Minimal incidence of neonatal/infancy onset diabetes in Italy is 1:90,000 live births

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Abstract Until early 2000, permanent and transient neonatal diabetes mellitus (NDM), defined as diabetes with onset within 6 weeks from birth that requires insulin therapy for at least 2 weeks, were considered exceedingly rare conditions, with a global incidence of 1:500,000–1:400,000 live births. The new definition of NDM recently adopted, that includes patients with diabetes onset within 6 months of age, has prompted studies that have set the incidence of the permanent form alone between 1:210,000 and 1:260,000 live births. Aim of the present work was to ascertain the incidence of NDM (i.e. permanent + transient form) in Italy for years 2005–2010. Patients referred to the Italian reference laboratory for NDM between years 2005 and 2010 and screened for mutations in common NDM genes ($KCNJ11$, $ABCC8$, and $INS$) and for uniparental isodisomy of chromosome 6 (UDP6) were reviewed. A questionnaire aimed at identifying NDM cases investigated in other laboratories was sent to 54 Italian reference centers for pediatric diabetes. Twenty-seven patients with NDM born between 2005 and 2010 were referred to the reference laboratory. In this group, a mutation of either $KCNJ11$, $ABCC8$ or $INS$ was found in 18 patients, and a case with UDP6 was identified. Questionnaires revealed 4 additional cases with transient neonatal diabetes due to UDP6. Incidence of NDM was calculated at 1:90,000 (CI: 1:63,000–1:132,000) live births. Thus, with the definition currently in use, about 6 new cases with NDM are expected to be born in Italy each year.

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Abbreviations
ISPED  Italian society for pediatric endocrinology and diabetes
MDI  Monogenic diabetes of infancy
NDM  Neonatal diabetes mellitus
TNDM  Transient neonatal diabetes mellitus
PNDM  Permanent neonatal diabetes mellitus
UPD6  Uniparental isodisomy of chromosome 6

Background

Neonatal/infancy onset diabetes mellitus (NDM) is a monogenic form of diabetes with onset within 6 months from birth. Two distinct types of NDM have been recognized: permanent (PNDM) and transient (TNDM) [1, 2]. In patients with TNDM, remission of hyperglycemia usually occurs within 3–6 months from diagnosis [1, 2]. In addition, in about 50% of individuals with TNDM, diabetes may relapse at adolescence.

Paternal isodisomy of chromosome 6 (UDP6), paternal duplication, or loss of maternal methylation of chromosome 6q24 have been reported as the most frequent causes of TNDM (>65% of cases) [1], followed by activating mutations in ABCC8 and KCNJ11 genes, which encode the two subunits of the ATP-sensitive potassium (K\textsubscript{ATP}) channel of pancreatic b-cell [1]. Differently, mutations of K\textsubscript{ATP} channel and INS genes are found in most patients with PNDM (also termed monogenic diabetes of infancy, MDI) [3, 4]. Many other genes are involved in exceedingly rare, recessive subtypes of PNDM/MDI [1, 2].

Until 2002, NDM (i.e. PNDM + TNDM) was considered very rare with an incidence of 1:400,000–1:500,000 live births [5–7]. At that time the cut-off in use to define NDM was hyperglycemia with onset within 6 postnatal weeks in patients born at term and treated with insulin for at least 2 weeks [5]. In 2002, a study from our group suggested that patients with diabetes onset in the first 6 months of life do not show the typical laboratory features of type 1 diabetes [8]. The subsequent discovery of activating mutations of KCNJ11 gene in individuals with diabetes onset within 6 months from birth confirmed those findings [9, 10]. Recently, the incidence of the permanent form alone has been calculated between 1:210,000 live births of Italy and Slovakia [3, 11] and 1:260,000 of other European countries [12]. These higher incidence rates can be attributed to the adoption of the new limit of 6 months of age for diagnosing neonatal/infancy onset diabetes and are not comparable to the increased incidence observed for type 1 diabetes, even of very early onset (i.e. 0–4 years) [13].

With the present study, we wanted to assess the minimal incidence of NDM (i.e. PNDM/MDI + TNDM) in Italy of a 6-year period (2005–2010).

