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False diagnosis of type 1 diabetes mellitus and its complications in Wolfram syndrome — is it the reason for the low number of reported cases of this abnormality?

Czy nieprawidłowe rozpoznanie zespołu Wolframa jako cukrzycy typu 1 i jej powikłań może być przyczyną rzadkiego rozpoznawania tego zespołu?

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Abstract

Wolfram syndrome (WS), also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness), is a rare autosomal recessive syndrome (1/770,000 in the United Kingdom), characterised by juvenile onset of diabetes mellitus, optic nerve atrophy, diabetes insipidus, sensorineural deafness, renal tract and neurological abnormalities, and primary gonadal atrophy. WS is caused mainly by biallelic mutations in the WFS1 gene, which encodes wolframin. Wide tissue distribution of wolframin and many mutations in the wolframin gene resulting in Wolfram syndrome may contribute to different phenotypes and the unusual combinations of clinical features. We describe a female patient with Wolfram syndrome diagnosed at the age of 25, with a previous false diagnosis of type 1 diabetes mellitus and misdiagnosed diabetic complications. The patient was found to be a compound heterozygote for two novel mutations in exon 8 of WFS1 gene: a 2-bp deletion AT at nt 1539 leading to a frameshift (Y513fs) and a single-base substitution 1174C > T resulting in a stop codon (Q392X). A detailed analysis of the patient's medical history and a review of the literature suggest that many cases of Wolfram syndrome may remain undiagnosed due to misdiagnosis as type 1 diabetes mellitus and incorrect interpretation of clinical symptoms of neurodegenerative abnormalities, especially in their early stages. **(Endokrynol Pol 2014; 65 (5): 398–400)**

Key words: *Wolfram syndrome; diabetes mellitus; optic atrophy; WFS1*

Streszczenie

Zespół Wolframa (WS), znany również jako DIDMOAD (moczówka prosta, cukrzyca, atrofia nerwu wzrokowego i głuchota), jest rzadkim zespołem dziedziczonym autosomalnie recesywnie (1/770000 w Wielkiej Brytanii), charakteryzującym się wystąpieniem cukrzycy w wieku młodzieńczym, zanikiem nerwu wzrokowego, moczówką prostą, głuchotą, niewydolnością oddechową i zaburzeniami neurologicznymi oraz pierwotną atrofią gonad. WS jest spowodowany głównie mutacją w genie WFS1, który koduje wolframinę. Obecność wolframiny w wielu tkankach organizmu oraz wiele różnych mutacji w genie wolframiny, których skutkiem jest wystąpienie zespołu Wolframa, może stanowić przyczynę różnych fenotypów tego zespołu oraz różnych kombinacji cech klinicznych.
W poniższej publikacji opisano przypadek pacjentki z zespołem Wolframa, której choroba początkowo była błędnie zdiagnozowana jako cukrzyca typu 1 i jej powikłania. W badaniach genetycznych wykazano, że pacjentka była heterozygotą w zakresie dwóch nowych mutacji w egzonie 8 genu WFS1: 2-bp delecji AT w regionie nt 1539, prowadzącej do mutacji zmiany ramki odczytu (Y513fs) oraz substytucji pojedynczej zasady 1174 C > T, czego skutkiem był stop kodon (Q392X).
Ze szczegółowej analizy historii medycznej pacjentki oraz przeglądu piśmiennictwa wynika, że duża liczba przypadków zespołu Wolframa może zostać niewłaściwie rozpoznana jako cukrzyca typu 1 lub zaburzenia neurodegeneracyjne, zwłaszcza w początkowej fazie ich rozwoju. **(Endokrynol Pol 2014; 65 (5): 398–400)**

Słowa kluczowe: *zespół Wolframa; cukrzyca; atrofia nerwu wzrokowego; WFS1*

Background

Wolfram syndrome (WS), described for the first time in 1938 and also known as DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness), is a rare autosomal recessive syndrome characterised mainly by the association of early-onset insulin-dependent diabetes mellitus and optic atrophy [1, 2]. Diabetes mellitus, as well as progressive, bilateral optic atrophy occur before the age of 15. Other clinical features of WS are diabetes insipidus, multiple neurological abnormalities, such as sensorineural deafness, neuropathic bladder, cerebellar ataxia, dysarthria, dysphagia, startle myoclonus, reduced limb reflexes, horizontal

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nystagmus, central apnoeas, loss of taste and smell, hemiparesis, mental retardation, psychiatric illness, and renal tract abnormalities [1, 3, 4]. Symptoms of WS may include primary gonadal atrophy and reduced fertility [1]. Patients usually die at the median age of 30 (range 25–49 years) as a result of brainstem atrophy or renal failure secondary to infections [1, 3]. The prevalence of the syndrome is 1/770,000 in the United Kingdom [1].

