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AUTHORS: Kemal FIDAN,Mehmet Zahid KOÇAK,Abdullah DOGAN,Huseyin KORKMAZ

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Ülseratif Kolitli Hastalarda Netrin-1 Düzeyinin Klinik ve Hastalık Aktivitesini Değerlendirmedeki Rolü ve TNF-alfa, IL-6 ile İlişkisi

The Significance of Netrin-1 Level in the Clinical Activity of Ulcerative Colitis, its Association between TNF-α and IL-6

[1]Kemal FİDAN,[2]Mehmet Zahid KOCAK, [3]Abdullah DOĞAN, [4]Hüseyin KORKMAZ

[1]Department of Internal Medicine, Subdivision of Hematology, Erciyes University, Medical Faculty, Kayseri, Turkey
[2]Selcuk University Medical School, Department of Internal Medicine, Konya, Turkey
[3]Department of Internal Medicine, subdivision of Rheumatology, Gulhane Researchand Training Hospital, Ankara, Turkey
[4]Selcuk University Medical School, Department of Gastroenterology, Konya, Turkey

Kemal Fidan: https://orcid.org/0000-0002-2186-4196
Mehmet Zahid Koçak: https://orcid.org/0000-0003-4419-409X
Abdullah Doğan: https://orcid.org/0000-0001-7721-3707
Hüseyin Korkmaz: https://orcid.org/0000-0002-3518-1943

ÖZ

Amaç: Bu çalışmada Ülseratif Kolit (ÜK)'de netrin-1 düzeylerinin hastalığın klinik aktivitesindeki önemi ve diğer proinflamatuar sitokinlerden IL-6 ve TNF-alfa ile ilişkisini araştırdık.

Materyal ve Metot: Bu çalışma bir vaka control çalışması olup çalışmaya ÜK'li 67 hasta (36'sı aktivasyonlu, 31'i remisyonda) ve 50 sağlıklı kontrol dahil edildi. ÜK hastaları; "Truelove Witts klinik aktivite indeksi"ne göre hafif aktivasyon (n=21), orta aktivasyon (n=6) ve şiddetli aktivasyon (n=9) gruplarına ayrıldı. Asemptomatik olan 31 hasta Montreal sınıflandırılmasına göre remisyonda kabul edildi. Plazma örneklerindeki netrin-1, IL-6 ve TNF-alfa ölçümleri, ELİSA test kiti kullanılarak yapıldı.

Bulgular: Hasta grubu ile kontrol grubu arasında; netrin-1, IL-6 ve TNF-alfa düzeyleri arasında istatistiksel olarak anlamlı bir fark vardı (p<0,05). Şiddetli aktivasyon grubunda plazma netrin-1 düzeyi hafif şiddetli grup, remisyon grubu ve kontrol grubuna göre istatistiksel olarak daha yüksekti (p<0,05). ÜK grupları arasında TNF-alfa düzeyi istatistiksel olarak anlamlı bulunmazken (p>0,05), IL-6 düzeyi ise gruplar arasında anlamlı bulundu (p<0,05). Ayrıca netrin-1 ile IL-6 arasında pozitif yönde bir korelasyon saptanırken, netrin-1 ile TNF-alfa arasında korelasyon saptanmadı.

Sonuç: Çalışmamız; plazma netrin-1 düzeylerinin, TNF-alfa ve IL-6 gibi proinflamatuar sitokinlere benzer şekilde ÜK aktivasyonu ile ilişkili olduğunu ortaya koymaktadır.

Anahtar Kelimeler: IL-6, netrin-1, TNF-alfa, ülseratif kolit

ABSTRACT

Objective: We investigated the importance of netrin-1 levels in Ulcerative Colitis (UC) in clinical activity of the disease, and its association with other proinflammatory cytokines IL-6 and TNF-alpha.

Materials and Methods: This study was a case-control study and included 67 patients with UC (36 activated, 31 in remission) and 50 healthy controls. UC patients were divided into mild activation (n=21), moderate activation (n= 6) and severe activation (n= 9) groups according to the "Truelove Witts clinical activity index". 31 asymptomatic patients were considered to be in remission. Netrin-1, IL-6 and TNF-alpha measurements in plasma samples were made using ELISA assay kit.

