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Review Article

Autoimmune Encephalopathy for Psychiatrists: When to Suspect Autoimmunity and What to Do Next

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Objective: *To provide a critical review of autoimmune encephalopathy—broadly defined as neuropsychiatric features directly related to an autoimmune process—relevant for psychiatric practice.* **Methods:** *We consulted rheumatology textbooks to define the scope of autoimmune conditions and identified recent reviews of rheumatic conditions, autoimmune vasculitis, and autoimmune encephalitis. We integrated these with primary reports to provide a clinically relevant overview of autoimmune encephalopathy. We focus on clinical features that should raise suspicion for autoimmunity.* **Results:** *Despite outlying conditions, 2 categories of autoimmune encephalopathy are described: (1) neuropsychiatric symptoms associated with rheumatic conditions and (2) antibody-associated autoimmune encephalitis. Rheumatic conditions principally include connective tissue disease and other vasculitides. These may present variously such as with unexplained delirium, cognitive decline, or depression. Autoimmune encephalitis may be diffuse or localized as in limbic, brainstem, or basal ganglia encephalitis. Unexplained delirium, psychosis, catatonia, strokes, and seizures are among common presenting symptoms.* **Conclusions:** *Prompt identification and management of autoimmunity are critical for optimal outcomes. The fact that undiagnosed and, therefore, untreated autoimmunity leads to debilitation demands vigilance for these conditions. Close attention to the unusual nature and course of neuropsychiatric symptoms, associated neurological features, and review of systems as reviewed here should guide the skillful clinician.*

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Key words: autoimmune encephalopathy, encephalitis, rheumatic disease, anti-NMDA receptor, limbic encephalitis, paraneoplastic encephalitis.

INTRODUCTION

Autoimmune encephalopathy is increasingly recognized for its early psychiatric symptoms.[1,2] It should be noted that many of the citations herein are from neurological sources, which prefer the term encephalopathy. Encephalopathy is not operationalized, so it is used here in its broadest sense to include any clinically significant neuropsychiatric features. However, the heterogeneity of symptoms encountered in autoimmune conditions makes recognition difficult. Delayed diagnosis may lead debilitating symptoms to persist or recur for decades,[3] and neurocognitive

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decline may become irreversible with prolonged brain inflammation.[4] The fact that prompt recognition of an autoimmune etiology can lead to effective treatment demands that psychiatric clinicians maintain a high degree of suspicion for autoimmunity, especially in unusual neuropsychiatric syndromes. Here, we identify key clinical features that raise suspicion for autoimmunity, provide an overview of autoimmune encephalopathies for the psychiatric clinician, and conclude with recommendations on evaluation and management.

TWO CATEGORIES OF AUTOIMMUNE ENCEPHALOPATHY

Despite several outlying conditions, 2 categories of encephalopathy due to the direct effect of autoimmunity are recognized: (1) rheumatic conditions with neuropsychiatric symptoms and (2) antibody-associated autoimmune encephalitis (AAE). Rheumatic conditions with neuropsychiatric symptoms include collagen vascular disease, vasculitides with cerebral involvement, and outliers such as neurosarcoidosis. These syndromes are defined by the nature and extent of systemic disease. Although psychiatric symptoms may be the presenting feature, systemic evidence of disease is typically evident concurrent with psychiatric symptoms.[5] Delirium and cognitive impairment are the most common neuropsychiatric presentations, but other psychiatric syndromes, such as depression and anxiety disorders, are defined.[6,7]

AAEs describe conditions of brain inflammation associated with IgG autoantibodies targeting either neuronal surface epitopes or intracellular antigens. Antineuronal surface epitope antibodies are infrequently paraneoplastic, whereas anti-intracellular antigen antibodies are often known as onconeural antibodies for their close association with malignancy.[8] Importantly, proposed diagnostic criteria for AAE identify psychiatric symptoms as a primary criterion for diagnosis. These criteria also allow for probable diagnosis and treatment of many types of AAE while awaiting antibody confirmation.[9]

CLINICAL OVERVIEW

Autoimmune encephalopathy usually has a subacute onset, progressing over the course of 1–3 months, though it may present acutely as in the case of acute disseminated encephalomyelitis. Further, the atypical nature of neuropsychiatric symptoms may alert clinicians to possible autoimmunity; diagnosis requires objective findings. Critically, computed tomography and magnetic resonance imaging (MRI) are insufficiently sensitive to rule out autoimmune encephalopathy. In fact, reviews indicate that a single brain MRI may have less than 50% sensitivity for detecting several of these conditions.[10]

Many rheumatic conditions have been associated with neuropsychiatric symptoms; however, multiorgan involvement, complex histopathology, and overlap syndromes make rheumatic conditions difficult to classify. Given intraclass and intrasyndrome diversity in these conditions, each syndrome has a unique pattern of associations with neuropsychiatric symptoms (Table 1).

The neuropsychiatric features of AAE often reflect brain regions affected, which may be *diffuse* or *focal* (Table 2). *Diffuse encephalitis* implies broad or multifocal inflammation. It may affect brain only (*encephalitis*), extend to the meninges (*meningoencephalitis*), or extend to the spinal cord (*encephalomyelitis*). Brain involvement presents with delirium and seizures. Involvement of the meninges and spinal cord causes meningismus and localizing neurological deficits, respectively.

Focal encephalitis may involve the medial temporal lobes (typically bilateral in AAE; *limbic encephalitis*), basal ganglia (*basal ganglia encephalitis*), or brainstem (*brainstem encephalitis* or *rhombencephalitis*). Limbic encephalitis is known for its common triad of anterograde amnesia, seizures, and psychiatric symptoms ranging from personality change to delirium. Features of brainstem encephalitis are variable because inflammation may involve any number of closely nestled brainstem tracts and nuclei. Cranial nerve palsies are seen in three-quarters of all patients with brainstem encephalitis, but the presence of altered arousal, long tract signs, cerebellar ataxia, or fever varies with cause.[11] *Basal ganglia encephalitis* is a poorly understood syndrome that causes dystonia, parkinsonism, chorea, emotional dysregulation, or psychosis.[12] Encephalitis lethargica may be one subtype.[13]

FEATURES THAT SUGGEST AUTOIMMUNITY

Unusual psychiatric symptoms often cue suspicion of an underlying autoimmune process (Table 3). These