DISSERTATION

ON

PERIPHERAL NEUROPATHY IN RHEUMATOID ARTHRITIS WITH SPECIAL EMPHASIS ON NERVE CONDUCTION STUDIES

A Dissertation Submitted to

THE TAMILNADU DR. M.G.R MEDICAL UNIVERSITY

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for the Award of the Degree of

M.D. (GENERAL MEDICINE) - BRANCH – I

GOVERNMENT KILPAUK MEDICAL COLLEGE & HOSPITAL

CHENNAI,TAMILNADU.

MAY – 2018.

BONAFIDE CERTIFICATE

This is to certify that this dissertation title "**PERIPHERAL NEUROPATHY IN RHEUMATOID ARTHRITIS WITH SPECIAL EMPHASIS ON NERVE CONDUCTION STUDIES"** submitted by **Dr.S.ASHOK KUMAR,** to the faculty of General Medicine**, "The Tamil Nadu Dr. M.G.R. Medical University"**, Chennai in partial fulfillment of the requirement for the award of **MD Degree Branch I (General Medicine)**, is a bonafide research work carried out by him under our direct supervision and guidance

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DECLARATION

I, **Dr.S.Ashok Kumar**, solemnly declare that the dissertation titled **"PERIPHERAL NEUROPATHY IN RHEUMATOID ARTHRITIS WITH SPECIAL EMPHASIS ON NERVE CONDUCTION STUDIES**" has been prepared by me under the guidance of **Prof.Dr.S.Chandrasekar, M.D.,** Department of Internal Medicine, Govt. Kilpauk Medical College and Hospital. This is submitted to **"The Tamil Nadu Dr. M.G.R. Medical University, Chennai"** in partial fulfillment of the requirement for the award of **MD Degree Branch I (General Medicine).**

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CERTIFICATE - II

This is to certify that this dissertation work titled **"PERIPHERAL NEUROPATHY IN RHEUMATOID ARTHRITIS WITH SPECIAL EMPHASIS ON NERVE CONDUCTION STUDIES**" of the candidate **Dr.S.ASHOK KUMAR,** Post graduate in **GENERAL MEDICINE** with registration Number **201511152** for the award of **M.D.GENERAL MEDICINE** in the **Branch I**. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **8%** percentage of plagiarism in the dissertation.

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CONTENTS

ABBREVIATIONS

ACR	-	American college of rheumatology
Anti-CCP	-	Anti cyclic citrulinated peptide
CMAP	-	Compound muscle action potential
CRP	-	C-Reactive protein
CTS	-	Carpel tunnel syndrome
DAS-28	-	Disease activity score.
DC	-	Differential count
DIP	-	Distal interphalangeal joint
DMARD	-	Disease modifying anti rheumatoid drug
ESR	-	Erythrocyte sedimentation rate
EULAR	-	European league of anti rheumatism
Hb	-	Hemoglobin
M	-	Motor
MCP	-	Meta carpophalangeal joint
MM	-	Mononeuritis multiplex
NDS	-	Neuropathic disease activity score
NSS	-	Neuropathic sensory symptoms
PIP	-	Proximal interphalangeal joint
PN	-	Peripheral neuropathy
RA	-	Rheumatoid arthritis
RF	-	Rheumatoid factor
SNAP	-	Sensory nerve action potential.
S	-	Sensory
TC	-	Total count
-ve	-	negative
+ve	-	positive

INSTITUTIONAL ETHICS COMMITTEE
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Protocol ID. No.03/2017 Meeting held on 03.03.2017

CERTIFICATE OF APPROVAL

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "**Peripheral Neuropathy in Rheumatoid Arthritis with Special Emphisis on Nerve Conduction Studies** " submitted by Dr.S.Ashok Kumar, M.D. General Medicine, PG Student, GKMC, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

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INTRODUCTION

Rheumatoid arthritis is a chronic immune-inflammatory systemic disease which affects synovial joints with possibility of extraarticular manifestations[1].

Rheumatoid arthritis prevalence is approximately 0.8% (0.3 to 2.1%) of population worldwide[2]. Our Indian data suggest prevalence to be around 0.65 to 0.75%.

Rheumatoid arthritis is primarily a joint disease, but extraarticular manifestation can be detected in any organ system and may occasional precede the onset of arthritis. Most common neurological manifestation in rheumatoid arthritis is entrapment neuropathy which is secondary to proliferative synovitis[3].

About 33.2% of the patients develop neurological problems during their lifetime[3].Peripheral nerve involvement in rheumatoid arthritis includes compressive neuropathy, which is by far the commonest , distal sensory and combined sensorimotor neuropathy[4].

Although the underlying pathology resulting in rheumatoid neuropathy is not clear, ischemia secondary to vasculitis with

characteristic axonal loss and humoral mechanisms such as the deposition of immune complexes and fixation of complement are thought to be important factors[5]. The arteritis of small vessels commonly fibrinoid type and immune globins are demonstrated in walls of the vessels[6].

The presence of peripheral neuropathy in patients with rheumatoid arthritis is difficult to recognize as patients often related neurological symptoms to joint disease. It is also difficult to assess neurological system in the presence of severe joint disease[5]. Hence our current study is undertaken to evaluate the prevalence and pattern of neuropathy in rheumatoid arthritis and to correlate it with disease parameter and other extraarticular involvement.

AIMS AND OBJECTIVES

1. To study the prevalence of peripheral neuropathy in Rheumatoid arthritis.
2. To know the pattern of neuropathy in Rheumatoid arthritis.
3. To correlate neuropathy with disease parameters and other extra articular involvement.

REVIEW OF LITERATURE

Rheumatoid arthritis a chronic inflammatory multisystem disease of unknown etiology with characteristic features of persistant inflammatory synovitis affecting mostly peripheral joints symmetrically. This inflammation leads on to cartilage destruction, bony erosions and presenting finally as joint deformity.

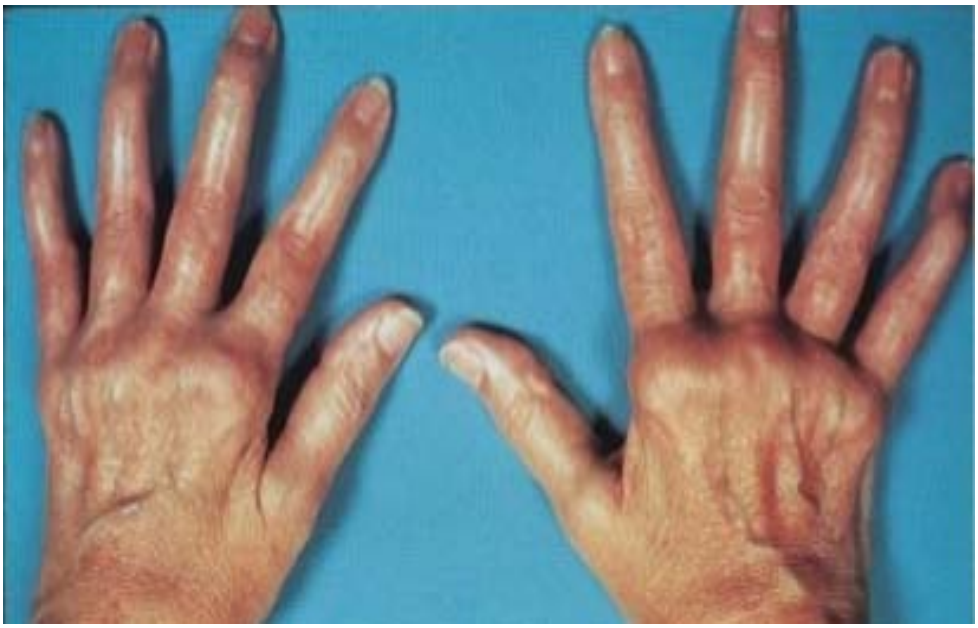
The main manifestations involve the joints, studies done before have reported that extra-articular manifestations occur in 10%–20%of RA patients. These symptoms correlate with increased mortality. Clinical neuropathy occurs in 0.5% to 85% of RA patients. They present in the form of mononeuritis multiplex, sensorimotor neuropathy and entrapment neuropathy. Clinical neuropathy may present with wide variety of symptoms like pain, paresthesias, and muscle weakness. These symptoms mimic and overlap those of arthritis, and hence difficult to distinguish peripheral neuropathy symptoms from arthritis symptoms.

Clinical research over two decades have revolutionized the contemporary paradigms for diagnosis and treatment of Rheumatoid arthritis. Serum antibodies to Cyclic Citrulinated peptides is used

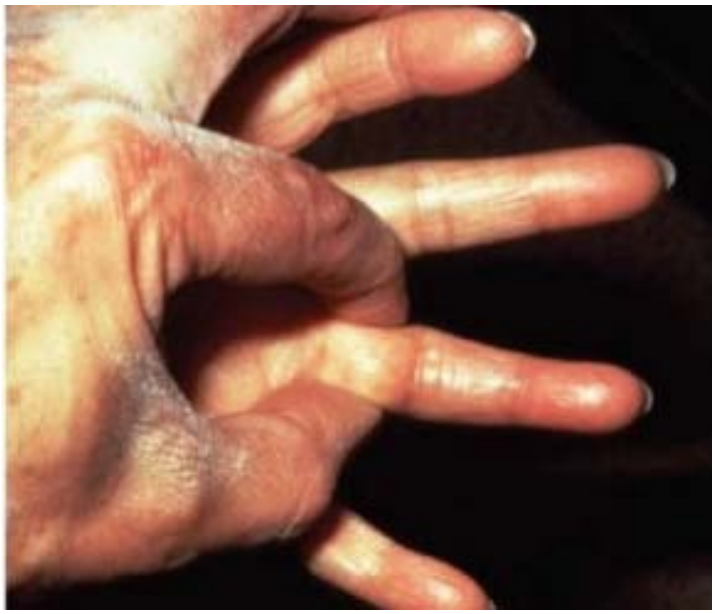
routinely along with rheumatoid factor for diagnostic and prognostic significance.

Newer imaging techniques improved our ability to detect joint inflammation and destruction in Rheumatoid arthritis. Incomplete understanding of initial pathogenic pathways remains seizable barriers to prevent and cure Rheumatoid arthritis. The description of crippling arthritis encountered less frequently due to therapeutic armamentarium plus adopting early treatment intervention leading to remarkable improvement in outcome of Rheumatoid arthritis. Early identification of problem and referring patients with inflammatory arthritis to rheumatologist for correct diagnosis and initiating treatment is of clinical significance.

Clinical presentation of rheumatoid arthritis starts increasing between 25 to 55 years of age, plateaus until 75 years of age and then decreases. Symptoms of rheumatoid arthritis results from inflammation of joints , tendon and bursae. Early morning stiffness of more than 1 hr which reduces with physical activity. Most common and early involvement seen in small joints of hand and feet. Pattern of joint involvements are monoarticular, oligoarticular ($\leq$4) joints, polyarticular (>5) joints usually in symmetric distribution.



Some inflammatory arthritis effects very few joints classified initially as undifferentiated Inflammatory arthritis later diagnosed to be rheumatoid arthritis having more joint involvement and having positive serum Rheumatoid Factor or Anti-CCP antibodies. They also show high scores for physical disability. Wrist joint, metacarpophalangeal joints, proximal interphalangeal joints are most frequently involved. Distal interphalangeal joints may be involved in rheumatoid arthritis but usually co-exist with osteoarthritis. Hallmark of Rheumatoid arthritis is flexor tendon tenosynovitis.



FLEXOR TENOSYNOVITIS

This leads to reduced range of movements ,reduced grip strength and trigger fingers. Destruction of joints and soft tissues progressively leads to chronic irreversible deformities. Subluxation of metacarpophalangeal joints with subluxation of proximal phalanx to volar side results in Ulnar deviation. Some of the deformities commonly seen in rheumatoid arthritis are,

“Swan Neck deformity” –hyperextension of proximal inter phalangeal joint with flexion of distal inter phalangeal joint.

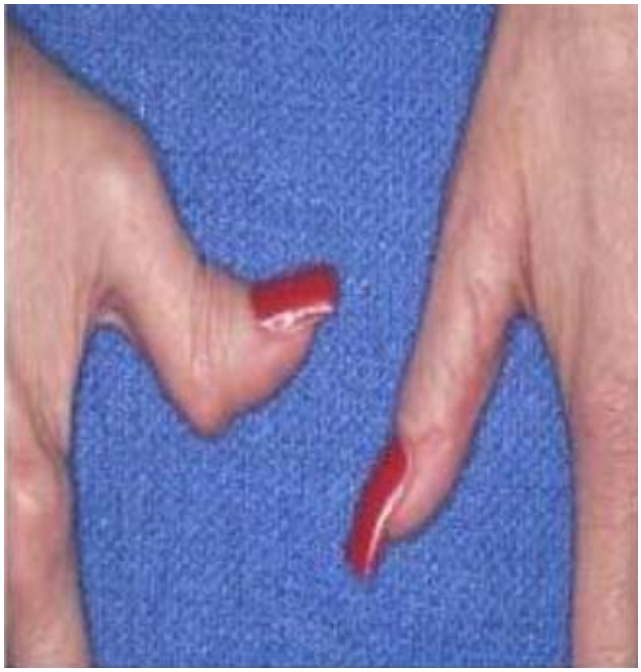
 ,

SWAN NECK DEFORMITY

"Boutonniere deformity" - flexion of proximal inter phalangeal joint with hyperextension of Distal inter phalangeal joint

BOUTONNIERE DEFORMITY

“ Z-LINE deformity ” – subluxation of first meta carpo phalangeal joint with hyper extension of first inter phalangeal joint.



Z-LINE DEFORMITY

In feet early feature of disease is metatarsophalangeal joint involvement. Inflammation of ankle and midtarsal regions chronically leads on to pesplanovalgus- Flat feet. Large joints like knee and shoulder joints affected in established disease and they remain asymptomatic for many years after onset. Cervical spine involvement is noteworthy as it is potential to cause compressive myelopathy and neurological dysfunction. Atlantoaxial involvement of cervical spine presents with signs and symptoms of neurological dysfunction with progressive instability of C1 on C2.

