Pediatric Endocrinology Diabetes and Metabolism
Endokrynologia, Diabetologia i Choroby Przemiany Materii Wieku Rozwojowego

Case Report | Praca kazuistyczna
Pediatr Endocrino Diabetes Metab 2017;23,2:107-110
DOI: 10.18544/PEDM-23.02.0081

redakcja@pediatricendocrinology.pl
www.pediatricendocrinology.pl
www.pteidd.pl

Previously unreported abnormalities in Wolfram Syndrome Type 2

Dotychczas niezgłaszane nieprawidłowości w zespole Wolframa typu 2

[1]Halis Kaan Akturk MD, [2]Seda Yasa MSc

[1]Assistant Professor of Medicine and Pediatrics, Barbara Davis Center for Childhood Diabetes, University of Colorado, Aurora, CO, USA [2]Ph.D. candidate. Department of Molecular Biology. Centre INRS-Institut Armand-Frappier, Laval, Quebec, Canada

Abstract

Wolfram syndrome (WFS) is a rare autosomal recessive disease with non-autoimmune childhood onset insulin dependent diabetes and optic atrophy. WFS type 2 (WFS2) differs from WFS type 1 (WFS1) with upper intestinal ulcers, bleeding tendency and the lack ofdiabetes insipidus. Li-fespan is short due to related comorbidities. Only a few familieshave been reported with this syndrome with the CISD2 mutation. Here we report two siblings with a clinical diagnosis of WFS2, previously misdiagnosed with type 1 diabetes mellitus and diabetic retinopathy-related blindness. We report possible additional clinical and laboratory findings that have not been pre-viously reported, such as asymptomatic hypoparathyroidism, osteomalacia, growth hormone (GH) deficiency and hepatomegaly. Even though not a requirement for the diagnosis of WFS2 currently, our case series confirm hypogonadotropic hypogonadism to be also a feature of this syndrome, as reported before.

Key words

type 1 diabetes, Wolfram syndrome, optic atrophy, growth hormone deficiency, hypoparathyroidism, hypogonadism, osteomalacia

Streszczenie

Zespół Wolframa jest rzadką chorobą dziedziczoną autosomalnie recesywnie, wiążącą się z występowaniem nieautoimmunizacyjnej cukrzycy insulinozależnej i atrofii nerwu wzrokowego. Typ 2 zespołu Wolframa (WFS2) różni się od typu 1 (WFS1) występowaniem owrzodzeń górnej części przewodu pokarmowego, skłonnością do krwawień i niewystępowaniem moczówki prostej. Czas przeżycia jest krótki ze względu na współwystępujące choroby. Dotychczas opisano tylko kilka rodzin z tym zespołem i mutacją *CISD2*. W obecnej pracy opisujemy przypadek rodzeństwa z kliniczną diagnozą WFS2, wcześniej zdiagnozowanego jako cukrzyca typu 1 z retinopatią powikłaną utratą wzroku. Opisujemy możliwe dodatkowe kliniczne i laboratoryjne parametry, które nie były wcześniej opisywane, takie jak: bezobjawowa niedoczynność przytarczyc, osteomalacja, niedobór hormonu wzrostu i hepatomegalia. Pomimo braku wymogu do rozpoznania zespołu WSF2 prezentowane przypadki potwierdzają również hypogonadyzm hypogonadotropowy jako cechę tego zespołu.

Słowa kluczowe

cukrzyca typu 1, zespół Wolframa, atrofia nerwu wzrokowego, niedobór hormonu wzrostu, niedoczynność przytarczyc, hypogonadyzm, osteomalacja

Received: 20.03.2017
Accepted: 15.07.2017
Conflict of interests: none declared.

Halis Kaan Akturk MD
Barbara Davis Center for Childhood Diabetes,
University of Colorado, Aurora, CO, USA.
e-mail: halis.akturk@ucdenver.edu

Introduction

Wolfram syndrome (WFS; MIM 222300) is a rare neurodegenerative disease with autosomal recessive inheritance and incomplete penetrance, the diagnosis of which requires diabetes mellitus (DM) and optic atrophy (OA). Two types of WFS, type 1 (WFS1; MIM 606201) and type 2 (WFS2; MIM 604928) characterized by different disease genes have been identified. The estimated prevalence of Wolfram syndrome type 1 is 1 in 500 000-770 000 people worldwide [1,2]. Only a few families from Jordan and a single case from Italy have been found to have WFS2 [3–5].

