Research Article

The Electrophysiological Evaluation of 70 Iranian Rheumatoid Arthritis Patients

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Abstract

Objectives: We have conducted an electrophysiological investigation to find out the incidence and patterns of peripheral nerves involvement in rheumatoid arthritis patients and to correlate them with some patients’ characteristics.

Patients and Methods: Using clinical examination and proper laboratory end electrophysiological tests, seventy unselected rheumatoid arthritis patients (50 female and 20 male) were evaluated for evidence of peripheral nervous system involvement. The results were correlated with clinical data (severity and duration of disease) using statistical tests.

Results: Clinical and electrophysiological manifestations of peripheral nervous system involvement were found in 33 patients (47.1%). Most of cases were asymptomatic. The most common disorder was entrapment neuropathy, which was predominantly carpal tunnel syndrome (17 patients, 24.3%). Polyneuropathy was detected in 14 patients (24%) and was mostly sensorimotor. Also, it was exclusively axonal type and was significantly common in severe cases. (p<0.05)

Conclusion: Electrophysiological findings of peripheral nerve damage, even in the absence of clinical evidences, are common in rheumatoid arthritis.

Keywords: Peripheral nervous system, electrophysiological study, Rheumatoid arthritis (RA)

Özet

Amaç: Romatoid artrit hastalarında periferik sinir tutułsunların görülme siklğ, şeklini ortaya çktırmak ve bazı hasta özelliklerini karșılâtırmak üzere bir elektrofizyolojik çalışma planladık.

Hastalar ve Yöntemler: Klinik muayene ve uygun laboratuvar ile elektrofizyolojik testler kullanarak gelişigüzel seçilmiş 50 kadın, 20 erkek olmak üzere toplam 70 romatoid artrit hastasında periferik sinir sistemi bozukluğunu araştırıldı. İstatistiksel testler uygunlarak hastalinin süresi ve ağrılığı göz önüne tutularak sonuçlar klinik verilerle irdelendi.

Sonuçlar: Periferik sinir sistemi tutułu 33 hastada (%47,1) klinik ve elektrofizyolojik bulgularla teyid edildi. Olguların çoğunluğ asemptomatik idi. En sık saptanan bozukluk bir tuzak nöropatisi olarak göre çaran karpal tünel sendromu (17 hastada, %24,3) oldu. Polinöropati 14 hastada (%24) saptandi ve genellikle sensorimotor tipteydi. Aynı zamanda, ağır vakalarda önemli bir oranda istisnasız olarak aksonal tipe gözlendi. (p<0.05)

Yarg: Periferik sinir hastaların elektrofizyolojik bulguları, klinik kanıtların bulunmaması durumunda bile, romatoid artritte yayındır.

Anahtar Kelimeler: Periferik sinir sistemi, elektrofizyolojik çalışma, Romatoid artrit (RA)
INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of undetermined etiology involving primarily the synovial membranes and articular structures of multiple joints. The disease is often progressive and results in pain, stiffness, and swelling of joints. In late stages, deformity and ankylosis develop. The diagnosis is based routinely on the persistence of arthritic symptoms over a time. Important factors associated with RA are the possibility of infectious triggers, genetic predisposition and autoimmune responses. The primary targets of inflammation are synovial membranes and articular structures but other organs are affected as well.

Organ systems that may be affected include the following: Cardiac involvement as carditis and pericarditis; pulmonary disorders as pleuritis and intrapulmonary nodules; hepatic disorders in the form of hepatitis; ocular involvement as scleritis, episcleritis and dryness of the eyes; vascular inflammation as vasculitis of various organs including brain and vasculitic neuropathy. RA is a diffuse systemic disease involving many areas of the body so that the presenting complaint may be remote from a joint.

One clinical hallmark of this systemic arteritis is the appearance of neurological findings. However, it is often difficult to diagnose these slight or early neuropathies due to pain in the joints and limitation of movement. Nevertheless, it is often possible to show objectively the existence and distribution of even subclinical neuropathies by means of electrophysiological study (16).

METHODS

The design of the study was observational and cross sectional. Patients with a diagnosis of RA according to the American College of Rheumatology (ACR) criteria (1) were eligible for inclusion in the study if the duration of their active disease was more than one year.