EXTRAARTICULAR MANIFESTATIONS:

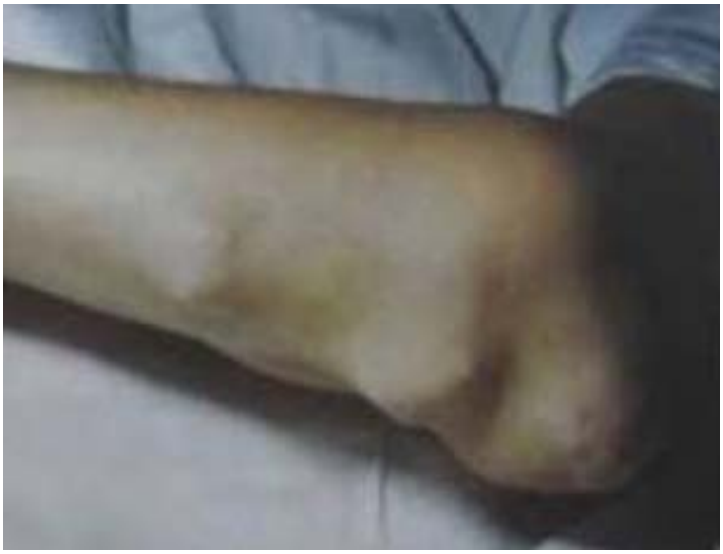
Extraarticular manifestations develop during clinical course of rheumatoid arthritis[7]. Patients with history of smoking develop extraarticular disease, early onset of significant disability and usually positive for serum Rheumatoid factor. Most frequently observed extraarticular manifestations are rheumatoid nodules ,secondary sjogren's syndrome, pulmonary nodules, cardiac manifestations ,haematological features ,vasculitis, neurological manifestations,osteoporosis , lymphoma and others.

SYSTEMIC SYMPTOMS:

Systemic features like fever, weight loss, fatigue, malaise, in severe cases cachexia. This reflects higher degree of inflammation.

Subcutaneous nodules seen in 30 to 40 % of patients. Typically benign may be associated with infection. Usually seen in height of disease activity with positive rheumatoid factor and x-ray evidence of joint erosions.

RHEUMATOID NODULES:



Nodules are firm, non tender, adherent to periostium, bursae or tendons. Occurs in the areas of repeated trauma or irritation such as forearm, achilles tendon and sacral prominences. Nodules sometimes seen in lungs, pleura, pericardium and peritoneum .

HEMATOLOGICAL

Patients often develops normocytic, normochromic anemia. It's the most frequent hematological abnormality. Anemia may not be that much evident clinically. Anemia usually correlates with the degree of inflammation, levels of c- reactive protein and ESR value. Platelet counts are elevated as an acute phase reactant.

In some patients, triad of neutropenia, rheumatoid nodules and splenomegaly is seen defined as Felty's syndrome. Typically occurs in white patients in late stage of severe disease and its incidence is decreasing due to aggressive treatment. Leukopenia may be seen but is most often due to drug treatment. Lymphomas are seen quiet commonly in patients with rheumatoid arthritis. Common type seen histopathologicaly is diffuse large B-cell lymphoma . Its incidence usually coorelates with disease activity.

PULMONARY MANIFESTATIONS :

Pulmonary manifestations like pleuritic chest pain ,dyspnea , pleural friction rub and pleural effusion are usually seen. Pleural effusion is usually exudative. Pulmonary nodules seen may be solitary or multiple. Interstitial lung disease may also occur, presenting with progressive dyspnea and dry cough. Pulmonary function test shows restrictive pattern. Diagnosis made by high resolution chest computer tomography.

ILD confers poor prognosis but responds favourably to immunosuppressive treatment than idiopathic ILD.

CARDIAC MANIFESTATIONS

Pericardium is the most frequent site of cardiac involvement. Pericarditis occur in less than 10% of patients with rheumatoid arthritis. Cardiomyopathy is another manifestation of rheumatoid arthritis. Heart muscle may contain rheumatoid nodules. Mitral regurgitation is the most common abnormality in rheumatoid arthritis.

VASCULITIS

Rheumatoid vasculitis seen most commonly in long standing case with positive serum rheumatoid factor and hypocomplementemia. Cutaneous signs include petechiae, purpura, digital infarcts, livedoreticularis, painful lower limb ulceration. Vasculitic ulcers treated successfully with immuno suppressants and skin grafting. Sensorimotor polyneuropathies like mononeuritis multiplex occur in association with rheumatoid vasculitis.

NEUROLOGICAL

Neuropathy occurs in 0.5% to 85% of rheumatoid arthritis patients. Clinically presents in the form of mononeuritis multiplex, sensory motor neuropathy and entrapment neuropathy. These patients presents with varied symptomatology like pain ,paresthesiaand muscle weakness. These

symptoms mimic and overlap with those of arthritis. Its difficult to distinguish arthritis symptoms from neuropathic symptoms. Entrapment neuropathies occur secondary to proliferative synovitis or joint deformities and commonly involve median, ulnar, radial or anterior tibial nerve.

Diagnosis of neuropathy is possible by nerve conduction study to show objectively the existence and distribution of subclinical neuropathies. They also provide quantitative and qualitative insight into neuromuscular function.

Rheumatoid arthritis affects about 0.5-1% of adult population globally. African and Asian population showed lower prevalence in the range of 0.2 – 0.4% . Rheumatoid arthritis occur commonly in females than males in 2-3:1 ratio.

Studies from Latin America and Africa shows female to male ratio 6-8:1. Various theories proposed preponderance in female is due to estrogen in disease pathogenesis. Theories centered the role of estrogen in enhancing immune response. Experimental studies shown than estrogen stimulate production of TNF-alpha, major cytokines in the pathogenesis of rheumatoid arthritis.

Genetic factors contribute to the occurence and severity of rheumatoid arthritis. First degree relatives of patient share the diagnosis of rheumatoid arthritis 2-10 times greater than general population . Twin studies showed that genetic factors explain upto 60% of occurence of rheumatoid arthritis. Genetic influence varies across studies due to environment – gene intractions.

Alleles known to cause greatest risk of rheumatoid arthritis located within Major Histo Compatibility (MHC)- HLA –DR B1 gene encodes MHC II beta chain molecule shows close association in genetic risk of rheumatoid arthritis.

Genomic studies have showed the possible identification of several non – MHC related genes in rheumatoid arthritis susceptibility. Non-MHC loci at risk alleles for rheumatoid arthritis has only modest effect on risk and also contribute to other autoimmune diseases like Type I Diabetes Mellitus, Systemic Lupus Erythematosus and Multiple Sclerosis. Non-HLA association also been described in patients with Anti CCP- antibodies positive disease. Risk alleles varies with ethnic groups. Risk alleles identified by non – MHC loci only account approximately 5% of genetic risk .This suggests other DNA varieties yet to found that contribute to overall risk model.

Environmental factors have been implicated in the pathogenesis of RA .Most reproducible of the environmental factor is cigarette smoking. Various cohort and case control studies demonstrated that smoking confers relative risk for developing.

Rheumatoid arthritis of 1.5–3.5. Women who smoke cigarettes have nearly 2.5 times greater risk of Rheumatoid arthritis, risk that persists even 15 years after smoking cessation. Twin who smoke will have significantly higher risk for Rheumatoid arthritis than his or her monozygotic co-twin. Interestingly risk from smoking is almost exclusively related to Rheumatoid Factor and anti-CCP antibody-positive disease. It been shown that smoking cessation, while having many health benefits, doesn't improves disease activity.

Researchers began to aggressively search an infectious cause for Rheumatoid arthritis after discovery in 1931 that sera from patients with this disease could agglutinate strains of streptococci. Viruses such as Epstein-Barr virus (EBV) have garnered most interest over past 30 years given their ubiquity, ability to persist many years in the host, and frequent association with arthritic complaints.

Titers of IgG antibodies against EBV antigens in the blood and saliva are significantly higher in patients with Rheumatoid arthritis than

general population. EBV DNA is also been found in synovial fluids and cells of Rheumatoid arthritis patients. The evidence for these links is largely circumstantial, it has not been possible to directly implicate infection as causative factor in Rheumatoid arthritis.

Rheumatoid arthritis affects synovial tissue, underlying cartilage and bone. Synovial membrane, which covers most articular surfaces, tendon sheaths and bursae, normally is a thin layer of connective tissue. Synovial membrane consists primarily of two cell types

1: Type A synoviocytes (macrophage-derived)

2: Type B synoviocytes (fibroblast-derived)

The synovial fibroblasts form the most abundant and produce structural components of joints, including collagen, fibronectin, laminin, and other extracellular constituents of synovial matrix. Pathologic hallmarks of Rheumatoid arthritis are synovial inflammation and proliferation, focal bone erosions, and thinning of articular cartilage.

Chronic inflammation leads on to synovial lining hyperplasia and formation of pannus, a thickened cellular membrane contains fibroblast-like synoviocytes and granulation-reactive fibrovascular tissue that invades underlying cartilage and bone. The inflammatory infiltrate is

made of not less than six cell types: T -cells, B- cells, plasma cells, dendritic cells, mast cells, and granulocytes. T-cells comprise 30–50% of the infiltrates. The topographical organization of these cells is complex and vary among individuals with Rheumatoid arthritis.

Structural damage to the mineralized cartilage and subchondral bone is mediated by osteoclast. Osteoclasts are multinucleated giant cells that are identified by the expression of CD68, tartrate resistant acid phosphatase, cathepsin K, and calcitonin receptor. They appear at pannus-bone interface where it eventually form resorption lacunae. These kind of lesions typically localize where synovial membrane inserts into periosteal surface at the edges of bones close to the rim of articular cartilage and at the attachment sites of ligaments and tendon sheaths. This most likely explains why bone erosions usually develop at radial sites of the MCP joints juxtaposed to insertion sites of the tendons, collateral ligaments and synovial membrane. Another form which leads to bone loss is periarticular osteopenia that occurs in joints with active inflammation. In recent years, concept of joint pathology in Rheumatoid arthritis has been extended to include the bone marrow cavity. Generalized osteoporosis, which results in the thinning of trabecular bone throughout the body, it’s a third form of bone loss found in patients with Rheumatoid arthritis .

PATHOGENESIS

Pathogenic mechanisms of synovial inflammation are likely to result from complex interplay of genetic ,environmental, and immunologic factors that produces dysregulation of immune system and breakdown in self-tolerance. What triggers these initiating events and genetic , environmental factors that disrupt the immune system remains a mystery. But detailed molecular picture is emerging of the mechanisms underlying the chronic inflammatory response and the destruction of the articular cartilage and bone.

Preclinical stage in Rheumatoid arthritis appears to be characterized by breakdown in self-tolerance. This is supported by the finding that autoantibodies, such as Rheumatoid factor and anti-CCP antibodies, may be found in sera from patients many years before clinical disease is detected. However, the antigenic targets of anti-CCP antibodies and Rheumatoid factor are not restricted to joints , and their role in disease pathogenesis remains speculative. Anti-CCP antibodies are directed against deaminated peptides, that result from posttranslational modification by the enzyme PADI4. It recognize citrulline-containing regions of several different matrix proteins, including filaggrin, keratin, fibrinogen and vimentin, and present at higher levels in the joint fluid

compared to the serum. Other autoantibodies have been found in minority of patients with Rheumatoid arthritis ,but they also occur in other types of arthritis. People who smoke display higher citrullination of proteins in bronchoalveolar fluid than those who do not smoke. It has been speculated that long-term exposure to tobacco smoke might induce citrullination of cellular proteins in lung and stimulate expression of neoepitope capable of inducing self-reactivity, which in turn, leads to formation of immune complexes and joint inflammation. Exposure to silicone dust and mineral oil , has also been linked to an increased risk for anti-CCP antibody-positive Rheumatoid arthritis.

The immune system is alerted by the presence of microbial infections through Toll-like receptors (TLRs). TLR 2,-3,and -4 are abundantly expressed by synovial fibroblasts in early Rheumatoid arthritis . Specific role for TLRs in disease pathogenesis is not been elucidated. Pathogenesis of Rheumatoid arthritis is built upon the concept that self-reactive T cells drive chronic inflammatory response. Self-reactive T-cells might arise in Rheumatoid arthritis from Abnormal central selection due to defects in DNA repair leading to Imbalance of T-cell death and life or defects in cell signalling apparatus lowering threshold for T-cell activation. Clinical diagnosis of Rheumatoid arthritis is largely based on signs and symptoms of chronic inflammatory arthritis,

with laboratory and radiographic results providing supplemental information.

Collaborative effort between American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) revised the 1987 ACR classification criteria for Rheumatoid arthritis in 2010,in an effort to improve early diagnosis with the goal of identifying patients who benefit from early introduction of disease-modifying therapy. Application of newly revised criteria yields a score of 0–10, with a score of ≥ 6 fulfilling the requirements for definite Rheumatoid arthritis. The new classification criteria differs in several ways from older criteria.

The new criteria include positive test for serum anti-CCP antibodies (ACPA--anti-citrullinated peptide antibodies) as an item, which carries greater specificity for diagnosis of Rheumatoid arthritis than positive test for Rheumatoid factor.

The newer classification criteria do not take into account whether the patient has rheumatoid nodules or radiographic joint damage because the findings occur rarely in early Rheumatoid arthritis.

It is important to emphasize, the new 2010 ACR-EULAR criteria are “classification criteria” as opposed to “diagnostic criteria” and serve

to distinguish patients at the onset of disease who have high likelihood of evolution to chronic disease with persistent synovitis and joint damage. The presence of radiographic joint erosions or subcutaneous nodules may inform the diagnosis in later stages of disease.

1987-REVISED CLASSIFICATION CRITERIA[11]

1. Morning stiffness in and around joints, atleast 1 hour before maximal Improvement.

2. Arthritis of 3 or more joint areas.

3. Symmetric arthritis

4. Arthritis of Hand joints (wrist, MCPs, PIPs)

5. Rheumatoid nodules

6. Rheumatoid Factor

7. Radiographic changes in hand and wrist joints.

Requirements: $\geq$ of the above 7 criteria. Criteria 1-4 must be present for atleast 6 weeks.

JOINT INVOLVEMENT	1-Large joint (shoulder, elbow, hip, knee, ankle)	SCORE 0
	2-10 large joints	1
	1-3 small joints (MCP,PIP, Thumb IP, MTP, wrist)	2
	4-10 small joints	3
	>10 joints (atleast 1 small joint)	5
SEROLOGY	Negative RF and negative Anti-CCP	0
	Low positive RF or low positive anti-CCP antibodies (≤ 3 times ULN)	2
	High positive RF or high positive anti-CCP antibodies (>3 times ULN)	3
ACUTE PHASE REACTANTS	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
DURATION OF SYMPTOMS	<6 weeks	0
	≥ 6 weeks	1

CLASSIFICATION CRITERIA FOR RHEUMATOID ARTHRITIS

Note: These criteria are aimed at classification of newly presenting patients who have at least one joint with definite clinical synovitis that is not better explained by another disease. A score of ≥6 fulfills requirements for definite RA.

DIAGNOSTIC MARKERS

Patients with systemic inflammatory diseases such as Rheumatoid arthritis will most often present with elevated nonspecific inflammatory markers such as ESR or CRP. Detection of serum RF and anti-CCP antibodies is most important in differentiating Rheumatoid arthritis from other polyarticular diseases, although RF lacks diagnostic specificity and may be seen in association with other chronic inflammatory diseases in which arthritis figures in clinical manifestations.

