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Wolfram Syndrome. Case report

Przypadek zespołu Wolframa

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Abstract
Wolfram syndrome is a rare neurodegenerative and genetic disorder, characterized by insulin-dependent diabetes mellitus, caused by non-autoimmune loss of β cells, as well as optic atrophy; the disease is also known as DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness). Patients that demonstrate diabetes mellitus are also affected by: optic atrophy in the first decade of their life, diabetes insipidus and sensorineural deafness in the second decade, and urinary tract and neurological abnormalities in the third decade of their life. Patients with Wolfram syndrome usually die due to central respiratory failures caused by brain stem atrophy in their third or at the beginning of their fourth decade of life. The authors present a case of two female siblings with diagnosed Wolfram syndrome that have been diagnosed with diabetes mellitus, optic atrophy, and urological abnormalities. Early diagnosis and adequate hormonal supplementation can improve their quality of life.
Key words:
Wolfram Syndrome, children, case report

Streszczenie
Zespół Wolframa jest to rzadka, uwarunkowana genetycznie choroba neurodegeneracyjna, charakteryzująca się współwystępowaniem cukrzycy insulinozależnej spowodowanej nieautoimmunologicznym zanikiem komórek β oraz zanikiem nerwu wzrokowego, znana również jako DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness). U pacjentów z cukrzycą insulinozależną postępuje zanik nerwu wzrokowego w pierwszej dekadzie życia, moczówka prosta i głuchota sensoryczna w drugiej dekadzie, zaburzenia neurologiczne i w układzie moczowym w trzeciej dekadzie. Pacjenci z zespołem Wolframa zwykle umierają z powodu niewydolności oddechowej w przebiegu zaniku pnia mózgu w trzeciej lub na początku czwartej dekady życia. Autorzy przedstawiają przypadek dwóch sióstr z rozpoznanym zespołem Wolframa, u których występuje cukrzyca insulinozależna, zanik nerwu wzrokowego i zaburzenia urologiczne. Wczesne postawienie diagnozy i odpowiednia suplementacja hormonów może poprawić jakość życia tych pacjentów.
Słowa kluczowe:
zespół Wolframa, dzieci, opis przypadku

Introduction

Wolfram Syndrome is a rare genetic neurodegenerative disease, inherited autosomally and recessively. It can be clinically diagnosed based on the fact that the patient has diabetes and that his/her optic nerves begin to deteriorate before the age of 15. In addition, patients can have diabetes insipidus (83%) and deafness (65%). Other symptoms may include [1, 2] • Neurological disorders and mental health-depression, psychosis (60%) • Urodynamic abnormalities, including neurogenic bladder (60%) • Hydronephrosis, megaureter • Peripheral vegetative neuropathy (cardiovascular and gastro-intestinal) • Hipergonadotrophic hypogonadism in men • An under active frontal lobe of pituitary • Diabetic retinopathy, youthful cataracts • Limitations of movable joints • Heart defects, cardiomyopathy •Short Stature • Megalo-and syderoblastic anemia, thrombocytopenia • Celiac Disease.

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Hence, another name for the disease is derived from the acronym of its syndromes and very often it is used interchangeably - DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness) [2]. Genetic basis of the disease is concerned with WFS gene mutation, which encodes wolfram protein and less-often mutations of mitochondrial DNA. Three forms of the disease are known: WFS1, WFS2, and the mitochondrial form. In the most common form (WFS1), mutation is located on chromosome 4 (4 p 16.1) and can be characterized by a mismatch, an insertion, transversion or transition [3– 6]. A less common form of the disease (WFS2) is associated with CISD2 gene mutation in locus 4q22-q24 [7]. The gene (WFS1) codes the protein (wolframin protein) which occurs in the endoplasmic reticulum. This protein is made from 890 amino acids and creates nine domains. The expression of this gene is particularly high in nerve cells, muscle cells of the pancreas, liver, kidney and the inner ear. Wolframin takes part in the transportation of cytoplasmic proteins, protein precursors treatment (insulin proinsulin) and the intra-cellular regulation of the calcium ion concentration [3, 6– 9]. Recently, mutations in *4 p 16.1* have been associated with disorders of the subunit beta *1 on*$^{+}$*/K*$^{+}$ *ATP aza*, which is essential for the beta cells of the pancreas to function properly [10].

