

# Neurological Involvement in Rheumatoid Arthritis

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## Abstract

Rheumatoid Arthritis (RA) is a chronic autoimmune disease of unknown aetiology. It is famous of affecting the synovial joints leading to its inflammation and deformity specially the small joints of the hands and feet. However other extra-articular manifestations do exist including nervous system affection.

Neurological affection in RA can be divided into central nervous system, peripheral nervous system and iatrogenic neuropathy which can cause central and/or peripheral nervous manifestations

**Keywords:** Rheumatoid Arthritis; Central Nervous System; Peripheral Nervous System; Cervical; Subluxation

## Central Nervous System Affection in Rheumatoid Arthritis

### Introduction

Rheumatoid Arthritis (RA) is a chronic progressive autoimmune disease which primarily targets the synovial joints leading to their destruction and deformity. A wide range of neurological manifestations can be found in RA patients including myelopathy, vasculitic neuropathy, encephalopathy and stroke. Some of these manifestations are reported to be asymptomatic and should be investigated for in order to be diagnosed This review aims at putting spotlight on this underestimated extraarticular manifestation in RA.

### Methods

A comprehensive review of the current literature on the neurological manifestations of RA was done. The searching engines were PubMed, Google scholar and Cochrane library.

### Results

A total of 29 review articles were chosen according to their clinical relevance.

### Discussion

Neurological affection in RA can be divided into central nervous system, peripheral nervous system and iatrogenic neuropathy which can cause central and/or peripheral nervous manifestations (Table 1).

**Table 1:** Neurological Manifestations of Rheumatoid Arthritis

Central Nervous System	Peripheral Nervous System
<ul style="list-style-type: none"> <li>• Cervical myelopathy</li> <li>• Meningitis,</li> <li>• Focal neurological dysfunction, - optic atrophy</li> </ul>	<p>a. Entrapment neuropathies: including</p> <ul style="list-style-type: none"> <li>• Carpal tunnel syndrome</li> <li>• Posterior interosseous nerve palsy</li> <li>• Cubital tunnel syndrome</li> <li>• Radial nerve palsy</li> <li>• Tarsal tunnel syndrome</li> </ul> <p>b. Non-entrapment neuropathies: including</p> <ul style="list-style-type: none"> <li>• Mononeuritis multiplex</li> <li>• Distal symmetric sensory neuropathy</li> <li>• Sensorimotor neuropathy</li> <li>• Morton's neuroma</li> <li>• Autonomic nervous system dysfunction</li> </ul> <p>c. Iatrogenic neuropathy</p>

## Central Neuropathy in Rheumatoid Arthritis

**Cervical myelopathy:** Compression of the spinal cord at the cervical spine level is one of the serious extraarticular manifestation of RA. The most common cervical affection in RA is Atlantoaxial Instability (AAI) with excessive movement at the junction between the atlas (C1) and axis (C2) because of either a bony or ligamentous abnormality. It can be anterior, posterior or lateral. the anterior type is the most common. Upward migrations of the odontoid and sub axial subluxation can also occur (Figure 1).

Mathews reported that 25-30% of patients with rheumatoid arthritis who were admitted to the hospital had radiographic evidence of cervical spine involvement [1].

Patients with AAI may be presented with upper motor neuron lesion with weakness, exaggerated reflexes and incontinence. Manifestations of vertebrobasilar insufficiency with vertigo, tinnitus, loss of equilibrium, visual disturbances, and dysphagia can be also found. Facial pain, auricular pain and occipital pain can result from compression on C2 sensory branches to the

