High Incidence of Childhood Type 1 Diabetes in Liguria, Italy, From 1989 to 1998

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OBJECTIVE — Assessing updated incidence of type 1 diabetes in 0- to 14-year-old children in Liguria, a Northwest region of Italy.

RESEARCH DESIGN AND METHODS — Incident cases were recorded prospectively from 1989 to 1998. Incidence rates (IRs) were standardized to the 1999 world population using the direct method. The independent effect of sex, age, residence, and calendar year was estimated with Poisson regression model. The degree of ascertainment was calculated in accordance to capture/recapture method.

RESULTS — During 10 full calendar years, 219 new cases of type 1 diabetes in children were diagnosed in Liguria. The standardized IR over the 10-year period was 12.56 cases per 100,000 per year (95% CI 11.0–14.3). The sex-specific IR among men and women was 14.15 and 10.88, respectively. The age-specific IR was higher in the 10- to 14-year-old age-group (15.01/100,000) than in 0- to 4-year-old age-group (9.01/100,000) and in the 5- to 9-year-old age-group (13.03/100,000).

CONCLUSIONS — The IR of type 1 diabetes in Liguria is among the highest in Southern Europe and approaches IRs of Northern European countries. In particular it is much higher than those reported in the surrounding Italian regions except for Sardinia. Therefore, the geographical distribution of type 1 diabetes does not seem to reflect the simple North-South gradient reported in several previous works.

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Type 1 diabetes is one of the most frequent chronic disease in children and is a major public health problem because of the long-term complications of type 1 diabetes. Monitoring the incidence of type 1 diabetes may provide important information about the etiology of the disease.

In a 5-year study, we previously demonstrated that the Liguria region had the highest incidence (11.72/100,000 per year) in Italy (1) after Sardinia (30.7/100,000 per year) (2). However, we realized that data from a longer period would be needed before these results could be fully confirmed.

This study aimed to update the 10-year incidence of type 1 diabetes in 0- to 14-year-old children in Liguria.

RESEARCH DESIGN AND METHODS

— Type 1 diabetic patients who were diagnosed between 1 January 1989 and 31 December 1998 and who were under the age of 15 years at the time of their first injection were included in the study. Diagnosis of type 1 diabetes was in accordance with the World Wealth Organization (3).

It was assumed that two alternative sources provided the information independently. As previously described (1), the data of the primary source have been obtained from records of 9 pediatric departments, 11 endocrinology and diabetes units, and 8 internal medicine departments in the hospitals of the four provinces of the Liguria region (Genoa, Imperia, La Spezia, and Savona), assuming that all patients were hospitalized at the onset of insulin therapy. Actually, the possibility that a child with the onset of type 1 diabetes before age 15 years could have been treated without any contact with a hospital department must be regarded as exceptional in Liguria as well as in Italy. We sent a study questionnaire and a letter to the chiefs of the departments explaining the purpose of the study and the data we required (name, age, sex, residence, data of first insulin injection, parent's age and profession, family history for type 1 or type 2 diabetes or other endocrinopathies, symptoms at onset, and if there were intercurrent infection or stress in the last 3 months before diagnosis.) The research was made easier because of the "Regional Assistance Network for type 1 diabetes."

This collaborative network was set up in 1986 under the supervision of the Pediatric Department of the University of Genoa, and it provides current and reliable epidemiological data of type 1 diabetes in childhood in the different provinces of Liguria by an active surveillance model.

The secondary source of validation was established through the review of type 1 diabetic patients' basic data (name, surname, date, and place of birth) of the five local health service units in the region. Each new case was notified to our center and personally identified to avoid multiple reports of the same patient. Age- and sex-specific incidence rates (IRs) were calculated for the four Ligurian

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Abbreviations: IR, incidence rate.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*IR (per 100,000/year) of type 1 diabetes in Liguria during 1989 to 1998*