Rotig et al. [11] suggested that some cases of the syndrome, especially the ones associated with an early disclosure of diabetes, atrophy of the optic nerve and deafness may have its source in the irregularities found in the mitochondrial DNA. Subsequent reports have confirmed the presence of mitochondrial mutations in Wolfram syndrome [12– 14].

It is estimated that the frequency of Wolfram syndrome occurrence is about 1:770000, with 1:350 being the chances of carrying the mutation [4].

Insulin dependent diabetes, non-autoimmune and atrophy of the optic nerve are usually recognized as first signs of the disease – these symptoms happen in the first decade of life. Diabetes insipidus and deafness occur in the second decade. Disorders of the urinary tract in the third decade, while disorders of the nervous system, such as the imbalance of cerebellum origin, convulsions, peripheral neuropathy, nystagmus, Parinaud syndrome, atrophy changes in the brain, dementia, depression, psychosis are found in the third, or at the beginning of the fourth decade of patient's life [18].

Wolfram syndrome patients usually die from respiratory failure in the course of the disappearance of the brainstem or due to complications from other neurodegenerative disorders in the third or fourth decade of their life. Cases of depression-caused suicides in the course of Wolfram syndrome have also been reported [4, 5, 18].

Description of the case

Two female siblings at the age of 18 and 15 with diabetes and atrophy of optic nerves had Wolfram syndrome which was diagnosed in their early childhood – Fig 1. Unbiased family medical history (i.e., there was no trace of genetically conditioned diseases, reproductive failures, birth defects or brain impairments in the family's medical records), parents are healthy and are not relatives. The elder sister with CI, PI, correct, born in 36 Hbd, with caesarean section due to rhythm abnormalities of the fetus. Birth weight 2590 g Apgar, 6/7/8. Hyperbilirubinemia was long present after the birth. At the age of 5 the girl was diagnosed with insulin-dependent diabetes, and next (the same year) with bilateral atrophy of the optic nerves without the characteristics of diabetic retinopathy (current visual acuity is 0.3). At the age of 13, the girl was hospitalized because of bed-wetting as well as urine-withholding problems during daytime, disorders of the urinary bladder and the suspicion of polyneuropathy. Laboratory tests revealed 8.7% HbA1c and microalbuminuria. USG examination of abdomen and kidneys revealed urine retention in the bladder. Consultation with ophthalmologist confirmed bilateral atrophy of the optic nerves and hyperopia of both eyes and neurological consultation concluded additional nystagmus. Echocardiogram examination led to ASD suspicion. Immunological studies on patomechanism diabetes found no presence of autoantibodies GAD, with reduced peptide concentration C in the glukagone test. Hearing test was normal. Genetic analysis confirmed the presence of gene mutation AGG/AGC WFS1 – with residual amino acid S R type substitution in 443 wolframin peptid chain – this definitely confirmed the Wolfram syndrome diagnosis. Intellectual development remained normal. Hearing was normal. Magnetic resonance examination revealed proper brain image.

The girl was discharged from the hospital with the recommendation to take insulin via insulin personal pump, the Minirin and to be under constant control by the Endocrine, Diabetes, Neurological, Cardiac, Ophthalmological and Nephrologic Clinics.

The younger sister of CIIPII, correct, born in 40 Hbd with caesarean section. Birth weight 4150 g and Apgar was 9/10. Hyperbilirubinemia was long present after the birth. At the age of 4 the girl was diagnosed with insulin-dependent diabetes and when 6 years old she was diagnosed with bilateral atrophy of the optic nerves (now visual acuity 0.1). At the age of 11 years the girl was hospitalized due to the suspicion of Diabetes Insipidus, dysuric symptoms, troubles with body balance and headaches. Laboratory tests found 7.7% HbA1c without microalbuminuria. Based on the low weights of the urine, fluid balance and urine density test urodynamic abnormalities were diagnosed. The USG examination of abdominal and reins revealed urine retention in the bladder. Consultation with ophthalmologist confirmed bilateral atrophy of the optic nerves, astigmatism and hyperopia of left eye as well as glaucoma. Echocardiogram examination resulted in ASD suspicion. Immunological studies on the patomechanism of diabetes found no presence of autoantibodies GAD, with reduced peptide concentration C in the test with glucagone. The genetic test confirmed that the patient is homozygous in terms of mutations in the WFS1 gene like her sister which confirmed the Wolfram syndrome diagnosis. Magnetic resonance examination showed no pathological changes in the brain. Audiogram was correct. Intellectual development was in order.