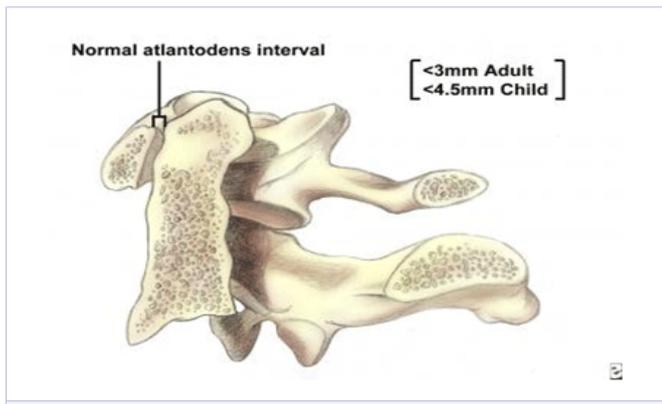


Figure 1: Normal Atlanto-Dens Distance

trigeminal tract, Greater auricular nerve and greater occipital nerve respectively.

Proper assessment of the atlantoaxial joint is advisable in all RA patients undergoing general anaesthesia to avoid cord damage during intubation of head positioning [2].

Other less common CNS affection in patients with RA includes aseptic pachymeningitis presented with aphasia and convulsions [3]. Cerebral vasculitis presenting with headache and gait disorders rheumatoid nodule formation and cerebral arteritis presenting with headaches, focal neurological dysfunction and optic atrophy, Cervical Spine Computed Tomography (CT) scanning and Magnetic Resonance Imaging (MRI) are not routinely performed and are generally reserved for either extreme cases or situations of diagnostic uncertainty [4-6].

### Peripheral Neuropathy in Rheumatoid Arthritis

In RA, peripheral neuropathy can be divided into entrapment neuropathies, non-entrapment neuropathies and iatrogenic neuropathies.

Peripheral nerve entrapment syndromes, including carpal tunnel syndrome (median nerve at the wrist), and tarsal tunnel syndrome (anterior tibial nerve at the ankle), are common in RA. Vasculitis can lead to a stocking and glove neuropathy or mononeuritis multiplex, both of which may require aggressive therapy.

### Entrapment neuropathies

Compression neuropathies are the most common and comprise between 50 and 90 % of all neuropathy in RA patients [7]. Whereas upper extremity entrapment neuropathy and RA may occur coincidentally, joint swelling and deformity resulting from synovitis and pannus formation frequently cause compression of adjacent structures [8, 9]. Furthermore, evidence has shown the intrinsic effects on nerve anatomy and physiology in patients with RA. Some studies showed electrophysiological abnormalities in asymptomatic RA patients [10, 11, 12].

Carpal Tunnel Syndrome (CTS) is the most commonly diagnosed upper extremity compression neuropathy and has been estimated to affect between 6 and 69 % of patients with RA

[13,14]. In RA patients, CTS can result from tenosynovitis of flexor tendons that pass inside the carpal tunnel. Volar Subluxation of the carpal bones is another cause [15,16] (Figure 2).

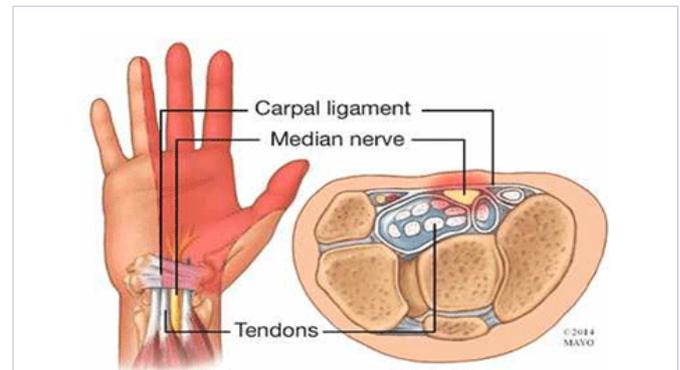


Figure 2: Cross section through the Carpal Tunnel

Patients with CTS complaint typically from pain and paraesthesia in distribution of median nerve in the hand which is the lateral three and half fingers. Weakness and wasting of the thinner muscles occur in severe cases [17]. Double crush syndrome (compression of the nerve at different level along its course) should be excluded when failure of CTS treatment is encountered.

