

Incidence rate and spatio-temporal clustering of type 1 diabetes in Santiago, Chile, from 1997 to 1998*

Taxa de incidência e agrupamento espaço-temporal de diabetes tipo 1 em Santiago, Chile, de 1997 a 1998

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Keywords

Diabetes mellitus, insulin-dependent, epidemiology.[#] Space-time clustering. Incidence. Child. Adolescence. Urban zones.

Abstract

Objective

To estimate the incidence rate of type 1 diabetes in the urban area of Santiago, Chile, from March 21, 1997 to March 20, 1998, and to assess the spatio-temporal clustering of cases during that period.

Methods

All sixty-one incident cases were located temporally (day of diagnosis) and spatially (place of residence) in the area of study. Knox's method was used to assess spatio-temporal clustering of incident cases.

Results

The overall incidence rate of type 1 diabetes was 4.11 cases per 100,000 children aged less than 15 years per year (95% confidence interval: 3.06–5.14). The incidence rate seems to have increased since the last estimate of the incidence calculated for the years 1986–1992 in the metropolitan region of Santiago. Different combinations of space-time intervals have been evaluated to assess spatio-temporal clustering. The smallest p-value was found for the combination of critical distances of 750 meters and 60 days (uncorrected p-value = 0.048).

Conclusions

Although these are preliminary results regarding space-time clustering in Santiago, exploratory analysis of the data method would suggest a possible aggregation of incident cases in space-time coordinates.

Descritores

Diabetes mellitus insulino-dependente, epidemiologia.[#]

Conglomerados espaço-temporais.

Incidência. Criança. Adolescência.

Zonas urbanas.

Resumo

Objetivo

Estimar a taxa de incidência de diabetes tipo 1 na área urbana de Santiago, Chile, entre os dias 21 de março de 1997 e 20 de março 1998, assim como a avaliação do agrupamento espaço-temporal dos casos incidentes no período.

Métodos

Foram localizados 61 casos incidentes no tempo (dia do diagnóstico) e no espaço (lugar de residência) na área do estudo. O método de Knox foi usado para avaliar o agrupamento dos casos no espaço e no tempo.

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Resultados

A taxa de diabetes tipo 1 foi estimada em 4,11 casos por 100.000 menores de 15 anos por ano (Intervalo de confiança 95%: 3,06 – 5,14). Essa taxa de incidência parece ter aumentado desde a última estimativa realizada na região metropolitana de Santiago, nos anos 1986-1992. Foram construídas diferentes combinações de intervalos de espaço e tempo para determinar a agregação espaço-temporal dos casos incidentes. A quase significativa agregação de casos foi detectada usando as distâncias críticas de 750 m e 60 dias (valor *p* não corrigido = 0,048).

Conclusões

Embora o estudo só mostre resultados preliminares do agrupamento espaço-temporal dos casos de diabetes tipo 1, em Santiago, a análise dos dados sugere uma possível agregação de casos incidentes nas coordenadas de espaço e tempo.

INTRODUCTION

Type 1 diabetes mellitus is characterized by autoimmune destruction of the insulin-secreting beta cells located in the pancreas. The incidence rates of this complex disorder vary greatly in different countries and ethnic groups, suggesting that both genetic and environmental factors participate in the etiological process of beta cell destruction (Akerblom et al,¹ 1997).

In the last years, the methodology provided by the World Health Organization DiaMond project¹⁵ has confirmed the existence of large geographic differences in the incidence rate of type 1 diabetes around the world. The highest incidence rates correspond to North European countries such as Norway, Finland, Denmark, and the island of Sardinia in Italy (Green et al,⁵ 1992). The Chilean population constitutes a melting pot of populations arising from different groups including Europeans predominantly from Spain, and Amerindians (mainly Mapuche and Aymara natives) (Carrasco et al,² 1996). It has been reported that Chile's aboriginal Mapuche population has a very low incidence of childhood diabetes (0.43 per 100,000 children per year) (Larenas et al,⁹ 1996), while the incidence rate found in the metropolitan region of Santiago was 2.36 per 100,000 children per year for the period 1986-1992 (Carrasco et al,² 1996).

