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Werner syndrome as a crossroads between lipodystrophy, escleroderma-like changes and torpid ulcers in lower limbs

Síndrome de Werner como encrucijada entre lipodistrofia, cambios esclerodérmicos y úlceras tórpidas en miembros inferiores

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Werner's syndrome (WS) or adult progeria is an autosomal recessive hereditary disorder with premature ageing beginning in the person's teens. Its incidence is less than $1/10^6$ births, although it is probably underdiagnosed.[1] Although it was originally described in 1904, its molecular basis was not established until 1996.[2] It is caused by mutations in the *WRN* or *RECQL2* gene, which encodes a DNA helicase. This enzyme is key in DNA repair processes and in maintaining telomere integrity, so a deficiency causes genomic instability, risk of cancer and cellular senescence.[2] The main clinical manifestations are the absence of a puberty growth spurt with short stature, thinning hair with early greying, skin changes, sarcopenia, osteoporosis and glucose and lipid metabolism abnormalities with accelerated atheromatosis.[3] Biallelic mutations in the *WRN* gene are found in 97% of patients. Clinically diagnosed cases in which no *WRN* mutations are found are called atypical WS and in a significant proportion of these, mutations in the *LMNA* gene are identified, with earlier symptoms and more rapid progression.[3]

We present a case of WS diagnosed after association and exclusion of signs and symptoms and the use of next-generation genetic sequencing techniques.

This was a 55-year-old woman who consulted with painful ulcers on both feet. She had never smoked and had been diagnosed with type 2 diabetes mellitus at the age of 29 years, requiring insulin and pioglitazone early, which provided adequate control (HbA1c around 7%). She had surgery for bilateral cataracts at age 50. The patient's height was 147 cm, weight 46 kg, and she had increased abdominal adiposity (circumference 94 cm) with a marked decrease in the fat panniculus around the edges. Her scalp hair was sparse and she had started to go grey in her 20 s. The skin on her hands and feet was thick and hard, with thinning of the underlying tissues, leading to suspicion of scleroderma. She did not have Raynaud's phenomenon and nailfold capillaroscopy showed isolated dilations and capillary ramifications. She had developed the ulcers five years earlier, preceded by hyperkeratosis, which were now chronic, with poor healing and frequent superinfection. The deepest ulcers were located both in the balls and backs of the first and second toes of both feet, some of them deep with bone exposure; ulcers had also developed on the metatarsal heads of the first and fifth toes and on the lateral aspects of her feet. She also had *hallux valgus* and claw toes. Sensitivity in her lower limbs and distal peripheral pulses were normal, with an indeterminate ankle-brachial index due to arterial stiffness. Transcutaneous oxygen pressures (TcPO2) in her feet were 8 and 2 mmHg. Her total cholesterol was 227 mg/dl and triglycerides 289 mg/dl. X-rays of her hands and feet detected osteoporosis and vascular and subcutaneous calcifications, and liver ultrasound revealed steatosis. Further investigations ruled out involvement of the gastrointestinal tract, heart, lungs or kidneys, and autoimmunity tests were negative. There were also no signs of diabetic nephropathy or retinopathy. Added to the intensive treatment of the ulcers (frequent dressings, discharge measures and antibiotics), the patient was started on treatment with bosentan (125 mg/12 h), but with no significant improvement. The associated pain and the need for functional rest had made the use of a wheelchair necessary.

The molecular study with next-generation sequencing of 27 genes associated with hereditary lipodystrophies identified a rare homozygous variant (c.3711del or p.K1237Nfs*11) in the *WRN* gene, classified as pathogenic in ClinVar (ID: 577673). None of the patient's children or siblings and neither of her parents had developed similar conditions. There was no known consanguinity between the parents, although their families were originally from the same town in the province of Ciudad Real.

Although Spain has had some reports of cases of patients with suspected WS, most are old and prior to the discovery of the causative gene. This is the first case in this country with a full clinical description and molecular confirmation. The mutation found in the *WRN* gene, although described as pathogenic, is very uncommon worldwide.[4] In addition, finding it as a homozygous variant has revealed the existence of some previously unknown degree of consanguinity in her parents.

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Table 1 Diagnostic criteria of the International Registry of Werner's Syndrome.

	Met by our patient[a]
I. Cardinal signs and symptoms (onset over 10 years old):	
1. Cataracts (bilateral)	+
2. Characteristic dermatological pathology (hard, tight skin, atrophic skin, pigmentary alterations, ulceration, hyperkeratosis, regional subcutaneous atrophy) and characteristic facies ('bird' facies)	+
3. Short stature	+
4. Parental consanguinity or affected sibling	?
5. Premature greying and/or thinning of scalp hair	+
II. Other signs and symptoms:	
1. Diabetes mellitus	+
2. Hypogonadism (secondary sexual underdevelopment, diminished fertility, testicular or ovarian atrophy)	?
3. Osteoporosis	+
4. Osteosclerosis of the distal phalanges	–
5. Soft tissue calcifications	+
6. Evidence of premature atherosclerosis (e.g., myocardial infarction)	–
7. Mesenchymal neoplasms, rare neoplasms or multiple neoplasms	–
8. Voice changes (high-pitched, squeaky or hoarse voice)	+
9. Flat feet	–

Source: Tsuge et al.[2]
Definite diagnosis: all the cardinal signs and two further signs.
Probable diagnosis: the first three cardinal signs and any two further signs.
Possible diagnosis: cataracts or dermatological signs and any four further signs.
Exclusion: onset of signs and symptoms before adolescence (except short stature).
[a] (+): yes; (-): no; (?): not sure.

