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REVIEW ARTICLE

Beyond the joints

Neurological involvement in rheumatoid arthritis

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Abstract Although arthritis is the most notable component, rheumatoid arthritis (RA) is a systemic inflammatory disorder where extra-articular manifestations are common; among them, central and peripheral nervous system involvement is frequent and associated with significant morbidity and, in some cases, reduced life span. It may produce a myriad of symptoms and signs ranging from subtle numbness in a hand, to quadriparesis and sudden death. Central and peripheral neurologic manifestations may arise from structural damage produced by RA in diarthroidal joints, by the systemic inflammatory process of the disease itself or by the drugs used to treat it. Neurologic syndromes may appear suddenly or developed slowly through months, and emerge early or after years of having RA. Neurologic manifestations may be easily overlooked or incorrectly assigned to peripheral arthritis unless the attending physician is aware of these complications. In this article, we review neurologic involvement in RA patients with emphasis on clinical approach for early detection.

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Introduction

Rheumatoid arthritis (RA) is a prevalent and complex disorder where the inflammatory process may persist active for decades [1], with a multidimensional impact ranging from pain, joint stiffness and the development of comorbid conditions such as cardiovascular diseases or cancer, to family distress and high societal costs [2].

Although the clinical hallmark of RA is arthritis that in many cases progress to destruction of the diarthroidal joints, it can also produce extra-articular manifestations in several organs and systems. Among them neurologic features involving both the central and peripheral nervous system are common and associated with significant morbidity and may indicate heightened disease activity. Neurological involvement may produce a myriad of symptoms and signs that may remain undetected or mistakenly assigned to peripheral arthritis unless the attending physician is aware of these complications. Moreover, some neurological manifestations are related to the drugs used to treat RA patients [3]. The reported frequency of neurologic involvement in RA patients depends on the used definitions, diagnostic methods, studied population and settings. For instance, Hanly et al. [4] reported that cumulative neuropsychiatric (NP) syndromes were more frequently found in RA patients than in systemic lupus erythematosus (SLE) when using ACR nomenclature and standard definitions for NP-SLE. We review here neurologic manifestations associated with RA or its treatment (Table 1) with emphasis on clinical manifestations and strategies for early detection.

Table 1 Neurological syndromes associated with rheumatoid arthritis

Neurologic syndromes	Assigned causes
Peripheral nervous system	
Mononeuritis multiplex	Vasculitis
Distal symmetric sensory neuropathy	Unknown
Sensorimotor neuropathy	
Carpal tunnel syndrome	Unknown, Vasculitis?
Posterior interosseous nerve palsy	Compression neuropathies, local joint changes
Cubital tunnel syndrome	
Compression of radial nerve	
Tarsal tunnel syndrome	
Morton's neuroma	
Autonomic nervous system dysfunction	
Diverse, related to dysautonomia	Unknown
Central nervous system	
Cervical myelopathy	Atlantoaxial subluxation
Meningitis, focal neurological dysfunction, optic atrophy	Subaxial subluxation
	Vasculitis, rheumatoid nodules
Drug-related neurologic manifestations	
Diverse, central and peripheral neurologic syndromes	Glucocorticoids
	NSAIDs
	Methotrexate
	Antimalarials
	Sulphasalazine
	Leflunomide
	Penicillamine
	Gold salts
	Cyclosporin
	Anti-TNF† agents
	Rituximab

NSAIDs non-steroidal anti-inflammatory drugs, *anti-TNF* anti-tumor necrosis factor

Peripheral neurologic manifestations

Involvement of the peripheral nervous system is common in RA. Clinical neuropathy occurs in up to 20% of RA patients [5–8] and presents in the form of entrapment neuropathies, mononeuritis multiplex, distal sensory neuropathy and sensorimotor neuropathy [9] (Table 1). Subclinical neuropathy has been reported to be prevalent in 65–85% of the RA patients [10, 11].

Noncompressive neuropathies

Noncompressive neuropathies in RA patients may be asymptomatic in the early stages of the disease or may present with a variety of symptoms including pain, paresthesias, and muscle weakness. These symptoms may mimic or overlap with those of arthritis. Yet the presence of noncompressive neuropathies increases the morbidity in RA patients [12].