Serum IgM RF has been found in 75–80% of patients with Rheumatoid arthritis, therefore a negative result does not exclude presence of this disease. It is also found in other connective tissue diseases, like primary Sjögren's syndrome, systemic lupus erythematosus and type II mixed essential cryoglobulinemia and also in chronic infections such as subacute bacterial endocarditis and hepatitis B and C.

Serum RF also be detected in 1–5% of the healthy population. The presence of serum anti-CCP antibodies has the same sensitivity as serum RF for diagnosing Rheumatoid arthritis, but its diagnostic specificity approaches 95%, so a positive test for anti-CCP antibodies in the setting of early inflammatory arthritis is useful for distinguishing Rheumatoid arthritis from other forms of arthritis.

Testing for the presence of both RF and anti-CCP, has some incremental effect as some patients with Rheumatoid arthritis are positive for RF but negative for anti-CCP and visa versa.

The presence of RF or anti-CCP antibodies has some prognostic significance, with anti-CCP antibodies showing the most value for predicting worse outcomes.

PERIPHERAL NEUROPATHY:

Patients with connective tissue diseases including Rheumatoid arthritis have different types of peripheral neuropathy like entrapment neuropathy, distal axonal, predominantly sensory polyneuropathy, mononeuropathy or multiple mononeuropathy, as well as fulminant sensorimotor polyneuropathy. When associated with Rheumatoid arthritis, vasculitis explain nerve injuries possibly by immune complex mediated damage to the vessel wall or myelinated nerves in some patients. Other possible causes for neuropathy may be mechanical affection of nerves by swelling of soft tissue, bone erosions and joint deformity or rheumatic nodules . Peripheral neuropathy associated with other connective tissue diseases like systemic lupus erythematosus and Sjogren’s syndrome is more frequently reported than Rheumatoid arthritis.

Peripheral nerves are composed of sensory, motor, and autonomic nerve fibres. Diseases can affect cell body of a neuron or its peripheral processes, the axons or the encasing myelin sheaths. Peripheral nerves are mostly mixed type and contain sensory and motor as well as autonomic fibers.

Nerves are subdivided into three major classes: large myelinated, small myelinated, and small unmyelinated. Motor axons are most often large myelinated fibers that conduct rapidly approximately 50 m/s. Sensory fibers may be any of the three types described above. Large-diameter sensory fibers conduct- proprioception and vibratory sensation to the brain, while the smaller-diameter myelinated and unmyelinated fibers transmit- pain and temperature sensation. Autonomic nerves are small in diameter. Thus, peripheral neuropathies impair sensory, motor or autonomic function, either singly or in combination.

Peripheral neuropathies are classified further into those that primarily affect the cell body (neuronopathy or ganglionopathy), myelin (myelinopathy), and axon (axonopathy). The different classes of peripheral neuropathies have distinct clinical and electrophysiologic features which is of practical significance.

Assessment of peripheral nerve function is important in detecting extraarticular neurological manifestations of Rheumatoid arthritis. Systemic vasculitis in Rheumatoid arthritis has been reported to increase the prevalence of peripheral neuropathy.

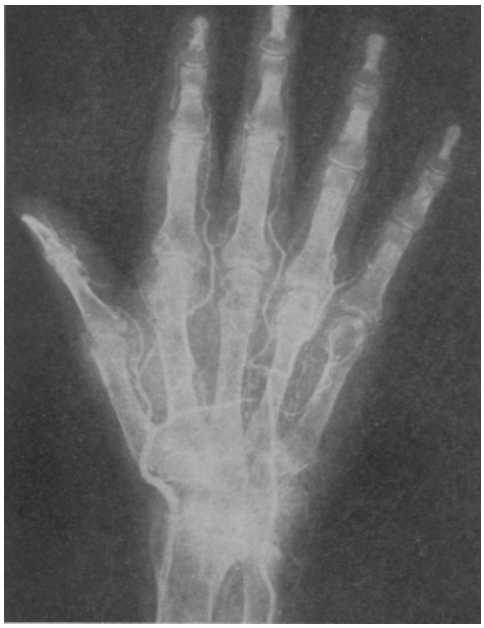
Assessment of amplitude of the motor and sensory nerves reflects both the number of fibres conducting and their degree of synchrony, while distal latency and conduction velocity measures conduction in the fastest myelinated motor nerve fibres. Slowing of conduction velocity reflects segmental myelin loss. Conduction of the proximal segments can be measured using F wave responses. Peripheral neuropathy associated with other connective tissue diseases like, systemic lupus erythematosus and Sjogren's syndrome is more frequently reported than in Rheumatoid arthritis. Peripheral neuropathy manifested as diffuse sensorimotor neuropathy or mononeuritis multiplex occurs in a small subset of patients with RA. The underlying mechanism is small-vessel vasculitis with ischemic neuropathy[9]

In pathology of mononeuropathies, our knowledge is somewhat more complete. Compression of nerve or its roots, local or segmental ischemia, stretch, and laceration of nerves are understandable mechanisms and their pathologic changes can be reproduced

experimentally. Tumor infiltration and importantly, vasculitis with ischemic infarction of nerve account for a proportion of cases of mononeuropathies.

Polyneuropathies are the result of axonal damage are characterized foremost by a relatively symmetric distribution of weakness that is, distal because the pathologic changes begin in the far distal parts of the largest and longest nerves and advance along the affected fibers toward their nerve cell bodies (dying-back neuropathy or "distal axonopathy")[8]. Muscles of the feet and legs are typically affected earlier and more severely than those of the hands and forearms. In milder forms of disease, only the feet and lower legs are involved. This shows the "length-dependent" pattern that is typical of axonal degeneration. The nutritional, metabolic, and toxic neuropathies assume this predominantly distal "axonal" pattern.

Some 1 to 5 percent of patients with rheumatoid arthritis have vasculitic involvement of one or more nerves at some point of time in their disease course[8], apart from more mundane pressure neuropathies as a result of thickened tendons and destructive joint changes.



BRACHIAL ARTERIOGRAM SHOWING WIDESPREAD OCCLUSION OF DIGITAL VESSELS[10].

The arteritis is of small-vessel fibrinoid type and immune globulins are demonstrable in the walls of blood vessels. Most of the neuropathic patients under our care have had severe rheumatic disease for many years and were strongly seropositive[8]. In addition to neuropathy, such patients often have rheumatoid Nodules, skin vasculitis, weight loss, and fever. The diagnosis of these group of neuropathies depends on the finding of motor, reflex, and sensory changes confined to the territory of a single nerve; of several individual nerves affected in a random manner (mononeuritis or mononeuropathy multiplex); or a plexus of nerves or part of a plexus (plexopathy).

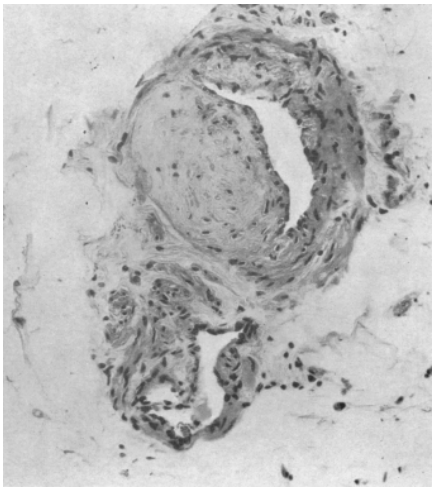
Compression of median nerve at the wrist (carpal tunnel syndrome) is the most common disorder affecting the median nerve and itsthe most frequent nerve entrapment syndrome. The problem arises usually as a result of excessive use of hands and occupational microtrauma. Infiltration of the transverse carpalligament with amyloid (as occurs in multiple myeloma and amyloidosis) or thickening of connective tissue in rheumatoid arthritis leads on to clinical features of carpal tunnel syndrome.

According to Kremer and colleagues, it was McArdle, in 1949, who first suggested the cause of this syndrome was compression of median nerve at the wrist and that the symptoms would be relieved by division of flexor retinaculum forming the ventral wall of the carpal tunnel. Dysesthesias and pain in the fingers, referred to for many years as "acroparesthesia" came to be recognized as syndrome of median nerve compression only in early 1950. The syndrome is essentially sensory one. The loss or impairment of superficial sensation affects palmar aspect of the thumb, the index and middle fingers especially the index finger and may or may not split the ring finger. Electrophysiologic testing confirms the diagnosis by demonstrating prolonged sensory conduction across the wrist. Surgical division of the carpal liga-ment with decompression of the nerve is curative but is required only in severe and protracted cases. Most

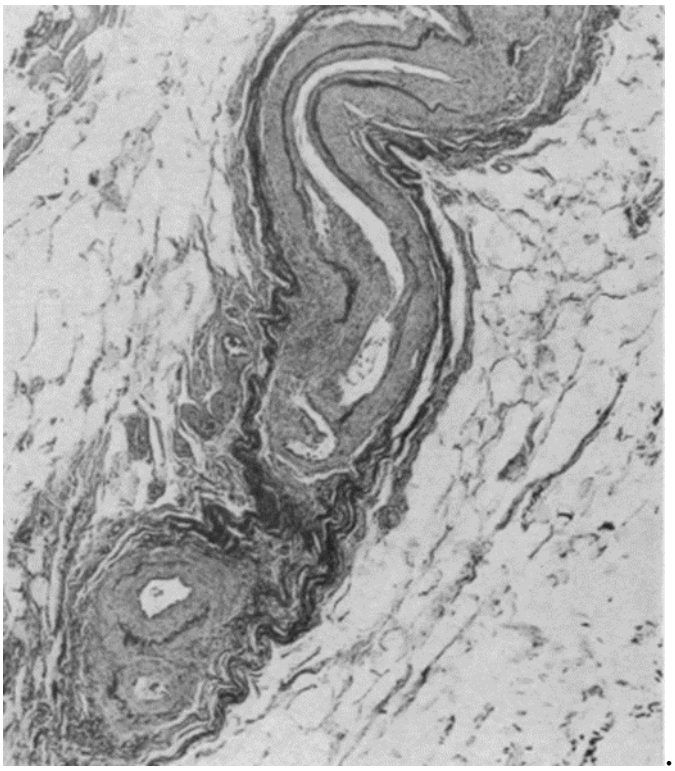
often, splinting and local steroid injections are very satisfactory in the short-term, especially if the symptoms are of recent onset.

ENTRAPMENT NEUROPATHY :

Reference has been made in several places in the preceding pages about the most frequently encountered entrapment neuropathies. A nerve passing through the tight canal is trapped and subjected to constant movement or pressure, forces not applicable to nerves elsewhere. The epineurium and perineurium become greatly thickened, strangling the nerve with additional possibility of demyelination



ARTERY WITHIN EPINEURIUM OF RIGHT POSTERIOR TIBIAL NERVE WITH SEGMENTAL DESTRUCTION OF WALL AND FIBROUS INTIMAL THICKENING ENCROACHING ON THE LUMEN

 .

Function is gradually impaired with sensory more than motor, and the symptoms fluctuate with activity and rest. The most frequently compressed nerves are median, ulnar, peroneal, tibial, and plantar in approximately that order. It is well to keep in mind that the systemic processes that enhance pressure palsies by infiltration of the nerve or surrounding tissues. Peripheral entrapment neuropathy, which tends to occur when the nerve is compressed by inflamed synovium against a fixed structure. Atlantoaxial subluxation may cause neurologic impairment in patients with Rheumatoid arthritis[9].

As with other extraarticular complications of Rheumatoid arthritis, earlier and more aggressive treatment of Rheumatoid arthritis has resulted

in decreased prevalence of neurologic complications that may be a result of disease activity. Mononeuritis multiplex is the least frequent neuropathies encountered in RA patients than other neuropathies and it is associated with high disease activity and requires immunosuppressive therapy. But the distal axonal sensory or sensorimotor polyneuropathies have been reported more frequently (up to 10% of RA patients) and are associated with lower disease activity and have an excellent prognosis. It can be managed symptomatically.

Compressive neuropathies are the most common neuropathies and they are described in 20% to 70% of patients. Carpal tunnel syndrome --affecting the median nerve and tarsal tunnel syndrome --affecting the posterior tibial nerve are the most common compressive neuropathies, respectively presenting as numbness in the first three digits of hands and feet. Compression neuropathies results from synovial or bursa inflammation or can occur due to joint deformities or posttraumatic fibrosis not stemming from active disease. Conservative strategies including splinting and tendon sheath injections, are tried before surgical release. In contrast to compressive neuropathies, inflammatory demyelinating neuropathies have been temporally associated with the use of tumor necrosis factor (TNF) inhibitors [9]. Despite the rarity of these inflammatory demyelinating neuropathies described in lesser than 100

RA patients treated with TNF inhibitors, such demyelinating neuropathies are otherwise not seen in RA patients, and therefore an etiopathogenic relationship is suggested. Some patients show improvement or stabilization when the offending TNF inhibitors are withdrawn, other patients require treatment with intravenous immunoglobulin or other therapies used for the treatment of primary demyelinating neuropathies.[9]

DRUGS CAUSING PERIPHERAL NEUROPATHY:

LEUFLONAMIDE

Leflunomide side effects include headache, dizziness, and paresthesia. The central nervous system adverse effects are usually mild to moderate and are not commonly a cause for stopping the drug. Case reports of peripheral neuropathy associated with leflunomide have been reviewed. Of 80 reported cases, symptoms began after a mean of 6 months of treatment. Electrodiagnosis was consistent with distal axonal, sensory, or sensorimotor polyneuropathy in most patients. Patients withdrawing from leflunomide within 30 days were more likely to show improvement. In a study to monitor potential clinical neurotoxicity in 113 patients treated with leflunomide, eight incident cases of peripheral neuropathy and two cases of worsening of preexisting neuropathy were diagnosed by nerve conduction studies .Compared with patients not

receiving leflunomide, patients receiving leflunomide were older (mean age, 69), most often diabetic (30%), and most often treated with potentially neurotoxic drugs (20%). Atleast one risk factor was found in about 50% of patients with neuropathy (positive predictive value- 56%; negative predictive value- 96%). The results suggest the need for careful monitoring of patient's neurologic status during leflunomide treatment. Patients became stable symptomatically and electrophysiologically on cessation of the drug.

PYRIDOXINE (VITAMIN B6) TOXICITY:

Pyridoxine is an essential vitamin that serves as a coenzyme for transamination and decarboxylation process. But, at high doses (116 mg/d), patients may develop severe sensory neuropathy with dysesthesias and sensory ataxia. Nerve conduction study reveal absent or markedly reduced Sensory nerve action potential amplitudes with relatively preserved compound motor action potentials. Nerve biopsy reveals axonal loss of fiber of all diameters.