Patients who had received agents with neurological side effects, including peripheral nervous system complications, were excluded from the study. Also patients with diabetes mellitus, alcoholism and other metabolic or toxic causes of neuropathy were excluded. None of the patients had other connective tissue disease. The patient is considered to have severe RA if the handicap is important, osteoarticular lesions are observed on the radiographs or extra-articular manifestations are present. Thus in this study severe disease was defined by the presence of one or more of the following criteria: severe functional status measured by the HAQ (HAQ score ≥1.5) (1), the presence of typical radiological lesions and/or the presence of extra-articular manifestations (5,18).

An expert internist and a neurologist interviewed and examined all the patients. Evaluation included a detailed medical history and neurological examination. Nerve conduction parameters (NC) of median, ulnar and radial motor and sensory nerves were studied in upper extremities. In the lower extremities, tibial and peroneal motor nerves and sural sensory nerves were also examined. We performed electromyography (EMG) with bipolar needle electrode in muscles of upper and lower extremities. The EMG/NC study apparatus was Toenniss® Neuroscreenplus, Erich Jaeger GmbH, Hoechberg, Germany.

Objectively detected hypoesthesia in a glove and stocking distribution with or without decreased or absent deep tendon reflexes were suggestive of sensory peripheral neuropathy. Also, motor neuropathy was defined as decreased or absent deep tendon reflexes, with or without cramps, weakness or atrophy of the muscles.

The electrophysiological criteria for carpal tunnel syndrome include: 1) Antidromic sensory conduction velocity for the wrist-second digit segment less than 48.2 m/s, 2)
The difference between median and ulnar sensory nerve distal latencies with recording from the fourth digit (recording-stimulation distance was kept 14 cm) exceeding 0.5 ms, 3) Distal motor latency to abductor pollicis brevis muscle greater than 4.2 ms (2). According to following electrophysiological testing results, the patients were grouped into mild, moderate or severe CTS: Mild CTS: Prolongation of median distal sensory latency >3.5 ms or relative prolongation of median compared to ulnar distal sensory latencies over identical distances. Moderate CTS: Reduced median SNAP amplitude (<50% compared to unaffected side or <25mv) or prolonged median motor distal >4.5 ms. Severe CTS: Reduced median CMAP amplitude (<50% compared to unaffected side or <4mv) denervation of median innervated muscles on needle exam (8).

The following criteria were used for diagnosis of the Cubital tunnel syndrome: 1) Slow motor conduction velocity in the ulnar nerve across the elbow (velocity less than 41 m/sec) compared with the velocity in the forearm segment; 2) Prolonged response duration with stimulation above elbow compared with stimulation below the elbow; 3) Motor latency from above the elbow more than 10.2msec and/or prolonged sensory latencies (7,15).

Tarsal tunnel syndrome criteria were: 1) Prolonged distal motor latency (lateral plantar nerve) more than 7.0 m/sec; 2) Terminal latencies of abductor hallucis (which is innervated by the medial plantar nerve) more than 6.2 msec (13). We considered three types of Guyon's canal entrapment, in type I, electrodiagnostic studies may reveal normal motor conduction velocity of the ulnar nerve in the across-the-elbow and elbow-to-wrist segments, prolonged distal latency to the abductor digiti minimi and first dorsal interosseous muscles, prolonged sensory latency and diminished evoked sensory responses. In type II, normal motor conduction velocity in the ulnar nerve in the across-the-elbow and elbow-to-wrist segments, normal sensory latency and sensory evoked responses, normal distal motor latency to the abductor digiti quinti minimi and prolonged latency to the first dorsal interosseous; denervation potentials in the first dorsal interosseous but not in the abductor digiti quinti. In type III, the location of compression is distal in the end of the Guyon's canal and only sensory abnormalities on palmar ulnar distribution; there is no motor deficit. It is the rarest of the three syndromes (3). When nerve conduction and electromyography studies showed damage to at least 2 separate nerves, it was distinguished as Mononeuritis multiplex.

Polyneuropathy types described as axonal or demyelinating. Axonal polyneuropathy was diagnosed when: 1) Conduction velocities were normal or slightly slow; 2) The size of the compound muscle action potentials (CMAP) and sensory nerve action potentials (SNAP) were decreased in at least two motors and one sensory nerve; and 3) Evidence of chronic partial denervation in at least two studied muscles. In general, demyelinating neuropathies were considered when the NC studies showed: 1) A reduction by more than 40 percent of mean motor and sensory conduction velocities, 2) Prolonged terminal motor latencies, 3) Partial conduction block or abnormal temporal dispersion in at least one motor nerve and finally 4) Absence of F waves or prolonged minimum F wave latencies in two or more motor nerves. The normal limits of these values derived from a famous practical textbook in electromyography (14).

