Full Length Research Paper

Seasonal variation by the onset of symptoms and health care seeking behaviour in 282 patients with Inflammatory Bowel Disease

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Environmental factors are believed to trigger the onset of Inflammatory bowel disease (IBD). We aimed to evaluate the seasonal variation in the onset of symptoms in patients with IBD and health care seeking behaviour. 282 patients were chosen from the charts. Demographic features, the month and the age at the onset of presenting symptoms and delayed diagnosis term for each patient were analyzed. Cumulative monthly averages analysed by Kruskal Wallis test and Roger’s test. Of the 282 patients with IBD, 181 were male (64%). Mean age was 40.1±14.7 years (median: 38, range: 14 to 79 years). The seasonal pattern showed peak in March with 57% and the lowest point in November with 36% (p <0.05). The delayed diagnosis term was 3.0 ± 2.3 months in males vs 3.2 ± 3.2 months in females (p >0.05). The seasonal pattern was not influenced by both genders and by age groups in patients with IBD or UC or CD (p >0.05). We investigated the etiologic environment of IBD and found an interaction between the etiopathogenesis of IBD and environmental risk factors. There was a delay in IBD, but no difference on the health care seeking behaviour between males and females.

Key words: Inflammatory bowel disease, Crohn’s disease, seasonal, cluster, health care seeking behaviour.

INTRODUCTION

IBDs (Inflammatory bowel diseases) including Crohn’s disease (CD) and ulcerative colitis (UC) are chronic diseases with an unknown etiology (Auslander et al. 2005). Environmental factors are believed to trigger the onset of either CD or UC in genetically susceptible individuals. In this regard, to investigate seasonal variation in IBD as an unknown etiopathogenesis does make sense. Seasonal variation studies are performed by scholars who are working to find particular infective agents such as gastrointestinal system infections or a specific time period (Evans and Acheson, 1965; Cave and Freedman, 1975; Don and Goldacre, 1984; Myszor and Calam, 1984; Sonnenberg et al., 1994; Moum et al., 1996; Aratari et al., 2006). For these reasons, seasonal variation studies in IBD are very timely and necessary.

Several studies have reported seasonal variations in the flare of IBD, previously (Mee and Jewell, 1978; Rampton et al., 1983; Isgar et al., 1983; Sellu, 1986; Riley et al., 1990; North et al., 1991; Tysk and Jarnerot, 1993). However, very few studies, all performed in Western countries, investigated seasonality in the onset of IBD (Auslander et al., 2005; Evans and Acheson, 1965; Cave and Freedman, 1975; Don and Goldacre, 1984; Myszor and Calam, 1984; Sonnenberg et al., 1994; Moum et al., 1996; Aratari et al., 2006). The studies reported conflicting results with a peak from August to
January for UC, and no seasonality for CD previously (Mee and Jewell, 1978; Rampton et al., 1983; Isgar et al., 1983; Sellu, 1986; Riley et al., 1990; North et al., 1991; Tysk and Jarnerot, 1993).

As previously noted by our group, the endoscopic diagnosis date should not be used to assess the occurrence of seasonal variation in a study that aimed to investigate the etiopathogenesis of the disease (Basaranoglu et al., 2006; Basaranoglu, 2006). Although few studies designed according to the above-mentioned criteria reported a seasonal variation in IBD, prior limited results are conflicting and the presence of a seasonal pattern in patients with IBD remains unestablished (Moum et al., 1996; Aratari et al., 2006).

So far the seasonality of IBD have not been reported from Eastern countries. Moreover, there is a belief that the risk factors of IBD in the East differ from those in the West. Thus, it would be important to document the characteristics of seasonality from Turkey, quite unique border of two continents, 97% lies in Asia and about 3 percent in Europe Demirkok et al. (2006). In this study, we aimed to evaluate the seasonal variation in the onset of symptoms in patients with IBD. Whether an interaction between seasonality and both age and gender was also questioned. Moreover, we investigated health care seeking behaviour in males and females patients with IBD.