Gene linkage and positional cloning analysis reveal that a subset of Wolfram syndrome patients belonging to the WFS1 group (MIM 606201) carry a loss-of- function mutation in the *WFS1* gene, which encodes a transmembrane protein, wolframin, localized in the endoplasmic reticulum (ER) [1,2]. WFS1 also referred to as DIDMOAD is characterized by diabetes mellitus (DM), optic atrophy, diabetes insipidus (DI), deafness, neurologic symptoms, renal tract abnormalities, psychiatric problems and primary hypogonadism.

In WFS2, diabetes insipidus and psychiatric disorders are not described, whereas bleeding upper intestinal ulcers, not reported in WFS1, are present [3]. The disease gene for WFS2 is *CISD2*. It was identified in three consanguineous Jordanian families carrying a point mutation in exon 2 [4]. Another mutation was found as a homozygous intragenic deletion of *CISD2* in an Italian female [5]. *CISD2* maps to chromosome 4q22-q24, close to a region implicated in human longevity [6]. *CISD2* plays an important role in intracellular Ca^{2+} homeostasis, which is required for the differentiation and functioning of adipocytes as well as the regulation of glucose homeostasis in mice [7].

Case presentations

We present 19-year-old male and 16-year-old female siblings of Turkish origin, sharing common findings, as described below. There was parental consanguinity since their parents were first-degree cousins. They had a healthy 17-year old sister. There was no other family history of DM or blindness.

Case-1

The 19-year-old male patient was seen in our clinic for high blood sugar levels. He was 154 cm (5'), 58 kg (128 lbs) (BMI: 24.4 kg/m^2) at presentation to our clinic. He was below the 3rd percentile curve for height (Turkish boys' growth chart used [8]). Bone age was 15 and delayed. Vital signs were normal. He was diagnosed with diabetes mellitus at the age 6 and he had had visual difficulties since the age of 9. He was legally blind since the age of 14. He had four episodes of upper gastrointestinal (GI) bleeding, the first one was at the age of 9. Repeated endoscopies during bleeding episodes showed several duodenal and peptic ulcers. He did not present with secondary sexual characteristics (Tanner stage 1) and testicular exam showed pre-pubertal size testicles.

Case-2

Case-2 is the sister of Case-1. She was 143 cm (4' 6''), 44kg (97lbs) (BMI: 21.5 kg/m^2) at presentation to our clinic. She was below the 3rd percentile curve for height (Turkish girls' growth chart used) [8]. Bone age was 12 and delayed. Vital signs were normal. A 16-year-old female who was diagnosed with diabetes mellitus at the age 8 and she had had visual difficulties since the age of 11. She was legally blind since the age of 15. She had two episodes of upper GI bleeding, the first one was at the age of 10. Endoscopy during a bleeding episode showed multiple duodenal ulcers. She did not have any menses and did not develop secondary sexual characteristics at the physical exam (Tanner stage 1).

Common findings of cases

They were clinically diagnosed with Type 1 DM without the antibody confirmation in their childhood, in a rural part of the country. Their parents had not had health insurance for many years, living in a low socioeconomic neighborhood. The children had not been seen by any endocrinologist before. Vision loss was attributed to uncontrolled DM without a proper ophthalmologic exam. The Wolfram syndrome had not been diagnosed until our evaluation. We stated that both siblings had non-autoimmune insulin dependent DM, optic atrophy related blindness, history of multiple upper GI bleeding in childhood, the absence of signs of puberty, short stature, mild hepatomegaly, osteomalacia. The funduscopic exam showed advanced bilateral optic atrophy but no signs of diabeticretinopathy despite poorly controlled DM, with HbA1c chronically over 12% in both siblings. The audiology exam was normal in both patients.

Laboratory findings

They both presented with hypogonadotropic hypogonadism and GH deficiency, based on low concentrations ofIGF--1and low growth hormone secretion in arginine stimulation tests but normal concentrations of cortisol, ACTH, and prolactin. Neither of them manifested DI, neurologic or psychiatric symptoms. In both siblings low concentrations of PTH were found, however no clinical signs of hypocalcemia were noted. Phosphorus concentrations were mildly elevated but calcium concentrations highly varied on different occasions from mildly low to normal.

Urine analysis revealed proteinuria of 640 mg protein/ 24h urine in Case-1 and 550 mg protein/ 24h urine in Case-2, likely related to a poorly controlled DM.

Both siblings had negative glutamic acid decarboxylase antibodies (GAD65) and islet cell antibodies (ICA) at our evaluation. Thyroid antibodies (TPO and TSI) were also negative and thyroid function assays (TSH and freeT4) were normal.

