CASE REPORT

Report of a Brazilian patient with Wolfram syndrome

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Abstract

Objective: to report a case of a patient diagnosed with Wolfram Syndrome and brachydactyly type E. Wolfram Syndrome is characterized by the presence of diabetes mellitus, diabetes insipidus, atrophy of the optic nerve, alterations of the urinary tract, deafness and neurologic and psychiatric disorders. However, not all manifestations are present at diagnosis, indicating the necessity of long-term follow-up of these patients. This long-term follow-up should be extended to the patients’ closest relatives, having in mind the increased risk of occurrence of psychiatric disorders and diabetes mellitus among the heterozygous carriers of Wolfram Syndrome.

Description: male, white patients, only child of non-consanguineous parents, was healthy until four years of age, when he presented with polydipsia and polyuria, being diagnosed with diabetes mellitus type I. Since then, he has needed regular insulin use, but has followed an inadequate diet due to socioeconomic problems. He was evaluated by the genetic service when he was 11 years old. Brachydactyly was observed on physical examination. In the course of the complementary investigation, bilateral atrophy of the optic nerve was observed; the visual evoked potential and the electroretinogram were compatible with extensive optic nerve injury. Both retinas were normal. The presence of insulin-dependent diabetes mellitus together with atrophy of the optic nerve is a sufficient criterion for the diagnosis of Wolfram Syndrome. The molecular investigation confirmed the diagnosis of Wolfram Syndrome.

Comments: the aim of the present report is to alert physicians about the association between diabetes mellitus and monogenic syndromes, such as Wolfram Syndrome.


Introduction

Wolfram syndrome (WS) or DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness) (OMIM - 222300)1 is a neurodegenerative disease, whose incidence is estimated at 1 in every 770,000 live births.2 Studies carried out up to the present day suggest that WS is caused by alterations in genes located on chromosome 4, (on 4p16.1 - gene WFS1, or on 4q22-q24 - gene WFS2)3; or, alternatively, in the mitochondrial DNA.4 The recently identified gene WFS1 (from wolframin) encodes a transmembrane protein with 890 amino acids, which is continually synthesized, especially in the endocrine pancreas.5,5 In cases of WS due to the mutation of the genes WFS1 (OMIM - 606201) and WFS2 (OMIM - 604928) the type of heredity is recessive and autosomal, with a risk of recurrence of 25%. On the other hand deletions and mutations at the tip of the mitochondrial DNA (OMIM - 598500) have also been described in patients with WS6 In this way, WS appears to be genetically heterogenetic.

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The diagnosis of WS is essentially clinical and based on the obligatory presence of juvenile, insulin-dependent diabetes mellitus, and atrophy of the optic nerve. Patients may also manifest central diabetes insipidus, sensorineural hearing loss, urinary tract atony and neurologic and/or psychiatric disorders.4

There is an increase in susceptibility to psychiatric diseases and to diabetes mellitus in its adult form in carriers of WS.4,7

In general, the disease evolves to the point of premature death due to respiratory failure, which is related to atrophy of the brainstem.

The current case study has the objective of drawing the attention of health professionals to the existence of this syndrome, since there are no case studies of Brazilian patients with WS in the available literature.

Case Study

A male patient, 11 years old, white, only child of non-consanguineous parents, with no family history of diabetes or psychiatric disorders, was healthy until four years of age when he manifested polydipsia and polyuria, being diagnosed as having diabetes mellitus type I. Since then he has needed regular insulin use and an appropriate diet to control diabetes mellitus. Due to socioeconomic difficulties the insulin is not used sufficiently and the diet is not appropriate, resulting in the patient being repeatedly hospitalized and not attending school. The grandfather who is responsible for the patient tells of a reduction in visual acuity from eight years of age onwards, which worsened last year.

A physical examination, performed when the patient was 11, revealed a good general state of health with an atypical face. When auscultated with a stethoscope, the heart rate was regular, in double phase, with no sign of murmur. At palpation, the abdomen showed no signs of visceromegaly. The upper and lower extremities exhibited brachydactyly. The genitalia were male, with appropriate-for-age development. The neurologic exam did not reveal any abnormalities. The following anthropometric measurements were taken: weight - 28kg (P10); height - 130cm (between P3 and P10); head circumference - 52.2 cm (P25); length of right hand - 13.5 cm (< P3); length of third finger of right hand - 5.3 cm (< P3); length of right foot - 19.3 cm (< P3). It was not possible to perform a physical examination of the parents.

The ophthalmologic evaluation did not show any evidence compatible with diabetic retinopathy; but identified bilateral papillary atrophy (Figure 1). The psychiatric assessment revealed difficulty in accepting limits, linked to depressive behavior.