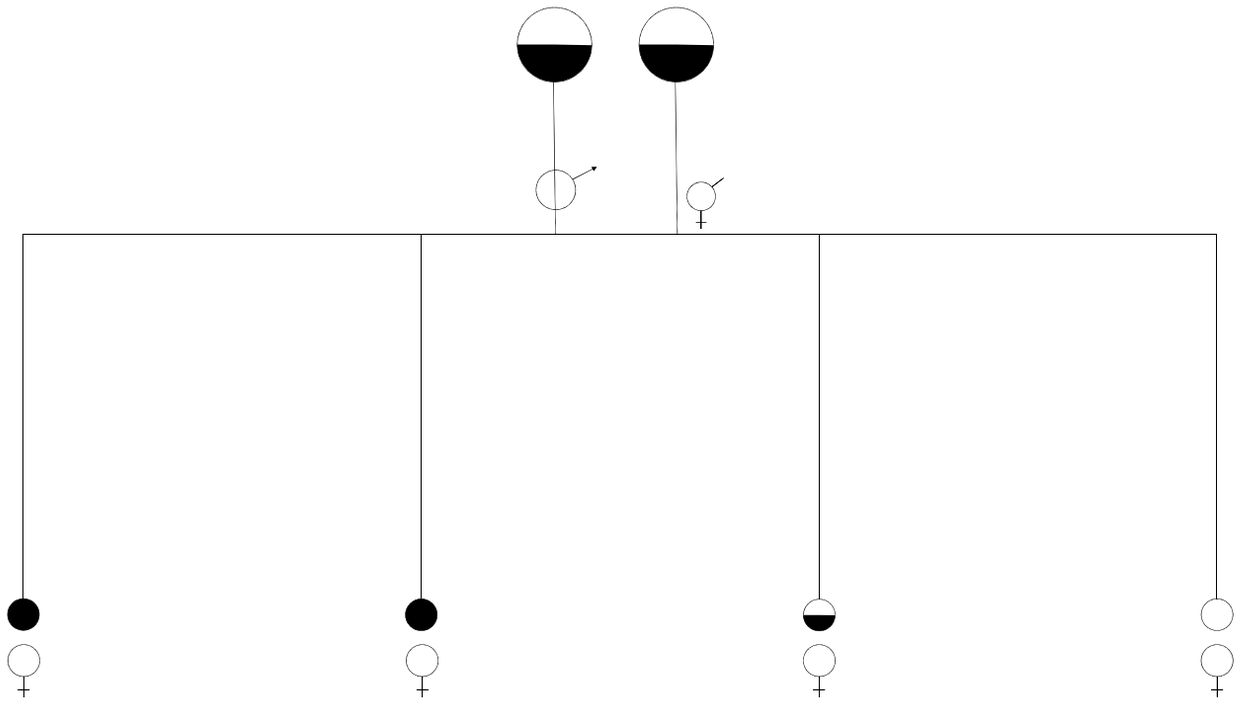

Fig. 1. Diagram of the family with Wolfram syndrome
Ryc. 1. *Diagram rodziny z zespołem Wolframa*

The girl was discharged from the hospital with the recommendation to take the insulin therapy using insulin personal pump, the Minirin, eye drops and to be under control by Endocrine, Diabetes, Cardiological, Neurological, Ophthalmological and Nephrological clinic.

Currently, both patients have recurrent urinary tract infections and bed-wetting; also amblyopia is progressing.

Conclusions

Although that Wolfram Syndrome is a very rare disease, it should be suspected whenever patients are diagnosed with diabetes and disappearance of optic nerves that occur in the first three decades of life. Identifying the mutations responsible for Wolfram syndrome not only confirms the diagnosis, but can also help to determine the phenotypic-genotypic correlation. Moreover, identifying of heterozygote carriers of the gene mutations WFS1 requires genetic counseling in the patients' families and it is vital to ensure that multi-specialist care for these patients is provided, mainly due to the risk of specific disorders [19].

