

CENTRAL NERVOUS SYSTEM MANIFESTATIONS IN RHEUMATIC DISEASES MANIFESTACIJE CENTRALNOG NERVNOG SISTEMA KOD REUMATSKIH BOLESTI

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Summary: Patients with multi-system rheumatic conditions may have a disease affecting the central nervous system (CNS). Central nervous system manifestations vary according to the location of the lesion and range from focal findings (e.g., stroke-like presentations), although serious neurological complications in rheumatic disease appear to be rare. The most prominent features of neurological involvement in rheumatic diseases include cerebral ischaemia and psychiatric symptoms. Little information is available on the prevalence of neurological disease in patients with a rheumatological diagnosis. Involvement of the CNS may be a striking early or presenting feature with a wide variety of manifestations. There is more clarity about the CNS syndromes attributable to systemic lupus erythematosus and new insights into the central mechanisms involved in the manifestations of Sjögren's syndrome and rheumatoid arthritis. Severe CNS involvement is associated with poor prognosis, and high mortality rate. We review the spectrum of neurological diseases in patients with a rheumatological diagnosis.

Keywords: neurological complications, rheumatic diseases

Kratak sadržaj: Pacijenti sa višesistemskim reumatskim stanjima mogu imati i bolest koja pogađa centralni nervni sistem (CNS). Manifestacije centralnog nervnog sistema razlikuju se prema lokaciji lezije i kreću se od lokalnih nalaza (npr. stanja slična šlogu), iako su ozbiljne neurološke komplikacije kod reumatskih bolesti naizgled retke. U najčešće odlike neuroloških poremećaja kod reumatskih bolesti ubrajaju se cerebralna ishemija i psihijatrijski simptomi. Postoji malo podataka o prevalenci neuroloških oboljenja kod pacijenata sa reumatološkom dijagnozom. Zahvaćenost CNS može biti upadljiva rana ili trenutna odlika, koja se može manifestovati na vrlo različite načine. Situacija je jasnija kod sindroma CNS koji se mogu pripisati sistemskom lupusu eritematodesu i u pogledu novih saznanja o centralnom mehanizmu uključenom u manifestacije Sjogrenovog sindroma i reumatoidnog artritisa. Velika zahvaćenost CNS ukazuje na lošu prognozu i visoku stopu smrtnosti. Dajemo pregled spektra neuroloških oboljenja kod pacijenata sa reumatološkim dijagnozama.

Ključne reči: neurološke komplikacije, reumatske bolesti

Introduction

Neurological involvement is associated with significant morbidity in patients with rheumatic diseases, and may indicate heightened disease activity. Connective tissue diseases result from immunologic or auto-immune reactions. However, involvement of the central nervous system (CNS) may be a striking early or presenting feature with a wide variety of manifestations.

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When the CNS is involved, a wide range of neurologic symptoms occurs, including epileptic seizures as well as headaches, confusion, and coma (1, 2).

Rheumatoid arthritis

A wide spectrum of neurological conditions occur in rheumatoid arthritis (RA), including peripheral neuropathy, encephalopathy, myelopathy, vasculitis causing neuropathy and stroke, myositis and denervation atrophy. Neurologic complications occur in moderate to severe RA either as a result of the disease's erosive effects on joints and bones or caused by the disease itself (e.g., compressive rheumatoid nodules, rheumatoid vasculitis). Rheumatoid vasculitis affecting the CNS is rare and may present with seizures, dementia, hemiparesis, cranial nerve palsy, blindness, hemispheric dysfunction, cerebellar ataxia, or dysphasia (3, 4).

Systemic lupus erythematosus

Neurological manifestations of systemic lupus erythematosus (SLE) are common. The most frequent conditions are psychiatric disorders, dementia and seizures. Psychiatric symptoms are the commonest form of neurological involvement. Epileptic seizures are an important feature of CNS lupus (5–7).

Despite the relatively frequent involvement of the CNS in SLE, presentation of this disorder with neurologic signs or symptoms appears to be uncommon (7). The neurologic diagnoses associated with SLE include stroke, seizure, dementia, psychosis, and peripheral neuropathy. CNS involvement has been reported in up to 75% of SLE patients, with seizures occurring in up to 50% of patients by the time of death. Chorea is a well-known phenomenon in SLE, shown to be strongly related to the presence of antiphospholipid (aPL) antibodies (9–11).

Antiphospholipid syndrome

Antiphospholipid antibodies have been found in patients with SLE with CNS involvement, including psychiatric disturbances. Neurologic disorders are among the most prominent clinical manifestations associated with the antiphospholipid syndrome. Such neurologic disorders are predominantly related to focal central nervous system thrombo-occlusive events (12, 13). Antiphospholipid antibodies have been associated with a variety of neurologic manifestations. Neurologic disorders are mainly, but not exclusively, linked to focal cerebral or ocular thrombo/occlusive events. One of the most prominent and grave features associated with aPL is cerebral ischemia, which manifests as single or multiple ischemic strokes or transient ischemic attacks (14, 15). Thrombo-occlusive events may manifest indirectly in various ways, such as with seizures or multiinfarct dementia secondary to arterial thrombosis,

or with intracranial hypertension secondary to cerebral venous thrombosis. However, aPL antibodies are identified in 2% to 7% of healthy young people and in higher rates among the elderly, complicating interpretation of associations with different neurologic manifestations. APL antibodies have been found in patients with SLE with CNS involvement, including psychiatric disturbances. Migraine headaches have been reported in patients with the APS. Among patients with SLE, there is a higher rate of seizures in those with aPL antibodies (16).