MATERIALS AND METHODS

Study population

We performed a retrospective cohort study among patients with IBD' medical records of our IBD Center at Ankara Yüksek Ihtisas Hospital Gastroenterology Clinic. In our IBD center, we have used chart review system since 1995. The study was approved by the ethics committee Ankara Yüksek Ihtisas Hospital Ethics Committee and confidentiality of records was maintained according to the guidelines issued by the health authorities. All patients were Turkish origin.

The patient selection

Of the 2220 patients with IBD, 282 patients (years: 1995 to 2010) who have full data which was defined by demographic features, the month and the age at the onset of presenting symptoms, and delayed diagnosis term (as month) for each patient were included in this study. We evaluated the pattern of seasonality only in the symptomatically diagnosed patients with IBD in this study. These patients are still being followed prospectively at the center. We had the dates of diagnosis for each patient as well. However, we did not use these dates in this study because we know that the onset of symptomatic presentation of IBD is more useful than the dates of diagnosis for a seasonality study.

The diagnosis of IBD was established when clinic, endoscopic and radiological findings were supported by histological evidence and exclusion of other disorders known to cause intestinal inflammation. Mycobacteria were excluded by tissue staining and cultures.

Climate features of Turkey and definition of seasons

This study was conducted in Ankara, Turkey, a city with a continental climate, and a quite wide temperature difference between summer and winter Demirkok et al. (2006). The month of presentation was determined as the month symptoms first appeared.

Data analysis

The data were presented as mean ± SD. The monthly distribution of diagnosis was used to study seasonal variation by cumulative diagnosis per month during the full 12 year period. The graphical data presentation was based on the cumulative monthly averages, expressed as the percentage above or below the average monthly value during the entire study period (Basaranoglu et al., 2006; Demirkok et al., 2006). The amplitude of seasonal variation was described by the total seasonal variation. Total seasonal variations were measured as the sum of the percentage above the average for the month with the highest value and the percentage below the average for the month with the lowest value.

Statistical methods

Cumulative monthly averages analysed by Kruskal Wallis test and Roger’s test. Roger's test for cyclic variation was used to determine the significance of any seasonal variation of incidence (Basaranoglu et al., 2006; Demirkok et al., 2006). This statistical analysis determines a simple harmonic cyclic trend, by dividing a circle into 12 equal sectors and plotting the monthly frequencies as co-ordinates (x and y) in the corresponding sectors in the circle. Otherwise, Chi-square, Student’s t-test and Mann-Whitney U analyses were used. Probability (p) values < 0.05 were considered as statistically significant.

RESULTS

IBD group

Of the 282 patients with IBD, 181were males (64%) and 101 were females (36%) and 98 were CD and 184 were UC. Mean age was 40.1±14.7 years (median: 38, range: 14 to 79 years) in the study group; 42.8 ± 14.6 years (median: 42, range: 17 to 78 years) in males vs. 35.4 ± 13.8 years (median: 33, range: 14 to 79 years) in females (p< 0.0001).

The seasonal pattern showed peak in March with 57% and the lowest point in November with -36% as shown in Table 1 and Figure 1 (p <0.05). The seasonal pattern was not influenced by both gender and by age groups (p >0.05).

The delayed diagnosis term (seeking health care behaviour) was 3.1±2.7 months (median: 2 and range: 0 to 18 months); 3.0±2.3 in males (median: 2 and range: 0 to 12 months) vs. 3.2 ± 3.2 months (median: 2 and range: 0 to 18 months) in females (p >0.05).
Table 1. Observed and expected number of cases among IBD patients according to months of the presentation.