References

1. Hansen L, Eiberg H, Barrett T, Bek T et al. *Mutation analysis of the WFS1 gene in seven Danish Wolfram syndrome families; four new mutations identified*. Europ J Hum Genet. 2005;13: 1275-1284.
2. Khanim F, Kirk J, Latif F, Barrett TG. *WFS1/Wolframin mutations, Wolfram syndrome, and associated diseases*. Hum Mutat. 2001;17: 357-367.
3. Osman AA, Saito M, Makepeace C, Permutt MA et al. *Wolframin expression induces novel ion channel activity in endoplasmic reticulum membranes and increases intracellular calcium*. J Biol Chem. 2003;278: 52755-52762.
4. Tessa A, Carbone I, Matteoli MC, Bruno C et al. *Identification of novel WFS1 mutations in Italian children with Wolfram syndrome*. Hum Mutat. 2001;17: 348-349.
5. Cryns K, Sivakumaran TA, Van den Ouweland JMW, Pennings RJE et al. *Mutational spectrum of the WFS1 gene in Wolfram syndrome, nonsyndromic hearing impairment, diabetes mellitus, and psychiatric disease*. Hum Mutat. 2003;22: 275-287.
6. Fonseca SG, Fukuma M, Lipson KL, Nguyen LX et al. *WFS1 is a novel component of the unfolded protein response and maintains homeostasis of the endoplasmic reticulum in pancreatic beta-cells*. J Biol Chem. 2005;280: 39609-39615.
7. Hofmann S, Bauer MF. *Wolfram syndrome-associated mutations lead to instability and proteasomal degradation of wolframin*. FEBS Lett. 2006;580: 4000-4004.
8. Inoue H, Tanizawa Y, Wasson J, Behn P et al. *A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome)*. Nature Genet. 1998;20: 143-148.
9. Hofmann S, Philbrook C, Gerbitz K-D, Bauer MF. *Wolfram syndrome: structural and functional analyses of mutant and wild-type wolframin, the WFS1 gene product*. Hum Molec. Genet. 2003;12: 2003-2012.
10. Zatyka M, Ricketts C, Xavier GS, Minton J et al. *Sodium-potassium ATPase beta-1 subunit is a molecular partner of Wolframin, an endoplasmic reticulum protein involved in ER stress*. Hum Molec Genet. 2008;17: 190-200.
11. Rotig A, Cormier V, Chatelain P, Francois R et al. *Deletion of mitochondrial DNA in a case of early-onset diabetes mellitus, optic atrophy, and deafness (Wolfram syndrome, MIM 222300).* J Clin Invest. 1993;91: 1095-1098.
12. Cagalinec M, Liiv M, Hodurova Z, Hickey MA et al. *Role of Mitochondrial Dynamics in Neuronal Development: Mechanism for Wolfram Syndrome*. PLoS Biol. 2016;19,14(7):e1002511.
13. Tanabe K, Matsunaga K, Hatanaka M, Akiyama M, Tanizawa Y. *[Wolfram syndrome: clinical features, molecular genetics of WFS1 gene]*. Nihon Rinsho. 2015;73:341-349.
14. Valero T. *Mitochondrial biogenesis: pharmacological approaches*. Curr Pharm Des. 2014;20:5507-5509.
15. Rendtorff ND, Lodahl M, Boulahbel H, Johansen IR et al. *Identification of p.A684V missense mutation in the WFS1 gene as a frequent cause of autosomal dominant optic atrophy and hearing impairment*. Am J Med Genet. 2011;155A: 1298-1313.
16. Sandhu MS, Weedon MN, Fawcett KA, Wasson J et al. *Common variants in WFS1 confer risk of type 2 diabetes*. Nature Genet. 2007;39: 951-953.
17. Moosajee M, Yu-Wai-Man P, Rouzier C, Bitner-Glindzicz M, Bowman R. *Clinical utility gene card for: Wolfram syndrome*. Eur J Hum Genet. 2016;24, doi:10.1038/ejhg.2016.49.
18. Sam W, Qin H, Crawford B, Yue D, Yu S. *Homozygosity for a 4-bp deletion in a patient with Wolfram syndrome suggesting possible phenotype and genotype correlation*. (Letter) Clin Genet. 2001;59: 136-138.
19. Zmyslowska A, Borowiec M, Antosik K, Szalecki M et al. *Wolfram syndrome in the Polish population: novel mutations and genotype--phenotype correlation*. Clin Endocrinol. 2011; 75:636-641.