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Increased prevalence of Down's syndrome in individuals with type 1 diabetes in Denmark: a nationwide population-based study

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Abstract *Aims/hypothesis:* In patients with Down's syndrome, dogma has long held that the prevalence of diabetes is increased. The aim of the present study was to determine the actual prevalence of Down's syndrome among type 1 diabetic patients. *Subjects, materials and methods:* The background population included all children born in Denmark between 1981 and 2000. Registry-validated and clinical data on type 1 diabetes and Down's syndrome diagnoses were obtained from the National Disease Register and Danish Cytogenetic Central Register, respectively. *Results:* The prevalence of Down's syndrome in the background population was 0.09%, whereas we identified a prevalence of Down's syndrome in type 1 diabetes patients of 0.38% (95% CI 0.17–0.75), corresponding to a 4.2-fold increased prevalence compared with the background population ($p=7.3\times 10^{-5}$). *Conclusions/interpretation:* To the best of our knowledge this is the first population-based study addressing the prevalence of Down's syndrome among verified type 1 diabetes patients. A more than fourfold increased prevalence of Down's syndrome among type 1 diabetes patients supports the notion that genes on chromosome 21 may confer risk for type 1 diabetes, probably also in the general population.

Keywords Chromosome 21 · Down's syndrome · Population-based · Prevalence · Type 1 diabetes

Introduction

Down's syndrome (trisomy 21) (MIM 190685) is characterised by mental retardation, well-defined dysmorphic features and increased prevalence of a number of autoim-

mune diseases [1]. Increased prevalence of diabetes in Down's syndrome is an established dogma that is described in textbooks [2] and is mainly based on observations from two 30-year-old studies [3, 4]. An earlier peak age of onset of diabetes has also been suggested previously [5]. However, the prevalence of Down's syndrome among type 1 diabetes patients has never been determined. The previous reports were not population-based, and were biased in that they originated from selected hospitals, were based on questionnaires with low reply-rates, and in addition did not distinguish between type 1 and type 2 diabetes. Denmark, with its complete disease registries, provides a unique opportunity for population-based studies like the current one. The aim of the present study was to determine the prevalence of Down's syndrome in type 1 diabetes.

Subjects, materials and methods

The background population included all children born in Denmark in 1981–2000. Numbers were obtained from 'Denmark's Statistics' (<http://www.statistikbanken.dk>). All individuals in Denmark have a unique social security number. From the Danish National Disease Register we obtained information on all cases of type 1 diabetes diagnosed among the 1,230,933 individuals born in 1981–2000. Data on type 1 diabetes diagnoses were validated through an independent database of childhood diabetes in Denmark (Danish Study group for Childhood Diabetes), in which information is collected from all (~99%) newly diagnosed type 1 diabetes individuals and their families. In Denmark, seven laboratories perform postnatal karyotyping, and the Danish Cytogenetic Central Register (<http://www.auh.dk/dccr>), founded in 1968, collects information on constitutional chromosomal abnormalities throughout Denmark, including statistics regarding number of individuals with Down's syndrome born each year. From all counties in Denmark, information about karyotypes and social security numbers is provided to the Danish Cytogenetic Central Register. However, in the county of Funen,

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from 1996 onwards, this information has been collected in a local registry. The registries are believed to be 100% complete, since karyotyping is usually performed at birth or later in life, whenever trisomy 21 or other chromosomal abnormalities are suspected. We cannot, however, completely rule out the possibility that some parents may have refused karyotyping of their child, but we believe it is unlikely, and that it confers no bias to the result, since the chances of such a child also developing type 1 diabetes are highly unlikely. Prevalences were compared using χ^2 statistics with a Yates correction. HLA was analysed on whole-genome amplified DNA extracted from dried blood spot samples (Guthrie cards). The *DQB1* genotyping assay was based on time-resolved fluorometry [6]; classification of alleles as conferring risk or protection are based on [7]. The study was approved by the local ethics committee as well as The Danish Data Protection Agency <http://www.datatilsynet.dk>, and the data are stored and handled in accordance with their guidelines. Furthermore the scientific board of the Danish Cytogenetic Central Register approved the project.

