CLINICAL STUDY

Seasonality of month of birth of patients with Graves' and Hashimoto's diseases differ from that in the general population

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Abstract

Objective: We aimed to test the viral hypothesis in the pathogenesis of autoimmune thyroid disease (AITD).

Design: We determined the pattern of month of birth (MOB) distribution in patients with AITD and in the general population and searched for differences between them.

Methods: A total of 1023 patients were included in this study; 359 patients had Graves' hyperthyroidism (GrH) and 664 had Hashimoto's hypothyroidism (HH). We divided the patients with HH into three subgroups according to their thyroid peroxidase (TPO) antibody titers at diagnosis: low levels (<500 IU/ml), high levels (500–1000 IU/ml), and extremely high levels (>1000 IU/ml). We used cosinor analysis to analyze the data.

Results: Overall, patients with GrH and HH had a different pattern of MOB distribution when compared with the general population and between groups. Furthermore, among both patients with GrH and HH, both genders had a different pattern of MOB distribution when compared with the general population and this pattern was also different between genders. Finally, only women with extremely high titers of TPO antibodies at diagnosis and men with low or extremely high TPO antibody levels showed rhythmicity in MOB, with a pattern of MOB distribution different from that in controls.

Conclusions: The different MOB seasonality in both GrH and HH points towards a similar maybe even common etiology with type 1 diabetes mellitus and multiple sclerosis, namely a seasonal viral infection as the initial trigger in the perinatal period, the clinical disease resulting from further specific damage over time.

European Journal of Endocrinology 156 631–636

Introduction

Graves' disease (GrD) and Hashimoto's thyroiditis (HT) are common disorders with an autoimmune origin and are also therefore alluded to as autoimmune thyroid diseases (AITD; (1, 2)). Like other organ-specific autoimmune endocrinopathies, they have a multifactorial but different etiology (3). It has been calculated that 21% of the cause to develop GrD can be attributed to environmental factors (1, 3). This is less documented for HT (4). Among the environmental factors, infections especially viruses have been mentioned (1) but so far only an association between congenital rubella infection and hyperthyroidism has been documented (5). Evidence for a link between viral infection and the autoimmune process has been repeatedly shown in type 1 diabetes (T1D) mellitus (6–11) and multiple sclerosis (MS; (12)). Since there is a high degree of association between T1D with both GrD and HT (13) and possibly MS (14), one can assume that autoimmune diseases have despite different antigens and antibodies a common trigger in the initiation of the autoimmune process, probably viral

infections in the perinatal period. Viral infections have been recognized to act in T1D as the last insult leading to the conversion of the subclinical to clinical disease thus showing a higher incidence of clinical diagnosis during seasons of endemic viral outbreaks, usually late autumn and winter (8, 15, 16).

Seasonal variations in the frequency of AITD are also known to support the viral hypothesis (17–20). Considering the strong link between T1D and AITD (13) and the finding that children and young adults who subsequently developed T1D had a different seasonality of month of birth (MOB) from that found in the general populations (21–23), we analyzed the seasonality of MOB in a large cohort of patients with Graves' hyperthyroidism (GrH) and Hashimoto hypothyroidism (HH). This article presents the results of this analysis.

Subjects and methods

We studied all patients who were first diagnosed with AITD from January 2003 up to November 2005 as well as all

patients who were being followed up at the Endocrine Out-patient Department of Panagia General Hospital, in Thessaloniki, Greece. The study population was subdivided according to the diagnosis of patients with GrH and HH.

A total of 1023 patients were included in this study; their characteristics are shown in Table 1. Male sex was more prevalent among patients with GrH than among those with HH ($P=0.015$). Patients with GrH were significantly older at diagnosis when compared with patients with HH ($P=0.003$). Age at diagnosis, overall and in GrH and HH separately, did not differ significantly between men and women.

MOB, thyroid stimulating hormone (TSH), and free thyroxine (FT_4) were recorded in all patients. Titers of antibodies against thyroid peroxidase (TPO) were determined in patients with HH at their initial visit. Patients with GrH had elevated levels of FT_4 and suppressed TSH, while patients with HH had elevated TSH levels (>10 mU/l, normal range = 0.4–4.0 mU/l), decreased levels of FT_4 (normal range = 7.0–18.0 pg/ml), and positive TPO antibodies (normal range <50 IU/ml). Most of the latter had a thyroid ultrasound scan, which was consisted with the diagnosis of autoimmune thyroiditis. The diagnosis of GrH was based, except for high levels of FT_4 and suppressed TSH, on one or more of the following: various degrees of diffuse goiter (clinically or by ultrasound scan), ophthalmopathy or elevated levels of thyroid receptor antibodies (TRAbs). The serum concentrations of FT_4 and TSH were measured by standard, commercial RIA kits (DiaSorin, 13040, Saluggia (VC), Italy). TPO antibody titers were determined by commercial RIA kit (Brahms, Henningsdorf, Germany).

