NEUROLOGICAL MANIFESTATIONS IN RHEUMATOID ARTHRITIS

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CERTIFICATE

This is to certify that the dissertation entitled "Neurological Manifestations in Rheumatoid arthritis" is a bonafide work of **Dr.P.S.ARUL RAJAMURUGAN** *during the period August 2004 to July 2007 in partial fulfilment of the requirement for the degree of DM-Rheumatology (Branch IX) of The Tamilnadu Dr. MGR Medical university.*

Dr.T.P.Kalaniti, MD.,
Dean,
Madras Medical College,
Chennai.

Dr.C.Panchapakesa Rajendran, DCH., MD., DM
Professor and Head
Department of Rhematology,
Madras Medical College, Chennai.

Dedicated
To my beloved
Teachers

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NEUROLOGICAL MANIFESTATIONS IN RHEUMATOID ARTHRITIS

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic multisystem disease of autoimmune aetiology. The characteristic feature is the persistent inflammatory synovitis usually involving peripheral joints in a symmetric distribution. Though it is considered a disease predominantly involving the joints it can cause a variety of extraarticular manifeststions.It can affect skin,eye,cardiovascular ,respiratory and nervous systems and may produce hematological complications including an increase in the risk of Hodgkin's disease,non Hodgkin's lymphomas, leukemias independent of the immunosuppressive drugs. One of the important extra articular manifestations is the involvement of nervous system. Neurological manifestations may be due to the involvement of central nervous system involvement, peripheral nervous system or autonomic nervous system. They may be either due to the vascular involvement, direct compression or immune mediated mechanism. It is often difficult to diagnose early neuropathies and the study of the peripheral nervous system is made difficult by symptoms resulting from pain in the joints and limitations of movement. It is nevertheless often possible by means of electroneuromyography to show objectively the existence and distribution of even subclinical neuropathies.

Epidemiology

RA is widely distributed all over the world and affects all races. The prevalence in the adult population is assessed at approximately 0.5 to 1.The prevalence and incidence is 3 times higher in the females than the males. The incidence of RA rises dramatically during adulthood. The average age at onset has shifted upward over the past five decades. There is a decline in the age specific incidence and is greatest in females (1).

Aetiopathogenesis

The genetic predisposition and the environmental factors importantly infections play a major role in the causation of RA. The class II molecule particularly HLA DR4 is associated with 70% of RA patients. The susceptibility to RA is associated with the third hypervariable region of the DR β chains from aminoacids 70 through 74 (2). Deficient galactosylation of the immunoglobulin G might also be a risk factor for the development of RA. Association with genetic polymorphisms have been demonstrated with tumour necrosis factor–alpha, chemokines and other cytokines. A single nucleotide polymorphism for the T-cell costimulatory molecule CTLA 4 is also associated with susceptibility. Infectious agents play an aetiologic role in the causation of RA. The bacterial organisms are pathogenic through molecular mimicry and viruses cause direct synovial infection or induce polyclonal activation as in Ebstein-Barr viral infection. Rheumatoid factor was the first evidence of autoimmunity in RA. Rheumatoid factor (RF) is an autoantibody against the antigenic determinant region in the Fc portion of the Ig G molecule. The Ig G becomes immunogenic through various mechanisms. First, new determinants on Ig G might be

exposed after polymerization of molecules or formation of Ig G complexes with specific antigens. Second structural anomalies in the Ig G of the RA patients may render it immunogenic. Finally changes in the relative extent of the galactosylation of the Ig G may give rise to auto antigenic reactivity (3). Production of high affinity RF leads to intra articular complement fixation and synovitis. High titer IgG RF is associated with vasculitis, IgA RF is associated with erosions and vasculitis. Apart from that autoantibodies directed against the components of the articular cartilage like type II collagen, gp39, cartilage link protein, proteoglycans and aggrecans and nonarticular antigens like citrullinated peptides, glucose 6-phosphoisomerase, HLA–DR, heatshock proteins, hnRNPA2 also play a vital role in the pathogenesis of RA. Patients with active rheumatoid disease may develop encephalopathy, myelopathy, peripheral neuropathy, and myopathy through a variety of tissue mechanisms. Brain involvement is usually characterized by the formation of rheumatoid nodules or by the development of vasculitis or its complications, and there is evidence to suggest that the trapping of immune complexes within the choroid plexus may be important in pathogenesis.

Structural damage to the spinal cord and lower brain stem, on the other hand, most commonly results from narrowing of the bony canal, leading either to direct compression of neural tissue or to compromise of its vascular supply or due to atlanto axial subluxation following the loss of support from the transverse, alar and apical ligaments due the inflammation at the synovial bursa which is present in between the transverse ligament and the odontoid process. The appearance of peripheral neuropathy generally signifies the presence either of inflammatory epineurial arterial disease or entrapment by neighbouring anatomical structures. Skeletal muscle

dysfunction may be due to vasculitis, myositis, or denervation atrophy. Both systemic and local anatomical factors, therefore, are of importance in determining the manner in which different parts of the nervous system may be affected in rheumatoid disease. Serum levels of soluble VCAM-1, soluble E-selectin, and Anti Endothelial Cell antibody are higher in patients with RA neuropathy than in patients with RA uncomplicated by neurological disease. These data suggest that development of peripheral neuropathy in RA is associated with increased endothelial cell activation (4).

Pathology

The primary site of immune activation in RA is the synovium of the joint. Infiltration of synovium with mononuclear cells, especially T cells and macrophages, and synovial intimal lining hyperplasia are the hallmarks of the disease.The increase in the synovial intimal lining cells is substantial.The two types of synoviocytes, type A and B are increased in RA with the predominance of type A macrophage like cells which express the markers CD 68,Fc receptors,CD14 and abundant HLA –DR molecule. In chronic RA the synovium contains a collection of T lymphocytes that can lead to an organizational structure resembling a lymphnode. These collections consist of small CD 4+ memory cells. T cells constitute about 50 % or more of cells in most RA synovia, and most are CD4+, only 5% or fewer of cells are B lymphocytes or plasma cells. Oligoclonal expansion of CD 4+ CD28- T cells are poor B cell stimulators and occur more frequently in patients with extra articular manifestation. Synovial lymphocytes also bear adhesion molecules of very late antigen and lymphocyte function associated antigen super family of integrins, which

may enable the inflammatory process to persist within the synovium. The cytokine milieu of the synovium induces the expression of ICAM-1, VCAM-1 and connecting segment -1 fibronectin on vascular endothelium. Chemokines and the chemokine receptor especially CCR 5 play a vital role in the accumulation of T cells independent of a particular antigen. Synovial B cells and plasma cell hyperactivity take part in the perpetuation and initiation phase of RA.Dendritic cells constitute around 5% of synovial cells which has resistance to the effects of IL-10.Other cells present in the synovium are polymorphonuclear cells, mast cells. Synovial tissue express Th1 cytokine bias which comprises IFN-γ, IL-2 and IL-17.Macrophages are the major source of cytokine secretion in the synovium.Activation of macrophages and fibroblasts occur also through cell to cell contact with T-lymphocytes.The pro inflammatory cytokines IL-1,IL-6,TNF-alpha,IL-15,colony stimulating factors, chemokines, platelet derived growth factor and fibroblast growth factor all play an important role in the establishment of the synovial pathology.Underproduction of suppressive cytokines like IL-1Ra ,IL-10,TGF-β and soluble cytokine receptors and binding proteins may also contribute for the synovial inflammation.The most important mechanism of the bone and cartilage destruction is the pannus formation which is a cellular layer .Aggressive degradation of the extracellular matrix occurs at the pannus cartilage junction. The enzymes induced by the factors IL-1, TNF-alpha, phagocytosis of debris by synovial cells and mechanic trauma cause the joint destruction. The MMP s and aggrecanases produced by the chondrocytes through IL-1 mediated mechanism destroy the proteoglycans and weakens the cartilage thereby predisposing for a cartilage destruction. Tissue inhibitor of metalloproteases which is a family of proteins block the activity of metalloproteases by directly binding

to them. Degradation of the bone occurs through binding of receptor activator of nuclear factor κ B ligand which is produced by the activated T cells and fibroblast like synoviocytes with the receptor ,RANK expressed in the osteclasts which in turn will activate the osteoclasts. Osteoprotegerin ,a decoy receptor binds with RANK and competes with RANK-L.Polymorphonuclear neutrophil activation leads to mobilization of membrane phospholipids and release of arachidonic acid metabolites. Proinflammatory product like leukotriene B4 plays a considerable role in in the induction of inflammation.

Clinical features

The clinical manifestations include articular and extra articular features. The articular manifestation may have an insidious onset in 55-65 % of patients, acute onset in 8-15% of patients and subacute in 15-20% of patients. The unusual pattern of onset may be adult onset Still's disease, palindromic onset, polymyalgia rheumatica type and arthritis robustus type. The joints most commonly involved first are metacarpophalangeal joints, proximal interphalangeal joints, metatarsophalangeal joints and wrists. The large joints become symptomatic after the small joints .The extra articular manifestation includes subcutaneous nodules, episcleritis, scleritis, myositis, vasculitis, pulmonary manifestations in the form of pleurisy, interstitial fibrosis, nodular lung disease, bronchiolitis, pulmonary hypertension and small airways disease. Cardiac complications include pericarditis, myocarditis, endocardial inflammation, conduction defects, coronary arteritis, granulomatous arteritis or valvular disease.