Results

The number of births in Denmark in 1981–2000 was 1,230,933. Based on this background population, we obtained registry-validated data about current diabetes status. A total of 2,094 had been diagnosed with type 1 diabetes by 1 May 2003. This corresponds to a prevalence of type 1 diabetes in this population of 2,094/1,230,933, i.e. 0.17% (95% CI 0.16–0.18%). From 1981–2000, the number of individuals with Down's syndrome registered was 1,151, corresponding to a prevalence of Down's syndrome of 1,151/1,230,933, i.e. 0.09% (95% CI 0.09–

0.10%). Unique social security numbers of the 2,094 type 1 diabetes cases were used to search the Danish Cytogenetic Central Register as well as the Funen register (from 1996) for individuals being registered here. Eight out of the 2,094 type 1 diabetes cases were identified as trisomic for chromosome 21 (Down's syndrome). Type 1 diabetes diagnosis was confirmed by medical records, summarised in Table 1.

We demonstrate a prevalence of Down's syndrome in type 1 diabetes of 8/2,094, i.e. 0.38% (95% CI 0.17–0.75%), in comparison with a prevalence of Down's syndrome in the background population, born in 1981–2000, of 0.09%, which corresponds to a 4.2-fold increased prevalence of Down's syndrome in type 1 diabetes ($p=7.3 \times 10^{-5}$). Among Down's syndrome patients this is equivalent to a prevalence of type 1 diabetes of 8/1,151, i.e. 0.7% (95% CI 0.3–1.36%), which is also more than fourfold higher than the type 1 diabetes prevalence in the background population (0.7% compared with 0.17%). In addition we observed an odds ratio of 4.12 (95% CI 2.1–8.2) for type 1 diabetes in the Down's syndrome group vs the non-Down's syndrome group. The median age at onset for type 1 diabetes in the eight trisomy 21 individuals was 6 years (range 0–13 years), whereas the median age at onset of type 1 diabetes in the background population of individuals born in 1981–2000 was 8 years (range 0–17 years) ($p=0.33$). HLA-*DQB1* genotyping was possible for six of eight identified Down's syndrome individuals with type 1 diabetes (Table 1). Of the four individuals carrying HLA risk alleles, one carried two risk alleles (302/0201), whereas the other three only carried one risk allele (302 or 0201) in combination with a neutral allele. One individual carried only neutral alleles, whereas the last one carried at least one allele normally considered dominantly protective (602 or 603).

Table 1 Clinical characteristics and HLA-*DQB1* genotypes for eight individuals with Down's syndrome and type 1 diabetes: information from medical records

No.	Age at onset	Insulin treated	DKA	Glucose (mmol/l)	Bicarbonate (mmol/l)	Autoantibodies	Other autoimmune diseases	Continuous insulin treatment since onset	HLA- <i>DQB1</i> genotype
1	5 years	Yes	Yes	NA	14	Not measured	None known	Yes	602/603/604/X ^a
2	7 months	Yes	Yes	74	17	Not measured	None known	Yes	0201/X
3	13 years	Yes	No	27.3	26	Not measured	None known	Yes	X/X
4	1 year	Yes	Yes	NA	18	Not measured	Coeliac+ hypothyroidism	Yes	302/0201
5	12 years	Yes	No	19	24	GAD65 positive, ICA negative	Hypothyroidism	Yes	302/604
6	11 years	Yes	Yes	NA	7	Not measured	None known	Yes	Not typed
7	7 years	Yes	No	NA	25	Not measured	Coeliac disease	Yes	Not typed
8	1 Year	Yes	Yes	96	15	Not measured	None known	Yes	302/X

^a602/603/604/X corresponds to four possible *DQB1* genotypes: 602/604 or 602/603 or 603/X or 603/60