Noncompressive neuropathies include mononeuritis multiplex and distal symmetric sensory or sensorimotor neuropathy [13]. Mononeuritis multiplex is a painful asymmetric asynchronous sensory and motor peripheral neuropathy involving isolated damage of at least two separate nerve areas [14, 15]. It results from necrotizing or occlusive vasculitis of the vasa nervorum producing axonal degeneration [10, 16]. The most common manifestations are foot and wrist drop [17, 18]. Mononeuritis multiplex occurring in a patient with longstanding RA is considered diagnostic of systemic vasculitis [12].

Primarily sensory neuropathy may present as axonal degeneration and demyelinization that affects the lower extremities in a symmetrical way. It is characterized by paresthesias, numbness, burning pain, and sometimes motor deficits. Electromyography can be used to confirm the neuropathy, but in doubtful cases a sural nerve biopsy is indicated [5]. Recently, Bayrak et al. [19] described that ten out of 60 patients with RA had electrophysiologically

changes compatible with polyneuropathy, the most common finding was mild symmetric sensoriomotor axonal polyneuropathy. RA disease duration and DAS-28 were associated with a 4- and 3-fold increase in the risk of polyneuropathy [19]. Vasculitis, especially of the epineurial and endoneural arteries, is observed in the sural nerve biopsy [20]. Alternatively, an indirect confirmation of the vasculitic origin of the neuropathy may be obtained by detecting vasculitis in other tissues, such as skin or skeletal muscle [12, 21].

Necrotizing vasculitis is responsible for the different patterns of noncompressive neuropathies in RA. The most common findings in the involved peripheral nerve are: fibrinoid necrosis of the media with infiltration by polymorphonuclear leukocytes, eosinophils, and mononuclear cells; perivascular infiltration with mononuclear cells; intimal proliferation with minimal cellular infiltrates and fibrosis. All these changes lead to vessel ischemia and subsequent axonal degeneration and neuronal demyelination [16].

Compression neuropathies

Compression (entrapment) neuropathies are often found with early disease and associated with local joint changes. Carpal tunnel syndrome (CTS) is the most frequently encountered compression neuropathy in RA patients; its frequency varies from 23% to 69% depending on the diagnosis methods [22]. Carpal tunnel is the anatomic space borderer posteriorly by the carpal bones and anteriorly by the transverse carpal ligament. Tenosynovitis of the flexor tendons of the fingers, which also travel within the tunnels, is the probable cause of median nerve compression in RA patients. Patients complain of pain and paresthesia in one or both hands. Pain has a burning or stinging quality and is made worse by repetitive activities of the hand and at night. Sensory symptoms are usually limited to the median nerve territory (thenar area and palmar aspects of first four digits) [23]. However, these symptoms may involve forearm, upper arm and even the shoulder due to Martin–Gruber anastomosis (median-to-ulnar crossover) [24].

Symptoms arising from CTS may start at any time during the course of RA, or even before RA is clinically evident. There are two commonly used provocative tests useful as screening for CTS. The Tinel's sign, light percussion at the flexor wrist triggers a shower of paresthesias down the involved fingers, and the Phalen's test, where the patient is asked to hold the forearms horizontally allowing the hands to drop into complete flexion at the wrist for 60 s; paresthesias in the median territory indicate a positive response. Phalen's test performs litter better, as it has a sensitivity of 64%, specificity of 75%, positive likelihood ratio of 2.54 and a negative likelihood ratio of 49% [25]. However, they may be found positive in asymptomatic individuals and in other local problems [26]. CTS may coexist with additional impingement(s) on the nerve, whether at the proximal forearm in the pronator syndrome or in the neck. Multiple compressions (double crush syndromes) are responsible for some of the treatment failures of carpal tunnel release. RA patients with suspected CTS should have image studies such as ultrasound or MRI, and electrodiagnostic testing before deciding conservative or surgical treatment.