Central nervous system (CNS)

i. ***Meningeal nodules, pachymeningitis and CNS vasculitis***

Rheumatoid nodules occur occasionally in the dura, falx cerebri, the leptomeninges and the choroid plexus (5). Some of the nodules adhere to the brain or spinal cord and compress structures but they do not intrude into the parenchyma and probably do not occur in the parenchyma of the nervous tissue. In some cases not only nodules are present, there is also a more widespread plaque like inflammation of the meninges with necrosis, lymphocytes, and a variable percentage of plasma cells. This aseptic pachymeningitis may also occur on its own without any rheumatoid nodules. Vasculitis extending in some from a region of pachymeningits into the brain has also been reported (6). Mental obtundation, organic brain syndrome, severe headache, seizures, cranial neuropathy including optic neuropathy, paresis and agnosia, thoracic myelopathy and radiculopathy due to pachymeningitis or rheumatoid nodules. Inflammatory CNS disease occurs usually but not exclusively in patients with long standing seropositive disease and considerable deformities. CSF examination reveals a raised protein content and a modest degree of pleocytosis. Imaging will show enhancement of meningeal structures. Meningeal rheumatoid nodules are sometimes discovered at autopsy in patients without any neurological manifestations.

ii. ***Cervical spine in Rheumatoid arthritis***

Cervical spine lesions in long standing RA is an important complication which may lead on to an emergency clinical situations .After approximately 10 years one

third of the patients have a form of cervical subluxation and after a mean disease

duaration of 15.7 years the prevalence of cervical subluxation is 52% (7).Neurologic compromise occurs in 11-58% of these patients (8) and is correlated to the levels of CRP, peripheral joint involvement and carpal collapse (9).The reason for the excessive vulnerability of the cervical spine is not definitely clarified but two factors likely to play a significant role; the extreme mobility of the cervical spine and the heavy load it has to carry. Cervical lesions may be atlantoaxial subluxation, subaxial subluxation or atlanto axial impaction.Neurological manifestations follow the bulbospinal compression .In myelopathy gnosic sensibility is more frequent than of vital sensibility. Patients have unilateral or bilateral astereognosis of the hands. Lhermitte's sign may be present. Pyramidal changes include exaggerated tendon reflexes with positive Babinski's sign, spasticity and muscle weakness. Severe nuchal pain due to radiculopathy is more frequent.Bulbar syndromes and cranial nerve lesions like dysphagia, dysarthria, vertigo, fainting, cerebellar signs, symptoms of V,IX,X,XII,VII and rarely III,IV and VI..Obstructive hydrocephalus and secondary inappropriate ADH secretion have also been reported.

Peripheral nerve lesions

Chronic or subacute compressive (entrapment) neuropathies

Mononeuropathies developing after prolonged mechanical damage to a nerve at a site of anatomical constriction are common, the most familiar of which is the median nerve in the carpal tunnel. Following localized demyelination, segmental demyelination occurs and progresses to wallerian degeneration. Varying degrees of slowing of nerve conduction velocities are found and in early or mild cases sensory nerve studies are more sensitive.

Needle sampling may reveal denervation in the relevant muscles in more severe cases. The common lesions encountered in rheumatological practice are summarised in **Table-1**.The following nerves are involved in the entrapment neuropathy in Rheumatoid arthritis due to arthritis.

Median nerve

Carpal tunnel syndrome is the commonest chronic nerve entrapment neuropathy. Although usually idiopathic, underlying causes have been well described and fortunately mild cases usually respond, initially at least, to conservative measures Electrodiagnosis is generally indicated if the clinical diagnosis is not secure or the lesion appears progressive. The following are the presenting features of carpal tunnel syndrome.

1. Weakness of thumb opposition and abduction and atrophy of abductor pollicis brevis.
2. Numbness and tingling in the digits 1-4
3 Pain in the median nerve innervated region of the hand which may radiate upto the elbow

The minimal diagnostic criterion is a prolonged median sensory conduction velocity with a normal ulnar sensory velocity. The distal motor latency to abductor pollicis brevis is normally also determined. Using these criteria, Boniface et al reported that nerve conduction studies excluded the clinical diagnosis of carpal tunnel syndrome in 36%, and the authors highlight the importance of the investigation for this clinical condition as part of good

clinical practice as well as health service costs (10).

Ulnar nerve

Ulnar neuropathy is the second most frequent entrapment neuropathy, the majority occurring at the elbow in the cubital tunnel. The aim of doing ulnar nerve studies are to find out

1. The degree and exact site of damage at the elbow
2. Whether the lesion is in the ulnar nerve or the 1st thoracic root
3. Whether an ulnar nerve lesion of the hand is proximal or distal to the bifurcation into deep muscle and superficial sensory branches
4. Part of work up for a peripheral neuropathy

Conduction studies of ulnar nerve lesions at the elbow correlate well with clinical severity and localization is correct in 95%. Electrical tests are an important adjunct to this clinical assessment.

Cervico thoracic nerve roots

Radicular symptoms may be due to rheumatoid involvement of the cervical spine (often silent). Displacement of the vertebra may narrow the space available for the radicles in the intervertebral foramen leading to compression.

Common peroneal nerves

The common peroneal nerve is vulnerable at the level of the fibula head as the nerve enters the peroneus muscle. Electrical studies are indicated if the lesion is complete and recovery is not apparent or appears very slow, decisions about the amount of physiotherapy actually required, planning of rehabilitation and type of leg appliances all require prognostic information early which can often only be obtained by electromyography. In distinguishing between a L5 root lesion and peroneal nerve palsy causing a foot drop, it is worth noting that the weakness of foot eversion which is found in peroneal nerve palsies is not always easy to demonstrate. The posterior tibialis is one of the few muscles innervated by the L5 root and not via peroneal nerve and therefore an important muscle to examine to distinguish these two lesions.

Posterior tibial nerve.

The tarsal tunnel syndrome is not common. The tibial nerve gets compressed behind and below the medial side of the ankle where it passes under the flexor retinaculum. Clinical manifestations are infrequent and comprise pain, tingling and numbness of the toes and soles .The tibial nerve divides in the tunnel into two or three branches. Not all these branches need to be compressed to the same degree. When only one of the branches is involved, differentiation is necessary of tarsal tunnel syndrome from plantar nerve compression distal to the tarsal tunnel.

Other less commonly affected nerves

The motor branch of the radial nerve separates from sensory branch at the level of the elbow and passes below the elbow between the superficial and the deep part of the supinator muscle. At the site of entrance in the supinator muscle, the nerve may be compressed by the fibrous arch of the superficial part of the supinator or by the extensor carpi radialis brevis muscle. It may also be compressed, at a slightly higher level by fibrous bands, which may form the radialis tunnel. In all these cases, the main symptom is very characteristic, and comprises inability to extend the fingers due to weakness of the extensor digitorum communis muscle and the extensor pollicis. Wrist extension is usually preserved and the sensibility remains intact. Rupture of the tendon of the extensor digitorum muscle is the main differential diagnosis. However tendon rupture occurs suddenly, which is in contrast to posterior interosseous nerve compression which progresses gradually. Tendon rupture concerns the fourth and fifth fingers mostly and not the thumb. Prevention of initiation of finger extension also may be due to metacarpophalangeal dislocation, but in this case, extension of the fingers can be maintained after passive stretching .In patients with RA ,the nerve is compressed or stretched by bulging, proliferating synovium, which is often palpable and best visualized by MRI.

Mononeuritis multiplex

Mononeuritis multiplex is a painful asymmetric asynchronous sensory and motor peripheral neuropathy involving isolated damage to at least 2 separate nerve

areas. Multiple nerves in random areas of the body can be affected. As the condition worsens, it becomes less multifocal and more symmetric. Mononeuropathy multiplex syndromes can be distributed bilaterally, distally, and proximally throughout the body. Mononeuritis multiplex exhibits equal incidence in men and women. This condition can become progressively worse over time. The damage to the nerves involves destruction of the axon (ie, the part of the nerve cell that is analogous to the copper part of a wire), thus interfering with nerve conduction. Common causes of damage include a lack of oxygen from decreased blood flow or inflammation of blood vessels. Approximately 33% of cases originate from unidentifiable causes. Pain often begins in the low back or hip and spreads to the thigh and knee on one side. The pain usually is characterized as deep and aching with superimposed lancinating jabs that are most severe at night. Other possible symptoms that may be reported by the patient include the following:

Numbness

Tingling

Abnormal sensation

Burning pain – Dysesthesia

Difficulty moving a body part – Paralysis

Lack of controlled movement of a body part

Loss of sensation and movement may be associated with dysfunction of specific nerves.

Examination reveals preservation of reflexes and good strength except in regions more profoundly affected. The involvement of the nerves is as follows.

Sciatic nerve dysfunction

Femoral nerve dysfunction

Common peroneal nerve dysfunction

Axillary nerve dysfunction

Radial nerve dysfunction

Median nerve dysfunction

Ulnar nerve dysfunction

Tardive ulnar palsy

Peroneal nerve palsy.