ISONIAZID :

Most common side effects of isoniazid (INH) is peripheral neuropathy. Standard doses of INH (3–5 mg/kg per day) are associated with 2% incidence of neuropathy, whereas incidence of neuropathy

increases to at least 17% of patients taking excess of 6 mg/kg per day. Elderly, malnourished, and “slow acetylators” are at increased risk for developing peripheral neuropathy. INH inhibits pyridoxal phosphokinase, resulting in pyridoxine deficiency and leading on to neuropathy. Prophylactic administration of pyridoxine 100 mg/d can prevent the development of neuropathy.

ANTIRETROVIRAL AGENTS

The nucleoside analogues like zalcitabine (dideoxycytidine or ddC), didanosine (dideoxyinosine or ddI), stavudine (d4T), lamivudine (3TC), and antiretroviral nucleoside reverse transcriptase inhibitor (NRTI) are used to treat HIV infection. The dose-limiting side effects of these medications is predominantly sensory, length-dependent, symmetrically painful neuropathy. Zalcitabine (ddC), at doses greater than 0.18 mg/kg per day, is associated with sub acute onset of severe burning and lancinating pains in feet and hands. NCS revealed decreased amplitudes of the sensory nerve action potentials with normal motor conduction studies. Nucleoside analogues inhibit mitochondrial DNA polymerase, which is the suspected pathogenic basis for the neuropathy. Because of “coasting effect,” patients continue to worsen even 2–3 weeks after stopping the medication. Following dose reduction, improvement in the neuropathy is seen in most patients several months later. NCS reveals

absent or markedly reduced Sensory nerve action potential amplitudes with relatively preserved CMAPs.

NUTRITIONAL NEUROPATHIES COBALAMIN (VITAMIN B12):

Pernicious anemiais most commonly caused by the deficiency of cobalamin. Other causes includes dietary avoidance, gastrectomy, gastric bypass surgery, inflammatory bowel disease, pancreatic insufficiency, bacterial overgrowth, and possibly histamine-2 blockers and proton pump inhibitors. An under appreciated cause of cobalamin deficiency is food-cobalamin malabsorption which typically occurs in older individuals and results from an inability to adequately absorb cobalamin from food protein. The use of nitrous oxide as anesthetic agent or as recreational drug can produce acute cobalamin deficiency neuropathy and subacute combined degeneration. Preferentially large-fiber sensory loss affecting proprioception and vibration with sparing of small-fiber modalities is present. Diagnosis is confirmed by reduced serum cobalamin levels. Antibodies to intrinsic factor is present in approximately 60%, and antiparietal cell antibodies in about 90%, of individuals with pernicious anemia.

Cobalamin deficiency is treated with various regimens of cobalamin. One regimen consists of 1000 μg of cyanocobalamin IM weekly for 1 month and monthly thereafter. Patients with food cobalamin malabsorption can absorb free cobalamin and therefore can be treated with oral cobalamin supplementation. An oral cobalamin dose of 1000 μg per day should be sufficient. Treatment for cobalamin deficiency usually does not reverse the clinical manifestations completely and at least 50% of patients exhibit some permanent neurologic deficit.

THIAMINE DEFICIENCY

Thiamine deficiency now most often seen as a consequence of chronic alcohol abuse, recurrent vomiting and total parenteral nutrition leading to peripheral neuropathy. Beriberi means “I can’t, I can’t” in Singhalese. Dry beriberi refers to the neuropathic symptoms. Wetberiberi is used when cardiac manifestations predominate in reference to edema. Symptoms of neuropathy follow prolonged deficiency and these begin with mild sensory loss and burning dysesthesias in the toes and feet and aching and cramping in the lower legs. Patients develop features of a nonspecific generalized polyneuropathy, with distal sensory loss in the feet and hands. Thiamine is given intravenously or intramuscularly at a dose of 100 mg/d. Neurologic improvement is usually more variable and less dramatic.

VITAMIN E DEFICIENCY :

Clinical features may not appear until many years after the onset of deficiency. Symptoms onset tends to be insidious, and progression is slow. Main clinical features are spinocerebellar ataxia and polyneuropathy. Vitamin E deficiency may present as an isolated polyneuropathy, but it's very rare. Diagnosis is made by measuring alpha-tocopherol levels in the serum. Electrodiagnosis shows features of axonal neuropathy. Treatment is with replacement of oral vitamin E 1500–6000 IU/d in divided doses.

VITAMIN B6 DEFICIENCY :

Vitamin B6 or pyridoxine, can produce neuropathic manifestations from both deficiency and toxicity as discussed above. Vitamin B6 deficiency is commonly seen in patients treated with isoniazid or hydralazine. The polyneuropathy of vitamin B6 is nonspecific and manifesting as generalized axonal sensorimotor polyneuropathy. Vitamin B6 deficiency is detected by direct assay. Vitamin B6 supplementation with 50–100 mg/d is suggested for patients being treated with isoniazid or hydralazine and also for replacement in cases of nutritional deficiency.

NIACIN DEFICIENCY:

Pellagra is produced by deficiency of niacin. Pellagra may be seen in alcoholics. Neurologic manifestations are variable; abnormalities can develop in the brain and spinal cord as well as peripheral nerves. When peripheral nerves are involved, the neuropathy is usually mild and resembles that of beriberi.

MATERIALS AND METHODS

STUDY DESIGN : Cross sectional study

STUDY PERIOD : 8 months

STUDY AREA **:** Govt. Kilpauk Medical College, Chennai.

STUDY POPULATION:

Rheumatoid arthritis patients in OPD and admitted in Govt. Kilpauk Medical College & Hospital, Chennai.

SAMPLE SIZE : 60

SOURCE OF DATA : The present study will be conducted in the Department of Medicine and Rheumatology, Govt. KMCH, Chennai.

Rheumatoid arthritis patients attending OPD or admitted to the hospital will be taken for the study.

METHOD OF COLLECTION OF DATA:

Definition of study

Study subjects : Sixty patients attending OPD or admitted to the hospital with diagnosis of rheumatoid arthritis, with or without clinical evidence of neuropathy, satisfying the inclusion and exclusion criteria will be taken for the study.

Inclusion criteria

Patients already diagnosed as Rheumatoid Arthritis as Per 1987 Revised ACR Classification Criteria and correlated with laboratory data.

Exclusion criteria:

1. Diabetes mellitus
2. Renal failure
3. Chronic alcoholism
4. Retro viral disease
5. Liver disease
6. Thyroid disease
7. Pregnancy
8. Drugs

STUDY METHODS: The present study is a clinical study.

1. The study period is from date of ethical clearance to 8 months.
2. A total of 60 rheumaroid arthritis patients are taken for study.
3. All these patients are evaluated thoroughly by clinical, laboratory methods. All patients will undergo nerve conduction study of median nerve, ulnar nerve, common peroneal nerve and sural nerves.

4. Compound muscle action potential, sensory nerve action potential, distal and proximal latencies and nerve conduction velocities are studied.

INVESTIGATIONS NEEDED FOR THE STUDY

- Hb%, TC, DC, ESR, platelet count.
- CRP, RF/Anti CCP Factor.

Electrophysiological studies

Nerve conduction studies were performed using the Medelec-Synergy EMG instrument . The skin temperature kept between 31and 32 degree Celsius. Nerve velocity increases by 2.4m/s per degree from 29 to 38°C skin temperature[12-18]

Median, ulnar, peroneal, and posterior tibial motor nerve conduction studies (NCSs), including F-waves, were performed on both sides.

Median, ulnar, superficial peroneal, and sural sensory NCSs were performed on both sides. Latency of the H-wave was measured bilaterally. Motor nerve conduction was performed using the bellytendon method. Sensory nerve conduction was studied antidromically.

All amplitudes were determined based on the base-to-peak value;. The conduction velocity of each nerve was measured. Findings were compared with the reference values used in our center .

Polyneuropathy was diagnosed when at least three Abnormal parameters were present. When the median CMAP latency was greater than 4.2 ms or the median SNAP was greater than 3.6 ms, we used the ‘mid-palm’ technique to diagnose carpal tunnel syndrome (CTS). The median nerve was then stimulated at the palm at a 14-cm distance (wrist). Presence of CTS was considered when the ratio of palm to wrist latency was lower than 50%. All of the patients gave informed consent, and the study was approved by the ethics committee of our university. The clinical and laboratory findings were analysed.

NERVE	**LATENCY (ms)**	**AMPLITUDE**	**CONDUCTION VELOCITY(m/s)**
MOTOR			
Median	<4.2	>5	>50
Ulnar	<4.2	>5	>50
Deep Peroneal	<6.2	>2	>40
Posterior Tibial	<5	>5	>40

NERVE	LATENCY (ms)	AMPLITUDE	CONDUCTION VELOCITY(m/s)
F- WAVE			
Median	<30	-	-
Ulnar	<30	-	-
Deep Peroneal	<50	-	-
Posterior Tibial	<50	-	-
SENSORY			
Median	<3.6	>20	-
Ulnar	<3.6	>10	-
Superficial Peroneal	<4.2	>5	-
Sural	<3.9	>10	-
H-REFLEX	<32	-	-

Reference values for nerve conduction study used in the present study

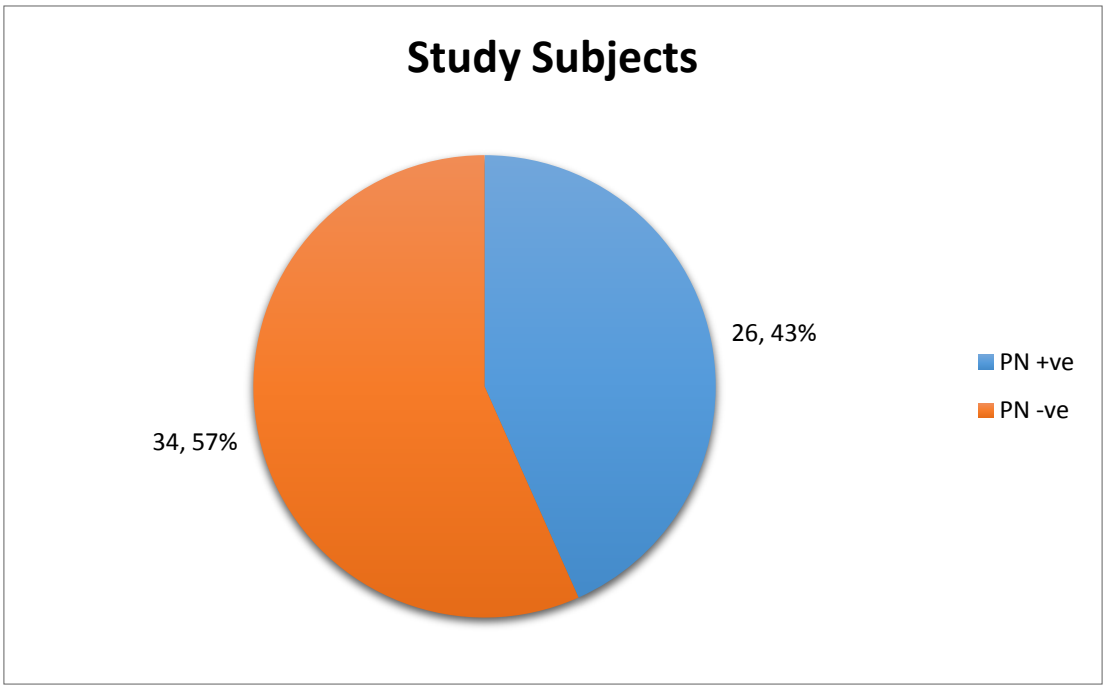
1. Peak latencies of all sensory nerves
2. Onset latencies of all motor nerves.
3. Amplitudes are measured in millivolt (mV, motor) and in microvolt (μV, sensory).

Statistical Analysis:

Statistical analysis done by Fishers exact test, Unpaired-t test. Multivariate analysis of factors determined by logistic regression. P value <0.05 is taken as significant correlation with confidence interval of 95%.

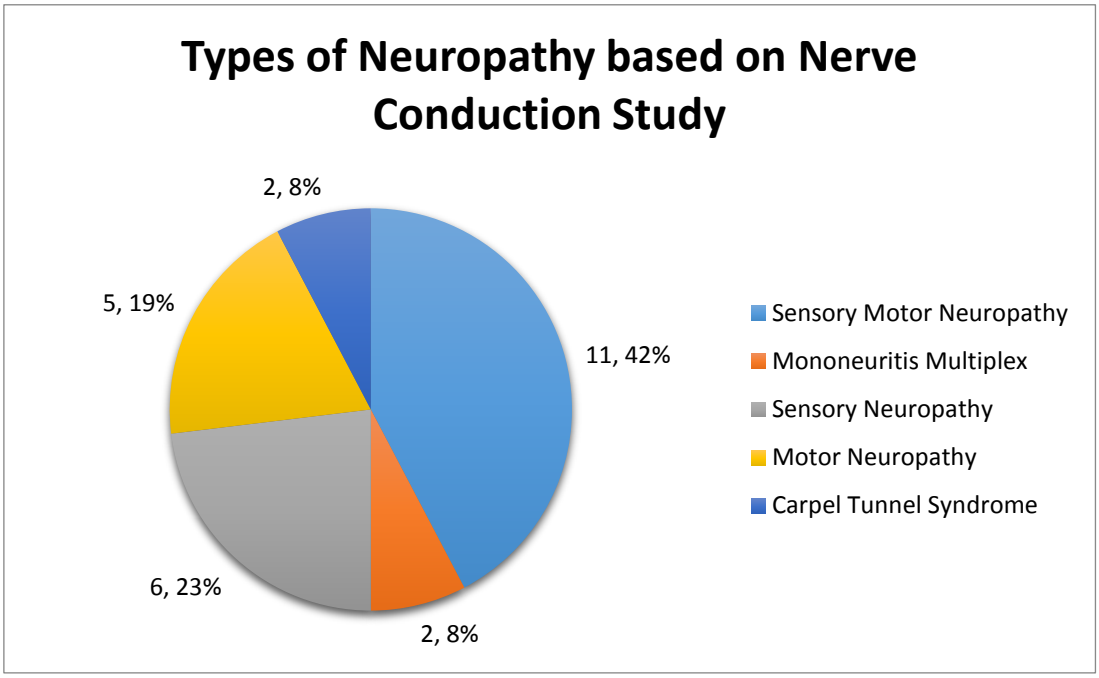
OBSERVATION AND RESULTS

Study Subjects



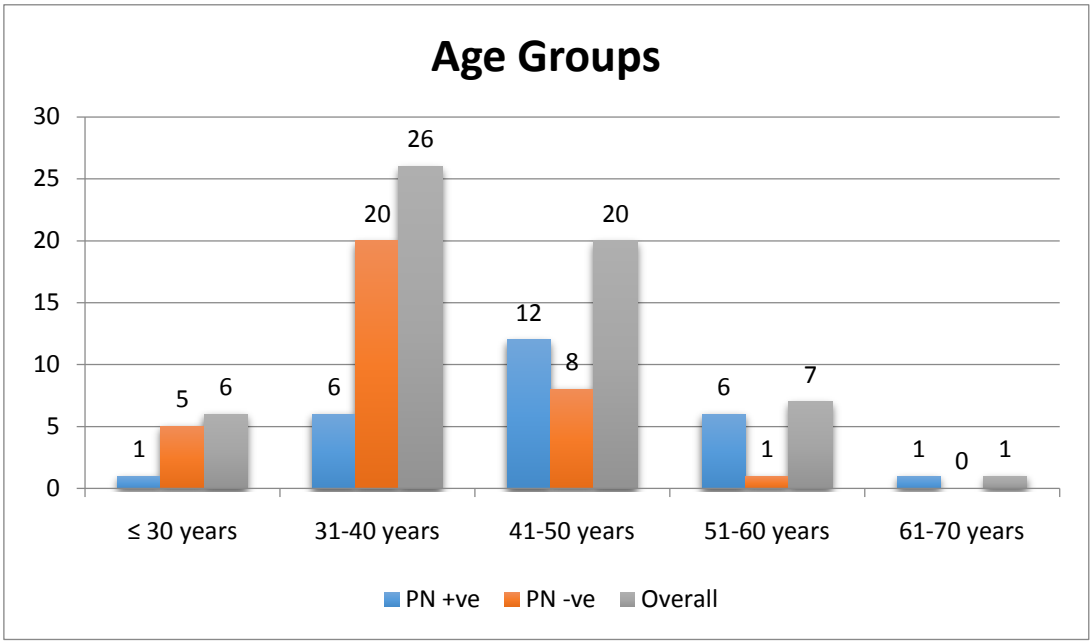
Study Subjects	Number	Percentage
PN +ve	26	43.33
PN -ve	34	56.67
Total	60	100.00