Results: Between the patient group and the control group; there was a statistically significant difference between netrin-1, IL-6, TNF-alpha, (p<0.05 for all). The plasma netrin-1 mean of UC with severe activation group was statistically significantly higher than that of the mild activation, remission group and control group (p<0.05). Plasma netrin-1 mean of UC with modarate activation group was statistically significantly higher than that of the mild activation and remission group.

Conclusion: We found that plasma netrin-1 levels increase with disease severity in UC, similar to proinflammatory cytokines such as TNF-alpha and IL-6.

Keywords: IL-6, netrin-1, TNF-alpha, ulcerative colitis

INTRODUCTION

Ulcerative colitis (UC) is a nonspecific inflammatory disease with chronic and idiopathic activation (exacerbation, recurrence) and remission episodes. Although the pathogenesis is not completely known, it is characterized by intestinal epithelial cell damage and leukocyte mucosal epithelial infiltration.[1] Interleukin-1 beta (IL-1b), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) released from macrophages have been shown to play a role in the pathogenesis of UC.[2] These cytokines are normally produced secondary to inflammation, but generally their production is stopped or at best inhibited to maintain tissue damage. Their activity in inflammatory bowel disease (IBD) is not regular, and imbalances between proinflammatory and anti-inflammatory cytokines arise. Netrin-1 is a laminin-like protein. It promotes spinal cord growth, axonal growth by secretion from neuronal basement membranes. It is also secreted from organs such as kidneys, liver, intestine, lungs and has been found to play a role in tissue morphogenesis, cell development, vascular development and tumorogenesis.[3] Many studies have demonstrated that netrin-1 inhibits inflammation in renal ischemic reperfusion injury, intestinal disease, anddiabetic nephropathy.[4] In a study investigating the role of netrin-1 in endothelial cells, it was observed that netrin-1 suppressed TNF-alpha-induced cytokines and blocked the adhesion of monocytes to the endothelium. It was also observed that the cytokine production of netrin-1 from monocyte chemoattractant protein-1(MCP-1), IL-1beta, IL-6 and TNF-alpha was suppressed.[5] In studies determined, it has been shown that netrin-1 has an anti-inflammatory effect in many acute and chronic diseases.[6,7] Increased netrin-1 in the intestinal mucosa was reported to be protective (anti-inflammatory effect) in animal experiments performed. It has been reported that the increase of netrin-1 is affected by inhibiting leukocyte migration and infiltration.[8-10] In these experimental studies, it was reported that netrin-1 may be a tissue-protective mediator in IBD and increased netrin-1 in the colon mucosa during experimental colitis.[8]

In animal experiments has been reported that netrin-1 reduces neutrophil infiltration, cytokine and chemokine production in the colon mucosa and kidney.Also predicted, this effect was to decrease IL-6 production and activity. Thus, it has been shown that netrin-1 may limit organ damage by suppressing apoptosis and inflammatory mediators.[11] It was also found that TNF-alpha released by macrophages stimulates the production of netrin-1, thus TNF-alpha contributes to the anti-apoptotic effect of netrin-1.[12]

In this study, we investigated the importance of netrin-1 levels in UC in the clinical activity of the disease, and its association with other proinflammatory cytokines IL-6 and TNF-alpha.

MATERIALS AND METHODS

Ethics Committee Approval: Written informed consent was obtained from all participants, and the local ethics committee approved the study protocol (Date: 26/05/2015, decision no: 2015/182). This cross-sectional study was carried out according to good clinical practice and the Declaration of Helsinki.

This study is a type of case-control study. The study included 67 patients with ulcerative colitis who applied to the Internal Diseases Gastroenterology Clinic or Emergency of Selcuk University Medical Faculty Hospital between 15.05.2015 and 01.01.2016, who had an acute attack and came for routine follow-up after the attack (remission). Fifty volunteer controls who applied to Selcuk University Medical Faculty Hospital Internal Diseases Clinic with nonspecific symptoms and worked in the hospital were included.

UC patients were evaluated according to the "Truelove-Witts (TW) Clinical Activity Index"and were divided into groups; mild activation (n=21), moderate activation (n=6) and severe activation (n=9). Thirty-one asymptomatic patients were considered to be in remission according to the Montreal classification. The ones with a history of cerebrovascular accident, neurological disease, cigarette smokers, with infection, pregnant women, ones with diagnosed liver failure, with previously diagnosed malignancy using anticonvulsant drugs, nephrotoxic drug users, and those with kidney diseases were excluded from the study. The blood samples were taken from the antecubital area and put into etilen diamine tetraacetic acid (EDTA) tubes. After centrifugation at 2800 rpm and at 4°C for 20 min, plasma samples were placed into the eppendorf tubes and were stored at −80°C until runtime. Netrin-1, IL-6 and TNF- alpha measurements in plasma samples were performed with Rayto-2100C Microplate Reader device using enzyme-linked immunosorbent assay (ELISA) kit (MyBioSource, USA). Hemogram, sedimentation and CRP were measured with standard laboratory testing.

