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Evaluation of peripheral nerves in patients receiving anti-tumor necrosis factor-alpha drug therapy

Anti-tümör nekroz faktör-alfa ilaç tedavisi alan hastalarda periferik sinirlerin değerlendirilmesi

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Abstract

Aim: Anti-tumor necrosis factor-alpha (TNF-α) drug treatments are widely used in many inflammatory diseases. Neurological complications have rarely been reported in these treatments. Our aim in this study was to investigate the neurological findings that occurred in our patients receiving this treatment.
Methods: A case-control study conducted in (institutional information was blinded) between September 2018-September 2019. The study included 35 patients receiving tumor necrosis factor-alpha blocker drug, and 37 healthy control subjects with similar demographic characteristics. The disease activity scores of the patient group and physical function scores of the patient and control groups were questioned. All patients underwent a detailed physical and neurological examination. Afterward, peripheral nerves were evaluated neurophysiologically. According to distribution Mann-Whitney U test or independent samples t-test was used when comparing groups. The relationship between Short Form-36 and age or body mass index was determined by using Spearman's rank correlation coefficient.
Results: The results obtained in sensory and motor nerve conduction examinations were compared between groups. Patients using anti-tumor necrosis factor-alpha had peripheral sensory neuropathy. Examination of peripheral motor nerves was within normal limits.
Conclusions: Anti-tumor necrosis factor-alpha drugs have good effects in inflammatory diseases. These patients should be carefully monitored for neurological findings.

Keywords: Tumor necrosis factor-alpha, nerve conduction, electromyography

Öz

Amaç: Anti-tümör nekroz faktör-alfa (TNF-α) ilaç tedavileri, birçok enflamatuar hastalıkta yaygın olarak kullanılmaktadır. Bu tedavilerde nadiren nörolojik komplikasyonlar bildirilmiştir. Bu çalışmadaki amacımız, bu tedaviyi alan hastalarımızda ortaya çıkan nörolojik bulguları araştırmaktı.
Yöntemler: Eylül 2018-Eylül 2019 arasında (kurumsal bilgi körlendi) yürütülen bir vaka kontrol çalışmasıdır. Çalışmaya tümör nekroz faktör-alfa bloker ilaç alan 35 hasta ve benzer demografik özelliklere sahip 37 sağlıklı kontrol deneği dahil edildi. Hasta grubunun hastalık aktivite skorları ile hasta ve kontrol grubunun fiziksel fonksiyon skorları sorgulandı. Tüm hastalara detaylı fiziksel ve nörolojik muayene yapıldı. Daha sonra periferik sinirler nörofizyolojik olarak değerlendirildi. Dağılıma göre gruplar karşılaştırılırken Mann-Whitney U testi veya Independent samples t-testi kullanıldı. Kısa Form-36 ile yaş veya vücut kitle indeksi arasındaki ilişki, Spearman'ın sıra korelasyon katsayısı kullanılarak belirlendi.
Bulgular: Duyusal ve motor sinir ileti incelemelerinde elde edilen sonuçlar gruplar arasında karşılaştırıldı. Anti-tümör nekroz faktör-alfa ilacı kullanan hastalarda periferik duyusal nöropati tespit edildi. Periferik motor sinirlerin incelemesi normal sınırlardaydı.
Sonuç: Anti-tümör nekroz faktör-alfa ilaçları enflamatuar hastalıklarda oldukça etkilidir. Bu ilaçları kullanan hastalar nörolojik bulgular açısından dikkatle izlenmelidir.

Anahtar kelimeler: Tümör nekroz faktör-alfa, sinir iletimi, elektromiyografi

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Introduction

Tumor necrosis factor (TNF) is a pleomorphic proinflammatory cytokine, which plays an important role in the pathogenesis of many chronic inflammatory diseases, mainly produced in monocytes, macrophages, and T-lymphocytes [1]. TNF has also been shown to be produced by natural killers, fibroblasts, granulocytes, keratinocytes, muscle cells, and neurons. It is the first cytokine to respond to tissue damage, bacteria, viruses, immune complex, tumor cells and is referred to as "fire alarm'' our body [2].