Statistical analysis

We analyzed the data using cosinor analysis (24). Cosine approximation Y_i (monthly number of births) = $M + A \times \cos(\omega t_i + \phi)$ yield the following parameters: M is the time series mean (Midline Estimating Statistic Of Rhythm), A is the amplitude (one-half of the peak to trough variation), and acrophase (ϕ) is the peak time of the calculated rhythm. T_i , the time in months; (ωt), the period of the rhythm (2D Table curve, Jandel Scientific, San Rafael, CA, USA). The data were compared with the pattern of total live births during 2003–2004 in Thessaloniki, Greece ($n=37\,119$). Information was

obtained from the national registry of Central Macedonia, Greece.

Results

The overall results are summarized in Table 2. The rhythmic patterns of the seasonality of MOB are graphically illustrated in Figs 1 and 2.

In the general population, in both males and females, the highest incidence of births was noticed during summer (Fig. 1; $P<0.01$ and $P<0.05$ respectively). In contrast, both genders with GrH had a different pattern of MOB distribution when compared with the general population, which also differed between the genders. More specifically, more males with GrH had been born during winter ($P<0.01$), whereas females showed two peaks in the distribution of births, one in spring and one in autumn ($P<0.01$).

Figure 2 illustrates the comparison between the distribution of MOB in patients with HH and the general population. It is clear that the pattern of both genders with HH differs from that of the general population and also that the pattern of MOB differs between the two genders. The males have two peaks, one in summer and one in winter ($P<0.01$), whereas the females have only one in winter ($P<0.01$).

To find out whether the pattern of MOB in patients with HH differs with the serum TPO antibody titers, we divided the patients with HH arbitrarily into three subgroups according to their TPO antibody titers at diagnosis: low levels (<500 IU/ml), high levels (500–1000 IU/ml), and extremely high levels (>1000 IU/ml; Fig. 2). In women, the only group that showed rhythmicity was the group with extremely high titers ($P<0.01$) with a pattern different from that of controls but identical with that of the entire female population with HH. In contrast, women with low or high levels showed no rhythmicity. In men, both groups with low ($P<0.01$) and extremely high TPO antibody levels ($P<0.01$) showed rhythmicity in MOB. The pattern of MOB distribution was different between these two subgroups as well as from the controls. In contrast, men with high levels showed no rhythmicity.

Discussion

To the best of our knowledge, the fact that the seasonal and monthly pattern of birth of patients with AITD differs from that of the general population has not been reported so far. Our study shows an abnormal seasonality of birth in a large independent Greek population with AITD, both GrH and HH. This is unlikely to be due to chance, and it is difficult to conceive of a bias that might account for the results. Of note, no reports are available from the local Department of Health stating that the prevalence of specific or

Table 1 Demographic characteristics of the patients.

	Overall (<i>n</i> = 1023)	GrH (<i>n</i> = 359)	HH (<i>n</i> = 664)
Mean age at diagnosis ± s.d. (years)	42.4 ± 14.4	44.5 ± 14.1	41.3 ± 14.5
Gender (%)			
Males	17.9	22.0	15.7
Females	82.1	78.0	84.3

GrH, Graves' hyperthyroidism; HH, Hashimoto's hypothyroidism.

Table 2 Rhythmic parameters of the seasonality of month of birth in patients with Graves' disease and Hashimoto's thyroiditis when compared with the general population.

	Graves'		Hashimoto's		Hashimoto's – low titer		Hashimoto's – extremely high titer		General population	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
n=	78	280	103	557	17	85	41	194	18 971	18 148
Correlation coefficient R	0.43	0.67	0.73	0.74	0.87	NS	0.80	0.80	0.70	0.39
Period (months)	12	6+4	6+4	8+12	12+4		8+12	6+4	8+12	8
Mesor	6.2	23.3	8.6	49.4	1.42		4.47	16.16	1533	1522
Amp	2.6	6 months=3.2 4 months=3.1	6 months=3.3 4 months=2.9	8 months=15.2 12 months=14	12 months=0.78 4 months=1.12		12 months=15.7 8 months=4.9	6 months=2.73 4 months=4.3	8 months=73.2 12 months=97	109.7
P value	<0.01	<0.01	<0.01	<0.01			<0.01	<0.01		
Peak at	March	April and September	July	January and July	March, July, and November		January and June	January and June	August	August

general viral infections in the area was different from usual 40–45 years ago, which is the age of most of our patients today.

