Seasonality of birth of patients with juvenile idiopathic arthritis

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Abstract

Objective

The aim of this study was to determine the seasonality of month of birth (MOB) in children with juvenile idiopathic arthritis (JIA) as compared to the general population.

Methods

Cosinor analysis was used to analyse MOB rhythmicity in 558 children with JIA from a simple rheumatology clinic compared with the MOB pattern of the general population in Israel (n=1.040558). Statistical differences between groups were also analysed by non-parametrical tests.

Results

Patients with JIA showed different patterns from that of the general population. A rhythmic pattern of 12 months was found in the MOB patterns of JIA patients. This rhythm with a peak between November to March and a nadir in summer was a mirror image of the rhythmic pattern observed for MOB of the healthy population. Males showed a pattern with combined rhythm of 8 and 6 months with peaks in winter, while females' MOB pattern showed no rhythmicity. Testing different JIA subtypes, only the patients with the enthesitis-related arthritis (ERA) subtype showed rhythmicity in MOB. Rhythmicity patterns were different for males and females, and differed according to several disease characteristics.

Conclusion

The observed pattern of MOB in JIA patients is distinctive and different from that in the healthy population supporting the hypothesis that autoimmune process may begin in utero or in the perinatal period due to seasonal environmental pathogenic agents.

Key words

juvenile idiopathic arthritis, seasonality, month of birth, perinatal factors, children, autoimmune

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Received on May 10, 2014; accepted in revised form on July 29, 2014.

Competing interests: none declared.

Introduction

Juvenile idiopathic arthritis (JIA), the most common chronic rheumatic disease of childhood, is a group of disorders characterised by chronic inflammatory arthritis. According to the current International League of Associations for Rheumatology (ILAR) classification, different subtypes of JIA can be distinguished on the basis of clinical manifestations (oligoarthritis – persistent and extended – rheumatoid factor (RF) positive and RF negative polyarthritis, systemic, psoriatic, enthesitis-related [ERA] and other, undifferentiated arthritis) (1). Each subtype is characterised by distinct clinical and laboratory manifestations and prognosis.

JIA is an autoimmune disease, caused or triggered by environmental factors such as infectious agents in a genetically susceptible host (2, 3). Infectious agents including viruses in concert with other factors (*e.g.* stressful life events, psychosociologic milieu, meteorological variations, and maternal smoking) may contribute to the pathogenesis of JIA (2). The aetiologic role of environmental factors is supported by data demonstrating a seasonal variation of disease onset in systemic-onset JIA (4, 5). The seasonal based increase in systemic JIA incidence correlated with enteroviral infections which also show a seasonal pattern (6).

If viral infections are linked to the initiation of JIA as suspected in other autoimmune diseases (7-11), children who develop JIA may have a different seasonality of month of birth (MOB) compared to the general population as was found in type 1 diabetes mellitus (T1DM) (7, 8, 10), coeliac disease (11) and other autoimmune diseases (9, 12). The aim of this study was to examine whether the seasonality of MOB is different for JIA patients compared to the general population. In addition, seasonality of MOB was compared among the different JIA subgroups. To the best of our knowledge, this is the first study of its kind.

Patients and methods

The study cohort consisted of all children attending the rheumatology clinic of the Lily & Edmond Safra Children Hospital, Sheba Medical Centre, a tertiary referral hospital in Israel during the years 2000–2010, who met the ILAR criteria for JIA. Date of birth, sex and age of arthritis onset, the disease subtype, history of uveitis and anti-nuclear antibody (ANA) status were recorded.

The MOB of the patients was compared to the MOB of the general population in Israel which served as a control group (n=1,040,558; 534,650 males, 505,908 females). Each JIA subgroup was analysed separately for each gender and for the total population. The data for MOB were obtained from the Israeli population registry at the Central Bureau of Statistics, Jerusalem. The MOB of the general population was obtained for a period of 13 years. The analysis of individual years during these representative 13 years yielded the same results as the whole period. The Institutional Review Board of Sheba Medical Centre approved the study protocol.