The WHO DiaMond Molecular Epidemiology Subproject tested the hypothesis that such geographic differences in the incidence of type 1 diabetes vary according to the frequency of alleles for disease susceptibility in the human leukocyte antigen (HLA) region (Dorman et al,³ 1996). Environmental risk factors, such as viral infections and diet, have been implicated in the etiology of type 1 diabetes by directly destroying beta cells or by inducing autoimmunity through molecular mimicry in genetically susceptible subjects (Akerblom et al,¹ 1997). Viral infections are one of the most accepted hypothesis to explain the

seasonal variation of type 1 diabetes, with fewer cases diagnosed in the summer months and relatively constant incidence in the other three seasons (World Health Organization DiaMond Project,¹⁵ 1992).

It has been shown that risk factors for childhood diabetes vary spatially due to differences in the exposure to environmental risk factors, and due to the population stratification by ethnicity, constituting geographically separated groups with different genetic susceptibility profile. Environmental risk factors such as viral infections also vary temporally. In this scenario, an aggregation of cases in space and time would be expected. Several articles have shown spatial, temporal and spatio-temporal clustering of childhood diabetes (Samuelsson et al,¹³ 1994; Law et al,¹¹ 1997). As far as it is known, there are no studies on spatio-temporal aggregation of type 1 diabetes in countries with low incidence of the disease such as Chile or in countries in the Southern hemisphere.

The aim of the present study was to estimate the incidence rate of type 1 diabetes in the urban area of Santiago, Chile, from March 21, 1997 to March 20, 1998, and to assess the spatio-temporal clustering of cases during that period.

METHODS

Study area

The metropolitan region of Santiago is in the central region of the country, and it concentrates close to 40% of the country's population. The Greater Santiago is the most important urban area of the metropolitan region, and is comprised of 34 highly urbanized districts called "comunas". According to 1992 census, the total population of Greater Santiago was 4,756,663 (Instituto Nacional de Estadísticas,⁶ 1993), living in an approximate area of 2,269 km². The population of less than 15 years old is considered as the population "at risk" in this study. According to post-

censal projections, the population less than 15 years in Greater Santiago in 1997 was 1,483,218 (Instituto Nacional de Estadísticas,⁶ 1993).

Regarding climate-related factors, climate in Greater Santiago is mild, with four well-defined seasons. As Santiago is in the Southern hemisphere, winter solstice is approximately on June 21, and summer solstice is on December 21. The March 21, June 21, September 21 and December 21 are the first day of autumn, winter, spring, and summer, respectively. The study comprises the four seasons, from March 21, 1997 to March 20, 1998.

Ascertainment of cases*

A search and confirmation method was used to ascertain cases of type 1 diabetes diagnosed from March 21, 1997 to March 20, 1998. To be included in the study, a case must fulfill the following requirements: age at onset 0-14 years, diagnosed with diabetes and on insulin treatment, diagnosed within the defined time period, and be resident of Greater Santiago at the time of the diagnosis. The day of the first insulin injection was considered as the date of diagnosis.

Newly diagnosed cases were obtained from two sources. Emergency services in hospitals, private clinics and pediatricians were collectively considered as the primary source. The secondary source of ascertainment was the volunteer registry of Juvenile Diabetes Foundation of Chile.*

Statistical methods

The incidence rate is expressed as the number of cases per 100,000 inhabitants aged less than 15 years per year. The number of newly diagnosed cases, corrected for underascertainment with the capture-recapture formula (LaPorte et al,¹⁰ 1992), were applied as the rate numerator. Ninety-five percent confidence intervals were calculated assuming a Poisson distribution. The age-standardized incidence rate was computed using the world population as reference (Murray & Lopez,¹² 1996). A chi-squared test for heterogeneity was utilized to assess seasonality in the occurrence of new cases of type 1 diabetes.

Knox method was used as an exploratory analysis to assess spatio-temporal clustering of incident cases of type 1 diabetes (Knox,⁸ 1964). Although there are more sophisticated and powerful statistical techniques to detect aggregation of cases in space and time, it is believed that in the preliminary analysis, Knox method provides an intuitive approach to visualize possible

clusters occurring simultaneously in space and time. All combinations of two cases are identified, and each of the $n(n-1)/2$ pairs are classified according to their spatial and temporal proximity to one another. The space coordinates (x-meters, y-meters) for each case were determined by plotting the place of residence of the case in a grid superimposed in the study area. Three different and arbitrary critical time intervals (30, 60 and 90 days) were used in combination with three arbitrary critical distances in space (500, 750 and 1,000 meters). For example, a pair of cases is said to be in time distance "30" and space distance "500" if they are diagnosed in the same 30 days-interval period, and in a distance less than or equal to 500 meters. The p-value is calculated assuming that the number of case pairs close in both space and time is distributed as a Poisson random variable.