TNF released from macrophages has been shown to have endotoxic shock development, cachexia in the course of infections as well as suppressing replication of viruses and facilitating the elimination of pathogens by macrophages [3]. TNF is first synthesized as membrane TNF-bound transmembrane TNF (tmTNF), and TNF is transformed into soluble-TNF (sTNF) by TNF-alpha converting enzyme (TACE) and released from the cell. Both tmTNF and sTNF are biologically active and have important roles [4].

Recently, anti-tumor necrosis factor-alpha (anti-TNF-α) drugs have been widely used as immunosuppressive agents in chronic inflammatory diseases such as rheumatoid arthritis (RA), juvenile rheumatoid arthritis, ankylosing spondylitis (AS), psoriasis, psoriatic arthritis, and Crohn disease. The five anti-TNF-α agents currently in clinical use are etanercept (circulating receptor fusion protein), infliximab, adalimumab, golimumab (Ig G monoclonal antibodies), and certolizumab (PEGylated Fab 1 fragment of an Ig G1 monoclonal antibody) [5]. TNF blockers are known to stimulate phagocytosis, degranulation, cytokine release, and antibody-mediated cellular cytotoxicity through which the cell bind to Fc receptors through Fc portions [6]. Anti-TNF drugs with monoclonal antibody features show their effects by suppressing proinflammatory cytokines, inducing cellular apoptosis, and stimulating cytotoxicity through complement [7]. In Etanercept, this effect is weak, and unlike other anti-TNFs, it also blocks lymphotoxin α (LTα3) [8]. Anti-TNF-α drugs were found to be faster and more effective in controlling disease activity and preventing underlying structural tissue damage than traditional disease-modifying drugs (DMARD) treatments [7].

Anti-TNF-α has been associated with different adverse effects, including infections (especially tuberculosis reactivation), local site reactions, hemocytopenia, congestive heart failure, T-cell lymphomas, lupus-like syndromes and vasculitis, autoimmune and neurological events [9-11].

Additionally, with the widespread use of anti-TNF-α drugs, an increasing number of demyelinating pathologies have been reported, including central nervous system (optic neuritis, multiple sclerosis, acute transverse myelitis) and peripheral nervous system disorders (Guillain-Barre syndrome, Miller Fisher syndrome, mononeuropathy multiplex, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, and axonal sensorimotor polyneuropathies) [12].

Our aim in this study was to investigate the patients with the chronic inflammatory disease using TNF-α blockers in terms of peripheral nerve damage.

Material and methods

The study includes patients with RA and Spondyloarthropathy (SpA) using TNF-α blocker drug and who applied to (institutional information was blinded) Physical Medicine and Rehabilitation clinic between September 2018-September 2019. The study was approved by the Local Ethical Committee (date, meeting and decision no: 09.01.2018, 18/05). Patients with RA were previously diagnosed according to the American College of Rheumatology (ACR) 1987, patients with SpA, according to the Assessment of SpondyloArthritis İnternational Society (ASAS) diagnostic criteria. The study included 35 patients receiving TNF-α blocker drug (20 SpA, 15 RA) and 37 healthy control subjects with similar demographic characteristics. Of the patients, 35 in the patient group, 14 were receiving adalimumab, 9 were etanercept, 6 were infliximab, and 5 were golimumab.

Patients with diabetes mellitus, hypertension, dyslipidemia, heart disease, iron, and B12 deficiency, endocrinological, neurological disease, atherothrombotic attack, head and neck trauma, and neurological surgery were excluded from the study. The control group was consisted of healthy individuals aged between 18-65 years and demographically compatible with the patient group that without any acute, chronic diseases and vitamin deficiency, using no medication, non-smoking and no alcohol consumption and not pregnant. Disease activity scores of the patient group and physical function scores of the patient and control groups were questioned. All patients underwent a detailed physical and neurological examination. Afterward, peripheral nerves were evaluated neurophysiologically by electromyography (EMG). Neurological examination and neurological tests were performed by a specialist neurologist.

