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Visual evoked potentials and pulse wave velocity in inflammatory bowel disease

BOWEL

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Original Article

ABSTRACT

Background/Aims: Data about the effects of inflammatory bowel disease (IBD) on various functions of the nervous and cardiovascular systems are limited. In this study, the visual neuronal and cardiovascular functions of patients with IBD were evaluated by measuring visual evoked potentials (VEP) and pulse wave velocity (PWV), respectively.

Materials and Methods: There were three study groups: the Crohn's disease (CD) group (n=25), the ulcerative colitis (UC) group (n=30), and a healthy control (C) group (n=25). The exclusion criteria were as follows: patients with IBD were in remission, had no extra-intestinal manifestations of the disease, had no additional chronic disease(s), and had been receiving medical treatment for their IBD without any previous surgical intervention. VEP amplitudes (mV) and the N2 and P2 latencies (ms) were recorded for visual-neuronal analysis of all study groups. For cardiovascular assessment in all study groups, PWV was measured noninvasively as follows: the carotid-femoral PWV with the Complior Colson device (The authors have no conflict of interest.) and the PWV along the aorta with two ultrasound strain-gauge pressure-sensitive transducers (TY-306 Fukuda pressure-sensitive transducers - Fukuda Denshi Co, Tokyo, Japan) fixed transcutaneously over the course of a pair of arteries separated by a known distance. The right femoral and right common carotid arteries were the ones used.

Results: The PWV levels of the CD and UC groups were significantly higher than those in the C group ($p<0.001$). In the bilateral recording of the VEP, the N2 latencies of the CD ($p<0.05$) and UC ($p<0.01$) groups were significantly longer than those in the C group.

Conclusion: In this study, we showed vascular and visual neuronal impairments at a subclinical stage in patients with both types of IBD.

Keywords: Inflammatory bowel disease, pulse wave velocity, arterial stiffness, visual evoked potentials, Crohn's disease, ulcerative colitis

INTRODUCTION

Inflammatory bowel disease (IBD) is a systemic disorder affecting all physiologic mechanisms negatively and not only the gastrointestinal system (1). IBD diminishes vital functions directly via its systemic inflammatory activity. Chronic inflammation damages the cardiovascular and nervous systems (2,3). Neurological and cardiovascular dysfunctions are the major comorbidities associated with this chronic disease (4-6).

Performing visual evoked potentials (VEP) is a noninvasive electrophysiological test used to evaluate the visual neuronal system from the eye to the occipital cortex. VEP are the electrical activities in the occipital (visual) cortex in response to flash stimulation (7). Noninvasive ultrasonographic techniques such as pulse wave velocity (PWV) are employed for the diagnosis of cardiovascular dysfunctions. PWV is calculated by measuring the spillover of arterial pressure onto the vessel wall (3). IBD could cause neuronal, heart, and blood vessel dysfunction via its harmful systemic effects. Data about the functions of the nervous and cardiovascular systems in IBD patients are limited. In this study, visual neuronal and cardiovascular functions of the IBD patients were evaluated by measuring VEP and PWV.

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MATERIALS AND METHODS

This study was performed with the approval of the Clinical Research Ethics Committee of İstanbul University Cerrahpasa Medical Faculty. The individuals who provided consent were included in the study prospectively. There were three study groups: the Crohn's disease (CD) group (n=25; 13 women, 12 men), the ulcerative colitis (UC) group (n=30; 15 women, 15 men), and the control (C) group (n=25; 13 women, 12 men). The C group members were healthy and had no chronic disease. The IBD patients had been receiving medical treatment, were in remission, and had no extra-intestinal manifestations of their disease, other chronic disease, or surgical intervention for IBD. All individuals enrolled in the study had normal visual acuity and no visual disturbances. Their clinical visual examinations were normal. Remission of IBD was determined using the Crohn's Disease Activity Index for the CD patients and the Seo Index for the UC patients (8,9).

