Schizophrenia Research 176 (2016) 36–40

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Review

Anti-NMDA receptor encephalitis, autoimmunity, and psychosis

Matthew S. Kayser [a,b,*], Josep Dalmau [c,d]

[a] Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, United States
[b] Center for Sleep and Circadian Biology, Perelman School of Medicine, University of Pennsylvania, United States
[c] Department of Neurology, Perelman School of Medicine, University of Pennsylvania, United States
[d] Department of Neurology, Hospital Clinic, Barcelona, Spain

ARTICLE INFO

Article history:
Received 16 July 2014
Received in revised form 6 October 2014
Accepted 8 October 2014
Available online 25 October 2014

Keywords:
NMDA
Encephalitis
Autoimmune
Schizophrenia

ABSTRACT

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is a recently-discovered synaptic autoimmune disorder in which auto-antibodies target NMDARs in the brain, leading to their removal from the synapse. Patients manifest with prominent psychiatric symptoms – and in particular psychosis – early in the disease course. This presentation converges with long-standing evidence on multiple fronts supporting the glutamatergic model of schizophrenia. We review mechanisms underlying disease in anti-NMDAR encephalitis, and discuss its role in furthering our understanding of neural circuit dysfunction in schizophrenia.

1. Introduction

Investigations into an autoimmune basis for schizophrenia and other psychiatric disorders date back well over a half century (Fessel, 1962). In the intervening years, a more intense focus has been on the role that dysregulation of specific neurotransmitter systems, such as glutamatergic signaling, might play in psychotic disorders (Coyle, 2012; Javitt, 2012). Yet, there has been limited ability to unite these seemingly disparate etiological possibilities. Since its initial description in 2007 (Dalmau et al., 2007), anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis has come to support the idea that abnormalities in both autoimmunity and glutamatergic signaling can be involved in causing psychosis. Anti-NMDAR encephalitis is a synaptic autoimmune disorder in which IgG auto-antibodies recognize the GluN1 subunit of NMDARs. Over the past 7 years, a tremendous effort has been made to understand issues related to diagnosis and clinical management, mechanisms of disease, and what this autoimmune disorder can teach us about psychosis and schizophrenia at large.

2. Demographics and clinical course

Anti-NMDAR encephalitis was originally identified linking a syndrome with prominent psychiatric manifestations in the context of encephalitis in four young women with ovarian teratoma (Vitaliani et al., 2005). It is now appreciated that children and males can be affected and that the same neurologic syndrome may develop either without a tumor or as a paraneoplastic manifestation of an underlying teratoma (Dalmau et al., 2008; Viaccoz et al., 2014). The frequency of an underlying teratoma, and very rarely other tumors, is dependent on patients' sex and age (Florance et al., 2009). Children under 12 years of age and male patients rarely have a tumor (Titulaer et al., 2013). Regardless, this disorder overwhelmingly affects young women, though patients as young as 2 months and as old as 85 years have been reported (Titulaer et al., 2013; Armangue et al., 2014). The clinical course begins in most instances with a viral prodrome, followed by prominent psychiatric symptoms such as psychosis (delusional thinking, hallucinations), agitation, and confusion (Fig. 1) (Dalmau et al., 2008; Kayser and Dalmau, 2011). Most cases progress to include severe neurological features like seizures, movement abnormalities, autonomic instability, or hypoventilation, often requiring ICU-level care (Dalmau et al., 2008; Irani et al., 2010; Titulaer et al., 2013). Recent work has demonstrated that early and aggressive immunosuppression along with removal of tumor (if present) lead to positive outcomes, with 80% of patients returning to near baseline level of function (Titulaer et al., 2013; Viaccoz et al., 2014). Relapse is less common than once thought, particularly with effective management, as only ~10–15% of patients relapse in a 2 year period (Titulaer et al., 2013). Overall, this once often-fatal encephalitis is now clinically recognizable, diagnosable by presence of antibodies in CSF, and treatable with immunosuppression, all due to a detailed understanding of the underlying disease process.

* Corresponding author at: Perelman School of Medicine, University of Pennsylvania, 10-160 Translational Research Center, 3400 Civic Center Blvd., Building 421, Philadelphia, PA 19104-5158, United States.
E-mail address: Matthew.Kayser@uphs.upenn.edu (M.S. Kayser).

