Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Clinical and genetic features of Argentinian children with diabetes-onset before 12 months of age: Successful transfer from insulin to oral sulfonylurea

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ARTICLE INFO

Article history:
Received 17 October 2015
Received in revised form
7 March 2016
Accepted 18 April 2016
Available online 26 April 2016

Keywords:
Genetics
Neonatal diabetes mellitus
Personalized Medicine
Pharmacogenetics

ABSTRACT

Aims: Neonatal diabetes mellitus (NDM) is a rare monogenic disorder, reported to affect less than 2 cases per 100,000 infants. There are two types, permanent (PNDM) and transient (TNDM). We describe our clinical experience in determining and comparing the genetic basis of diabetes in children with onset before 6 months versus those diagnosed between 6 and 12 months of age.

Methods: We reviewed medical records of children with diabetes diagnosed before 12 months of age. Genetic testing was performed in all cases.

Results: 12 patients were diagnosed with diabetes before 6 months of age (PNDM = 6; TNDM = 6), and 11 patients between 6 and 12 months (all with permanent diabetes). Among children with PNDM, we identified three different *KCNJ11* mutations in 5 patients, and one novel *ABCC8* mutation in a single patient. Among children with TNDM, we detected a *KCNJ11* and *ABCC8* mutation each in a single patient and methylation abnormalities at chromosome 6q24 in 4 patients.

Among children with diabetes diagnosed between 6 and 12 months, 1 patient had an *INS* mutation and one patient was homozygous for an *SLC19A2* mutation which confirmed a diagnosis of thiamine-responsive megaloblastic anaemia syndrome. Five of the patients with an *ABCC8* or *KCNJ11* mutation have successfully transferred from insulin to glibenclamide whist 1 child demonstrated a partial response to sulfonylurea treatment.

Conclusions: Investigating the underlying genetic basis of diabetes in children with onset before 1 year is useful for choosing the most efficient treatment, the basis of Personalized Medicine.

Abbreviations: NDM, neonatal diabetes mellitus; PNDM, permanent neonatal diabetes mellitus; TNDM, transient neonatal diabetes mellitus; UPD6, paternal isodisomy of chromosome 6.

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http://dx.doi.org/10.1016/j.diabres.2016.04.005
0168-8227/

1. Introduction

Neonatal diabetes mellitus (NDM) is a rare monogenic disorder, with an incidence of less than 2 cases per 100,000 infants [1,2]. In countries such as Turkey and Saudi Arabia where consanguineous unions are common there is an increased incidence of NDM (~1:30,000 live births), a likely reflection of an increase burden of recessively inherited disease in these populations [3,4]. NDM is diagnosed in most individuals within the first 6 months of life with the majority of cases resulting from a nonautoimmune aetiology with low or undetectable C-peptide and low birth-weight.

Two distinct types of NDM have been recognized, transient (TNDM) and permanent (PNDM). Most cases of NDM result in impaired beta-cell function rather than insulin action. Among patients with TNDM, remission of hyperglycemia usually occurs within 3–6 months from diagnosis but will relapse in around 50% of these individuals during adolescence or early adulthood [5].

The most frequent cause of TNDM is genetic and epigenetic defects at the imprinted region on chromosome 6q24 (71% of cases). These include paternal uniparental isodisomy (UPD6), paternal duplication and loss of maternal methylation [5]. Other important causes of TNDM are mutations in the *KCNJ11* (13%) and *ABCC8* (10%) [5–7] genes which encode the two subunits of the β-cell ATP-sensitive potassium (K_{ATP}) channel. Mutations in 22 different genes are known to cause PNDM with heterozygous mutations in *KCNJ11*, *ABCC8* and *INS* occurring most frequently [8].

While the vast majority of NDM cases are diagnosed in the first 6 months of life, diabetes can sometimes present in individuals between the ages of 6 and 12 months. Indeed, monogenic DM is the second most common cause of diabetes, after type 1 diabetes, within this age group. For this reason some authors have suggested to move the threshold for genetic testing to 9 months [9,10].

The current scientific knowledge of NDM and other monogenic forms of diabetes, has led to the birth of the *Personalized Diabetology*, thus allowing for optimal therapeutic choice in selected patients, and thereby improving quality of life [7,11,12]. As few reports exist on NDM from Latin American countries, the aim of our study was to explore among Argentinian children the impact of genetic testing for NDM on *Personalized Diabetology*, and to compare the genetic basis of DM in children according to the age of onset (before 6 months versus between 6 and 12 months of age).

2. Material and methods

2.1. Patients

We reviewed medical records of 23 children (9 girls and 14 boys) born between 1996 and 2012 with diabetes-onset before 12 months of age referred to the Unit of Nutrition and Diabetes of the Children's General Hospital "Dr. Pedro de Elizalde" in Buenos Aires, Argentina. The patients were recruited on a voluntary basis, and their parents were contacted and invited to take part in the genetic study by phone and mail. Consanguinity was not reported in any family. The current diagnostic threshold of diabetes within the first 6 months of life for NDM is highly specific, clearly identifying almost all cases of monogenic origin. Nevertheless, patients with diabetes carrying mutations in NDM genes (especially *KCNJ11*, *ABCC8* and *INS*) can present with diabetes later [9,10,13–15], even in the age range typically seen in the so-called Maturity Onset Diabetes of the Young. For this reason we included in our study patients who presented with diabetes diagnosed within the first 12 months of life.

The DEND syndrome was defined as PNDM, developmental delay (mental retardation, impaired motor development, muscle weakness and/or hypotonia) and early-onset epilepsy (<12 months), while the intermediate DEND (iDEND) as PNDM with milder developmental delay (language delay and dyspraxia, mainly) and without epilepsy in the first 12 months of life [16]. Clinical and genetics characteristics of patients were obtained from medical records (Tables 1–3).

Ethical approval

The study was approved by the Ethics Committee of our hospital, and informed consent was obtained from all parents.

3.1. DNA analyses

Genomic DNA from patients and their parents was extracted from EDTA-stabilized peripheral leukocytes using a commercial kit (Wizard Genomic DNA Purification kit, Promega, Madison, WI). DNA was sent to the University of Exeter Medical School Molecular Genetics Laboratory, UK for *ABCC8*, *KCNJ11*, *INS* and *SLC19A2* sequence analysis as previously described [6,17,18]. Studies to investigate methylation status at chromosome 6q24 were performed at Wessex Regional Genetics Laboratory, Salisbury, UK, using previously described methods [19].

3.2. Transfer from insulin therapy to glibenclamide

Transition from insulin therapy to glibenclamide was undertaken according to a previously reported transfer protocol from the University of Exeter Medical School, UK (www.diabetesgenes.org/content/transferring-patients-diabetes-due-kir62-mutation-insulin-sulphonylureas), with advice kindly provided by Prof. Andrew T. Hattersley [12], either during patient admission to the Children's General Hospital "Dr. Pedro de Elizalde" at Buenos Aires, Argentina, or through close communication with the outpatient's parents. Glycemic control and beta-cell function were evaluated, respectively, with HbA1c (Siemens DCA 2000 Systems Hemoglobin A1c Reagent Kit) and fasting C-peptide (Immulite 2000 C-peptide Assay, Siemens) measurements, before and 3 months after transfer to glibenclamide, in order to evaluate its efficacy.

3.3. Statistical analysis

Quantitative data is given as mean values ± standard deviations (SD) and range, where appropriate. We used Wilcoxon test to compare HbA1c and C-peptide levels before and after transition from insulin to glibenclamide in patients with