The performance of any procedure, such as a nerve biopsy, is dictated by the history and physical examination. The purpose of any procedure is to determine the primary pathologic process. A nerve biopsy may be performed to help distinguish between demyelination (destruction of parts of the myelin sheath covering the nerve) and axonal degeneration (destruction of the axon portion of the nerve cell), to identify inflammatory nerve conditions (neuropathies), or to confirm specific diagnoses. In some cases, a nerve biopsy may be appropriate to determine the underlying cause (eg, a combination of perivascular inflammation and axonal loss or demyelination and axonal loss with multinucleated inflammatory cells). A pattern of necrotizing vasculitis of epineural arteries may be observed.

Multifocal pathology

This may be suspected clinically for example in mononeuritis multiplex, but more often is revealed by the appropriate electrical tests. Certain conditions characterised by mild generalised neuropathic changes, which are

often subclinical, are also prone to localised entrapment neuropathies because of mechanical pressure as in diabetes, hypothyroidism, chronic alcoholism, inflammatory arthritis, and familial pressure palsies.

Autonomic dysfunction

A wide range of symptoms may indicate abnormal function of the autonomic nervous system.The characteristic autonomic symptoms are blurred vision due to defective pupillary accommodation,optic nerve or brain ischemia due to orthostatic hypotension, dry eyes or mouth due to impaired parasympathetic innervation to lacrimal or salivary glands, orthostatic lightheadedness with dull shoulder aching due to muscle ischemia as a result of hypotension; early satiety or alternating diarrhea and constipation due to gastrointestinal dysmotility; and urinary retention or sexual dysfunction due to sympathetic and parasympathetic denervation. Small fiber dysfunction which can cause burning or lancinating pains of the hands and feet, may also cause hypohidrosis, anhidrosis or compensatory hyperhidrosis.

Diagnosis

The diagnosis of RA is by using the 1988 revised American Rheumatism Association classification criteria (11) that are based on the effective clinical history and examination, laboratory tests and diagnoses that exclude it. Though the criteria should not be used for diagnosing the individual case ,the requirement that the objective evidence of synovitis must be present for atleast 6 weeks is an important one. The diagnosis of RA should be confirmed or ruled out within 2 months after the onset of synovitis. Anti cyclic citrullinated antibody test is the latest addition to the

list of laboratory investigations. It may be positive in 60% of seronegative RA if second generation ELISA kit is used. Diagnosis of neurological manifestations depend on the type of involvement assessed with the history and clinical examination. Imaging plays an important role in diagnosing the cervical spine and the cerebral lesions. Dynamic x-rays of the cervical spine like lateral view in flexion ,extension,neutral may be useful, in diagnosing the atlantoaxial subluxation. CT and MR imaging have a vital role in delineating the involvement of the cervical spines. An atlanto dental distance greater than 3.5 cm is considered abnormal in an adult. Atlanto axial impaction or superior migration of odontoid is diagnosed by using the Mc Gregor's line (12) or Ranawat's index (13). McGregor's line is drawn from the posterior edge of the hard palate to the most caudal part of the occipital curve of the skull.The tip of the odontoid should be not more than 4.5 mm above the Mc Gregor's line.Another line named Fischgold and Metzger's line (14) is drawn between the two digastric grooveswhich passes 10.7mm above the tip of the odontoid process normally.Diagnosis of peripheral nerve lesions requires neurophysiological studies .

Neurophysiological studies

The principal application of electrical studies to rheumatic diseases is in the diagnostic and prognostic assessment of the neurological and myopathic features that can complicate inflammatory and connective tissue disorders. The electro-physiological tests can detect and distinguish between disorders of anterior horn cells, nerve roots, plexus, peripheral nerves, neuromuscular junction and muscles. They are also useful in defining the location, extent and severity. The nerve conduction studies can assess the motor conduction velocity, amplitude, sensory conduction velocity and

reflex latencies. The demyelination is reflected in the slowing of the conduction and the prolonged distal latencies. Entrapment neuropathies will have segmental demyelination at the site of compression. Normal or slightly reduced conduction velocities in the presence of reduced amplitudes or absent sensory, motor and /or mixed action potentials are characteristic of axonal degeneration. Varying degree of slowing of nerve conduction velocities are found and in early or mild cases sensory nerve studies are more sensitive. Needle sampling may reveal denervation in the relevant muscles in more severe cases. Two varieties of peripheral neuropathy are well recognized features of rheumatoid disease .Low amplitudes and slowing of sensory conduction suggest segmental demyelination found in the more common mild distal sensory neuropathy which has a good prognosis. It is not unusual to record normal electrical values in patients who present with features of peripheral neuropathy. The indications for neuropysiological studies are given in **Table 2** .Not only can electrical studies determine the exact site and severity of a lesion in these conditions, they may also help to assess prognosis and response to treatment, depending on the nature and site of lesion. However, correlation of clinical and electrical findings are not always straight forward as shown by the lack of uniformity in reported studies of electrical assessment and monitoring of recovery following injury and surgical decompression. For diagnosis it is important to demonstrate that delay in conduction distal to the site of compression is disproportionate to any mild proximal slowing . Electrodiagnostic demonstration of an isolated motor nerve root lesion can be achieved by finding evidence of denervation in a group of muscles corresponding to the distribution of the spinal segment rather than the

peripheral nerve. A preganglionic root lesion will not affect the distal sensory action potential whereas a postganglionic lesion may do so because the integrity of the peripheral nerve fibre may be affected.

1. The optimum diagnostic yield depends on thorough clinical evaluation of the patient's symptoms and signs, with the appropriate radiology and laboratory tests

2. It only provides supplement to the studies of pathological (e.g. biopsy) or structural disturbances (e.g. radiology)

3. It is uncomfortable for the patient, but safe.

4. It requires specialised equipment and expertise.

General principles and methods

Motor nerve conduction velocity

This is measured by stimulating a motor nerve with a surface (skin) electrode and recording the response from the appropriate muscle with a surface electrode placed over the muscle belly (only occasionally is a concentric needle electrode inserted into the muscle belly required). A supramaximal stimulus is delivered at least two sites along the peripheral nerve. The onset of the muscle response, the motor action potential, gives the distal motor latency. If the distance between the two stimulating sites is measured, the motor nerve conduction velocity of that segment of nerve can be calculated from the formula:

Speed (m/s) = distance (cm) / time (ms)

The amplitude, duration and shape of the potential is examined and all

these findings are compared with the contralateral side and other peripheral nerves, and also to the normal values available in standard tables.

Sensory nerve conduction velocity

This is normally measured by stimulating the sensory nerve and recording the sensory nerve action potential with surface electrodes distally i.e. antidromically.The responses are of much lower amplitudes (normally measured in microvolts) and more difficult to elicit, and may require averaging techniques. The amplitude, shape and duration are recorded. The velocity is calculated in the normal way, and the distal (to onset) or peak (to peak response) latency standardized for distance.

Mixed nerve potential

The mixed motor and sensory nerves are tested by stimulating a mixed fibre nerve proximally (e.g. in median fossa for median nerve) and recording the amplitude and latency of the compound nerve action potential distally (at the wrist for median nerve). When a motor nerve is stimulated, impulses travel proximally to the anterior horn cells followed by recurrent conduction back down the nerve where the small muscle response (known as the 'F wave') can be detected over muscles of the appropriate root distribution. This latency is measured and compared to the other side or height related normal values. They are sometimes technically difficult to elicit but a delayed F wave in the presence of normal peripheral conduction implies slowing of proximal motor fibres at plexus or root level.

Sensory Evoked Potentials

Very small potentials, evoked by repetitive percutaneous stimulation of peripheral nerves can be detected with averaging techniques by surface electrodes over the skin of spinal cord or scalp. Somatosensory evoked potentials have also been used in investigations of peripheral neuropathies, and are particularly well suited to the investigation of proximal lesions of the brachial plexus and spinal nerve roots, which are so inaccessible to normal recording methods.

Clinical application

The usefulness of these studies in clinical evaluation depends very much on the nature, site and chronicity of the lesion, the clinical information available, and the knowledge of other features, which may affect the electrical findings, for example the presence of neurological anomalies or dual pathology. In some cases this investigation can be crucial in decisions regarding surgery, but in others the diagnostic and prognostic yield may be minimal.

Three main pathological processes result in the electrical abnormalities of conduction studies:

demyelination

axonal degeneration

metabolic effects

It is customary to use the term demyelination for neuropathies with a primary disorder of the myelin sheath. The degree of slowing parallels the degree of demyelination, and conduction velocities are usually reduced by at least 30%. Segmental demyelination is found to be localized to one segment of a nerve in the entrapment neuropathies at the site of compression. More prolonged compression of a peripheral nerve results in further damage to the axons distal to the lesion causing wallerian degeneration. Normal or slightly reduced conduction velocities in the presence of reduced amplitudes or absent sensory, motor and/or mixed action potentials are characteristic of axonal degeneration. This is because, as in most peripheral neuropathies, the disease process affects fast conducting, large diameter fibres preferentially and the remaining smaller diameter fibres have only slightly slower velocities. Motor conduction velocities of less than 40 metres per second are unusual. In rheumatological practice axonal degeneration is typical of the vasculitides, for example mononeuritis multiplex seen in rheumatoid arthritis. The degree and site of these changes (**Table 3)** are an indication of the presence of axonal degeneration or widespread or segmental demyelination and this helps to narrow down the differential diagnosis. Electrical studies also help to distinguish the relative importance of the coexistence of these processes, for example entrapment neuropathies in the presence of generalised neuropathies of rheumatoid arthritis. Timing of the investigation may be

important, and serial studies may be helpful.

