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SHORT COMMUNICATION

Prevalence of monogenic diabetes amongst Polish children after a nationwide genetic screening campaign

W. Fendler · M. Borowiec · A. Baranowska-Jazwiecka · A. Szadkowska · E. Skala-Zamorowska · G. Deja · P. Jarosz-Chobot · I. Techmanska · J. Bautembach-Minkowska · M. Mysliwiec · A. Zmyslowska · I. Pietrzak · M. T. Malecki · W. Mlynarski

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Abstract
Aims/hypothesis The aim of this study was to study dynamic changes in the prevalence of different types of diabetes in paediatric populations in Poland, with a specific focus on monogenic diabetes (MD).
Methods Using epidemiologic data (PolPeDiab Collaboration) and nationwide genetic test results (TEAM Programme), we compared the prevalence of type 1, type 2 and cystic fibrosis-related diabetes (CFRD) and MD. Genetically confirmed MD included MODY, neonatal diabetes and Wolfram and Alström syndromes. The study covered all children aged 0–18 years treated for diabetes between 2005 and 2011 in three regions, inhabited by 23.7% (1,989,988) of Polish children, with a low prevalence of childhood obesity (<5%).
Results The prevalence of type 1 diabetes showed a continuous increase, from 96 to 138/100,000 children. The prevalence of type 2 diabetes and CFRD also increased, from 0.3 to 1.01/100,000 children and from 0.1 to 0.95/100,000 children, respectively. The prevalence of MD was stable at between 4.2 and 4.6/100,000 children, accounting for 3.1–4.2% of children with diabetes, with glucokinase (*GCK*)-MODY being the most frequent type, amounting to 83% of patients with MD. The percentage of positive test results decreased with the number of referrals, suggesting that children with the highest probability of MD were referred initially, followed by those with a less clear-cut phenotype. The prevalence of neonatal diabetes equalled 1 in 300,000 children.
Conclusions/interpretation The prevalence of MD in a paediatric population with a low prevalence of obesity remains stable and is nearly fivefold higher than that of type 2 diabetes and CFRD, justifying a need for increased access to genetic diagnostic procedures in diabetic children.

Keywords DNA sequencing · MODY · Monogenic diabetes · Neonatal diabetes · Paediatrics · Wolfram syndrome

Abbreviations
CF Cystic fibrosis
CFRD Cystic fibrosis-related diabetes

W. Fendler and M. Borowiec contributed equally to this study.

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W. Fendler · M. Borowiec · A. Baranowska-Jazwiecka · A. Szadkowska · A. Zmyslowska · I. Pietrzak · W. Mlynarski (✉)
Department of Paediatrics, Oncology, Haematology and Diabetology, Medical University of Lodz,
36/50 Sporna Str.,
91-738 Lodz, Poland
e-mail: Wojciech.Mlynarski@umed.lodz.pl

E. Skala-Zamorowska · G. Deja · P. Jarosz-Chobot
Department of Paediatrics, Endocrinology and Diabetes,
Silesian Medical University of Katowice,
Katowice, Poland

I. Techmanska · J. Bautembach-Minkowska · M. Mysliwiec
Department of Paediatrics, Oncology, Haematology and Endocrinology, Medical University of Gdansk,
Gdansk, Poland

M. T. Malecki
Department of Metabolic Diseases,
Collegium Medicum Jagiellonian University of Cracow,
Cracow, Poland

GCK Glucokinase
HNF Hepatocyte nuclear factor
MD Monogenic diabetes

Introduction

The literature reports a wide range of prevalence of monogenic diabetes (MD), making it difficult to perform economic analyses and estimate the feasibility of genetic screening procedures [1–3]. Efforts to estimate the prevalence of paediatric type 2 diabetes mellitus are similarly challenging, there being a wide range of estimated values [1, 2]. To improve on this situation, we report here accurate prevalence estimates of different types of childhood diabetes based on extensive epidemiological and genetic data from three major academic paediatric diabetes clinics [4, 5].

