Topic: Neurovascular and neuroinflammation mechanisms associated with bipolar disorder

Psychotic and nonpsychotic mood disorders in autoimmune encephalitis: diagnostic issues and research implications

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ABSTRACT

Recent research on autoimmune disorders suggests additional links between systemic and central nervous system (CNS) pathophysiology, among which the identification of antibody-induced limbic encephalitis provided the strongest evidence for the potential involvement of autoimmunity in the pathogenesis of severe mood and psychotic symptoms. In these illnesses, psychiatric symptoms predominate in the initial phase of the disorder in up to 70% of the cases, and they often lead patients to early psychiatric evaluation. For this reason, it is very important to increase the limited knowledge among psychiatrists about these autoimmune neuropsychiatric diseases, which can mimic psychiatric syndromes, in particular, those typically presented in severe mood disorders and schizophrenia. On the other hand, similarities in clinical presentation suggest that neuroinflammation and systemic immune dysregulation may play a role in the pathophysiology of severe mood and psychotic disorders. A complex interaction between periphery and immune cells of the CNS may result in cellular damage through mechanisms involving excitotoxicity, oxidative stress, and mitochondrial dysfunction. These pathways are possibly shared between comorbid medical disorders and severe mood and psychotic disorders and may reflect common underlying vulnerability.

Key words: Autoimmune encephalitis, mood disorders, psychosis

INTRODUCTION

The connection between autoimmunity and neuropsychiatric symptoms has long been acknowledged, and William Osler provided a description of psychosis in systemic lupus erythematosus in 1895. The myasthenic syndromes are good examples of how autoantibodies can cause neurological symptoms.[1] As another example, some paraneoplastic syndromes such as cerebellar degeneration or limbic encephalitis (LE) are associated with highly specific antibodies against intracellular neuronal proteins and aggressive cytotoxic T-cell responses that usually lead to irreversible deficits.[2]

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Access this article online	
Quick Response Code:	Website: www.nnjournal.net
	DOI: 10.4103/2347-8659.160986

In recent times, the discovery of a range of autoantibodies acting on specific synaptic sites in the brain has been an important development for the identification of different forms autoimmune encephalitis, often characterized by the initial psychiatric presentation. The predominance of a psychopathological expression often leads patients to early psychiatric evaluation and treatment.[3] As a result, in many cases, the correct diagnosis may be delayed because of the limited knowledge among psychiatrists about these autoimmune neuropsychiatric diseases mimicking psychiatric syndromes, in particular, severe mood disorders and schizophrenia.[4-6] Moreover, the fact that a variety of neuropsychiatric disorders may initially present with

Cite this article as: Quaranta G, Bucci N, Toni C, Perugi G. Psychotic and nonpsychotic mood disorders in autoimmune encephalitis: diagnostic issues and research implications. Neuroimmunol Neuroinflammation 2015;2:228-36.

Received: *12-03-2015*; **Accepted:** *13-04-2015*

psychiatric symptoms very similar to classical mood and psychotic disorders reinforced the hypothesis that innate inflammation/autoimmunity may be relevant to the pathogenesis of psychiatric symptoms at least in a subset of patients with bipolar disorder[7] or schizophrenia.[8]

AUTOIMMUNE ENCEPHALITIS

Since 1974, Mitsuda and Fukuda[9] described "atypical psychosis" as some acute and transient psychotic disorders, which cannot be easily classified as either schizophrenia or mood disorder with psychotic features. Some important clinical characteristics of atypical psychosis include acute onset, emotional and psychomotor disturbances, alternations of consciousness, high prevalence in women, and well-adjusted premorbid personality. In these conditions, an involvement of neurologic brain changes has been hypothesized.