Types of Neuropathy based on Nerve Conduction Study



Types of Neuropathy based on Nerve Conduction Study	Number	Percentage
Sensory Motor Neuropathy	11	42.31
Mononeuritis Multiplex	2	7.69
Sensory Neuropathy	6	23.08
Motor Neuropathy	5	19.23
Carpel Tunnel Syndrome	2	7.69
Total	26	100.00

Age



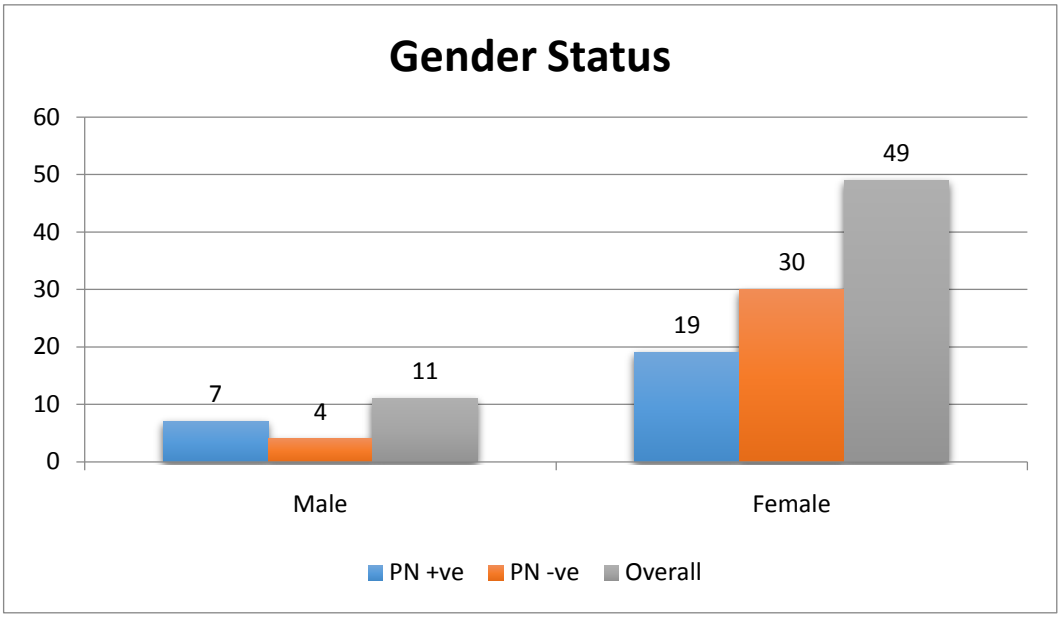
Age Groups	PN +ve	%	PN -ve	%	Overall	%
≤ 30 years	1	3.85	5	14.71	6	10.00
31-40 years	6	23.08	20	58.82	26	43.33
41-50 years	12	46.15	8	23.53	20	33.33
51-60 years	6	23.08	1	2.94	7	11.67
61-70 years	1	3.85	0	0.00	1	1.67
Total	26	100.00	34	100.00	60	100.00

Age Distribution	PN +ve	PN -ve	Overall
Mean	45.85	36.65	40.63
SD	8.99	6.87	9.04
P value Unpaired t Test		<0.0001	

It is evident from the age distribution table that most of the PN +ve group subjects were in 41-50 years age group (46.15%) with a mean age of 45.85 years. Similarly in PN -ve group majority were in 31-40 years age group (58.82%) with a mean age of 36.65 years. (p= <0.0001). The data subjected to unpaired t test reveals the existence of statistically significant association between age distribution and intervention groups ($p < 0.05$)

In our study age distribution between the PN +ve group and PN –ve group was meaningfully significant. This is evident by the increased mean age in PN +ve group compared to PN –ve group (mean difference of 9.20 years, 20% higher). Age is a known risk factor for polyneuropathy [19]

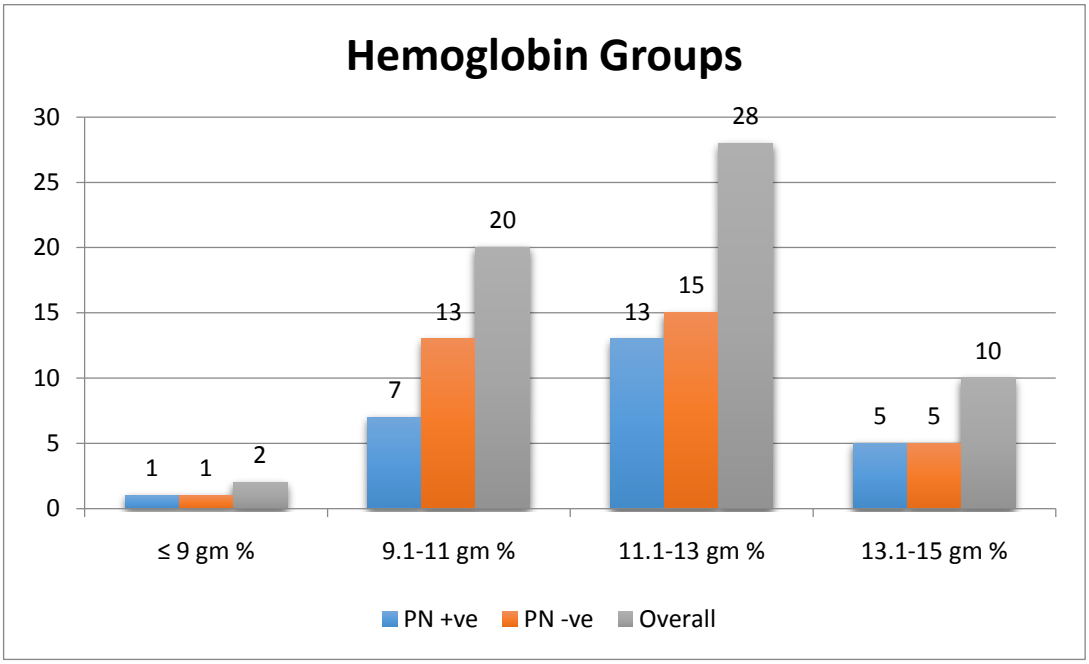
Gender



Gender Status	PN +ve	%	PN - ve	%	Overall	%
Male	7	26.92	4	11.76	11	18.33
Female	19	73.08	30	88.24	49	81.67
Total	26	100.00	34	100.00	60	100.00
P value Fishers Exact Test				0.1329		

It is evident from the gender status table that most of the PN +ve group subjects were females (73.08%) and in PN -ve group majority too were females (88.24%) (p= 0.1329). The data subjected to fishers exact test reveals the existence of statistically insignificant association between gender status and intervention groups (p >0.05)

Hb

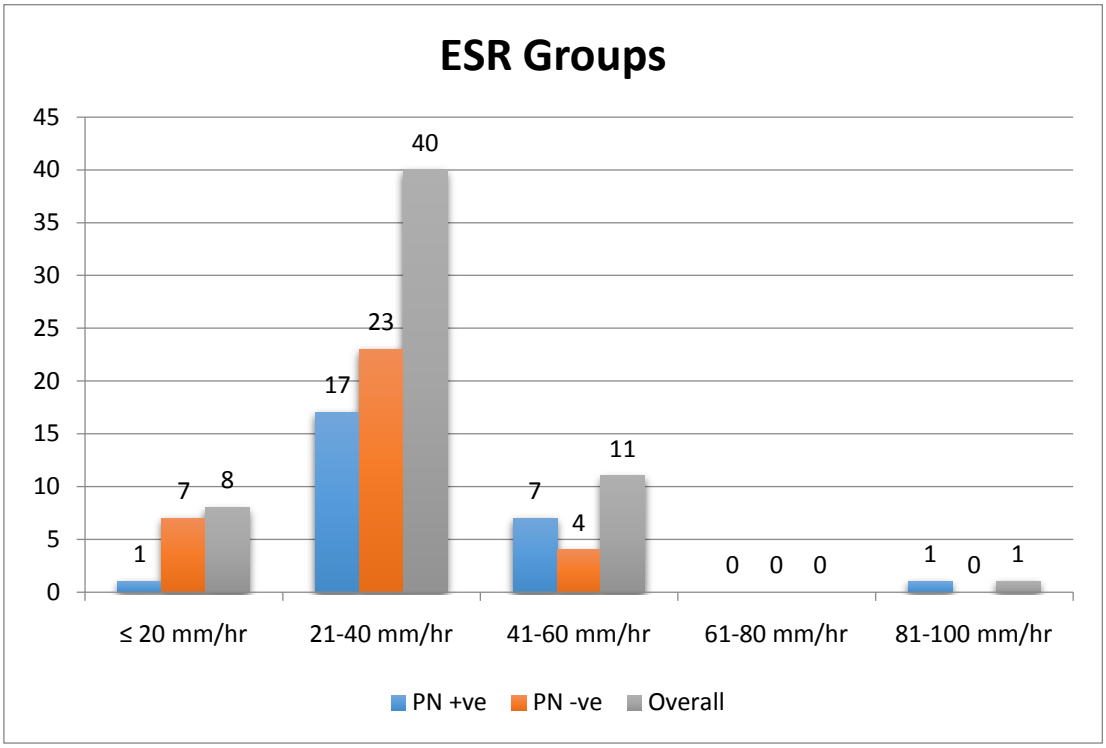


Hemoglobin Groups	PN +ve	%	PN - ve	%	Overall	%
≤ 9 gm %	1	3.85	1	2.94	2	3.33
9.1-11 gm %	7	26.92	13	38.24	20	33.33
11.1-13 gm %	13	50.00	15	44.12	28	46.67
13.1-15 gm %	5	19.23	5	14.71	10	16.67
Total	26	100.00	34	100.00	60	100.00

Hemoglobin Distribution	**PN +ve**	**PN -ve**	**Overall**
Mean	11.68	11.59	11.63
SD	1.53	1.44	1.47
P value Unpaired t Test		0.8231	

It is evident from the hemoglobin distribution table that most of the PN +ve group subjects were in 11.1-13 gm % group (50%) with a mean Hb of 11.68 gm%. Similarly in PN -ve group majority were in 11.1-13 gm % group (44.12%) with a mean Hb of 11.59 gm% (p= 0.8231). The data subjected to unpaired t test reveals the existence of statistically insignificant association between age distribution and intervention groups ($p > 0.05$)

ESR



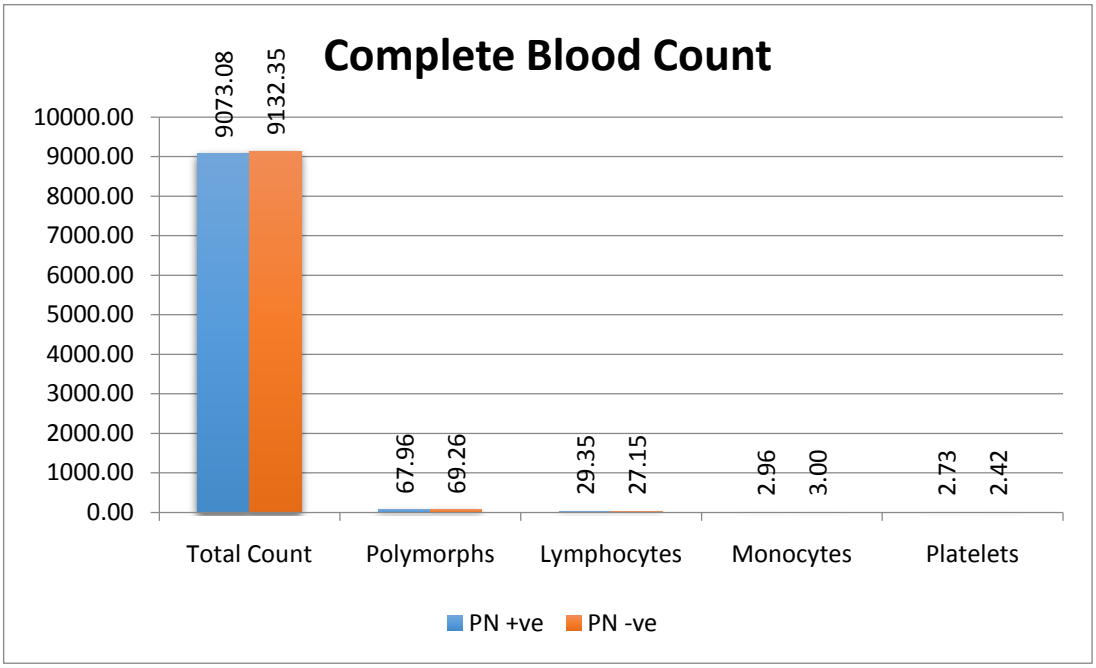
ESR Groups	PN +ve	%	PN - ve	%	Overall	%
≤ 20 mm/hr	1	3.85	7	20.59	8	13.33
21-40 mm/hr	17	65.38	23	67.65	40	66.67
41-60 mm/hr	7	26.92	4	11.76	11	18.33
61-80 mm/hr	0	0.00	0	0.00	0	0.00
81-100 mm/hr	1	3.85	0	0.00	1	1.67
Total	26	100.00	34	100.00	60	100.00

ESR Distribution	PN +ve	PN -ve	Overall
Mean	39.77	28.97	33.65
SD	14.48	8.63	12.63
P value Unpaired t Test		0.0007	

It is evident from the ESR distribution table that most of the PN +ve group subjects were in 21-40 mm/hr group (65.38%) with a mean ESR of 39.77 mm/hr. Similarly in PN -ve group majority were in 21-40 mm/hr group (67.65%) with a mean ESR of 39.77 mm/hr. (p= 0.0007). The data subjected to unpaired t test reveals the existence of statistically significant association between ESR distribution and intervention groups ($p < 0.05$)

In our study ESR distribution between the PN +ve group and PN –ve group was meaningfully significant. This is evident by the increased mean ESR in PN +ve group compared to PN –ve group (mean difference of 10.80 mm/hr, 27% higher).