In the present study, nerve conduction studies were performed with a Medelec Synergy model device. Sensory nerve conduction was performed antidromically. Peak amplitude values, conduction velocities were measured and compared in the sensory nerve examinations between the patient and control groups. In sensory nerve examinations, distal latency was accepted as the time until the first positive peak of the potential generated by the stimulation artifact. The amplitude was evaluated as the amplitude measured between the first electronegative peak and the second electropositive peak. Compound muscle action potentials, distal motor latency, peak amplitude values, conduction velocities recorded by distal and proximal stimulation in motor nerve examinations were measured and compared between groups. Latency was evaluated as the time between the warning artifact and the point where the potential left the baseline in an electronegative direction. The amplitude was evaluated as the amplitude of the oscillation between the baseline and the electronegative peak. While calculating the motor nerve conduction velocity, the proximal latency of the compound muscle action potential obtained by proximal stimulation was obtained by subtracting the distal latency of the compound muscle action potential obtained by distal stimulation, and the conduction velocity was calculated by dividing the distance between the two stimulation points by this difference latency [13].

Statistical analysis

All statistical analyses were performed by using IBM SPSS 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). While reporting categorical variables number and percentage n (%) was used. Continuous variables were reported as mean±standard deviation (SD) and median (minimum-maximum). The normality assumption for variables was checked with the Kolmogorov-Smirnov test. When data were not normally distributed Mann-Whitney U test, otherwise independent

samples t-test, was used. The relationship between SF-36 and Age or BMI was determined by using Spearman's rank correlation coefficient. For correlation coefficient 0,0-0,19 was accepted as no correlation, 0,20-0,39 as weak correlation, 0,40-0,69 as moderate, 0,70-0,89 as strong and 0,90-1,00 as perfect correlation.

Results

The average age of the patient group who participated in our study was similar to the control group (p=0.683). Besides, BMI was similar between the patient group and the control group (p=0.123). In patients undergoing neurophysiological evaluation, the mean duration of disease was 124.3±80.3 (months), and mean duration of drug use was 35.6±19.9 (months). The demographic information is shown in Table 1.

Table 1. Demographic and Biochemical Findings of Study Groups.

	Case	Control	p
Age (years)	43.2±13.0	44.6±15.1	0.683†
BMI	27.4±4.4	26.1±2.8	0.123†
SF-36 (Physical)	5.0 (50.0-95.0)	90.0 (80.0-100.0)	<0.001
Duration of disease (months)	120.0 (24.0-360.0)	-	-
Duration of drug use (months)	36.0 (6.0-96.0)	-	-
RF (IU/mL)	8.8 (8.8-316.0)	-	-
CCP (U/mL)	4.7 (0.5-161.9)	-	-
CRP (mg/L)	3.2 (2.4-44.7)	3.0 (3.0-6.8)	0.002
Sedimentation (mg/dL)	10.0 (2.0-45.0)	8.0 (2.0-34.0)	0.623
AST (U/L)	21.0 (12.0-71.0)	20.0 (14.0-30.0)	0.709
ALT (U/L)	22.0 (9.0-91.0)	20.0 (11.0-42.0)	0.826
GGT (U/L)	28.3±12.7	22.5±6.3	0.018†
Urea (mg/dL)	28.0±6.2	28.5±6.9	0.731†
Creatinine (mg/dL)	0.9±0.1	0.9±0.2	0.154†
WBC (10^3/μL)	7.4 (4.2-12.2)	6.8 (5.2-10.2)	0.216
HGB (g/L)	13.4 (11.0-16.8)	14.1 (12.0-16.4)	0.263
HCT (%)	41.8±4.7	42.7±3.9	0.367†
PLT (10^3/mL)	274.1±67.2	271.9±59.1	0.888†

BMI: Body mass index, SF: Short form, RF: Rheumatoid factor, CCP: Cyclic citrullinated peptide, CRP: C- reactive protein, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, GGT: Gamma-glutamyl transferase, WBC: White blood cell, HGB: Hemoglobin, HCT: Hematocrit, PLT: Platelets. Results were presented as mean ± standard deviation value or median (minimum-maximum) value. †Independent samples t-test was performed; Otherwise Mann-Whitney U test was used. Statistically significant (p<0.05).

