

Prevalence of subclinical peripheral neuropathy in rheumatoid arthritis patients in Eastern India: A hospital based clinical study**Rakhi Sanyal¹, Manjit Kumar Dhrubprasad², Sagnik Dutta Sarma³, Goutam Dutta Sarma^{4*}, Uma Mohan⁵, Ratneswar Bhattacharyya⁶**¹*Assistant Professor, Department of General Medicine, ICARE Institute of Medical Sciences and Research, Haldia, Purba Medinipur, West Bengal, India*²*Assistant Professor, Department of General Medicine, ICARE Institute of Medical Sciences and Research, Haldia, Purba Medinipur, West Bengal, India*³*Resident Medical Officer, Critical Care Medicine, AMRI Hospitals – Saltlake KB 24, KB Block, Sector III, Salt Lake City, Kolkata, West Bengal, India*⁴*Assistant Professor, Department of Obstetrics & Gynaecology, ICARE Institute of Medical Sciences and Research, Haldia, Purba Medinipur, West Bengal, India*⁵*Resident Medical Officer, Bindubasini Nursing Home, 76, Madhusudan Banerjee Road, Pratiraksha Nagar, Birati, Kolkata, West Bengal, India*⁶*Associate Professor, Department of General Medicine, ICARE Institute of Medical Sciences and Research, PO-Balughata, Haldia, Purba Medinipur, West Bengal, India***Received: 20-07-2020 / Revised: 23-08-2020 / Accepted: 30-08-2020****Abstract**

Background: It is difficult to diagnose the slight or early neuropathy and study of peripheral nervous system is often made difficult by symptoms resulting from pain in the joints in the patients with rheumatoid arthritis (RA). Therefore inclusion of electro-neuro-physiological examination of the RA patient is usually carried out in routine diagnostic procedure. Taking all these in consideration, the aim of our study was to detect subclinical neuropathy by electrophysiological testing in RA patients from Eastern India. **Materials & Methods:** This was a type of cross-sectional study which was undertaken to show the prevalence of subclinical neuropathy in patients of RA. This study was conducted over a period 18 months in the Rheumatology out-patient department. The technique employed was systematic sampling method. Fifty one patients between 35 to 79 years comprising of 44 females and 7 males were enrolled for the study in the first 12 months and then subsequently followed up for 4 visits at an interval of 6 weeks up to another 6 months. Patients were selected on the basis of confirmation of RA as per the American Rheumatological Association/ ARA revised criteria 1987. **Results:** The prevalence of subclinical peripheral neuropathy is more than 1/3rd of the rheumatoid patients. The neuropathy has definite relationship with RF positivity and high titres of anti CCP antibody. It also showed significant correlation with the disease duration, a sharp rise in ratio between neuropathy present and neuropathy absent groups after around 6 years of the disease. It did not show any significant correlation with age, sex, disease activity index. Fisher exact test P value= <0.0001, statistically significant association between Anti-CCP and presence of sub-clinical neuropathy. **Conclusion:** The prevalence of subclinical peripheral neuropathy is more than 1/3rd of the rheumatoid patients. Electrophysiological studies can diagnose subclinical peripheral neuropathy at a quite early stage. A very small percentage of patients developed overt clinical neuropathy, when followed up over a very small period of time of 6 months. The neuropathy has definite relationship with RF positivity and high titres of anti CCP antibody.

Keywords: Rheumatoid arthritis, peripheral neuropathy, rheumatoid factor, anti- CCP titre, electrophysiological testing.