Detailed lab results are reported in table I. Genetic analysis was not done due to the cost and lack of availability in Turkey.

Imaging

Both patients presented with normal neck US and normal size of the thyroid.The abdominal US showed only mild hepatomegaly, otherwise it was normal in both cases. MRI of the

Pediatr Endocrinol Diabetes Metab 2017;23,2:107-110

Table I. Lab results of both siblings with Wolfram Syndrome Type 2. Lab normal ranges are age and gender adjusted
Tabela I. *Wyniki badań laboratoryjnych rodzeństwa z zespołem Wolframa 2. Zakresy referencyjne badań podane są w odniesieniu do wieku i płci*

Age	19	16
Gender	M	F
HbA1c (N<6.5%)	12.8	12.1
Day–1 PTH (15–65 pg/ml)	5.53	4.84
Day–3 PTH (15–65 pg/ml)	3.89	6.81
Day–7 PTH (15–65 pg/ml)	8.05	7.46
Day–1 P (2.3–4.7 mg/dl)	5.3	4.9
Day–3 P (2.3–4.7 mg/dl)	5.1	5.2
Day–7 P (2.3–4.7 mg/dl)	5.0	5.2
Day–1 Ca	8.0	8.6
Day–3 Ca	8.2	8.4
Day–7 Ca	8.7	8.2
Day–1 25OH Vitamin D (30–100 ng/ml)	36	38
Day–1 1,25OH Vitamin D (19.6–65 pg/ml)	50	44
Testosterone (250–800 ng/dl)	18	-
Estradiol (24–273 pg/ml)	-	12
FSH (Male 1.27–19.2 mIU/ml) (Female 3.85–22.1 mIU/ml)	1.0	1.9
LH (Male 1.24–8.62 mIU/ml) (Female 2.12–86.4 mIU/ml)	0.06	0.2
IGF-1 (91–442 ng/ml)	46	-
IGF-1 (153-611 ng/ml)	-	68
GH (Arginine stimulated, N>5 ng/ml)	0.2	0.3

brain showed bilateral optic atrophy and normal pituitary gland and brain structures in both cases. On X-rays Looser's zones were noted in the femur bilaterally in Case-1 and in the right tibia and the femur in Case-2.

Discussion

WFS2 is rarer than WFS1 and consanguinity is a known risk factor for this syndrome, considering autosomal recessive inheritance. Even though we could not do the genetic analysis for WFS2, the clinical picture is consistent with WFS2. Like all previously reported cases, our patients had non-autoimmune insulin dependent DM, optic atrophy and like most reported cases they also experienced upper GI bleeding. However, our patients did not have any hearing loss, which may be due to the relatively early stage of the syndrome. In a follow-up case series of WFS2 families, after many years hearing loss is reported in patients who did not manifest it at the diagnosis [4,9].

We report additional findings to previously defined WFS2, such as asymptomatic low concentrations of PTH with mildly elevated phosphorus (P), mildly low to normal calcium (Ca), high levels of bone-specific alkaline phosphatase (BS-ALP) with radiologic evidence of osteomalacia, the growth hormone (GH) deficiency with short stature and mild hepatomegaly.

Differential diagnosis includes Kearns-Sayre Syndrome, Thiamine-responsive megaloblastic anemia, mutant *WFS1* gene-induced deafness, autosomal dominant optic nerve atrophy, Friedreich ataxia, Bardet–Biedl syndrome, and Alström syndrome.

Hypoparathyroidism, DM and rarely optic atrophy can also be seen in Kearns-Sayre Syndrome, inherited by a mitochondrial gene defect. However, the lack of ptosis, ophthalmoplegia, neurologic and cardiac symptoms, retinal pigmentation at funduscopic exam and autosomal recessive inheritance pattern make this diagnosis unlikely [10]. Thiamine-responsive megaloblastic anemia syndrome is a rare autosomal-recessive condition characterized by a non-autoimmune DM, sensorineural hearing loss,megaloblastic anemia and rarely optic atrophy [11]. The lack of megaloblastic anemia, and the presence of GI bleeding make this diagnoses unlikely in our patients.Bardet–Biedl and Alström syndromes cause severe obesity, insulin resistance and type 2 diabetes rather than non-autoimmune insulin dependent diabetes seen in WFS.

WFS2 should be suspected in non-autoimmune type 1 diabetes mellitus, history of early siblings' death, family history of Wolfram syndrome or type 1 diabetes mellitus and optic atrophy with upper GI bleeding, and history of parental consanguinity [12].