	Population	Cases	Rate	95% CI
Male age-group (years)				
0–14	898,427	126	14.15*	11.9–16.9
0–4	284,708	23	8.08	5.1–12.1
5–9	284,360	46	16.18	11.8–21.6
10–14	329,359	57	17.31	13.1–22.4
Female age-group (years)				
0–14	855,991	93	10.88*	8.9–13.3
0–4	270,311	27	9.99	6.6–14.6
5–9	268,004	26	9.71	6.3–14.3
10–14	317,676	40	12.59	9.0–17.1
Both sexes age-group (years)				
0–14	1,754,418	219	12.56*	11.0–14.3
0–4	555,018	50	9.01*	6.7–11.9
5–9	552,364	72	13.03*	10.2–16.4
10–14	647,035	97	15.01*	12.2–18.3
Province				
Genoa	980,050	131	13.44*	11.3–15.9
Imperia	239,219	19	8.10*	5.2–12.7
La Spezia	244,377	27	11.11*	7.6–16.2
Savona	290,772	42	14.48*	10.7–19.6

*Standardized rates.

provinces. Census data are collected in Italy the first year of each decade, so in our study we only used real census data for 1991. Estimates of the resident population in non-census years are directly provided by the National Institute of Statistics based upon statistical modeling.

IRs were standardized to the 1999 world population using the direct method (4). The independent effect of age, sex, residence, and calendar year was estimated with Poisson regression model (5). The choice among different regression models was suggested by Kleinbaum et al. (6). The calculation of rate ratios and 95% CI was performed by the generalized linear interactive modeling statistical software (7). Completeness of ascertainment was estimated with the capture/recapture method.

RESULTS — During 10 calendar years, 219 new cases of type 1 diabetes who met all eligibility criteria were identified. Of these, 22 (10.04%) were found by primary source only, 31 (14.15%) by secondary source only, and 166 (75.8%) by both sources. The combination of both sources provided a degree of ascertainment of 98.16%.

The age- and sex-standardized IR from 1989 to 1998 was 12.56 cases per 100,000 per year. The adjusted IR for completeness of ascertainment (crude IR/degree of ascertainment) was 12.99 cases per 100,000 per year. Number of eligible cases, population, and standardized IRs by sex and age-groups from 1989 to 1998 are reported in Table 1. The division of cases by age of diagnosis (groups 0–4, 5–9, and 10–14 years) has shown that the number of cases increases gradually during infancy (50, 72, and 97, respectively, in age-groups 0–4, 5–9, and 10–14 years).

The only covariate that significantly affected the IR of type 1 diabetes is age. A significant excess was found for both the age-groups 5–9 years (RR 1.58; 95% CI 1.07–2.32) and 10–14 years (2.09; 1.46–3.01) when compared with the age-group 0–4 years (Table 2). IRs by year of diagnosis were examined, but no significant variation was seen during the 10 years. The highest IR was reported between 1994 and 1995 (1.13; 0.74–1.71), and the lowest IR was reported in 1992 (0.94; 0.61–1.45).

Regarding the sex differences, we observed that incidence was somewhat higher, even if not significant, for boys than for girls (14.15 vs. 10.88). In age subgroups, female rates were higher than male rates in the age-group 0–4 years and lower in the age group 5– 9 and 10–14 years, whereas male rates gradually increased during childhood. None of the described differences reaches significance.

Genoa and Savona provinces showed the highest rates (13.44 and 14.48, respectively), whereas La Spezia and Imperia showed the lowest (11.11 and 8.10, respectively).

The percentage of distribution of cases by month of diagnosis showed a winter time peak (34.25% in winter vs. 18.72% in spring, 24.20% in summer, and 22.83% in autumn). The highest number of new cases was recorded in January and March, and the lowest was recorded in June. There was no significant difference in seasonal pattern.

CONCLUSIONS — In the last 2 decades, worldwide epidemiological research has shown an increase of the incidence of type 1 diabetes in all pediatric populations (8,9) with a major increase in populations with a low incidence (10). Furthermore, a large geographical variation in the incidence of type 1 diabetes in childhood has been reported with the widest range of intracontinental variation being observed in Europe (11).

