AUTOIMMUNE ENCEPHALITIS ALLIANCE

Psychiatry plays a pivotal role in the diagnosis and management of AE

Autoimmune encephalitis (AE) is an emerging group of autoimmune or paraneoplastic diseases with complex neuropsychiatric presentations. Patients often present primarily or even solely with psychiatric symptoms such as fulminant psychosis, and as such, awareness amongst mental health practitioners is paramount in identification and timely treatment.

Currently, limited exposure and knowledge of these disorders for providers in many disciplines leads to delays in appropriate diagnostic evaluation and management. Our goal is to raise awareness and enhance knowledge as to how to initiate testing and appropriately manage suspected cases – psychiatrists and psychiatric providers will certainly be an integral component of this process.

While reports and descriptions of AE date back to the 1960s, our understanding of this entity has expanded dramatically over the past 15 years with the recognition and identification of pathogenic, neuronal autoantibodies. In 2007, Dr. Josep Dalmau and his team first described anti-N-methyl-D-aspartate (NMDA) receptor encephalitis, a neuropsychiatric disorder of proven autoimmune etiology that almost universally presents with psychosis.

Since that time, many more neuronal autoantibodies associated with AE have been described, and clinical criteria have been published to guide clinicians in making a diagnosis of AE prior to receiving autoantibody panel results or in the event that no autoantibody is detected. The spectrum of psychiatric symptoms that may be seen with AE now includes changes in behavior (e.g., agitation and aggression) or mood, hallucinations, delusions, mutism, and disorganized thinking.

Complementing this research has been increasing evidence for an inflammatory basis to many other neuropsychiatric disorders, particularly those of psychosis such as schizophrenia, in which complement C4 involvement has been implicated. While there is currently limited direct evidence for specific inflammatory mechanisms and no clear biomarkers of prognosis in individuals with schizophrenia or at clinical high risk for psychosis, there is extensive research being undertaken in these areas.

Despite the improved awareness that autoimmune mechanisms may underlie the development of neuropsychiatric illnesses, there remains a lot that we do not know. Autoantibodies against neuronal receptors have been identified in the systemic circulation of patients with presumed primary psychiatric disorders, however, the significance of this finding and whether they play a pathophysiologic role remains unclear. Additionally, there is no clear consensus regarding which patients with predominantly psychiatric symptoms warrant further investigations for an autoantibody or other autoimmune cause.

Psychiatrists play a pivotal role in the diagnosis and treatment of AE. As psychiatric symptoms often dominate the symptoms that occur at onset of this disease, patients may present initially to a psychiatrist who are tasked with identifying abnormal features of psychosis presentations, including alterations in mental status, seizures, and dysautonomia, which may prompt consideration of AE and consultation with a neurologist. Furthermore, for patients with suspected AE undergoing immunotherapy, psychiatric symptoms are frequently ongoing and may require symptomatic pharmacologic and non-pharmacologic symptoms.

The Autoimmune Encephalitis Alliance is dedicated to raising awareness of AE and recognizes the importance of a multi-disciplinary approach to the diagnosis and management of these patients, which includes psychiatrists in addition to neurologists and rheumatologists. What follows is a compilation of scientific articles that may be of specific interest to psychiatrists, and we invite you to join our Clinicians Network to increase awareness of AE and to improve the care provided and outcomes for individuals with this disease.

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Publications on Autoimmune Encephalitis with a focus on Psychiatry

Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin.

Pollak TA, Lennox BR, Vincent A, Najjar S, Bechter K, Lancet Psychiatry. 2020 Jan;7(1):93-108.

> *There is increasing recognition in the neurological and psychiatric literature of patients with so-called isolated psychotic presentations who have tested positive for neuronal autoantibodies and who have responded to immunotherapies. Although these individuals are sometimes described as having atypical, mild, or attenuated forms of autoimmune encephalitis, some authors fell that these cases are sufficiently different from typical autoimmune encephalitis to establish a new category of so-called autoimmune psychosis. We briefly review the background, discuss the existing evidence for a form of autoimmune psychosis, and propose a novel, conservative approach to the recognition of possible, probable, and definite autoimmune psychoses for use in psychiatric practice.*

The psychopathology of NMDAR-antibody encephalitis in adults: a systematic review and phenotypic analysis of individual patient data.

