

Is there Autonomic Dysfunction in Inflammatory Bowel Disease in Turkish Population?

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Received: May 20, 2014

Revised: July 4, 2014

Accepted: July 6, 2014

Published online: August 21, 2014

in enteric nervous system in inflammatory bowel disease, it does not seem to correlate with a defect in the central autonomic nervous system.

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Key words: Inflammatory bowel disease; Inflammation; Enteric nervous system; Autonomic nervous system; Heart rate variability

Topal F, Yuksel ES, Kahya N, Cekiç C, Ekinci N, Akpınar Z, Unsal B. Is there Autonomic Dysfunction in Inflammatory Bowel Disease in Turkish Population? *Journal of Gastroenterology and Hepatology Research* 2014; 3(8): 1202-1205 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/817>

ABSTRACT

AIM: Autonomic dysfunction is accused as one of the factors in the pathogenesis of inflammatory bowel disease. We have aimed to find out if there is a concordance between autonomic dysfunction and inflammatory bowel disease.

METHODS: In this study, we have evaluated 10 colon and/or small bowel resection materials from ulcerative colitis (UC) and Crohn's disease (CD) patients. Inflammatory cells (leuko-plasmocytes) cumulated around and in the enteric ganglia were shown. After that, we have taken one step forward and examined autonomic dysfunction by heart rate variability in 26 ulcerative colitis patients in remission and 24 healthy volunteers in order to evaluate if there is a simultaneous autonomic dysfunction.

RESULTS: There was infiltration of lymphocytes and mast cells in the myenteric plexus in 8 (5 CD, 3 UC) of the 10 resection specimens but no destruction in ganglia. There were not any statistically significant differences between HRV variables of the IBD group and the control group in our analysis.

CONCLUSION: In conclusion, even though there is inflammation

INTRODUCTION

Modulating motility, secretion and microcirculation of the gastrointestinal tract, and regulating mucosal immune and inflammatory responses are major roles of autonomic nervous system (ANS)^[1]. Abdominal pain and diarrhea in patients with disease in remission can be attributed to functional changes, including abnormal colonic motility and transit in inflammatory bowel disease. These motor disturbances are suggestive of alterations in colonic neuromuscular components including enteric neurons^[2]. In some of the studies, inflammatory bowel disease (IBD) seem to be related with hyperfunction in ANS^[3,4]. The increased sympathetic activity may contribute to the augmentation of the bowel inflammation^[4,5]. The host immune system has been identified as an important factor in the pathogenesis and chronicity of IBD. The autonomic nervous system (ANS) and the immune system are shown to interact in the pathogenesis of IBD in several studies^[6]. For example, patients with UC have a greater density of adrenergic nerves and adrenalin in the rectal mucosa than control subjects or irritable bowel syndrome (IBS) patients. Focal destruction of autonomic nervous system (ANS) axons is present in inflamed and non-inflamed CD patients' small bowel

tissue. Myenteric plexitis is a predictor for postoperative recurrence in CD. The presence of neuronal hypertrophy in Meissner's plexus is more common in UC than CD^[7]. Enteric neurons and glial cells regulate the patterns of smooth muscle activity^[8,9]. The neural/myogenic network is altered in the setting of bowel inflammation, resulting in gut dysmotility^[10,11].

Despite the increasing incidence of inflammatory bowel disease, few studies have focused on the motility disorders related to the dysfunction in ENS. It is not very clear if the inflammation of ENS is the starter of the ethiopathogenetic cascade or ENS is an innocent bystander which is affected by the process. Differences have been reported in ANS function between patients with IBD and healthy volunteers^[12]. Both hypofunction (autonomic neuropathy) and hyperfunction (autonomic hyperreflexia) have been described in IBD. In previous studies, autonomic neuropathy was detected with high prevalence in IBD, ranging from 40 to 50%^[10]; this was later considered to be an overestimation due to the study design^[4]. In further studies, using strict diagnostic criteria, cardiovascular autonomic neuropathy was found to be rare in IBD, with prevalence rates of about 5%^[3,4]. In a study of 40 patients with UC, 33 with CD, 25 with IBS and 56 healthy controls, subjects with UC had significantly impaired parasympathetic function ($P < 0.05$) as compared to patients with IBS or controls^[3]. These changes were only present in a subset of the UC patients and did not correlate with objective markers of disease activity such as C-reactive protein or serum orosomucoid.

The changing intervals between heartbeats in normal sinus rhythm are evaluated as a normal physiologic event. The reasons are respiration, thermoregulation and some kind of baroreflex mechanisms. Although the automaticity in the heart is associated with the intrinsic pacemaker tissue, the heart rate and rhythm are basically under control of ANS. Heart rate variability (HRV) depends on the analysis of the intervals between normal heart beats. SDNN, SDANN, Pnn50, RMSSD parameters are used^[13]. SDANN is the standard deviation of mean 5 minutes-NN intervals during 24 hours, SDNN is the standard deviation of differences between adjacent R-R intervals, RMSSD is the root mean square of successive differences between adjacent R-R intervals and Pnn50 is the percentage of number of R-R intervals with differences ≥ 50 ms. A decrease in HRV means parasympathetic hyperactivation.