The registries of type 1 diabetes in Italy established in 1997 recently demonstrated a wide incidence variation of type 1 diabetes not only between Sardinia and other Italian regions but also among different areas of the country (12). It is note-

Table 2—*Results of fitting Poisson regression model to data on diabetes incidence in Liguria*

Covariates	RR	95% CI
Sex		
Female	1.00	—
Male	1.30	0.99–1.69
Age (years)		
0–4	1.00	—
5–9	1.58	1.07–2.32
10–14	2.09	1.46–3.01
Province		
Genoa	1.00	—
Imperia	0.59	0.37–0.96
La Spezia	0.82	0.54–1.24
Savona	1.07	0.76–1.52
Calendar year		
1989/1990	1.00	—
1991/1992	0.94	0.61–1.45
1993/1994	1.13	0.74–1.71
1995/1996	1.13	0.74–1.71
1997/1998	1.08	0.71–1.65

worthy to say that the within-country variation in incidence found in Italy approaches the highest in the world, despite the supposed genetic homogeneity and very similar environmental condition, diet, and lifestyle habit.

The age-standardized IR we found over the 10-year period was 12.56/100,000 per year, and it is almost the same reported in our previous study. The degree of ascertainment is very high (98.16%), allowing the reliability of these data.

Based on this information, Liguria confirms one of the highest IR in Italy after Sardinia (33.2) (13). In particular, the calculated IR approaches the incidence in Friuli VG (12.8) (14), but it is higher than those reported in other Italian regions such as Sicilia (Catania, 10.2) (15), Umbria (10.2) (16), Toscana (10.2) (17), Lombardia (Pavia, 9.5) (18), Marche (9.5) (16), Abruzzo (9.4) (19), Piemonte (9.4) (20), Lazio (7.9) (21), and Campania (6.07) (22). This is surprising, and it represents a challenging clue for further epidemiological research to provide more information about the distribution of genetic markers and the role of environmental factors in etiology.

The Sardinian population is genetically distinct from all other Mediterranean and European populations (23). An interesting large study in Sardinian migrants to Lazio showed that, although Sardinian children born and living in Lazio retain the same high IR as children born and living in Sardinia, children from Lazio have a very low incidence (24). Therefore, this situation might also affect our data because of the nearness between Liguria and Sardinia and the possibility of Sardinia migrants to Liguria. However, we were not able to collect the data regarding all of our patients.

The comparison with available rates in other countries shows that Liguria region has an intermediate type 1 diabetes risk. IR in Liguria is lower than those reported in Finland (36.5), Sweden (27.5), Canada (24.0), Norway (21.2), U.K. (from 15.3 in Leicestershire to 24.0 in Aberdeen), and Denmark (15.5) (9), but it is similar to those of other Northern European countries such as Netherlands (13.0), Belgium (11.6), and Luxembourg (11.4) (9). Indeed IR in Liguria is, excluding Sardinia, the highest in Southern Europe as in Portugal (Algarve) (16/100,000), Spain (12.8/100,000), and Malta (15.6/100,000) (25).

These data offer a further exception to the hypothesis that latitude (North-South gradient) may be critical to explain the considerable geographical variation of type 1 diabetes within Europe and throughout the World. However, the North-South gradient does not seem to be as strong as previously supposed (9).

A greater incidence was found in boys in our study (the average sex-specific IR among boys and girls was 14.15 and 10.88 per 100,000 per year, respectively) according to the data from Northern Europe (9) and from Piedmont region (26) but not to the data observed in another study (20).

The highest IRs are found at the age of puberty in both boys and girls. This is consistent with the typical pattern of type 1 diabetes occurrence by age, which shows a peak in correspondence of the pubertal spurt (2,27).

We confirmed that the onset of type 1 diabetes is affected by seasonality, although the variability is not large. The percentage of distribution of cases by month of diagnosis showed a wintertime peak. A higher incidence of viral infections during winter season or climatic factors, such as cold, might influence the time of onset of type 1 diabetes by increasing the need of insulin supporting this hypothesis.

In conclusion, this prospective 10-year study showed an IR of type 1 diabetes in Liguria to be among the highest in Southern Europe, approaching those reported in several Northern European countries.

On this basis, Liguria region confirms to be a further exception to "North-South gradient" and may contribute toward a more complete map of geographical distribution of childhood-onset diabetes in Europe.

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