There are few reports of posterior interosseous nerve (PIN) palsy, cubital tunnel syndrome and compression neuropathy of the deep branch of the radial nerve in RA patients. PIN palsy presents with inability to extend the fingers, whereas wrist extension is normal. The mechanism of nerve impingement is an anterior synovial bulge due to synovitis of the elbow joint [27]. Differential diagnosis of PIN includes extensor tendon rupture, metacarpophalangeal joint dislocation and cervical neuropathy [22]. Cubital (ulnar) nerve palsy results when the ulnar nerve is compressed at the medial elbow. An early complaint is waking up with paresthesias in the ulnar portion of the hand (fourth and fifth digits). Symptoms are promptly relieved by extending the extremity. Sensory loss, weakness of intrinsic muscles, and muscle atrophy are markers of late disease [23]. Compression neuropathy of the deep branch of the radial nerve is a rare condition. Symptoms include shooting paresthesias up and down the course of the radial nerve for several days or weeks followed by paresis of extensor digitorum communis and extensor carpi ulnaris [23]. There is an inability to extend the index, long, ring, and little fingers. Wrist dorsiflexion is weak and results in dorsoradial deviation. This clinical picture may be confused as extensor tendon rupture. Passive flexion of the wrist by automatically extending the fingers (tenodesis effect) rules out tendon rupture.

RA patients may have major structural changes in the midfoot and foot due to combination of chronic synovitis and weight bearing. Tarsal tunnel syndrome and Morton's neuroma may develop in these patients. Tarsal tunnel syndrome refers to the entrapment of posterior tibial nerve resulting from tenosynovitis of the tibialis posterior, flexor digitorum longus, and flexor hallucis longus. It is characterized by dysesthetic pain in the toes, sole, and heel. Tinel sign posterior to the medial malleolus may be present [23]. Morton's neuroma is a tender thickening of the digital nerve between the third and fourth toes or the second and third toes, causes forefoot pain. Two finger compression (one dorsal and one plantar) at the symptomatic intermetatarsal space may suggest Morton's neuroma, and may be felt as a tender fusiform swelling under the plantar skin [23]. Clinical assessment may perform better than ultrasonogra-

phy and MR imaging in the preoperative evaluation of Morton's neuroma [28].

Autonomic nervous system dysfunction

Autonomic nervous system dysfunction or dysautonomia has been reported in several non-rheumatic and rheumatic conditions. 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.

The dysfunction of the autonomic nervous system in RA patients has been recognized for almost 50 years [29]. Most of the reports are cross-sectional studies with small samples, using heterogeneous methods to assess it, and including patients with no specific neurologic symptoms. Although dysautonomia has been well characterized and associated with short-term mortality in diseases such as diabetes mellitus, its frequency, clinical features, pathogenic mechanisms, treatment and prognosis in RA patients remain largely unknown.

Central nervous system (CNS) involvement in RA patients

There are several CNS syndromes associated with RA, including cervical myelopathy, vasculitis, meningitis, optic atrophy, and rheumatoid nodules (Table 1). The prevalence of cervical involvement among those with RA varies with the patient subset studied ranging from 4% to 61% [30, 31], and cervical myelopathy from either atlantoaxial subluxation (AAS) or subaxial subluxation is the most frequent CNS involvement found in RA patients. An increased risk of radiographic cervical involvement has been associated with the presence of either rheumatoid factor or an elevated C-reactive protein level [32, 33].

Atlantoaxial subluxation

AAS has been classified as congenital, traumatic, or spontaneous. Spontaneous AAS usually occurs in association with an infectious or inflammatory process, and has been described as a complication of various rheumatic conditions [34–45], including RA [46–50].

The reported frequency of AAS in RA varies across studies depending on definitions, methods to diagnose it and settings. In one recent study, AAS was found in 21% of 165 consecutive RA patients [51]; as for the rest (68.7%) [52], and in another study combining standard radiography, CT scan and MRI, AAS was found in 45% (anterior in 25%, lateral in 15%, and vertical or rotatory in 10% each) [53].