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Introduction

Rheumatoid arthritis is a chronic autoimmune disease that causes inflammation of the joints and may cause inflammation of other tissues in the body. The exact aetiology is unknown. It is marked by symmetric peripheral polyarthritis. It is the most common form of chronic inflammatory arthritis and often results in joint damage and physical debility. The synovium is the primary target in the autoimmune process resulting in synovitis causing thickening and erosion of the synovium [1]. The surrounding structures like underlying cartilage and bone can also be involved leading to joint deformities. The synovial membrane which covers most articular surfaces, tendon sheaths, and bursae, normally is a thin layer of connective tissue. In joints, it faces the bone and cartilage, bridging the opposing bony surfaces and inserting at periosteal regions close to the articular cartilage [2]. The presenting symptoms of RA typically results from inflammation of the joints, tendons and bursae. Patients complain of early morning stiffness lasting for more than one hour and getting better with physical activity. The earliest involved joints are typically the small joints of hand and feet. Progressive destruction of the joints and soft tissues may lead to chronic irreversible deformities. Large joints, including the knees and shoulders, are often affected in established disease, although these joints may remain unaffected for many years after onset [2, 3]. Atlantoaxial joint involvement is also common and is very important because it can lead to compressive myelopathy and neurological dysfunction. Unlike the spondylo-arthropathies RA does not affect the thoracic and lumbar spine usually. Temporomandibular joint may also be involved but rarely associated with significant-symptoms or functional impairment. Varieties of extra-articular systemic manifestations involving lungs, cardiovascular system, skin, eyes and alteration of haematological parameters are common in rheumatoid arthritis. This can occur even prior to onset of arthritis. RA affects several organ systems, as follows: cutaneous, cardiac, pulmonary, renal, gastrointestinal (GI), vascular, hematologic, neurologic and ocular. There are associated conditions like, cardiovascular disease, osteoporosis and hypoandrogenism with RA [4, 5]. There are studies which show that nervous system is also involved in RA and the clinical hallmark is the appearance of neurological findings [6, 7]. It is difficult to diagnose the slight or early neuropathy and study of peripheral nervous system is often made difficult by symptoms resulting from pain in the joints in the

patients with RA. Therefore inclusion of electro-neuro-physiological examination of the RA patient is usually carried out in routine diagnostic procedure.

Symptomatic neuropathy is thus uncommon in RA but though compressive and vasculitic neuropathy are reported in longstanding RA and most patients are asymptomatic clinically but there is high prevalence of subclinical neuropathy in patients with RA [8, 9]. Taking all these in consideration, the aim of our study was to detect subclinical neuropathy by electro-physiological testing in RA patients from Eastern India.

Materials & methods

This was a type of cross-sectional study which was undertaken to show the prevalence of subclinical neuropathy in patients of RA. This study was conducted over a period 18 months in the Rheumatology out-patient department. The technique employed was systematic sampling method. Fifty one patients between 35 to 79 years comprising of 44 females and 7 males were enrolled for the study in the first 12 months and then subsequently followed up for 4 visits at an interval of 6 weeks up to another 6 months. Patients were selected on the basis of confirmation of RA as per the American Rheumatological Association/ ARA revised criteria 1987 [10], which states:

- a) Morning stiffness: Stiffness in and around joints lasting 1 hour before maximum improvement.
- b) Arthritis of 3 or more joint areas: At least 3 joint areas observed by a physician simultaneously, having soft tissue swelling or joint effusion. The 14 joint areas are right and left PIPs, MCPs, wrists, elbow, knee, ankle and MTP joints.
- c) Arthritis of hand joints.
- d) Symmetric arthritis: Simultaneous involvement of the same joint areas of both sides of the body.
- e) Rheumatoid nodules: Subcutaneous nodules over the bony prominences, extensor surfaces.
- f) Serum Rheumatoid Factor,
- g) Radiographic changes: Typical changes of RA on P-A view, including erosions or unequivocal bony decalcification.

Criteria (a to d) must be present for at least 6 weeks and a four out of seven criteria were required to classify a patient as having RA. A detailed rheumatological history like morning stiffness and