Clinical conditions

Mononeuritis multiplex

The following tests are done for the mononeuritis multiplex.

Sensory nerve conduction studies

The lesion or lesions are distal to both the motor and sensory cell bodies and result in either axonal disruption/degeneration or abnormal axonal conduction. Sensory nerve conduction studies (NCS) show abnormalities of decreased amplitude in the presence of axonal disruption. Physical examination will direct the electromyographic examination. Sensory NCS are beyond the reference range for amplitude and/or latency only if a large enough percentage of the sensory axons are damaged. A lesion that eliminates conduction in less than 10% of the sensory axons produces a loss of amplitude that may not be detectable.

Motor nerve conduction studies

Abnormalities are similar to those seen in axonal polyneuropathies and entrapment neuropathies with the exception of the anatomic distribution. A reduction

in the sensory and motor action potential amplitudes and minimal alterations in nerve conduction velocity will be seen. Velocity may be slightly reduced compared with the reference range, but it does not usually decrease below 70-80% of the lower limit of the reference range. Additionally, the loss of motor axons should generate a reduced number of motor unit action potentials (MUAP) firing at high rates (ie, reduced recruitment). Abnormal findings directly depend on the severity and aggressiveness of the underlying disease. A decrement of motor amplitude may be seen if there is significant denervation.

Needle electrode examination

Results of needle electrode examination can vary, depending on the time course of the disorder. Findings are typically neuropathic and may include abnormal spontaneous membrane activity (positive sharp waves and fibrillation potentials) and increases in MUAP duration, amplitude, and polyphasia.

Carpal tunnel syndrome

The minimal diagnostic criterion is a prolonged median sensory conduction velocity with a normal ulnar sensory velocity. The distal motor latency to abductor pollicis brevis is normally also determined. Using these criteria, Boniface et al (10) reported that nerve conduction studies excluded the clinical diagnosis of carpal tunnel syndrome in 36%.

Peripheral neuropathies

Motor, sensory and mixed conduction studies in both arms and legs

are essential if a generalized neuropathy is suspected. Sensory investigations are more sensitive than motor studies, especially the sural sensory and peroneal mixed action potentials in sensory neuropathies. The differential diagnosis is narrowed down by careful appraisal of the clinical features, the degree of slowing and magnitude of amplitude responses, and which sensory and/or motor nerves are affected. Differentiation between the numerous possible causes of peripheral neuropathies on the basis of electrical findings alone is possible in only a few cases. Two varieties of peripheral neuropathy are well recognised features of rheumatoid disease (15). Low amplitudes and slowing of sensory conduction suggest segmental demyelination found in the more common mild distal sensory neuropathy which has a good prognosis. Reduced amplitudes with or without widespread denervation in the presence of relatively normal conduction suggest axonal degeneration found in the more severe sensorimotor neuropathy. This may start as an isolated neuropathy and progress as part of a vasculitic process as in mononeuritis multiplex. Electrical studies are clearly valuable in distinguishing the two and demonstrating the extent of involvement which may not be apparent clinically because of joint deformity or synovitis.

Pitfalls in electrodiagnosis.

The normal ranges for motor nerve conduction were first established by Hermann von Helmolz in the summer months of the early 1850s. Subsequent studies by him in the winter demonstrated the significant effect of temperature on nerve conduction and present day electromyographers are well aware of

the necessity to provide standard temperatures (preferably warm ones) for this examination. In some circumstances cold patients need to be warmed up to obtain real results for example in peripheral neuropathy. Another factor which can influence electrical readings is age, with maximal conduction velocities seen in the teens. Full term neonates have half the normal adult ranges, and there is a reduction of 0.5-1.8 metres per second per ten years after the age of 20. Amplitude decay increase with age. Anomalies of neurological arrangements occasionally make the life of an electromyographer difficult, the most common of which is the Martin-Gruber anastomosis between ulnar and median nerves which probably occurs more frequently than the 6% quoted by Hopf and Hense. Conventional electrical tests will be essentially normal in patients with upper motor neuron lesions or with non organic signs. In the latter, when the hysteria-conversion reaction or malingering posture makes clinical examination so difficult, electrical testing can be extremely helpful in excluding severe organic disease, but occasionally reveals a genuine underlying pathological lesion.

Table 1. Common entrapment neuropathies

Nerve	Site of entrapment
median	carpal tunnel at wrist
ulnar	palm, wrist or elbow (cubital tunnel)
radial	spiral groove in upper arm
cervical nerve root/plexus	cervico thoracic outlet
common peroneal	head of fibula
posterior tibial	tarsal tunnel
lumbar sacral roots	lumbosacral spinal canal or foramina

Table 2. Indications for electrodiagnosis in rheumatoid arthritis

Clinical feature	Pathophysiology	Examples
Muscle weakness or wasting	Atrophic	Rheumatoid joint
	Neuropathic	Rheumatoid or entrapment neuropathy
Sensory symptoms	Peripheral neuropathy	Rheumatoid arthritis
	Entrapment neuropathy	Ulnar neuropathy
Pain	Entrapment neuropathy	Carpal tunnel syndrome
	Nerve injury	Causalgia
Deformity	Entrapment neuropathy	Ulnar nerve claw hand

Table 3. Summary of electrical findings of conduction studies in neuropathy

Electrical features	**Axonal degeneration**	**Segmental demyelination**
Amplitude	markedly reduced	normal/slight reduction
Distal latency	normal/slight delay	marked delay
Velocity	,,	,,
Examples	vasculitis	diabetes

Treatment

Treatment of rheumatoid arthritis comprises of non pharmacological and pharmacological therapies. It should have comprehensive regime directed towards treating the basic disease and the complications Non drug therapy includes patient education, counseling and rehabilitative measures that that focus on pain control, patient adherence, rest, joint protection principles and exercise therapy. Drug therapy includes analgesics, nonsteroidal anti-inflammatory drugs, corticosteroids either intra articular or systemic. Systemic steroids which are used as, low dose daily therapy, high dose short course therapy for drug induced thrombocytopenia, mononeuritis multiplex and interstitial lung disease, coronary arteritis. It can be used as a principal therapy during pregnancy when needed. Disease modifying antirheumatic drugs are used according to the algorithmic approach put forward by the American College of Rheumatology. The combination therapy is supported by the evidence shown in the two trials, COBRA (17) and FIN- RACO (18). The drugs used in the combination triple drug therapy are methotrexate, hydroxychloroquine and sulphasalazine. Other drugs like leflunomide,cyclosporine,azathioprine,D-penicillamine and gold salts are used either alone or in combination when the conventional DMARD combination therapy fails. The TNF-alpha inhibitors, Etanercept which is a fusion protein of the soluble portion of the human TNF p75 chain of the receptor and the Fc portion of the human Ig G1.This drug is used in patients who fail to respond to first line drugs and is shown to have higher improvement at ACR 20,50,70 responses, infliximab a chimeric monoclonal antibody has also been shown to reduce the clinical signs and symptoms along with slowing the radiological progression. Adalimumab is a fully humanized monoclonal antibody against TNF. Other drugs like abatacept, a fusion protein of

CTLA4 with IgG, Rituximab, an anti CD 20 B cell depleting agent have shown to have favorable results on the clinical as well as radiological progression of the disease. Statins were found to have beneficial effects in RA. Drugs which are under trial include p38 MAP kinase inhibitor, anit B cell stimulator (BLyS) and other anti cytokine therapies.

REVIEW OF LITERATURE

The studies done on the various neurological manifestations at various centres in different countries were reviewed. There are no larger studies on CNS vasculitis in RA and most of them are case reports. Cerebral vasculitis in rheumatoid arthritis has been reported rarely and spinal cord vasculitis not at all. **Watson P** *et al* reported a patient with rheumatoid arthritis and necrotizing vasculitis affecting only the central nervous system. Clinical and pathological involvement by this process was shown in both cerebral hemispheres, the pons and spinal cord (19). **Mandybur TI** *et al* reported three cases of cerebral amyloid angiopathy. There was also a chronic cerebral vasculitis characterized by segmental fibrinoid necrosis, chronic adventitial inflammatory infiltrates, obliterative "endarteritis" and hyaline arteriolar change, resembling rheumatoid vasculitis. Two of these cases had rheumatoid arthritis, and one had unspecified "arthritis" at the onset of dementia. Both vasculitis and amyloidosis involved the leptomeningeal and cerebral cortical vessels. In the two autopsy-verified cases, the vascular disease was limited to the brain. In the third case, only a brain biopsy was available. Amyloid-containing neuritic plaques were present in the cerebral cortex in all three cases, but they were abundant only in one, which also showed numerous Alzheimer tangles (20).**Kim RC** *et al* have reported extensive rheumatoid lesions in the cranial dura, falx, and choroid plexus in a 63-year-old woman a case of RA who presented with confusional state as well as persistent cerebrospinal fluid pleocytosis and hypoglycorrhachia (21). **Beck DO** *et al* reported a case of seizures due to central nervous system rheumatoid meningovasculitis. Infection was excluded as a cause of the seizures and cerebrospinal fluid abnormalities, which resolved with corticosteroids and azathioprine therapy

(22).**Kamio N** *et al* reported a 78-year-old man with severe arthritis showing the formation of rheumatoid nodule-like granulomas in the dura and subarachnoid space along with the spleen .The characteristic morphological finding of the granulomas was the presence of neutrophils and the absence of definite fibrinoid necrosis, which differed from the typical features of rheumatoid nodules previously described. Additionally, they have noted systemic necrotizing vasculitis in the dura and multiple cerebral infarcts (23). **Wolf** *et al* studied the increase in cerebrovascular disease in RA. They have compared the incidence of cerebrovascular disease in RA with OA adjusting for age, sex, education level, smoking, income, hypertension, and body mass index and reported that the patients with RA had the following increased risks: current CVA 1.70 (1.29, 2.24), and lifetime CVA 1.005 (0.931, 1.196 0.86 and 3.02% (RA) versus 0.50 and 3.03% (OA) for CVA with RA as compared to OA (24).