Data were processed using the SPSS statistical package (version 11.05). Descriptive analysis was undertaken for all variables. Continuous variables were reported using mean and standard deviation. Data were analyzed by the X² or Fisher’s exact test if frequencies were small. Continuous variables were analyzed using Student’s t test or ANOVA and P<0.05 considered significant.
RESULTS
After screening for exclusion criteria, 70 unselected consecutive patients with RA were evaluated. Among 70 patients, 50 (71.4%) were female with mean age of 51.4±13.37 years and disease duration of 7.9±5.3 years. Twenty (28.6%) were male with mean age of 47±18.28 years and mean disease duration of 5.7±0.6 years. Using the predefined criteria of severity, 33 patients (47%) were considered to have severe disease.

Peripheral nervous system involvement was found in 33 patients (47.1%). Detected peripheral nervous system disorders are summarized in table 1.

Entrapment neuropathies: Electrophysiologically detected entrapment of various nerves was the most common type of peripheral nerves disorder, which found in 21 (30%) patients. The most common injured nerve was median nerve (17 patients, 24.3% of all patients). Most of patients with carpal tunnel syndrome (CTS) were asymptomatic. Severity of CTS in 8 cases (11.42%) was mild and in the other 9 patients (12.8%) was moderate and none of them had severe CTS. None of patients with CTS had previous surgery for nerve release.

Ulnar nerve was compressed in cubital canal in examination of 2 patients (2.86%) and in one other case (1.43%) this nerve was entrapped in Guyon’s canal. Asymptomatic Tarsal tunnel syndrome (tibial nerve entrapment) was detected in one case (1.43%). We could not diagnose peroneal and radial nerves entrapments in our cases.

Polyneuropathies: Fourteen patients (20%) had peripheral neuropathy: eight of them (57.1%) had mixed sensorimotor neuropathy and five patients (35.7%) had sensory only. None of cases had pure motor neuropathy. All neuropathies were axonal type and we could not find criteria of demyelination in electrophysiological studies. In one case, small fiber neuropathy was suspected. Most of cases (11 cases, 78.6%) had subclinical neuropathy. Two patients (14.3%) had paresthesia and numbness in their extremities in a glove and stocking distribution and the deep tendon reflexes were decreased or absent in six patients (42%).

Mononeuritis multiplex: Two patients (2.86%) presented with mononeuritis multiplex. In one patient neurological examination revealed right-sided paresis of dorsiflexion and eversion of the right foot and tendon reflexes were normal. The other patient complained of hyperpathy in the dorsum of the right foot. In the former case, EMG/NC studies revealed axonal injury with spontaneous activity in the muscles innervated by the common peroneal nerve and partial interference pattern. Nerve conduction studies excluded entrapment of the common peroneal nerve. In the latter case, EMG/NC showed axonal neuropathy with spontaneous activity, and was consistent with mononeuritis multiplex involving the peroneal, tibial and radial nerves.

<table>
<thead>
<tr>
<th>Table 1: Peripheral nervous system involvement in 70 cases of RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNS involvement:</td>
</tr>
<tr>
<td>Entrapment neuropathy*</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Ulnar</td>
</tr>
<tr>
<td>Tibial</td>
</tr>
<tr>
<td>Mononeuritis multiplex</td>
</tr>
<tr>
<td>Polyneuropathy**</td>
</tr>
<tr>
<td>33 (47.1%)</td>
</tr>
<tr>
<td>21 (30%)</td>
</tr>
<tr>
<td>17</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2 (2.86%)</td>
</tr>
<tr>
<td>14 (20%)</td>
</tr>
</tbody>
</table>

*The most common type was median nerve entrapment (carpal tunnel syndrome)
**All cases of neuropathy were axonal type
The mean age of patients with PNS involvement was 52.6±8.75 years and that for patients with normal electrophysiological studies was 48±14.8 years. There was no significant correlation between neurophysiological involvement of peripheral nerves and age (p=0.42). Seven of 20 male patients (35%) showed PNS involvement while in female group, 26 of 50 female cases (52%) had electrophysiologic injury to PNS (p=0.198). Based on above findings it can be concluded that there isn’t significant correlation between sex and PNS injury.

Mean duration of disease was 7.1±3.1 years in the group of patients with documented PNS involvement and it was 6.4±2.1 years in normal PNS group. Statistical analysis did not show significant correlation (p>0.05).

