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The prevalence of Wolfram syndrome in a paediatric population with diabetes

Ocena częstości występowania zespołu Wolframa w populacji dzieci z cukrzycą

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Abstract

Introduction: Wolfram syndrome (WFS) is the most frequent syndromic form of monogenic diabetes coexisting with optic atrophy and many other disorders. The aim of this study was to estimate the prevalence of Wolfram syndrome among children with diabetes in Poland.
Material and methods: These calculations were performed among Polish diabetic children, aged 0–18 years, from three administrative regions between January 2005 and December 2011. Epidemiological data was obtained by matching the results from the EURO-WABB-Poland Project and the PolPeDiab Registry.
Results: Throughout the study period, we confirmed genetic diagnosis of Wolfram syndrome in 13 patients from Poland. Three patients originated from the studied regions with complete epidemiological data on paediatric diabetes. The total number of patients with diagnosed diabetes in the study equalled 2,568 cases. The prevalence of Wolfram syndrome among Polish children with diabetes is 0.12% (95% Confidence Interval 0.04–0.34%).
Conclusions: We estimate that Wolfram syndrome is 26 to 35 times less frequent than monogenic diabetes (MODY and neonatal diabetes) in the Polish paediatric population. **(Endokrynol Pol 2014; 65 (4): 295–297)**

Key words: *Wolfram syndrome; monogenic diabetes; type 1 diabetes*

Streszczenie

Wstęp: Zespół Wolframa (WFS) jest najczęstszą syndromiczną formą cukrzycy monogenowej, gdzie oprócz cukrzycy występuje zanik nerwów wzrokowych oraz wiele innych zaburzeń. Celem pracy była ocena częstości występowania zespołu Wolframa na tle innych rodzajów cukrzycy w populacji pediatrycznej.
Materiał i metody: Ocena chorobowości została przeprowadzona wśród dzieci chorych na cukrzycę, pochodzących z trzech polskich województw (łódzkie, pomorskie i śląskie) w wieku 0–18 lat, w okresie czasu pomiędzy styczniem 2005 roku i grudniem 2011. Dane epidemiologiczne uzyskano poprzez połączenie danych pochodzących z Rejestru EURO-WABB dla Polski oraz Rejestru PolPeDiab.
Wyniki: W badanym okresie czasu potwierdzono genetycznie rozpoznanie zespołu Wolframa u 13 pacjentów na terenie Polski. Do niniejszej analizy włączono 3 pacjentów z zespołem Wolframa pochodzących z badanego regionu. Całkowita liczba przypadków cukrzycy zdiagnozowanych w tym okresie czasu wyniosła 2568. Prewalencję zespołu Wolframa wśród pacjentów pediatrycznych z cukrzycą oszacowano na 0.12% (95% Przedział Ufności 0.04–0.34%).
Wnioski: Oceniono, że zespół Wolframa występuje w polskiej populacji pediatrycznej 26- do 35-krotnie rzadziej niż pozostałe typy cukrzycy monogenowej (MODY i cukrzyca noworodkowa). **(Endokrynol Pol 2014; 65 (4): 295–297).**

Słowa kluczowe: *zespół Wolframa; cukrzyca monogenowa; cukrzyca typu 1*

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Introduction

Wolfram syndrome (WFS) is the most frequent syndromic form of monogenic diabetes coexisting with optic atrophy and many other disorders. This syndrome is a result of mutations in the wolframin gene (*WFS1*) and is inherited as an autosomal recessive trait [1].

The aim of this study was an estimation of the prevalence of Wolfram syndrome among children with diabetes.

Material and methods

An evaluation of the prevalence of Wolfram syndrome was performed among Polish diabetic children aged 0–18 years between January 2005 and December 2011.