Inomata-Terada S *et al* reported the first case of cerebral thromoembolism in a 45-year-old woman who had rheumatoid arthritis for 12 years and a rheumatoid nodule in the heart .She was reported to have had three attacks and died after the final attack. Her autopsy revealed a nodule at the base of the aortic valve which was pathologically proved to be a rheumatoid nodule and thrombus at the top of the nodule. It was easily ablated and a small amount of fibrin stuck the nodule.They concluded that the embolism has arisen from the thrombus in on the nodule (25). **Ramos M** *et al* reported a case of cerebral vasculitis a 63-year-old man with severe, untreated rheumatoid arthritis and pleuritis who developed an unusual neurological syndrome similar to Gerstman syndrome, followed by dementia and blindness, six weeks before his death. An autopsy showed extensive necrotizing vasculitis, resembling polyarteritis nodosa, involving the brain and resulting in numerous

infarcts. The disease was most severe in the posterior portion of the cerebral hemispheres. Other organs were only slightly involved. Severe amyloidosis of cerebral arterioles and senile plaques were noted in the areas of brain with most severe vasculitis (6).

There are many studies on the assessment of progression and the compressive myelopathy in cervical spine involvement in RA which discuss the correlation between the disease duration, activity and the severity of peripheral joint involvement.

J. C. Stevens *et al* studied atlanto-axial subluxation and cervical myelopathy in rheumatoid arthritis in one hundred patients, 27 males and 73 females, suffering from rheumatoid arthritis have been studied radiologically and clinically to establish the incidence of atlanto-axial subluxation (A.A.S.) and of cervical myelopathy. The diagnosis of A.A.S. was made in 36 patients on the basis of an atlanto-odontoid separation of 3 mm or more on the lateral tomogram in flexion but no particular features of the disease were identified which predisposed to this complication except that it was more common in those with subcutaneous nodules and hand deformities. Neck symptoms were not more conspicuous in those with A.A.S. Twenty-four of the 36 patients with A.A.S. had cervical myelopathy as judged by a pathological increase in the deep tendon reflexes and this became increasingly common the greater the degree of atlanto-odontoid separation. Ten patients without subluxation also had myelopathy and in only three of these was there radiological evidence of moderate or severe subaxial spondylosis (26). **Castro S** *et al* studied fifty patients with definite rheumatoid arthritis for cervical spine involvement by a clinical neurological examination, a somatosensory evoked potential (SEP) study and different radiological

techniques including tomograms, computerized tomography (CT) and magnetic resonance imaging .Two patients presented a posterior atlantoaxial subluxation due to complete erosion of the dens. Both had cervical cord compression and one of them had hypoglossal nerve paresis. The delineation of peridental pannus formation was clearly demonstrated by MRI. In the majority of cases cervical cord compression was caused by pannus formation or by vertical atlantoaxial subluxation (27).

Oda T *et al* studied the natural course of cervical spine involvement in rheumatoid arthritis by serial radiographs. The purpose was to determine the pattern of progression of cervical spine lesions in rheumatoid arthritis and predictors for the extent of progression. Subluxation frequently occurs as a result of rheumatoid involvement of the cervical spine. It may be severe in patients with mutilans deformities in the hands and feet. The extent of progression in a given patient is still unpredictable. Serial cervical radiographs in 49 patients with rheumatoid arthritis were analyzed. The extent of progression was evaluated by rheumatoid arthritis subset defined previously, which reflected the final extent of joint erosion in this systemic disease and could be roughly classified during early stages of the disease. In the upper cervical spine, reducible anterior atlantoaxial subluxation occurred first. Vertical subluxation of the axis appeared next. Irreducible change of preceding anterior atlantoaxial subluxation was a sign of the start of vertical subluxation. In subaxial lesion, subluxation occurred less frequently (22.4%) than upper cervical lesion (77.6%). The extent of progression was different with the rheumatoid arthritis subset. In the upper cervical spine, none of the subset with least erosive disease developed vertical subluxation, whereas 52% of the subset with more erosive disease and 88% of the subset with mutilating disease advanced to vertical subluxation. The extent of

progression was well correlated with the number of joints with erosion. Subaxial subluxation was often seen and became irreducible in mutilating disease and more erosive disease, but not in least erosive disease. A progressive pattern of the upper cervical subluxations was clarified. That is, upper cervical lesions progressed from reducible anterior atlantoaxial subluxation to irreducible anterior atlantoaxial subluxation with vertical subluxation. This extent of progression was different with the rheumatoid arthritis subset, which was also related to the development of subaxial subluxation. The most aggressive arthritis classification, a subset with mutilating disease, had the more severe subluxation in both upper and subaxial cervical spine (28). **Chellapandian** *et al* studied the frequency of cervical spine involvement in patients with rheumatoid arthritis (RA) and its correlation with the clinical and laboratory markers of disease severity. X-rays of the cervical spine in 75 consecutive cases of RA fulfilling the 1988 revised ACR criteria were done. X-rays of cervical spine in the antero-posterior with open mouth and lateral views with the neck in neutral position and in flexion were taken. In addition X-rays of hands and feet werealso taken. Results: The abnormalities in cervical spine due to RA were found in 32 cases (42.7 percent). They were odontoid erosions in 19 (25.3 percent), anterior atlanto-axial subluxation in 15 (20 percent), lateral subluxation in 1 (1.3 percent) and osteoporosis in 2 (2.6 percent) patients. No patient had neurological deficit. There was a statistically significant correlation of cervical spine involvement with duration of the disease, tender and swollen joint counts, rheumatoid nodules, joint deformities, extra articular manifestations, rheumatoid factor (RF) positivity and erosions in X-rays of hands and feet. Conclusion: The involvement of cervical spine in RA is common. Since the patient may remain asymptomatic, the cervical radiographs should be

included in the initial evaluation of patients with RA and repeated if necessary in those with the above risk factors (29). **Schwarz-Eywill M** et al studied the involvement of the cervical spine in rheumatoid arthritis .The cervical myelopathy due to pannus formation and/or subluxation can be fatal. Aim of this study was to demonstrate the possible changes seen by MRI, and to establish a risk-profile for the individual patient. Within a period of 24 months 214 patients with active RA were included. Clinical and laboratory data were obtained and plain radiographs of the cervical spine were taken. In patients with pathological findings on X-ray an MRI was performed (36 patients). Within the group of 214 patients 36 were identified to get an cervical spine MRI. In 10 (27.8 %) a cervical myelopathy due to pannus or subluxation was present. There was no correlation of the MRI-results with symptoms and findings by examination. The patients with cervical spine disease were in all stages of RA. The majority was rheumatoid-factor positive. 5 out of 10 patients with cervical myelopathy showed neurological deficits.They concluded that the the early detection of a cervical spine involvement in RA is essential to avoid possibly fatal complications (30).

There are many neurophysiological studies on the evaluation of peripheral nerve lesions with different protocols in selection of the study population.

Frenay J *et al* have done nerve conduction studies, analysed the sensory action potential (110 nerves investigated) and demonstrated abnormalities in 15 to 20 patients with rheumatoid arthritis. It is concluded that moderate, often subclinical peripheral neuropathy is a common complication in rheumatoid arthritis (31).