The identification of autoimmune encephalitis, a new category of neuropsychiatric diseases that occurs with focal or widespread involvement of the nervous system in association with antibodies against extracellular epitopes of neuronal cell-surface or synaptic proteins, have led to changed paradigms for the diagnosis and treatment for some neuropsychiatric disorders, and reclassification of syndromes previously defined as idiopathic or with descriptive terms.[10] Since 2005, there have been 1-2 discoveries of novel syndromes and associated autoantigens per year, including autoantigens the *N*-methyl-D-aspartate receptor (NMDAR),[11,12] the subunits Kv1.1 and Kv1.2 of the voltage-gated potassium channels (VGKCs), the α-amino-3-hydroxy-5-methyl-4-isoxazol-pro pionic acid receptor (AMPAR),[13] metabotropic glutamate receptor 5,[14] or the γ-amino-butyric acid B-receptor (GABAbR),[15] leucine-rich glioma inactivated 1 (Lgi1),[16] contactin associated protein 2 (CASPR2).[17] The study of these disorders has revealed novel mechanisms of how antibodies might alter memory, behavior, cognition and cause mood disorders, psychosis, seizures or abnormal movements.[18,19] However, though obtaining serum to test for autoantibodies is extremely convenient and relatively noninvasive, the caveats of using serum antibodies as a diagnostic tool need to be considered. Neuronal surface antibodies are not 100% specific.[20-25] In particular, lower serum titers should be interpreted with caution, and the role of evaluating cerebrospinal fluid (CSF) neuronal surface antibodies rather than serum titers may increase diagnostic specificity.[10] The presence of neuronal surface antibodies should always be correlated with the clinical picture.

One important clinical feature of autoimmune encephalitis is the strong association between autoantibody production and the presence of teratoma or other neoplasms. Comorbidities of autoimmune encephalitis with small cell lung carcinoma, neuroblastoma, ovarian carcinoma, breast carcinoma, thymoma, and testicular cancers have also been reported.[26] These findings suggested that the autoantibody syndrome may be triggered by cross-reaction between antibodies produced in response to tumor presence and antigenically similar synaptic proteins within the central nervous system (CNS). Autoimmune encephalitis can develop, however, with or without an underlying tumor, and in the largest case series to date, no teratoma or other type of tumor was detected in 41% of cases.[3,27]

Different forms of autoimmune encephalitis can affect patients of all ages although some of them seem to preferentially occur in late childhood and young adulthood.[28,29] The onset of the symptomatology shows a substantial overlap among the different types. Sometimes associated with headache or mild hyperthermia, the initial clinical picture is characterized by a rapid development of a set of psychiatric and/or neurological symptoms. Mood disorders, usually manic or mixed-manic symptoms, anxiety, behavioral problems, psychotic features, mild to moderate disorders of consciousness, and memory loss occur in most types of autoimmune encephalitis, often associated with seizures. Demographic information (such as gender and race), presence or absence of a underlying tumor, brain magnetic resonance imaging (MRI) findings, CSF examination, and the severity and predominance of some symptoms over others can suggest a specific subtype.

Ultimately, two approaches have been proposed for the diagnosis of autoimmune encephalitis: one based on the laboratory examination as proposed by Lancaster and Dalmau[10] and the other based on clinical diagnostic criteria as proposed by Zuliani *et al.*[30] The latter recommend that one should suspect a diagnosis of an autoimmune encephalitis when a patient presents with acute or subacute onset of symptoms, evidence of inflammation supported by CSF examination, imaging, or histopathological investigations, and the exclusion of other infectious, metabolic, and toxic etiologies. Supportive criteria include a history of other autoimmune comorbidities, and preceding infectious prodromes. Using a combination of these criteria as well as test of response to therapy, they suggest a model whereby patients can be classified as having definite, probable or possible neuronal cell surface antibody related pathology.[30,31]

Anti-NMDAR encephalitis

Anti-NMDAR encephalitis, among all the autoimmune encephalitis, is the best-understood variant and the most frequently associated with almost exclusively psychiatric presentation. The illness was first described as a distinct clinical entity in an observational study in 2005 by Vitaliani *et al*.[11] in four young women who developed acute psychiatric symptoms, seizures, memory deficits, decreased level of consciousness, autonomic instability, and hypoventilation in association with the presence of an ovarian teratoma. Two years later, a paper by this group described the underlying pathology, mediated by auto-antibodies directed against the NR1 subunit of the NMDAR.[12] These antibodies cause a decrease in the number of NMDARs in target cells by inducing cross-linking and internalization of NMDARs by autophagy.[32] Therefore, anti-NMDAR encephalitis represents a state of NMDA-R hypofunction, associated to glutamate dysregulation.[33] Initially, it was classified as a paraneoplastic syndrome[12] due to the strong association (upwards of 60%) with a teratoma or other tumor types.

