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Permanent Neonatal Diabetes Mellitus: Prevalence and Genetic Diagnosis in the SEARCH for Diabetes in Youth Study

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Abstract

Background—Neonatal diabetes mellitus (NDM) is defined as diabetes with onset before 6 months of age. Nearly half of individuals with NDM are affected by permanent neonatal diabetes mellitus (PNDM). Mutations in KATP channel genes (*KCNJ11*, *ABCC8*) and the insulin gene (*INS*) are the most common causes of PNDM.

Objective—To estimate the prevalence of PNDM among SEARCH for Diabetes in Youth (SEARCH) study participants (2001-2008) and to identify the genetic mutations causing PNDM.

Methods—SEARCH is a multi-center population-based study of diabetes in youth < 20 years of age. Participants diagnosed with diabetes before 6 months of age were invited for genetic testing for mutations in the *KCNJ11*, *ABCC8* and *INS* genes.

Results—Of the 15,829 SEARCH participants with diabetes, 39 were diagnosed before 6 months of age. Thirty five of them had PNDM (0.22% of all diabetes cases in SEARCH), 3 had transient neonatal diabetes that had remitted by 18 months and one was unknown. The majority of them (66.7%) had a clinical diagnosis of type 1 diabetes by their health care provider. Population

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prevalence of PNDM in youth <20 years was estimated at 1 in 252,000. Seven participants underwent genetic testing; mutations causing PNDM were identified in five (71%), (two *KCNJ11*, three *INS*).

Conclusions—We report the first population-based frequency of PNDM in the US based on the frequency of PNDM in SEARCH. Patients with NDM are often misclassified as having type 1 diabetes. Widespread education is essential to encourage appropriate genetic testing and treatment of NDM.

Keywords

neonatal diabetes; *KCNJ11*; *INS*; *ABCC8*; infant

Introduction

Neonatal diabetes mellitus (NDM) is defined as diabetes with onset before 6 months of age (1). The population frequency of NDM has been estimated at 1 in 300,000 to 1 in 400,000 (2), although more recent reviews have estimated a higher frequency, at 1 in 90,000 (3). Many of these cases are transient but nearly half of them develop permanent neonatal diabetes mellitus (PNDM) (4).

Autoimmune diabetes is rare before 6 months of age (5, 6). PNDM is a monogenic form of diabetes that predominantly occurs before 6 months, largely determined by genetic mutations that affect beta-cell number, survival or function (7). Activating mutations in genes encoding the KATP channel of the beta-cell, *KCNJ11* (encoding the Kir6.2 subunit) and *ABCC8* (encoding the SUR1 subunit), alter the KATP channel function by reducing its sensitivity to ATP, causing hyperpolarization of the beta-cell and impaired insulin secretion, resulting in PNDM (8, 9). Additionally, mutations in the insulin gene (*INS*) affect the folding of peptide precursors resulting in endoplasmic reticulum stress and beta-cell apoptosis (10). Mutations in the *KCNJ11*, *INS*, and *ABCC8* genes account for the majority (60%) of patients with PNDM (11). Other rare genetic determinants of PNDM include mutations in genes that encode transcription factors such as *EIF2AK3*, *FOXP3*, *IPF-1*, *HNF1B*, *GLIS 3* and *PTF1A* (7, 11). Homozygous mutations in the *GCK* gene are also a rare cause of PNDM (12).

Patients with PNDM due to KATP channel mutations often respond to sulfonylurea therapy and have been transitioned successfully from insulin to oral sulfonylureas with improvement in glycemic control (13, 14). Treatment with sulfonylureas, acting through closure of KATP channels in the neurons, has also been shown to improve neurologic symptoms in patients with developmental delay, epilepsy and neonatal diabetes (DEND) phenotype. Neurological symptoms due to KATP channel mutations have been observed in up to 20% of PNDM cases, and there is evidence to suggest that early sulfonylurea therapy may prevent or delay the onset of these symptoms (15-17).

The treatment strategy in patients with PNDM due to KATP mutations is significantly different than that for children with autoimmune diabetes. Thus it is important that clinicians

recognize the genetic basis of PNDM. We describe the frequency of NDM in the SEARCH for Diabetes in Youth study.

