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Autoimmune Etiologies with The Potential to Transform Psychiatric Practice: Experiences from a Neuropsychiatry Unit

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The relationship between neurology and psychiatry has a rich history rooted in the groundbreaking work of pioneers like Constantin von Economo. His early 20th-century investigations into encephalitis lethargica —an illness that significantly influenced the field—shed light on the complex interplay between neurologic and psychiatric manifestations (1). Today, autoimmune conditions are again challenging the boundaries between the classical distinction of psychiatry and neurology.

Highlights

- **Autoimmune causes challenge traditional psychiatric and neurological divisions.**
- **Early diagnosis of autoimmune conditions can prevent life-threatening delays.**
- **CSF analysis is crucial in identifying autoimmune neuropsychiatric disorders.**
- **Empirical immunotherapy in psychiatric settings is vital for selected patients.**
- **A multidisciplinary approach is essential for accurate diagnosis and treatment**

The increasing recognition of autoimmune encephalitis (AE) and related autoimmune psychiatric syndromes has led to the emergence of concepts such as autoimmune psychosis and autoimmune catatonia (2,3,4). Anti-NMDA receptor encephalitis, a well-characterized form of AE first identified by Dalmau and colleagues in 2007, exemplifies the critical overlap between neurology/neuroimmunology and psychiatry (5,6). This disorder typically presents with subacute-onset psychiatric symptoms—psychosis, agitation, catatonia, and cognitive disturbances—before progressing to seizures, autonomic dysfunction, and potentially life-threatening neurological deterioration. Given that nearly 80% of patients with anti-NMDA receptor encephalitis first seek psychiatric services, there is growing concern that many cases may be misdiagnosed as primary psychiatric disorders, resulting in delays in life-saving immunotherapy (7, 8, 9). This diagnostic challenge extends beyond classic AE syndromes. Many case reports have documented the etiology of AE without established autoantibodies -so-called seronegative AE- presenting solely with psychiatric symptoms, which increases diagnostic complexity (2, 3, 8).

Accumulating evidence has emphasized the need for psychiatrists to recognize autoimmune neuropsychiatric conditions and to initiate immunotherapy when appropriate to prevent complications such as treatment-resistant neurocognitive impairments, prolonged psychiatric illness, or even mortality (8, 9). In this respect, several diagnostic frameworks have been proposed to aid early identification. The classification of autoimmune psychosis into "possible," "probable," and "definite" categories provides a structured approach to assessing isolated psychiatric presentations with suspected autoimmune pathology (2). Graus criteria also provide a level of evidence for diagnosing the forms of "AE—"possible AE," "probable but autoantibody (-) AE," "definite LE," "definite NMDAR encephalitis," and "probable NMDAR encephalitis" (10). Additionally, "red flag" and "yellow flag" features have been suggested to guide further extended medical and diagnostic work-ups in selected cases (11).

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Despite these advancements, practical issues remain. The presence of autoantibodies in cerebrospinal fluid (CSF) is often considered proof of an autoimmune process, but clinical decisions regarding treatment are not solely dependent on definite serological markers (8, 10). Expert consensus reports suggest that meeting the diagnostic threshold for "possible AE" and probable NMDA receptor encephalitis may be sufficient to justify empirical immunotherapy after excluding infectious causes (8, 9, 10). Our clinical experience at our inpatient clinic aligns with these recommendations. Over the past two years, among patients presenting with isolated severe neuropsychiatric signs and symptoms and suspected autoimmunity, 17 cases exhibited indirect CSF markers of central nervous system (CNS) inflammation despite established definitive autoantibodies. Initiating empirical immunotherapy for five to seven consecutive days in these patients—typically empirical high-dose corticosteroids—led to rapid and significant clinical improvement. Moreover, two additional patients were diagnosed with definite NMDA receptor encephalitis after the confirmation of NMDA receptor autoantibodies in CSF. Experiences from our center highlight the importance of conducting routine CSF analysis in some psychiatric patients with symptoms and signs suggesting a potential autoimmune condition.

Several scoring systems and diagnostic algorithms have been proposed to facilitate the identification of autoimmune cases without definitive autoantibody confirmation (4), (12). Based on our clinical experience and diagnostic algorithms adapting these scores to adult psychiatric patients may be a helpful approach in guiding diagnostic considerations, particularly in cases with isolated psychiatric symptoms, catatonia, and delirium-like presentations where an underlying autoimmune pathology is suspected. Furthermore, the concept of "autoimmune psychosis" can provide a structured framework for identifying patients with isolated psychiatric manifestations indicative of autoimmunity (2). These criteria assist psychiatrists in systematically evaluating cases and considering immunotherapy for selected patients. Another challenge is the strict adherence to existing diagnostic criteria for AE. Although the Graus criteria for probable NMDAR encephalitis are widely recognized, they may unintentionally exclude cases that primarily present with psychiatric symptoms (10). By contrast, concerns have been raised in recent years regarding overusing, overdiagnosing, and subsequently misclassifying primary psychiatric disorders as autoimmune syndrome. The lack of adequate CSF analysis has been viewed as a major contributor to overdiagnoses or false positive diagnoses of AE, indicating the necessity for rigorous diagnostic protocols that balance sensitivity and specificity (13). Given these complexities, a multidisciplinary approach is imperative with neurology, rheumatology, and radiology. Psychiatrists must actively participate in AE diagnosis and treatment, integrating neuroimmunology principles into routine psychiatric assessments, requiring expanding psychiatric training to include core competencies in neurology, including proficiency in conducting lumbar punctures, interpreting neuroimaging data (MRI, EEG, FDG-PET), and assessing inflammatory markers in CSF.

From von Economo's early insights on the inseparability of psychiatric and neurologic conditions to contemporary advances in autoimmune-mediated neuropsychiatric clinical conditions, our understanding of mental illness is extending beyond the constraints of traditional Neo-Kraepelinian diagnostic models. The integration of neuropsychiatric and neuroimmunologic approaches in psychiatric settings promises more accurate diagnoses for patients suggestive of an underlying autoimmune condition. Psychiatrists should have experience and capability in the routine differential diagnosis and management of immune-mediated neuropsychiatric presentations.

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