Vasculitis

The CNS may be affected in 20 to 40% of patients with systemic vasculitis. Vasculitis is characterized by multi-organ involvement, and the disease often presents with significant constitutional symptoms (17, 18). The CNS may be affected with systemic vasculitis, resulting in stroke, cerebral hemorrhage (intraparenchymal or subarachnoid), encephalopathy, seizures, or a meningitis or meningoencephalitis picture (19, 20). Stroke and seizures due to cerebral vasculitis are the most frequent clinical manifestations. Other manifestations of cerebral vasculitis include headaches, confusion, or transient neurologic events, such as paresthesia, blackouts or visual loss. In Churg-Strauss syndrome, granulomatous disease may erode through the nasopharynx and lead to basilar meningitis, dural venous thrombosis, or optic neuropathy due to compression. Asymptomatic anterior ischemic optic neuropathy in the setting of systemic disease has also been reported (21).

Behçet's syndrome

Neurological involvement is classified into: 1) inflammation of CNS tissue, or 2) vasculitis with a stroke-like presentation and sinus venous thrombosis. The wide variety of neurological findings that occur are headaches, ocular and other cranial nerve palsies, seizures, cerebrovascular insufficiency, brainstem syndrome leading to cerebellar ataxia and pseudobulbar palsy. Spinal cord disease, hemisphere lesions and meningoencephalitis also occur. The most common presentation of parenchymal CNS involvement is a subacute brainstem syndrome with cranial nerve findings, dysarthria, and cerebellar or corticospinal tract signs (22, 23).

Sjögren's syndrome

Central nervous system involvement with Sjögren's syndrome remains an area of controversy. The cause of CNS disease in Sjögren's syndrome is unknown, but it is likely immunologically mediated (24, 25).

There is wide variation in reported neurological involvement in primary Sjögren's syndrome. Neurolo-

gical complications may be seen in about 40% of patients. The involvement of the CNS can present with progressive multifocal neurological symptoms, spinal cord dysfunction, motoneuron disease (with the involvement of upper and lower mononeurons), and cortical or subcortical cognitive decline. The cognitive deficits frequently involve frontal executive functions, and manifest as dysinhibition and difficulties with attention and abstraction. Memory deficit and visuospatial dysfunction are also often present (26, 27).

Idiopathic inflammatory myopathies

Idiopathic inflammatory myopathies share the histopathological feature of inflammation in striated muscle. The three major subgroups are dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM). The exact cause of the idiopathic inflammatory myopathies is unknown, but they are generally accepted to be the result of an immune-mediated process. Evidence supporting this hypothesis includes the association of idiopathic inflammatory myopathies with other autoimmune diseases such as thyroiditis, vitiligo, myasthenia gravis, and other connective tissue diseases (1, 2).

Progressive systemic sclerosis (scleroderma)

Neurologic involvement is rare, with myopathy and cranial neuropathies being the most frequently reported manifestations. Brachial plexopathy, lumbosacral radiculopathy, and polyneuropathy have also been reported. CNS manifestations are even more rare and may be due to hypertension, renal or pulmonary dysfunction caused by scleroderma, or primary vascular changes. These manifestations include encephalopathy, aphasia, dementia, psychosis, anxiety disorder, grand mal seizures, and transient ischemic attacks. Spontaneous intracerebral hemorrhages have been rarely reported (28, 29).

Ankylosing spondylitis

The main neurological complications in ankylosing spondylitis occur due to axial disease with spinal cord impingement at multiple levels (1).

Pediatric rheumatic diseases

Central nervous system manifestations are not rare in pediatric rheumatic diseases. They may be a relatively common feature of the disease, as in SLE and Behçet's disease. Direct CNS involvement of a systemic rheumatic disease primary CNS vasculitis, indirect involvement secondary to hypertension, hypoxia and metabolic changes, and drug associated adverse events may all result in CNS involvement. The manifestations are diverse; ranging from headache, seizures, chorea, changes in personality, depression, memory and concentration problems, cognitive impairment, cerebrovascular accidents to coma, and death (30).

Anti-rheumatic drugs associated with neurological side-effects

A full drug history in patients with an existing rheumatological diagnosis is imperative, since a number of drugs used in the rheumatology clinic are associated with neurological side-effects. Of particular concern are the reports of demyelinating disorders reported in patients taking cytokine inhibitors, although the risk of developing this side-effect appears low (2).

Conclusion

The spectrum of conditions includes stroke, dementia, migraine and hemiparetic somatization. Neurological involvement in rheumatic disease is associated with high morbidity and in some cases can be life-threatening. Early assessment and a high index of suspicion for recognized complications are essential in managing such patients.

A better understanding of the clinical, radiographic, and serologic characteristics of various central nervous system complications of rheumatologic diseases has been gained in the past year. A thorough knowledge of the rheumatic diseases and therapy-related adverse events is mandatory for the management of a patient with rheumatic disease and CNS involvement.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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