



Association of Peripheral Neuropathy with Inflammatory Markers in Rheumatoid Arthritis Patients : An Electrophysiological Study

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ABSTRACT

Aim: To evaluate the involvement of peripheral nervous system by means of nerve conduction studies (NCSs) in RA patients and to see the alterations in the neurophysiological parameters with presence and absence of inflammatory markers.

Methods: 100 RA patients diagnosed under ACR criteria 2010 were included in this study and matched with 100 normal subjects regarding age and gender. Both the groups went through the NCSs for the assessment of the median, ulnar, tibial and peroneal nerves bilaterally and they were compared with each other with the help of t-test. Within the study group itself the alterations in electrophysiological parameters were observed in the presence and absence of some inflammatory markers e.g. RA factor, C- reactive protein (CRP), erythrocyte sedimentation rate (ESR) and joint. To see the associations tMann-Whitney test was performed with categorical variables e.g. RA factor, CRP and correlation analysis was done with continuous variables e.g. ESR.

Results: Electrophysiologically neuropathy was detected in RA patients with or without the clinical signs and symptoms. The parameters of NCSs were significantly affected due to the presence of inflammatory markers mainly CRP, ESR and joint deformities and less likely RA factor.

KEYWORDS

INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic multisystem disease with characteristic feature of persistent inflammatory synovitis, usually involving peripheral joints in a symmetric distribution. The potential of synovial inflammation is enough to cause cartilage damage, bone erosion and subsequently joint deformities. Clinically synovial inflammation causes swelling, tenderness and limitation of motion which gradually affects several joints especially those of hands, wrists, knees and feet.(1)

The course of RA is quite variable from patient to patient. Some of them may experience a mild oligo-articular illness of brief duration with minimal joint damage whereas others will have relentless progressive polyarthritis with marked functional impairments and extra-articular manifestations. These extra-articular manifestations are all the conditions and symptoms which are not directly related to locomotor system. It can produce the inflammation in lung, pleura, pericardium, sclera and subcutaneous tissues (2). The extra articular manifestations occur in 40% of patients, either in the beginning or during the course of the disease (3). These extra-articular manifestations include rheumatoid nodules, rheumatoid vasculitis and pleuro-pulmonary, neurologic, digestive, cardiovascular, cutaneous, haematologic complications.(1)

Due to the disability and functional limitation of the patients with long standing RA, the presence of peripheral neuropathy as an extra-articular manifestation is often an overlooked aspect. Nerve entrapment secondary to proliferative synovitis or joint deformities may produce neuropathies of median, ulnar, radial (interosseous branch) or anterior tibial nerves (1). However it is difficult to diagnose these slight or early neuropathies due to the symptoms resulting from pain in joints and limitation of movements. But on the other hand if diagnosed later the damage may be irreversible.

Nevertheless it is often possible by means of electrodiagnosis to show objectively the existence and distribution of even sub-clinical neuropathies. As a fundamental component of electrodiagnostic evaluation, nerve conduction studies provide valuable qualitative and quantitative insight into neuromuscular function.(4)

With the help of nerve conduction studies the involvement of

peripheral nerves (either clinical or subclinical) in RA patients can be assessed and further it can be correlated with inflammatory markers of disease e.g. erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and RA factor.

MATERIALS AND METHODS:

This was a retrospective case control study which was conducted in the Department of Physiology, Dr. D. Y. Patil Medical College, Pimpri, Pune and Department of Medicine, S.P. Medical College and associated hospitals, Bikaner. 100 patients of rheumatoid arthritis were consecutively enlisted and enrolled from the medicine OPDs and they were matched with 100 normal individuals, grouped as controls, regarding age and gender. All of them had given the written consent for participating in the research project. The prior permission of institutional ethics committee had been taken.

Patients with clinical diagnosis of rheumatoid arthritis according to ACR 2010 criteria, in between the age of 20-70 years, disease duration more than 12 months and were on regular medication either DMARDs (disease modifying anti-rheumatoid arthritis drugs) or steroids, were included as the study group. Those who were having any evidence of malignancy, pregnancy, diabetes mellitus, renal and hepatic diseases, history of alcoholism / smoking, obesity, malnutrition, evidence of heavy metal intoxication, history of any other collagen vascular disease were excluded from the study.

A proforma sheet was prepared for getting the information of each patient regarding the age, sex, occupation and residential address with contact numbers. After screening patients were subjected to complete all parameters related to rheumatological and peripheral nervous system assessment including:

- 1) RA factor (> 30 IU / ml was considered as +ve)
- 2) CRP (> 5mg / lt was considered as +ve)
- 3) ESR (> 28 mm/hr was considered as abnormal)
- 4) Sensory and motor examination of upper and lower limb
- 5) Electrophysiological studies of ulnar, median, tibial and peroneal nerves

The nerve conduction studies were done with the help of "synergy systems" at the temperature maintained at 25 degree centigrade. The validity and reliability of the instrument

was checked. The placements of electrodes were done as per Mishra etal (5). The parameters recorded were:

a) Motor conduction studies / compound muscle action potential (CMAP)

- distal and proximal latency (dl and pl)
- amplitude (A)
- velocity (v)
- f- wave latency (fw)

b) Sensory conduction studies / sensory nerve action potential (SNAP)

- Distal latency

Amplitude

- Velocity

Statistical analysis

In between the control and study group the electrophysiolog-

ical findings were compared with the help of Mann- Whitney test. This test was also performed to see the associations of electrophysiological findings with categorical variables e.g. RA factor and CRP. Spermear's correlation analysis was done to see the correlation between electrophysiological findings with continuous variables e.g. ESR.

