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Neurological Complications of Rheumatic Disease

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Rheumatic disease represents a broad spectrum of systemic conditions manifested by multisystem involvement and mediated by autoimmunity and inflammation. Their neurological complications may occur at any point in the disease process and are diagnostically challenging. For years central nervous system (CNS) was considered as a system uniquely protected from effects of the immune system because of the blood-brain barrier. Indeed, under physiological conditions immune access to CNS is tightly regulated. Over the past decade, new scientific discoveries highlighted pathways by which immune and neurological systems interact, including a variety of mechanisms controlling permeability of blood-brain barrier, and specific roles that $CD4^+$ and $CD8^+$ T-lymphocytes play in initiation of specific adaptive immune response to neural specific antigens. This leads to release of proinflammatory cytokines (interleukin 1, interleukin 6, and tumor necrosis factor alpha). In addition, B-cells involved in CNS inflammation produce antibodies against membrane bound and soluble antigens. This article describes specific neurological manifestations of the most common autoimmune rheumatic disorders.
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Introduction

Children with rheumatic diseases often have a broad constellation of clinical features above and beyond arthralgias and arthritis. Neurological manifestations are not uncommon, may be severe, and in some of these disorders represent the primary clinical disturbance, or in others exist as a part of the clinical disease spectrum. Additionally, neurological involvement may occur during the course of management because of secondary thrombosis, hemorrhage or infection, offering significant challenges to the clinician. In this article, we will review the central nervous system (CNS) and peripheral nervous system (PNS) manifestations of the common rheumatic disorders of childhood.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder characterized by multiple organ involvement and the presence of autoantibodies to native DNA. It usually presents with a chronic course manifested by periods of flares and remissions. Approximately 20% of patients develop SLE in childhood. Both adults and children with SLE have similar clinical characteristics, but children are known to have a more severe disease course and to accumulate more disease damage. CNS and PNS involvement occurs in approximately 20%-95% of patients with pediatric SLE, depending on the population studied, inclusion criteria (particularly the inclusion or exclusion of headaches, discussed later), and the period of observation, and is collectively considered as neuropsychiatric SLE (NPSLE).[1,2] Patients may develop neurological manifestations at any time during the course of the illness, however, most frequently NPSLE develops within one year from the initial SLE presentation.

In 1999, the American College of Rheumatology (ACR) developed case definitions of 19 NPSLE manifestations for adult patients, which are also applicable to children (Table).[3] Headache is the most common symptom that occurs in approximately 50% of patients with lupus and may or may not be associated with more serious neuropsychiatric involvement. New onset or worsening headache in a patient with SLE deserves further investigation as it may represent CNS vascular events or increased intracranial pressure. Psychosis has been described in approximately 30%-50% of patients with NPSLE. Lim et al[4] reported that, in a cohort of 40 pediatric patients

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Table The 1999 American College of Rheumatology Nomenclature and Case Definitions for Neuropsychiatric SLE (Adapted From Ref. 3)

Central nervous system
Aseptic meningitis
Cerebrovascular disease
Demyelinating syndrome
Headache
Migraine
Benign intracranial hypertension
Movement disorder (chorea)
Myelopathy
Seizure disorder
Acute confusional state
Anxiety disorder
Cognitive dysfunction
Mood disorder
Psychosis
Peripheral nervous system
Acute inflammatory demyelinating polyneuropathy (Guillain-Barre syndrome)
Autonomic disorder
Mononeuropathy, single/multiplex
Myasthenia gravis
Neuropathy, cranial
Plexopathy
Polyneuropathy