Although many patients have been diagnosed with anti-NMDAR encephalitis to date, the exact prevalence of this disorder is unknown. A study of 100 patients revealed that although most patients are young women, the disorder can occur in men and children.[34] In fact, with increasing awareness of the syndrome, the number of pediatric cases has steadily grown and appears to represent about 40% of all cases.[28] The younger the patient, the less likely an underlying tumor will be detected at the time of presentation.[34]

A stereotypical clinical course with different phases is noted for patients with anti-NMDAR encephalitis.[35] In 70% of patients, the illness begins with a prodromal phase lasting 5-14 days.[3,36] This nonspecific flu-like prodrome is characterized by subfebrile temperature, fatigue, malaise, headache, nausea, diarrhea, vomiting. This is followed by other clinical phases, which may vary in sequence, presentation and severity.

After the initial phase, psychiatric manifestations go on to develop, including emotional and behavioral disturbances such as apathy, anxiety, panic attacks, fear, depression, decreased cognitive skills, sleep disorders. In most cases, an excited manic or mixed manic symptomatology develops in a variable lapse of time, from hours to days; mood disorders and agitation are almost invariably associated with psychotic features such as grandiose delusions, Capgras syndrome, paranoid interpretation, and different types of hallucinations. From mild to moderate cognitive disorders are frequently presented.[18,37] During this phase, patients are often referred to psychiatric assessment and may receive treatment with psychoactive agents or admission to psychiatric facilities.

This psychotic phase can be followed by physical decompensation involving autonomic instability (less common in children), with hypo- or hypertension, hypo- or hyperthermia, hypoventilation, cardiac arrhythmia, decreased responsiveness, and occasionally short-term memory loss. Some patients may also have seizures, most commonly generalized tonic-clonic, but also partial and/or complex type. In some patients, early treatment with antiepileptic drugs may mask seizures. Dyskinesias, extrapyramidal signs, and stereotyped motor automatisms may also be observed.[38] During this phase, patients not already admitted to the hospital often present to the emergency department because they no longer follow verbal commands and may appear mute (with language disintegration) and akinetic. Patients may maintain gaze as if in a catatonic state, smile inappropriately, or demonstrate stereotyped athetosic movements.[34,39]

Since the initial descriptions, further studies have expanded the clinical phenotype of this syndrome. Some patients with anti-NMDAR antibodies have predominant or isolated psychiatric features, dystonia, or epilepsy, without the classic multistage presentation, potentially representing a *forme fruste* of anti-NMDAR encephalitis, mimicking a psychiatric disorder.[3,40]

The diagnosis of anti-NMDAR encephalitis is confirmed by the detection in serum or CSF of antibodies to the NR1 subunit of the NMDA receptor. After treatment or in advanced stages of the disease, the CSF antibodies usually remain elevated if there is no clinical improvement, whereas serum antibodies may be substantially decreased by treatments. The titer of CSF antibodies appears to correlate more closely with the clinical outcome. Patients with anti-NMDAR encephalitis may have abnormalities of both CSF and MRI. 80% of patients with confirmed anti-NMDAR encephalitis have abnormal CSF with the majority of them exhibiting a lymphocytic pleocytosis, but over a half also show raised proteins. There may also be the presence of isolated oligoclonal bands in the CSF of patients with autoimmune encephalitis (around 60%).[3] In contrast to the consistency of the clinical picture, MRI findings are less predictable; only 55% of patients had increased fluid-attenuated inversion recovery (FLAIR) or T2 signal in one or several brain regions, without significant correlation with patients' symptoms. MRI can be normal or demonstrate medial temporal involvement or focal areas of hyperintensity in the frontal or parietal cortex. Other studies demonstrated that [18F]-fluorodeoxyglucose positron emission

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