Peripheral Neuropathy in Rheumatoid Arthritis Patients: An Electroneurophysiological Study

Romatoid Artritli Hastalarda Periferik Nöropati: Elektronörofizyolojik Çalışma

Lale Akbulut Aktekin[1], Hilmi Gözlükaya[2], Hatice Bodur[1], Pınar Borman[3], Özlem Köz[4]

[1]Ankara Numune Eğitim ve Araştırma Hastanesi, Fizik Tedavi ve Rehabilitasyon Kliniği, Ankara, Türkiye

[2]Ordu Devlet Hastanesi, Fizik Tedavi ve Rehabilitasyon Kliniği, Ordu, Türkiye

[3]Ankara Eğitim ve Araştırma Hastanesi, Fizik Tedavi ve Rehabilitasyon Kliniği, Ankara, Türkiye

[4]Ankara Numune Eğitim ve Araştırma Hastanesi, Göz Hastalıkları Kliniği, Ankara, Türkiye

Abstract

Objective: The aim of this study was to evaluate the frequency of peripheral nervous system involvement with electrophysiological studies in rheumatoid arthritis (RA) patients whose neurological examination findings were within the normal range.

Material and Methods: Fifty-six RA patients and 32 healthy control subjects were included. Demographic characteristics, duration of disease and drug use of the patients were recorded. Laboratory variables and Ritchie articular index were used to evaluate disease activity. Electrophysiological studies were performed in all patients and control subjects. Median, ulnar and peroneal nerve motor nerve conduction studies (CVs), F wave, and median, ulnar, and sural nerve sensory CVs were recorded.

Results: The frequency of neuropathy was higher in the patients with RA than in the control group. Neuropathy was detected in 20 (36%) RA patients: 3 (5%) had sensorimotor polyneuropathy, 7 (13%) had low sural sensory nerve conduction or absence of action potentials, 2 (4%) had carpal tunnel syndrome, 6 (11%) had low amplitude peroneal compound muscle action potentials, 1 (2%) had low amplitude peroneal compound muscle action potential and low ulnar sensory nerve conduction, and 1 (2%) had low sural and ulnar sensory nerve conduction. Neuropathy was determined in 5 of 13 patients using corticosteroids and in 15 of 43 patients who were not using corticosteroids. There was no statistically significant difference between the electrophysiologic findings of subgroups in terms of the corticosteroid therapy and positivity of Schirmer test and rheumatoid factor. There was no correlation between the electrophysiological parameters and disease activity in patients with RA. In the control group, 2 (6%) cases had electrophysiologically determined neuropathy; frequency of neuropathy was higher in the patients with RA when compared with the control group, and the difference was statistically significant ($p<0.01$).

Conclusion: Clinical evaluation of neuropathy in RA patients is difficult since neuropathic symptoms are frequently confused with arthritis. To detect neuropathy earlier in patients with RA, electrophysiological studies are recommended as routine diagnostic procedure even in the absence of clinical nerve involvement. *(Turk J Rheumatol 2009; 24: 62-6)*

Key words: Rheumatoid arthritis, neuropathy, ENMG

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Özet

Amaç: Bu çalışmanın amacı, nörolojik muayenesi normal olan Romatoid Artrit'li (RA) hastalarda periferik sinir sistemi tutulumunun elektrofizyolojik çalışmalarla değerlendirilmesidir.

Yöntem ve Gereçler: Çalışmaya 56 RA'li hasta ve 32 sağlıklı kontrol dahil edildi. Hastaların demografik özellikleri, hastalık süreleri ve kullandıkları ilaçlar kaydedildi. Hastalık aktivitesini belirlemede laboratuvar verileri ve Ritchie Artiküler İndex (RAİ) kullanıldı. Tüm hastalar ve kontrol grubunda, median, ulnar, and peroneal sinir motor sinir iletim çalışmaları, F dalga latansı ve median, ulnar, and sural sinir duyu sinir ileti çalışmaları kaydedildi.