In an electroneurographic study done by **Lang AH** *et al* to assess the sensory

neuropathy in rheumatoid arthritis in a selected series of twenty-three RA patients, aged from 23 to 56 years, mean 41, six sensory nerves were measured and the results were correlated with clinical and laboratory data. Significant changes in the functions of one or more nerves were found in 10 patients, 2 of whom had no symptoms of clinical neuropathy. There was a highly significant correlation between neurophysiological symptoms and clinical neuropathy symptoms, although the combination of the clinical and electrophysiological findings was variable. On the other hand, there was no significant correlation between neurophysiological / neurological findings and clinical/laboratory data (age, sex, duration of disease, stage of disease, rheumatoid factor and erythrocyte sedimentation rate). Manifest or sub-clinical mono-neuropathies in n. medianus were found in 5 patients. In the light of these results it would seem in order to recommend the inclusion of an electro-neurophysiological examination of the median nerves of RA patients in routine diagnostic procedures (32). **Canesi B** *et al* studied latent neuropathy in rheumatoid arthritis with the electrophysiological study of 45 cases. Thirty (88.2%) of thirty four patients with rheumatoid arthritis showed evidence of latent neuropathy, as judged by the following tests: measurements of motor and sensory conduction velocity; analysis of single motor units at various sites and under different conditions. All patients demonstrating electrophysiological signs of involvement of nervous functions showed no clinical signs of peripheral neuropathy. On the basis of the present results it is proposed that neurophysiological alterations could depend on a widespread (? mmunologically mediated) injury of the axonic membrane (33). A clinicopathologic and prognostic study of thirty-two patients done by **Puechal X** et al to assess the peripheral neuropathy with necrotizing vasculitis in rheumatoid arthritis analysed 32

patients with RA and peripheral neuropathy whose nerve and/or muscle biopsy specimens exhibited necrotizing vasculitis. Morphologic analysis of nerve specimens included light and electron microscopy studies and teased fiber preparation. Survival was evaluated, and the prognostic values of clinical, biologic, and pathologic features were assessed by Cox proportional hazards model. A prognostic assessment based on the significant variables was devised to estimate the probability of survival of any individual patient. Epi- and/or perineurial vasculitis was observed with the same frequency in the 17 patients with sensory and motor deficit and the 15 patients with sensory neuropathies and was associated with axonal degeneration of an average of 77.7% of the nerve fibers. They concluded that the necrotizing vasculitis is responsible for the different patterns of noncompressive neuropathies in RA, including mononeuritis multiplex and distal symmetric sensory or sensorimotor neuropathy. Cutaneous vasculitis, multifocal neuropathy, and depressed C4 level were the 3 independent variables which best predicted mortality. They propose a prognostic assessment according to these variables, to stratify patients to receive more aggressive or less aggressive therapy (34). **Murthy** *et al* studied the prevalence of carpal tunnel syndrome in South India. They have reported 7% prevalence among the patients referred for nerve conduction study (35). **Bekkelund SI** performed nerve conduction studies in 52 patients with rheumatoid arthritis (RA) and 77 healthy controls. Nerve conduction studies (NCS) including recordings of motor and sensory amplitudes, the nerve conduction velocities and the distal latencies were investigated in both groups. The mean summed amplitude of compound muscle action potentials was 30.3 mV (SD = 7.9) in the patients compared with 35.9 mV (SD = 6.8) in the controls ($p = 0.0001$). Contrary to this, the mean values for motor distal latency was 14.3 msec (SD

= 2.0) in the patients and 15.9 msec (SD = 1.8) in the controls (p = 0.0001). Decreased values for nerve conduction studies found in the patients may indicate impaired nerve functions in RA. However, the summed motor and sensory distal conduction were in fact better in the patient group (36). **Bekkelund SI** *et al* did a controlled study of quantified clinical neurological examination, including psychophysical assessment of sensory thresholds, in patients with rheumatoid arthritis (RA). Fifty-five women with seropositive RA living in North Norway and 83 healthy controls underwent clinical neurological examination quantified by neurological symptom score (NSS) and neurological deficit score (NDS). Vibration threshold (VT), warm-cold detection threshold (limen) as well as heat pain detection threshold (HPDT) were performed to evaluate afferent myelinated and unmyelinated fibre functions. Higher scores on NSS and NDS were seen in RA patients compared with the controls. Higher index finger and big toe VT was demonstrated in the patients, while results from warm-cold limen and HPDT were not significantly different in the two groups. Among the disease-related variables, the most prominent finding was a positive association of index finger VT with disease duration in the patients (P = 0.01). Maximum walking time (15 m) was a significant predictor of big toe VT in the patient group (P = 0.0001). This study suggests impaired peripheral nerve function in afferent myelinated fibres. However, involvement of dorsal column fibres cannot be excluded, although patients with radiological atlantoaxial subluxation were not included in this study (37). **Nadkar MY** *et al* assessed the neuropathy in rheumatoid arthritis. They did this study to find out the incidence and pattern of neuropathy and to correlate it with disease parameters and other extra-articular involvement. They 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. Electrocardiograph (ECG), pulmonary function tests (PFT) and ophthalmological examination were also carried out to ascertain extra-articular involvement. Ten out of 31 RA patients had neuropathy of which five each were overt and 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. Nine of the ten neuropathic patients had RA for more than 2 years. Seven patients had other extra-articular features along with neuropathy. One-third of patients with RA had evidence of neuropathy. Disease parameters such as activity, rheumatoid factor and functional and radiological grade did not correlate with neuropathy. Non-entrapment sensori-motor type of neuropathy is the most common type (38).

In order to evaluate the neurophysiological functions of RA patients by means of the peripheral nerve conduction and somatosensory evoked potential studies, 33 RA patients and 20 healthy controls were studied by **Sivri A** *et al*. Two (6%) patients were found to have carpal tunnel syndrome, while 6 (18%) patients had mononeuritis multiplex. Delayed N12, N13, N1 and P1 latencies were detected in 6 (18%) of 33 RA patients suggesting central nervous system involvement with intact peripheral nervous system. Our results confirm earlier observations that symptoms of neuropathy are fairly common in cases of RA without there being any clear correlation with any clinical variable. They recommend electroneurophysiologic examination of the RA patients as a routine diagnostic procedure (39).

Lanzillo B *et al* assessed the clinical involvement of the peripheral nervous system in forty RA patients who did not have clinical signs. They were examined neurologically and electrophysiologically, and sural nerve biopsies were performed in 4.No patient reported symptoms or signs of peripheral nerve involvement. Twenty-six patients (65%) exhibited electrophysiologic findings consistent with a sensorimotor neuropathy (in 2 of them a carpal tunnel syndrome was also present), while 3 patients showed isolated carpal tunnel syndrome. There was a moderate loss of myelinated fibers in 3 of the 4 nerve biopsy samples, and all showed an increased number of endo- and perineurial vessels and some signs of axonal degeneration. They concluded that the patients with RA may have electrophysiologic and histologic findings of peripheral nerve damage, even in the absence of clinical evidence of peripheral nerve involvement (40). **Sherifa A. HAMED** *et al* studied the occurrence of subclinical cranial and peripheral nerve involvement in 55 patients with RA.Patients had a mean age of 43.1 years and a mean duration of illness of 6.4 years. All patients presented with electrophysiological findings suggestive of peripheral neuropathy. In addition, 69.1% of them had entrapment neuropathies, in which carpal tunnel syndrome was the most common (54.6%). Sensorimotor neuropathy at sites other than usual entrapment sites was diagnosed in 70.9%, while bilateral distal sensory neuropathy in lower limbs was identified in 29.1%. Among cranial nerves examined, optic and vestibulocochlear neuropathies were common (29.1% of eyes and 40% of ears examined). Spinal accessory neuropathy was reported in 21.8% of records. Neither facial nor trigeminal nerves were affected. Electrophysiological characteristics of neuropathies were indicative of axon loss. Significant association was identified between neuropathy and patients' ages ($P < 0.01$), duration of the illness ($P < 0.001$), presence of rheumatoid

nodules ($P < 0.001$) and disease stages ($P < 0.001$).The authors concluded that their results indicate that cranial and non-compressive neuropathies are not uncommon in RA (41). **Giovanni Albany et al** have studied 92 consecutive patients with RA (69 females, 23 males, mean age 59 ± 12 years) with the mean disease duration 8 ± 7 years. Disease activity was assessed using the DAS on 44 joints. Twenty one patients (23%,12 females and nine males) had some form of peripheral neuropathy. The most common form was pure sensory neuropathy, sensory motor neuropathy in nine patients (4 females and 5 males). The pattern of sensory motor neuropathy was demyelinating in males and axonal in females. In their study age was found to be the most important independent predictor of peripheral neuropathy. The presence of erosions and of additional extraarticular manifestations were associated with four fold increase in the risk of peripheral neuropathy. DAS ,HAQ and pVAS values were not significantly related to PN (42).

