenotype, with arteriopathic presenting signs and striking ischemic events as major features, together with other progeroid signs.

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 cardiac 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.

Acknowledgments
The authors gratefully acknowledge Professor Patrick Calvas (CHU Toulouse) for sending them the conserved DNA sample of the patient’s father, and Dr Nancy Uhrhammer (CHU Clermont-Ferrand) for RECQL2 sequencing in the patient.

Sources of Funding
This work has been supported by the French Ministry of Health, Youth and Sport, in the context of the 2005 Clinical Research Hospital Programme (PHRC) “Caractéristation et explorations cliniques, génomiques et fonctionnelles des Laminopathies systémiques : vers l’identification de syndromes candidats et la mise en place d’essais thérapeutiques.”

Disclosure
None.

References
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*Stroke.* published online December 18, 2008;

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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