of sustained tachycardia throughout hospitalisation and diastolic hypertension; anorexia and postprandial fullness may also be considered autonomic symptoms. Orthostatic hypotension and vasovagal syncope are the most frequently described autonomic symptoms;[3,4] these were not recorded in our patient, probably due to the low clinical suspicion during hospitalisation. Secondly, he showed a 5.9-point decrease in HbA1c in less than 2 months. And thirdly, symptoms appeared following glycaemic control.

TIDN should be distinguished from other acute neuropathies presenting in these patients, especially diabetic neuropathic cachexia,[5] which may be associated with similar clinical manifestations: subacute, symmetrical sensory, and motor alterations in varying degrees, associated with autonomic dysfunction. Diabetic neuropathic cachexia is characterised by anorexia, involuntary, severe weight loss, and emotional instability; these symptoms resolve completely with weight gain. The pathophysiology of diabetic neuropathic cachexia is not fully understood, and no clear diagnostic criteria have been established; the literature only includes isolated cases. We cannot rule out the possibility that our patient was affected by both conditions, given the marked involuntary weight loss and emotional lability, which was initially thought to be a response to pain.

In conclusion, TIDN or insulin neuritis is a rare, little-known entity requiring a high level of suspicion. The condition may be prevented by administering a less aggressive treatment for glycaemic control. Although TIDN is self-limiting, pain may be disabling, leading to hospitalisation.

References

1. Caravati C. Insulin neuritis: case report. Va. Med. Mon. 1933;59:745—6.
2. Gibbons CH, Freeman R. Treatment induced diabetic neuropathy, a reversible painful autonomic neuropathy. Ann. Neurol. 2010;67:534—41.
3. Gibbons CH, Freeman R. Treatment-induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes. Brain. 2015;138:43—52.
4. Hwang YT, Davies G. ''Insulin neuritis'' to ''treatment-induced neuropathy of diabetes'': new name, same mystery. Pract Neurol. 2016;16:53—5.
5. Naccache DD, Nseir WB, Herskovitz MZ, Khamaisi MH. Diabetic neuropathic cachexia: a case report. J Med Case Rep. 2014;8:20.

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A new mutation in a patient with Wolfram syndrome☆

Descripción de una nueva mutación en una paciente con síndrome de Wolfram

Dear Editor:

Wolfram syndrome is a neurodegenerative disease characterised by the appearance of diabetes mellitus and optic atrophy in young patients. In the years following onset, patients also usually present such other symptoms as sensorineural hypoacusia, diabetes insipidus, progressive neurological anomalies (cerebellar ataxia, peripheral neuropathy, dementia), psychiatric disorders, and atonia of the urinary tract. The syndrome was described in 1938 by Donald J. Wolfram, who reported 4 cases of diabetes mellitus and optic atrophy in members of the same family, who subsequently developed hearing loss, incontinence, and ataxia.[1] Prevalence is estimated at one case per 770 000 population.[2]

Wolfram syndrome is caused by a mutation of the *WFS1* gene, located in chromosome region 4p16.1, which codes for the transmembrane protein wolframin. This protein is located in the endoplasmic reticulum and is expressed in practically all tissues of the body, although at higher concentrations in the beta cells of pancreatic islets and the brain. The function of the protein is not well understood; wolframin is believed to be involved in cellular transport and calcium homeostasis in the endoplasmic reticulum.[3] Given the disease's rareness and its considerable genetic and clinical heterogeneity, the term ''Wolfram syndrome spectrum'' is frequently used. Disorders associated with the *WFS1* gene include Wolfram syndrome,[4] which follows an autosomal recessive inheritance pattern, and Wolfram-like syndrome and low-frequency sensorineural hearing loss (LFSNHL), which follow an autosomal dominant inheritance pattern. Wolfram-like syndrome is characterised by the combination of sensorineural hearing loss, diabetes mellitus, psychiatric disorders, and variable optic atrophy. LFSNHL is characterised by congenital, nonsyndromic, slowly progressive, low-frequency sensorineural hearing loss.[5]

Treatment is symptomatic and depends on the clinical manifestation. Mean age at death is 30 years; death is