Methods

Study Design

SEARCH for Diabetes in Youth (SEARCH) is a multi-center study conducting population-based ascertainment of cases of non-gestational diabetes in youth aged 0-19 years with the goal of identifying all prevalent cases in 2001 and all incident cases in subsequent calendar years. A detailed description of SEARCH methodology has been published elsewhere (18). SEARCH collected data from 4 geographically defined populations in Ohio, Washington, South Carolina and Colorado and among health plan enrollees in Hawaii and California. Cases were validated on the basis of physician reports and medical record review. The diabetes 'type' was assigned by the health care provider and recorded as part of the case validation process. Completeness of case ascertainment was assessed for the 4 geographic centers using the capture-recapture method and a 2-mode ascertainment model (19, 20). Using a protocol that conformed to the Health Insurance Portability and Accountability Act of 1996 (HIPAA), youth with diabetes (or their parents/guardians if <18 years) were asked to complete a brief survey that asked for their age at diagnosis, race/ethnicity, and a limited health history. Those who completed the survey were invited to participate in a SEARCH study visit at which written informed assent and/or consent were obtained according to the guidelines established by the local institutional review board (IRB) from participants 18 years of age and participants and their parents/guardians for participants < 18 years of age. The consent process included an option to have a DNA sample stored for future genetic testing. At the study visit, additional clinical information was collected including symptoms at presentation, family history of diabetes, and medication use. A physical examination was performed and participants had blood drawn for laboratory testing, including measurement of the diabetes autoantibodies [glutamic acid decarboxylase 65 (GAD65) and insulinoma-associated- 2 (IA2)], glycosylated hemoglobin (A1c) and fasting C-peptide. DNA was extracted from peripheral leukocytes and stored for genetic studies. For participants with identified genetic mutations causing PNDM, additional information was obtained on treatment regimen and glycemic control before and after a monogenic etiology for their diabetes was identified.

Participants

All SEARCH participants with a diagnosis of diabetes before 6 months of age from the 2001 prevalence cohort and 2002-2008 incidence cohorts were eligible for genetic testing. For eligible participants who had participated in a SEARCH study visit, DNA samples had already been collected and stored if the participant/parent had consented for future DNA studies. We attempted to contact eligible participants who did not have a DNA sample in storage, as well as those who had previously refused to participate in a SEARCH study visit (when permitted by the local IRB), to ask if they would be willing to come in for a visit to provide a DNA sample for testing for PNDM. Informed consent and blood sample was obtained from those who agreed. Testing was performed for *KCNJ11*, *ABCC8* and *INS* mutations in that order. Participants in whom genetic mutations were identified were invited

to undergo confirmatory testing using standard clinical procedures. Outcomes for those whom the genetic diagnosis dictated a treatment change were abstracted by chart review. Since the case finding methodology in SEARCH is likely to have missed cases of transient neonatal diabetes (TNDM), any participant whose diabetes had remitted by 18 months of age was reclassified as TNDM for the purpose of the analysis in this paper.

Laboratory methods

Samples were analyzed for GAD65 and IA2 antibodies using a standardized protocol (21). Fasting C-peptide was measured by a two-site immunoenzymetric assay (TOSOH 1800, TOSOH Bioscience Inc., San Francisco, CA). Glycated hemoglobin (A1c) was measured by a dedicated ion exchange high-performance liquid chromatography instrument (TOSOH G7, TOSOH Bioscience Inc., San Francisco, CA). HLA class II genotyping (HLA DRB1 and DQB1) was performed with a PCR-based sequence-specific oligonucleotide probe system in the laboratories of Drs. L. Gaur (Genomic Research Laboratory, Puget Sound Blood Center, Seattle, WA) and H. Erlich (Roche Molecular Systems, Pleasanton, CA). Blood samples were processed locally and shipped within 24 hours to the central laboratory (Northwest Lipid Metabolism and Diabetes Research Laboratories, Seattle, WA), where they were analyzed.

Mutation Analysis

Genomic DNA was extracted from peripheral leukocytes using standard procedures. Standard PCR and sequencing techniques were used to amplify the coding sequences of the *KCNJ11* (NM 000525), *ABCC8* (NM 000352 which incorporates the alternatively spliced residue in exon 17; L78208, L78224) and *INS* (NM 000207) genes and Mutation Surveyor v.3.98 software was used for mutation detection. Identified variants were checked against known polymorphisms and mutations (22), published mutations (HGMD) and variant databases (dbSNP132 and 1000 genomes) Molecular analysis was undertaken at the Molecular Genetics Laboratory, Peninsula Medical School, Royal Devon and Exeter Hospital, Exeter, United Kingdom.