Statistical Analysis: SPSS (Statistical Package for Social Sciences) for Windows 16.0 statistical software was used. Median (min, max) values are reported for continuous non-normal data, mean ± SD is reported otherwise. Chi-square tests were used to assess the relationship between control and patient groups with categorical variables. Student's t-test was used to compare the measurements of a particular variable of two separate groups and for normal scattered groups, the Mann–Whitney U test was

used for abnormally distributed groups. Tamhane's T2 test together with the one-way Analysis Of Variance (ANOVA), was used to compare multiple groups. The Kruskal-Wallis test was used for non-normally distributed data to compare multiple groups. Bonforoni correction was used when assessing significance between subgroups. Pearson correlation analysis was used to determine the relationship between numerical variables for normally distributed groups, and Spearman test was used for abnormally distributed groups. Correlation coefficient (r), between 0.000 and 0.249 was considered as weak relation; middle from 0.250 to 0.499, strong from 0.500 to 0.749, and very strong relation between 0.750 and 1.000. P value lower than 0.05 is considered as statistically significant.

RESULTS

Individuals enrolled in the study were divided into two as 67 patients with UC (36 activation, 31 remission) and 50 control group. The individuals study and control group in both groups were equal in terms of age, gender, and BMI. Characteristics of study group were summarized in Table 1.

Laboratory parameters of the patient group and control group were summarized in Table 2. Between the patient group and the control group, there was a statistically significant difference in levels netrin-1, IL-6, TNF-alpha, CRP, ESR, WBC, neutrophil, platelet ($p<0.05$).

The laboratory parameters of the remission, mild, moderate, severe activation groups and the healthy control group were summarized in Table 3.

Table 1. Similar features of study and control group.

Parameters	Activation n=36	Remission n=31	Control n=50	x^2/f	p
Age(year)	45.77±13.84	43.83±12.65	42.56±16.64	0.493	**0.612**
BMI(kg/m^2)	25.67±4.03	26.93±4.28	26.27±3.96	0.799	**0.452**
Gender -Female -Male	12(33.3%) 24(66.7%)	13(41.9%) 18(58.1%)	21(42%) 29(58%)	0.780	**0.677**
Total	36(100%)	31(100%)	50(100%)		

Table 2. Laboratory parameters between patient-control group.

Parameters	Control (n=50)	Patient (n=67)	x^2/f	p
Netrin-1 (pg/ml)	71.00±35.46	91.87±51.98	10.09	**0.011**
IL-6 (pg/ml)	4.28±1.45	7.45±12.08	10.501	**0.036**
TNF-αlpha (pg/ml)	7.36±8.88	20.02±9.16	0.886	**0.000**
ESR(m/h)	16.48±13.29	25.68±18.75	8.54	**0.002**
CRP(mg/L)	4.72±4.05	9.90±14.93	13.84	**0.008**
WBC(K/Ul)	6.90±1.54	8.18±2.80	13.31	**0.002**
HGB(g/dL)	13.40±2.40	13.24±1.94	0.689	**0.701**
PLT(K/uL)	244.11±64.55	286.97±82.97	0.833	**0.002**
Neutrophil (K/uL)	3.94±1.20	5.31±2.44	16.32	**0.000**
Lymphocyte K/uL)	2.19±0.58	1.99±0.67	0.455	**0.088**

TNF-αlpha: Tumor necrosis factor-alpha; IL-6: Interleukin 6; HGB: Hemoglobin; ESR: Erythrocyte sedimentation rate; WBC: White Blood Cell; CRP: C-Reactive Protein.

Table 3. Laboratory parameters of all groups.