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All patients fulfilled the clinical criteria of Wolfram syndrome – the coexistence of diabetes mellitus and optic atrophy. Diagnosis of Wolfram syndrome was definitely confirmed by direct sequencing of *WFS1* gene and/or MLPA (SALSA MLPA P163 GJB-WFS1 probemix, MRC-Holland, Amsterdam, the Netherlands), as described previously [2]. Sequence information of the *WFS1* gene was derived from GenBank (www.ncbi.nlm.nih.gov). For sequencing, all exons, including exon-intron boundaries and 900 bp from the 5′ and 3′ untranslated region (UTR)/promoter region of *WFS1* were amplified by 12 primer pairs and analysed by terminator cycle sequencing using Big Dye v3.0 chemistry on an ABI PRISM 310 capillary DNA sequencer (Applied Biosystems, Foster City, CA, USA) [2].

Epidemiological data was obtained by matching results from the EURO-WABB-Poland Project and the PolPeDiab Registry. Data of frequency of Wolfram syndrome was provided from the EURO-WABB-Poland Registry. The EURO-WABB Project started in 2011 as the European Union Rare Diseases Registry for Wolfram-, Alstrom-, Bardet Biedl syndrome and other rare syndromes and deals with the recruitment and genetic identification of patients. The Department of Paediatrics, Oncology, Haematology and Diabetology, Medical University of Lodz is the nationwide co-ordinator of the EURO-WABB Project (Fig. 1).

Diagnosis of type 1, type 2, other monogenic types of diabetes (MODY, neonatal diabetes), and cystic fibrosis-related diabetes (CFRD), was performed according to the WHO classification. Data showing the effects of these efforts was reported previously [3–6].

Prevalence calculations for all analysed types of diabetes: type 1, type 2, other than WFS monogenic diabetes, and CFRD, were performed using the epidemiological data from the Polish PolPeDiab Registry. Three academic paediatric endocrinology/diabetology centres submitted complete data on the prevalence of diabetes in their respective regions. In the Slaskie and Pomorskie regions, the study centres (in Katowice and Gdansk) were the main reference departments and supervised the treatment of all children with diabetes in those administrative districts. In the Lodzkie administrative region, there are two academic centres for paediatric diabetes care. However, the study centre was in charge of epidemiological data collection from both regional centres and is responsible for the treatment of approximately 85% of children with diabetes in the region. Generally, owing to the centralised structure of diabetes care in the studied regions, we were able to maintain approximately 100% coverage of the three regions in terms of the number of children treated for diabetes throughout the study period.

Table I. ***Prevalence of Wolfram syndrome among a paediatric population with diabetes in three regions of Poland in 2005–2011***

Tabela I. ***Częstość występowania zespołu Wolframa na tle innych rodzajów cukrzycy w populacji paediatrycznej w trzech regionach Polski w latach 2005–2011***

Type of diabetes	Number of diabetes cases (overall from three regions)
Wolfram syndrome	3
Other monogenic diabetes	97
Type 1 diabetes	2,425
Type 2 diabetes	25
CFRD	18

The study protocol was approved by the University Bioethics Committee at the Medical University in Lodz, Poland (RNN/124/11/KE and RNN/133/10/KE).

Results

In the study period, we confirmed diagnosis of Wolfram syndrome by genetic analysis in 13 patients from Poland (11 females and two males aged: 6–33, mean 18.7 ± 6.7 years). Three patients with Wolfram syndrome who originated from the three administrative regions (three females) aged: 6–18, mean 13.1 ± 6.3 years were entered into the study. Two individuals were homozygous for the W540X mutation and one was a compound heterozygote with both S167E and W648X mutations. All three mutations were reported earlier to be pathogenic [2, 7].

Epidemiological data for all analysed types of diabetes: type 1, type 2, other than WFS monogenic diabetes, and CFRD, is summarised in Table I. The total number of patients with diabetes equalled 2,568 cases. Comparing the epidemiological data from the EURO-WABB-Poland Project and the PolPeDiab Registry, we found that the prevalence of Wolfram syndrome among paediatric patients with diabetes is 0.12% (95% Confidence Interval [CI] 0.04–0.34%). After combining that data with that from our earlier epidemiological report which showed the prevalence of monogenic diabetes to range from 3.1 to 4.2% of diabetes [5], we estimated that Wolfram syndrome is 26 to 35 times less frequent than monogenic diabetes in the Polish paediatric population.