RESULTS

The total number of cases in the studied period was 61 (31 boys and 30 girls). The mean age of cases was 8.8 years old with a standard deviation of 3.9 years. Eleven cases were diagnosed in the autumn, 22 cases in the winter, 14 cases in the spring and 14 cases in the summer. Although these are results from a single year, they suggest an increased number of cases in the winter months ($p < 0.001$). A total of 57 cases were ascertained by both the primary and secondary sources. A total of 53 diabetic patients were ascertained both through the primary and the secondary sources. The number of cases corrected by multiple ascertainment using the capture-recapture formula was 61.3.

The overall incidence rate of type 1 diabetes was 4.11 cases per 100,000 children per year (95% CI: 3.06–5.14). The incidence rate in both sexes was also 4.11 per 100,000 children per year. When data were stratified by age, the incidence rate in the group 0-4 years was 3.28 per 100,000 children per year (95% CI: 1.91-5.25), in the 5-9 years group was 2.97 (95% CI: 1.81-5.14), and in 10-14 years group was 6.10 (95% CI: 4.05-8.82). The age-standardized incidence rate was 4.03/100,000.

A total of nine different combinations of space-time intervals have been evaluated in the study (Table). The smallest p-value was found using the critical distances of 750 meters and 60 days (p -value=0.048). However, multiple statistical hypotheses have been tested simultaneously in the analysis. After using Bonferroni's method to adjust multiple comparisons, there was no more a statistical significance in the critical combination of 750 meters and 60 days.

*This research project was approved by the University of Chile Ethics Committee.

Table - Knox's Method applied to pairs of cases of type 1 diabetes in the Gran Santiago, Chile (March 21, 1997 - March 20, 1998).

Distance space (mts)	Distance time (days)		
	30	60	90
500	1*	2	2
	0.24**	0.68	1.09
	0.21***	0.15	0.29
750	1	4	4
	0.48	1.35	2,186
	0.38	0.048	0.18
1,000	2	5	5
	0.84	2.3	3,826
	0.21	0.09	0.34

*Observed pairs of cases close in space and time.

**Expected pairs of cases under the null hypothesis of random distribution of cases in space and time.

***p-value obtained by Knox's method.

DISCUSSION

The overall incidence of type 1 diabetes seems to have increased since the last estimate of the incidence in the years 1986–1992, calculated for the whole metropolitan region of Santiago (Carrasco et al,² 1996). This would be consistent with the observation that the incidence of type 1 diabetes is increasing worldwide (Vaananen et al,¹⁴ 1998). Seasonality in the incidence rate is suggested by these data, with a higher number of cases occurring in the winter. Several reports from both Northern and Southern hemisphere have indicated that the incidence of type 1 diabetes is higher in the months of autumn, winter and spring than in the summer time (Durruty and García de los Ríos,⁴ 1979). This increased frequency of type 1 dia-

betes in colder months was previously related to a higher number of viral episodes occurring in such months (World Health Organization DiaMond Project,¹⁵ 1992).

Identification of disease clustering is important in public health studies, since it allows adequate strategic planning in the primary prevention and the development of new etiological hypotheses. Studies on spatio-temporal clustering of childhood diabetes has been exclusively conducted in countries with moderate or high incidence of type 1 diabetes, with results that are consistent with early exposure to infectious agents or localized environmental sources (Samuelsson et al,¹³ 1994; Law et al,¹¹ 1997, Joner et al,⁷ 1998). This preliminary analysis suggests a possible aggregation of cases in specific critical points of time and space in the city of Santiago. However, the present report only represent a detailed description of the spatio-temporal clustering of type 1 diabetes during a single year. As a conclusion, it is expected that this study will be able to increase the power of detecting space-time aggregation of type 1 diabetes by identifying new cases of the disease in the following years and by using more sophisticated statistical methods for this purpose.

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