its duration, clinical type of articular involvement i.e. whether affecting small or large joints or both, whether symmetric or asymmetric, additive or migratory, predilection for lower or upper extremities, PIPs or DIPs, MCPs and MTPs, wrists or other joints. Associated features like skin lesions, nodules, mouth ulcers, axial involvement, a positive family history, any relevant drug history were taken. Then a detailed neurological history was obtained, which specifically included symptoms like numbness, tingling, burning feeling, sensation of pins and needles of the extremities as well as motor symptoms like weakness and thinning out of extremities. This was followed by a clinical examination to rule out overt neuropathy. History and clinical examination for autonomic dysfunction and subsequently followed by Autonomic testing like heart rate variation with deep breathing, valsalva response, orthostatic B.P recordings were also performed to rule out autonomic neuropathy. The patients were also examined for the presence of extra-articular involvement in the form of subcutaneous nodules, interstitial lung disease, and features of vasculitis like Raynauds phenomenon, digital infarctions and palpable purpura. Past treatment records were examined and all patients were asked about the intake of steroids and disease modifying anti-rheumatic drugs (DMARDs) whether continuously or intermittently. The following investigations were done: CBC with ESR, liver function test, prothrombin time (PT) / partial thromboplastin time (PTT), fasting blood sugar, blood urea nitrogen and creatinine, thyroid function test, C reactive Protein (CRP), and Rheumatoid Factor (RF). Anti-CCP titre done using commercially available ELISA kit and less than 6RU/ml was considered normal. Hand and chest x-rays P.A. view and x-ray lumbo-sacral spine was taken. ECG in 12 leads was done in every patient. Vitamin B12 level and lipid profile, were estimated. Finally electrophysiological studies were performed in all patients and the results were assessed according to the American Diabetes

Association diabetic neuropathy protocol [11]. The electrophysiological studies were carried by device. Median, ulnar, peroneal nerve motor nerve conduction studies, F wave, and median, ulnar and sural nerve conduction velocities were recorded and room temperature was maintained at 22-24^o C. The palm-wrist conduction were done on patients for detection of carpal tunnel syndrome. Standard nerve conduction velocity was used.

Polyneuropathy types were described either axonal or demyelinating [7].

Axonal neuropathy was diagnosed by [7]:

1. Conduction velocities were normal.
2. The size of compound muscle action potential (CMAP) and sensory nerve action potentials (SNAPs) were decreased in at least 2 motor and 1 sensory nerves.

Demyelinating neuropathy showed [7]:

1. A reduction of CVs of at least 40% in at least 2 motor or 1 sensory nerves
2. Prolonged terminal motor latencies
3. Partial conduction block
4. An absent F wave or prolonged F wave latencies in 2 or more motor nerves

The exclusion criteria were the presence of conditions which can give rise to neuropathy and acted as confounding factors like: Diabetes, Kidney disease, Liver disease, Alcohol abuse, Nutritional deficiencies like Vitamin B₁₂, family history of peripheral nerve diseases, malignancies, those on neurotoxic drug, current toxin exposure, other autoimmune disorders and patients on leflonamide. Unconscious and severely ill patients were excluded from the study. Patients who were mentally impaired and or unable to give consent were also excluded. Data were collected and charts were made showing the baseline demographic parameters and statistical analysis was done by EPI-INFO software for chi-square and Fischer's exact tests keeping α level to 0.05.

Results

Demographics and baseline characteristics have been described in Tables 1-4.

Table 1: Age and sex distribution of the study population

Parameter (n=51)	Values
Age (in years)	
Range	35 – 79
Mean \pm SD	49.96 \pm 10.52
Sex	
Female	44 (86.3%)
Male	7 (13.7%)

Duration of Disease (in years)	
Range	3 - 13
Mean \pm SD	6.46 \pm 3.34

Table 2: Disease profile of the study population

Parameter (n=51)	Values
Rheumatoid Factor [Positive]	29 (56.9%)
Polyarthritis	20 (39.2%)
Early Morning Stiffness	19 (37.3%)
Joint Deformity	13 (25.5%)
Other Symptoms [Present]	21 (41%)
ESR (mm/hr)	
Range	10 - 60
Mean \pm SD	26.67 \pm 14.86
Anti CCP antibody	
0 - 100	15
101 - 200	21
>200	15
CRP	
<6	11
6 - 10	10
>10	30
VAS	
Range	0 - 70
Mean \pm SD	24.51 \pm 23.77

The prevalence of subclinical peripheral neuropathy is more than 1/3rd of the rheumatoid patients. Electrophysiological studies can diagnose subclinical peripheral neuropathy at a quite early stage. A very small percentage of patients developed overt clinical neuropathy, when followed up over a very small period of time of 6 months [Table 1-2].