There are some example studies using HRV to assess autonomic dysfunction in UC and CD^[14]. In this study, our aim was to describe the disturbances in ENS and/or ANS in the ethiopathogenesis of inflammatory bowel disease in Turkish population.

METHODS

Histopathology

10 (6 CD, 4 UC) intestinal resection materials from inflammatory bowel disease patients were evaluated focusing on the ganglionic area. The paraffin sections were stained with Hematoxylin Eosin (H&E) for general histologic examination for ganglia destruction and inflammation.

Autonomic dysfunction investigation

Patient And Healthy Group Selection: 26 UC and 24 healthy volunteers were included in the second step of the study. The UC patients were selected among the ones in remission proven by biochemical results, clinical and endoscopic findings who were treated with mesalazine peroral and/or enema forms. The exclusion criteria consisted fever, infection, history of anti-diarrheals, steroids, any cardiac drug, diabetes mellitus and any kind of cardiac and/

or neurologic disorder, smoking and alcohol use since all of these conditions would interfere with the ANS.

Heart Rate Variability: Autonomic function was investigated with HRV because it is non-invasive and capable of quantitative assessment of parasympathetic and sympathetic systems. Although autonomy in the heart is related to the intrinsic pacemaker tissue, most of the control on the heart rate and rhythm belongs to ANS. HRV can be evaluated with 24 hour ambulatory monitoring. NN interval is the interval between two consecutive beats. SDNN, SDAN, RMSSD and Pnn50 can be calculated from NN intervals in 24 hour holter monitorization.

Heart rate variability (HRV) is the physiological phenomenon of variation in the time interval between heartbeats. It is measured by the variation in the beat-to-beat interval (RR variability using the peak of the QRS complex of the ECG wave). The term "NN" is used in place of RR to emphasize the fact that the processed beats are "normal" beats.

One of the most widely used method for HRV analysis is the time-domain method. This method is based on NN intervals, which are analysed to give variables such as: (1) SDNN, the standard deviation of NN intervals and is calculated over a 24-hour period; (2) SDANN, the standard deviation of the average NN intervals calculated over short periods, usually 5 minutes; (3) RMSSD ("root mean square of successive differences"), the square root of the mean of the sum of the squares of the successive differences between adjacent NNs; (4) pNN50, the proportion of NN50 (the number of pairs of successive NNs that differ by more than 50 ms) divided by total number of NNs.

Statistical Analysis: The data analysis was done with SPSS Windows 11.5. Numeric variable distribution was analysed with Shapiro Wilk test. Descriptive statistics were shown for numeric variables as mean \pm standard deviation or median (minimum-maximum). Nominal variables were shown as observation numbers or percentage. Student's *t* test was used to determine the statistical difference between the groups. Mann Whitney U test was used to determine the statistical difference between median variables. If $p < 0.05$ was accepted as statistically significant in Pearson's chi-square test.

RESULTS

We found infiltration of lymphocytes and mast cells in the myenteric plexus in 8 (5 CD, 3 UC) of the 10 resection specimens. The lymphocytes were located as peri- and intraganglionic. The average number of lymphocytes per ganglia and/or nerve was more than 10/HPF for the ones with ganglioneuritis. All the patients had increased number of intraepithelial lymphocytes and mast cells. On the other hand, there was no destruction in the ganglion cells. (Figures 1-2).

In the second part of the study, 26 ulcerative colitis and 24 control patients were recruited. The mean age was 43.5 ± 15.0 in the patient group and 36.9 ± 12.1 in the control group ($p = 0.098$). Age and gender did not differ significantly between the two groups (Table 1).

Median SDNN level was 145.5 ms in the control group and 137.5 ms in the patient group ($p = 0.541$). Median SDANN level was 133.5 ms in the control group and 119.5 ms in the patient group ($p = 0.260$). Median RMSSD level was 46.5 ms in the control group and 43.5 ms in the patient group ($p = 0.808$). Median Pnn50 value was 8.0% in the control group and was 9.1% in the patient group ($p = 0.497$) (Table 2).

DISCUSSION

In the present study, we found ganglioneuritis in 8 of 10 intestinal resection materials and carried the study one step forward

hypothesizing that autonomic dysfunction is more prevalent in IBD patients compared to the normal population. In the remission phase, an interruption and inflammation in the local or systemic autonomic nerves compared to controls can be accused of the chronic symptoms of IBD such as bloating and abdominal pain. In practical life, it seems unattainable to acquire full thickness intestinal biopsies from IBD patients in remission hence it seems reasonable to investigate autonomic dysfunction by indirect methods such as HRV. Nevertheless, there were not any statistically significant differences between HRV variables of the IBD group and the control group in our analysis.