<table>
<thead>
<tr>
<th>Month of the year</th>
<th>Onset of symptoms in patients with UC</th>
<th></th>
<th>Observed (%)</th>
<th>Expected</th>
<th>Observed (%)</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>January</td>
<td>23 (12.5)</td>
<td></td>
<td>15.3</td>
<td>30 (10.6)</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>February</td>
<td>12 (6.5)</td>
<td></td>
<td>15.3</td>
<td>23 (8.6)</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>March</td>
<td>25 (13.6)</td>
<td></td>
<td>15.3</td>
<td>37 (13.1)</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>April</td>
<td>23 (12.5)</td>
<td></td>
<td>15.3</td>
<td>27 (9.6)</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>May</td>
<td>15 (8.2)</td>
<td></td>
<td>15.3</td>
<td>22 (7.8)</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>June</td>
<td>15 (8.2)</td>
<td></td>
<td>15.3</td>
<td>26 (9.2)</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>July</td>
<td>14 (7.6)</td>
<td></td>
<td>15.3</td>
<td>25 (8.9)</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>August</td>
<td>16 (8.7)</td>
<td></td>
<td>15.3</td>
<td>23 (8.2)</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>September</td>
<td>13 (7.1)</td>
<td></td>
<td>15.3</td>
<td>18 (6.4)</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>October</td>
<td>8 (4.3)</td>
<td></td>
<td>15.3</td>
<td>17 (6.0)</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>November</td>
<td>9 (4.9)</td>
<td></td>
<td>15.3</td>
<td>15 (5.3)</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>December</td>
<td>11 (6.0)</td>
<td></td>
<td>15.3</td>
<td>19 (6.7)</td>
<td>23.5</td>
<td></td>
</tr>
</tbody>
</table>

P value: $P < 0.05$

Figure 1. Shows the distribution of symptomatic onset of disease each month over fourteen years in patients with IBD.
Crohn’s disease group

Of the 98 patients with CD, 51 was male (52%). Mean age was 37.8±13.6 years (median: 36, range: 17 to 79 years); 38.3 ± 13.6 years (median: 38, range: 17 to 75 years) in males vs 37.2 ± 13.7 years (median: 36, range: 18 to 79 years) in females (p >0.05).

The seasonal pattern in the patients with CD showed peak in February, March, June and July and the lowest point in April and September (p > 0.05) as shown in Figure 2. The seasonal pattern was not influenced by both gender and by age groups (p >0.05).

Delayed diagnosis term was 3±2.8 months (median: 2.0 months; 0 to 18 months) in patients with CD. There was no difference for delayed diagnosis between males 3.0±2.7 months (median: 2.0; 0-10 months) vs females 3.0±3.0 months (median: 2.0; 0 to 18 months) (p >0.05).

Ulcerative colitis group

Of the 184 patients with UC, 130 was male (71%). Mean age was 41.4±15.2 years (median: 40.5, range: 14 to 78) in the study group. Mean age was 44.5±14.7 years (median: 44.5, range: 19 to 78 years) in males vs. 33.9 ± 13.8 years (median: 30.5, range: 14 to 67 years) in females (p< 0.0001).

The seasonal pattern in the patients with UC showed peak in October and November and the lowest points in January, March and April (p <0.05) as shown in Table 1 and Figure 3. The seasonal pattern was not influenced by both gender and by age groups (p >0.05).

Delayed diagnosis term was 3.2±2.6 months (median: 2.0 months; 0-15 months) in patients with UC. There was no difference for delayed diagnosis between males 3.1±2.2 months (median: 3.0; 0-12 months) vs females
3.4±3.4 months (median: 2; 0 to 15 months) (p >0.05).

**DISCUSSION**

To the best of our knowledge, our study group with 282 patients with IBD is one of the biggest groups in the literature. In this study, differently from the most of the previously published papers, we evaluated the pattern of seasonality only in the symptomatic, recently diagnosed patients with IBD instead of endoscopic diagnosis date. Although we had the records of endoscopic diagnosis date for each patient, we did not use these records as we know that the onset of symptomatic presentation of IBD is more useful than the dates of endoscopic diagnosis for a seasonality study. The exact cause and the disease pathogenesis of IBD have not been fully understood, so far. Very few studies which concerned the aetiology of IBD performed and reported conflicting results (Auslander et al., 2005; Evans and Acheson, 1965; Cave and Freedman, 1975; Don and Goldacre, 1984; Myszor and Calam, 1984; Sonnenberg et al., 1994; Moum et al., 1996; Aratari et al., 2006). There should be reasons of these reported differences. We concern regarding the methodology of the previously published studies which includes the patient selection criteria and statistic methods. Some scholars used endoscopic diagnosis date of the patients or only IBD patients with a disease history of 12 months or less. These strategies include riskies. We considered that we should evaluate the seasonal variability of IBD cohort with known date of onset of symptoms over a many years to decrease chance factor in these type of studies. In this regard, we evaluated the seasonal variability of a large sample of Turkish IBD cohort with known date of onset of symptoms over a 15-year period in our study. Of the 2200 patients with IBD in our IBD center, we reached to 282 patients with IBD who had full record. We strongly recommend this strategy to increase the homogeneity of the IBD cohort and decreased the chance factor in seasonality studies.