WS is caused mainly by biallelic mutations in the WFS1 gene, which encodes wolframin, located in chromosome 4p16.1 and consisting of 8 exons [5, 6]. Wolframin plays a role in the biosynthesis of protein, regulation of charged calcium ions homeostasis in the ER, and is involved in the regulation of ER stress [7, 8]. To date, about 130 mutations of the WFS1 gene resulting in Wolfram syndrome have been reported [9, 10].

Case report

A 25-year-old female patient with a previous diagnosis of type 1 diabetes mellitus complicated by blindness related to retinopathy, with nephropathy and neuropathy as well, gave birth to her first child (first pregnancy, first labour, caesarean section) in the 38th week of pregnancy. A few days after the labour, the patient was admitted to the Department of Diabetology because of high glycaemia levels.

The laboratory results were as follows: glycated haemoglobin (HbA1C) - 52 mmol/mol (6.8%), morphology, ionogram, serum creatinine and glomerular filtration rate (GFR), albumin concentration in urine sample and gasometry within normal ranges, C-peptide — 0.068 ng/mL (normal range: 1.1–4.4).

On the first day, the glycaemia levels ranged from 80 to 240 mg/dL. Afterwards, during further hospitalisation, fasting glycaemia levels were: 79–221 mg/dL, postprandial glycaemia: 97–250 mg/dL. The patient was treated with insulin administered intravenously for the first 20 hours of hospitalisation (0.5–3 IU/h), then subcutaneously: before meals and NPH in the morning and before bedtime (total insulin dose: 0.5 IU/kg/24 hours).

Despite significant glycaemic improvement and almost normal serum glucose levels, polyuria (6.7–8.2 litres per 24 hours) was observed, accompanied by a low specific gravity of the urine (1.010). In fundoscopic examination, no signs of retinopathy were found, but bilateral optic atrophy was diagnosed and confirmed through FVER (visually evoked response) examination. No sign of peripheral neuropathy was found in a detailed clinical assessment. All these findings and clinical features pointed to Wolfram syndrome with the presence of diabetes insipidus. The patient was given desmopressin (0.5 mg p.o. per 24 hours), which resulted in a decreased diuresis: 2–3 litres per 24 hours, and higher specific gravity of urine: 1.020. That confirmed the diagnosis of diabetes insipidus. The patient did not complain of any problems with hearing; no pathologies were found during the otoscopic examination. Audiometry showed bilateral high frequency (more than 1,500 Hz) sensorineural hearing loss. An ultrasonography of the abdominal cavity was performed, showing a slight dilation of the pyelocalyceal systems on both sides.

In this paragraph, we present the patient`s past medical history. She was diagnosed with diabetes at the age of seven and insulin treatment was introduced at diagnosis, with the following doses: 0.7–1.0 IU/kg, with varying glycaemic control (HbA1c in the past in the range 55–70 mmol/mol [7.2–8.6%]) and no episodes of ketoacidosis. At the age of 15, reduced visual acuity occurred and progressed gradually. Fundoscopic examination was performed several times as the deterioration of the subject`s vision progressed, and no features of diabetic retinopathy were observed. At the age of 17, the ophthalmologist described bilateral optic atrophy for the first time, together with divergent squint and nystagmus. The patient`s visual fields at that time showed peripheral constriction. When blindness occurred at the age of 20, the ophthalmologist attributed it to bilateral maculopathy.

The patient had been complaining of polyuria for many years. However, glucose levels during that time were rather low, and it was regarded by the patient as a symptom of diabetes mellitus. Low urine specific gravity was observed a number of times.