Table 3: Neuropathy present in patient under study

	Present (n=51)	Percentage
Neuropathy present	22	43.1%
Sensory neuropathy	1	2%
SMD	1	2%
CTS	8	15.7%
TTS	2	3.9%
L5R	3	5.9%
L5S1R	3	5.9%
MN	3	5.9%

Table 4: Relationship between neuropathy and Rheumatoid factor

Data Analyzed	Neuropathy Present	Neuropathy Absent
RF positive	19	10
RF absent	3	19
Total	22	29

Fischer exact test: $p < 0.0004$, statistically significant association between RF positivity and presence of sub-clinical neuropathy [Table 4].

Table 5: Relationship between neuropathy and Anti CCP antibody

Anti CCP	Neuropathy present/ total in that Anti-CCP group
0-100	0/15
101-200	9/21
>200	13/15

Table 6: Relationship between neuropathy and Anti-CCP antibody

Anti CCP	Neuropathy Present	Neuropathy Absent
0-100	0	15
101-200	09	12
>200	13	02

Fisher exact test P value= <0.0001, statistically significant association between Anti-CCP and presence of sub-clinical neuropathy [Table 6].

Table 7: Relationship between neuropathy and CRP

CRP	Neuropathy present/ total in that CRP group
<6	5/11
6 – 10	14/30
>10	3/10

Table 8: Relationship between neuropathy and CRP

	Neuropathy present	Neuropathy absent
CRP <6	5	6
CRP [6 – 10]	14	16
CRP >10	3	7

P value = 0.664, p values are statistically not significant

The neuropathy has definite relationship with RF positivity and high titres of anti CCP antibody. It also showed significant correlation with the disease duration, a sharp rise in ratio between neuropathy present and neuropathy absent groups after around 6 years of the disease. It did not show any significant correlation with age, sex, disease activity index [Table 5-8].

Discussion

RA affects approximately 0.5-1.0% of the adult population in the world. There is evidence that the overall incidence of RA has been decreasing in recent decades, whereas prevalence has remained the same since the patient with RA are living longer. The prevalence of clinical RA is popularly believed to be about 1% worldwide [12]. Nervous system is also affected among the extra-articular manifestations of RA, mostly in the form of peripheral nervous system involvement. The presence of peripheral neuropathy in patients with RA constitutes significantly to the functional limitation, and has impact on lost work days with far reaching social and economic impacts. But it is an overlooked aspect [13]. Nadkar et al

studied 31 patients of rheumatoid arthritis (RA) classified by ACR criteria. Electromyography and nerve conduction studies (EMG/NCV) were done in all the patients apart from routine laboratory and radiological investigations [14]. Ten out of 31 RA patients had neuropathy of which five patients had overt and five patients had subclinical respectively. Only one patient had entrapment neuropathy. Four of the ten patients had pure motor neuropathy whereas the other six were sensori-motor neuropathies. Four patients had mononeuritis multiplex and five had symmetrical peripheral neuropathy. Seven patients had other extra-articular features along with neuropathy. They concluded that one-third of patients with RA have evidence of neuropathy. Disease parameters such as activity, rheumatoid factor and functional and radiological grade do not correlate with neuropathy. Non-entrapment sensori-motor type of neuropathy is the most common type. Agarwal V et al. studied one hundred eight patients of RA, fulfilling American College of Rheumatology 1987 criteria and were examined clinically and electrophysiologically for evidence of peripheral neuropathy [15]. About 57.4% patients had electrophysiologic evidence of neuropathy.

Of these 85.5% patients had pure sensory or sensory motor axonal neuropathy, while 14.5% had demyelinating neuropathy. Carpal tunnel syndrome was seen in 10.1% patients [15]. Bely M *et al* studied the frequency and histopathological characteristics of systemic vasculitis in autopsy material of 161 patients with RA. Systemic vasculitis was observed in 22.4% (36 cases). In percentage of all cases with systemic vasculitis, most frequently involved organs were the heart (66.7%), skeletal muscles (54.8%), and peripheral nerves (52%). The skin was involved only in about 36%. In most cases the arterioles and the small arteries were affected by vasculitis [16].