DKA Diabetic keto-acidosis NA Not applicable

Discussion

To the best of our knowledge, this is the first proper demonstration of an increased prevalence of Down's syndrome in patients with type 1 diabetes. The present study is nationwide and population-based, using validated and complete registers, as well as confirmed diagnoses of type 1 diabetes. We demonstrate a prevalence of Down's syndrome in type 1 diabetes of 0.38%, which corresponds to a 4.2-fold increased prevalence of Down's syndrome in type 1 diabetes, compared with the background population. And in line with some of the previous studies addressing type 1 diabetes in Down's syndrome, we also demonstrate an increased prevalence of type 1 diabetes in Down's syndrome of 0.7%, compared with 0.17% in the general population, a prevalence which is increased more than fourfold in Down's syndrome individuals.

Previous studies regarding this issue were biased in several ways. Milunsky and Neurath [3] demonstrated a prevalence of type 1 diabetes in Down's syndrome of 0.43%; however, the study was based on questionnaires to hospitals, with reply rates of around 50%, no age distribution was provided and only some of the cases were treated with insulin, hence several were probably type 2 diabetics [3]. A second study [4] reported a prevalence of 1.7%, but was based on a subgroup of Down's syndrome patients attending a training centre, used glucosuria for diagnosis and did not differentiate between type 1 and type 2 diabetes. A Dutch study [8] identified three cases in Down's syndrome children aged 0–9 years (prevalence 0.34%), but did not differentiate between type 1 and type 2 diabetes either. In a Scottish study, based on interviews and a clinical database in a region of Scotland [9], a prevalence rate of diabetes in Down's syndrome of between 1.4 and 10.6% was observed, which is considerably higher than reported elsewhere. The prevalence is based on identification of 13 individuals with Down's syndrome and diabetes, which was compared with previous estimates calculating the presumed numbers of individuals with Down's syndrome in the region. No clinical or biochemical information regarding diabetes onset are provided. Down's syndrome diagnoses were based on clinical examination and in only two of the cases on confirmatory chromosomal analysis.

Differentiation between type 1 and type 2 diabetes is important. Pathogenesis and mechanisms underlying diabetes in Down's syndrome are unclear. However, signs of premature ageing as well as life-style factors may create bias when simple age criteria are used for diagnosis. Increased autoimmunity in general in Down's syndrome has been proposed, and especially thyroid and coeliac disease have increased prevalences, including demonstration of autoantibodies [10, 11]. In a study of nine Down's syndrome patients, with slightly impaired glucose tolerance, it was impossible to detect insulin autoantibodies, as an indication of autoimmune damage of pancreatic beta cells [12]; however, no information about age was given.

Since the observation time for type 1 diabetes diagnosis in the present study is limited to the end of the year 2003, we cannot exclude the possibility that we are underestimating the number of cases of type 1 diabetes and type 1 diabetics who also have Down's syndrome, since we do not know everyone who will eventually become type 1 diabetic in this cohort. We observed a median age at diagnosis of type 1 diabetes in Down's syndrome of 6 years, lower than the general median age at onset for type 1 diabetes of 8 years; however, the numbers are small and the difference does not reach statistical significance. In order to evaluate the significance of the usual major type 1 diabetes risk locus, the HLA region, in Down's syndrome individuals with type 1 diabetes, we evaluated HLA-*DQB1* genotypes. Although our numbers are small, one carried a dominantly protective allele, one carried only neutral alleles, and three just one classic risk allele, whereas just one carried two classic risk alleles. This suggests that other genetic risk loci, such as chromosome 21, are important for type 1 diabetes in this group and it is tempting to speculate that the explanation for the increased prevalence, or part of it, might be due to the trisomy 21. The more than fourfold increased prevalence of verified type 1 diabetes in people with Down's syndrome further supports the possibility that chromosome 21 may confer a risk of type 1 diabetes in the general population.

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