Bulgular: Elektrofizyolojik olarak nöropati sıklığı RA'li hasta grubunda kontrol grubuna göre daha sıktı. RA'li hastaların 20'sinde (%36) nöropati tespit edildi. Üç hastada (% 5) sensorimotor polinöropati, 7 hastada (% 13) sural sinir duyu ileti hızında yavaşlama veya duyusal aksiyon potansiyeli elde edilememe, 2 hastada (%4) karpal tünel sendromu, 6 hastada (%11) peroneal sinir bileşik kas aksiyon potansiyeli amplitüdünde azalma, 1 hastada (%2) peroneal sinir bileşik kas aksiyon potansiyeli amplitüdünde azalma ve ulnar sinir duyu iletiminde yavaşlama ve 1 hastada (% 2) ulnar ve sural duyu iletiminde yavaşlama tespit edildi. Kortikosteroid tedavi alan, almayan ve Schirmer testi ile romatoid faktör pozitifliğine göre hastalar gruplandırıldığında nöropati yönünden istatistiksel anlamlı farklılık tespit edilmedi. Elektrofizyolojik parametreler ile hastalık aktivitesi arasında da korelasyon tespit edilemedi. Kontrol grubunda 2 kişide (%6) elektrofizyolojik olarak nöropati tespit edildi, RA'li hastalarla karşılaştırıldığında aradaki farklılık istatistiksel olarak anlamlı idi ($p<0.01$).

Sonuç: RA'li hastalarda nöropatinin klinik olarak değerlendirilmesi sıklıkla nörolojik semptomların artrit nedeni ile ayırt edilememesi yüzünden zordur. RA'li hastalarda nöropatinin erken tanınabilmesi için, klinik olarak tutulum olmasa bile elektrofizyolojik çalışmaların rutin tanısal yöntem olarak kullanılması önerilmektedir. *(Turk J Rheumatol 2009; 24: 62-6)*

Anahtar sözcükler: Romatoid artrit, Periferik nöropati, ENMG

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Address for Correspondence/Yazışma Adresi: Dr. Lale Akbulut Aktekin, Ankara Numune Eğitim ve Araştırma Hastanesi, Fizik Tedavi ve Rehabilitasyon Kliniği, Ankara, Türkiye Phone: +90 312 508 48 03 E-mail: laleakbulut@yahoo.com

Introduction

Rheumatoid arthritis (RA) is a systemic disease of unknown etiology that primarily affects the joints, but involves nonarticular sites, including the skin, heart, lungs, eyes and the nervous system. Nervous system involvement can be variable in RA patients. The most common lesion is peripheral neuropathy, including entrapment neuropathy, distal axonal predominantly sensory polyneuropathy, mononeuropathy or multiple mononeuropathy, as well as fulminant sensorimotor polyneuropathy (1).

In this study, we evaluated the frequency of peripheral nervous system involvement with electrophysiological studies in RA patients whose neurological examination findings were within the normal range.

Materials and Methods

Fifty-six RA patients who fulfilled the 1987 criteria of the American Rheumatism Association (ARA) (2) were included in the study. Patients with diabetes mellitus, kidney, liver, and thyroid diseases, amyloidosis, chronic heart failure, malignancies, or abuse of alcohol and patients diagnosed to have peripheral nervous system diseases were not included in the study. Demographic characteristics, duration of disease and drug use were recorded. The control group consisted of 32 healthy subjects recruited from hospital staff volunteers. A complete neurological examination was performed in patients with RA, and disorders of deep tendon reflexes (DTR) and vibration threshold were evaluated for assessing peripheral nervous system involvement (1). Patients with vibration defects or disorders of DTRs on their neurological examination were not included in the study. The presence of keratoconjunctivitis sicca (KCS) was evaluated with the Schirmer test and wetness under 5 mm was accepted as positive (3).