AAS in RA is explained by inflammation of the synovial tissue. Four synovial articulations occur between the atlas and axis: two lateral atlantoaxial joints, one on each side, between the inferior facet of the lateral mass of the atlas and the superior facet of the axis; and two median synovial joints, one minor between the anterior arch of the atlas and the odontoid process of the axis and a second and larger lies between the cartilage-covered anterior surface of the transverse ligament of the atlas and the grooved posterior surface of the odontoid process [54]. The joints are stabilized by a large number of ligaments [55].

AAS can occur anteriorly, posteriorly, vertically, laterally and/or rotationally. Anterior AAS is characterized by an increase in the atlas-dens interval on a plain radiograph taken in the neutral position or with the neck flexed (Fig. 1). There is no consensus on the definition of the minimal distance required to diagnose anterior AAS, but

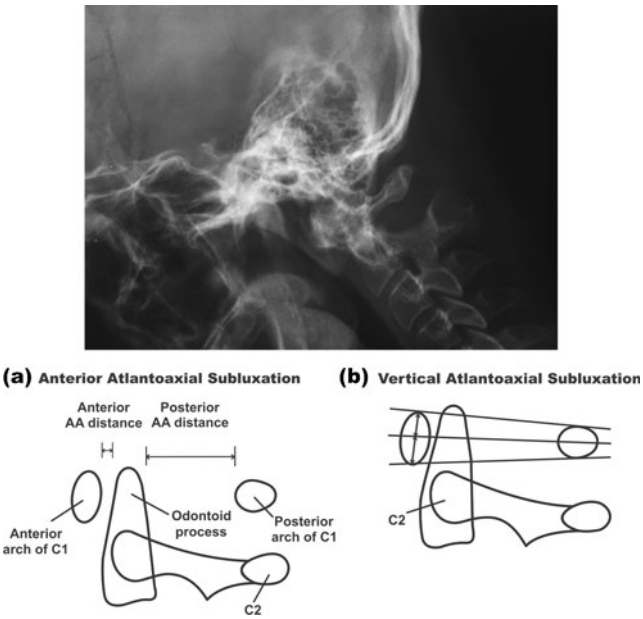

Fig. 1 Anterior atlantoaxial subluxation. A 50-year-old female with rheumatoid arthritis of 18 years duration; she was hospitalized because of severe neck pain and dizziness; X-ray in lateral view shows anterior atlantoaxial subluxation. Anterior atlantoaxial interval is the distance between the anterior aspect of the odontoid and the posterior aspect of the anterior arch of the atlas (**a**). Posterior atlantoaxial interval is the distance between the posterior margin of the odontoid and the anterior rim of the posterior arch of C1 (**a**). **b** Sakaguchi-Kauppi method to assess vertical atlantoaxial subluxation. Under normal situation (grade I), the tips of the facets of the axis are situated under a line drawn from the lower part of the posterior atlas arch to the lowest part of the anterior atlas arch (the *lower atlas arch line*). Vertical subluxation is diagnosed when the atlas falls around the axis; it is categorized into grades II, III, or IV

commonly a distance of more than 3 mm after the age of 44 and more than 4 mm in younger people should be considered [47], yet other definitions have been also proposed [56–59]. On the other hand, Boden et al. [60] found that the distance between the posterior margin of the odontoid and the anterior rim of the posterior arch of C1 (posterior atlas-odontoid interval) (Fig. 1) showed stronger correlation with the risk of neurological compromise than the atlas-odontoid interval; all of their RA patients whose posterior atlas-odontoid interval was smaller than 14 mm had neurological abnormalities [60], and surgery should be considered promptly in these cases [61].

Superior migration of the odontoid process, or vertical AAS, is better assessed in lateral films taken in neutral position. Several measurements has been used to determine it, including Chamberlain's line, McRae's line, McGregor's line, Ranawat's method, Redlund's method and Sakaguchi–Kauppi method (reviewed by Kauppi et al. [62]). McRae and McGregor's lines may be both less sensitive if the apex of the odontoid is eroded. If the apex of the odontoid cannot be identified, these methods cannot be used. Ranawat's method has not gained wide acceptance because the radiological landmarks are difficult to define. Redlund's method is based on measurements of the distance from the endplate of the axis to the McGregor's line. Although these landmarks are easy to find and this is a good method to follow-up vertical AAS, unfortunately it is not satisfactory for screening because results depend on the height of the axis which has a wide distribution in healthy individuals [63]. For screening proposes we use the Sakaguchi–Kauppi method [62]; vertical AAS is diagnosed when the atlas falls around the axis; it is categorized into grades II, III, or IV [62] (Fig. 1).