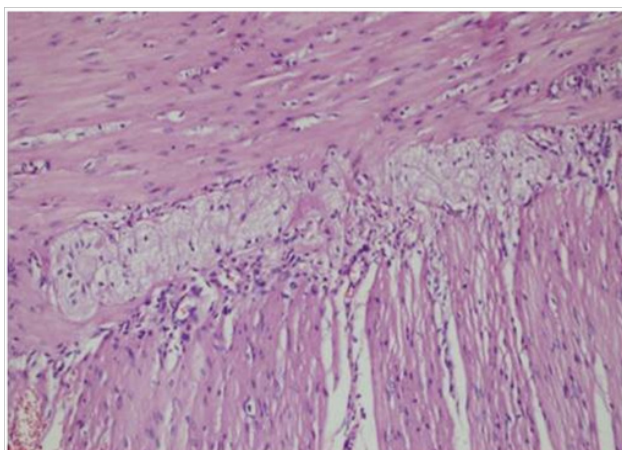


Figure 1 Lymphoplasmacytes in the ganglion in a UC material.

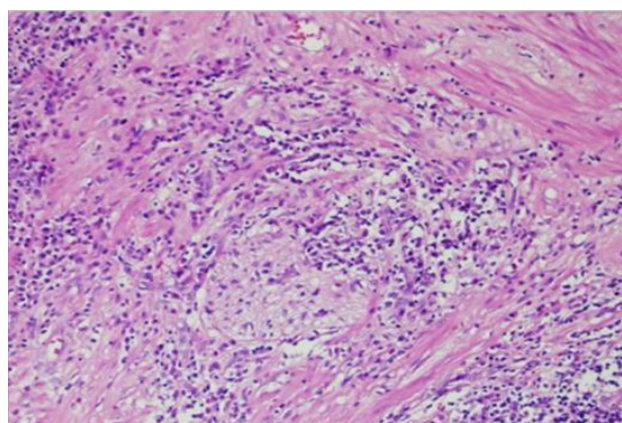


Figure 2 Ganglioneuritis-mast cells and lymphoplasmacytes in the ganglion in a CD material.

Table 1 Demographic data.

Variables	Control group (n=24)	Patient group (n=26)	p-value
Age	36.9±12.1	43.5±15.0	0.098 ¹
Gender			0.166 ²
Female	12 (%50.0)	8 (%30.8)	
Male	12 (%50.0)	18 (%69.2)	

¹ Student's *t* test; ² Pearson's chi-square test.

Table 2 HRV values.

Variables	Control group (n=24)	Patient group (n=26)	p-value ¹
SDNN	145.5	137.5	0.541
SDANN	133.5	119.5	0.260
RMSSD	46.5	43.5	0.808
Pnn50	8.0	9.1	0.497

¹ Mann Whitney U test.

Gastrointestinal motility and function require coordination between the intrinsic and extrinsic nervous systems, the interstitial cells of Cajal (ICCs) and smooth muscle cells^[15,16]. Enteric ganglioneuritis has been found in some patients with severe IBS and IBS symptoms are more frequent in patients with CD and UC than in the general population. In CD and UC, proliferation and injurious changes can occur in ENS. These observations suggest that autonomic enteric neuropathy may be present in CD and UC and thus could be responsible for the IBS-typical symptoms. This hypothesis was supported by the finding that chronic intestinal pseudo-obstruction (CIPO), secondary to enteric neuropathy, has been observed in patients with CD or UC^[17]. Bernardini *et al* investigated the myenteric ganglia in UC patients and concluded that the quantitative variations of myenteric neuro-glial cells indicate considerable alterations of the colonic neuromuscular compartment in the setting of mucosal inflammation associated with UC, and provided a morphological basis for better understanding the motor abnormalities often observed in UC patients^[2].

Maule *et al* declared that they have investigated eleven UC patients for autonomic dysfunction with head-up tilt, valsalva maneuver and deep breathing and the results were negative for dysfunction. On the other hand, they have acquired a decrease in HRV compared to the controls and concluded that UC patients have perpetuated sympathetic activity^[1]. Sharma *et al* have also shown a decrease in parasympathetic activity in IBD patients and expressed that autonomic dysfunction might be responsible for the chronicity of the disease^[14]. Additionally Ganguli *et al* notified an increase in the sympathetic activity independent of the bowel disease activity^[7].

In summary we did not find any significant difference in ANS function between IBD patients and controls. Our results must be interpreted with caution due to some drawbacks in the study. The most important limitation is the selection of patients, all of them in remission. The idea behind this selection was to hinder the effect of components related to activation such as hypotension, infection, fever, bleeding and abdominal cramping on autonomic nervous system. Additionally investigations other than HRV might have been included such as orthostatic hypotension. On the other hand, this is an important study which investigates the role of autonomic dysfunction in IBD pathogenesis and reminds it as a therapeutic target for the future if more thorough research is done concluding a positive relationship.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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