Methods

The study aimed to estimate the prevalence and relative frequency of type 1, type 2 and other specific types of diabetes (according to the ADA classification) in children of a European country with a low prevalence of overweight and obesity [6]. The diagnosis of MD was defined to cover the following genetic diagnoses with at least one confirmed case amongst Polish children in the period between January 2005 and December 2011: MODY, persistent neonatal diabetes mellitus and Wolfram and Alström syndromes. This study protocol was approved by the Bioethics Committee of the Medical University of Lodz. Guardians of all study participants gave informed consent.

Epidemiological data were obtained from the publicly available online database of the Central Statistical Office of Poland (www.stat.gov.pl/bdlen/app/strona.html?p_ name-indeks, accessed 5 January 2012). The paediatric population covered by the study constituted 23.7% of children in Poland. To assure the uniformity of data, only patients aged 0–18 years with diabetes entered the analysis.

Classification of the type of diabetes in patients covered by this analysis was based on a joint expert opinion of the diabetologists at the respective centres. Uniform recruitment criteria for MODY described by Ellard et al were adopted in 2008 by all participating centres [7]. Clinical characteristics used before that date are described in the electronic supplementary material (ESM Methods 1). Children with a suspicion of neonatal diabetes entered genetic screening if their diabetes manifested during the initial 6 months of life. Phenotypic characteristics suggestive of Wolfram or Alström syndromes were evaluated by the attending diabetologist and verified by members of the research team within the principal study centre in Lodz. The diagnostic criteria for type 2 diabetes were based on OGTT, the absence of signs of diabetic ketoacidosis at diagnosis, obesity (>2 SD-BMI), a high level of endogenous insulin production assessed by fasting C-peptide level, marked insulin resistance, detection of acanthosis nigricans, a family history of diabetes and obesity and, if possible to ascertain, the absence of autoantibodies.

The primary method used in screening for genetic defects causative for diabetes was DNA sequencing performed using fluorescent-labelled terminating deoxynucleoside triphosphates with gene-specific oligonucleotide primers, and multiplex ligation-dependent probe amplification was used

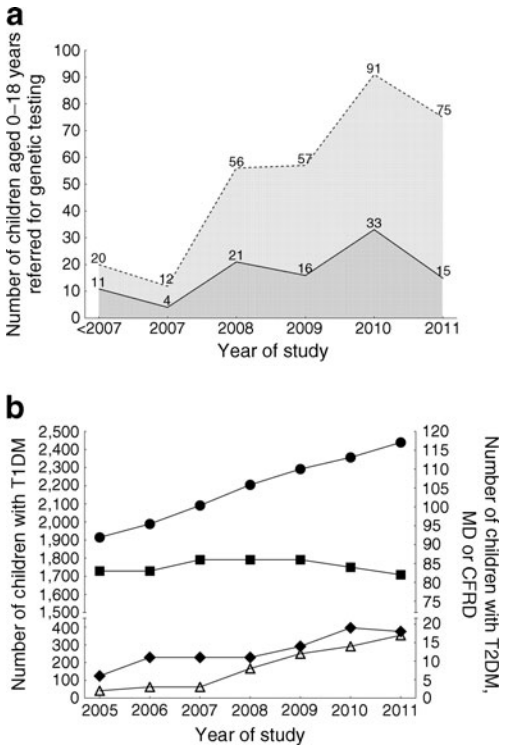

Fig. 1 (**a**) Increase of referral rate throughout the study period. The lower area (dark grey) represents patients with positive genetic test results for any kind of MD. The upper area (light grey) represents children referred for genetic testing and with negative genetic test results. GCK-MODY was the most commonly observed form, detected in 83% of children referred for genetic screening, followed by neonatal diabetes (7%), *HNF1A*/*HNF4A*-MODY (4%), *HNF1B*-MODY (2%) and diabetes in Wolfram and Alström syndromes (2% and 1%, respectively). (**b**) Number of children with type 1 diabetes (T1DM, circles), type 2 diabetes (T2DM, diamonds), monogenic diabetes (MD, squares) and CFRD (triangles) treated at the three study centres throughout the study region. Owing to the rapidly increasing number of children with type 1 diabetes, the percentage of diabetic patients with MD relative to the overall population of diabetic children decreased from 4.1% in 2005 to 3.2% in 2011, while the percentages of type 1 diabetes, type 2 diabetes and CFRD all increased. The left hand axis depicts the number of children with type 1 diabetes, while the right hand axis shows the number of children with monogenic or type 2 diabetes or CFRD

for detecting exon deletions (MRC-Holland, Amsterdam, the Netherlands). Details of the molecular methods are provided in ESM Methods 2. Prevalence calculations were performed for all four analysed types of diabetes: type 1, type 2, monogenic and cystic fibrosis (CF)-related diabetes (CFRD). A p value lower than 0.05 was considered statistically significant.