We agree the previously recommended diagnosis criteria for WFS2 (Non-autoimmune insulin dependent DM, optic atrophy and GI bleeding/ulcers/bleeding tendency and no DI) [3,4]. Our patients also had hypogonadotropic hypogonadism with delayed puberty as reported in previous two cases in the literature [4,5].

Our patients were treated with multiple daily injections of insulin therapy for diabetes. Female patient was started on combined estrogen and progesterone. Male patient started to use testo sterone. They were recommended to have annual hearing exam with audiogram and annual PTH with calcium tests. They were placed on the proton pump inhibitor for GI bleeding prophylaxis.

Conclusion

Although WFS2 is a very rare entity, clinicians should suspect this syndrome with childhood onset insulin dependent diabetes mellitus, early onset blindness and multiple GI bleeding episodes. We report possible additional clinical and laboratory findings that have not been previously reported. We believe hypogonadotropic hypogonadism can be an additional diagnostic feature of WFS2. We recommend checking gonadotropins and PTH in future cases since we report additional findings that may be related to this rare syndrome. We suggestgenetic analysis for all suspected patients with acknowledging high cost of the test anddifficult access to capable labs. Unfortunately, there are currently no effective treatments that can delay or reverse the progression of Wolfram syndrome Early diagnosis, monitoring and supportive care can relieve the associated symptoms [13]. Wolfram syndrome affects multiple organs and systems. Multidisciplinary care by physicians and healthcare professionals from a range of disciplines is recommended [13].

Further case series and studies are required to confirm these features.

References

1. Inoue H, Tanizawa Y, Wasson J et al. *A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome)*. Nat Genet. 1998;20:143-148.
2. Strom TM, Hortnagel K, Hofmann S et al. *Diabetes insipidus, diabetes mellitus, optic atrophy and deafness (DIDMOAD) caused by mutations in a novel gene (wolfram) coding for a predicted transmembrane protein*. Hum Mol Genet. 1998;7:2021-2028.
3. Al-Sheyyab M, Jarrah N, Younis E et al. *Bleeding tendency in Wolfram syndrome: a newly identified feature with phenotype genotype correlation*. Eur J Pediatr. 2001, 160(4):243-246.
4. Amr S, Heisey C, Zhang M et al. *A homozygous mutation in a novel zinc-finger protein, ERIS, is responsible for Wolfram syndrome 2*. Am J Hum Genet. 2007;81(4):673-683. doi:10.1086/520961.
5. Mozzillo E, Delvecchio M, Carella M et al. *A novel CISD2 intragenic deletion, optic neuropathy and platelet aggregation defect in Wolfram syndrome type 2*. BMC Med Genet. 2014 Jul 24;15:88. doi: 10.1186/1471-2350-15-88.
6. Chen YF, Kao CH, Chen YT et al. *Cisd2 deficiency drives premature aging and causes mitochondria-mediated defects in mice*. Genes Dev. 2009; 23:1183-1194.
7. Wang CH, Chen YF, Wu CY et al. *Cisd2 modulates the differentiation and functioning of adipocytes by regulating intracellular Ca2+ homeostasis*. Hum Mol Genet. 2014. doi:10.1093/hmg/ddu193.
8. Neyzi O, Furman A, Bundak R et al. *Growth references for Turkish children aged 6 to 18 years*. Acta Paediatr. 2006 Dec;95(12):1635-1641.
9. El-Shanti H, Lidral AC, Jarrah N, Druhan L, Ajlouni K. *Homozygosity mapping identifies an additional locus for Wolfram syndrome on chromosome 4q*. Am J Hum Genet. 2000; 66:1229-1236.
10. Barrett TG, Bundey SE. *Wolfram (DIDMOAD) syndrome*. J Med Genet. 1997;34:838-841.
11. Astuti D, Sabir A, Fulton P et al. *Monogenic diabetes syndromes: Locus-specific databases for Alström, Wolfram, and Thiamine-responsive megaloblastic anemia*. Hum Mutat. 2017 Jul;38(7):764-777. doi: 10.1002/humu.23233. Epub 2017 Jun 1.
12. Rigoli L, Bella C Di. *Wolfram syndrome 1 and Wolfram syndrome 2*. Curr Opin Pediatr. 2012;24(4):512-517.
13. Urano F. *Wolfram Syndrome: Diagnosis, Management, and Treatment*. Curr Diab Rep. 2016 Jan;16(1):6. doi: 10.1007/s11892-015-0702-6.