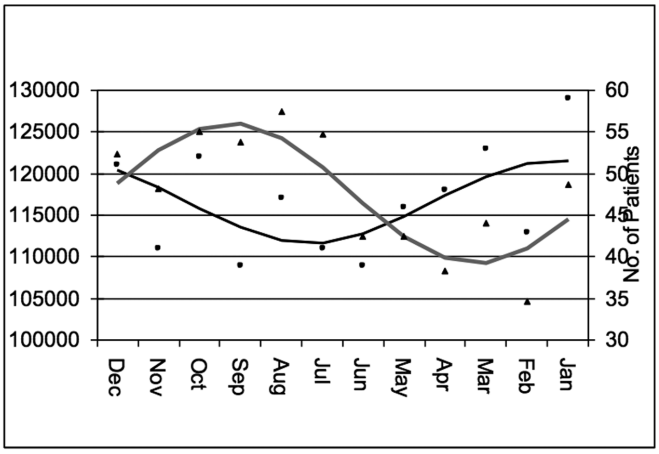
Statistical analyses

Biological rhythms rely on two types of time series analytical approaches. One approach involves the fit of time series data by a mathematical model (*e.g.* cosine function) 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 using the Poisson regression (13) or the Walter and Elwood test (14) were found to be of limited value for small populations (15, 16). The advantage of the cosinor analysis

Table I. Characteristics of the 558 JIA patients enrolled in the study.

Clinical feature	Mean±SD
Females, n (% of patients)	377 (67.6)
Patients with positive ANA*, n (%)	172 (30.8)
Patients with uveitis, n (%)	64 (12.9)
Oligoarthritis	380 (68.1)
RF-negative polyarthritis	54 (9.7)
RF-positive polyarthritis	14 (2.5)
Systemic subtype	59 (10.6)
Psoriatic arthritis	16 (2.9)
Enthesitis-related arthritis	35 (6.3)

*ANA anti nuclear antibodies.

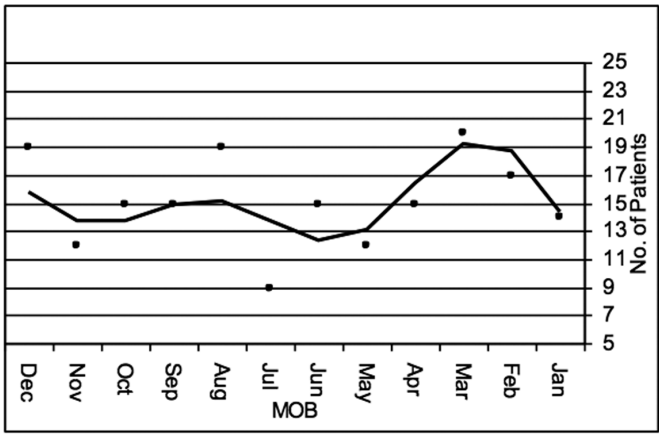


Grey triangle: general population. Black circle: JIA patients

General population 12 months rhythm: R=0.86, p<0.001 Mesor 86713 Amplitude = 6312.4

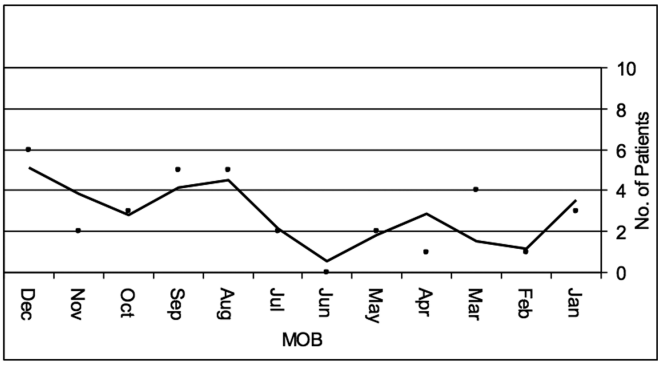
JIA patients 12 months rhythm: R=0.58, p<0.05 Mesor 46.58 Amplitude = 4.96

Fig. 1. Month of birth of JIA patients and general population.



Eight and 6 months rhythm: R=0.65 p<0.05 Mesor 14.8, Amplitude = 3.1

Fig. 2. Month of birth of male JIA patients.