Complete blood count (CBC) and levels of erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), and C-reactive protein (CRP) were measured. ESR was measured with the Westergren method and nephelometric method was used for CRP and RF. Stoke disease activity index (SDAI) (4) and Ritchie articular index (RAI) (5) were used to evaluate disease activity and tenderness, respectively, in the study group.

Electrophysiological studies were performed in all patients and control subjects and the results were assessed according to the American Diabetes Association diabetic neuropathy protocol (6). Electrophysiological studies were carried out by Nihon Kohden Neuropack 2 EMG device. Median, ulnar and peroneal nerve motor nerve conduction studies (CVs), F wave, and median, ulnar, and sural nerve sensory CVs were recorded, and room temperature was maintained at 22-24°C. Standard nerve CV techniques were used. The EMG examination was performed by an experienced physiatrist (LAA).

The demographic and clinical characteristics of the patients were summarized by descriptive statistics. The categorical variables were evaluated by chi-square or Fisher's exact test, where applicable. Nonparametric Mann-Whitney U test was used in comparison of subgroups of patients taking different drugs. Spearman test was used to assess the correlation between EMG variables and clinical parameters. A value of $p<0.05$ was reported as statistically significant. All statistical analyses were performed by SPSS 11.0 version, statistical package.

Results

A total of 56 patients with RA [48 F (86%), 8 (14%) M] were included in the study. Their mean age was 51.0±11.8 (range: 21-76) years. The control group consisted of 29 (91%) females and 3 (9%) males, with a mean age of 47.4±12.7 (range:22-78) years. There was no significant difference between the patient and control groups in terms of age and gender ($p>0.05$). The mean disease duration was 8.4±6.1 (range: 0.5-27) years. Twenty-eight patients were using methotrexate, 15 chloroquine, 2 sulfasalazine, 4 methotrexate and chloroquine, 1 methotrexate and sulfasalazine, 1 chloroquine and sulfasalazine, and 1 chloroquine, methotrexate and sulfasalazine, and 13 patients were on low-dose corticosteroid therapy. Four patients were not receiving any disease-modifying antirheumatic drug (DMARD) treatment.

The clinical characteristics and disease variables are listed in Table 1.

Positive correlations were found between RF level and age ($r=0.59$, $p<0.05$), RF level and ESR ($r=0.38$, $p<0.05$), ESR and CRP ($r=0.59$, $p<0.001$), RAI and ESR ($r=0.56$, $p<0.05$), RAI and CRP ($r=0.40$, $p<0.05$), RAI and RF ($r=0.40$, $p<0.05$), and SDAI and RF ($r=0.56$, $p<0.001$).

In the RA group, electrophysiologically diagnosed neuropathy was detected in 20 (36%) patients: 3 (5%) had sensorimotor polyneuropathy, 7 (13%) had low sural sensory CV or absence of sensory action potentials (SAP), 2 (4%) had carpal tunnel syndrome (CTS), 6 (11%) had low amplitude peroneal compound muscle action

Table 1. The clinical and laboratory characteristics of patients with RA

	n	Min	Max	Mean	± SD
Age (years)	56	21	76	51.0	11.8
Duration of disease (years)	56	0.5	27	8.4	6.1
ESR (mm/hr)	56	7	120	38.4	21.3
RF (IU/ml)	56	6.5	656	140.3	159.7
CRP (mg/L)	56	0.64	136	21.9	24.5
Ritchie Index	56	0	49	18.6	9.3
Stoke Index	56	1	17	7.9	4.5

RA: Rheumatoid arthritis, ESR: Erythrocyte sedimentation rate, RF: Rheumatoid factor, CRP: C-reactive protein, Min: Minumum, Max: Maksimum, SD: Standard deviation

potentials, 1 (2%) had low amplitude peroneal compound muscle action potential and low ulnar sensory nerve conduction, and 1 (2%) had low sural and ulnar sensory nerve conduction. In the control group, 2 (6%) cases had electrophysiologically determined neuropathy: 1 had low sural sensory CV and 1 had absent sural SAP. Frequency of neuropathy was higher in the patients with RA when compared with the control group, and the difference was statistically significant ($p<0.01$). Results of the electrophysiological studies of both the patient and the control groups are given in Table 2.