http://dx.doi.org/10.1016/j.schres.2014.10.007
0920-9964/

3. Mechanisms of disease

The cellular mechanisms underlying anti-NMDAR encephalitis are increasingly well understood. Binding of IgG antibodies to NMDARs induces a reversible internalization of the receptors from both synaptic and extrasynaptic space, with relative sparing of other glutamate receptors and excitatory scaffolding proteins; the number of synapses remains unchanged, and dendritic structure and cell survival is not perturbed (Hughes et al., 2010). Internalization of NMDARS occurs through antibody binding, capping, and cross-linking of the receptors, and loss of NMDARs from the cell surface correlates with antibody titer (Hughes et al., 2010). Notably, CSF antibody titers correlate better than serum titers with clinical outcome and relapses (Gresa-Arribas et al., 2014). The removal of NMDARs from the cell surface is supported not only by immunohistochemical evidence in vitro and in vivo, but also electrophysiological measures, indicating a decrease of synaptic NMDAR-mediated currents due to the low level of receptors induced by auto-antibodies rather than a direct antibody blockade (Hughes et al., 2010; Moscato et al., 2014). Decreased synaptic NMDAR content also leads to reduced synaptic plasticity, as treatment of rodent neurons with patient CSF blocks molecular signatures of long-term potentiation (LTP) (Mikasova et al., 2012). The effect on NMDARs does not appear to be specific to excitatory neurons, as NMDARs on inhibitory neurons are similarly internalized (Moscato et al., 2014). Interestingly, in vitro investigations into the time frame of these cellular phenomena show that in neurons continuously exposed to patients' CSF antibodies, the process of NMDAR internalization becomes microscopically visible in 2 h, reaching the lowest level of NMDAR receptor density after 12 h; subsequently there is a steady state of low levels of synaptic NMDAR for as long as the neurons are exposed to patients' antibodies (Moscato et al., 2014). These effects were independent of receptor activity. Moreover, while patient NMDAR auto-antibodies did not induce compensatory changes in glutamate receptor gene expression, they caused a decrease in inhibitory synapse density onto excitatory hippocampal neurons (Moscato et al., 2014). These findings suggest a potential mechanism of increased excitability, which is in line with the in vivo effects (increase of extracellular glutamate) of patients' antibodies after injection in the premotor cortex of rats (Manto et al., 2010).

Does exposure to antibodies in animal models result in similar behavioral effects as in humans? Recent work has found that prolonged cerebroventricular infusion of patient antibodies into mice results in progressive memory deficits, anhedonia, and depressive-like behaviors (Planaguma et al., in press). These behavioral changes correlated with detection of a progressive (over days) increasing concentration of brain-bound NMDAR antibodies and parallel decrease of the density of synaptic and extrasynaptic NMDAR clusters. After the infusion of antibodies stopped there was progressive (over days) clinical improvement associated with restoration of NMDAR levels, a feature strikingly conserved from in vitro work to the clinical experience of patients. In sum, multiple lines of evidence now demonstrate that anti-NMDAR antibodies in this disorder cause reversible internalization of NMDARs from the synapse in humans and rodent models, resulting in behavioral manifestations across species.

4. Anti-NMDAR antibodies and psychosis

The prominence of psychotic symptoms in anti-NMDAR encephalitis has been of tremendous interest to the psychiatric community by raising the possibility of an identifiable, treatable subtype of psychosis. This is unlikely to be the case if prominent neurological symptoms always accompany psychiatric manifestations in the presence of CSF auto-antibodies. Do patients with known anti-NMDAR encephalitis experience isolated psychiatric symptoms either at initial presentation or even in relapse? Examination of nearly 600 cases (Kayser et al., 2013) has shown that, while rare, some patients may demonstrate only psychiatric symptoms without any neurological involvement during the first disease episode or in a relapse episode. Fig. 2 demonstrates NMDAR antibodies in a single patient at two different time points: during the recovery phase of the initial presentation (severe neurological involvement with ICU-level care and intubation) and during a relapse episode two years later (pure psychiatric symptoms with prominent psychosis and aggression). Remarkably, NMDAR titers were higher in relapse (1:80 dilution with continued reactivity) than during the recovery phase of initial presentation (1:5 dilution). Prolonged time to treatment in some cases with isolated psychiatric symptoms confirms that isolated psychiatric episodes are truly monosymptomatic and not simply a result of early intervention that spared clinical worsening (Kayser et al., 2013). These patients do not differ with regard to demographics, presence or absence of tumor, psychiatric symptoms constellation, or outcomes from the population of anti-NMDAR encephalitis as a whole (Kayser et al., 2013). It seems possible, therefore, that

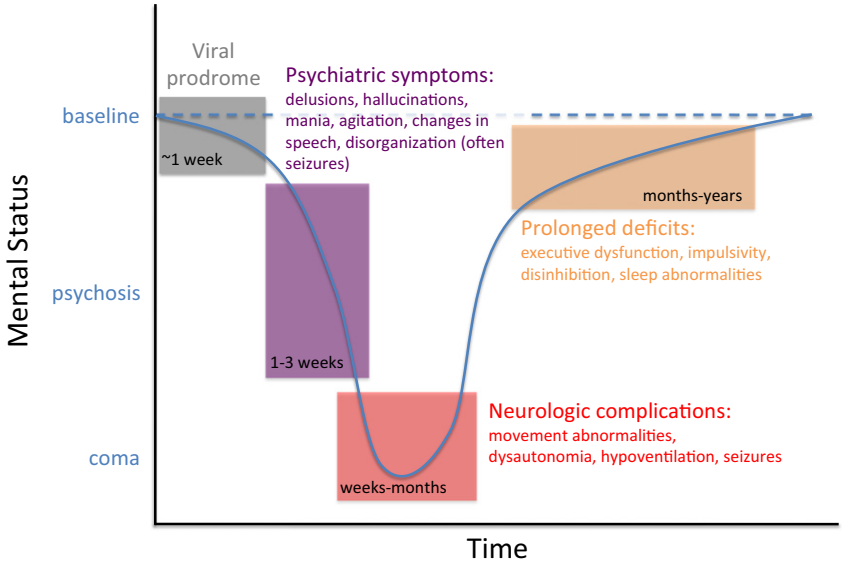

Fig. 1. Typical clinical course of illness in anti-NMDAR encephalitis. Following a viral prodrome, patients experience prominent psychiatric symptoms in the early weeks of the disorder. This is followed by progressive neurological involvement, often requiring ICU-level care. Prolonged behavioral and cognitive and behavioral symptoms are common, though most patients make a near complete recovery with early and aggressive treatment (from Kayser, M.S., Dalmau, J., 2011).