Statistical Analysis

Analysis is descriptive due to small numbers of participants. The Chi-square test was used to determine if the race/ethnicity distribution of NDM (non-Hispanic white was compared to all other race/ethnicity due to small sample size) was significantly different compared with the race/ethnicity distribution in the total SEARCH population. Fischer's exact test was used to compare characteristics between participants who underwent genetic testing and participants who were unable to be genetically tested. All statistical analyses were conducted using SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Out of a total of 15829 persons registered for the SEARCH study from 2001-2008, forty were diagnosed before 6 months of age (Figure 1). One of these participants had developed diabetes secondary to pancreatectomy and was excluded. Hence frequency of NDM in SEARCH was 39/15,829 (0.25%). Three participants had recognized transient diabetes that

had remitted. Thirty five of the remaining participants had a diagnosis of NDM that had not remitted by 18 months of age, suggesting that they had PNDM, while clinical history was unknown for one participant (Figure 1). Hence frequency of PNDM in SEARCH was 35/15829 (0.22%). SEARCH estimated the prevalence of all forms of diabetes in 2001 to be 1.8 youth per 1,000. Based on these numbers, the frequency of PNDM in youth was estimated to be 1 in 252,000. The prevalence estimates were 1 in 145,000 in the 2001 prevalence cohort and 1 in 476,000 in the 2002-2008 incidence cohorts (Figure 1).

Mean age at diagnosis of NDM was 2.6 months (standard deviation: 2.6 months) and 26/39 (66.7%) had a diagnosis of type 1 diabetes assigned by their health care provider. The remainder (13/39) were assigned other (N=5) / hybrid (N=2) /type 2 diabetes (N=2) / unknown (N=2) /missing (N=2). The race/ethnicity distribution in those with NDM did not significantly differ from the non-NDM diabetes participants in SEARCH (p=0.08) (Table 1). Of the three participants with TNDM, only one was available for genetic testing, was negative for the tested genes (*KCNJ11*, *ABCC8* and *INS*) and was subsequently found to be positive for the 6q24 duplication. Seven of the remaining 36 participants were available for genetic testing and a mutation was identified in 5/7 (71%) participants (Table 2). The 2 participants, who did not have the *KCNJ11/ABCC8/INS* mutations, did not have any specific clinical features to suggest testing for other rare causes of PNDM. All the identified mutations in the 5 individuals have been previously reported except the *INS* G32C mutation which has not been previously published. All 5 of these participants had been treated with insulin since diagnosis. Diabetes autoantibodies were negative in all of those screened (4/5). HLA genotyping was available on two participants and one participant had a neutral genotype (DR 1/1), while the other had a genotype known to confer susceptibility to type 1 diabetes (DR 3/3) (T1D) (23). The latter participant was negative for both GAD65 and IA-2 autoantibodies, suggesting that this participant's diabetes was nonautoimmune in etiology. This participant's diabetes duration at the time of evaluation was >5 years, so positivity for autoantibodies could have been missed. Family history, when available, was positive for diabetes in the parents for half (2/4) of the participants with mutations. The mother of the participant with the *INS* G32C mutation had diabetes and carried the same mutation while the father of the patient with the *KCNJ11* G53D mutation was found to be a non-diabetic carrier of the mutation. Fasting C-peptide concentrations (normal range: 0.5-3 ng/mL) were low (similar to type 1 diabetes) in all participants tested, with no clear differences between *KCNJ11* and *INS* mutation carriers.

The participants with *KCNJ11* mutations were diagnosed at a younger age and had a lower birth weight compared with those with *INS* mutations. These participants were ages 8 years (Case 1) and 2 years (Case 2) at the time of genetic testing. Both participants were on approximately 0.5 units/kg/day of insulin and after genetic diagnosis, were switched to oral sulfonylurea therapy (requiring glyburide 1.5mg/kg/day and 1.3mg/kg/day respectively when insulin was discontinued). They had improved glycemic control (A1c decreased from 7.3% to 6% and 7.8% to 6.7% respectively, reference range 3.9-6.1%) when insulin was discontinued. On follow up at least one year later, both participants remained off insulin, on glyburide doses of 1.4 mg/kg/day and 0.25 mg/kg/day respectively, and had A1c values of 5.6% and 5.8% respectively.

The participant with the *KCNJ11* G53D mutation (Case 1) also had a history of hypotonia and motor developmental delay, and was diagnosed with the iDEND syndrome. Therapeutic switch to sulfonylureas was associated with some improvement in upper limb co-ordination and manual dexterity but no improvement in fine motor precision and integration in the short term. The participant's father was found to have the same mutation in 20% of his peripheral blood lymphocytes, also had a history of hyperactivity and learning difficulty, but had normal results on the oral glucose tolerance test (fasting 86 mg/dL, 2-hour 69 mg/dL). This is the first report of somatic mosaicism (and inferred germline mosaicism) in an asymptomatic parent causing iDEND syndrome in the offspring.