According to BASDAI, 11 (55%) of AS patients had low disease activity, and 9 (45%) had high disease activity. According to ASDAS, one out of 9 patients had very high disease activity. The functional level of those with low disease activity, according to BASFİ, is good; the functional level of those with high disease activity was moderate. According to the DAS 28 score, 3 (20%) of 15 RA patients had low, and 12 had moderate disease activity. The SF-36 physical function score was higher in the control group than the patient group for both genders.

A moderate negative relationship was found between age and SF-36 physical functional score (r =-0.54, p < 0.001). Similarly, a weak negative relationship was found between BMI and SF-36 physical functional score (r=-0.36, p=0.002). Five (33.3%) of the patients with RA were RF positive, and 10 (66.7%) were RF negative; Anti-CCP was positive in 7 (46.7%) of patients and negative in 8 (53.3%) of patients. HLA B27 was positive in 16 (80.0%) of patients with AS and negative in 4 (20.0%).

The EMG results of sensory nerve conduction between the patient and control groups for left median, right median, ulnar and sural nerves were presented in for Table 2.

Table 2. Sensory Nerve Conduction Values of Study Groups.

		Case	Control	p
Left Median Nerve	NP-amplitude	24.3 (5.9-54.7)	34.4 (9.4-76.1)	0.060
	Velocity	54.9 (38.1-90.3)	56.5 (31.3-73.7)	0.761
	Latency	2.5 (1.6-3.2)	2.3 (1.7-4.2)	0.020
Right Median Nerve	NP-amplitude	22.5 (3.0-68.7)	31.2 (9.3-65.2)	0.008
	Velocity	55.6±8.5	56.0±6.9	0.842†
	Latency	2.4 (2.0-4.5)	2.3 (1.8-3.7)	0.025
Ulnar Nerve	NP-amplitude	25.8 (10.1-52.9)	26.8 (9.0-49.8)	0.685
	Velocity	58.9±6.3	61.3±5.8	0.091†
	Latency	2.0 (1.6-2.6)	1.8 (1.5-2.5)	<0.001
Sural Nerve	NP-amplitude	12.8 (4.4-44.4)	19.5 (9.3-38.6)	0.001
	Velocity	48.8 (29.4-68.6)	60.6 (46.8-69.0)	<0.001
	Latency	2.1 (1.6-4.2)	1.6 (1.2-2.4)	<0.001

NP: Negative-peak. Results were presented as mean ± standard deviation value or median (minimum-maximum) value. †Independent samples t-test was performed; Otherwise Mann-Whitney U test was used. Statistically significant (p<0.05).

Similarly, EMG results of motor nerve conduction between the study groups for left median, right median, ulnar, common peroneal and tibial nerves were presented in for Table 3.

Table 3. Motor Nerve Conduction Values of Study Groups.

		Case	Control	p
Left Median Nerve	NP-amplitude	10.5 (4.2-16.6)	9.8 (7.7-15.5)	0.191
	Velocity	59.5 (53.4-70.3)	61.2 (51.9-76.2)	0.237
	Latency	3.0 (2.1-4.7)	3.0 (2.3-5.3)	0.883
Right Median Nerve	NP-amplitude	10.9±4.0	9.4±2.7	0.076†
	Velocity	57.4 (45.7-70.8)	59.2 (51.4-73.0)	0.289
	Latency	3.1±0.6	3.1±0.6	0.368†
Ulnar Nerve	NP-amplitude	10.4±2.2	10.0±2.0	0.380†
	Velocity	63.2±7.1	64.7±6.3	0.355†
	Latency	2.3±0.3	2.4±0.4	0.353†
CP Nerve	NP-amplitude	4.9 (2.2-13.2)	5.0 (2.4-8.1)	0.644
	Velocity	51.5±6.8	49.8±5.4	0.240†
	Latency	3.8±0.7	3.8±0.6	0.833†
TIB Nerve	NP-amplitude	9.2±4.3	8.0±2.6	0.140†
	Velocity	48.6 (24.0-67.3)	47.4 (42.6-54.8)	0.090
	Latency	4.3±1.0	4.5±0.7	0.179†