Lateral AAS may also occur in RA patients. In this situation, C1 is displaced laterally resulting in abnormal head posture, and indicates unilateral or asymmetric involvement of the lateral atlantoaxial joint. The diagnosis is provided by an anteroposterior open-mouth radiograph, which shows involvement of one or both C1–C2 joints with a greater than 2-mm shift of C2 on C2 and tilting of C1 on C2. The degree of tilting reflects the extent of the damage to the lateral mass of C2 [64]. The lateral view shows no evidence of lateral AAS.

Rotatory AAS has been also reported in RA patients and results from unilateral C1–C2 joint damage with disruption of the transverse ligament. The best incidence for demonstrating the dislocation by plain radiography is the open-mouth incidence, which shows lateral displacement of the odontoid, asymmetry of the C1 lateral masses with respect to the odontoid, and abnormal lateral mass geometry (the anteriorly displaced mass seems larger and closer to the odontoid, whereas the other mass seems smaller and farther from the odontoid). Persistence of these abnormalities when the neck is rotated confirms the diagnosis. Computed tomography (CT) scan is helpful because it shows rotation of C1 on C2. CT images in maximum inverse rotation are particularly useful [64].

Posterior AAS is when the anterior arch of C1 moves upward and the posterior arch tilts downward until it lodges in front of the spinous process of C2. On imaging studies, the posterior margin of the anterior arch of C1 lies posterior to the anterior edge of the C2 vertebral body.

CT scan can demonstrate spinal cord compression by revealing the loss of posterior subarachnoid space, attenuation of the transverse ligament, and bony and soft tissue changes [65, 66]. Magnetic resonance imaging (MRI) is particularly valuable in the assessment of cervical spine disease in RA, because it permits visualization of the pannus producing cord compression, the spinal cord, and bone [67, 68]. A dynamic (flexion–extension) MRI clearly delineates the relationship between the odontoid, foramen magnum, and cervical spinal cord, but flexion should be performed with caution because of the risk of cord compression [69].

AAS may produce a myriad of symptoms and signs that may range from neck pain on motion and occipital headache, to a broad range of neurologic or vascular manifestations, such as weakness (including quadriparesis), sphincter dysfunction, sensory deficits, pathologic reflexes, lower cranial nerve palsies, transient ischemic attacks with fluctuations of blood pressure and breathing. When is severe the clinical picture of AAS is characteristic, but in less severe degrees of displacement when the diagnosis is not to obvious, symptoms including those due to neurological changes may remain unexplained or mistakenly assigned to side effects of drugs or as a part of peripheral arthritis, unless this complication is considered. The clinical expression and severity of AAS depends on three factors: the individual variation between the spinal cord volume and space available in the bony canal, and the swiftness and type of AAS. These factors may explain that there is no clear relationship between the radiological features and the neurologic signs [55].

However, AAS may be present with no symptoms, so it is advisable to properly assess C1–C2 stability in every patient with RA before undergoes surgical procedures to avoid damage to cervical cord or brainstem during intubation or as the patient is transferred while asleep [70, 71]. Tracheal intubation with the aid of the fiber-optic bronchoscope is considered useful in RA patients as it diminishes the number of complicated intubations and reduces the intubation trauma considerably [72]. It has been also reported that AAS in RA patients is a predictor of reduced lifetime expectancy [73, 74].

Occipitocervical lesions in RA patients are an independent risk factor for sleep apnea. Small atlantodental interval

and short neck, secondary to the vertical translocation by RA, may be the cause of obstructive sleep apnea, probably through mechanical or neurological collapse of the upper airway [75].