Patients who were excluded from the study had previous myocardial infarction; constrictive, restrictive, or dilated cardiomyopathy; heart failure; valvular heart disease; hypertension; renal failure; diabetes mellitus; peripheral arterial disease; cerebrovascular disease; a hematocrit <0.30; electrocardiogram conduction and rhythm disorders; systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg; body mass index (BMI) >30 kg/m^2; and waist-to-hip ratio ≥1. BMI was calculated by dividing body weight in kilograms by the square of body height in meters. Waist-to-hip ratios were calculated by dividing the circumference of the waist by the circumference of the hips. Blood pressure was measured after 20 min of rest, using a mercury sphygmomanometer with a cuff appropriate to the arm circumference, in compliance with World Health Organization guidelines (Korotkoff phase I for SBP and phase V for DBP). Whole blood levels of total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), triglycerides, white blood cells, C-reactive protein, hemoglobin, hematocrit, albumin, total protein, glucose, platelet number, and erythrocyte sedimentation rate were also evaluated in the study.

Recording of the pulse wave velocity

The carotid-femoral PWV was assessed with the Complior Colson the device (Complior Colson; Createch Industrie, Garges les Gonesses, France), the technical characteristics of which have been previously described (10). PWV along the aorta was measured noninvasively by two ultrasound or strain-gauge pressure-sensitive transducers (TY-306 Fukuda; Fukuda Denshi Co, Tokyo, Japan) fixed transcutaneously over the course of a pair of arteries separated by a known distance; the right femoral and right common carotid arteries were used. During preprocessing analysis, the gain of each waveform was adjusted to obtain an equal signal for the two waveforms. During the actual PWV measurements, after pulse waveforms of sufficient quality were recorded, the operator initiated the digitalization process to start automatic calculation of the time delay between two upstrokes. Measurements were repeated over 10 different cardiac cycles and the mean value was used for the final analysis. PWV was calculated from measurements of the distance traveled by the pulse between the two recording sites (D) and the pulse transit time (T):

$$PWV\ (m/s) = \frac{D\ (m)}{T\ (s)}$$

Recording of the visual evoked potentials

Subjects were placed in a dark, light-reflecting, sound-attenuating, electrically shielded room. Three standard disposable silver-silver gluey chloride electrodes were used for recording VEP. The electrode impedances were set below 5 kO to reduce electrical interference. One electrode was fixed onto the left ear, one onto the right ear, and a third onto the occipital part of the scalp (above the visual cortex). Electroencephalogram paste gel was used for better conductivity. The bilateral (both left and right eyes open) and the unilateral left and right eye VEP's were recorded. Black carbon paper and a cotton patch were used appropriately for to block light from the eye not being tested.

After 5 min of dark adaptation, a photic stimulator of the lowest intensity was employed to provide flash stimuli at a distance of 30 cm, which lit up the entire pupil from the temporal visual field. Dilation of the pupils and use of suprathreshold flash intensity are simple procedures to control these parameters in human or animal testing (11-13). The photic stimulation was delivered 100 times by a general evoked response stimulator at a frequency of 0.5 Hz. Five hundred sweeps each of 350-ms duration at 1 Hz were averaged with the software (MP 150 Manager Version 3.7.3; Biopac Systems Inc., Santa Barbara, CA, USA). Illumination of the reflecting surface was approximately 40 Lux. The gain was set at 50AV/div. At least two averages were obtained to ensure response reproducibility. The responses were amplified with high- and low-filter settings of 1-45 Hz, respectively, using a band-pass technique and the Blackman-61 db method. The amplitudes of VEP were measured as the voltage (P-P) between two successive peaks and the N_2 and P_2 latencies (ms).

Statistical analyses

Power analysis was performed before the study to determine the minimum patient number needed for generalizability of the study's findings. The required sample size for each group (n=16) was determined based on the following four assumptions: a) a difference of at least 10% in the percentage rise in heart rate is significant, b) a difference of at least 10% in the percentage rise in SBP is significant, c) α error=0.05, and d) β error=80%. All values were expressed as the mean±standard deviation. ANOVA with *post hoc* comparison (Tukey) was used for statistical analysis of the study's all-numerical parameters. Values were considered significant when p was ≤0.05. SPSS 12.0 (Statistical Package for Social Sciences; SPSS Inc., IL, USA) was used for assessing the significance of differences between the groups.

RESULTS

Characteristics of the patients, laboratory findings, and PWV levels are summarized in Tables 1 and 2. The mean blood pressure (MBP) levels for the UC ($p<0.001$) and CD ($p<0.05$) groups were significantly higher than those in the C group. The mean triglyceride, hemoglobin, and hematocrit levels of the UC and CD groups were significantly lower than those in the C group. The albumin and total protein levels of the CD group were significantly lower than those in the C group ($p<0.05$ and $p<0.001$, respectively). In addition, total protein and total cholesterol levels of the CD group were also significantly lower than those in the UC group ($p<0.05$). PWV levels of the UC and CD groups were significantly higher than those in the C group ($p<0.001$).