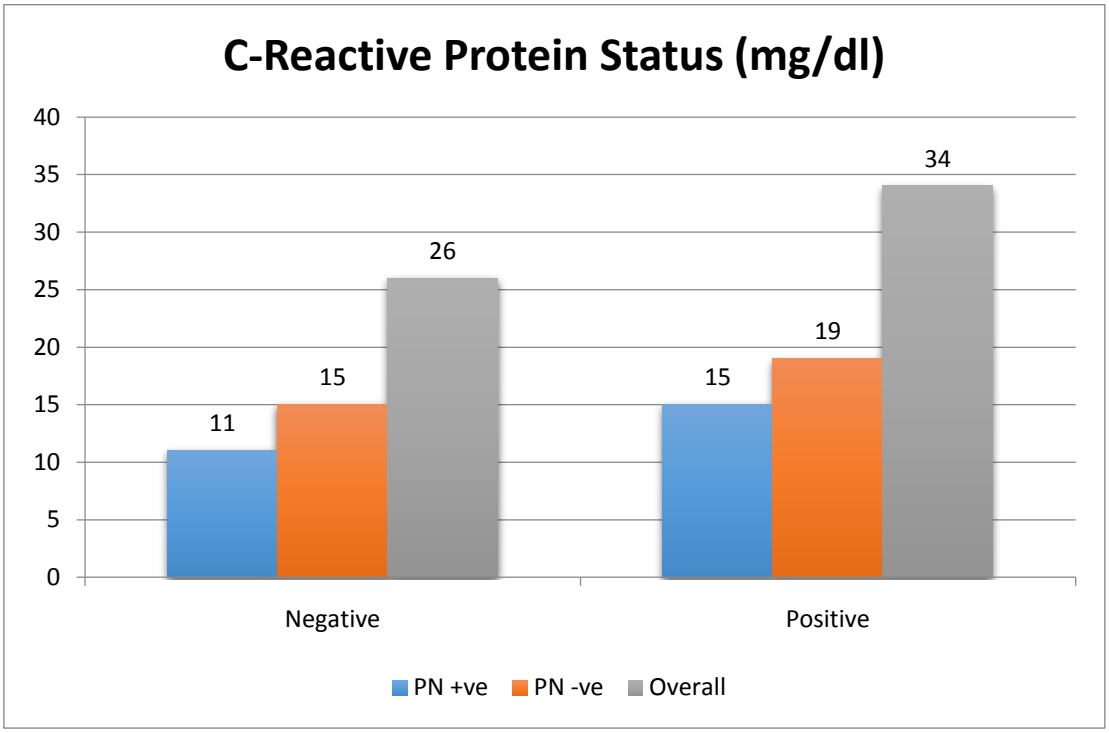
CBC



Complete Blood Count		Total Count	Polymorphs	Lymphocytes	Monocytes	Platelets
PN +ve	Mean	9073.08	67.96	29.35	2.96	2.73
	SD	1708.59	5.64	5.95	1.84	0.77
PN -ve	Mean	9132.35	69.26	27.15	3.00	2.42
	SD	2249.00	7.97	7.34	2.89	0.82
P value Unpaired t Test		0.9113	0.4814	0.2178	0.9530	0.1421

It is evident from the complete blood count distribution table that the mean total count, polymorphs count, lymphocytes count, monocytes count and platelets count were 9073.08, 67.96, 29.35, 2.96 and 2.73. Similarly in PN -ve group it was 9132.35, 69.26, 27.15, 3.00 and 2.42. ($p= 0.9113$, 0.4818, 0.2178, 0.9530 and 0.1421). The data subjected to unpaired t test reveals the existence of statistically insignificant association between complete blood count distribution and intervention groups ($p > 0.05$)

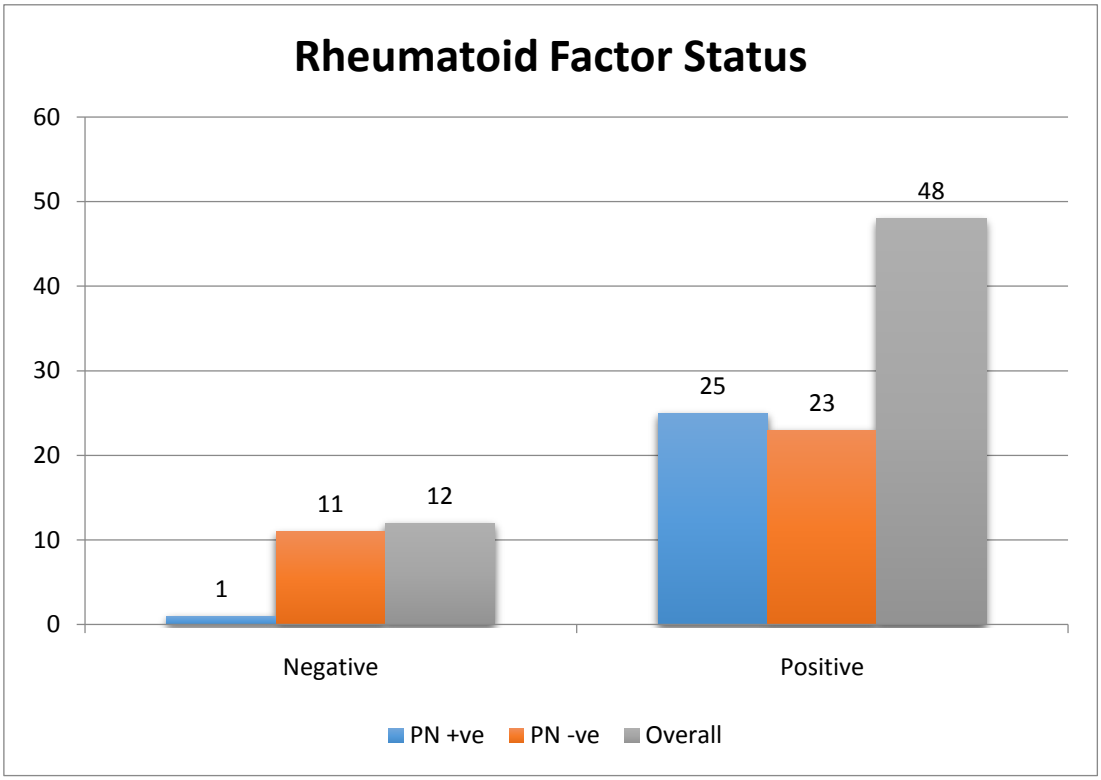
CRP



C-Reactive Protein Status (mg/dl)	PN +ve	%	PN -ve	%	Over all	%
Negative	11	42.31	15	44.12	26	43.33
Positive	15	57.69	19	55.88	34	56.67
Total	26	100.00	34	100.00	60	100.00
P value Fishers Exact Test				0.8891		

It is evident from the C reactive protein status table that most of the PN +ve group subjects were CRP negative (57.69%) and in PN -ve group majority too were CRP negative (55.88%) (p= 0.8891). The data subjected to fishers exact test reveals the existence of statistically insignificant association between C reactive protein status and intervention groups (p >0.05)

RF

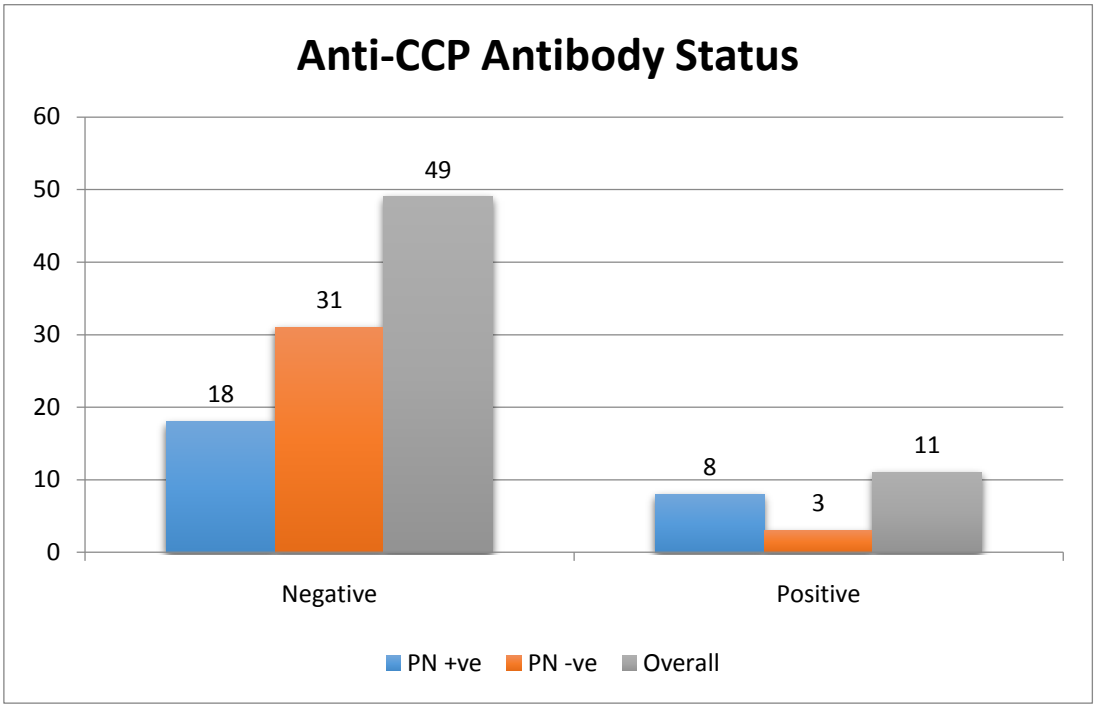


Rheumatoid Factor Status	PN +ve	%	PN -ve	%	Overall	%
Negative	1	3.85	11	32.35	12	20.00
Positive	25	96.15	23	67.65	48	80.00
Total	26	100.00	34	100.00	60	100.00
P value Fishers Exact Test					0.0064	

It is evident from the rheumatoid factor status table that most of the PN +ve group subjects were RA factor positive (96.15%) and in PN -ve group majority too were RA factor positive (67.65%) (p= 0.8891). The data subjected to fishers exact test reveals the existence of statistically significant association between rheumatoid factor status and intervention groups ($p < 0.05$)

In our study rheumatoid factor status between the PN +ve group and PN –ve group was meaningfully significant. This is evident by the increased incidence of RA factor positivity in PN +ve group compared to PN –ve group (percentage difference of 28.51, 30% higher).

Anti-CCP Antibody

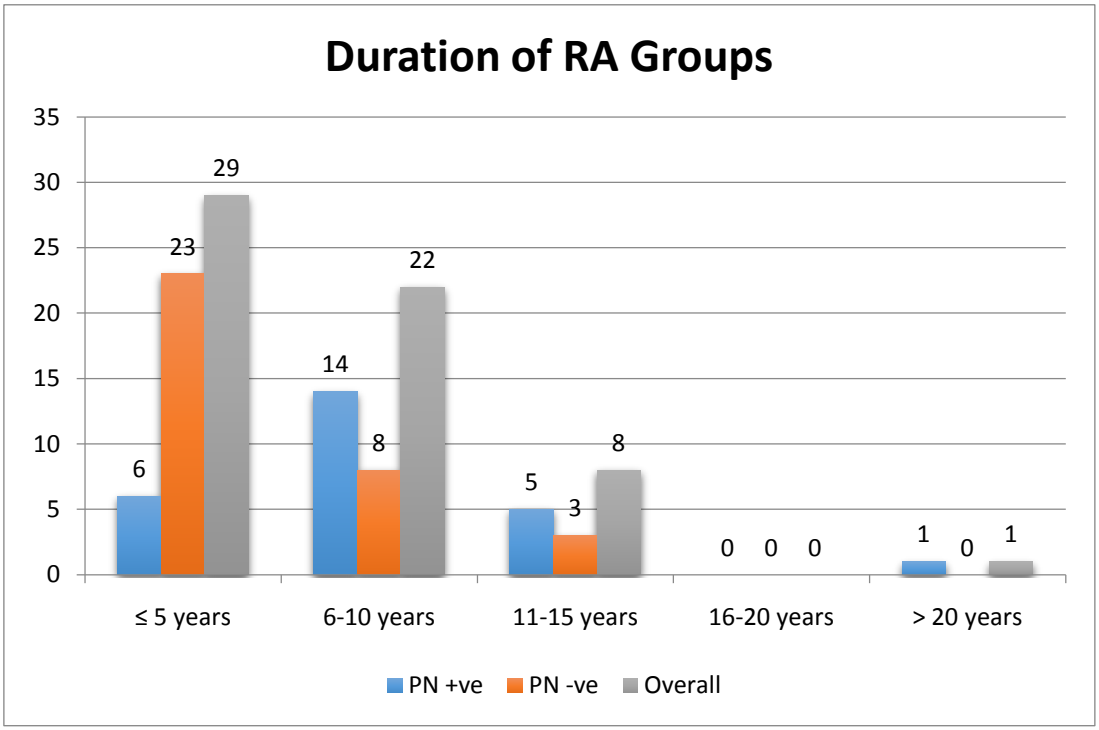


Anti-CCP Antibody Status	PN +ve	%	PN -ve	%	Overall	%
Negative	18	69.23	31	91.18	49	81.67
Positive	8	30.77	3	8.82	11	18.33
Total	26	100.00	34	100.00	60	100.00
P value Fishers Exact Test					0.0288	

It is evident from the anti CCP antibody status table that most of the PN +ve group subjects were anti CCP antibody negative (69.23%) and in PN -ve group majority too were anti CCP antibody negative (91.18%) ($p= 0.0288$). The data subjected to fishers exact test reveals the existence of statistically significant association between anti CCP antibody status and intervention groups ($p <0.05$)

In our study anti CCP antibody status between the PN +ve group and PN –ve group was meaningfully significant. This is evident by the increased incidence of anti CCP antibody positivity in PN +ve group compared to PN –ve group (percentage difference of 21.95, 71% higher).