Despite the patient meeting the criteria for typical WS (Table 1), the delay of more than 25 years from onset of the syndrome to it being recognised is remarkable. One of the aspects that most pointed to the diagnosis was her general physical appearance, with regional lipodystrophy (severe lipoatrophy of the extremities and truncal obesity). About twenty progeroid syndromes with different molecular mechanisms are known; along with premature ageing, they are associated with different patterns of lipodystrophy[5] and ectopic fat deposition, which can lead to the development of insulin resistance, type 2 diabetes, fatty liver and atherogenic dyslipidaemia.[6,7] Our patient had this metabolic constellation, although her blood glucose control was adequate and she had no signs of diabetic microangiopathy. In addition to the elevated risk of malignancy, these metabolic complications contribute to the premature death of patients with WS due to accelerated atheromatosis.

The signs of scleroderma were also striking. Unlike scleroderma, however, she did not have Raynaud's phenomenon, the capillaroscopy pattern was atypical, the autoantibody screening was negative and there was no evidence of internal organ involvement. The distribution of the scleroderma was also very characteristic of WS. Nevertheless, the differential diagnosis with systemic sclerosis can be difficult.[8]

However, the main associated disorder is chronic ulcers, severely limiting the patient's quality of life and functional autonomy. The pathogenesis of these ulcers is more complex and multifactorial than that of the simple diabetic foot ulcer.[9] In addition to vascular mechanisms or neuropathy, which were not decisive in our case, gene transcription dysfunction and cellular senescence hinder tissue repair. One extensive review on ulcers in WS patients noted their frequency (more than 40%), calluses as a prodrome, their refractory nature and the frequent need for surgical procedures.[10]

In conclusion, the manifestations of WS are multisystemic and nonspecific, which delays correct diagnosis and management. However, understanding WS alerts us to suspect the diagnosis and order the confirmatory molecular tests. Despite the lack of a specific treatment, identification is essential for appropriate follow-up and genetic counselling.

Ethical responsibilities

The patient gave her written informed consent, both for the molecular study and for taking clinical images. The Independent Ethics Committee raised no objections to this publication.

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Ultra-rapid insulin in mitochondrial diabetes: Two clinical cases

Insulina ultrarrápida en diabetes mitocondrial: dos casos clínicos

Mitochondrial diseases are a group of genetic disorders characterised by defects in oxidative phosphorylation and caused by mutations in genes in the nuclear DNA or mitochondrial DNA. Mitochondrial DNA mutations occur in 1 per 5000 adults and are transmitted through maternal inheritance.[1] Diabetes is the most common endocrinopathy among mitochondrial disorders. Defects in the tricarboxylic acid cycle and electron transport chain lead to reduced oxidative phosphorylation, resulting in inefficient and suboptimal glucose-stimulated insulin secretion.[1] Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS), and maternally inherited diabetes and deafness (MIDD) are the most common mitochondrial diabetes disorders,[2] Although the m.3243A>G mtDNA pathogenic variant is more frequently linked to diabetes, other mutations can occur. Mitochondrial diabetes typically affects adults over 35 years, and most patients require insulin treatment a few years after its onset.[3,4] The severity of diabetes has been strongly associated with increasing age, consistent with the clinical picture of a progressive disease.[5] Hearing loss in MIDD frequently precedes the diagnosis of diabetes and tends to develop in early adulthood.[6,7]

To our knowledge, no studies exist on ultra-rapid insulin therapy in mitochondrial diabetes. Two cases of mitochondrial diabetes under basal-bolus insulin therapy with fast-acting insulin aspart will be discussed.

Patient 1 is a 50-year-old male with a chronic kidney disease known since childhood, and currently undergoing peritoneal dialysis and waiting for a kidney transplant. Notwithstanding occupational noise exposure, bilateral sensorineural hearing loss was identified in childhood. Diabetes was diagnosed during a routine evaluation when he was 30 years old (normal weight, c-peptide level 2.2 ng/mL, and negative beta-cell antibodies), and insulin was started at diagnosis. To determine diabetes aetiology, he was submitted to genetic testing that revealed MT-TL1 mutation, m.3243A>G, 20% heteroplasmy in peripheral blood leucocyte DNA. He was on basal insulin alone for 17 years after his diabetes diagnosis. During this period, sitagliptin 25 mg od was started. However, HbA1c levels started to rise to 7.5–8.0%, and the flash glucose monitoring device Freestyle Libre was employed, showing significant post-prandial hyperglycemia with insulin glargine U-100 9 IU/day. He was then started on fast-acting insulin aspart before the three main meals, according to pre-prandial glucose levels. His basal insulin is now glargine U-100 3 IU in the morning, and his daily insulin dose (TDI) is 10–15 IU/d (0.15–0.23 IU/kg/d). Glucose control has significantly improved, as shown by monitoring reports, and basal insulin needs are now less than 30% of TDI (Fig. 1). Apart from chronic kidney disease, no other target-organ diabetes complications were present years before the diabetes diagnosis. A family history of diabetes was present in Patient 1's mother and two siblings.

Patient 2 is a 56-year-old male with bilateral sensorineural hearing loss. A family history of hearing loss was present