Geographical variability of the incidence of Type 1 diabetes in subjects younger than 30 years in Catalonia, Spain

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ORIGINAL

RESUMEN

Fondo y objetivo: El objetivo de este estudio ha sido evaluar la variabilidad geográfica en la incidencia de la diabetes de tipo 1 en sujetos menores de 30 años de edad al inicio de la enfermedad, durante el periodo de 1989 a 1998, en Cataluña (España). También se ha analizado el efecto del sexo, la edad al inicio de la enfermedad, los períodos de años y la densidad de la población.

Material y métodos: Los datos se obtuvieron del registro prospectivo catalán de diabetes mellitus. Se utilizaron modelos mixtos lineales generalizados a fin de determinar los efectos de los factores de riesgo y de conocer la distribución geográfica. El mejor modelo se seleccionó según el criterio de información de AKAIKE.

Resultados: La incidencia cruda de la diabetes de tipo 1 en personas menores de 30 años de edad fue de 11,8 cada 100.000 sujetos por año (intervalo de confianza del 95%: 11,4–12,3). En el grupo de entre 0 y 14 años de edad, la incidencia en el sexo masculino y en el sexo femenino fue similar, pero en adultos jóvenes se observó una preponderancia en los varones. No se observaron variaciones anuales en las tasas de incidencia. La incidencia no estaba asociada a la densidad de la población. Tampoco presentaba un patrón espacial a lo largo del territorio catalán sino que había una variabilidad geográfica no estructurada.

Conclusiones: Algunas regiones de Cataluña presentaron valores de incidencia de diabetes de tipo 1 más elevados o más bajos de lo que se esperaba. Estas regiones con incidencias extremas eran específicas de cada grupo demográfico estudiado y, en ningún caso, se obtuvieron agrupaciones que sugirieran factores explicativos con patrones de distribución geográfica. La incidencia de la diabetes en adultos jóvenes en algunas comarcas fue similar a la de los países europeos con una incidencia elevada.

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Introduction

Type 1 diabetes is a common chronic disease of childhood, and presents with acute, sometimes life-threatening, symptomatic hyperglycemia. Type 1 diabetes is a multifactorial disease in which environmental risk factors trigger an immune-mediated destruction of the pancreatic beta cells in genetically susceptible individuals. Studies of the epidemiology of Type 1 diabetes in different populations may provide important clues about its etiology. Data collected from the WHO Multinational Project for Childhood Diabetes (DIAMOND) Project, showed that the incidence of Type 1 diabetes increased by 2.8% per year during the years 1990–1999 worldwide, with a marked geographic variation from an age-adjusted incidence of 0.1 per 100,000/year in China and Venezuela to 40.9 per 100,000/year in Finland. The EURODIAB ACE study group revealed a very wide range of incidence rates of childhood diabetes across Europe, varying from the highest in Finland and Sardinia to the lowest (4.6 per 100,000) in northern Greece. Within-country variations have also been reported in several European countries, including Finland, Norway, Sweden, Austria, and Germany. On the other hand, an association between the degree of urbanization and the incidence of Type 1 diabetes has been described. In Northern Ireland and Yorkshire, England, a low incidence of diabetes was observed among children living in urban districts, while in Italy and Finland a high incidence was found in urban areas.

Therefore, there is evidence that environmental factors are an important cause of childhood diabetes, but factors influencing variations between and within ethnic groups are unknown. Moreover, information is scarce regarding the incidence of Type 1 diabetes, to examine the effect of the incidence of Type 1 diabetes on the age groups over 14 years at diabetes onset. It has been suggested that the epidemiology of Type 1 diabetes is not the same in young adults as in children.

The incidence of Type 1 diabetes in Catalonia (Spain) from 1987–1990 has been previously described by Goday et al. and no differences were found in the incidence of the disease in the four provinces of Catalonia. To contribute further to the knowledge of variations and trends in the incidence of Type 1 diabetes, we performed an epidemiological study over a longer period than that of the study by Goday et al.

The aims of this study were to analyze the temporal trends of the incidence of Type 1 diabetes, to examine the effect of the density of population on the incidence, and to present a descriptive and geographical analysis of the incidence of Type 1 diabetes in the 0–29 years of age group in the autonomous community of Catalonia (Spain) from 1989 to 1998. This analysis allowed studying the variability of the incidence that was not explained by the variables sex and age at onset (considered in the study conducted by Goday et al.). Moreover, we obtained smoothed rates of incidence, which eliminate the instability of crude rate and identify geographic regions with high rates of incidence. This provides information to optimize healthcare planning and to generate hypotheses about the factors that influence the risk.

