The Libyan International Medical University
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Encephalitis
Anti-N-Methyl-D-Aspartate Receptor Encephalitis

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Abstract

NMDA-type glutamate receptors are ligand-gated ion channels that mediate a Ca2+-permeable component of excitatory neurotransmission in the central nervous system (CNS). They are expressed throughout the CNS and play key physiological roles in synaptic function, such as synaptic plasticity, learning, and memory. NMDA receptors are also implicated in the pathophysiology of several CNS disorders and more recently have been identified as a locus for disease-associated genomic variation.NMDAR encephalitis is a common cause of autoimmune encephalitis, predominantly affecting young adults. Current data supports the idea that autoantibodies targeting NMDARs are responsible for disease pathogenesis. While these autoantibodies occur in the setting of underlying malignancy in approximately half of all patients, initiating factors for the autoimmune response in the remainder of patients are unclear Although the majority of patients achieve good outcomes. Common clinical features include auditory and visual hallucinations, delusions, behavioural change (frequently with agitation), impaired consciousness, motor disturbance (ranging from dyskinesia to catatonia), seizures, and autonomic dysfunction. for Further advances in our understanding of this disease and underlying triggers are necessary to develop treatments which improve outcomes.

Introduction

The vast majority of the excitatory neurotransmission in the central nervous system (CNS) is mediated by vesicular release of glutamate, which activates both pre and postsynaptic G-protein–coupled metabotropic glutamate receptors and ionotropic glutamate receptors (iGluRs). iGluRs are ligand-gated cation channels that are divided into three major structurally distinct functional classes: the α-amino-3-hydroxy-5-methyl-4-isoxasolepropionic acid (AMPA) receptors, kainate receptors, and NMDA receptors.

NMDA receptors are unique among synaptic receptors in their requirement for the binding of two agonists, glutamate and glycine (or d-serine; Johnson and Ascher, 1987; Kleckner and Dingledine, 1988; Benveniste and Mayer,

1991; Clements and Westbrook, 1991, 1994). Synaptic NMDA receptors are temporally controlled by the synaptic release of glutamate for activation, because extracellular glycine (or d-serine) is thought to be continuously present at fairly constant concentration[2]. Encephalitis is an acute inflammation of the brain. The majority of cases are caused by either a viral infection or the immune system mistakenly attacking brain tissue, my focus in these report on immune encephalitis. Here are some key points about encephalitis. Early symptoms are fever, photophobia, and headache Encephalitis is rarely life-threatening Encephalitis most often affects children, older adults, and those with compromised immune systems Only a handful of antiviral medications can help treat encephalitis Complications of encephalitis can include epilepsy and memory loss A severe form of encephalitis associated with antibodies against NR1–NR2 heteromers of the NMDA receptor was recently identified. potentially lethal, but treatment-responsive encephalitis that associates with autoantibodies to the NMDA receptor (NMDAR) and results in behavioral symptoms similar to those obtained with models of genetic or pharmacologic attenuation of NMDAR function. The N-methyl-D-aspartate receptor (also known as the NMDA receptor or NMDAR), is a glutamate receptor and ion channel protein found in nerve cells[3]. The study aims to analyze the incidence, pathogenesis, clinical features, investigation findings of anti-N-methyl-d-aspartate receptor encephalitis.

Keywords

NMDA receptor, Encephalitis ,anti-NMDA receptor encephalitis, autoimmune encephalitis.