Posterior Interosseous Nerve (PIN) palsy can also be found in RA patients secondary to elbow joint synovitis. It presents with finger drop with normal wrist extension [18]. Synovial bulge of elbow synovitis could also compress the ulnar nerve in the cubital groove causing cubital tunnel syndrome. Other causes include instability or valgus deformity of the elbow, inflammatory swelling of the medial collateral ligament, or a geode (subarticular cystic lesion) of the olecranon [9,19,20]. Munoz, et al. reported a case referred as olecranon bursitis, in which the diagnose of rheumatoid nodule was established after histological study of the respected tissue [21]. It manifests itself as pain and paraesthesia in the medial one and half finger. weakness and wasting of hand muscles and clawing can occur in severe cases [22]. Clinical evaluation is paramount in the diagnosis of cubital tunnel syndrome as Electromyography (EMG) and Nerve Conduction Study (NCS) are not adequately sensitive to detect changes associated with nerve compression [23,24].

Entrapment of the posterior tibial nerve behind the medial malleolus (tarsal tunnel syndrome) has been reported in RA patients. It is caused by tenosynovitis of the tibialis posterior, flexor hallucis longus or flexor digitorum longus. Patients with tarsal tunnel syndrome may complain from pain and paraesthesia in the toes, sole and heel (Figure 3).

Morton's neuroma is another neurological event in RA. Although it is not a true neuroma, it causes neuropathic pain in the distribution of the interdigital nerves. The most common sites are the third web space followed by the second one with rare involvement of the other web spaces (Figure 4).

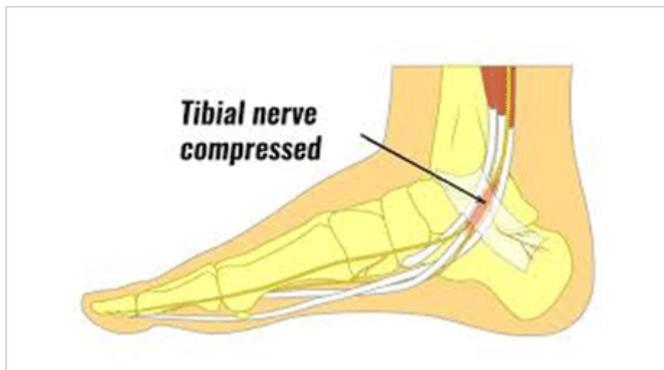


Figure 3: Tarsal Tunnel Syndrome



Figure 4: Morton Neuroma in the 3<sup>rd</sup> Web Space

Patient with Morton’s neuroma usually complains from intermittent burning pain and paraesthesia in the forefoot and corresponding toes adjacent to the neuroma. Musculoskeletal ultrasonographic diagnosis of Morton’s neuroma has comparable sensitivity as that of MRI [25].

### Non-compressive neuropathies

Although non- compressing neuropathies are asymptomatic in early stages of the disease, its presence adds to its morbidity [26]. In RA, non-compressive neuropathy includes mononeuritis

multiplex and distal symmetric sensory or sensorimotor neuropathy [27].

Mononeuritis multiplex is a painful, asymmetrical, asynchronous sensory and motor peripheral neuropathy involving isolated damage to at least 2 separate nerve areas [28].

In RA, the suggested cause is vasculitis of the vasa nervorum resulting in axonal degeneration [29]. It is presented as dysfunction of the involved nerve (Figure 5).