Several important conclusions can be drawn from our observations. Whereas both genders in the general population had a rhythmic seasonal pattern with an excess of births in the summer and early autumn months, the pattern of MOB distribution in both genders with HH differs from that of the general population. In the general population, in both males and females, the highest incidence of births was noticed during summer; whereas male patients with HH had two peaks, one in summer and one in winter, and the females had only one in winter.

Regarding patients with GrH, both genders had a different pattern when compared with the general population, with an additional difference between them (the peak in the males being in winter and the females having two peaks, in spring and autumn). The findings of two periods of excess births may suggest the existence of more than one subpopulation in the groups analyzed. This may be due to genetic or environmental factors.

In addition, we observed variation in MOB seasonality in patients who had extremely high TPO titers when compared with those with low titers. Of note is that antibody measurements were performed only at the initial visit. In addition, it has to be mentioned that the term autoimmune thyroiditis encompasses several different entities whose interrelationships remain unclear. This supports the heterogeneous nature of the disease.

Our findings are in line with observations for T1D mellitus (T1DM) that the clinical onset follows an infection with an increased incidence in autumn and winter, i.e., during the months of the yearly virus epidemics (15). Further epidemiological studies showed that patients who subsequently developed T1DM (21–23) or MS (25) had a different seasonality pattern in MOB than the general population, the peak prevalence being in the spring and summer months. These findings were interpreted as support of the 'viral hypothesis' assuming that the viral infections in autumn and winter trigger the autoimmune process in genetically susceptible fetuses conceived during those periods of the year. Graves' disease and Hashimoto's thyroiditis are autoimmune diseases (26) and the different pattern of MOB found in these patients when compared with the general population raises the possibility that the GrH and HH have the same or a similar trigger as in T1DM or MS.

It is of interest that the patterns of MOB between patients with GrH or HH differ. This may be due to a different type of autoimmune etiology despite a common trigger. The finding of a different MOB in patients with a very high titer of TPO is similar to findings reported in T1DM patients with high or multiple titers of anti-β-cell antibodies (27).

Seasonal factors, other than viral epidemics, which could be implicated are u.v. radiation and vitamin D (28), a deficiency of which is suspected to relate with the

Figure 1 Comparison of month of birth distribution between patients with Graves' disease and the general population. TLB, total live births.

etiology of autoimmune diseases (29). Although Greece is a sunny country, a recent study has showed that a substantial percentage of the population suffers from vitamin D deficiency, particularly during winter (30).

It must be remembered that genetic and environmental factors have been shown to play a key role in the development of these diseases. It is likely that a genetic predisposition is necessary for the development of AITD and a seasonal viral infection acting as a sole

environmental pathogen or synergistically with other pathogens has a predominant role in controlling whether a genetically predisposed individual progresses to clinically overt disease. Other environmental factors such as iodine intake or smoking may act as triggers leading to the conversion of the subclinical to clinical disease.

Most studies of biological rhythms rely on two types of time series analytical approaches. One approach involves the fit of time series data by a mathematical

Figure 2 Comparison of month of birth distribution between patients with Hashimoto's thyroiditis and the general population. TLB, total live births.

model (e.g., cosine function; (24)) with a predetermined period. The other approach involves subjecting the data to spectral analysis to ascertain information on the different ranges of cycles in the data. Epidemiological studies on yearly MOB distribution used the Poisson regression (31) or the Walter and Elwood test (32) methods, which are of limited use for small populations (33–37). The advantage of the cosinor analysis is that in addition to statistical significance it provides parameters regarding the rhythm (36, 37). Therefore, we analyzed the data by using cosinor analysis (24).

In conclusion, the different MOB seasonality in both GrH and HH point towards a similar, perhaps even common etiology with autoimmune diabetes and MS (38), namely a seasonal viral infection as the initial trigger in the perinatal period, the clinical disease resulting from further specific damage over time.

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Received 11 January 2007

Accepted 20 March 2007