Neuropathy was determined in 5 of 13 patients using corticosteroids and in 15 of 43 patients who were not using corticosteroids. There was no statistically significant difference between the electrophysiological findings of subgroups in terms of the corticosteroid therapy ($p>0.05$).

The proportion of RF-negative patients was 16% (9 patients). Neuropathy was determined in 2 RF-negative patients and in 18 of the 47 RF-positive patients. Incidence of neuropathy was 22% for RF-positive patients and 38% for RF-negative patients. Although the number of RF (+) patients with neuropathy was higher than the number of RF (-) patients with neuropathy, the difference was not statistically significant ($p>0.05$).

In the patient group, disease activity according to the Stoke index was minimal in 10 patients, mild in 18 patients, moderate in 16 patients, and severe in 12 patients. Distribution of the electrophysiological findings according to the Stoke index is shown in Table 3.

There was no significant difference between patients with and without neuropathy in terms of laboratory parameters.

Schirmer test was performed in 46 patients; 35 had negative and 11 had positive results. Neuropathy was determined in 4 patients with positive Schirmer test and in 11 patients with negative Schirmer test. There was no statistically significant difference between these two subgroups ($p>0.05$).

Table 2. Results of electrophysiological work up of the patient and control groups

	Patient Group (N=56)	Control Group (N=32)
Normal range	36	30
Sensorimotor polyneuropathy	3	0
Low sural sensory conduction velocity or absence of sensory action potentials	7	2
Carpal tunnel syndrome	2	0
Low amplitude of peroneal compound muscle action potentials	6	0
Low sural and ulnar sensory nerve conduction	1	0
Low amplitude peroneal compound muscle action potential and low ulnar sensory nerve conduction	1	0

Discussion

Patients with connective tissue disease including RA may have different types of peripheral neuropathy, including entrapment neuropathy, distal axonal, predominantly sensory neuropathy, mononeuropathy or multiple mononeuropathy, and fulminant sensorimotor polyneuropathy (7). Although the incidence of peripheral neuropathy in RA was reported between 0.5-30%, electrophysiological studies, biopsy and angiography indicated that the actual incidence was higher (1, 7). Some studies reported that in patients with RA, mild sensorial neuropathy could be seen at a rate of 75% (8, 9). Neurological changes were found to be mostly due to vasculitis in autopsy studies of patients who did not have clinical neuropathy (10). Incidence of clinically serious vasculitic neuropathy was reported as 1-10% (10). Peripheral nerve involvement in RA includes several mechanisms. Peripheral neuropathy due to vasculitis is

Table 3. The distribution of electrophysiological findings, according to the Stoke index

	Minimal	Mild	Moderate	Severe
Normal range	7	9	12	8
Sensorimotor polyneuropathy	2	-	1	-
Low sural sensory conduction velocity or absence of sensory action potentials	-	6	-	1
Carpal tunnel syndrome	1	-	1	-
Low amplitude of peroneal compound muscle action potentials	-	3	-	3
Low sural and ulnar sensory nerve conduction	-	-	1	-
Low amplitude peroneal compound muscle action potential and low ulnar sensory nerve conduction	-	-	1	-
Total	10 (30%)	18 (50%)	16 (25%)	12 (33%)

explained by immune complex-mediated damage of the vessel wall or myelinated nerves. Other possible causes of neuropathy may be mechanical compression of nerves by swelling of soft tissue, bone erosions and joint deformity or rheumatoid nodules (7). However, it is often difficult to diagnose slight or early neuropathies with any certainty, and the study of the peripheral neuromuscular system is made difficult by symptoms resulting from pain and stiffness of peripheral joints (11). Patients with evident joint pain can describe additional symptoms like muscle weakness and paresthesia that can suggest neuropathy (1, 11-13).