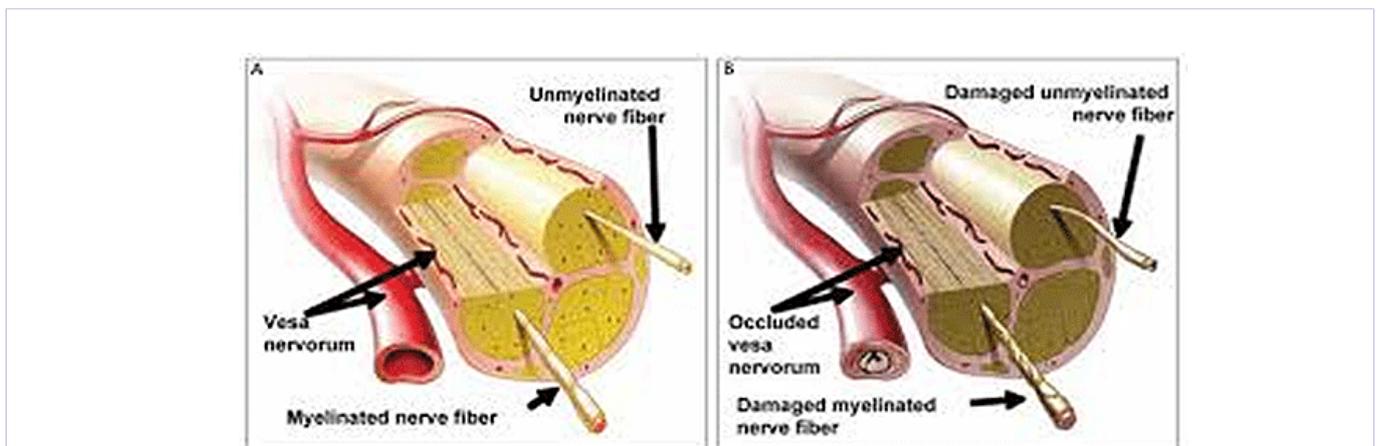


Figure 5: Vasculitis and Occlusion of the Vasa Nervorum

Motor and sensory nerve conduction studies are the standard methods of diagnosis. Distal symmetric sensory or sensorimotor neuropathy usually affects the lower limbs in the form of symmetric numbness and burning sensation with or without muscle weakness.

It is often difficult to diagnose these early neuropathies clinically due to symptoms resulting from pain in the joints and limitation of movement. However, by means of electroneuromyography, it is possible to show objectively the existence and distribution of even subclinical neuropathies [30].

Signs of autonomic dysfunction, although not always clinically apparent and measurable only with specific tests, have been found in RA patients [31]. Occurrence of autonomic dysfunction may be linked to the presence of auto antibodies targeted against ANS structures [32]. It is manifested by a variety of symptoms that may occur in isolation or in various combinations and relate to abnormalities of blood pressure regulation, thermoregulatory, gastrointestinal function, sweating, sexual function, sphincter control, ocular function and respiration [33].

## Iatrogenic Neuropathy

Drug induced neuropathy has been reported in RA in several literatures.

## Biologicals

Tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitors such as etanercept, infliximab or adalimumab, inhibit TNF- $\alpha$  by combining ligands of the TNF- $\alpha$  receptor with the Fc-fragment of IgG1 (etanercept) or as monoclonal antibodies (infliximab, adalimumab).

Different mechanisms have been proposed for the association between TNF- $\alpha$  inhibitors and neuropathy. Among these are, T-cell or induced autoantibody attack against myelin, ischaemic processes or inhibition of axon signalling. The presentation includes axonal, symmetric sensory polyneuropathy or as mononeuropathy simplex or multiplex or even as a conduction block [34,35]. A post-marketing report from US Food and Drug Administration (FDA) showed 15 patients developing Guillain-Barre Syndrome (GBS) after TNF- $\alpha$  inhibitor treatment [36].

## Leflunomide

Leflunomide is an immunomodulating agent that inhibits the mitochondrial dihydroorotate dehydrogenase and is essential in the synthesis of pyrimidine antibodies, thereby inhibiting the proliferation of activated T cells. Headache, dizziness, numbness or tingling are reported common neurological side effects. Richards, et al. reported, in a cohort of RA patients, an association between the use of leflunomide with an increase in the clinical symptoms of peripheral neuropathy; electromyographic studies showed an axonal, predominantly sensory or sensorimotor, polyneuropathy [37]. Carulli and Davies also reported two cases of peripheral neuropathy in patients commenced on leflunomide therapy, which was associated with NCS changes [38].