Discussion

After comparing the epidemiological data from the EURO-WABB-Poland Project with data from three Polish administrative regions for other types of diabetes in children and adolescents, we determined the preva-

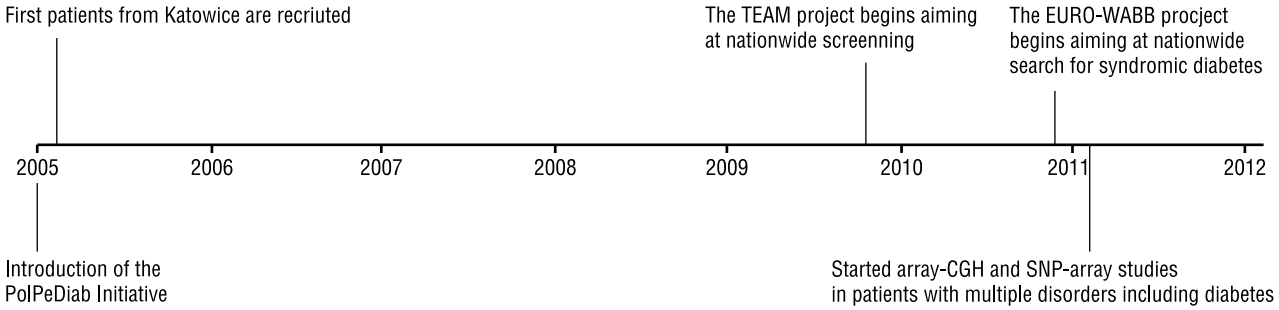

Figure 1. *Milestones for integrative epidemiology studies among paediatric patients with diabetes in Poland*

Rycina 1. *Kluczowe wydarzenia integrujące w Polsce badania epidemiologiczne wśród pacjentów pediatrycznych z cukrzycą*

lence of Wolfram syndrome among diabetic paediatric patients in Poland. We found that this value was 0.12%.

According to some researchers, the prevalence of this syndrome in European population is estimated to be 1 in 770,000 individuals in the UK and 1 in 500,000 in Germany [7, 8], so our findings are similar to those of other European countries. In other populations, the prevalence of Wolfram syndrome is assessed as up to 1 in 68,000 cases in Lebanon, due to a higher frequency of consanguinity among parents of children with this syndrome [9, 10].

The frequency of *WFS1* mutations in patients misdiagnosed as having the most frequent type of diabetes in paediatric populations — type 1 diabetes — ranges from about 0.57% in the UK population up to 5.5% in Lebanon [8, 10].

Other researchers have estimated that the prevalence of diabetes in Wolfram syndrome among patients with diabetes younger than 21 years in Europe is about 1:730 [7]. In our study, the prevalence of WFS among children with diabetes below 18 years old was about 1:860, which is concordant with those reports.

In view of earlier epidemiological reports of the group, we were also able to show the ratios of prevalence between the most frequent types of monogenic diabetes in children with that of Wolfram syndrome, underlining the rarity of the latter disorder.

There are however several limitations to our study, intrinsic to studies on rare diseases. Wolfram syndrome proved to be an exceptionally rare clinical entity, and we were thus unable to achieve a large sample size. Consequently, we were unable to estimate the yearly incidence of Wolfram syndrome and focused on its prevalence among paediatric diabetic patients instead. However, the aim of the study was to match two registries: EURO-WABB-Poland and PolPeDiab Registry. Moreover, the number of patients with Wolfram syndrome may have been underestimated as the natural history of this disease shows that the onset of diabetes generally precedes the development of optic atrophy and other disorders [11, 12]. Therefore some patients with Wolfram syndrome may be present within the dataset but are still treated as type 1 diabetes. However, as the study covered a long period of time, and the cohort was periodically evaluated for possible new cases of Wolfram syndrome, this scenario seems rather unlikely.

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