Subaxial subluxation

Translational displacement may occur at subaxial levels. It is named subaxial subluxation and may produce also pain, radicular pain, and myelopathy. Subaxial subluxation may be developed spontaneously or associated with AAS in approximately 10% [52, 76] to 43% [51] of RA patients or as a complication after atlantoaxial transarticular screw fixation for AAS. In this last scenario, the increase of the atlantoaxial angle at the operation can lead to a decrease in the C2–C7 angle, followed by anterior subluxation of the upper cervical spine and possibly neurological deterioration [29, 77].

Miscellaneous conditions

There are rare conditions affecting the CNS that may develop in RA patients: vasculitis presenting with headache and gait disorders [78], meningitis and arteritis presenting with headaches, spells of focal neurological dysfunction and optic atrophy [79–82], and rheumatoid nodule formation [82]. Other unusual conditions reported in RA patients are aseptic pachymeningitis presented with aphasia and convulsions[83], normal pressure hydrocephalus with impaired mental status, urinary control and gait [84], cranial pachymeningitis with headache, hemiparesis, aphasia and confusion [85], and rheumatoid leptomeningitis with emotional lability, fever and myoclonic seizure [86]

Drug-related neurologic involvement in RA patients

A number of drugs used in RA patients are associated with a wide range of neurological side effects (Table 2). A full drug history, including the use of non-conventional remedies [87, 88], is essential in any RA patients with a neurologic syndrome since drug-related neurological symptoms and signs may mimic and/or overlap RA associated neurological problems. Drug-related neurological manifestations may be as simple as a common headache or as complicated as progressive multifocal leucoencephalopathy (PML). We present a review of the principal drugs used in the treatment of RA patients and the reported neurological effects.

Corticosteroids

It is well known that glucocorticoid drugs may produce psychiatric symptoms such as hypomania, mania, depression, mood disturbances, psychosis and cognitive dysfunction [89–91]. While certain clinical groups may be at greater risk of corticosteroid-induced psychiatric effects, toxicity is remarkably unpredictable [92, 93]. Although high levels of endogenous glucocorticoids secreted during prolonged stress may induce hippocampus atrophy [94, 95], it is possible that glucocorticoid drugs may produce neuronal degeneration and reactive gliosis [96, 97].

Non-steroidal anti-inflammatory drugs (NSAIDs)

These drugs may cause serious adverse events, including neurologic syndromes, such as aseptic meningitis, psycho-

Table 2 Drug-related neurologic involvement in rheumatoid arthritis patients

Drugs	Side effects
Corticosteroids	Hypomania, mania, depression, psychosis, myopathy, and cognitive dysfunction
NSAIDs	Aseptic meningitis, psychosis, and cognitive dysfunction
Methotrexate	Headache and impaired ability to concentrate
Antimalarials	Retinopathy. Ototoxicity: sensorineural hearing loss, tinnitus, cochleovestibular manifestations. Headaches, lightheadedness. Myopathy
Sulphasalazine	Headache, peripheral neuropathy and vertigo
Leflunomide	Peripheral neuropathy and headache
Penicillamine	Myopathy
Gold salts	Peripheral neuropathy, Guillain–Barré-type syndrome, cranial nerve palsies, and encephalopathy
Cyclosporin A	Tremor and headache. Myopathy. Leukoencephalopathy, cerebellar syndrome, extrapyramidal syndrome, and pyramidal weakness
Anti-TNF	Guillain–Barré syndrome, Miller Fisher syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, mononeuropathy multiplex, and axonal sensorimotor polyneuropathies
Rituximab	Progressive multifocal leucoencephalopathy

NSAIDs non-steroidal anti-inflammatory drugs, *anti-TNF* anti-tumor necrosis factor

sis, and cognitive dysfunction [98–100]. Psychosis and cognitive impairment are more prevalent in elderly patients, particularly with the use of indomethacin. Aseptic meningitis seems to be more prevalent in patients with SLE but cases are reported in RA patients who are treated with ibuprofen [101]. High doses of salicylates have been associated with tinnitus [100], although it can occur with all of the available NSAIDs.

Methotrexate (MTX)

MTX associate neurological toxicity includes headache, fatigue, or impaired ability to concentrate. It has been suggested that the neurotoxicity of MTX may be related to the accumulation of adenosine due to the inhibition of purine synthesis [102]. A rare complication, aseptic meningitis, has been reported in a RA patient using intramuscular MTX [103].

