Seasonality of Month of Birth of Children and Adolescents with Type 1 Diabetes Mellitus in Homogenous and Heterogeneous Populations

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Key words: childhood-onset diabetes mellitus, seasonality of month of birth, virus etiology

Abstract

Background: Type 1 childhood-onset diabetes mellitus has a multifactorial origin involving an interplay between genetic and environmental factors. We have previously shown that many children who subsequently develop T1DM have a different seasonality of birth than the total live births of the same population, supporting the hypothesis that perinatal viral infection is a trigger for the autoimmune process of T1DM.

Objectives: To compare the seasonality of children with T1DM in different populations around the world for which data were available.

Methods: We analyzed large cohorts of T1DM patients with a clinical disease onset before age 14 or 18 years.

Results: We found a seasonality pattern only in ethnically homogenous populations (such as Ashkenazi Jews, Israeli Arabs, individuals in Sardinia and Canterbury, New Zealand, and Afro-Americans) but not in heterogeneous populations (such as in Sydney, Pittsburgh and Denver).

Conclusions: Our findings attempt to explain the controversial data in the literature by showing that ethnically heterogeneous populations comprising a mixture of patients with various genetic backgrounds and environmental exposures mask the different seasonality pattern of month of birth that many children with diabetes present when compared to the general population.

IMAJ 2005;7:381–384

Type 1 childhood-onset diabetes mellitus has a multifactorial origin involving an interplay between genetic and environmental factors, resulting in a wide spectrum of incidence rates between various populations. Epidemiologic studies by our group have shown that many children who subsequently develop T1DM have a different seasonality of birth than the total live births of the same population, supporting the hypothesis that perinatal viral infection during the yearly epidemics is a major initiating trigger for the autoimmune process of T1DM.

Reviewing the whole country register of childhood onset (0–18 years) type 1 diabetes in Israel between the years 1965 and1993, we found different incidence rates in various ethnic groups. Yemenite Jews had a very high incidence rate, Ashkenazi Jews (East European origin) an intermediate incidence rate, and Arabs a low rate [1]. Similar differences in incidence were found in other populations: Finns and Sardinians have a very high incidence [2], West Europeans an intermediate incidence, with the Scottish higher than the English [2,3], and the Hispano and the Asian a low incidence [3]. Further analysis of the seasonality of the month of birth of children with T1DM in the different ethnic groups in Israel revealed that the pattern in the Jewish population differed from that in the general population [4], and that in the high incidence group (Yemenite Jews) it mirrored the seasonality of the clinical onset [5]. In the low incidence Arab population there was no yearly seasonality when analyzed for the 12 month period.

Since the transition from the subclinical to the clinical form of type 1 diabetes frequently follows an infection, we hypothesized that viruses passing from the mother to the fetus during or after conception in the period of the yearly viral epidemics in autumn and winter initiate the autoimmune process in the pancreas. These babies are born in spring or summer and the progressive destruction of their beta cells results in the development of the disease [6]. To test our observations and hypothesis we performed collaborative epidemiologic investigations in other countries. We report here a comparative and enlarged analysis of month of birth of children with diabetes (compared to the general population) in the Arab and Ashkenazi Jewish populations in Israel; in Sardinia [7], in Canterbury, New Zealand [8]; in Sydney, Australia; and in three large medical centers in the United States.

Subjects and Methods

The patients in this study are from ethnically homogenous and ethnically heterogeneous populations that have a high, intermediate, or low incidence of childhood-onset type 1 diabetes [1–5,7,8]. All were previously diagnosed with type 1 insulin-dependent diabetes