Patients and methods

Description of the area under study

Catalonia is an autonomous community of northeastern Spain (32,091 km²) bordering on France to the north and the Mediterranean see to the east (580 km of coastal strip). The total population of Catalonia is 7,134,697 and the population density 222.3 inhabitants/km² (2006 Municipal Inhabitant Census). From an administrative point of view, the state division into provinces (Barcelona, Tarragona, Lleida, and Girona) overlaps with the division of the Catalan Administration into 41 regions (counties). There are currently 946 municipalities in Catalonia. Of these, 28 have less than 100 inhabitants: 492 between 100 and 1,000; 254 between 1,001 and 5,000; 120 between 5,001 and 20,000; 31 between 20,001 and 50,000; and 21 have more than 50,000 inhabitants. Nevertheless, 70% of the Catalan population lives in the 45 municipalities with more than 20,000 inhabitants. Approximately, 60% of the population in Catalonia lives in the Barcelona metropolitan area. The birth rate/year is 11.1% and the death rate/year 9.1%. The Catalan Health Service provides healthcare for 99% of inhabitants. Other hospitals or private practices cover the remainder.

Definition of study subjects and geographical units

All diabetic patients, diagnosed between 1st January 1989 and 31st December 1998, who were under 30 years of age at the time of onset, were included in the study. They had to be living in Catalonia for at least 6 months prior to onset. The date of the first insulin injection was used as the date of onset of Type 1 diabetes. Diabetes was defined according to the WHO criteria. Type 1 diabetes was defined as the presence of ketonuria, and the need for permanent insulin therapy. All the reported cases were on insulin treatment. A strict classification by e.g. C-peptide levels, islet cell antibodies, and insulin autoantibodies was not performed in all the cases. Nevertheless, most of the endocrinology, diabetes and pediatric units of Catalonia perform, at onset, a glucagon test measuring C-peptide levels, islet cell antibodies and insulin autoantibodies. Using this clinical and laboratory data, the physician can diagnose a case as Type 1 diabetes. Secondary diabetes and maturity onset diabetes of the young (MODY) were excluded.

The geographical units considered corresponded to the 41 administrative regions into which Catalonia is divided.

Population at risk

The population at risk from each region was obtained from the 1996 census provided by the Statistical Institute of Catalonia.

Collection of data

Data on the incidence of Type 1 diabetes in Catalonia were obtained from the prospective Catalan Registry of Type 1 Diabetes for the period 1989–1998. Because this registry took part in the EURODIAB ACE study since 1989, the standard protocol for prospective surveillance of insulin-dependent diabetes mellitus developed in this collaborative European study was followed. The recorded variables included sex; age at onset (first insulin injection) categorized as aged groups 0–14 years and 15–29 years; place of residence grouped into the 41 administrative regions; study period (calendar time categorized into two 5-year periods: 1989–1993, 1994–1998); and population density, which was calculated by dividing the total population of each group of study by the area of the region in square kilometres. The incidence of diabetes according to age at onset, sex, and calendar period was obtained for each region. The incidence in males, age group of 15–29 years, and 1994–1998 study periods were used as a reference.

Validation of ascertainment

Completeness of ascertainment was assessed by the capture-recapture method. The degree of case-ascertainment of the
Catalan Registry of Type 1 Diabetes is around 90%. The primary source of ascertainment was based on all recorded cases of newly diagnosed Type 1 diabetes in the 0–29 year age group through the hospital medical records, and notifications from physicians working with Type 1 diabetes included in the Catalan Diabetes Epidemiology Study Group. A secondary independent source of ascertainment was summer camps for diabetic children, patient associations, and prescription data.

Statistical analysis

The incidence rate for Catalonia and according to the covariates (sex, age, and calendar period), was calculated and expressed per 100,000 persons at risk and year. The 95% confidence intervals (CI) for these incidence rates were estimated assuming a Poisson distribution. To fit the incidence rate for the effects of the covariates we first considered a generalized linear model in which the number of new cases with diabetes in each region was assumed to be Poisson distributed. The population by region and group of study was considered in the offset term of the model. Assessment of the significance for the covariates was done by the Wald F test. Then, we extended the model to take into account the extra Poisson variability, incorporating random effects into the linear predictor by using generalized linear mixed models. In particular, four models with the same fixed covariates effect, yet different random effects were considered. The first model (model 1) incorporated a regional random effect without a structured pattern. This effect allowed for the heterogeneity of the incidence rate across regions. The second model (model 2) included two random effects: the first random effect had an unstructured variability and the second had an intrinsic conditional autoregressive structure. This effect is a spatially structured pattern, and measured the spatial correlation among regions (spatial variability). The existence of this spatial correlation means that the incidence rate of geographically close areas (neighbours) tends to be similar. The third model (model 3) was also a model with two random regional effects: one was unstructured and other was unstructured and different for each group of sex and age at onset. The last effect was a random sex-by-age interaction representing the risk of diabetes for each age at onset and sex group changed randomly across regions. And finally, model 4 was only composed for the sex-age random effect interaction. To estimate the models, we used the penalized quasi-likelihood estimation method and to choose the model which best fit the data, the Akaike Information Criterion statistics was applied. Moreover, we checked the model using a plot of the predicted values (in logarithm scale) versus the conditional standardized Pearson residuals. The Statistical Analysis Systems (SAS Institute, Cary, NC) software package was used for the analysis of data.