NP: Negative-peak, CP: Common peroneal nerve, TIB: Tibial nerve. Results were presented as mean ± standard deviation value or median (minimum-maximum) value. †Independent samples t-test was performed; Otherwise Mann-Whitney U test was used, Statistically significant (p<0.05).

Groups compared in terms of sensory nerves results. Right median nerve amplitude and sural nerve amplitude were considerably difference (p=0.008, p<0.001, respectively). Amplitudes were lower in the patient group. When the groups are compared in terms of conduction velocities, only the difference between the sural nerves were detected (p<0.001). Conduction velocity was lower in the patient group. When the groups were compared in terms of latency values, a statistical difference was found between the left median, right median, ulnar and sural nerves (p = 0.020, p = 0.025, p <0.001, p <0.001, respectively). Latency values were longer in the patient group. When the motor nerve findings were compared between the groups, no statistical difference was found in terms of amplitude values, nerve conduction velocities and latency.

Discussion

Nowadays, anti-TNF-α drugs are widely used in the treatment of autoimmune inflammatory diseases. It has been demonstrated that these anti-TNF-α drugs have a faster effect in reducing disease activity and the capacity to retard radiographic progression compared DMARD. Anti-TNF-α drugs in rheumatic diseases have rarely been reported to have neurological side effects. Peripheral neurological side effect is one of these and may cause drug discontinuation [14, 15]. Tektonidou et al., reported peripheral neuropathy in the form of mono neuritis multiplex or axonal sensorial polyneuropathy in two RA patients during infliximab therapy. Peripheral neuropathy has been described in RA either in vasculitis or as a side effect from medications and comorbid conditions. RA was on remission when peripheral neuropathy developed, and there were no risk factors associated with the development of rheumatoid vasculitis. Infliximab therapy, conduction block, and multifocal motor neuropathy, as well as the discontinuation of infliximab therapy, have been associated with axonal sensory polyneuropathy that returns with intravenous gamma globulin therapy [16]. In a French survey study, Seror et al., reported demyelinating findings in 33 patients receiving anti-TNF-α therapy. As a result of the study, they stated that peripheral neurological demyelinating complications might occur during the anti-TNF-α treatment [17]. Makol et al., presented a rheumatoid arthritis patient who received treatment with adalimumab and who had symptoms of mononeuritis multiplex as a case report and stated that mononeuritis multiplex and adalimumab therapy might be related [18].

In the present study, it was investigated whether there was any effect on the peripheral nervous system in patients using TNF-α inhibitors. TNF-α a has many effects on neurons [19]. It prevents the increase of Reactive Oxygen Species (ROS) in the cell. Thus, it prevents ROS from being toxic to neurons. Anti-TNF-α drugs can cause ROS increase and It has been reported that this situation may cause neuronal toxicity [20]. Studies have reported polyneuropathies in which both motor and sensory nerves are affected. Reports of only sensory polyneuropathy are limited in patients using anti-TNF-α [11]. In many studies, the results are controversial. In the presented study, it was observed that sensory nerves were affected in patients using anti-TNF- α drugs, but motor nerves were within normal limits. In the peripheral sensory nerve examination, in the patient group, longer latency values, lower amplitude values, and slower conduction velocity were measured. Motor nerve conduction velocity examination was evaluated within normal limits. It has been observed that sensory polyneuropathy occurs as a result of the use of anti-TNF-α drugs. In present study, pathological conditions in peripheral nerves were investigated primarily in patients using anti-TNF-α drug. Results suggesting that peripheral sensory nerves are affected.

This study has some limitations. A small sample size is the major limitation of the current research.

