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Review

Neuropsychiatric manifestations in rheumatoid arthritis☆

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic disease characterized by persistent synovitis, systemic inflammation, and the presence of autoantibodies. Neuropsychiatric manifestations are quite common in RA, including depression, cognitive dysfunction, behavior changes, spinal cord compression and peripheral nerve involvement. Potential causes include systemic inflammatory process, neural compression due to bone and joint destruction, side effects of medications and copying difficulties due to the chronicity of the disease. A high level of suspicious is required for an adequate diagnosis and treatment. In this review, we will discuss topographically the main neuropsychiatric manifestations described in RA patients, in an attempt to help in the management of these complex and multifaceted disease.

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Contents

1. Introduction

Rheumatoid arthritis (RA) is a chronic disease characterized by persistent synovitis, systemic inflammation, and autoantibodies (particularly to rheumatoid factor and citrullinated peptide) [1]. Extra-articular features are observed in up to 40% of patients and are associated with increased morbimortality [2,3]. The estimate incidence of neurological symptoms in rheumatic diseases is about 11%, but in RA it can reach up to 70% when mood disorders are included [4–8]. Extra-articular manifestations are associated with disease severity, disease duration, presence of autoantibodies and comorbidities (e.g. smoking) [9,10]. With earlier diagnosis and more aggressive treatment many extra-articular manifestations such as rheumatoid nodules, have been declining [11–13]. However little is known about neuropsychiatric manifestations. In a recent study, rheumatoid vasculitis has been shown to remain a serious complication of RA and associated with significant mortality [10].

Some of the reasons for a higher incidence of neurological symptoms in RA patients compared with the normal population are:

1) RA disease by itself, with inflammation, autoantibodies, pain, fatigue and disability leading to psychiatric diseases [4,6].

Abbreviations: BA, biological agents; DMARD, disease-modifying antirheumatoid drugs; RA, rheumatoid arthritis.

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2) The systemic inflammatory processes involving all organs and systems, which can involve the neural tissue (e.g. pachimeningitis or vasculitis) [14].
3) Joint and bone destruction leading to neural compression (e.g. cervical myelopathy symptoms caused by destruction of the atlanto-axial joints and subsequent atlantoaxial subluxation) or the presence of rheumatoid nodules compressing peripheral nerves [3,15–17].
4) Potential side effects of the medication used to obtain disease control, such as corticosteroids, disease modifying drugs (DMARDS) and biological agents (BA) [17].
5) Accelerated atherosclerosis associated with systemic inflammation and autoantibodies [18,19].

Clinical presentation of neurological symptoms may vary from a sudden and emergent vertebrobasilar stroke to a slowly and insidious process of peripheral neuropathy. The intensity of the symptoms is influenced by the degree of the inflammatory process, the size of the vessel involved, medication and comorbidities [1,2].

To better understand and treat neurological diseases in patients with RA it is important to identify the primary cause of the symptoms, which may not be an easy task [13].

In this review, we discussed the most common neurological manifestations during the course of RA as well as their most probably etiology, in an attempt to help physicians in the management of these complex and multifaceted disease. The clinical manifestations are presented topographically, according to the main involved site.

2. Methods

We performed a review in the MedLine Database (National Library of Medicine), without time restriction. The following search strategy was used: ("Rheumatoid arthritis" AND "Neurological" OR "Neural" OR "Central Nervous System" OR "Spinal Cord" OR "Peripheral nerves" OR "Cognitive impairment" OR "Vasculitis" OR "Seizure" OR "Depression" OR "Anxiety" OR "Stoke").

Abstracts were then reviewed and we included articles in English language discussing about the incidence, prevalence, diagnosis and management of neurological diseases in the setting of RA with no time restriction, according to the purpose of our review. The included articles were dividing in two groups:

1) Central nervous system: divided in brain (neurological and psychiatric manifestations) and spinal involvement
2) Peripheral nerve involvement: divided in compressive and non compressive neuropathies.

3. Results

3.1. Central nervous system

3.1.1. Brain involvement

The exact incidence of brain involvement in RA is not known but is probably low compared with spine and peripheral nerve involvement.