Al-Diwani A, Irani SR, Lancet Psychiatry. 2019 Mar;6(3):235-246.

> *Early immunotherapy administration improves outcomes in patients with N-methyl-D-aspartate receptor (NMDAR)-antibody encephalitis. As most patients with NMDAR-antibody encephalitis present to psychiatrists, the psychopathology of NMDAR-antibody encephalitis needs to be clearly defined to encourage accurate clinical identification and prompt treatment.*

Evaluation and Management of Autoimmune Encephalitis: A Clinical Overview for the Practicing Child Psychiatrist.

Mooneyham GC, Gallentine W, Van Mater H., Child Adolesc Psychiatr Clin N Am. 2018 Jan;27(1):37-52.

> *Medical conditions that present with psychiatric symptoms are becoming increasingly well-recognized in response to the emergence of the field of neuroimmunology. As the availability of testing for novel antineuronal antibodies has increased, so too has the clinical awareness of this diagnostic spectrum.*

In the clinic: autoimmune encephalitis

Shaw G., Neurology Today. 2018 June 7;18(11):16-17.

> *Researchers found that children and adolescents had persistent neuropsychological and behavioral problems even after recovery from pediatric anti-NMDAR encephalitis, which should be monitored and treated.*

Autoimmune encephalitis and psychiatric disorders

Honnorat and Plazat, Revue Neurol. 2018; 174:228–36.

> *Autoimmune encephalitis (AE) refers to a rare, newly described, group of diseases associated with specific circulating autoantibodies directed against neuronal proteins used as biomarkers of the disease. As psychiatric symptoms may predominate at the onset or over the course of these diseases, the diagnosis is frequently delayed. Yet, patients' prognoses depend on the speed with which the disease is detected, identified and managed.*

Antibody-mediated encephalitis

Dalmau and Graus, N Engl J Med. 2018 Mar 1;378(9):840-851.

> *The category of autoimmune encephalitides constitutes disorders with relatively distinct characteristics such as psychosis, seizures, abnormal movements, coma, and dysautonomia. Specific autoantibodies can be identified, and the disorders can be successfully treated.*

A clinical approach to new-onset psychosis associated with immune dysregulation: the concept of autoimmune psychosis

Najjar et al., J Neuroinflammation. 2018;15:40.

> *Growing data point to the overlap between psychosis and pathological processes associated with immunological dysregulation as well as inflammation. Notably, the recent discovery of antibodies against synaptic and neuronal cell membrane proteins such as anti-N-methyl-d-aspartate receptor provides more direct evidence of the etiological connection between autoimmunity and subsequent hazard of psychosis.*

Autoimmune encephalitis in children: clinical phenomenology, therapeutics, and emerging challenges.

Dale, R, Gorman M, Lim M., Curr Opin Neurol. 2017 Jun; 30(3):334-344.

> *Auto-antibodies that bind to conformational extracellular epitopes of neuronal receptors or synaptic proteins have provided clinicians with essential biomarkers in acute neurology. This review summarizes the current status and challenges in the field.*

The clinical challenge of autoimmune psychosis: learning from anti-NMDA receptor autoantibodies

Ellul P et al., Frontiers in Psychiatry. 2017 April;8:54.

> *Schizophrenia is a heterogeneous and complex psychiatric disorder affecting up to 1% of the population worldwide. Although the precise development of schizophrenia is not yet fully understood, it is now admitted to be underpinned by the entanglement of genetic, environmental, and immuno-inflammatory factors.*

Red flags: clinical signs for identifying autoimmune encephalitis in psychiatric patients

Herken et al, Front Psychiatry. 2017 Feb 16;8:25.

> *Autoimmune mechanisms causing diverse psychiatric symptoms are increasingly recognized and brought about a paradigm shift in neuropsychiatry. Identification of underlying antibodies against neuronal ion channels or receptors led to the speculation that a number of patients go misdiagnosed with a primary psychiatric disease.*

Autoimmune encephalopathy for psychiatrists: when to suspect autoimmunity and what to do next

Oldham M., Psychosomatics. 2017 May-Jun;58(3):228-244.