Toussirot E et al tested autonomic nervous system involvement in 50 cases of rheumatoid arthritis excluding all patients liable to develop dysautonomia or having a treatment interfering with ANS. They were investigated by cardiovascular tests of heart rate variations in deep breathing, Valsalva maneuver and orthostatic change in posture. These quantified tests were reported as ratios: breathing, Valsalva and 30/15. A control series of 82 healthy subjects were tested to determine the abnormal threshold for each one of the 3 tests and allowed a correlative study. Dysautonomia was defined when 2 of the 3 tests were pathological. According to these criteria, 30 patients with RA with ANS dysfunction were retained. The clinical examination of these patients showed no neurological sign or autonomic sign but there was an inflammatory syndrome. Rheumatoid factors (RF) were frequently present as were

slowly progressive articular destructions. The statistical study revealed a significant difference between the series of RA patients and the control series, only for the Valsalva maneuver ($p < 0.01$) and there was no obvious correlation between ANS dysfunction in RA and markers of inflammation, presence of RF, duration of disease or degree of articular destructive lesions. This study is claimed to be in agreement with the literature which reports an ANS involvement in RA with a same frequency but remaining primarily subclinical and probably isolated from other peripheral or central nervous system damage (43). **Nadkar MY** *et al* have studied autonomic dysfunction in 35 RA patients using the deep breathing, orthostasis, Valsalva manouvre, cold pressor and handgrip tests and heart rate response to atropine and correlated with disease duration ,activity and severity of the disease process and presence of rheumatoid factor.Fifteen patients had autonomic dysfunction.twelve (80%) had efferent parasympathetic lesions,7(46.7%) had efferent sympathetic and 7(46.7%) had total sympathetic arc lesions.They concluded that there was no correlation between the disease duration ,activity and severity of the disease process or rheumatoid factor and found autonomic dysfunction in asymptomatic patients (44). **Evrengul H** *et al* have studied heart rate variability (HRV) as a tool for the detection of sympathetic-parasympathetic balance in the autonomic nervous system. Short-term analysis of HRV was performed for time-domain frequency in 42 patients with RA and 44 matched controls. In this analysis, patients displayed lower standard deviation of the mean than healthy subjects ($P<0.0001$). Patients tended to display higher pNN50 and root-mean-square of successive difference values than did healthy subjects, but these differences were not statistically significant ($P >0.05$). In frequency domain analysis, the spectral measures of HRV showed reduced high-

frequency (HF) values and an higher low-frequency (LF) values; as a result, the ratio between low and high frequencies (LF/HF), representative of sympathovagal modulation, was significantly increased (P=0.001, P=0.012, and P=0.003, respectively). Their data suggest an increase in sympathetic control of the heart rate in patients with RA (45).

AIM OF THE STUDY

1) To study the various neurological manifestations in patients with rheumatoid arthritis.

2) To assess the subclinical neuropathy using the neurophysiological studies.

3) To correlate neurological involvement with Rheumatoid factor positivity and the DAS 28 score.

MATERIALS

Sixty eight consecutive patients (15 males, 53 females) with rheumatoid arthritis who attended the department of rheumatology, Madras Medical College were included as the study population. This a prospective study done during September 2004 -April 2007. Thirty four age and sex matched persons were taken as controls for the autonomic function testing.

Inclusion criteria

Patients who fulfilled 1988 revised American Rheumatism Association criteria for rheumatoid arthritis.

Exclusion criteria

1) Age above 60 years
2) Endocrine and metabolic disorders
3) Hypertension
4) Treatment with drugs influencing the adrenergic nervous system
5) Liver, renal, respiratory and cardiac diseases
6) Pregnancy
7) Severe anemia

METHODS

All the selected patients were subjected for detailed clinical examination.

Hematological evaluation included complete hemogram and peripheral smear study.

Biochemical parameters including blood glucose, urea, serum creatinine, liver function tests and fasting lipid profile

Immunological evaluation included rheumatoid factor and CRP by latex agglutination method, ANA by Indirect immunofluorescence using the mouse liver substrate and Hep 2 cells if negative by mouse liver substrate

Cryoglobulin was tested by preparing the centrifuged serum, keeping it at 4^0C and reading it after 72 hours.

Anticardiolipin antibodies Ig G and Ig M by ELISA and Lupus anticoagulant tests activated partial prothrombin time, dilute Russel viper venom test and Kaolin clotting time were done if appropriate.

Radiological evaluation included X-Rays of the hands, feet, and cervical spine AP, lateral flexion and neutral, skull AP open mouth views.

CT scan and MR Imaging were done if the patients had neurological signs or symptoms. Nerve conduction study was done for all patients.

Nerve conduction study

- *Motor nerve studies done in median, tibial, peroneal and ulnar nerves on both sides.*
- *F wave studies done in tibial nerve, median nerve and peroneal nerve on both sides.*
- *Sensory nerve conduction study done in median nerve*

Sensory nerve conduction study in median nerve

The recording electrodes are placed over the index finger and median nerve is stimulated at the wrist **(figure 1**). The amplitude is measured in microvolts and distal latency (to onset), or peak velocity (to peak response) in milliseconds. Values on both sides are compared. Normal tracing is shown in **figure 2**.

Stimulation and recording sites of ulnar nerve

The stimulation points of the ulnar nerve are at the wrist, below and above the elbow, in the axilla, and at Erb's point in the supraclavicular fossa. Recordings of the muscular response are over the adductor digiti minimi. The distance between the stimulation and recording sites is measured in centimetres.

Motor conduction studies

For motor conduction study in the median nerve recording electrode is placed over the abductor pollicis brevis and a supramaximal stimulus is given at the wrist 3 cm proximal to the distal palmar crease and for the tibial nerve

recording electrode is placed over the abductor hallucis and the stimulus given at the ankle. Peroneal nerve conduction study is done keeping the recording electrode over the extensor digitorum brevis and the stimulus is given at 2 cm distal to the fibular neck, at the neck of fibula, 5-8 cm above the fibular neck. Normal tracing is shown in **figure 3**.

Autonomic nervous system testing

Autonomic nervous system testing was done using the INCO-HRV analysis software.

Patients were asked to relax in a quiet room for atleast 10-20 minutes before testing. Thirteen patients who were not able to perform the tests were excluded.

The tests included

1) Analysis of heart rate, systolic and diastolic blood pressure, low frequency and high frequency ratio of the beat to beat variability at rest.

2) Reflex tests including orthostatic standing test to assess the 30^{th} and 15^{th} heart beat ratio of the RR interval, systolic and diastolic blood pressure difference

3) Expiratory, inspiratory ratio with deep breathing

4) Valsalva ratio- the ratio of the longest R-R interval during phase IV and to the shortest R-R interval during phase II.

5) Heart rate, diastolic blood pressure difference at 1 and 5mts with isometric hand grip

6) Cold pressor stimulation and assessment of heart rate and diastolic blood pressure difference at 1and 5 minutes.

The data were analysed comparing the age and sex matched healthy controls using the Anova Software.

RESULTS

A total of 68 patients were evaluated. The male, female ratio was1: 3.5, the mean age was 39.5 yrs. Mean duration of the disease was 3.6 yrs. Out of 68 patients 27 (male-3, female-24) patients had neurological symptoms in the form of paraesthesia of the hands and feet, numbness, weakness or radicular pain. Seven patients had signs of neurological involvement on clinical examination. Two patients had quadriparesis due to cord compression. One patient had lateral medullary syndrome. Two patients had absent ankle jerk. Two patients had positive Tinel's sign due to carpal tunnel syndrome. One patient had rheumatoid nodules, 10 patients had deformities in the form of boutonnier's deformity in 1, swan neck deformity in 1, finger drop in 1, jaccoud's arthropathy in 1, hallux valgus in 2,hammer toes in 1, instability of the knees in 2, foot drop in 1. Two patients had quadriparesis due to cord compression.

Laboratory evaluation showed anemia in ten patients, elevated ESR in 64 (92%), elevated CRP in 62 (91%). Rheumatoid factor (RF) was positive in 53 (77%) patients. Antinuclear antibody (ANA) was positive in 7 (10%) patients. Cryoglobulin was positive in 7 (10%) patients. Radiological examination showed juxta articular osteopenia in 52 (75%) patients, joint space loss in 24 (35%), erosive changes in 8(10.2%) patients. MR Imaging of the spinal cord showed atlanto axial subluxation (**Figure 5**) in 2 patients. Erosion of odontoid was seen in 3 patients (**Figure 6**) and pannus formation in one. MRI brain showed brainstem infarct in one patient. DAS 28 was in the range of 3-8.48 with a mean of 6.5 (**Figure 7**). The mean DAS28 score was 6.3 in patients with neurological involvement. Other system involvement in the form of interstitial lung disease was seen in 5 patients. Secondary Sjogren's syndrome was present in 2 patients.

Neurolgical involvement was present in 29 (42%) patients. Central nervous

system involvement was seen in 3 (4.4%) patients in the form of Brainstem infarction in 1, spinal cord compression and quadriparesis in 2. The mean age was 48 years, mean disease duration was 10.7 yrs. Anemia of chronic disease was present in one patient. The ESR was elevated in 2 patients, CRP was elevated in all the 3 patients. None of the patients had ANA or cryoglobulin positivity. Radiological evaluation showed erosions in all the patients. Atlantoaxial subluxation (AAS) was seen in 2 patients. The mean DAS 28 score was 7.1. (**Figure 8**) One patient had cervical pannus formation with radiculopathy.

Nerve conduction study was abnormal in 8 (12%) patients. Nerve conduction study was abnormal in the form of prolonged conduction velocity and conduction block in median nerves in 5 patients. Delayed nerve conduction velocity in both tibial nerves and reduction in the amplitude in one patient each. Decreased CNAP amplitude in common peroneal neves **(Figure 4)**, absent SNAP in both sural nerves in 2 patients. The mean age was 49 years and the mean disease duration was 3 years. Anemia of chronic disease was noted in 3 patients. Six patients had elevated ESR and CRP.Rheumatoid factor was positive in 5 patients. ANA was positive in one patient. None of the patients had cryoglobulinemia. Radiological evaluation showed erosion in one patient. The mean DAS 28 score was 5.56 (**Figure 9**).