RA is associated with vasculopathy, peripheral, autonomic and entrapment neuropathy resulting in distal sensory, combined sensory and sensorimotor neuropathy [6, 17]. Bekkelund S *et al* [18] studied 40 seropositive women with RA and revealed an increased prevalence of neurogenic but not myogenic changes in patients with RA compared to the controls. Nadkar MY *et al* [14] studied 31 patients of RA classified by ACR criteria. The study showed one-third patients with RA have evidence of neuropathy. Disease parameters such as activity, rheumatoid factor and functional and radiological grade did not correlate with neuropathy and it was also revealed that nonentrapment sensori-motor type of neuropathy is the most common type. In the present study, electrophysiological studies can diagnose subclinical peripheral neuropathy at a quite early stage. A very small percentage of patients developed overt clinical neuropathy, when followed up over a very small period of time of 6 months. The neuropathy has definite relationship with RF positivity and high titres of anti CCP antibody. It also showed significant correlation with the disease duration, a sharp rise in ratio between neuropathy present and neuropathy absent groups after around 6 years of the disease. It did not show any significant correlation with age, sex, disease activity index. Agarwal V, *et al* studied the clinical, electro-physiological neuropathy and pathological changes in the sural nerve in patients of RA. About 108 patients fulfilling American College of Rheumatology 1987 Criteria were examined clinically and electrophysiologically for evidence of peripheral neuropathy. It was shown that neuropathy in RA was mostly subclinical and predominantly axonal [15]. Sivri A *et al* studied 33 RA patients and compared them with 20 healthy controls. The results confirm earlier observations that symptoms of neuropathy were fairly common in cases of RA without there being any clear correlation with any clinical variable and by means of

electrophysiological studies; it is to evaluate the integrity of the peripheral nerve. Therefore the inclusion of electroneurophysiological examination of the RA patients is recommended in routine diagnostic procedure [6]. Lanzillo B *et al* studied with 40 RA patients who were examined neurologically and electrophysiologically and sural nerve biopsies were done in 4. They concluded that patients with RA may have electrophysiological and histological findings of peripheral nerve damage and even in the absence of clinical evidence of peripheral nerve involvement [9].

Aneja *et al* studied 100 newly diagnosed patients with RA (ACR criteria 1987 revised). Their study revealed that most patients of RA over a period of 3 years were asymptomatic clinically but there is high prevalence of subclinical neuropathy among them [19]. Lang *et al* studied with a group of patients in the age group 23 to 56 years with a mean age of 41 years and concluded that there was no significant correlation between neurological findings and clinical and laboratory data (age, sex, RF, ESR, etc) [20]. Our study found no significant association between presence of peripheral neuropathy and any of the conventional markers of severe rheumatoid disease such as 28 joint disease activity score, presence of erosions in hand x-ray, extra-articular manifestations like subcutaneous nodules, interstitial lung disease and features of vasculitides. Our findings are similar to the study conducted by Agarwal *et al* [15], Nadkar *et al* [14] and Lanzillo *et al* [9]. Our study had certain practical limitations. The major weakness of the study is that we could not perform nerve biopsy which is the pathological gold standard for determination of the presence and types of neuropathy. Further studies are needed to see the fate of the subclinical neuropathy. If overt neuropathy occurs, then the duration for its development. In future study may be planned to know whether any biological markers can be estimated, which can detect the subclinical neuropathy at a very early stage.

Conclusion

The prevalence of subclinical peripheral neuropathy is more than 1/3rd of the rheumatoid patients. Electrophysiological studies can diagnose subclinical peripheral neuropathy at a quite early stage. A very small percentage of patients developed overt clinical neuropathy, when followed up over a very small period of time of 6 months. The neuropathy has definite relationship with RF positivity and high titres of anti CCP antibody. It also showed significant correlation with the disease duration, a sharp rise in ratio between neuropathy present and neuropathy absent groups after

around 6 years of the disease. It did not show any significant correlation with age, sex, disease activity index.

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