Results

Throughout the study period the number of children with diabetes in the studied voivodeships (major administrative regions of Poland) increased from 2,008 to 2,568, whereas the total number of children decreased linearly, resulting in a net reduction of more than 200,000 (ESM Table 1). During the period of analysis, 1,351 individuals from 597 families were referred for genetic tests from 28 hospitals and clinics throughout the entire country. Of that number, 311 children (23.01%) from 238 families originated from the three voivodeships, with the largest number of referrals and complete epidemiological data for type 1 diabetes. Children were referred for genetic testing on a suspicion of: *GCK*-MODY (n=259) (involving the gene encoding glucokinase [GCK]), *HNF1A/HNF4A*-MODY (n=28) and *HNF1B*-MODY (n=4) (involving genes encoding hepatocyte nuclear factor [HNF]), neonatal diabetes due to *KCNJ11*, *ABCC8*, *GCK* or *INS* mutations (n=15), Wolfram syndrome (n=3), Alström syndrome (n=1) or an unspecified syndrome of neonatal diabetes with congenital heart defect and cytogenetic abnormalities (n=1). A pathogenic mutation was confirmed in 100 cases (details on the accuracy of specific genetic diagnoses are presented in ESM Results). The overall accuracy of clinical diagnosis, defined as the percentage of positive genetic confirmations of suspected MD, was 32.15% (range 25.55–44.00%). The number of children referred to genetic studies showed a steady, linear increase throughout the study period (Pearson's r=0.893; p=0.017), but the percentage of positive genetic tests decreased with the number of referred patients (Fig. 1a). The group of patients with positively confirmed MD was greater than those with newly diagnosed type 2 diabetes or CFRD (Fig. 1b and Table 1). Prevalence calculations confirmed earlier findings of an increase in the number of patients with type 1 diabetes. The prevalence of type 2 diabetes increased from 0.3/100,000 to 1.0/100,000 children—these values were, respectively, 13.9 and 4.3 times lower than the prevalence of MD in the study group, which equalled 4.2–4.6/100,000 children. The final prevalence of neonatal diabetes due to *KCNJ11* or *ABCC8* mutations was 1/300,000–400,000 children, yielding a number similar to an earlier collaborative epidemiological report [8].

Discussion

Results of the current study confirm our clinical observations that MD is a much more common phenomenon than paediatric type 2 diabetes in settings with low frequencies of obesity. We observed that the prevalence of MD differed considerably from earlier reports, probably because of protocol differences and unrestricted access to genetic studies

Table 1 Number of new diagnoses of type 2 diabetes, CFRD and MD made in the study centres during the analysed period

Variable	Lodz (Lodzkie voivodeship)	Katowice (Slaskie voivodeship)	Gdansk (Pomorskie voivodeship)	Overall
Number of new type 2 diabetes diagnoses	3	8	14	25
Number of new CFRD diagnoses	4	10	4	15
Number of MD diagnoses				
MODY	26	35	29	90
GCK	25	32	27	84
HNF1A/4A	1	3	0	4
Other	0	0	2	2
Neonatal diabetes	3	1	3	7
WFS and ALMS	2 and 1	0	0	3
Median delay between diagnosis of diabetes and genetic testing (25–75%) (years)	1.27 (0.21–4.65)	0.80 (0.16–1.64)	0.73 (0.22–2.39)	0.84 (0.19–2.70)
Median age of patients with MD at genetic examination (25–75%) (years)	10.10 (3.12–16.21)	10.86 (7.33–17.55)	13.79 (6.21–16.89)	11.05 (6.65–16.56)

Duration of the delay between the diagnosis of diabetes and referral for genetic tests did not differ between study centres, probands or siblings, nor between patients with positive and negative genetic test results, and was not correlated with the year of the study (all p values >0.2 in Mann–Whitney U test)

