Seasonal Variation in the Time of Disease Manifestation in Finnish Children with Type 1 Diabetes

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Short Report

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Abstract

We tested the hypothesis of a more aggressive disease process at diagnosis of type 1 diabetes during autumn and winter, the colder seasons with consistently observed higher incidence of type 1 diabetes, compared to spring and summer. Seasonality in the manifestation of type 1 diabetes was examined in 4993 Finnish children and adolescents participated in the nationwide register. Clinical and metabolic characteristics, beta cell autoantibodies and HLA class II genetics were analysed at clinical diagnosis. Significant seasonality was observed with higher number of new cases during autumn and winter ($n=1353/27.1\%$ and $n=1286/25.8\%$) compared to spring and summer ($n=1135/22.7\%$ and $n=219/24.4\%$) ($p<0.001$). The youngest children (aged 0.5-4 years) differed from the older ones (aged 5-14 years) as their frequency of diagnoses was highest in autumn and the fewest cases were found in winter ($p=0.019$) while the older children followed the same pattern as that seen in the total series. Ketoacidosis was more frequent in children diagnosed during spring or summer compared to those diagnosed in autumn (18.8% and 19.9% vs. 15.8%, respectively; $p=0.036$) and weight loss was highest if diagnosed in summer (6% vs. 4.7–5.4%; $p<0.001$). No relationship was observed between the season of disease presentation and diabetes-associated autoantibodies or HLA genotypes.

Conclusions: Contrary to our working hypothesis, more severe metabolic decompensation was seen during seasons with lower number of new cases. The heterogeneity in the seasonality of diabetes manifestation between younger and older children suggests that there could be different environmental factors triggering the disease at different ages.

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What Is Known:

- Seasonal variation in the presentation of type 1 diabetes has been consistently observed with the highest incidence rate of the disease found in autumn and winter and the lowest rate in spring and summer.
- Seasonality has been more pronounced in high-incidence countries and associated with male sex in addition to older age.

What is new:

- There is heterogeneity in the seasonality of type 1 diabetes manifestation between younger and older children as the number of new diagnoses peaked in autumn and reached a nadir in winter among the youngest children (aged 0.5-4 years) in contrast to the older children (aged 5-14 years) with peaks both in autumn and in winter.
- Signs of a more severe metabolic derangement was observed during the seasons with fewer diagnoses, i.e. in spring and in summer, but a clear link between seasonality, metabolic changes and

immunology seems to be missing.

Introduction

Seasonal variation in the incidence of type 1 diabetes has been reported with a peak in the autumn and winter months [1-5]. The phenomenon seems to be more pronounced in high-incidence countries [4]. Some studies suggest seasonality to be more prominent in males and absent in the youngest children [2, 4, 6] while others disagree [1, 3]. However, studies discussing the association of seasonality and the clinical characteristics of type 1 diabetes at diagnosis are sparse.

We set out to delineate the seasonal variation in the manifestation of type 1 diabetes in Finnish children and the association of seasonal timing of diagnosis with clinical presentation, markers of beta cell autoimmunity and HLA genetics. We also wished to analyse whether seasonal variation is dependent on sex or age. We hypothesized that the clinical presentation is more aggressive in the cold months given the higher number of new cases in that period.

Materials And Methods

Study design and subjects

In total, 4993 patients, aged between six months and 15 years (56.6% male, median age 8.2) and diagnosed with type 1 diabetes between 2003 and 2016 were derived from the Finnish Pediatric Diabetes Register (FPDR). Participants with no samples available for the autoantibody and HLA analyses were excluded ($n=1747$) as described previously [7] (Table S1).

Study subjects were divided into four groups by season of disease presentation. Seasons were classified according to the calendar months: spring (March to May), summer (June to August), autumn (September to November) and winter (December to February).

Metabolic factors, autoantibodies and HLA genetics at diagnosis

Markers of metabolic decompensation at diagnoses were analysed in the local laboratories. Insulin autoantibodies (IAA), antibodies to glutamic acid decarboxylase (GADA), islet antigen 2 (IA-2A), and zinc transporter 8 (ZnT8A) were analysed using specific radiobinding assays, and islet cell antibodies (ICA) with indirect immunofluorescence. We excluded samples taken later than 30 days after diagnosis (255/4993, 5.1%). PCR-based amplification followed by hybridization with lanthanide-labeled probes and time-resolved fluorometry detection was used for HLA typing of the major DR-DQ haplotypes. [7] See Online Resource Methods for details.