OBSERVATION AND RESULTS:

In the study group 18 were males and 82 were females whereas in control group 19 were males and 81 were females. In both the groups the gender distribution is comparable

All the parameters of nerve conduction studies were showing the significant differences in between the study and control group. Due to the lower values of velocity, amplitude and higher values of latencies, very well presentation of electro physiological neuropathy is observed whether the clinical signs and symptoms are present (in 10% of our study population) or absent.

Table 1: Associations of inflammatory markers with findings of nerve conduction studies in upper limb

Manifestati-ons of RA	Median nerve						Ulnar nerve					
	Motor			Sensory			motor			Sensory		
	Latency	amplitude	Velocity	latency	amplitude	velocity	latency	amplitude	velocity	latency	Amplitude	velocity
ESR		*			*							
RA factor								*				
CRP	*			*				*				

Table 2: Associations of inflammatory markers with findings of nerve conduction studies in lower limb

Manifestations of RA	tibial nerve						peroneal nerve					
	Motor			Sensory			motor			Sensory		
	Latency	amplitude	Velocity	latency	amplitude	velocity	latency	amplitude	velocity	latency	Amplitude	velocity
ESR								*				
RA factor												
CRP								*		*		*

*Denotes the electrophysiological parameter significantly affected by inflammatory markers.

The above two tables are showing the associations in upper and lower limb respectively in a summarized manner.

In median nerve conduction studies due to the presence of CRP, motor latency (2.926 ms with CRP -ve and 3.184 ms with CRP +ve, p-value is 0.042) and motor velocity (58.8 m/s with CRP -ve and 56.5 m/s with CRP +ve, p- value is 0.029) are showing significant differences. Due to the presence of higher ESR median nerve motor amplitude (-ve correlation with 0.031 level significance), sensory amplitude (-ve correlation with 0.04 level of significance) are affected.

In ulnar nerve conduction studies due to the presence of RA factor motor amplitude (5.92 mv with RA -ve and 4.98 mv with RA +ve, p-value is 0.015) is affected significantly. Due to the presence of CRP motor amplitude (5.92 mv with CRP -ve and 4.917 mv with CRP +ve, p-value is 0.022) is showing significantly lower values.

In peroneal nerve conduction studies due to the presence of CRP, motor amplitude (4.637 mv with CRP -ve and 3.81 mv with CRP +ve, p-value is 0.04), sensory latency (3.765 ms with CRP -ve and 4.652 ms with CRP +ve, p-value is 0.044) and sensory velocity (39.69 m/s with CRP -ve and 34.99 m/s with CRP +ve, p-value is 0.045) are showing the significant differences. Due to the presence of higher ESR motor amplitude (-ve correlation with 0.013 level of significance) is significantly affected.

DISCUSSION:

A total number of 100 RA patients were selected and included in this study irrespective of their sex, religion, habits and socio-economic status. Along with the patients 100 normal individuals were enrolled, matched with the patients regarding

age and sex. The group of patients was considered as study group and group of normal individuals as control group. All the subjects had given the written consent and there was no drop out in our study.

The motor and sensory NCSs findings of all four nerves were compared in between the two groups and it was statistically significant. These findings are supported by the study of Mohd. E. Sulaman etal where they had found the significant differences in the parameters of nerve conduction studies, the distal latency of compound muscle action potential and conduction velocity in RA patients and in normal subjects. They performed the nerve conduction studies in median, ulnar, radial, common peroneal and out of which except radial all the nerves were showing the significant difference in their parameters(6). In order to investigate subclinical involvement of peripheral nervous system Aktekin etal excluded the RA patients with the symptoms of muscle weakness, paraesthesia and hypoesthesia and found that 20 out of 56 RA patients (36%) who did not have any signs or symptoms of peripheral nerve 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 group was statistically significant (7).

In case of median nerve the presence of higher levels of CRP affected the motor latency and velocity. The higher ESR values affected the motor and sensory amplitude. In ulnar nerve conduction, due to the presence of RA factor and CRP motor amplitude was showing significantly lower values. In case of peroneal nerve higher levels of CRP affected the motor amplitude, sensory latency and velocity. Due to the presence of higher ESR values the motor amplitude significantly decreased. In case of tibial nerve no parameter was affected by any of the inflammatory markers. As shown by the above tables CRP is the marker which is maximally associated with electrophysiological parameters.

The involvement of peripheral nerves in RA might be in the form of compressive neuropathy or by vasculopathy, resulting in distal sensory or combined sensory-motor neuropathy.(8). This vasculitis is generated by interactions of leukocytes with endothelium and mediated by multiple pairs of adhesion molecules. Miedaney YM et al detected the higher expression of vascular cellular adhesion molecules (sVCAM) and E-selectin in RA patients complicated with neuropathy. The expression of such molecules are upregulated by immune activation and inflammation.(9). Mason JC et al reported the higher levels of sVCAM-1 in the sera from the patients with activated RA and the levels are well correlated with ESR and c-reactive proteins. (10). More recently Salih et al did the study on the levels of antiganglioside antibodies in RA patients complicated by peripheral neuropathy. They found the patients with greater neurological deficit had higher anti-IgM against GM1 ganglioside and sulphatide molecules. They also found the presence of rheumatoid factor was not different in the patients with or without the peripheral neuropathy which suggests that it is

not an important factor in aetiology of neuropathy (11). This finding is supporting to our findings in which RA factor affects the electrophysiological parameter less likely as compare to CRP and ESR.

CONCLUSIONS:

Peripheral nervous system is affected during the course of RA as an extra-articular manifestation and it is associated with inflammatory marker predominantly CRP. Thus the assessment of peripheral nervous system with the help of nerve conduction studies should be an important part of routine clinical examination of RA especially for the patients who are having higher inflammatory rate.

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