Taken together, although it is concluded that the only peripheral sensory involvement mentioned in the literature is rare and may occur under the influence of multiple factors [18], there is a need for a large number of multicenter studies involving a large number of patients.

References

1. Feldmann M, Steinman L. Design of effective immunotherapy for human autoimmunity. Nature. 2005;435:612-619.
2. Monaco C, Nanchahal J, Taylor P, Feldmann M. Anti-TNF therapy: past, present and future. Int Immunol. 2015;27:55-62.
3. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacol Ther. 2008;117:244-279.
4. Keystone EC. Tumor necrosis factor-α blockade in the treatment of rheumatoid arthritis. Rheum Dis Clin North Am. 2001;27:427-443.
5. Horiuchi T, Mitoma H, Harashima Si, Tsukamoto H, Shimoda T. Transmembrane TNF-α: structure, function and interaction with anti-TNF agents. Rheumatology. 2010;49:1215-1228.
6. Meroni PL, Valesini G. Tumour necrosis factor α antagonists in the treatment of rheumatoid arthritis: an immunological perspective. BioDrugs. 2014;28:5-13.
7. Kirchner S, Holler E, Haffner S, Andreesen R, Eissner G. Effect of different tumor necrosis factor (TNF) reactive agents on reverse signaling of membrane integrated TNF in monocytes. Cytokine. 2004;28:67-74.
8. Grom AA, Murray KJ, Luyrink L, Emery H, Passo MH, Glass DN, et al. Patterns of expression of tumor necrosis factor α, tumor necrosis factor β, and their receptors in synovia of patients with juvenile rheumatoid arthritis and juvenile spondylarthropathy. Arthritis Rheum. 1996;39:1703-1710.
9. Strangfeld A, Listing J. Bacterial and opportunistic infections during anti-TNF therapy. Best Pract Res Clin Rheumatol. 2006;20:1181-1195.
10. Kemanetzoglou E, Andreadou E. CNS demyelination with TNF-α blockers. Curr Neurol Neurosci Rep. 2017;17:36.
11. Tristano AG. Neurological adverse events associated with anti-tumor necrosis factor alpha treatment. J Neurol. 2010;257:1421-1431.
12. Bosch X, Saiz A, Ramos-Casals M, Group BS. Monoclonal antibody therapy-associated neurological disorders. Nat Rev Neurol. 2011;7:165.
13. Benatar M, Wuu J, Peng L. Reference data for commonly used sensory and motor nerve conduction studies. Muscle Nerve: Official Journal of the American Association of Electrodiagnostic Medicine. 2009;40:772-794.
14. Magnano M, Robinson W, Genovese M. Demyelination and inhibition of tumor necrosis factor (TNF). Clin Exp Rheumatol. 2004;22:134-140.
15. Mohan N, Edwards ET, Cupps TR, Oliverio PJ, Sandberg G, Crayton H, et al. Demyelination occurring during anti–tumor necrosis factor α therapy for inflammatory arthritides. Arthritis Rheum. 2001;44:2862-2869.
16. Tektonidou MG, Serelis J, Skopouli FN. Peripheral neuropathy in two patients with rheumatoid arthritis receiving infliximab treatment. Clin Rheumatol. 2007;26:258-260.
17. Seror R, Richez C, Sordet C, Rist S, Gossec L, Direz G, et al. Pattern of demyelination occurring during anti-TNF-α therapy: a French national survey. Rheumatology. 2013;52:868-874.
18. Makol A, Grover M. Adalimumab induced mononeuritis multiplex in a patient with refractory rheumatoid arthritis: a case report. Cases J. 2008;1:1-2.
19. Cámara Lemarroy CR, Guzmán de la Garza FJ, Fernández Garza NE. Molecular inflammatory mediators in peripheral nerve degeneration and regeneration. Neuroimmunomodulation. 2010;17:314-324.
20. Park KM, Bowers WJ. Tumor necrosis factor-alpha mediated signaling in neuronal homeostasis and dysfunction. Cell Signal. 2010;22:977-983.