Statistical analyses

We used IBM SPSS Statistics 24 (IBM Corp., Armonk, N.Y., USA) and the R Software for Statistical Computing for Windows, version 3.5.0 (R foundation, Vienna, Austria, <https://cran.r-project.org/>) for

statistical analyses. We compared the observed frequencies of seasons/months to the expected frequencies of the same variables considering the number of days in each season/month to account for the unequal lengths of months. A mean number of 365.25 days per year and 28.25 days in February was assumed in order to rule in the leap years. Cross-tabulation and the χ^2 -test were used for frequencies of categorical variables. Differences in levels of parametric variables were analysed with Student's *t* test or one way ANOVA and Mann-Whitney U test or Kruskal-Wallis test for nonparametric variables. Adjustment for age at diagnosis and sex was performed with logistic/ordinal/multinomial regression for dichotomous/ordinal/categorical variables and quantile regression in R (package quantreg) for nonparametric variables. A two-tailed *p* value <0.05 was considered statistically significant (see Online Resource Methods for details).

Results And Discussion

A majority of the children were diagnosed in autumn or winter ($n=1353/27.1\%$ and $n=1286/25.8\%$) vs. in spring or summer ($n=1135/22.7\%$ and $n=1219/24.4\%$) ($p=0.001$). Spring was the season with the lowest number of new cases compared to the other seasons ($p=0.006$). Analyses by month revealed significant seasonality, with a peak frequency of diagnoses in January followed by August and September, the lowest frequency being observed in May ($p<0.001$) (Fig. S1). The observed frequency of new diagnosis in the cold season (52.9%) is in line with a report from Sweden (53%) [5] while in general, comparisons with previous studies are challenging because of differences in the research designs and methods. We did not observe any difference in the seasonality of diabetes manifestation between the sexes. There is a male-to-female excess in patients with type 1 diabetes [7], and the reason for pronounced seasonality in males observed in some reports might reflect stronger statistical power.

To exclude potential changes in the environment over the years possibly contaminating the results, we looked for the difference in seasonality between those diagnosed during ≤ 2009 and >2009 but found no significant differences. The season of birth was not related to the time of disease manifestation.

We further divided the study population into two groups by age at diagnosis (0.5-4 years and 5-14 years) and observed significant seasonality in the group of older children but not among the younger children (additional information is given in Online Resource Results). A previous report by Weets et al. agree with that finding [6]. Between-group analysis showed a clear difference as the youngest children had a peak of disease presentation in autumn and, surprisingly, a nadir in winter contrary to the older children with peaks both in autumn and in winter (Fig. 1). Furthermore, this observation was significant in boys but not in girls. A link between certain enteroviruses and progression to clinical type 1 diabetes has been implicated (reviewed in [8]). Enteroviruses more often affect younger children, and in Finland, more than 80% of enterovirus infections are diagnosed between August and December [9]. This may explain the peak of type 1 diabetes during autumn and the low frequency of disease presentation in winter among the younger children. Some seasonal cycling exists also in the 25(OH)D concentrations, as in Finnish children, they are observed to be decreased in winter in parallel with the decreased amount of sunlight [10]. Moreover, decreased 25(OH)D concentrations were associated with multipositivity for diabetes-

related autoantibodies. Compared to the older children, the vitamin D intake in the younger children might be more closely controlled by the parents and the health care professionals due to more frequent contacts in the child health clinic during early childhood. Our results together with the current observation about the decreasing trend in the incidence rate of the disease only among younger children [11] suggest different environmental factors triggering the disease in children of different age.