In an Indian study, 150 patients with rheumatoid arthritis suited for therapy with disease-modifying antirheumatic drugs (DMARD) were assigned to one group treated with leflunomide with or without methotrexate ( $n = 50$ ), while the other group was treated with other DMARDs such as methotrexate or hydroxychloroquine [39]. The leflunomide group, showed a significantly higher incidence of polyneuropathy than the methotrexate group (5/50 versus 2/100), which was confirmed by reduced nerve conduction velocity in all seven patients showing motor axonal neuropathy. All neuropathic manifestations disappeared completely within 3 months after treatment was stopped. Nerve biopsies performed on three patients showed epineural perivascular inflammation and prominent neovascularisation compatible with an axonal neuropathy and vasculitis.

## Glucocorticoids

Literature reports several cases of depression related to the use of corticosteroid therapy with an incidence of 40.5%; mania, psychosis, and delirium are also very frequent [40]. However, approximately 20% of patients receiving high doses of corticosteroids develop psychiatric disorders including

depression, mania, and psychosis requiring pharmacological treatment, while 75% report psychiatric symptoms reversible upon discontinuation of therapy [41, 42].

Steroid receptors are expressed in different areas of the brain and their role is related to the regulation of various neurotransmission, including serotonin and dopamine [43]. A set of psychiatric symptoms attributed to prolonged treatment or high-dose corticosteroids, catatonia was assessed with muscle stiffness, insomnia, and abnormal behaviours such as silence and stillness. Emotional lability and irritability are common symptoms sometimes accompanied by auditory hallucinations and paranoia [44].

Rarely, altered consciousness and disorientation may be observed.

In some cases, cognitive deficits, difficulty to maintain concentration, and poor memory, especially after prolonged treatment with high doses of corticosteroids, were observed [40]. The incidence rate of psychiatric disorders is directly correlated to dose and time of glucocorticoids exposure.

The beginning of the appearance of symptoms induced by corticosteroids is variable. They may arise in the first phases of treatment, during, or even at the end of therapy [45]. In most cases (86%), they occur within the first 5 days of treatment.

The mechanism of corticosteroid induced neurotoxicity is not known but glucocorticoids are known to affect cellular glucose metabolism and decrease glucose utilization in peripheral tissues and the brain [42].

There is some evidence to suggest that glucocorticoids may increase the release or enhance the effects of excitatory amino acids such as glutamate [46].

## Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Aseptic meningitis is the most widely recognised CNS adverse effect associated with NSAIDs. Cognitive dysfunction is also reported, most commonly with indomethacin. Inhibition of cyclo-oxygenase with a prostaglandin-mediated mechanism seems unlikely as a mechanism of NSAID-induced aseptic meningitis, since patients who develop the disorder with one NSAID can usually be successfully treated with another one [47]. In addition to aseptic meningitis, NSAIDs can cause a wide range of psychiatric and neurological problems including headache, dizziness, cognitive dysfunction, memory loss, confusion and irritability. Such CNS effects have been reported in 1 to 4% of all patients receiving a NSAID, but most frequently with indomethacin [48].

Spontaneously reported psychiatric events associated with NSAIDs include such diverse disorders as depression, hallucinations, paraesthesia, paroniria (bad dreams), emotional lability, anxiety and amnesia. These events are not limited to the elderly but can occur in all age groups [49].

## Methotrexate

MTX can cause acute, subacute, and long-term neurotoxicity

[50]. Central nervous disturbances, including headache, dizziness, vertigo, light-headedness, and mood alterations were reported in up to 36% of patients in long-term studies [51,52]. Advanced age and elevated serum creatinine are predisposing risk factors [51].