Duration of RA



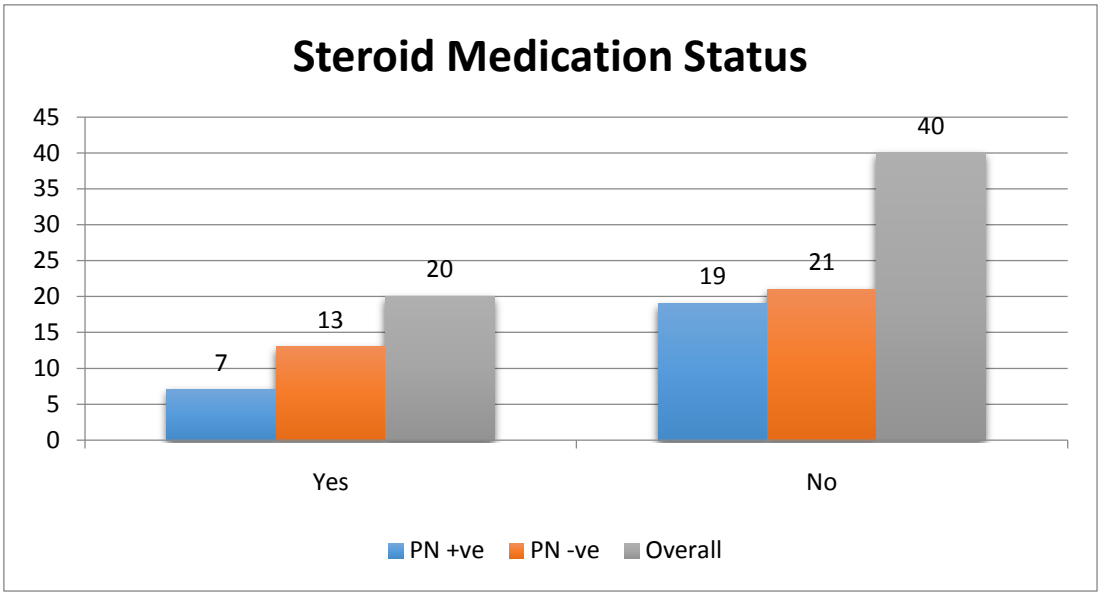
Duration of RA Groups	PN +ve	%	PN - ve	%	Overall	%
≤ 5 years	6	23.08	23	67.65	29	48.33
6-10 years	14	53.85	8	23.53	22	36.67
11-15 years	5	19.23	3	8.82	8	13.33
16-20 years	0	0.00	0	0.00	0	0.00
> 20 years	1	3.85	0	0.00	1	1.67
Total	26	100.00	34	100.00	60	100.00

Duration of RA Distribution	PN +ve	PN –ve	Overall
Mean	8.23	5.06	6.43
SD	3.73	2.84	3.60
P value Unpaired t Test		0.0004	

It is evident from the duration of RA distribution table that most of the PN +ve group subjects were in 6-10 years group (53.85%) with a mean duration of RA of 8.23 years. Similarly in PN -ve group majority were in ≤ 5 years group (67.65%) with a mean duration of RA of 5.06 years (p= 0.0004). The data subjected to unpaired t test reveals the existence of statistically significant association between duration of RA distribution and intervention groups ($p < 0.05$)

In our study duration of RA distribution between the PN +ve group and PN –ve group was meaningfully significant. This is evident by the increased mean duration of RA in PN +ve group compared to PN –ve group (mean difference of 3.17 years, 39% higher).

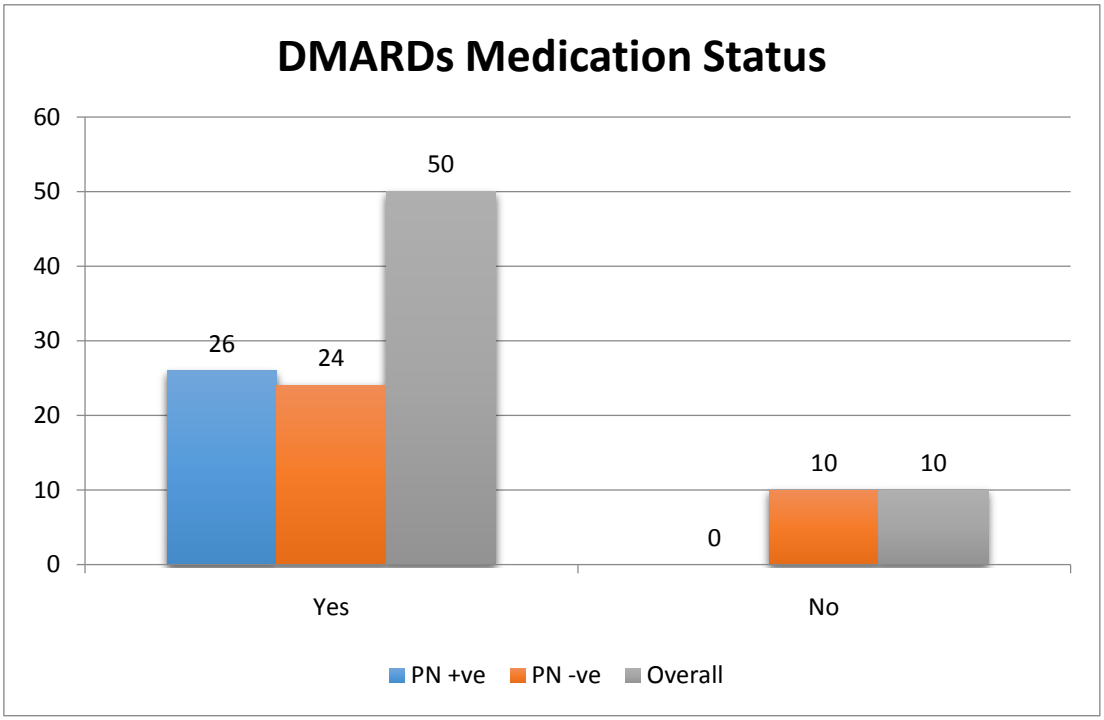
Steroid



Steroid Medication Status	PN +ve	%	PN -ve	%	Overall	%
Yes	7	26.92	13	38.24	20	33.33
No	19	73.08	21	61.76	40	66.67
Total	26	100.00	34	100.00	60	100.00
P value Fishers Exact Test				0.3573		

It is evident from the steroid medication status table that most of the PN +ve group subjects did not take steroids (83.08%) and in PN -ve group majority too did the same (61.76%) (p= 0.3573). The data subjected to fishers exact test reveals the existence of statistically insignificant association between steroid medication status and intervention groups (p >0.05)

DMARDs

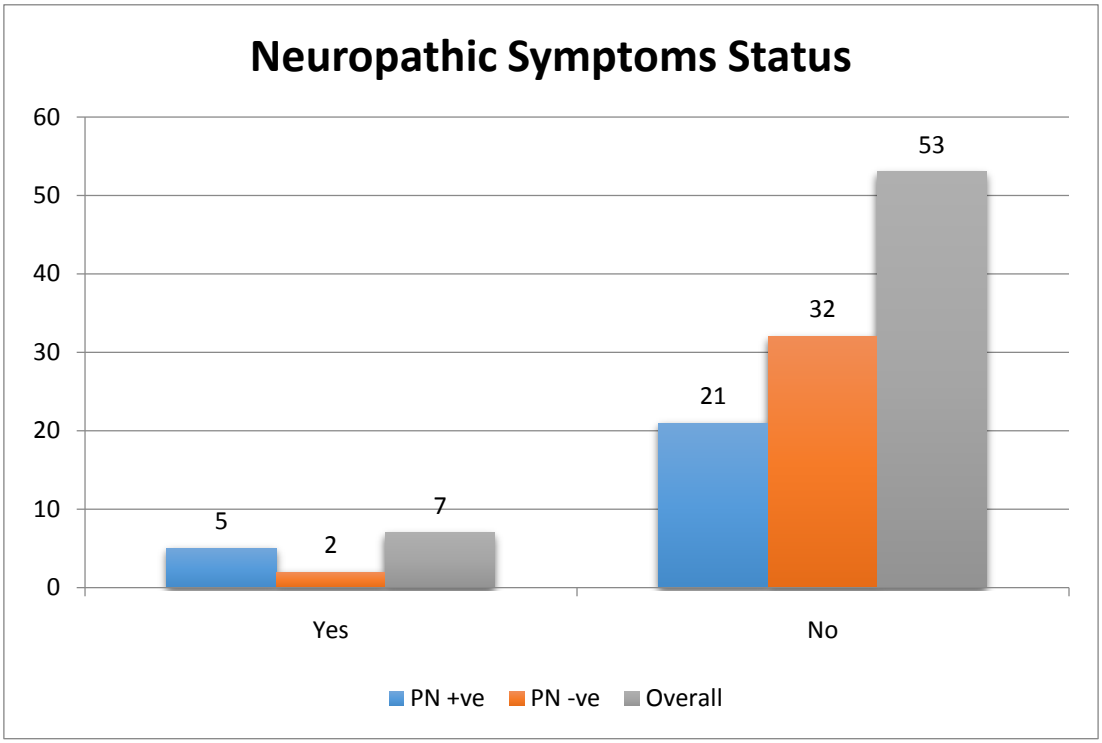


DMARDs Medication Status	PN +ve	%	PN -ve	%	Overall	%
Yes	26	100.00	24	70.59	50	83.33
No	0	0.00	10	29.41	10	16.67
Total	26	100.00	34	100.00	60	100.00
P value Fishers Exact Test					0.0022	

It is evident from DMARDs medication status table that most of the PN +ve group subjects took DMARDs medication (100%) and in PN -ve group majority too took DMARDs medication (70.59%) (p= 0.0288). The data subjected to fishers exact test reveals the existence of statistically significant association between DMARDs medication status and intervention groups ($p < 0.05$)

In our study DMARDs medication status between the PN +ve group and PN –ve group was meaningfully significant. This is evident by the increased incidence of intake of DMARDs medication in PN +ve group compared to PN –ve group (percentage difference of 29.41, 29% higher).

Neuropathic Symptoms



Neuropathic Symptoms Status	PN +ve	%	PN -ve	%	Overall	%
Yes	5	19.23	2	5.88	7	11.67
No	21	80.77	32	94.12	53	88.33
Total	26	100.00	34	100.00	60	100.00
P value Fishers Exact Test					0. 1198	

It is evident from the neuropathic symptoms status table that most of the PN +ve group subjects did not have neuropathic symptoms (80.77%) and in PN -ve group majority too did not have neuropathic symptoms (94.12%) ($p= 0.1198$). The data subjected to fishers exact test reveals the existence of statistically insignificant association between neuropathic symptoms status and intervention groups ($p >0.05$)

Multivariate analysis of factors associated with peripheral neuropathy in RA as determined by logistic regression

Variable	Odds ratio	95% CI	*P*-value
Age (> 40 years)	2.43	1.47-4.01	0.0112
Gender (Male)	1.75	1.04-2.93	0.1141
Hemoglobin> 11 gm%	1.02	0.85-2.87	0.1026
ESR >40 mm/hr	2.65	1.67-4.79	0.0457
CRP +ve Status	1.75	1.04-2.93	0.4421
RF +ve Status	2	1.21-3.32	0.0966
Anti-CCF Antibody +ve status	3.49	0.88-5.87	0.0322
Duration of RA > 10 years	2.07	0.74-4.47	0.0145
Steroid Intake	2.15	0.87-3.39	0.6832
DMARDs Intake	2.94	0.91-5.05	0.0751

Multivariate analysis demonstrated that after adjusting of basic variables and rheumatoid arthritis.

- The risk of developing peripheral neuropathy in patients with rheumatoid arthritis is 2.43 times significantly more when age is greater than 40 years than in patients less than 40 years. It is statistically significant with a p-value of 0.0112
- The risk of developing peripheral neuropathy in patients with rheumatoid arthritis is 2.65 times significantly more when ESR is greater than 40 mm/hr than in patients less than 40 mm/hr. It is statistically significant with a p-value of 0.0457
- The risk of developing peripheral neuropathy in patients with rheumatoid arthritis is 1.49 times significantly more when anti CCF antibody positivity exists than in patients less than in patients with anti CCF antibody negativity. It is statistically significant with a p-value of 0.0322
- The risk of developing peripheral neuropathy in patients with rheumatoid arthritis is 2.07 times significantly more when the duration of RA is more than 10 years than in patients with less than 10 years duration. It is statistically significant with a p-value of 0.0145

DISCUSSION

The prevalence of peripheral neuropathy and their relationship with demography, clinical findings, and laboratory values have not been clearly demonstrated in the literature. The prevalence of peripheral neuropathy vary among previous studies, as shown in Table below. Furthermore, it is difficult to compare studies on peripheral neuropathy in RA because the inclusion criteria and neuropathy assessment methods varies between previous studies. In our present study, we reported a frequency of peripheral neuropathy, including entrapment neuropathy of 43.3% in RA patients, which appears to be lower than that in previous studies with a large series of patients. The frequency of peripheral neuropathy in our study was higher than the frequency of idiopathic polyneuropathy of 8%, reported previously in a population-based epidemiological study[19]. We included RA patients with neurological symptoms in our current study, the prevalence of neuropathy in the electrophysiological study was more than that in other studies. There was no relationship between the neuropathic symptoms and the presence of peripheral neuropathy, which may be because the neuropathic symptoms consists of questions that focus on positive symptoms, such as burning and tingling, which are subjectively reported by the patients and also neuropathic symptoms mimic the symptoms of arthritis. Because of all

these reasons, neuropathic symptoms of patients might show a poor correlation with results of electrophysiological studies.

Comparison between electrophysiological studies of peripheral neuropathy and associated factors in the present and previous studies

Study	No. of patients	Types of peripheral neuropathy					Associated factors
		SM	S	M	MM	CTS	
Fleming etal. [29]	102	0	15	3	0	53	*
Agarwal et al. [27]	108	25	28	0	7	11	Absence of DTR, Presence of vasculitis
Lanzillo et al. [28]	40	26	0	0	0	3	*
Nadkar et al.[26]	31	6	0	4	4	1	*
Bayrak et al. [30]	60	8	2	0	0	*	Duration of RA, NSS, NDS, DAS 28
Mi Kyung Sim, et al.	30	2	1	0	0	7	Age, anti-CCP antibody
Present study	60	11	6	5	2	2	Age,ESR,Anti-CCPantibodyDuration of RA

SM - sensorimotor; S- sensory; M- motor;

MM - mononeuritis multiplex;

CTS - carpal tunnel syndrome;DTR- deep tendon reflex;

RA - rheumatoid arthritis; NSS- neuropathy symptom score;

NDS- neuropathy disability score; DAS 28 - 28-joint disease activity score Anti-CCP - anti-cyclic citrullinated peptide.