All the analyses were then adjusted for age at diagnosis and sex. Contrary to our hypothesis, those diagnosed in spring or summer suffered from ketoacidosis more often than those diagnosed in autumn (Table 1). Furthermore, weight loss at diagnoses was highest in summer. Hanberger et al. reported similar findings of HbA1c as the levels were the highest in late spring and summer when the number of children diagnosed with type 1 diabetes was the lowest [5]. The results might be due to the higher risk for dehydration in the seasons with higher temperature leading to more severe metabolic decompensation, or due to the delay of diagnosis during summer holidays and poorer availability of health services. Interestingly, a few studies have reported a positive correlation between high-incidence seasons and C-peptide levels at diagnosis, suggesting variation in the secretory capability of remaining beta cells by season [12, 13]. As classical symptoms and weight loss present less often in children with higher C-peptide concentrations at diagnosis [13], possibly this could explain our observation of better clinical condition in autumn/winter. Unfortunately, we were unable to test this hypothesis as the FPDR does not provide information on the C-peptide concentrations at diagnosis. Nevertheless, the above-mentioned observations might let us to expect that there should be milder signs of autoimmunity during the high-incidence seasons reflecting heterogeneity on the pathogenic process according to the season of diagnosis.

However, we failed to show seasonality in the number of positive autoantibodies at diagnosis and the only notable relationship between season of disease presentation and autoantibodies was higher ICA titers observed in autumn (Table S2). In a small Slovakian study, IA-2A positivity at diagnosis showed seasonal cycling with a peak in autumn [14]. Similar seasonality has not been observed in IAA [14] or GADA at diagnosis [14, 15]. In a Belgian cohort, seasonality in the diagnosis of type 1 diabetes was restricted to HLA DR3/DR4-negative males [6]. However, we did not find any differences in the HLA genetics between the seasons (Table S3).

A strength of this cross-sectional observational study is the large sample derived from the nationwide register including more than 90% of all children diagnosed with diabetes. The retrospective nature of this study is a limitation. There is a possibility of selection bias as 1747 children were excluded because of the lack of samples for analyses [7]. However, the frequencies of seasons of disease presentation did not differ between the included and the excluded children.

In conclusion, our results from the country with the highest incidence of type 1 diabetes confirmed the seasonality of type 1 diabetes manifestation with peaks in autumn and winter. Seasonality of disease presentation was similar in both sexes. Younger children were most seldom diagnosed in winter whereas the peak of the diagnoses continued from autumn to winter in older children, suggesting heterogeneity in

environmental factors contributing to the development of type 1 diabetes in children of different ages. Signs of a poorer metabolic status was observed during the seasons with fewer diagnoses, in spring and summer. However, based on the results from this and previous studies, no clear link can be discerned between seasonality, metabolic decompensation and beta cell autoimmunity at diagnosis.

Abbreviations

FPDR	Finnish Pediatric Diabetes Register
GADA	Antibodies to glutamic acid decarboxylase
IAA	Insulin autoantibodies
IA-2A	Antibodies to islet antigen 2
ICA	Islet cell antibodies
ZnT8A	Zinc transporter 8 autoantibodies

Declarations

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Conflicts of interest The authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Availability of data and material The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability N/A

Authors' contributions MT collected and analyzed the data, contributed to the study conception and data acquisition, wrote the first version of the manuscript, edited and approved the final manuscript as submitted. TH was responsible for the autoantibody laboratory, reviewed the manuscript, contributed to the data acquisition and discussion and approved the final manuscript as submitted. JI was in charge of HLA genotyping, reviewed the manuscript, contributed to the data acquisition and discussion and approved the final manuscript as submitted. AP reviewed the manuscript, contributed to the data acquisition and discussion and approved the final manuscript as submitted. MK planned the study, reviewed the manuscript, contributed to the data acquisition and discussion and approved the final

manuscript as submitted. MK is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics approval The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa.

Consent to participate A legal caretaker gave a written informed consent, and participants 10-15 years of age an informed assent.

Consent for publication Informed consent was obtained from the legal caretaker and an assent from the participants aged 10-15 year.

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Supplementary Information The online version contain supplementary information.