In the bilateral recording of the VEP, N_2 latencies of the UC ($p<0.01$) and CD ($p<0.05$) groups were significantly longer than those in the C group. P_2 latencies of the UC and CD groups were significantly longer than those in the C group ($p<0.05$). Results of the VEP are summarized in Table 3.

DISCUSSION

The assessment of VEP is a reliable technique for evaluating visual neuronal functions in patients with neurological or systemic diseases (14). Delayed latencies were observed in VEP of our patients with IBD. However, the amplitudes of their VEP were normal. Essentially, low VEP amplitudes suggest severe disease of the visual pathways. We focused mainly on amplitudes during VEP evaluation, but abnormal latencies could also be a marker of probable pathology and therefore should be followed up regularly and analyzed further. The finding of delayed VEP latency reveals a significant deceleration in visual neuronal functions. Ocular manifestations such as episcleritis, scleritis, and anterior uveitis occur in about 4-10% of IBD patients (15,16). Various neurologic abnormalities have been reported in IBD without being an extraintestinal manifestation (17). Optic disc edema and arterial thrombosis have been reported in patients with ulcerative colitis (18). Systemic inflammatory activity could affect visual neuronal functions directly or indirectly during active periods of IBD. This and other chronic relapsing multisystem inflammatory disorders could cause neuronal physiologic abnormalities in VEP (19,20). To our knowledge, our study is the first to report subclinical visual neuronal dysfunction in IBD patients who were in a remission and had no extraintestinal disease. The subclinical dysfunction we uncovered could predispose IBD patients to subsequent major visual and neurological pathology.

Pulse wave velocity is used to assess widening of the arterial walls due to atherosclerosis. Increased PWV means increased arterial stiffness, which is an independent conventional risk factor for atherosclerosis (17,21). Decreased distensibility and compliance cause elevated PWV levels, which indicate vascular dysfunction due to arterial stiffness (13). Systemic inflammation is known to impair vascular functions by inducing atherosclerotic activity (20). Inflammatory pathologies can cause decreased distensibility, compliance, and elasticity of arteries by damaging their walls (21). Increased arterial stiffness has been reported in chronic inflammatory diseases (22).

There is limited knowledge about atherosclerotic activity in IBD (23). The reports on cardiovascular risk in IBD are controversial. In various studies, it has been suggested that IBD patients have normal arterial intima-media thickness and, therefore, IBD is not a risk factor for cardiovascular disease mortality (24-26). However, Dagli et al. (27) and Papa et al. (28) have found in-

Table 1. Characteristics and biochemical analyses of IBD patients and controls

	Control (n=25)	Ulcerative colitis (n=30)	Crohn's Disease (n=25)
Age (year)	42.07±6.55	44.71±11.51	38.94±10.14
Body mass index (kg/m^2)	25.4±1.92	24.85±4.12	22.95±5.09
Waist hips ratio	0.82±0.02	0.84±0.06	0.84±0.07
Glucose (mg/dL)	105.8±7.86	105.14±7.29	104.47±7.03
Total cholesterol (mg/dL)	169.07±17.81	177.25±24.51	154.53±33.71†
High density lipoprotein (mg/dL)	45.47±9.3	47.75±6.63	43.94±12.1
Low density lipoprotein (mg/dL)	96.53±17.86	106.71±24.79	100.18±29.92
Triglyceride (mg/dL)	135.67±42.23	80.36±36.22***	89.65±24.91***
Hemoglobin (g/dL)	14.87±1.64	13.4±1.95*	13±1.91*
Hematocrit (%)	43.27±3.71	37.29±4.81***	38.65±4.91*
White blood cells (/mm^3)	6353.33±708.99	7000.36±2402.08	7172.94±2118.86
Sedimentation (mm/h)	9.4±1.12	19.25±14.87	23.65±15.98*
C- reactive protein (mg/L)	2.13±0.83	8.17±8.04	19.08±17.49**
Albumin (g/dL)	4.4±0.2	4.15±0.45	4.04±0.46*
Total protein (g/dL)	7.77±0.26	7.43±0.45	6.79±1.2***†

Significant difference between control group and other groups defined with *; $p<0.05$*, $p<0.01$**, $p<0.001$***.
Significant difference between ulcerative colitis group and Crohn's Disease group defined with†; $p<0.05^{\dagger}$.