Laboratory tests revealed the following: Ht - 37.7 %, Hb - 12 g/dL, MCV - 85 fl, Lactate (fasting) - 0.94 mmol/L (Normal), Cortisol - 11.5 mg/dL (Normal). Simple urine test: density - 1010; pH - 5; other results showed no peculiarities. The brainstem auditory evoked potential was normal. The visual evoked potential and the electroretinogram were consistent with severe lesions of the optic nerve and retina with no abnormalities. X-rays of the hand and wrist revealed short metacarpi and phalanges, while bone age assessment (left hand) showed delayed bone maturity greater than three standard deviations (Figure 2). The abdominal echography showed bilateral pyelocalyceal and ureteral dilation and an increased urinary bladder volume with irregular contours and parietal thickness; while the urethrocystography showed an irregular, trabeculated bladder, with pseudodiverticula, without reflux or urethral involvement. Brain computed tomography was normal.

The molecular investigation, performed at the West Midlands Regional Genetics Laboratory, Birmingham - UK detected a homozygous nonsense mutation C647X in exon 8 of the WFS1 gene.

Discussion

Not all patients with juvenile-onset diabetes mellitus and optic atrophy have WS. Other diagnoses include congenital rubella syndrome, Leber’s hereditary optic neuropathy thiamine responsive anemia with diabetes mellitus and deafness.4 These hypotheses were rejected as the patient showed neither evolution nor a clinical picture consistent with any of these diagnoses.

Patients with WS show progressive ophthalmologic symptoms that usually occur after diabetes mellitus. Deterioration in visual acuity is observed, with peripheral constriction of the field of vision and with or without central scotomata and bilateral atrophy of the optic disc; however,
The behavioral problems have been attributed to the patient’s and his/her family’s economic situation, but the possibility that this is a manifestation of WS cannot be excluded. Nevertheless, psychiatric disorders have been described as being later manifestations of WS. The diagnosis of brachydactyly related to WS is in agreement with the observations reported by Bale et al. (1985), who suggested that both disorders could be related, and that brachydactyly could be one of the manifestations of WS.

The molecular investigation demonstrated a homozygous nonsense mutation C647X in exon 8 of the WFS1 gene, confirming molecularly the diagnosis of WS. The analysis of base sequences showed the substitution of base A for base C at codon 647 (nucleotide 1941), converting the amino acid cysteine into a stop signal, resulting in a premature termination of translation on both chromosomes. The nonsense mutation is the pathogenic cause of this disease.

On diagnosing WS the physician should be alert to the clinical manifestations that occur with age progression. It is also necessary to investigate and identify manifestations that are not yet expected, but which could be present at an earlier age (Table 1).

Less frequently, gonadal atrophy and changes to gastrointestinal motility are found.

In the current case, diabetes mellitus and optic atrophy manifested at the expected age. The loss of auditory acuity and the neurologic changes, as expected, have not yet manifested in our patient. However, the renal tract abnormalities, which would be expected in the fourth decade of life, are already present. The dilation of the renal tract can be partially attributed to the increased production of urine due to diabetes insipidus, which was not possible to diagnose in the current report. Some patients have recovered from the dilation upon the institution of treatment for diabetes insipidus with antidiuretic hormones; however the presence of a neuropathic bladder suggests that this too could be caused by autonomic dysfunction.

Psychological support for the patients and their family is essential due to the high morbidity and mortality of this illness. This support is also important because of the behavioral disorders and psychiatric illnesses the patient may develop over the course of time. Family members should not only receive psychological support, due to their own increased risk of developing the adult form of diabetes mellitus and psychiatric illness, but should also be attentively monitored in order to identify and treat these disorders.
In that this is a disease with serious consequences for the patient, genetic counseling should be extremely cautious. In cases where there is proven mutation in the genes WFS1 and WFS2 heredity is recessive and autosomal, with a risk of recurrence of 25% in siblings. In cases where the mutation is in the mitochondrial DNA the risk of recurrence is harder to quantify. There is no way of clinically identifying which gene is responsible for the phenotypical alterations. Therefore, in order to perform genetic counseling based on reliable information on the risk of recurrence, those patients suspected of WS should undergo a molecular investigation.

We believe that WS is underdiagnosed in our setting. For genetic counseling purposes, we suggest that every patient with juvenile-onset diabetes mellitus be evaluated in order to rule out this possible diagnosis, as, sometimes, diabetes mellitus is not an isolated condition, with multiple hereditary factors. It is possible that a lack of knowledge of medical professionals with respect to the relationship between diabetes mellitus and monogenic syndromes could be one of the principal reasons for the underdiagnosis of illnesses such as WS.

References

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