3.1.1.1. Psychiatric symptoms. Depression and anxiety are also reported as highly prevalent in RA patients [4,5,20–22]. The prevalence varies according to the many factors, such as population characteristics, definitions and methodologies applied. Prevalence is up to 40% when considering patients with mild and moderate symptoms [23–26]. Although the prevalence of depression is higher in RA than in the normal population (RR 2.06–95% IC, 1.73–2.44, $p < 0.001$), it is similar to other chronic and disability diseases [26–29]. Potential causes for depression in RA include more advanced age, severe forms of disease, pain, work disability [25,28,30]. However depression in RA is associated with a higher risk of suicide and mortality [25].

Similarly, anxiety is also extremely prevalent in RA varying from 21 to 70% [27,28,31]. Some studies reported that depression and anxiety may frequently coexist [5]. The prevalence of anxiety in RA patients is associated with increased sensitivity to pain and suffering [5,6]. Although mood disorders have been associated with inflammatory markers in major depression and other autoimmune diseases, such association has not been extensively investigated in RA so far [32,33]. Regular screening for depression and anxiety is recommended in early treatment and offering psychological support enhances treatment outcome and increases quality of life [31,34]. Secondary causes of mood disorders have to be excluded, such as hyperthyroidism, and side effect of corticosteroids [35].

3.1.1.2. Cognitive dysfunction. Cognitive dysfunction has been described to occur in RA patients and early diagnosis and treatment is of paramount importance [36,37]. Cognitive dysfunctions are more frequently observed in RA when compared to controls especially in visual–spatial and planning functions [7,8]. Potential risk factors for cognitive dysfunction in RA are 1) the presence of low education (odds ratio [OR] 6.18, 95% confidence interval [95% CI] 1.6–23.87), 2) low income (OR 7.12, 95% CI 1.35–37.51), 3) use of oral glucocorticoids (OR 2.92, 95% CI 1.05–8.12), and 4) increased cardiovascular disease (CVD) risk factors (OR 1.61, 95% CI 1.19–2.17 per risk factor) [38].

Patients with cognitive impairment have increased functional difficulties, less adherence and poorer quality of life [7,8,38]. When cognitive complains are present, an extensive clinical and radiological investigation should be performed, including neuropsychiatric testing, screening for mood disorders, accessing disease activity as well as a brain MRI to identify potential causative factors. Finally, some biological agents are associated with leukoencephalopathy that may present as cognitive impairment, such as Toclilizumab, a humanized anti-human interleukin-6 receptor antibody [39].

In the setting of cognitive or psychiatric dysfunction, an additional evaluation of all the medication used to treat RA is important once all the drugs may have potential side effects that can lead to these symptoms. When symptoms have a temporal relation to drug start and discontinuation, the diagnosis of drug-induced neurological disorders should be considered. As some examples, methotrexate is associated with persistent headaches, especially in high doses [40]. Demyelination of the white matter fibers has been described in patients with RA, especially using rituximab, gold salts and anti-TNF drugs [41,42]. Some anti-TNF drugs were associated with some reports of demyelination, clinically manifested as cognitive dysfunction, speech difficult and sight problems [41]. The radiological findings of the demyelination are white matter hyperintense lesions in the T2 sequence of the brain MRI [41].

Finally, the repeated treatment of RA with Rituximab, a monoclonal antibody that targets the CD20 molecule on the surface of B cell, has been associated with progressive multifocal leukoencephalopathy [42]. Symptoms are diverse, varying from progressive weakness, visual and speech impairment, as well as personality changes, also associated with white matter lesions at the MRI [42].

3.1.1.3. Headaches. Headaches are common symptoms in the context of RA and can be secondary to many etiologies [43]. Although primary headaches are still the most common association in RA, physicians should pay attention to other causes, especially in the setting of progressive and disability symptoms or in the presence of other focal neurological deficits. Secondary causes of headaches in patients with RA are side effects of medication, intracranial pathology with space occupying lesions (such as tumor or infections), meningeal inflammation due to the disease itself or infection and central venous sinus thrombosis. A cranial MRI and evaluation of the cerebrospinal fluid (CSF) liquid may be necessary in some cases to rule out secondary causes of headaches in patients with RA [43].

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