T1DM = type 1 childhood-onset diabetes mellitus
MOB = month of birth

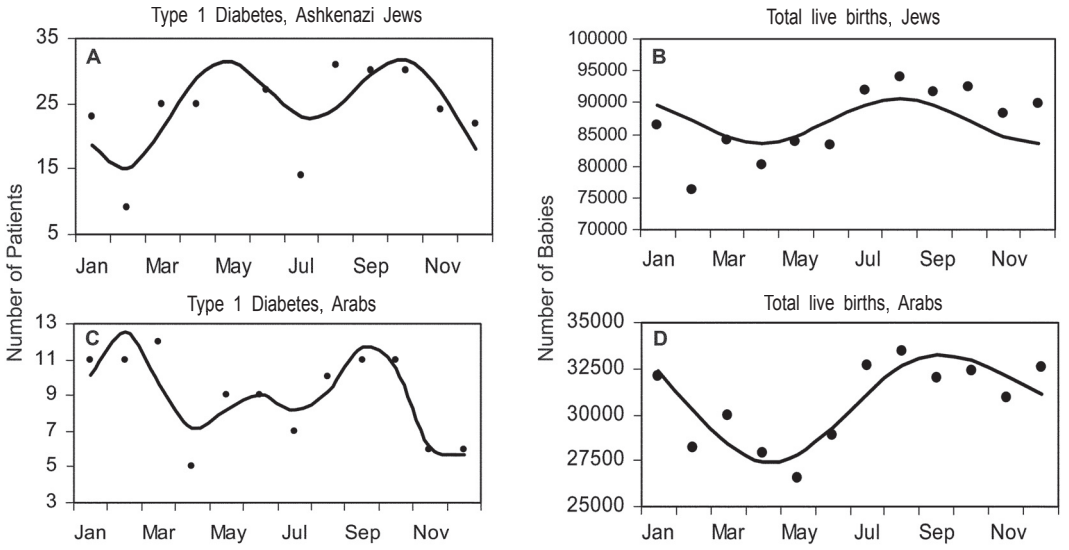

Figure 1. Monthly distribution of month of birth (MOB) of Jewish-Ashkenazi and Arab children and adolescents with type 1 diabetes in Israel (age 0–18 years)

[A]. MOB in Ashkenazi Jews. Combined rhythm of 8 + 6 months, $R = 0.74$, $P < 0.01$, mesor = 25.8, n=296, amplitude 8 months = 6.7, amplitude 6 months = 9.7.

[B]. Total live births of the Jewish population in Israel. Rhythm of 8 months, $R = 0.47$, $P < 0.05$, mesor = 87,185, n=1,042,148, amplitude 8 months = 3504.6

[C]. MOB in Arabs. Combined rhythm of 4 + 6 months, $R = 0.85$, $P < 0.01$, mesor = 9, n=108, amplitude 4 months = 1.94, amplitude 6 months = 2.02

[D]. Total live births of the Arab population in Israel. Combined rhythm of 8 + 12 months, $R = 0.83$, $P < 0.01$, mesor = 30,842, n=367,494, amplitude 8 months = 1,281, amplitude 12 months = 2,205

mellitus. The diagnosis was verified since all had participated in all-country or regional incidence surveys.

A homogenous population is considered to consist exclusively, or at least by a large majority, of the same ethnic group. Heterogeneous populations comprise a mixture of ethnic groups. We included in this study children and adolescents with T1DM aged up to 14 or 18 years belonging to populations of both types. Their distribution by continent was as follows:

- Europe (n=4842), which included: Sardinia (n=1118) [7], Sicily (n=273) [9], Ireland (n=303) [10], Belgium (n=2663), Berlin (n=570) [11], Slovenia (n=849) [12], and Baden-Wuerttenberg (n=1184) [13]
- USA (n=4509), which included: Pittsburgh: whites (n=1715) and Afro-Americans (n=189), Denver (n=1282), and St. Louis: whites (n=1098) and Afro-Americans (n=225)
- Sydney, Australia (n=621), and Canterbury, New Zealand (n=275)
- Israel (n=1868).

Some of the data from European countries, Israel and New Zealand [7,9–11] were previously analyzed using a different statistical method (as well as by Cosinor analysis) [8,12,13] and were re-analyzed in this study.

Statistical analysis

Rhythm analyses were evaluated using the compatibility of the data to a mathematical model (a Best Fit Formula) composed of up to four cosine functions with a set of predetermined periods (e.g., cosine-fit: 2D Table curve, Jandel Scientific, USA) [14,15]. The degree of fitness was determined by the statistical parameters *R* and *P*. The data were compared to the pattern of total live births in the respective regions with the exception of St. Louis where the data were not available.

Results

We present illustrative examples from our study. Figure 1 shows the seasonality of month of birth of Ashkenazi Jewish and Arab children and adolescents in Israel (0–18 years) – both ethnically highly homogenous populations. Two findings were evident: in both Jews and Arabs the seasonality of MOB in the children with diabetes [Figure 1 A–C] differs from that in the general population [Figure 1 B–D]. The Ashkenazi Jews with T1DM (n=296) have a combined rhythm with periods of 8 + 6 months with peaks in May and October [Figure 1A, mesor = 25.8, amplitude 8 months = 6.7, amplitude 6 months = 9.7, $R = 0.74$, $P < 0.01$), while the total live population of Jews (n=1,042,148) shows a rhythmicity of 8 months with a peak in August [Figure 1B, mesor = 87,185, amplitude 8 months = 3504.6, $R = 0.47$, $P < 0.05$).