Table 2. Hemodynamic parameters of IBD patients and controls

	Control (n=25)	Ulcerative colitis (n=30)	Crohn's Disease (n=25)
Systolic blood pressure (mmHg)	108±10.14	125.71±15.97**	115.29±17.36
Diastolic blood pressure (mmHg)	59.33±7.04	78.57±10.44***	71.47±13.44**
Mean blood pressure (mmHg)	75.55±6	93.94±11.26***	84.96±14.39*†
Pulse pressure (mmHg)	48.67±11.87	48.21±12.19	45.29±13.17
Heart rate (bpm)	79.73±8.75	77.57±9.85	78.47±13.5
Pulse wave velocity (m/s)	7.59±0.29	9.28±1.31***	9.56±1.41***

Significant difference between control group and other groups defined with *; $p<0.05$*, $p<0.01$:**, $p<0.001$:***.
Significant difference between ulcerative colitis group and Crohn's Disease group defined with†; $p<0.05^{\dagger}$.

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Table 3. VEP results for the patients

		Ulcerative Control (n=25)	Crohn's colitis (n=30)	Disease (n=25)
Bilateral	N_2 (ms)	56.71±2.97	77.12±21.42**	74.72±26.75*
	P_2 (ms)	91.32±2.11	110.16±19.87*	110.06±27.1*
	PP (μV)	11.36±4.53	14.18±5.57	10.88±3.66
Right eye	N_2 (ms)	64.18±4.94	78.76±15.74*	79.67±25.81*
	P_2 (ms)	90.18±4.59	118.56±21.69***	118.22±24.45***
	PP (μV)	9.34±4.52	11.76±5.89	9.66±3.73
Left eye	N_2 (ms)	61.77±4.79	78.28±15.88**	83.39±17.79***
	P_2 (ms)	93.27±4.78	116.4±19.49***	115.5±15.33***
	PP (μV)	8.28±4.01	12.05±5.46*	7.42±4.34††

Significant difference between control group and other groups defined as follows: p<0.05*, p<0.01**, p<0.001***.
Significant difference between ulcerative colitis group and Crohn's Disease group defined with†; p<0.05†.

creased carotid intima-media thickness and carotid artery stiffness in IBD patients and reported that they are at risk of early atherosclerosis.

We observed increased PWV, an objective marker of atherosclerosis, in IBD patients. Inflammation causes vascular dysfunction (28).

We also observed mildly increased mean, SBP, and DBP levels that could result from vascular and also neurohormonal dysregulation in IBD. The stage of these increased blood pressures was not clinically significant, overall, but the blood pressures of some of these patients were at borderline high levels. High blood pressure directly causes abnormal PWV.

The literature is unclear about the etiology of hypertension in IBD patients. Chronic inflammation is a driving force for premature atherosclerosis (29). Atherothrombotic complications are related to early atherosclerosis (30,31). Microvascular endothelial dysfunction with diminished vasodilatory capacity causes reduced perfusion, impairs wound healing, and triggers inflammation in IBD (32). Venous and arterial thromboembolism is the major cause of morbidity and mortality in IBD patients (33). Some genetic factors and drugs used in treatment could also promote the pathophysiology of neuronal and vascular damage in IBD (34,35). Diminished blood vessel functions could also be an etiologic factor in visual neuronal dysfunctions associated with IBD.

We observed reduced hemoglobin, hematocrit, total cholesterol, albumin, and triglyceride levels in our IBD patients. The levels of some of these parameters were lowest in the CD group. These results were not predictable by us in the preparation period of the study because the patients had no additional symptoms or pathology besides IBD. However, mild anemia and low blood protein levels could be observed in IBD patients as a result of chronic blood loss via the gastrointestinal tract, malabsorption, and chronic inflammation (36). These findings related to malabsorption were more severe in Crohn's disease than that in ulcerative colitis because of differences in disease localization in their gastrointestinal tracts. Chronic anemia and diminished nutritional absorption are probable problems for IBD patients and also can cause direct neuronal and cardiovascular dysfunctions independently (37,38). The nutritional status and blood counts of the IBD patients in our study were satisfactory to maintain their vital functions without additional treatment. Certainly, our data are insufficient to warrant further comment about the possible effects of different blood levels of hemoglobin and proteins on neuronal and cardiovascular functions.