Sufficient electrophysiological tests can identify asymptomatic peripheral neuropathy. Electrophysiological tests are the primary approach in the early diagnosis and treatment of the subclinical neuropathy in patients with systemic vasculitis who are neurologically asymptomatic (1).

In order to investigate the subclinical involvement of the peripheral nervous system, we excluded patients with diminished DTR and vibration defects and previous peripheral nervous system involvement. Patients with symptoms of muscle weakness, paresthesia, and hypoesthesia were not taken into consideration, and neuropathy was defined according to electrophysiological studies. In our study, 20 of 56 RA patients (36%) who did not have any signs or symptoms of peripheral nervous system involvement had electrophysiologically determined neuropathy. Among the healthy control group, 2 of 32 cases had electrophysiological evidence of neuropathy. The difference between patient and control groups was statistically significant. Good et al. (9) reported electrophysiologic signs of peripheral neuropathy in 85% of their patients, including mild slowing of motor conduction velocity along the peripheral nerve. However, they included the RA patients with diabetes. Lanzillo et al. (1) investigated the occurrence of electrophysiologically evident peripheral nerve involvement in patients free of neuropathic symptoms. Sixty-five percent of their patients exhibited electrophysiologic findings consistent mostly with a sensorimotor neuropathy. However, their patients had neurologic clinical findings like absent DTR or vibration disorders.

Low amplitude sensory nerve action potential and multifocal compound muscle action potential and normal or minimally decreased velocity were reported in the previous studies with RA patients (14-16). In our study group, 1 (2%) patient had low amplitude peroneal compound muscle action potential and low ulnar sensory nerve conduction, 1 (2%) had low sural and ulnar sensory nerve conduction, 6 had low amplitude peroneal compound muscle action potentials, and 7 had low sural sensory conduction rates or absent SAP. We think that these findings may represent the preliminary picture of any peripheral neuropathy pattern.

The incidence of CTS in RA was reported at different rates between 2.5-40% by different authors (1, 11, 17-19). The incidence was defined as 4% in our study group, which is lower than previously reported. It is likely that edema or the swelling of synovial tissue in the carpal tunnel finally resulted in the compression of the median nerve.

The poor correlation between electrophysiological findings and clinical findings in our study was similar to previous data. Good et al. (9) did not report a relation between disease duration and neuropathy; similarly, Salih et al. (20) could not find a relation between neuropathy in RA patients and age, disease duration, RF positivity, CRP, complement (C) levels or antinuclear antibody (ANA) positivity. Nadkar et al. (21) failed to find any correlation between neuropathy and disease activity, RF, and disease parameters like functional and radiological state, which is consistent with our results. Lanzillo (1) and Sivri (11) reported that there was no correlation between the electrophysiological consequences of peripheral nerve system involvement and the clinical parameters of RA. These findings suggest that rheumatoid neuropathy is not associated with long-term disease duration or seropositive nodular destructive disease.

Bekkelund et al. (7) compared the frequency of neuropathy in RA patients with and without corticosteroid therapy and could not find any significant difference, similar to our results. In our study, electrophysiologic studies revealed neuropathy in 5 of 13 patients on low-dose (<15 mg) corticosteroid therapy and in 15 of 43 patients on steroid therapy. There was no statistically significant difference in neuropathy frequency between groups in terms of steroid intake.

Neuropathy is also associated with Sjögren syndrome, and peripheral neuropathy was more commonly reported in RA patients with Sjögren syndrome or sicca complex (22). We performed Schirmer test in 46 patients for KCS, and results were negative in 35 patients and positive in 11 patients. Four patients with positive Schirmer test and 11 patients with negative Schirmer test had neuropathy. The difference between these subgroups had no statistical significance.

As a result, we conclude that peripheral nerve involvement is one of the striking extra-articular involvements of RA, with no apparent correlation with the clinical parameters. As subclinical peripheral nerve involvement is common in RA, clinical examination alone may fail to detect early peripheral neuropathy.

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