Discussion

We present the first population-based study to assess the frequency of PNDM in the United States. Our estimate of the frequency of PNDM (defined in our study to be diagnosis at <6 months of age with persistence beyond 18 months of age) in the US, of 1 in 252,000 in youth <20 years, is comparable to the incidence estimates from the United Kingdom, Netherlands and Poland of 1 in 260,000 (24) as well as the 1 in 214,000 estimated from the Slovakian diabetes register(25). SEARCH estimated the completeness of diabetes case ascertainment to be >96% for all the geographic sites for years 2001-2007 for diagnosis of diabetes in the 0-4 year age group. Hence the population estimates of the prevalence of PNDM in the US would be expected to be reasonable.

The major limitation of this study was the inability to obtain DNA samples to perform genetic testing, from all eligible participants. The majority of cases ascertained by SEARCH did not have in-patient visits or stored samples for DNA testing in SEARCH. Further, due to local IRB restrictions on re-contacting participants who initially refused and the inability to locate some participants many years later limited our ability to obtain genetic testing on all participants identified through SEARCH. However, the frequency of mutations identified among those tested (71%) is similar to other case series reported in the literature (26, 27). Of the 32 participants who were not available for genetic testing, 25 of them did not have an in-patient visit and 1 did not have a blood draw. The remaining 6 had an in-patient visit but either did not consent to genetic testing or the sample was insufficient for DNA testing. Also, there were no differences in age at diagnosis ($p=0.66$), race/ethnicity (non-Hispanic white vs. other, $p=0.43$), gender ($p=1$) or provider diagnosed type ($p=0.59$) between those who underwent genetic testing and those who were unavailable for testing.

TNDM was not studied systematically since the SEARCH case ascertainment design would have likely excluded several transient cases of diabetes. We did however identify 3 participants with remission of diabetes by 18 months of age, one of whom had undergone genetic testing prior to remission.

Type 1 diabetes due to autoimmunity is very rare in patients diagnosed at less than 6 months of age (5, 6). Despite this, we found that the majority of participants with NDM were classified by the providers as having type 1 diabetes (66.7%). It is possible that the misclassification occurred prior to the knowledge of NDM, since SEARCH participants identified with NDM came from the 2001-2008 cohorts, while the first *KCNJ11* mutation

causing neonatal diabetes was not reported until 2004 (8). However, it is important to recognize that among older patients who are currently being treated for type 1 diabetes, there are likely to be a small number who were diagnosed at less than 6 months of age. Many of these individuals will have KATP channel mutations causing PNDM, and they will likely be able to transition from insulin to sulfonylurea therapy. For this reason, genetic testing is indicated in all patients, regardless of their current age, if their initial onset of diabetes was prior to 6 months of age. Thus, increased awareness is essential to ensure that providers recognize the age at onset of diabetes and direct appropriate genetic testing and treatment.

Conclusions

Prevalence of permanent neonatal diabetes in the United States in youth was estimated to be 1 in 252,000 in a population-based study of diabetes. PNDM accounted for nearly 0.22% of all cases of diabetes in youth <20 years of age. The majority of participants with NDM were misclassified as having type 1 diabetes. Widespread education about the importance of genetic testing and its implication for clinical treatment is essential.