Our study has several limitations, including relatively small patient numbers and short follow-up time. However, we have created three homogenous patient groups with strict exclusion criteria to evaluate subclinical abnormalities in patients with IBD. It would be impractical to collect larger number of patients by applying more comprehensive exclusion criteria.

In this study, we have shown that even IBD patients who are in remission could be at risk for vascular and visual neuronal impairments. In addition, the results of the study suggest that IBD patients are at risk for early atherosclerosis compared to healthy individuals. Further prospective studies with a larger patient number could clarify the pathophysiologic mechanisms of premature atherosclerosis and visual neuronal dysfunctions in IBD patients.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University Cerrahpasa Medical Faculty.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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REFERENCES

1. Rothfuss KS, Stange EF, Herrlinger KR. Extraintestinal manifestations and complications in inflammatory bowel diseases. World J Gastroenterol 2006; 14: 4819-31.
2. Seymen P, Selamet U, Aytac E, Trabulus S, Seymen HO. Evaluation of visual evoked potentials in chronic renal failure patients with different treatment modalities. J. Nephrol 2010; 23: 705-10.

3. Yildiz M, Masatlioglu S, Seymen P, Aytac E, Sahin B, Seymen HO. The carotid-femoral (aortic) pulse wave velocity as a marker of arterial stiffness in familial Mediterranean fever. Can J Cardiol 2006; 22: 1127-31. [CrossRef]
4. Druschky A, Heckmann JG, Druschky K, Huk WJ, Erbguth F, Neundörfer B. Severe neurological complications of ulcerative colitis. J Clin Neurosci 2002; 9: 84-6. [CrossRef]
5. Keene DL, Matzinger MA, Jacob PJ, Humphreys P. Cerebral vascular events associated with ulcerative colitis in children. Pediatr Neurol 2001; 24: 238-43. [CrossRef]
6. Yilmaz S, Aydemir E, Maden A, Unsal B. The prevalence of ocular involvement in patients with inflammatory bowel disease. Int J Colorectal Dis 2007; 22: 1027-30. [CrossRef]
7. Hayton SM, Kriss A, Wade A, Muller DP. The effects of different levels of all-rac- and RRR-a-tocopheryl acetate (vitamin E) on visual function in rats. Clin Neurophysiol 2003; 114: 2124-31. [CrossRef]
8. Seo M, Okada M, Yao T, Ueki M, Arima S, Okumura M. An index of disease activity in patients with ulcerative colitis. Am J Gastroenterol 1992; 87: 971-6.
9. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976; 70: 439-44.
10. Asmar R, Benetos A, Topouchian J, et al. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. Hypertension 1995; 26: 485-90. [CrossRef]
11. Odom JV, Bach M, Barber C, et al. Visual evoked potentials standard. Doc Ophthalmol 2004; 108: 115-23. [CrossRef]
12. Otto D, Hudnell K, Boyes W, Janssen R, Dyer R. Electrophysiological measures of visual and auditory function as indices of neurotoxicity. Toxicology 1988; 49: 205-18. [CrossRef]
13. Otto DA, Hudnell HK. The use of visual and chemosensory evoked potentials in environmental and occupational health. Environ Res 1993; 62: 159-71. [CrossRef]
14. Turker H, Terzi M, Bayrak O, Cengiz N, Onar M, Us O. Visual evoked potentials in differential diagnosis of multiple sclerosis and neurobehcet's disease. Tohoku J Exp Med 2008; 216: 109-16. [CrossRef]
15. Karlinger K, Györke T, Makö E, Mester A, Tarján Z. The epidemiology and the pathogenesis of inflammatory bowel disease. Eur J Radiol 2000; 35: 154-67. [CrossRef]
16. Mintz R, Feller ER, Bahr RL, Shah SA. Ocular manifestations of inflammatory bowel disease. Inflamm Bowel Dis 2004; 10: 135-9. [CrossRef]