Parameters	Remission n=31	Mild activation n=21	Moderate activation n=6	Severe activation n=9	Control n=50	p
Netrin-1 (pg/ml)	75.15±41.15	75.61±48.57	100.35±49.5[a,b,d]	139.21±48.09[a,b,d]	71.00±35.46	**0.011**
IL-6 (pg/ml)	4.28±1.45	5.51±3.49	6.95±6.95	25.61±26.41[a,b,c,d]	3.59±1.79	**0.001**
TNF-alpha (pg/ml)	18.47±7.17 [d]	18.67±11.99 [d]	24.86±9.46 [d]	25.27±4.64 [d]	7.36±8.88	**0.000**
ESR (m/h)	13.12±8.83	27.66±14.62[a,c,d]	46.83±15.35[a,b,d]	50.22±17.10 [a,b,d]	16.48±13.29	**0.000**
CRP (mg/L)	5.06±3.20	6.41±5.64 [d]	13.44±21.37[d]	32.36±27.15 [a,b,c,d]	4.72±4.05	**0.000**

TNF-αlpha: Tumor necrosis factor-alpha; IL-6: Interleukin 6; HGB: Hemoglobin; ESR: Erythrocyte sedimentation rate; [a]: There was a significant difference between the groups with the remission activation group ($p<0.05$); [b]: There was a significant difference between the groups with mild activation ($p<0.05$); [c]: There was a significant difference between the groups with the middle activation group ($p<0.05$); [d]: There was a significant difference from the control group ($p<0.05$).

The plasma netrin-1 mean of UC with severe activation group (139.21±48.09) was statistically significantly higher than that of the mild activation (p=0.037), remission group (p=0.001) and control group (p=0.011). The plasma netrin-1 mean of UC with moderate activation group was statistically significantly higher than that of the mild activation (p=0.045) and remission group (p=0.004). There was no statistically significant difference between the severe activation group and the moderate activation group (p=0.054). Additionally, there was a statistically significant difference between the moderate activation group and mild activation (p=0.045), remission (p=0.004) and control groups (p=0.026) of netrin-1. There was no statistically significant difference between the mild activation group of netrin-1 and the remission (p>0.05) and control groups (p=0.096). There was no statistically significant difference between the netrin-1 remission group and the control group (p>0.05). The TNF-alpha mean of control group (7.36±8.88pg/ml) was statistically significantly lower than the remission group of UC (p<0.01). In patients with ulcerative colitis, the mean of TNF-alpha in the severe activation group (25.27±4.64 pg/ml) was not statistically significant compared to those in the mild activation (p=0.640), moderate activation (p>0.05) and remission group (p=0.621). The IL-6 mean of UC with activation group (10.78±15.72pg/ml) was statistically significantly higher than that of the remissin group (p=0.008) and the control group (p=0.003). The IL-6 mean of UC with severe activation group (25.61±26.41 pg/ml) was statistically significantly higher than that of the mild activation (p=0.001), moderate activation group (p<0.01) and remission group (p<0.01).

There was a positive statistically significantly correlation between the clinical activity of the disease and netrin-1 (p=0.008), TNF-alpha (p=0.034) and IL-6 (p<0.01). Besides, there was a positive statistically significantly correlation between IL-6 and netrin-1 (p<0.05) and TNF- alpha (p<0.05). There was no correlation between netrin-1 and TNF-alpha (p>0.05). They were summarized in Table 4.

There was no significant correlation between netrin-1 and ESR and TNF-alpha (p>0.05). A moderately strong positive correlation was found only between netrin-1 and IL-6 and CRP (p<0.05). There was a moderately strong positive correlation between IL-6 and netrin-1 and ESR, a very strong positive correlation with CRP, and a weak positive correlation with TNF-alpha (p<0.05). There was no significant correlation between TNF-alpha and netrin-1, ESR and CRP (p>0.05). A moderately strong positive correlation was found between ESR and IL-6 and CRP (p<0.01). A moderately strong positive correlation was found between CRP and netrin-1 and ESR, and a strong positive correlation was found with IL-6 (p<0.01). They were summarized in Table 5.

Table 4. Examining the correlation between disease activity and laboratory parameters.

Parameters	r
Netrin-1(pg/ml)	0.320**
IL-6 (pg/ml)	0.550**
TNF-alpha (pg/ml)	0.187*
ESR (m/h)	0.741**
CRP (mg/L)	0.382**

*: p<0.05; **: p<0.01.

Tablo 5. Investigation of the patient group "continuous variables" correlation coefficients (r).