> *To provide a critical review of autoimmune encephalopathy—broadly defined as neuropsychiatric features directly related to an autoimmune process—relevant for psychiatric practice.*

The diagnosis and treatment of autoimmune encephalitis

Eric Lancaster, J Clin Neurol. 2016 Jan; 12(1): 1-13.

> *Autoimmune encephalitis causes subacute deficits of memory and cognition, often followed by suppressed level of consciousness or coma. A careful history and examination may show early clues to particular autoimmune causes, such as neuromyotonia, hyperekplexia, psychosis, dystonia, or the presence of particular tumors.*

Anti-N-Methyl-D-Aspartate Receptor Encephalitis: A new challenging entity for consultation-liaison psychiatrist

Maccaferri et al, Brain Disord Ther 2016 May; 5(2):215

> *Anti-N-methyl-D-aspartate receptor encephalitis is a relatively newly identified autoimmune neuropsychiatric disorder that predominantly affects children and young adults. Although psychiatric symptoms are highly prevalent and frequently severe, it has mainly been reported in neurological, but not psychiatric, literature. Understanding this form of encephalitis, its quick diagnosis and which treatment to provide are of utmost importance for consultation-liaison psychiatrists.*

A clinical approach to diagnosis of autoimmune encephalitis

Graus F, Titulaer MJ, et al., Lancet Neurology 2016 Apr; 15(4):391-404

> *Encephalitis is a severe inflammatory disorder of the brain with many possible causes and a complex differential diagnosis. Advances in autoimmune encephalitis research in the past 10 years have led to the identification of new syndromes and biomarkers that have transformed the diagnostic approach to these disorders. However, existing criteria for autoimmune encephalitis are too reliant on antibody testing and response to immunotherapy, which might delay the diagnosis.*

Autoimmune encephalitis in psychiatric institutions: current perspectives

Bost et al., Neuropsychiatr Dis Treat. 2016; 12: 2775–2787.

> *Autoimmune encephalitis is a rare and newly described group of diseases involving autoantibodies directed against synaptic and neuronal cell surface antigens. As neurological symptoms are fairly well described in the literature, this review focuses on the nature of psychiatric symptoms occurring at the onset or during the course of the diseases.*

Anti-N-methyl-D-aspartate receptor encephalitis: A targeted review of clinical presentation, diagnosis, and approaches to psychopharmacologic management

Kruse et al, Annals of Clinical Psychiatry. 2014 Feb;26(1):e1-9

> *Anti-N-methyl-d-aspartate receptor encephalitis was formally described in 2007 and includes a range of psychiatric and neurologic symptoms. Most patients with anti-NMDAR encephalitis initially present to psychiatrists for diagnosis and treatment. However, there is limited literature summarizing treatment strategies for psychiatric symptoms. In an effort to improve identification and treatment, this review article provides an overview of anti-NMDAR encephalitis, with a focus on psycho- pharmacologic treatment strategies.*

Autoimmune Encephalitis

Leypoldt F, Wandinger K-P, Bien CG, Dalmau J., European neurological review. 2013;8(1):31-37.

> *The term autoimmune encephalitis is used to describe a group of disorders characterized by symptoms of limbic and extra-limbic dysfunction occurring in association with antibodies against synaptic antigens and proteins localized on the neuronal cell surface. Since many patients respond well to immunosuppressive treatment, the recognition of these disorders is of utmost importance.*

Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study

Titulaer MJ, McCracken L, et al. , Lancet Neurology; London 12.2 (Feb 2013): 157-65.

> *Anti-NMDA receptor encephalitis is an autoimmune disorder in which the use of immunotherapy and the long-term outcome have not been defined. We aimed to assess the presentation of the disease, the spectrum of symptoms, immunotherapies used, timing of improvement, and long-term outcome.*

Antibodies to surface dopamine-2 receptor in autoimmune movement and psychiatric disorders

Dale et al, Brain. 2012 Nov;135(Pt11):3453-68.