with NPSLE having psychosis, visual hallucinations were the most common symptom. Insight was preserved in the majority of these patients, and this was thought perhaps to be a unique feature of pediatric SLE. Cognitive dysfunction such as impairment of attention, memory, and decline in academic performance may be quite subtle in presentation and challenging to recognize. Brunner et al[5] reported that when children with SLE without previous NPSLE diagnosis were systematically screened with neurocognitive testing, subclinical cognitive dysfunction was detected in 59%. Cerebrovascular disease occurs in up to 30% of patients with NPSLE and may affect small or large vessels, involving both the arterial and venous circulations, taking the form of inflammatory vasculitis or vaso-occlusive events.[6] Cerebrovascular disease often occurs in the presence of antiphospholipid antibodies particularly with the presence of a lupus anticoagulant. Seizures in pediatric NPSLE are strongly associated with other manifestations such as headaches and cerebrovascular disease. Generalized seizures are more common than partial seizures. It is critically important to recognize that seizures can also be a manifestation of a CNS infection, uremia or hypertension, and evolved posterior reversible encephalopathy syndrome. Among movement disorders chorea is the most common feature and almost universally associated with presence of antiphospholipid antibodies. An underlying diagnosis of SLE or isolated antiphospholipid syndrome should be considered in any pediatric patient presenting with new onset chorea.[7]

Cranial and PNS involvement has been described in case reports only. Acute transverse myelitis may be the initial symptom of SLE, often associated with the presence of antiphospholipid antibodies and is suspected when patients present with muscle weakness and areflexia.[8]

Several antineuronal antibodies have been described in association of NPSLE. Anti-NR2 glutamate receptor antibodies, N-methyl-D-aspartate (NMDA) receptor antibodies, and antiribosomal-P antibodies have been identified in the serum and cerebrospinal fluid (CSF) of patients in NPSLE.[9] However, the presence of antibodies does not correlate with clinical disease activity; also antibodies may be present in patients who do not have any CNS involvement. The clinical usage of measuring these antibodies is therefore low. On the contrary, the detection of antiphospholipid antibodies in patients with SLE is quite important as it may offer insight into symptoms and also affect ongoing and future treatment.

Neuroimaging studies indicate that magnetic resonance imaging (MRI) abnormalities are detected in 25% of newly diagnosed patients with SLE and up to 60% of newly diagnosed patients with NPSLE, suggesting that brain damage occurs very early in the disease process. The most common MRI findings are white matter hyperintensities and cerebral atrophy.[10] The clinical usage of these findings is still questionable as they are reported both in patients with NPSLE and in patients with SLE without evidence of neurological involvement, therefore, these changes should be correlated with other clinical manifestation of neurologically active disease.[11] A brain MRI is most useful to demonstrate arterial or venous occlusion in the evaluation of patients with strokes or seizures. Piga et al[12] demonstrated in a 20-year follow-up study of brain MRI's of patients with SLE that a higher number of deep white matter hyperintensities was associated with an increased risk of stroke. However, the brain MRI may also be completely normal in spite of the overt presentation of wide variety of NPSLE symptoms, as shown in a study where 27 patients presented with symptoms fulfilling the 1999 American College of Rheumatology case definitions for neuropsychiatric lupus but only 41% had an abnormal MRI.[11]

Treatment decisions for SLE depend on the constellation of symptoms. The presence of NPSLE most often requires aggressive management with corticosteroids and other immunosuppressive medications such as cyclophosphamide and rituximab.

Sjogren's Syndrome

Sjogren's syndrome (SS) is a chronic autoimmune disorder that targets primarily exocrine glands. Inflammatory changes of salivary and lacrimal glands leads to dryness of oral mucosa and conjunctiva. Exocrinopathy can extend to involve skin, respiratory tract, and urogenital mucosa. SS is considered to be primary when it is not associated with another autoimmune illness or secondary, when another autoimmune illness is present, most frequently SLE or rheumatoid arthritis. SS is more common in adults, it may present in children and adolescents, usually with recurrent parotid swelling.[13,14] Extraglandular manifestations include fatigue, arthritis, purpura, pulmonary, and neurological involvement of both CNS and PNS. Immunologic features include the presence of anti-Ro (SSA) and anti-La (SSB) antibodies, high titer of antinuclear antibodies, and rheumatoid factor (RF).