Four and 12 months rhythm. R=0.77, p<0.01 Mesor 2.83 Amplitude = (4 months) 1.37 Amplitude = (12 months) 1.36

Fig. 3. Month of birth of patients with enthesitis-related arthritis.

is that in addition to statistical significance, it provides parameters regarding the rhythms (13).

We analysed the data using the cosinor method (17). Cosine approximation $Y_i = M + A \times COS(\omega t_i + \phi)$ yield the following parameters: M=the time series mean (Midline Estimating Statistic Of Rhythm, MESOR), A=Amplitude (one half of the peak to trough variation), and Acrophase (ϕ) - the peak of the calculated rhythm (ωt)- the period of the rhythm (2D Table curve, Jandel Scientific, USA). The data were compared to the pattern of total live births. The degree of fitness was determined by the statistical parameters R and p-value. The statistical significance was calculated using these parameters and the degrees of freedom.

Statistical differences between the examined groups were determined by χ^2 analysis.

Results

A total of 558 patients with JIA (377 females, 67.6%) were included in this study (Table I).

A rhythmic pattern of 12 months was found in the MOB patterns of JIA patients (n=558, p<0.05, R=0.58). This rhythm with a peak between November to March and a nadir in summer was a mirror image of the rhythmic pattern observed in MOB of the healthy population (n=1412000, p<0.01, R=0.927) (Fig. 1).

As the JIA population is heterogeneous and different JIA subgroups may differ in their aetiology, we analysed the data according to gender and JIA subtypes, ANA positivity and presence of uveitis. Rhythmicity patterns were different for males and females. Males showed a pattern with combined rhythm of 8 and 6 months with peaks in winter (February) (Fig. 2), while females MOB pattern showed no rhythmicity. Only the patients with the ERA subtype showed rhythmicity in MOB (Fig. 3). The rhythm was composed of two components 12 and 4 months that resulted in peaks in August and December (n=34, p<0.01, R=0.77). No significant differences were found for other subtypes, ANA positivity and uveitis when analysed for all patients. As the total cohort showed a difference in MOB rhythmsbetween males and females, subgroup analyses based on gender were performed for patients with the most common oligoarticular JIA subtype and for those with ANA positivity. The patterns observed were similar with these of the total JIA population. The males with oligoarticular disease showed a two component rhythmicity in MOB of 12 and 4 months (n=101, p<0.01, R=0.86, Fig. 4A), while MOB of the females were non-rhythmic (n=279).

In the ANA positive patients both males and females were rhythmic with 8 and 4 months components and 8 and 6 months rhythmic components respectively. Furthermore, the peaks of the rhythmic pattern in these two populations were different (males: n=27,

$p<0.01$, R=0.768; females: n=145, $p<0.05$, R=0.565). In the males the major peak was in July, while for females two peaks were observed: March and December. These results explain the non-rhythmic pattern obtained when the two genders were analysed as one group and indicate that males and females with ANA may be sensitive to different environmental factors (Fig. 4B).

Four + 12 months rhythm:
R=0.74, $p<0.01$
Mesor 8.41
Amplitude = (4 months) 1.1
Amplitude = (12 months) 2.55

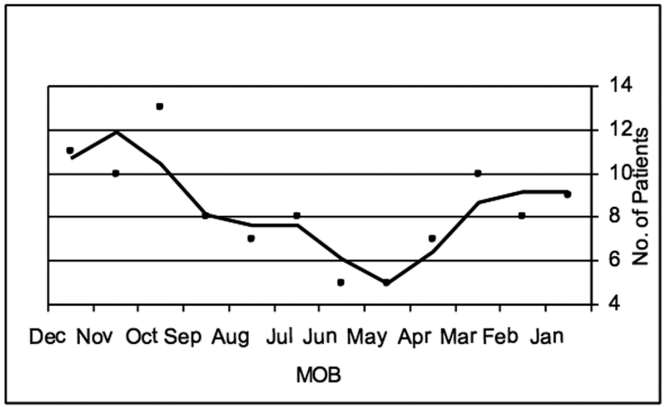


Fig. 4a. Month of birth of male JIA patients with oligoarthritis

Grey triangle = males
8+4 months rhythm:
R=0.77, $p<0.01$.
Mesor 2.78
Amplitude = (8 months) 0.7
Amplitude = (4 months) 0.67