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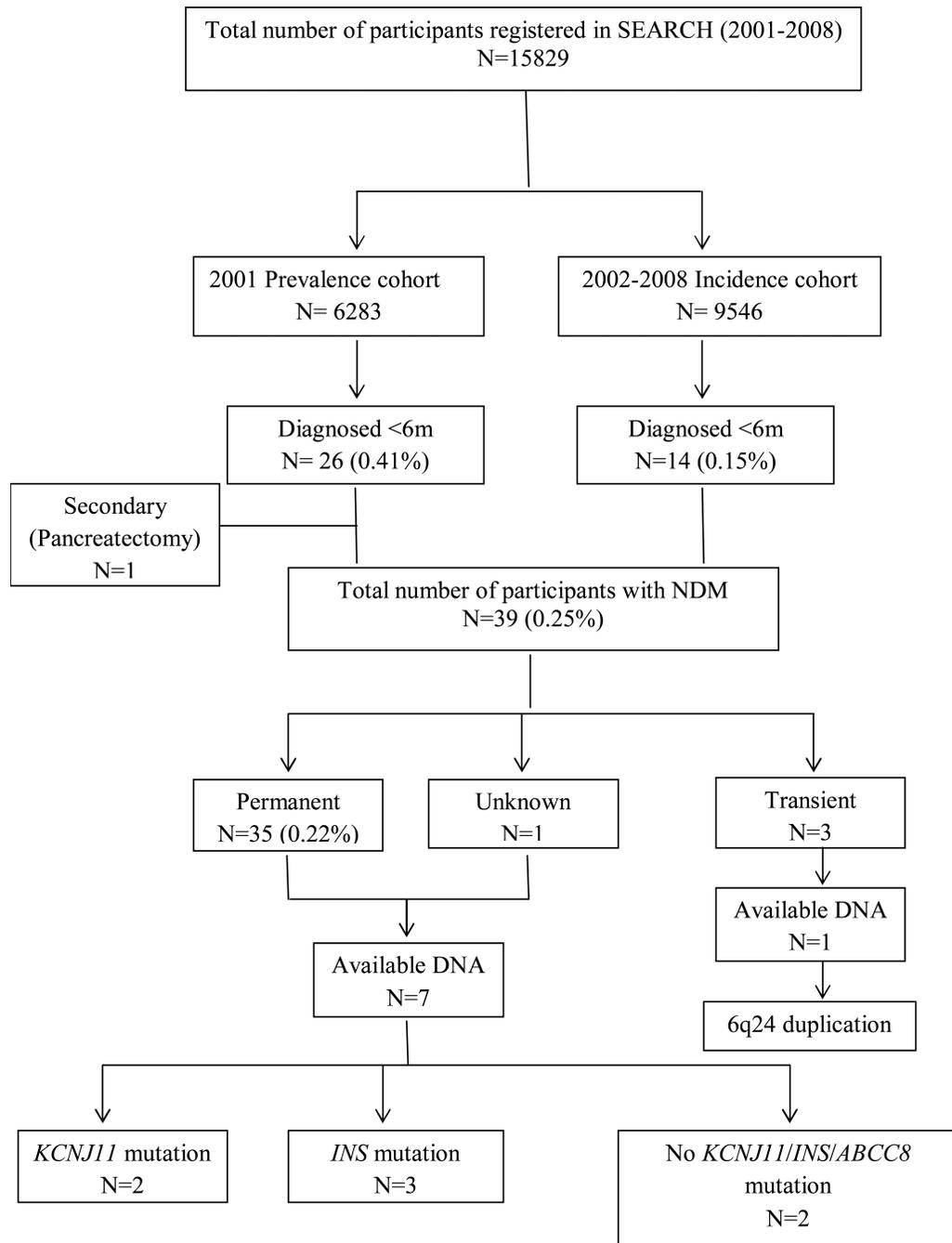


Figure 1.
Proportion of participants with Neonatal Diabetes (NDM) in SEARCH

Table I

Race/Ethnic distribution of participants with NDM compared with other participants in the SEARCH Study

Ethnicity	NDM (N=40)		SEARCH (N=15790)	
	N	%	N	%
Non-Hispanic White	18	46.3	9441	59.8
Other race/ethnicity	21	53.7	6348	40.2

P= 0.08

Table II

Characteristics of the five participants with identified genetic mutations causing PNDM.

	Case 1	Case 2	Case 3	Case 4	Case 5
Mutation	KCNJ11 G53D	KCNJ11 R201C	INS G32C	INS R89C	INS R89C
Age at diagnosis (months)	3.32	0.66	5.39	4.27	1.51
Provider diagnosis	Type 1	Other	Type 1	Type 1	Type 1
Insulin Dose (units/kg/day)	0.44	0.5	0.97	0.76	na
Birth weight (kg)	2.58	2.21	2.72	3.75	2.99
Family history of diabetes	Negative [#]	positive [*]	positive ^{**}	negative	na
HLA genotyping	na	na	DQB1*0501-DRB1*0101/DQB1*0504-DRB1*0101	DQB1*0201-DRB1*0301/DQB1*0201-DRB1*0301	na
GAD-65 antibody	negative	negative	negative	negative	na
IA-2 antibody	negative	negative	negative	negative	na
Fasting C-peptide (ng/mL) (Ref range: 0.5-3)	0.2	0.07	0.3	0.2	na
Duration diabetes (months)	24	15	129	87	na
A1c (%) (Ref range: 3.9- 6.1)	8.7	7.6	7.6	8.1	na

na = not available; Case 5 did not participate in 301 SEARCH study visit.

* Mother with gestational diabetes and maternal grandfather with Type 2 diabetes

** Mother and maternal grandfather with "Type 1" diabetes. Mother was reportedly diagnosed with diabetes at 9 days of age, treated with insulin for "type 1 diabetes" and was noted to have the same mutation as the child. Maternal grandfather was reportedly diagnosed at 3 months of age and is deceased, with no known details on treatment regimen or mutation status.

[#] Father was a non-diabetic carrier of the mutation.