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Autonomic nerve dysfunction in patients with inflammatory bowel disease

İnflamatuvar barsak hastalıklı hastalarda otonom sinir fonksiyon bozukluğu

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ÖZET: *Otonom nöropati (ON) Crohn hastalıklı (CH) 11, ülseratif kolitli (ÜK) 48 hastada ve 20 sağlıklı kontrolde non-invaziv kardiak otonom refleks testlerle araştırılmıştır. CH'nın ortalama yaşı 30 (22-55 arasında), ÜK'li olguların ise 35 (19-68) dir. ON varlığı ile yaş, hastalık süresi, hastalık aktivitesi ve lokalizasyon arasındaki ilişki araştırılmıştır. ON, CH'lı olguların %63.7'sinde, ÜK'li olguların %29.3'ünde izlenirken, sağlıklı kontrol olgularının hiçbirisinde saptanmamıştır. Gruplar arasındaki fark istatistiki olarak anlamlı bulunmuştur (p<0.001). ON ile hastanın yaşı, hastalık süresi, aktivitesi ve lokalizasyonu arasında anlamlı bir ilişki bulunamamıştır. ÜK'li olgularda vagal nöropati, CH'lı olgularda sempatik nöropati izlenmiştir. Sonuç olarak; ON inflamatuvar barsak hastalığının özellikle de CH'nın yaygın görülen barsak dışı komplikasyonu olarak kabul edilebilir..*

Anahtar Kelimeler: **İnflamatuvar barsak hastalığı, otonom nöropati, ülseratif kolit, Crohn hastalığı**

SUMMARY: *Autonomic neuropathy (AN) was evaluated in 11 patients with Crohn's disease (CD), 48 patients with ulcerative colitis (UC) and 20 healthy subjects (mean age 35 years, range 17-19 years) by non invasive cardiac autonomic reflex tests. Mean age of CD patients was 30 (range 22-55) and mean age of UC patients was 35 (range 19-68). Relation of presence of AN with age, disease duration, disease activity and extent of illnesses are assessed. Autonomic dysfunction was present in 63.7% of CD and 29.3% of UC while none in healthy control group (p<0.001). No relationship has been found between AN and the patients age, duration of sickness, localization and activity. UC cases had mainly vagal AN, while CD cases had mainly sympathetic. In conclusion; these results suggest AN can be accepted as an extensive extra intestinal manifestation of inflammatory bowel diseases (IBD) especially in CD.*

Key Words: **Inflammatory bowel disease, autonomic neuropathy, ulcerative colitis, Crohn's disease**

IBD is a general term for group of chronic inflammatory disorders of unknown etiology involving the gastrointestinal tract. Chronic IBD may be divided into two major groups; chronic UC and CD. CD and UC are associated with a spectrum of extraintestinal manifestations.

The autonomic nervous system regulates the visceral organs and vegetative functions. Usually AN is a manifestation of a more generalized polyneuropathy also affecting somatic peripheral nervous function, as in diabetic neuropathy, Guillain Barre syndrome and alcoholic neuropathy. Symptoms of dysautonomia are mainly negative (i.e, loss of function) and include postural hypotension with faintness or syncope, anhidrosis, hypothermia, bladder atony, obstipation, dry mouth and dry eyes from failure of salivary and lacrimal glands to secrete, blurring of vision from lack of pupillary and ciliary regulation, and sexual impotence in males. Hyperfunction may also occur and include episodic hypertension, diarrhea, hyperhidrosis and either tachycardia or bradycardia (1-3). There are a variety of nonintestinal symptoms and signs which may be associated with IBD and occur in both UC and CD (4). Large studies have demonstrated that 25-35% of patients with either type of IBD have at least one such associated complication (5).

The aim of this study was to evaluate the possible occurrence of AN in patients with IBD. Noninvasive tests of cardiovascular autonomic nerve function were carried out and correlated with the age, the duration, the extend and the severity of the disease.

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Table 1. Scoring of the tests

	0	*1*	*2*
TEST 1	*<100*	–	*>100*
TEST 2	*>1.21*	*1.11-1.21*	*<1.10*
TEST 3	*>15*	*11-14*	*<11*
TEST 4	*>1.04*	*1.01-1.03*	*<1.00*
TEST 5	*<10*	*11-29*	*>30*

Total score: <2 Negative >4 Positive

Table 2. Patients and controls

Female	*Male*	*Mean*	*Age*	*Duration*	*AN*
UC(46)	31	17	35+1.7	49+3.1	15(29%)*
CD (11)	7	4	30+0.7	48+2.1	7(63%)
Controls (20)	8	12	35.3+1.5	–	0(0%)

AN: Autonomic neuropathy *p<0.001

SUBJECTS AND METHODS

Between January 1,1994 and March 31, 1995, 59 patients were entered into the IBD Registry of Yüksek İhtisas Hospital. 48 (31 female, 17 male) of these patients were UC, 11 (7 female, 4 male) of others were CD. Patients with UC ranged in age from 29 to 68 years (mean; 35 years). Mean disease duration was 49±3.1 (range 12-240) months. The mean age of CD was 30 years (range 22-55), mean disease duration was 48±2.1 (range 12-60) months. The diagnosis was based on clinical, radiological and/or endoscopic and histologic criteria. The control population consisted of 20 healthy subjects (mean age, 35 years, range 17-69 years). Using a questionnaire the patient were asked for symptoms of AN. None of the patients or control were diabetic.

Autonomic nerve function tests;

1- Resting heart rate; Patients who stayed in the supine position for 15 minutes were recorded on ECG. The average five different R-R interval was calculated.