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Tables

Table 1 Seasonal variation in demographic, clinical and metabolic characteristics in type 1 diabetes affected children diagnosed in spring, summer, autumn and winter

	<i>n</i>	1. Spring, <i>n</i> =1135 (22.7 %)	2. Summer, <i>n</i> =1219 (24.4 %)	3. Autumn, <i>n</i> =1353 (27.1 %)	4. Winter, <i>n</i> =1286 (25.8 %)	<i>p</i> value	Adjusted <i>p</i> value ^a
Demographics							
Sex, male, % (95%CI)	4993	56.0 (53.1- 58.9)	58.4 (55.6- 61.2)	55.7 (53.0- 58.3)	56.2 (53.5- 58.9)	0.506	
Familial, % (95 % CI)	4993	10.1 (8.4- 11.9)	11.2 (9.4- 12.9)	9.5 (8.0- 11.1)	10.8 (9.1- 12.5)	0.541	0.531
Pubertal, % (95%CI)	3764	17.8 (15.3- 20.3)	16.4 (14.0- 18.7)	17.6 (15.3- 20.0)	16.8 (14.4- 19.1)	0.819	0.279
Metabolic decompensation at diagnosis							
Duration of symptoms, %	4614					0.067	0.041
No symptoms		1.5	0.5	1.0	0.8		
< 1 week		21.0	22.8	23.1	23.2		
1-4 weeks		60.2	55.7	55.8	58.5		
> 4 weeks		17.4	20.9	20.2	17.5		
							1 vs. 2: <0.050
Impaired consciousness, % (95%CI)	4784	5.2 (3.9- 6.6)	6.5 (5.1- 7.9)	4.9 (3.7- 6.1)	5.2 (4.0- 6.4)	0.331	0.327
Ketoacidosis, % (95%CI)	4817	18.8 (16.5- 21.2)	19.9 (17.6- 22.2)	15.8 (13.9- 17.8)	17.5 (15.4- 19.6)	0.051	0.036
							1 vs. 3: <0.050
							2 vs. 3: <0.050
Severe ketoacidosis, % (95%CI)	4817	3.8 (2.7- 5.0)	5.6 (4.3- 7.0)	4.4 (3.3- 5.5)	4.6 (3.4- 5.7)	0.212	0.183
Weight loss, %, median (range)	4610	4.9 (0- 33.2)	6.0 (0- 32.3)	4.7 (0- 40.0)	5.4 (0- 28.3)	< 0.001	<0.001
							1 vs.

							2:0.017
							2 vs. 3: <0.001
							3 vs. 4:0.003
pH, median (range)	4817	7.38 (6.82- 7.53)	7.38 (6.82- 7.54)	7.38 (6.82- 7.53)	7.38 (6.72- 7.57)	0.122	0.112
β-Hydroxybutyrate, mmol/L, median (range)	4384	1.6 (0- 18.4)	1.9 (0- 17.4)	1.7 (0- 27.0)	1.7 (0- 23.5)	0.234	0.330
Plasma glucose, mmol/L, median (range)	4869	24.2 (3.2- 93.2)	24.5 (3.6- 83.2)	23.4 (3.5- 97.6)	23.5 (3.6- 94.6)	0.079	0.070
HbA1c, mmol/mol, median (range)	841	93.2 (40.0- 176.0)	91.0 (38.0- 164.0)	90.0 (36.0- 189.0)	89.0 (37.7- 171.0)	0.700	0.427
HbA1c, %, median (range)	841	10.7 (5.8- 18.3)	10.5 (5.6- 17.2)	10.4 (5.4- 19.4)	10.3 (5.6- 17.8)	0.696	0.392

In case of significant differences in the analyses between the four groups of season, paired comparisons by groups were also performed. Only significant *p* values are presented from the paired analyses

^aAdjusted for sex and age at diagnosis

Figures

Figure 1

Seasonal variation in diabetes onset among children aged 0.5-4 and 5-14 years. The between-group analyses showed a significant difference in the distribution of diagnosis frequencies by season. There was a peak in the frequency of diagnoses during autumn and a drop-down during winter among the younger children while the older children were most often diagnosed in autumn followed by winter ($p=0.019$) (a). The phenomenon was more pronounced in the subgroup of boys ($p=0.020$) (b) and not seen in the subgroup of girls ($p=0.347$) (c). Significance was evaluated using Cross-tabulation and the χ^2 -test

Supplementary Files

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