According to above criteria, patients who were in clinically severe condition were 24 cases (72.7%) in the PNS involved group and in group with normal electrophysiological study, 9 (24.3%) patients had severe RA. There was significant correlation between severity of disease and PNS disorders (p<0.042). Also, this correlation was statistically significant for sensorymotor neuropathy (p<0.03). (Fig 1)

A comparison of the 33 patients’ characteristics with PNS involvement and the remaining 37 without it were presented in Table 2.

![Graph showing comparison of PNS and polyneuropathy](image)

**Fig 1:** Significant correlation between severity of disease and PNS disorders (p<0.042) is shown. Also, this correlation was statistically significant for sensorymotor neuropathy (p<0.03).

**Table 2:** Characteristics of the RA patients with PNS involvement and those without

<table>
<thead>
<tr>
<th>PNS disorder</th>
<th>Yes (n=33)</th>
<th>No (n=37)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA Severity (stag&gt;2)</td>
<td>24</td>
<td>9</td>
<td>&lt;0.042</td>
</tr>
<tr>
<td>RA duration (y)</td>
<td>7.1±3.1</td>
<td>6.4±2.1</td>
<td>ns</td>
</tr>
<tr>
<td>Age (y)</td>
<td>52.6±8.75</td>
<td>48±14.8</td>
<td>ns</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>7/26</td>
<td>13/24</td>
<td>ns</td>
</tr>
</tbody>
</table>

RA, Rheumatoid arthritis; PNS, Peripheral nervous system
DISCUSSION

Extra-articular complications are common in the course of RA so that physicians should monitor patients with RA for potential complications. Patients with connective tissue disease can present with systemic necrotizing vasculitis or hypersensitivity vasculitis. Rheumatoid arteritis (RA) is a connective tissue disease that most often causes vasculitis. Vasculitis develops in about 8-25% of patients with RA, usually 10-15 years after onset of RA. Overall, vasculitic neuropathy occurs in 40-50% of patients with systemic vasculitis.

Our study purpose was detection of PNS diseases in RA. The importance of such studies has been recognized for a long time and various researches with different results have been presented in literature. Our results indicated that PNS diseases, mainly manifest as mild sensory and mixed neuropathy are common. It should be emphasized that in the most of our patients these disorders were only detected by careful physical examination and using specific electrophysiological methods and suggesting that these abnormalities usually are subclinical. Only two of our patients presented with mononeuritis multiplex.

In study of Lanzillo et al, 65% of patients exhibited electrophysiologic findings consistent with a sensorimotor neuropathy. Other authors have reported less frequency as Nadkar et al reported neuropathy in about 30% of cases. They showed entrapment neuropathy only in one case of 31 patients. McCombe reported 3 patients with severe sensorimotor neuropathy complicating rheumatoid arthritis occurred early in the course of disease. Two patients had axonal neuropathy but the third patient had a demyelinating neuropathy with a high cerebrospinal fluid protein level, and is a probable example of a chronic inflammatory neuropathy occurring in RA.

All patients improved or were stabilized with corticosteroid therapy. Hawke et al evaluated the clinical, electrophysiological and pathological features and prognosis of 34 RA patients with peripheral neuropathy caused by necrotizing vasculitis. Mononeuritis multiplex was the most common clinical presentation, followed by asymmetrical polyneuropathy and distal symmetrical polyneuropathy.

Canesi et al detected evidence of latent neuropathy in thirty (88.2%) of thirty four patients with RA and concluded that neurophysiological alterations could depend on a widespread injury of the axonic membrane.

In conclusion our results confirm that asymptomatic PNS disorders are common in RA. Polyneuropathy in RA is usually an axonal type. Pathophysiologically, this finding shows that ischemic and/or vasculitic injuries to nerves exclusively result to an axonal disorder that usually this type of injury is irreversible. Also, polyneuropathy in RA has significant correlation with advanced stages of disease. Therefore, the inclusion of an electrodiagnostic examination of the RA patients is recommended in routine diagnostic evaluation.

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Received by: 26 December 2006
Revised by: 25 May 2007
Accepted : 31 May 2007

The Online Journal of Neurological Sciences (Turkish) 1984-2007
This e-journal is run by Ege University Faculty of Medicine, Dept. of Neurological Surgery, Bornova, Izmir-35100TR as part of the Ege Neurological Surgery World Wide Web service.
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