2- Deep breathing test; The subjects performed six maximal expirations and inspirations in the supine position during recording of a continuous electrocardiogram. The respiratory-inspiratory difference was calculated from the mean value of the longest R-R interval during inspiration. This is an established test of parasypathetic vagal nerve function (6).

3- Heart rate respond to Valsalva's maneuver; ECG was recorded during difficulty expiration for 20 seconds and the end of the test for one minute. The R-R ratio was calculated for Valsalva's maneuver and resting (VR>1.21 accepted normal).

4- Orthostatic test; The subject was tilted rapidly to the upright position (90°) and the heart rate changes were recorded on the ECG and the 30'th R-R/15'th R-R (30/15) ratio was calculated on the basis of the R-R intervals. The 30/15 ratio evaluate not only parasympathetic nervous tone but also sympathetic nerve function (7).

5- The blood pressure reaction to tilt; It was measured 4 min before and every minute after up to 8 min. The average blood pressure was taken. It was also used as a test of sympathetic nerve function (Table 1).

Statistical analysis; Fisher's exact x^2 test, Stu-

Table 3. Autonomic neuropathy in age related values (SD) in relation to age, duration, extent, and activity of UC and CD patiens.

	Patients	*Age*	*Duration*	*Extent*			*Activity*	
	(59)	(years)	(months)	pancolit	left	distal	A	R
UC	AN (+) (15)	35.6±5.9	49.6±3.2	7	5	3	8	7
(48)	AN (-) (33)	33.2±3.8	48.5±2.2	8	13	12	17	16
	p	**0.54**	**0.172**	**0.266**			**0.755**	
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CD	AN (+) (7)	29.5±2.6	51.4±4.2	4	3		3	4
(11)	AN (-) (4)	30.7±3.8	45±5.8	2	2		2	2
	p	**0.54**	**0.06**	**0.65**			**0.46**	

AN: Autonomic neuropathy A: active R:remission

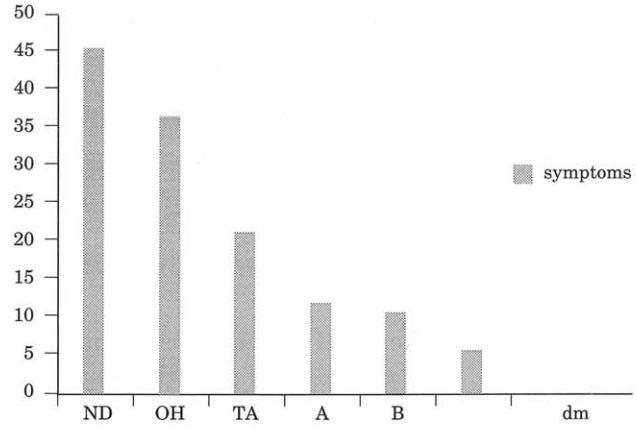

Figure 1. *Symptoms of AN*
(ND: nocturnal diarrhea, OH: ortostatic hypotension, TA: tachicardic attacks, A: anhidrosis, DM: dry mouth)

dent's t and compare percentiles tests were used.

RESULTS

Autonomic dysfunction was present in 63.7% of CD and 29.3% of UC patients while none in control group. The difference between them was statistically significant ($p<0.001$) (Table 2).

No relationship has been found between autonomous neuropathy and the patients age, duration of sickness and activity. When evaluated for localization, 46.6% of the UC cases determined to have autonomous dysfunction had pancolitis, whereas 24.2% of the group with AN (-) had pancolitis (Table 3).

The patients were evaluated for AN symptoms and a high relationship between nocturnal diarrhea and AN positivity have been found (Fig 1).

When the relationship between the disease type and AN type are examined the AN (+) 7 CD patients had 76.9% positive sympathetic tests and 53.6 vagal tests. In UC patients 53.1% sympathetic tests and 62.5% vagal tests found positive. The difference was not significant ($p>0.05$).

DISCUSSION

The determination of non-invasive methods and the designation of their capasities for sensitivity and predictivity especially for diabetic patients and the determination of AN in various disease has enlarged the clinical definitions (8). In the diseases related to the autonomous system the diseases are generally diffuse (3,9,10).

The major finding in this study was that patients with IBD especially CD demonstrated disturbed autonomic nerve function compared with controls. In the study done in our country demonstrated that 20.4% of patients with UC, 56.25% with CD, have AN(11). In the other study done by Lindgren et al. the percentages in CD and UC were found 48% and 30% to be respectively. The vagal tests in UC and the sympathetic teste in UC were primarily disturbed (12,13). In our study, the difference between the two groups was not significant for this aspect. According to our knowledge today it is not so easy to separate the isolated sympathetic and vagal functions of ANS and many tests measuring the autonomous functions are not totally reliable. No relationship has been found between the AN percentage and the patient age, duration of sickness and activity. It seems that the development of AN is not related to active inflammation. The studies in patients with total colectomy have shown that AN were also present in that group of patients (13). Even though damage was observed in neurons containing peptides in the colon of patients with UC, autonomous nervous dysfunction is not limited to the neurons in the colon but is also present systematically (14). In the intramural fibers of CD patients, changes including the peptidergic nervous fibers were observed (15).

In conclusion; autonomous neuropathy, especially for CD, is a common extraintestinal manifestation of IBD and it is not related to age, sex, disease activity or duration. The relationship of AN and IBD is not yet clearly verified in all aspects. We need more experimental studies for this clarification.

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