Antimalarials

Hydroxychloroquine (HCQ) and chloroquine (CQ) are used as disease modifying anti-rheumatic drugs (DMARD) in the treatment of RA; CQ is claimed to be more toxic than HCQ, although the evidence is scarce [104, 105]. HCQ and CQ may be more toxic in patients with renal and/or liver insufficiency; therefore, these medications should be used with caution in patients with renal/liver failure.

Retinopathy is the most important ophthalmologic complication of antimalarial therapy [33]. Antimalarials bind to melanin in the pigmented epithelial layer of the retina that may damage rods and cones and lead to permanent vision loss. The exact incidence of retinopathy is unknown but it probably occurs in about 3–4% of patients taking HCQ and up to 10% taking CQ after 10 years of use [104, 105].

Both HCQ and CQ use has been also associated with ototoxicity [106, 107]. Some reports have described sensorineural hearing loss, tinnitus, sense of imbalance, and cochleovestibular manifestations. CQ ototoxicity results from variable injuries such as decrease in neuronal cells, loss of supporting hair cells, and atrophy of stria vascularis [108]. Brain-evoked response audiometry seems to be the most sensitive test in detecting early manifestations of cochlear injury caused by CQ when still in a reversible stage [109]. The reversibility of CQ ototoxicity has been controversial, but it may reverse if the drug is stopped. Other manifestations are headaches, lightheadedness [110], insomnia, nervousness, psychosis and convulsions; the last two in the context of malaria treatment [111].

Myopathy is a rare complication of antimalarial drugs; one study estimated the incidence to be 1 in 100 patient-years [112]. HCQ causes a vacuolar myopathy that is usually of mild to moderate severity. HCQ neuromyotoxicity is a rare complication characterized by proximal muscle weakness, normal creatinine kinase levels, and characteristic ultrastructural changes on muscle biopsy of curvilinear body formation. Casado et al. [113] evaluated the prevalence of antimalarial myopathy in a cohort of 119 patients with rheumatic diseases and found a higher prevalence of myopathy than previously recognized when muscle enzyme determination is used as a screening method.

Leflunomide

Cases of toxic neuropathy have been observed in RA patients treated with leflunomide. Richards et al. [114] 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. Antonio-Valdiviezo et al. [115] reported segmental demyelination polyneuropathy and retrograde axonal degeneration with predominance of the thoracic members in a patient with RA and diabetes mellitus treated with leflunomide. Case reports suggest that early discontinuation (within 30 days of the onset of symptoms) is associated with a better outcome than stopping at a later time [116], and symptomatic improvement follows after discontinuation of the drug [117–119].

Gold salts

Gold therapy is responsible for many neurological complications [120]. Diagnostic confusion may arise because the neuropathy induced by gold can resemble some features of rheumatoid neuropathy. Typical findings include peripheral neuropathy, a Guillain–Barré-type syndrome, cranial nerve palsies including ophthalmoplegia, and, in rare cases, encephalopathy [121]. Neurologic toxicity arises after 3 months of weekly injections; myokymia (irregular muscle twitching) is a characteristic clinical sign. Neurologic complications of gold therapy are rare and reversible. Petiot et al. [122] reported a case of neuromyotonia, polyradiculoneuritis and Morvan's fibrillary chorea.

Cyclosporin A (CsA)

CsA induces neurological side effects in up to 40% of patients. Most common side effects are tremor and headache. Neurotoxicity is more frequent with high CsA blood levels. Dose reduction or withdrawal of CsA usually results in resolution of clinical symptoms. Adverse reactions involving skeletal muscle are not uncommon, and sometimes myopathy may occur, requiring discontinuation of the drug [123–125]. A reversible posterior leukoence-

phalopathy syndrome is the most serious complication [126]. Symptoms include headache, altered mental functioning, seizures, and cortical. Neuroimaging studies show white matter changes in the posterior regions of the brain. Other neurological side effects of CsA include cerebellar syndrome, extrapyramidal syndrome, and pyramidal weakness. Hypertension, hypomagnesemia, hypocholesteremia, and the vasoactive agent endothelin may all play a role in the pathogenesis of CsA neurotoxicty [127].