Research design and methods

We reviewed cases with NDM born between 2005 and 2010 and referred to the laboratory of Mendelian Diabetes in Rome, the reference laboratory for NDM of the Italian Society of Pediatric Endocrinology and Diabetology (ISPED). From this database, we included only cases with the following features: (1) diabetes onset within 6 months from birth and (2) hyperglycemia treated with insulin for at least 2 weeks. Two exceptions were represented by cases positive to the molecular genetic screening, but with insulin therapy of shorter duration (10 and 12 days, respectively). In addition, to ascertain whether any patient with NDM could have been referred to other laboratories, we sent a questionnaire to 54 pediatric diabetes clinics that are the referral centers for the diagnosis and treatment of diabetes in childhood in Italy. These 54 clinics are scattered throughout the country and provide a rather complete coverage. Cases identified through the questionnaire whose medical records could not be revised were not included in the study.

Incidence rates per 100,000 live births were computed combining cases from the laboratory of Mendelian diabetes and from the questionnaire.

Results

Twenty-seven cases (16 with PNDM/MDI and 11 with TNDM) born between 2005 and 2010 and referred to the laboratory of Mendelian Diabetes matched the clinical criteria we used to define NDM. In patients with NDM, we identified a causative mutation in 11 cases with permanent diabetes (7 KCNJ11 and 4 INS) (3,4; and the frequent KCNJ11/R201H mutation in a patient born in September 2010) and 7 with transient diabetes (mutations: ABCC8/S459R, ABCC8/R1380C, ABCC8/V1523M, KCNJ11/R50Q (twice), KCNJ11/E229K, and 1 case with UDP6). Transient neonatal diabetes mutations KCNJ11/R50H, KCNJ11/E229K, and ABCC8/R1380C have been previously reported [14], while ABCC8 mutations in same residue as ours, but with different amino acid change such as V1523A/L have been described associated with permanent
neonatal diabetes [14]. Mutation ABCC8/S459R appears to be novel.

Fifty centers out of 54 replied to the questionnaire (92%). Data collected revealed that 4 additional patients born between 2005 and 2010 and unknown to us had received a diagnosis TNDM; defects of chromosome 6 were identified in all of them. In two of the latter cases, insulin therapy duration was 10 and 12 days, respectively.

Minimal incidence of NDM (i.e. PNDM/MDI + TNDM) in Italy for years 2005–2010 was calculated at 1:90,000 (CI: 1:63,000–1:132,000).

Discussion/conclusions

Cases with the transient form of neonatal/infancy onset diabetes mellitus may be lost at follow-up, during the period of remission, while cases with the permanent form are obviously less prone to this problem. For this reason, we decided to investigate, to the purpose of epidemiological assessment, a period of time reasonably long, but also as close as possible to the present days and posterior to the discovery of the main gene causing NDM, i.e. KCNJ11 [9]. In addition, we also distributed a questionnaire for data collection to all Italian clinics for pediatric diabetes, in order to identify cases with NDM that could have not been referred to the reference laboratory in Rome. Questionnaire’s results showed that this was in fact the case and four patients with TNDM born between 2005 and 2010 had been diagnosed with UDP6 in other laboratories. Nevertheless, in patients with transient diabetes, we observed—in contrast with the literature [1]—a higher prevalence of $K_{\text{ATP}}$ mutations compared to defects of chromosome 6 ($K_{\text{ATP}} = 6/15$ vs. UDP6 = 5/15). Therefore, it is still possible that we could have missed some TNDM cases associated with UDP6, maybe referred to the 4 centers that have not sent back the questionnaire. In addition, the short duration of insulin therapy observed in two cases with UDP6 should alert about the thin line separating “true” cases with transient neonatal diabetes (i.e. cases by definition treated with insulin for at least 2 weeks) from patients with mild hyperglycemia due to other genetic causes and treated with insulin for short period [15].

A similar incidence of NDM of 1:89,000 has been recently reported from Germany [16]. However, though incidence rates were almost identical, we noticed three major differences with our study: (1) patients with TNDM represented only 10% of the total, (2) type 1 diabetes autoantibodies were present in seven patients with permanent diabetes, and (3) a mutation was found in only 30% of cases. In our study, patients with PNDM and TNDM accounted for about 50% of cases each, a mutation was found in 74% of patients (23/31), and all cases were negative for type 1 autoantibodies. We can not offer at this time any explanation for all the discrepancies observed between the two studies.

In conclusion, the present study and our previous results [3] indicate that a genetic diagnosis can be reached in most patients with NDM and confirms robustness to our epidemiological data. At an incidence rate of 1:90,000 live births, about six individuals presenting with neonatal diabetes are expected to be born in Italy each year.

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