Out of 55 patients who were subjected for autonomic nervous system tests, 18(32%) patients had 2 or more abnormal tests. Fifteen patients were females and 3 were males. The mean age was 35 years and the mean disease duration was 2.7 years. Anemia of chronic disease was noted in 4 patients. Seventeen patients had high ESR, 16 patients had elevated CRP. Fourteen patients had RF positivity. ANA and

cryoglobulin were positive in one patient each. Two patients had peripheral nerve involvement. The mean DAS 28 score was 6.38 (**Figure 10**). Three patients had radiological erosions.

DISCUSSION

Neurological involvement in rheumatoid arthritis is one of the extraarticular manifestations frequently reported in the literature. This study was undertaken to assess the neurological complications including the subclinical form, especially the peripheral nerve lesions and the autonomic dysfunction. The study patients were below 60 years of age so that the neurological problems due to aging was minimized. Central nervous system involvement was assessed after detailed history, clinical examination and with appropriate imaging studies. Autonomic tests were not done in patients who could not perform all the tests. In our study neurological involvement was seen in 29 (42%) patients. Eight patients had seronegative rheumatoid arthritis. Central nervous system involvement was noted in 3 (4.4%) patients. One patient had seronegative rheumatoid arthritis. The DAS 28 score was high and all of them had active disease. All the 3 patients had radiological erosions. Two patients (2%) had high cervical cord compression due to atlanto axial subluxation. They had severe neck pain, weakness of all the four limbs, sensory impairment below C4, exaggerated deep tendon reflexes and positive Babinski's sign. Somato sensory evoked potentials were not done for these patients. Prevalence of cord compression in RA due to atlanto axial subluxation reported in the previous studies were 4% (27) and 24% (26). In one study myelopathy was reported in patients who did not have radiological evidence of AAS (26). Both the patients had RA for more than 10 years. In a previous study from our center reported no neurological involvement in patients who had cervical spine involvement (29). The correlation of disease duration and the cervical complication has been reported in many studies In a study MRI of the cervical spine showed 27.8% of patients having cervical myelopathy due to pannus (30). The reason for the low

prevalence may be due to the exclusion of patients above 60 years of age and the number of patients subjected for CT or MRI cervical spine. One patient who presented with vertigo, dysarthria, ipsi lateral numbness of the face and Horner's syndrome, contralateral sensory impairment due to spinothalamic involvement was diagnosed to have lateral medullary syndrome due to brainstem infarct. As she is an young female without any other risk factors except active RA, the cause is probably a cerebral vasculitis which has produced the infarct. The prethrombotic conditions including antiphospholipid syndrome were excluded in this patient. She had severe arthritis with high ESR, elevated CRP and a high DAS 28 score. Patients with RA have a higher risk for cerebrovascular accidents due to premature atherosclerosis (24), other comorbid conditions, increased thrombogenicity due to drugs and cerebral vasculitis. Cerebral vasculitis has been reported to be very rare either because of the rarity of this entity or difficulty in proving the vasculitis. There are a few case reports of CNS vasculitis proved by meningeal biopsy or a brain biopsy or autopsy. MR Imaging is reported to be highly sensitive for diagnosing CNS vasculitis which will show multiple lesions with equal distribution among cortical and subcortical white matter regions (46). In our patient MR imaging showed a brainstem infarct which is rarely reported. Involvement of posterior circulation is very rare in CNS vasculitis due to RA.

None of our patients had neurological manifestations due to meningeal nodules or pachymeningitis due to localized immune process which are reported as the rare causes of neurological manifestations. Though CNS involvement is very rare in RA it causes death in 18.7% cases.

Peripheral nervous system involvement seems to be frequent among the extra articular manifestations of RA. The reported frequency, electrophysiological patterns and associated disability of peripheral nerve lesions in RA are widely variable (42). The reported frequency of peripheral neuropathy ranges from 23% to 65% including the subclinical form (42,40). Necrotising vasculitis in the nerve biopsy tissue has been reported in patients with peripheral nerve involvement not due to entrapment. In the present study peripheral nerve lesions were seen in 8 patients (12%). The mean duration of the disease was 3 years. Rheumatoid factor was positive in 5 cases. Elevated CRP and high ESR were seen in 6 patients. The mean DAS 28 score was 5.56 which is high indicating the active disease. None of the patients had radiological erosions.

Median nerve involvement was seen in 5 (7.3 %) patients. Mononeuritis multiplex was seen in one patient who presented with bilateral foot drop. Sensory motor neuropathy and motor neuropathy in one patient each. Carpal tunnel syndrome was reported to be of 6% (39) in one study. In the present study carpal tunnel syndrome was seen in 7.3% of the patients and it constitutes 37% of peripheral nerve lesions. All the patients had symptoms suggestive of carpal tunnel syndrome. An Indian study has reported a prevalence of carpal tunnel syndrome as 7% among the patients referred for neurophysiological evaluation (35). Mononeurits multiplex was seen in one patient (1.4%) .The reported prevalence of mononeurits multiplex are 12% in an Indian study (38) and 18% (39) in another study done in Turkey. The prevalence of mononeurits multiplex is very rare in this study.

Sensory motor neuropathy was seen in one patient whereas it has been

reported to be the commonest (69%) type of subclinical peripheral neuropathy in one study (40) and it constituted 18% in an Indian study (38).

Pure motor neuropathy involving the common peroneal nerve was seen in one patient who was asymptomatic. There was no significant association of peripheral nerve involvement with rheumatoid factor positivity as noted in an Indian study (38).

Autonomic dysfunction was reported to be 60% in a study done by Toussirot E et al (43). One Indian study reported a prevalence of 42.8% of patients with RA. In the present study 18 (32%) patients had autonomic dysfunction. Among the reflex tests **(Tables 6-11)** valsalva ratio, orthostatic 30:15 ratio and Expition:inspiration ratio had the high significance value. Fourteen patients had RF positivity. High ESR and elevated CRP were noted in 17 patients. Only 3 patients had radiological erosion. Twelve patients had single test abnormality, and only 18 patients had abnormalities in 2 or more tests. Among the 18 patients 2 had peripheral nervous system involvement.

CONCLUSION

- There was a female predominance in the patients with neurological manifestations due to rheumatoid arthritis.
- Autonomic nervous system dysfunction was the commonest manifestation
- Among the peripheral nerve lesions carpal tunnel syndrome was the commonest lesion
- One patient had subclinical neuropathy
- Cervical myelopathy due to atlantoaxial subluxation alone correlated with the duration of the disease
- Rheumatoid factor positivity was not associated significantly with the CNS and PNS lesions.
- Active disease was seen in 66% of patients with central nervous system involvement, 75% of patients with peripheral nervous system involvement and 94% of patients with autonomic dysfunction.

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47)Proforma For RA and Neurological Involvement

Name **AGE** **SEX** **OP / IP NO:**

R

CC NO:

DATE:

Arthritis Hand MCP Duration EMS
PIP
DIP

Elbow Nodules / forearm sign

Wrist
Raynaud's
Shoulder

TM Eye—red ,,Dry

SC
Rash
Hip

Knee Ulcers

Ankle
Gangrene
ST
Numbness/ paraesthesia
MT

Spine Nail fold infarct

Past history

TB, Hepatitis, DM, HT, IHD

Personal history

Smoking, Alcohol, Exposure to STD

Occupation----

Family history

Yes / No

Obstetric history

SYSTEM EXAMINATION

RS/ creps PNS CNS

CVS

ABD

Muscles DAS 28 PGA

<u>INVESTIGATIONS</u>

HEMATOLOGY RENAL LIPIDS

LIVER THYROID PROFILE

ANA Cryoglobulins/ cryofibrinogen

HIV

RF CPK VDRL

CRP URIC ACID

ECG

X-RAYS

USG **ECHO** **CT**

MRI

DOPPLER

NCS

EMG

ANS SYMPTOMS

Sympathetic	***Parasympathetic***
Orthostatic hypotension	Blurred vision
	Dilated pupils
Blurred vision	Dry eyes
Lightheadedness	Dry mouth
Coat hanger pain	Fixed heart rate
	Resting tachycardia
Nonreactive pupils	Abdominal pain
Sexual dysfunction	Early satiety
	Nausea/vomiting
Hypohidrosis	Constipation
Anhidrosis	Ileus
	Diarrhoea
Urinary retention/frequency Incontinence	Heat intolerance
Hyperhidrosis	Sexual dysfuntion

ABBREVIATIONS FOR THE MASTER CHART

ABN	-	Abnormal
ANA	-	Antinuclear antibody
ANS	-	Autonomic nervous system
Bou	-	Boutonnier's deformity
CNS	-	Central nervous system
CRP	-	C-reactive protein
Cry	-	Cryoglobulin
DOD	-	Duration of the basic disease
DOS	-	Duration of neurological symptoms
ERO	-	Erosion
ESR	-	Erythrocyte sedimentation rate
FFD	-	Fixed flexion deformity
Hb	-	Hemoglobin
HV	-	Hallux valgus
ILD	-	Interstitial lung disease
JAO	-	Juxta articular osteopenia
JSL	-	Joint space loss
Numb	-	Numbness
Paraes	-	Paraesthesia
PNS	-	Peripheral nervous system
RF	-	Rheumatoid factor
Sec Sjo	-	Secondary Sjogren's syndrome