Since the diagnosis of diabetes mellitus, sonography of the abdomen was performed several times and pelvicalyceal dilatation was always found in both kidneys. Dilated renal outflow tracts were diagnosed early, when the patient was about seven years old. A few months before the current hospitalisation, the patient was hospitalised in the urology ward due to pyelonephritis with bilateral hydronephros I^{o} and voiding difficulty.

In the patient`s family, the grandfather (the patient`s mother`s father) suffered from type 2 diabetes.

A detailed analysis of the medical history pointed to WS and a false diagnosis of type 1 diabetes mellitus and its complications.

A genetic test was performed in the patient and in some members of her family. The gene analysed was WFS1. The patient was found to be a compound heterozygote for two novel mutations in exon 8: a 2-bp deletion AT at nt 1539 leading to a frameshift (Y513fs) and single-base substitution 1174C > T resulting in a stop codon (Q392X). The patient`s mother was heterozygous for Q392X and her father was heterozygous for Y513fs. The subject`s younger sister was found to be a carrier of Y513fs and her older sister a homozygous wild type.

At present, the patient undergoes regular examinations at diabetes outpatient clinic, her condition is good and stable, and the desmopressin treatment is continuing.

Discussion

The typical sequence of the occurrence of the pathologies in patients with Wolfram syndrome is: diabetes mellitus in the first decade of life, optic atrophy in the first or early in the second decade, diabetes insipidus and sensorineural hearing loss in the second decade, dilated renal outflow tracts early in the third decade and neurological abnormalities early in the fourth decade of life [11, 12].

In our study, the patient`s age at diagnosis of diabetes mellitus was typical for Wolfram syndrome (seven years). The clinical course of diabetes was also characteristic, with low insulin requirement, fairly good metabolic control, and no episodes of ketoacidosis. The first symptoms of optic atrophy also occurred at a usual age, when the patient was about 15. Our patient demonstrated typical symptoms: reduced visual acuity with progressive sight deterioration, no features of diabetic retinopathy, peripheral constriction of visual fields, fundoscopic signs of optic nerve atrophy. All these symptoms, together with the lack of retinopathy, are usually reported in Wolfram syndrome patients [13]. The symptoms of diabetes insipidus were present in our patient already in her childhood, which is also typical for this abnormality in WS patients. The diagnosis of a sensorineural hearing defect was established at 25 years of age and based on audiometry, with no previous complaints of hearing problems from the patient. What was not typical was the very early (the patient was aged seven) appearance of urodynamic disorders. Usually, Wolfram syndrome patients present renal tract disorders, with urinary frequency, incontinence and recurrent infections, at the median age of 20 years (10–44 years) [3]. In our patient, there was no problem with conception and no complications occurred during pregnancy. Despite the fact that primary gonadal atrophy and reduced fertility occur in a number of patients suffering from Wolfram syndrome, successful pregnancies ending with the birth of healthy children have been reported as well [1]. Wide tissue distribution of wolframin and many mutations in the wolframin gene resulting in Wolfram syndrome may contribute to different phenotypes and atypical sequences of clinical features.

Although all the symptoms occurred in our patient quite early, the proper diagnosis of WS was established late — at the age of 25. The false diagnosis of type 1 diabetes and mistaking the typical features of Wolfram syndrome as diabetic complications may result in the very rare incidence of WS and a low vigilance of medical staff toward this syndrome. Assuming that the prevalence of Wolfram syndrome in young people with diabetes in Europe is 1/730, as was reported recently in a multicentre study, the number of subjects diagnosed with this syndrome should be much higher than that given in the literature [14]. Genetic studies of WS performed in different European countries usually have included relatively small numbers of patients — 41 in the UK [15], 22 in Spain [16], and six in Poland [17].

Conclusions

Although Wolfram syndrome is rare, it should be considered in a case of the presence of diabetes mellitus accompanied by symptoms of progressive optic atrophy and hearing loss, diabetes insipidus or renal tract disorders. Some of the cases diagnosed as type 1 diabetes mellitus are in fact subjects with Wolfram syndrome. Genetic tests should be performed in all patients in whom there is a suspected presence of Wolfram syndrome, as well as among their family members.

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