Black circle = females
8+6 months rhythm:
R=0.56, $p<0.05$
Mesor 11.52
Amplitude = (8 months) 4.1
Amplitude = (6 months) 2.46

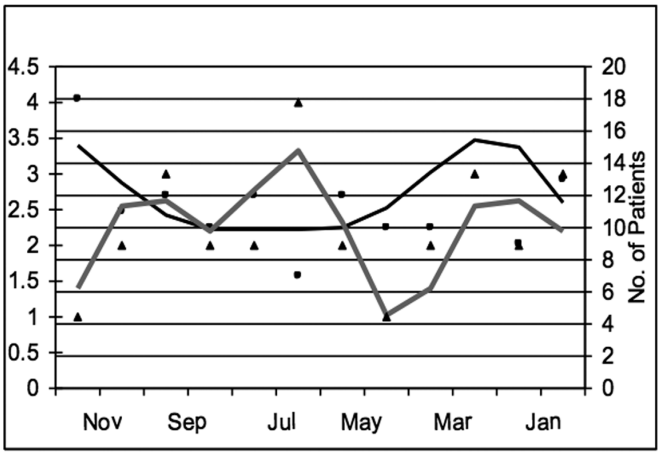


Fig. 4b. Month of birth of male and female ANA positive JIA patients.

Discussion

Seasonality of MOB in children with JIA differs significantly from the pattern in the general population. The rhythmic 12-month pattern in our JIA patients was a mirror image of the rhythmic pattern observed in the healthy population. These observations resemble seasonality of birth reported in several autoimmune diseases in children: T1DM (7, 8, 10), Graves disease, Hashimoto thyroiditis (9), multiple sclerosis (12) and coeliac disease (11). In all of these disorders, the pattern of MOB seasonality was different from that of the general population. In autoimmune diseases such as T1DM, the variation between the specific disease population and the general population was attributed to a variety of factors.

As a possible explanation for this finding it was suggested the parallel seasonality of endemic viral infections, such as enteroviruses, rotaviruses, and influenza during the late autumn and winter (11, 18). The suggested seasonality of autoimmune diseases assumes that the infected mother transmits a viral pathogen to the foetus, and if the foetus is genetically susceptible, a specific autoimmune disease process will be triggered (19). Similarly, viral seasonal infection contemporaneous with the vulnerable period of a developing embryo may explain this excess birth of JIA patients in winter months.

Other possible contributory factors for this difference in the birth seasonality between our JIA patients and the general population may be explained by seasonal environmental factors, such as solar exposure and vitamin D. Solar ultraviolet radiation can suppress directly T cell immunity. Solar exposure increases the synthesis of vitamin D, a steroid hormone with multiple immunosuppressant properties. Vitamin D deficiency has been linked to several autoimmune diseases, including JIA (20, 21) and serum levels of vitamin D show a similar seasonal variation with patterns similar to that of children with rheumatologic disorders (21). Vitamin D is an important factor even in solar-rich environments as there are still considerable rates of vitamin D deficiency in the general population living in these environments (22).

Another significant finding of our study is a rhythmicity of 8 and 6 months with peaks in the winter only in males with JIA and an absence of the MOB rhythmicity in female patients. Most JIA patients are females except for enthesitis-related (ERA) subtype. Gender is associated with uveitis prevalence and severity. Our finding may indicate a different etiopathology of the JIA between genders, and the requirement for a second environmental or genetic insult in males who are known to be less predisposed for JIA. Similar findings were observed in Crohn's disease, in which the pattern of MOB seasonality also differed between girls and boys, between those who were diagnosed before or after age 24 months, and between children with and without Crohn's disease in first-degree family members (11).

The the non-rhythmic pattern observed in females with JIA, which is also different from the general healthy population, may show that females are either sensitive to a factor that is not environmental or sensitive to environmental factors that do not have seasonal variation.

Conclusion

The observed pattern of MOB in JIA patients different from that in the healthy population support the hypothesis that autoimmune process may begin *in utero* or in the perinatal period due to a seasonal environmental pathogenic agent.

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