*Figure 3. Shows the distribution of symptomatic onset of disease each month over fourteen years in patients with UC.*
The role of environmental factors in triggering IBD has been the focus of attention for a long time, particularly with respect to bacterial infections which induce bursts of immune diseases and that is supported by the presence of antibodies against the oligomannan of Saccharomyces cerevisiae or ANCA. In the Turkey, bacterial infections show a seasonal pattern of occurrence that peaks in the winter. We found that the seasonal pattern of IBD was based on the exceedingly high occurrence of symptoms in March, and on the lower frequency than expected in November. Bacterial infections, particularly respiratory tract infections show a seasonal distribution with higher frequencies in the winter in Turkey. Thus, we consider that bacterial infections may have associated with the onset of IBD. The results of our study supported the hypothesis that the onset of IBD is precipitated by pathogens with known seasonality.

Another mechanism is that increased use of antibiotics in the winter period according to the Turkish Ministry of Health reports could also support that the use of this kind of drugs could induce the development of IBD (Demirkok et al., 2006). By contrast, enteric infections are most common in Turkey during the summer (Demirkok et al., 2006). However, we found the lowest peak in November and fall. These fundings did not support the hypothesis that enteric infections can precipitate the onset of IBD.

Adrenal corticosteroids peaks in the spring and summer and the lowest in the autumn and winter (Don and Goldacre 1984; Myszor and Calam, 1984). It may play a role in the onset of IBD. Additionally, immune function decreases during the winter with a lower production of proinflammatory cytokines and an increased TH1/TH2 ratio. The warmer temperature can facilitate the activation of leukocytes. These fluctuations in immune function in the different seasons may explain the seasonal variations in the onset of IBD.

Vitamin D receptors are present in cells and adequate vitamin D status is essential for optimal functioning of human cells (Myszor and Calam, 1984; Sonnenberg et al., 1994). Vitamin D is involved in the functioning of the immune system and vitamin D insufficiency is linked to bacterial and viral infections as well as autoimmune diseases. Calcitriol is a hormone that regulates both adaptive and innate immunity. These fluctuations in vitamin D status in the different seasons may explain the seasonal variations in the onset of IBD.

We also questioned the interaction between IBD seasonality and both age and gender which has not been investigated, previously. We found no interaction for the seasonal variation of the patients by both gender and age groups.

Statistical method is one of the most important points in seasonality studies. We used Roger's test for cyclic variation to prove that this seasonal variation was more than chance in our study (Demirkok et al., 2006).

In this study seasonal variation in the onset of symptoms was found only in UC as previously reported, not in CD. The numbers of UC patients seem to have been sufficient to obtain valid data for UC. However, seasonality of CD cannot be ruled out due to the comparatively smaller number of patients with CD.

For the first time, health care seeking behaviour in patients with IBD has been investigated by our study group. There was a delay for seeking health care among the patients with IBD, UC and CD. There was a tendency in females with a longer delaying period, too.

Conclusion

The environmental factors that contribute to the onset of IBD in the natural history of IBD have not been well defined, so far. By this study, we investigated the etiologic environment of IBD. Our data strongly support a seasonal pattern to the natural history of IBD. We also showed that there is a delay, but no difference between males and females regarding health care seeking behaviour. Further well-designed and large prospective studies are required to better understand the importance of these findings presented here.

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REFERENCES