> *Recent reports of autoantibodies that bind to neuronal surface receptors or synaptic proteins have defined treatable forms of autoimmune encephalitis. Despite these developments, many cases of encephalitis remain unexplained. We have previously described a basal ganglia encephalitis with dominant movement and psychiatric disease, and proposed an autoimmune aetiology. Given the role of dopamine and dopamine receptors in the control of movement and behavior, we hypothesized that patients with basal ganglia encephalitis and*

other putative autoimmune basal ganglia disorders harbored serum autoantibodies against important dopamine surface proteins.

Central nervous system neuronal surface antibody associated syndromes: review and guidelines for recognition

Zuliani et al., J Neurol Neurosurg Psychiatry. 2012 June; 83(6): 638-645.

The concept of antibody mediated CNS disorders is relatively recent. The classical CNS paraneoplastic neurological syndromes are thought to be T cell mediated, and the onconeural antibodies merely biomarkers for the presence of the tumor. Over the past 10 years, identification of autoimmune forms of encephalitis with antibodies against neuronal surface antigens, particularly the voltage gated potassium channel complex proteins or the glutamate N-methyl-D-aspartate receptor, have shown that CNS disorders, often without associated tumors, can be antibody mediated and benefit from immunomodulatory therapies.

Anti-NMDA Receptor Encephalitis in Psychiatry

Kayser et al., Curr Psychiatry Rev. 2011; 7(3):189-193.

Anti-NMDA receptor encephalitis is an autoimmune disorder in which antibodies attack NMDA (N-methyl-D-aspartate)-type glutamate receptors at central neuronal synapses. Symptoms include a highly characteristic set of neurologic deficits, but also prominent psychiatric manifestations that often bring mental health professionals into the course of care. Distinct phases of illness have become increasingly appreciated, and include a range of psychotic symptoms early in the course of the disease followed by more severe fluctuations in consciousness with neurologic involvement, and ultimately protracted cognitive and behavioral deficits. We provide an up to date review of this disorder and highlight the role of psychiatry in diagnosis, symptomatology, and treatment.

Emily's AE Story

It was almost exactly ten years ago that I rushed home from a coffee shop, paranoid and terrified, and my journey with autoimmune encephalitis began. A college sophomore, I ended up in the ER and then a psychiatric ward, eventually "diagnosed" with Psychosis: Unknown.

There have been a lot of unknowns along the way. My primary concern at the time was *when could I go back to school?* I desperately craved a normal life. After almost two months of inpatient hospitals, I was enrolled in a day program for adults – the farthest thing from normal for me. I did move back to school that fall semester. No longer paranoid, I was weighed down by a cocktail of psych meds. Daily life was like pushing through wet sand – heavy and hard.

For my parents, every day was an unknown. They worried about what would happen to me if I stopped taking my meds; if I would ever graduate or have a normal life, since my psychiatrist seemed convinced that I wouldn't.

And then one day, my body decided it had enough of this mistreatment and rebelled against me. I began slurring my words and lost basic motor functions. The right side of my face drooped – eventually I was unable to walk or even speak. I was diagnosed (or misdiagnosed, we now know) with Multiple Sclerosis, which left us wondering what my future would be like as the disease progressed. I didn't respond to the treatment and grew less responsive and less capable of doing anything.

My parents drove me to a local ER, where doctors checked me in and immediately started tests. These doctors admitted something everyone feared – they didn't know what was wrong with me. A few days later, a helicopter flew me to the University of Pennsylvania, where hopefully they would have an answer.

Weeks went by – I was in such critical condition that I couldn't even be tested for Anti-NMDA Receptor Encephalitis, although that's what everyone suspected. A grand mal seizure left me on a ventilator, unable to breathe on my own for almost a week. Even after I received a diagnosis and began treatment, my parents went to sleep every night not knowing what to expect the next day. I went to sleep afraid and alone in a hospital. I was there for two and a half months.

But I recovered; worked hard at physical, occupational, and speech therapy; and went on to graduate with a double major and then my Master's degree. I started a full-time job at a pharmaceutical company and became a certified yoga teacher. It was a long, hard-fought journey, but I'm back.

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