Results

During the 10-year study period, a total of 2771 new cases of type 1 diabetes were diagnosed in Catalonia, with a crude average annual incidence per year of 11.8/100,000 population (95% CI 11.4–12.3). In children aged 0–14 years at the time of onset, the incidence of the disease was 14.4/100,000/year (95% CI 13.61–15.20), whereas in young adults (15–29 age group) a somewhat lower incidence was found (10.2/100,000/year; 95% CI 9.71–10.76).

Fig. 1 shows the observed specific incidence rates for the 0–14 and 15–29 age groups according to sex and study period. In the whole group, the incidence was higher in the 0–14 age group than in the 15–29 age group. In addition, a male preponderance was noted in the 15–29 age group. This effect should be modelled introducing in the model an interaction between the variables sex and age. The incidence of Type 1 diabetes was significantly different according to sex (F = 42.93, p < 0.001) and age at onset (F = 93.28, p < 0.001). A statistically significant sex-by-age interaction was also observed (F = 45.34, p = 0.017).

The risk of type 1 diabetes was not significantly different in the 1989–1993 and 1994–1998 study periods (relative risk [RR] = 1.05, 95% CI 0.95–1.13). No significant annual differences were observed in the incidence of the disease during the 10 years of the study (mean annual RR = 0.99, 95% CI 0.98–1.1), neither was the density of the population significant, with an estimated mean of 1.1 (F = 1.84, p = 0.1773).

The model with sex and age and the interaction of them had an extra Poisson dispersion of 1.17 that was significantly higher than one (χ² = 437.50, p < 0.001). This model was named as base model. Accordingly, sex and age at onset did not explain all the variability in the incidence of Type 1 diabetes. Thus, the base model was extended including different random effects, and four models were fitted. Table 1 shows the variance estimate, their 95% CI, and the AIC for each model. The best AIC was obtained in model 4 (AIC = 743.7), in which incidence of Type 1 diabetes depended on sex, age at onset, and study region. The effect of the study region was random and different for each group of sex and age at onset. The residual plot showed that the model fit the data properly (not shown), and only four observations presented a residual value > 2 or < –2. In region 24 (males and females in the 15–29 age group) the risk was overestimated, whereas in regions 18 and 37 (females in the 15–29 age group) the risk was underestimated.

According to the estimation of the parameters of the sex and age variables (and their interaction) for model 4, we found that the incidence of the disease in the 0–14 age group was not significantly higher in males than in females (RR = 1.04, CI 0.85–1.28), and in the 15–29 age group, the risk for Type 1 diabetes was 1.5-fold higher in males than in females (95% CI 1.21–1.85).

Fig. 2 shows the regions that had regional random effects (exponential of random effects) significantly superior or inferior to the overall mean.
to 1 for the four demographic groups. In the 0–14 year old age group of males, the overall mean rate of diabetes was 13.75/100,000/year. In this group only one county showed a regional random effect significantly superior to one with an estimated incidence of 18.952/100,000/year. Concerning females the overall mean rate was 13.80/100,000 year. This figure is within the range of most of other studies undertaken in Spain so far. In our study we also found that possible factors triggering diabetes in Catalonia did not change along the study period.

The incidence of Type 1 diabetes for children in the 0–14 age group did not differ between males and females, being 14.4/100,000/year. This figure is within the range of most of other studies undertaken in Spain so far. However, in a recent study determining the incidence of type 1 diabetes in children and adolescents aged less than 15 years in the provinces of the autonomous region of Castilla-Leon, the values found in three provinces, Segovia (38.77/100,000/year), Valladolid (32.07/100,000/year), and Avila (23.21/100,000/year), were similar to those reported in Northern Europe. In our study we also found counties with high incidences (maximum estimated rate 18.952/100,000 year) but none with such high levels of incidence.

Compared to the incidence of diabetes in children in Europe, the rate in Catalonia is intermediate, being lower than the countries with the highest incidence such as Finland (37.7/100,000/year) and Sardinia (33.2/100,000/year) but higher than in Letonia which has a rate of 6.9/100,000/year. During this 10-year study, no annual variation was observed in the incidence of Type 1 diabetes, which may indicate that possible factors triggering diabetes in Catalonia did not change along the study period.

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In the young adults (15–29 years of age) the incidence in males (10.61/100,000/year) was greater than in females (7.04/100,000/year). We could not compare these rates with other studies undertaken in Spain because this is the first study to include Spanish subjects up to the age of 29 years.

The incidence of diabetes in Catalonia in young adults for both sexes is not the highest in Europe. Nevertheless, the estimated rate for males by counties showed that some regions, such as 7
and 41, had incidences of around 18/100,000/year, similar to the high values reported in Sardinia (16.8/100,000/year) and Leicestershire, UK (15.3/100,000/year). On the other hand, the incidence by counties for females did not show rates as high as those in European countries presenting a high incidence.

It is important to study the geographic variability of the incidence of diabetes since despite the lack of a pattern of geographic distribution this type of study demonstrates the regional heterogeneity of the incidence and identifies the geographical areas with a high incidence and, in practice, this information allows optimization of the healthcare planning.

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