The Arab children with T1DM (n=108) showed a shorter rhythmicity of combined 4 + 6 months than those observed in the Jewish population [Figure 1C, mesor = 9, amplitude 4 months = 1.94, amplitude 6 months = 2.02, $R = 0.85$, $P < 0.01$), with peaks in February and September, while the total live births in the Arab population (n=367,494) showed a rhythmicity of 8 + 12 months [Figure 1D, mesor = 30,842, amplitude 8 months = 1,281, amplitude 12 months = 2,205, $R = 0.83$, $P < 0.01$) with a peak only in September.

In Sardinia (n=2249), a homogenous population with a high incidence of T1DM [2,3], the MOB pattern of children with T1DM also demonstrated a statistically significant rhythmicity of 6 months (mesor = 190.12, amplitude = 22, $R = 0.76$), differing from the total live births (n= 270,747) which did not demonstrate any rhythmicity (not shown).

Similar findings were registered in Canterbury, New Zealand (n=275) [Figure 2], which also has a homogenous population with a medium incidence of childhood T1DM [16]. New Zea-

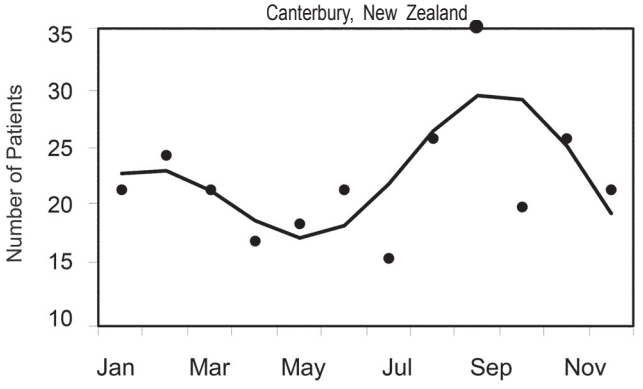

Figure 2. Monthly distribution of MOB of children and adolescents with type 1 diabetes in a combined rhythm of 12 + 8 months, $R = 0.62$, $P < 0.01$, mesor = 22.2, n=275, amplitude 12 months = 2.6, amplitude 8 months = 3.5. Reproduced with permission from Willis et al. [8]

land is located in the southern hemisphere and therefore has an inverse order of the yearly seasons. The rhythm of MOB was 12 + 8 months with a peak in October ($R = 0.62$, mesor = 22.2, amplitude 12 months = 2.6, amplitude 8 months = 3.5). This rhythm was also different from the total live births in Canterbury, New Zealand (n=91,394), which showed no rhythmicity (not shown). We also found a difference between the seasonality of month of birth from that in the general population in Sicily [9], Ireland [10], Slovenia [12], Berlin [11] and Baden-Wuerttenberg [13] – all considered to have mostly ethnically homogenous populations.

The populations in Pittsburgh and Denver (USA) and Sydney (Australia) are a mixture of several ethnic groups, i.e., non-homogenous populations. Analysis of the MOB of children with T1DM from these cities revealed no rhythmicity. In St. Louis, a different pattern of MOB seasonality was found between white children with T1DM ($R = 0.62$, mesor = 91, amplitude = 13) in June and the Afro-American children with T1DM ($R = 0.63$, mesor = 18.8, amplitude = 3.88) with a peak in September [Figure 3]. No such pattern was found in Pittsburgh, which has a relatively small number of Afro-American children [Table 1].

The total live births showed rhythmicity in Pittsburgh and Denver but not in Sydney [Table 1]. For St. Louis, no data were available. Nevertheless, it can be concluded that in Pittsburgh and in Denver the pattern of month of birth in the children with T1DM differed from that in the general population.