Anti-tumor necrosis factor (TNF) agents

TNF-alpha antagonists such as infliximab, etanercept and adalimumab are indicated for the treatment of some RA patients. Case-report and case-series report the association between anti-TNF-alpha treatment and various disorders such as Guillain–Barré syndrome (acute immune-mediated polyneuropathy characterized by progressive, symmetric muscle weakness accompanied by absent or depressed deep tendon reflexes), Miller Fisher syndrome (ophthalmoplegia with ataxia and areflexia), chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, mononeuropathy multiplex, progressive multifocal leukoencephalopathy [128] and axonal sensorimotor polyneuropathies [129–133]. Demyelinating disease's symptoms included confusion, ataxia, dysesthesia and paresthesia [134].

The United States Food and Drug Administration (FDA) Adverse Events Reporting system found 17 cases of demyelinating disease that occurred in patients receiving etanercept from 1998 to 2000 [131]. During that time, 77,152 patients received etanercept therapy. The incidence of demyelinating disease reported was of 31 per 100,000 patients per year of exposure. This prevalence appears to be higher than in the general population (4–6 per 100,000 per year). The proposed pathogeneses of TNF-alpha-associated neuropathies include both a T-cell and humoral immune attack against peripheral nerve myelin, vasculitis-induced nerve ischemia, and inhibition of signaling support for axons. Most neuropathies improve over a period of months by withdrawal of the TNF-alpha antagonist, with or without additional immune-modulating treatment. Preliminary observations suggest that TNF-alpha antagonists may be useful as an antigen-nonspecific treatment approach to immune-mediated neuropathies but further studies are required.

Also, CNS is affected is through a cerebral tuberculoma described in a patient treated with adalimumab [135].

Rituximab

Rituximab has been recently licensed for RA patients failing initial TNF inhibitor therapy. PML is a rare and often fatal opportunistic infection that has been well reported in patients with diverse rheumatic diseases. The predisposing factors such as underlying disease and immunosuppressive drug selection are incompletely understood but it would appear that patients with SLE may be at highest risk [136]. On December 18, 2006, the FDA in conjunction with Genentech and BiogenIdec issued a warning to health care providers and consumers, informing that two patients receiving rituximab for the treatment of SLE (an unapproved indication) had developed PML [137]. Additionally, in September 2008, a second letter was issued describing a patient with RA who died from PML 18 months after receiving rituximab, corticosteroids, and methotrexate therapy [138].

PML is a demyelinating disease of the CNS that occurs almost exclusively in immunosuppressed individuals. This disease is caused by a reactivation of the polyomavirus JC (JCV), usually manifests with subacute neurologic deficits including altered mental status, motor deficits (hemiparesis or monoparesis), limb ataxia, gait ataxia, and visual symptoms such as hemianopia and diplopia. Although PML lesions are located in the white matter, symptoms may be mistaken for a cortical disorder. Seizures are usually thought to be a manifestation of cortical injury rather than white matter disease, they occur in up to 18% of patients with PML [139].

Other drugs used in RA may also produce neurological symptoms. For instance, sulphasalazine has been associated with headache in up to 30%, and in rare cases with peripheral neuropathy and vertigo [140]. D-Penicillamine myopathy has been observed in 1.2% of treated RA patients [141, 142]. The development of myositis appears not been related to either dose or the duration of therapy [141, 143]. Affected patients present with symmetric proximal muscle weakness, muscle enzymes are elevated, and muscle biopsy reveals perifasicular cellular infiltrates and muscle fiber necrosis and regeneration [143, 144]. Muscle weakness resolves and muscle enzymes return to normal within a few weeks after stopping the drug but some cases require treatment with corticosteroids.

Conclusions

RA patients may develop several neurological syndromes, either by the structural damage to the joints, by the systemic inflammatory process of the disease itself, or as consequence of the drugs used to treat it. In some cases, neurological involvement is associated with high morbidity and even be life-threatening. Early assessment and a high index of suspicion for recognized complications are essential in managing such patients.

Disclosures None.

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