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usually due to disease complications (hypoglycaemic coma, status epilepticus, advanced renal failure, suicide, central respiratory failure, etc.).[2]

Our patient was a 14-year-old girl with a history of a year and a half of progressively decreasing visual acuity. She had been diagnosed with type 1 diabetes mellitus the previous year and had been receiving treatment with insulin since that time. Her psychomotor development was normal and she performed well academically. The patient presented tics, and reported dry eyes and lips despite drinking 4 litres of water daily. She had no other history of interest. Her 4-year-old brother was healthy; no family history of consanguinity was known. However, history of adult-onset type 1 diabetes mellitus was reported in cousins on the mother's side of the family. In the preceding 18 months, she began experiencing progressively decreasing visual acuity and presented bilateral optic atrophy. Physical examination revealed no abnormalities. The ophthalmological examination showed decreased visual acuity in both eyes (0.3 to 0.5 in the right eye and 0.4 to 0.5 in the left eye) with a preserved visual field; direct ophthalmoscopy revealed pallor and atrophy in both optic discs. The neurological examination, including eye movements, motor system, sensitivity, coordination, and gait, yielded normal results. An optical coherence tomography study confirmed bilateral optic atrophy. Visual evoked potentials with checkerboard stimulation showed a signal of forked and asynchronous morphology, decreased amplitude, and normal latencies. Flash visual evoked potentials yielded normal results. Full field electroretinography showed no alterations. Suspecting Wolfram syndrome, we requested a genetic study of the *WFS1* gene; the patient was heterozygous for variants c.2643_2646del and c.1703_1704del in exon 8. Variant c.1703_1704del has not previously been described as a mutation or a polymorphism in the most commonly used genetic variant databases.[6–10] This deletion causes synthesis of a truncated protein; we therefore consider that this variant is probably pathogenic.

Wolfram syndrome is a rare disease which should be suspected in young patients with progressive bilateral optic atrophy and diabetes mellitus. It is a clinically and genetically heterogeneous neurodegenerative disease whose pathophysiological mechanism is not well understood. More than 200 mutations of the *WFS1* gene in chromosome region 4p16.1 have been described as causing the disease,[6] which follows an autosomal recessive inheritance pattern. One of the variants identified in our patient has not previously been described in this syndrome; therefore, we consider the c.1703_1704del variant in exon 8 of the *WFS1* gene to be a probably pathogenic mutation. Early diagnosis of Wolfram syndrome is important in order to provide adequate genetic counselling.

References

1. Wolfram DJ, Wagener HP. Diabetes mellitus and simple optic atrophy among siblings: report of four cases. Mayo Clin Proc. 1938;13:715–8.
2. Barrett TG, Bundey SE, Macleod AF. Neurodegeneration and diabetes. UK nationwide study of Wolfram (DIDMOAD) syndrome. Lancet. 1995;346:1458–63.
3. Inoue H, Tanizawa Y, Wasson J, Behn P, Kalidas K, Bernal-Mizrachi E, et al. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). Nat Genet. 1998;20:143–8.
4. Cryns K, Sivakumaran TA, van den Ouweland JM, Pennings RJ, Cremers CW, Flothmann K, et al. Mutational spectrum of the WFS1 gene in Wolfram syndrome, nonsyndromic hearing impairment, diabetes mellitus, and psychiatric disease. Hum Mutat. 2003;22:275–87.
5. Tranebjærg L, Barrett T, Rendtorff ND. WFS1-related disorders. 2009 Feb 24 [accessed 19.12.13]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle, WA: University of Washington, Seattle; 1993–2016.
6. Leiden Open Variant Database. Available from: https://lovd.euro-wabb.org/home.php?select_db=WFS1.
7. Human Gene Mutation Database. Available from: http://www.biobase-international.com/product/hgmd.
8. Deafness Variation Database. Available from: http://deafnessvariationdatabase.org.
9. SNP Database. Available from: http://www.ncbi.nlm.nih.gov/snp.
10. NCBI ClinVar Database. Available from: http://www.ncbi.nlm.nih.gov/clinvar/.

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