Table 1. Lack of seasonality of month of birth (MOB) in children and adolescents with type 1 diabetes (T1DM) in cities with ethnically heterogeneous populations

	Type 1 diabetes		Total live births	
Center	No. of patients	Rhythm	No. of babies	Rhythm period
Pittsburgh				
Whites	1,715	Non-rhythmic	56,573	12 months
Afro-Americans	189	Non-rhythmic	13,729	8 months
Sidney	621	Non-rhythmic	881,700	Non-rhythmic
Denver	1,282	Non-rhythmic	54,835	12 months

Note difference from the pattern in the total live births in the same populations

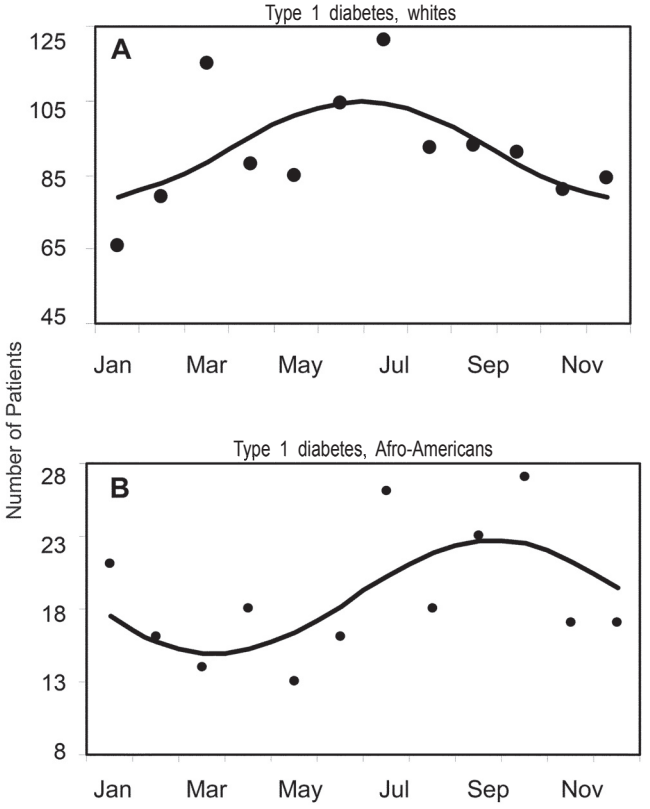

Figure 3. Monthly distribution of MOB of whites and Afro-American children and adolescents with type 1 diabetes in St. Louis.

MOB in whites: rhythm of 12 months, $R = 0.62$, $P < 0.05$, mesor = 91, n=1325, amplitude = 13

MOB in Afro-Americans: rhythm of 12, $R = 0.63$, $P < 0.05$, mesor = 18.8, n=226, amplitude = 3.38

Discussion

The statistical analysis of epidemiologic studies that we performed in many populations spreading over four continents clarifies the inconsistency of findings with regard to differences in month of birth seasonality in children with type 1 diabetes compared to the total population [17]. We observed that in homogenous ethnic populations – such as Ashkenazi and Yemenite Jews in Israel, in Sardinia, Ireland, Canterbury (New Zealand), etc. – that have a medium or high incidence of T1DM, there is a significant yearly rhythm with a peak in spring or summer. Others have reported similar findings in homogenous groups in five counties in the UK [18] and the Netherlands [19]. Heterogeneous populations of mixed ethnic origin and varying genetic susceptibility, such as in Pittsburgh, Denver and Sydney, did not show the above pattern. These differences are most probably due to the genetic and lifestyle differences between ethnic groups that became evident when each homogenous population was analyzed separately, such as the difference between white and Afro-American children with T1DM in St. Louis.

When mixing the data from different ethnic groups such as the Jewish and Arab T1DM populations in Israel [4,5] or the male and female data in Ireland [10], the rhythmicity observed in the individual ethnic groups in the first case or in the male diabetic children in the second case [10] was lost. This seems the most probable explanation for why we could not find a rhythmic seasonality pattern in the month of birth in cities with a heterogeneous, multiethnic population having various degrees of T1DM incidence and different genetic susceptibilities.

Conclusion

Our analysis of large cohorts of children with T1DM in various parts of the world revealed that in ethnically homogenous populations the children and adolescents who subsequently develop the disease have a MOB seasonality that differs from the pattern of the total live births. This adds support to the theory that the first trigger for beta cell destruction occurs in genetically susceptible ethnic groups already in the perinatal period, which is caused by viruses transmitted by the pregnant mother to the fetus during the yearly viral epidemics in late autumn and winter [6,19–23]. While mother's milk has mainly a protective effect against pathogens, it may also transmit viruses [24]. In the low incidence ethnic groups there may be an interplay between genetic protection and antivirus antibodies transmission by the mother to the fetus and newborn [25].

Acknowledgments. We thank Mrs. Sara Assa, PhD, for her assistance with the Israeli data. This study was partially supported by a grant-in-aid by Mr. E. Kaufman (EFD Ltd) to Z. Laron.

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