In present study we found significant correlation between peripheral neuropathy and the age of the patients, ESR, duration of RA and Anti-CCP antibodies. In present study, we did not find significant association between peripheral neuropathy and Gender, Neuropathic symptoms, CRP and type of medication. We found that RA patients with peripheral neuropathy were older than RA patients without peripheral neuropathy. Age is a known risk factor for polyneuropathy[20], and RA patients with peripheral neuropathy in our study showed similar results. However, the prevalence of peripheral neuropathy in patients with RA in this study was higher than that of peripheral neuropathy in patients without the underlying disease.

The most important finding of our study was that patients who were positive for anti-CCP antibody showed an increased risk of peripheral neuropathy. The anti-CCP antibody has become a focus of attention for diagnosis and it is a marker of severe RA[21]. New study reported that anti-CCP antibody is associated with human leukocyte antigen (HLA) class II RA-related susceptibility alleles and also with severe disease manifestations[22]. Some authors have observed a tendency

for positive association between anti-CCP antibody titer with extraarticular manifestations in RA, but there is no data on the effects of anti-CCP antibody on the development of peripheral neuropathy[23-25]. Our present study is one of the study to investigate the relationship between anti-CCP antibody and the development of peripheral neuropathy in RA patients. In our study anti CCP antibody status between the PN +ve group and PN –ve group was meaningfully significant. This is evident by the increased incidence of anti CCP antibody positivity in PN +ve group compared to PN –ve group (percentage difference of 21.95, 71% higher). Also, the effect of anti-CCP antibody on peripheral neuropathy seems to increase with age. Our study was limited by small sample size and cross-sectional design. We were unable to conduct an electrophysiological study for the same duration from symptom onset. Also, we were unable to determine the definite cause of peripheral neuropathy and CTS in this study, whether it was due to direct nerve injury or due to joint deformity or it was an independent disease. Furthermore longitudinal studies in a large population are needed.. It is difficult to distinguish the symptoms of peripheral neuropathy and those of arthritis, also the subjective symptoms of patients do not correlate with electrophysiological results. Hence, electrophysiological studies should be performed in patients with RA, particular in older patients and anti-CCP antibody positive patients.

CONCLUSSION

We can conclude that:

Gender, hemoglobin levels, complete blood counts, CRP, steroid medication and neuropathic symptoms had no statistically significant role to play on deciding peripheral neuropathy in rheumatoid arthritis patients

On internal comparison (PN +ve group and PN -ve group) the following conclusions were observed

- Peripheral neuropathy in rheumatoid arthritis patients is common among higher age group
- Enhanced ESR levels among rheumatoid arthritis patients with peripheral neuropathy
- Higher incidence of RA factor positivity among rheumatoid arthritis patients with peripheral neuropathy
- Higher incidence of Anti CCP antibody positivity among rheumatoid arthritis patients with peripheral neuropathy
- Longer duration of RA in peripheral neuropathy patient in rheumatoid arthritis is common among higher age group
- Higher incidence of DMARDs medication among rheumatoid arthritis patients with peripheral neuropathy

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The ideal individual with high risk of developing peripheral neuropathy in rheumatoid arthritis patients

- Age > 40 years
- Duration of RA greater than 10 years
- ESR greater than 40 mm/hr
- Anti-CCF Antibody positive status

This study is a hypothesis proving study.

Hence results have high clinical significance.

PROFORMA

Name:

Age:

Sex:

Educational status:

Occupation:

Address:

Clinical presentation on admission or OPD:

Time of onset of symptoms/Duration:

PAST HISTORY:

Diabetes

CKD

Thyroid diseases :

PERSONAL HISTORY :

Alcohol:

FAMILY HISTORY:

Rheumatoid arthritis :

Diabetes:

GENERAL EXAMINATION

Anemia:

Arthritis { DAS 28 SCORING SYSTEM}:

Extra articular manifestations:

VITALS: - Pulse rate

- Blood pressure

EXAMINATION OF CARDIOVASCULAR SYSTEM:

EXAMINATION OF RESPIRATORY SYSTEM:

EXAMINATION OF ABDOMEN:

EXAMINATION OF CENTRAL NERVOUS SYSTEM:

- Level of consciousness:

Peripheral nervous system examination :

Motor :

- Bulk.
- Tone.
- Power.
- Reflexes.

Sensory :

- Touch .
- Pain .
- Temperature .
- Vibration and joint position sense .

Autonomic system

INVESTIGATIONS

BLOOD

TC / DC :

ESR :

HB :

Platelet count :

Peripheral smear study :

RBS :

RFT :

CRP:

RF/Anti -CCP FACTOR:

LFT with lipid profile:

ELISA FOR HIV :

NERVE CONDUCTION STUDY :

- Median nerve .
- Ulnar nerve .
- Tibial nerve.
- Common peroneal nerve.
- Sural nerve

1	NAME	AGE	SEX	HB(gm%)	ESR	TC/DC(P/L/M)	PLATELET COUNT	CRP	RF	ANTI-CCP	DURATION	NERVE CONDUCTION STUDY	STEROIDS	DMARDS	NEUROPATHIC SYMPTOMS
2	PARIMALA	50	F	12.7	12/22	9600-74/25/1	3.1	+VE	_VE	0	13		NO	YES	YES
3	VIJAYA	35	F	11.8	18/34	8400-68/30/2	2	_VE	_VE	0	6		NO	NO	NO
4	SHANTHI	46	F	11	10/20	8700-74/24/2	1.7	_VE	+VE	0	11		YES	YES	NO
5	LATHA	29	F	12	12/38	7400-70/28/2	2.3	+VE	+VE	+VE	7	SMN	NO	YES	NO
6	SUNDHARI	45	F	11	20/36	8600-78/22	2.4	_VE	+VE	0	8		YES	YES	NO
7	AMSA	38	F	13	16/32	8500-66/30/4	3.7	+VE	+VE	0	7	CTS	YES	YES	NO
8	RAJAKUMARI	34	F	10.4	14/26	6500-70/28/2	1.25	_VE	_VE	0	4		NO	NO	NO
9	PREMA	45	F	12.2	16/28	7200-67/32/1	4	+VE	+VE	0	9	SMN	NO	YES	YES
10	ANGAMMA	37	F	10.9	15/32	10100-63/37/1	3.72	+VE	+VE	0	5		NO	YES	NO
11	GOWRI	37	F	11.7	18/36	8100-60/32/8	3.18	_VE	+VE	0	7	SN	NO	YES	NO
12	KUMARI	40	F	10.3	14/26	7800-75/24/1	2.8	+VE	+VE	+VE	11		YES	YES	NO
13	SAKUNTHALA	35	F	11.1	12/23	9500-76/21/3	3.63	+VE	+VE	0	5	MN	NO	YES	NO
14	RAVI	49	M	12.3	24/48	13100-85/10/5	2.86	+VE	+VE	0	6		NO	YES	NO
15	PADMAVATHY	70	F	12.7	21/36	5600-68/30/2	1.87	+VE	+VE	0	21	SMN	YES	YES	YES
16	KANNAKI	46	F	11.2	30/60	10460-66/27/7	3.03	_VE	+VE	0	7	SN	NO	YES	NO
17	SAMSHED BEGAM	50	F	12	12/24	11200-71/28/1	2.9	_VE	+VE	0	15	CTS	YES	YES	YES
18	SEEMAKANI	52	F	9.5	35/70	7500-59/37/4	2.28	_VE	+VE	0	12	MN	YES	YES	NO
19	MURUGAN	49	M	12.6	16/42	10300-75/23/2	1.9	_VE	+VE	+VE	5	MN	NO	YES	NO
20	RANI	60	F	8.4	45/90	12140-68/30/2	4.1	+VE		+VE	11	MN	YES	YES	YES
21	CHANDRU	31	M	9.7	23/46	9800-80/18/2	2.1	_VE	_VE	0	4		NO	NO	NO
22	HAIRUNISHA	36	F	12.6	18/36	8700-65/33/2	1.7	_VE	+VE	+VE	8	SN	NO	YES	NO
23	MENAKA	34	F	12.2	11/24	6200-62/35/3	2.03	+VE	+VE	0	5	SMN	NO	YES	NO
24	JEYANTHI	38	F	12.1	12/25	14300-76/20/4	3.73	_VE	+VE	+VE	4		YES	YES	NO
25	KAVITHA	31	F	13.6	8/20	9400-73/26/1	2.8	+VE	+VE	0	2		NO	YES	NO
26	RAJU	48	M	14.3	22/46	10200-79/20/1	2.09	+VE	+VE	0	7	MNM	NO	YES	NO
27	MALAR	41	F	12.9	14/28	11300-56/39/5	1.9	+VE	+VE	0	7		YES	YES	NO
28	SHANTHI	33	F	13.2	12/22	9100-67/30/3	1.3	-VE	_VE	0	3		NO	NO	NO
29	KUMAR	30	M	14.6	11/20	6700-71/28/1	2.7	_VE	+VE	0	4		NO	YES	NO
30	SUDHAKAR	52	M	11.3	14/36	10100-74/25/1	3.2	+VE	+VE	+VE	12	SMN	NO	YES	NO

31	NITHYA	26	F	13.7	21/42	12000-67/31/2	2	+VE	_VE	0	2		NO	NO	NO
32	PRIYA	34	F	9.7	14/26	8500-71/21/8	2.4	+VE	+VE	+VE	5		NO	YES	YES
33	SHYAMALA	45	F	10.4	8/18	10400-77/20/3	1.2	_VE	+VE	0	6		YES	YES	NO
34	GAYATHRI	51	F	9.8	12/26	4600-56/34/10	2.5	_VE	+VE	0	10		YES	YES	NO
35	RATHI	38	F	12.1	14/28	9900-82/16/2	1.8	+VE	+VE	0	4		NO	YES	NO
36	GOVINDHAN	52	M	14	24/36	11700-72/25/3	1.5	+VE	+VE	0	7	SN	NO	YES	NO
37	KRITHIKA	36	F	12.5	11/26	13200-67/30/3	2.5	_VE	+VE	0	5		NO	YES	NO
38	RAJAMMAL	46	F	10	20/38	8500-69/27/4	3.1	+VE	+VE	+VE	11	SMN	NO	YES	NO
39	KOKILA	33	F	12.7	17/34	9300-65/30/5	4	+VE	+VE	0	4		YES	YES	NO
40	BANU	29	F	8.9	12/20	10300-69/30/1	2.3	+VE	_VE	0	2		NO	NO	NO
41	DIVYA	31	F	11.2	8/16	6300-57/40/3	3.4	_VE	+VE	0	4		NO	YES	NO
42	RAJENDRAN	37	M	13.5	12/34	9800-71/26/3	3.9	+VE	+VE	0	5	SN	YES	YES	NO
43	THILAGAVATHY	32	F	12.8	15/30	10200-72/26/2	1.5	+VE	+VE	0	2		NO	YES	NO
44	PORKODI	42	F	12.1	21/42	9800-83/15/2	4.3	+VE	+VE	0	6		YES	YES	NO
45	BALAJI	28	M	14	11/22	9900-72/27/1	2.3	_VE	+VE	0	2		NO	YES	NO
46	MANORMANI	45	F	11.3	12/54	10100-77/20/3	2.8	_VE	+VE	0	7	SMN	NO	YES	NO
47	SUBHA	31	F	10.6	16/32	8900-59/30/11	1.7	_VE	+VE	0	3		YES	YES	NO
48	MALLIGA	35	F	11.2	20/40	9600-68/30/2	1.3	+VE	+VE	0	5		NO	YES	NO
49	PAVITHRA	34	F	9.7	10/24	10100-70/27/3	2.6	+VE	_VE	0	3		NO	NO	NO
50	DAMODHARAN	44	M	13.8	24/58	9400-64/34/2	3.2	+VE	+VE	+VE	6	SMN	NO	YES	NO
51	AGALYA	28	F	12.2	12/28	8700-58/30/12	3.1	_VE	_VE	0	2		NO	NO	NO
52	VASANTHI	39	F	9.3	8/16	4700-73/27	2.6	_VE	+VE	0	4		YES	YES	NO
53	RAJALAKSHMI	56	F	10.2	18/56	9900-69/30/1	1.8	+VE	+VE	0	8	SMN	NO	YES	NO
54	DEVIKA	32	F	11	18/38	8600-55/45	1.5	+VE	_VE	0	3		YES	NO	NO
55	SHILPA	43	F	9.6	12/42	9400-63/34/3	3.2	_VE	+VE	0	4	MNM	YES	YES	NO
56	MADHAVI	45	F	10.3	16/32	10100-59/35/6	1.9	_VE	+VE	0	5	SMN	NO	YES	NO
57	NIRMALA	42	F	11	11/38	9800-59/47/4	2.2	_VE	+VE	+VE	6	MN	NO	YES	YES
58	THANGARAJ	45	M	13.2	14/28	5800-69/30/1	2.8	+VE	+VE	0	7	SMN	NO	YES	NO
59	RADHA	34	F	11.3	20/40	4900-78/20/2	3.1	+VE	_VE	0	4		NO	NO	NO
60	GAJALAKSHMI	56	F	10	13/32	8300-69/27/4	2.7	_VE	+VE	0	10	SN	NO	YES	NO

CRP				ESR	TC- TOTAL COUNT						**NERVE CONDUCTION STUDY**	
(+)VE - MORE THAN 6				ERYTHROCY	P- POLYMORPHS						SMN- SENSORY MOTOR NEUROPATHY	
(-)VE - LESS THAN 6				SEDIMENT.	L- LYMPHOCYTES						MNM-MONONEURITIS MULTIPLEX	
				RATE	M- MONOCYTES						SN-SENSORY NEUROPATHY	
RF											MN-MOTOR NEUROPATHY	
(+)VE - MORE THAN 15 IU/ml											CTS- CARPEL TUNNEL SYNDROME	
(-)VE - LESS THAN 15 IU/ml												
ANTI-CCP												
(+)VE - MORE THAN 20 µunits/ml												
(-)VE - LESS THAN 20 µunits/ml												

சுயஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு:

மடக்குவாதம் உள்ள நோயாளிகளுக்க நரம்பு கோளாறு

உள்ளதை நரம்புக்கடத்துதல் ஆய்வு மூலம் ஆராய்தல்

இடம்: பொது மருத்துவ துறை,

அரசு கீழ்பாக்கம் மருத்துவக் கல்லூரி மருத்துவமனை,

சென்னை.

பங்குபெறுபவரின் பெயர் :

பங்குபெறுபவரின் வயது : பங்குபெறுபவரின் எண் :

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. நான் இவ்வாய்வில் தன்னிச்சையாக பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த சட்டசிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக்கொள்ளல்லாம் என்றும் அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும்போதும் இந்த ஆய்வில்பங்கு பெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக்கொள்ள மறுக்க மாட்டேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக்கொள்கிறேன். இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன்.

பங்கேற்பவரின் கையொப்பம் ஆய்வாளரின் கையொப்பம்

இடம் :

தேதி :