Parameters	CRP	ESR	TNF-alpha	IL-6
Netrin-1(pg/ml)	0,400**	0,068	0,118	0,281*
IL-6 (pg/ml)	0,756**	0,442**	0,175*	
TNF-alpha (pg/ml)	0,192	0,229		
ESR (m/h)	0,453**			

*: p<0.05; **: p<0.01.

DISCUSSION AND CONCLUSION

Netrin-1 is a laminin-like protein that has been shown to play a role in inflammation regulation in IBD.[13-16] Researchs has shown that netrin-1 can actively attenuate the acute inflammatory response and accelerate pro-resolving mechanisms, which cease the inflammation and help the inflamed tissue to return to homeostasis.[17,18] In animal studies, it has been shown that netrin-1 increases during inflammation in the intestinal mucosa of colitic mice's epithelial cells and myenteric neurons, and plays a key role in balancing the acute inflammatory (anti-inflammatory) response.[8,19] Laura Ziegon et al. was reported that netrin-1 expression is both induced and suppressed depending on the stimulus and organ in acute abdominal inflammation (acute pancreatitis, acute peritonitis).[20] Xueli Xia et al. stated that netrin-1 has different effects (anti-inflammatory, pro-inflammatory) on various receptors. It has been stated that netrin-1 on UNC5B/Adora2b receptors reduces inflammation by reducing leukocyte migration in multiple acute inflammatory events (such as sepsis, colitis). Moreover, urinary netrin-1 may even be a marker in diabetic nephropathy and acute kidney injury, close stated that netrin-1 may play a role in the clinical diagnosis and treatment of inflammatory diseases in the future.[21] In another study, immuno-histochemically netrin-1 expression was shown in epithelial cells with inflammation in the colonic mucosa of 30 IBD patients and netrin-1 levels in the infected mucosa were higher than normal mucosa.[15]

The relationship of netrin-1 to inflammatory cytokines and clinical activity of the disease in IBD is unclear. This study was designed to see the significance of plasma netrin-1 level in the clinical activity of UC and relationship between TNF-alpha and IL-6.

Plasma levels of netrin-1 with in patient's group were significantly higher than in the control group. When we divided the subjects participating in the study into groups as control, remission, and active patients, we determined that netrin-1 was higher in the active patient group than in the other groups, and we found a statistically significant difference between them. Additionally, we classified the patient group as mild, moderate and severe activation group according to the Truelove-Witts Clinical Activity Index. We found that the level of netrin-1 was higher in the severe activation group than in the other groups.

Our study is the first to investigate the relationship between the clinical activity of the disease and the level of netrin-1. In the correlation between the clinical activity of the disease and the netrin-1 level, there was a moderate positive correlation between them. As the clinical severity of the disease increased, the netrin-1 level increased. Although previous studies have shown that the level of netrin-1 increases only in the disease, no research has been donebetween the severity of the disease and the level of netrin-1. In this study, we found that there is a direct relationship between disease severity and netrin-1. It is known that the activation of immunocytes in UC secrete inflammatory cytokines.[2,10,22] Funakoshi et al. showed that the expression of IL-1beta, IL-6 and TNF-alpha in mucosal lesions in ulcerative colitis increased and these inflammatory cytokines played an important role in the pathogenesis of ulcerative colitis.[2]

In our study, we found higher TNF-alpha and IL-6 levels in UC patients compared to the control group. In addition, when we divided our study into groups according to clinical activity, we found that IL-6 and TNF-alpha were positively related to disease activation. There are very few studies investigating the relationship of netrin-1 with TNF-alpha and IL-6 in IBD. There was also a positive correlation between netrin-1 and IL-6 in the patient group, but we did not detect any correlation between netrin-1 and TNF-alpha. We found a weak positive correlation between TNF-alpha and IL-6.

Our study has some limitations. First, it was a relatively small study. A prospective study with larger groups of patients should be performed to better show the relations of plasma netrin-1 levels with UC. Second, only plasma netrin-1 level has been investigated, can be displayed better in a study comparing intestinal mucosal netrin-1 levels in the same patients. Our study was the first study to investigate the association of clinical involvement of disease with peripheral netrin-1 in UC with IL-6 and TNF-alpha, which are other proinflammatory factors. Our results reveal that plasma netrin-1 levels areto be associated with disease activation, similar to proinflammatory cytokines such as TNF alpha and IL6, in UC. Further randomized, prospective studies with larger samples are required to support our findings.

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