## Antimalarials

Chloroquine (CQ) and Hydroxychloroquine (HCQ) are among the conventional Disease Modifying Anti-Rheumatic Drugs (DMARD) in the treatment of RA; CQ is claimed to be more toxic than HCQ [53].

Long-term use of Hydroxychloroquine (HCQ) may lead to irreversible and potentially blinding retinal toxicity [54]. However, it is not possible to predict in which patients and in what proportion of patients an early retinopathy will progress to blindness.

The mechanism of CQ and HCQ toxicity is not well understood. High experimental doses have acute effects on the metabolism of retinal cells, but it is not clear how these short-term metabolic effects relate to the slow and chronic damage that characterizes the clinical state of toxicity. Binding to melanin in the RPE may serve to concentrate the agents and contribute to, or prolong, their toxic effects.

Hydroxychloroquine is used widely for the treatment of Systemic Lupus Erythematosus (SLE), rheumatoid arthritis, and related inflammatory and dermatologic conditions. It is now being considered for new applications in diabetes mellitus, heart disease, and adjunct cancer therapy. Thus, it is important for ophthalmologists and other physicians to understand the prevalence and risk factors for retinopathy.

Hydroxychloroquine and CQ retinopathy can progress even after the drugs are stopped, although the amount of progression and the risk to vision are functions of the severity of retinopathy at the time it is detected. [55, 56]. The typical picture is that of the "bull's eye," an intact foveal area surrounded by a depigmented ring, the whole lesion being enclosed in a scattered hyperpigmented area. At this stage the retinal vessels are contracted, there are changes in the peripheral retinal pigment epithelium, and the optic disk is atrophic. The resulting functional defects are varied: difficulty in reading, scotomas, defective colour vision, photophobia, light flashes, and a reduction in visual acuity. Symptoms do not parallel the retinal changes. By the time that visual acuity has become impaired, irreversible changes will have taken place.

New guidelines and recommendations for screening for Chloroquine and Hydroxychloroquine Retinopathy have been developed by the American Academy of Ophthalmology. It states that for baseline examination, All patients beginning long-term HCQ or CQ therapy should have a baseline ophthalmologic examination within the first year of starting the drug to document any complicating ocular conditions and to establish a record of the fundus appearance and functional status. Most critical is fundus evaluation of the macula.

Although baseline visual fields and Spectral-Domain Optical Coherence Tomography (SD OCT) are always useful, it is not

critical to obtain them at baseline unless abnormalities are present (e.g., focal macular lesion, glaucoma) that might affect screening tests.

As regards the annual screening, given the initial low risk of HCQ or CQ retinopathy, with a proper dose and in the absence of major risk factors, annual screening can be deferred until there has been 5 years of exposure. Screening should begin sooner if the risk is high [57].

Sulphasalazine has been associated with headache in up to 30%, and in rare cases with peripheral neuropathy and vertigo [58].

Cyclosporin A (CsA) induces neurological side effects in up to 40% of patients. A reversible posterior leukoencephalopathy syndrome is the most serious complication. Symptoms include headache, altered mental functioning, seizures, cortical blindness, and other visual disturbances, with hypertension. Neuroimaging studies show white matter changes in the posterior regions of the brain. Other neurological side effects of CsA include tremor, diffuse encephalopathy, cerebellar syndrome, extrapyramidal syndrome, pyramidal weakness, and peripheral neuropathy. Dose reduction or withdrawal of CsA usually results in resolution of clinical symptoms and of neuroimaging abnormalities [59].

## Conclusion

A wide spectrum of neurological manifestations can be found in RA ranging from myelopathy to peripheral neuropathy. Rheumatologists should put the nervous system in the back of their minds while examining a rheumatoid case in order not to miss an important system which affection could have a major impact on the patient's quality of life.

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