17. Villain MA, Pageaux GP, Veyrac M, Arnaud B, Harris A, Greenfield DS. Effect of acetazolamide on ocular hemodynamics in pseudotumor cerebri associated with inflammatory bowel disease. Am J Ophthalmol 2002; 134: 778-80. [CrossRef]
18. Rouleau J, Longmuir R, Lee AG. Optic disc edema with adjacent cilioretinal artery occlusion in a male with ulcerative colitis. Semin Ophthalmol 2007; 22: 25-8. [CrossRef]
19. Anlar O, Akdeniz N, Tombul T, Calka O, Bilgili SG. Visual evoked potential findings in Behcet's disease without neurological manifestations. Int J Neurosci 2006; 116: 281-7. [CrossRef]
20. Munro JM, Cotran RS. The pathogenesis of atherosclerosis: Atherogenesis and inflammation. Lab Invest 1988; 58: 249-61.
21. Cohn JN. Arterial compliance to stratify cardiovascular risk: More precision in therapeutic decision making. Am J Hypertens 2001; 14: 258-63. [CrossRef]
22. Imura T, Yamamoto K, Kanamori K, Mikami T, Yasuda H. Non invasive ultrasonic measurement of the elastic properties of the human abdominal aorta. Cardiovasc Res 1986; 20: 208-14. [CrossRef]
23. Roman MJ, Devereux RB, Schwartz JE, et al. Arterial stiffness in chronic inflammatory diseases. Hypertension 2005; 46: 194-9. [CrossRef]
24. Rachapalli SM. Inflammatory bowel diseases and atherosclerosis: do we need more studies? Inflamm Bowel Dis 2005; 11: 705. [CrossRef]
25. Maharshak N, Arbel Y, Bornstein NM, et al. Inflammatory bowel disease is not associated with increased intimal media thickening. Am J Gastroenterol 2007; 102: 1050-5. [CrossRef]
26. Dorn SD, Sandler RS. Inflammatory bowel disease is not a risk factor for cardiovascular disease mortality: results from a systematic review and meta-analysis. Am J Gastroenterol 2007; 102: 662-7. [CrossRef]
27. Dagli N, Poyrazoglu OK, Dagli AF, et al. Is inflammatory bowel disease a risk factor for early atherosclerosis? Angiology 2010; 61: 198-204. [CrossRef]
28. Papa A, Santoliquido A, Danese S, et al. Increased carotid intima-media thickness in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2005; 22: 839-46. [CrossRef]
29. Sappati Biyyani RS, Fahmy NM, Baum E, Nelson KM, King JF. Inflammatory bowel disease and coronary artery disease. Indian J Gastroenterol 2009; 28: 28-30. [CrossRef]
30. Selzer F, Sutton-Tyrrell K, Fitzgerald SG, et al. Comparison of risk factors for vascular disease in the carotid artery and aorta in women with systemic lupus erythematosus. Arthritis Rheum 2004; 50: 151-9. [CrossRef]
31. Van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis. An extraarticular feature of rheumatoid arthritis? Arthritis Rheum 2002; 46: 862-73. [CrossRef]
32. Hatoum OA, Binion DG, Otterson MF, Gutterman DD. Acquired microvascular dysfunction in inflammatory bowel disease: loss of nitric oxide-mediated vasodilation. Gastroenterology 2003; 125: 58-69. [CrossRef]
33. Di Fabio F, Obrand D, Satin R, Gordon PH. Intra-abdominal venous and arterial thromboembolism in inflammatory bowel disease. Dis Colon Rectum 2009; 52: 336-42. [CrossRef]
34. De Bleecker JL, Leroy BP, Meire VI. Reversible visual deficit and Corpus callosum lesions due to metronidazole toxicity. Eur Neurol 2005; 53: 93-5. [CrossRef]
35. Jarand J, Zochodne DW, Martin LO, Voll C. Neurological complications of infliximab. J Rheumatol 2006; 33: 1018-20.
36. Oustamanolakis P, Koutroubakis IE, Messaritakis I, Kefalogiannis G, Niniraki M, Kouroumalis EA. Measurement of reticulocyte and red blood cell indices in the evaluation of anemia in inflammatory bowel disease. J Crohns Colitis 2011; 5: 295-300. [CrossRef]
37. Hare GM, Tsui AK, McLaren AT, Ragoonanan TE, Yu J, Mazer CD. Anemia and cerebral outcomes: many questions, fewer answers. Anesth Analg 2008; 107: 1356-70. [CrossRef]
38. Simsek H, Gunes Y, Demir C, Sahin M, Gumrukcuoglu HA, Tuncer M. The effects of iron deficiency anemia on p wave duration and dispersion. Clinics (Sao Paulo) 2010; 65: 1067-71. [CrossRef]