ALMS, Alström syndrome; WFS, Wolfram syndrome

provided by our project. Understandably, if such access is not readily available, the discrepancy between observed and actual prevalence is vast. A good example is a recent surveillance study in Canada, which showed a prevalence of type 2 diabetes similar to that in our study (1.5/100,000 children) but differed considerably in that of MD, by reporting a value 20 times lower than in our population (0.2/100,000 children) [2]. Studies focused on adult patients unequivocally show that *HNF1A/HNF4A*-MODY is two to four times more frequent than *GCK*-MODY, which is more prevalent in children and adolescents [3, 9]. This discrepancy results from a difference between the stable clinical course of *GCK*-MODY and progressive loss of beta cell function in MODY types caused by mutations in transcription factor genes [10]. Moreover, the delay between onset of diabetes and genetic confirmation was probably shorter than in the adult population, further contributing to the over-representation of *GCK*-MODY (Table 1). However, if one considers that *GCK*-MODY constitutes a proportion of MODY convergent with studies on adults (~20–50% [7]), then the prevalence of genetic defects causative for MD in the whole Polish population would ultimately exceed 1 in 10,000, which agrees with the estimate by Shields et al (108/1,000,000) [3]. As referral of patients to genetic tests for MD is generally based on clinical grounds, the apparent non-linear relationship between the number of referrals and percentage of subsequent genetic confirmations of the clinical diagnosis suggests that children with the highest probability of MD were referred initially, followed by those with a less clear-cut phenotype. Obviously, this does not undermine the importance of searching for children with unusual clinical presentations of diabetes, but it does show a high potential for other, yet undefined genetic defects, which we were unable to detect using available methods.

The rise in prevalence of CFRD observed over the study period could be a result of improved care of children with CF, increased awareness of its diabetogenic potential (more frequent OGTT) and reduced mortality [11]. Unfortunately, because of the lack of centralised or region-specific databases of children with CF, we were unable to provide detailed prevalence and annual incidence characteristics for CFRD with regard to the whole group of children with CF.

Throughout the whole study period MD was more frequent than both type 2 diabetes and CFRD. The prevalence of type 2 diabetes was lower than that reported in countries with higher rates of overweight and obesity [1, 2]. In the Polish population, epidemiological reports on the matter estimate that between 1.9% and 5.0% of children meet the criteria for childhood obesity [6]. The prevalences of MODY and type 2 diabetes in German children were reported to be almost equal [1]. However, as obesity in German children was 1.7 times more prevalent than in Poland [6], it may have been a major driving factor altering the MODY/type 2 diabetes ratio in the paediatric population. One might, however, suspect that the prevalence of type 2 diabetes was underestimated because of the fluid distinction between type 1 and type 2 diabetes, coupled with an increasing rate of childhood obesity. Surprisingly, despite the fact that 20% of patients from the Lodz centre underwent examination using hyperinsulinaemic–euglycaemic clamp testing to measure insulin resistance, the observed number of cases with type 2 diabetes was the lowest among the three centres. This may result from regional discrepancies but also from an over-representation of type 2 diabetes in children without access to more sophisticated examination procedures that would allow the diabetologist to rule out the insulin resistance component in a patient with an ambiguous diagnosis.

Conclusions

The prevalence of MD in a paediatric population with a low prevalence of obesity is nearly fivefold higher than those of type 2 diabetes and CFRD, justifying a need for increased access to genetic diagnostic procedures in diabetic children.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement WF compiled the epidemiologic and genetic data, performed statistical analysis and wrote the manuscript; MB performed all critical laboratory studies and revised the manuscript; AB-J, ASz, ES-Z, GD, PJ-Ch, IT, JB-M, MM and IP collected and verified the clinical data in the study centres and revised the manuscript drafts; AZ provided clinical data on Wolfram and Alström syndromes on behalf of the EURO-WABB consortium and revised the manuscript drafts; MTM provided data on patients with neonatal diabetes and revised the discussion; WM coordinated genetic and clinical data collection, verified the statistical analysis and wrote the manuscript. All authors approved the final version.

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