Methods

Charts of 300 patients aged 18 to 35 years admitted to the intensive care unit (ICU) during a 5-year period were retrospectively reviewed for criteria of encephalitis of unknown etiology. These included encephalitic signs with psychiatric symptoms (agitation, paranoid thoughts, irritability, or hallucinations), seizures, CSF inflammation; and exclusion of viral or bacterial infection. Archived serum and CSF samples of patients fulfilling these criteria were

examined for NMDAR antibodies. Follow-up visits allowed the analysis of the natural disease course and estimation of prognosis.[4]

Result

Seven patients (all women) fulfilled the indicated criteria, 6 of them had NMDAR antibodies. Ovarian teratomas were detected in 2 patients, in one 3 years after the onset of encephalitis. Outcome was favorable in all patients. One patient without teratoma improved spontaneously along with disappearance of NMDAR antibodies.[4]

Discussion

The N-methyl-D-aspartate receptor (also known as the NMDA receptor or NMDAR), is a glutamate receptor and ion channel protein found in nerve cells. The NMDA receptor is one of three types of ionotropic glutamate receptors The NMDA receptor channels play an important role in synaptic plasticity and synapse formation underlying memory, learning and formation of neural networks during development in the central nervous system .The amino acid glutamate (Glu) plays a central role in both the normal and abnormal functioning of the central nervous system (CNS). Glu is recognized to be the main excitatory neurotransmitter in the CNS, estimated to be released at up to half of the synapses in the brain. In addition, Glu is also an excitotoxin that can destroy CNS neurons by excessive activation of excitatory receptors on dendritic and small surfaces.[5]

Two major classes of Glu receptors, ionotropic and metabotropic, have been identified. Glu exerts excitotoxic activity through three receptor subtypes, which belong to the ionotropic family. These three receptors are named after agonists to which they are differentially sensitive, Ar-methyl-D-aspartate (NMDA), amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainic acid (KA). Of these three, the NMDA receptor has been the most extensively studied and the most frequently implicated in CNS diseases.[5]

Encephalitis can develop as a result of a direct infection to the brain by a virus, bacterium, or fungus, or when the immune system responds to a previous infection , the immune system mistakenly attacks brain tissue. Primary infectious encephalitis can be split into three main categories of viruses: Common viruses, including HSV herpes simplex virus and EBV Epstein-Barr virus Childhood viruses, including

measles and mump Arboviruses spread by mosquitoes, ticks, and other insects, including Japanese encephalitis, West Nile encephalitis, and tick-borne encephalitis. Secondary encephalitis: Could be caused by a complication of a viral infection. Symptoms start to appear days or even weeks after the initial infection. The patient's immune system treats healthy brain cells as foreign organisms and attacks them. We still do not know why the immune system malfunctions in this way. In more than 50 percent of encephalitis cases, the exact cause of the illness is not tracked down. Encephalitis is more likely to affect children, older adults, individuals with weakened immune systems, and people who live in areas where mosquitoes and ticks that spread specific viruses are common. We recently described a severe, lethal, encephalitis that associates with autoantibodies to the NMDA receptor (NMDAR) and results in behavioral symptoms similar to those obtained with models of genetic or pharmacologic attenuation of NMDAR function. Here, we demonstrate that patients NMDAR antibodies cause a selective and reversible decrease in NMDAR surface density and synaptic localization that correlates with patients' antibody titers.(6) The mechanism of this decrease is selective antibody-mediated capping and internalization of surface NMDARs, as Fab fragments prepared from patients' antibodies did not decrease surface receptor density, but subsequent cross-linking with anti-Fab antibodies recapitulated the decrease caused by intact patient NMDAR antibodies. Moreover, whole-cell patch-clamp recordings of miniature EPSCs in cultured rat hippocampal neurons showed that patients' antibodies specifically decreased synaptic NMDAR-mediated currents, without affecting AMPA receptor-mediated currents. In contrast to these profound effects on NMDARs, patients antibodies did not alter the localization or expression of other glutamate receptors or synaptic proteins, number of synapses, dendritic spines, dendritic complexity, or cell survival. In addition, NMDAR density was dramatically reduced in the hippocampus of female Lewis rats infused with patients antibodies, similar to the decrease observed in the hippocampus of autopsied patients. These studies establish the cellular mechanisms through which antibodies of patients with anti-NMDAR encephalitis cause a specific, titer-dependent, and reversible loss of NMDARs. The loss of this subtype of glutamate receptors eliminates NMDAR-mediated synaptic function, resulting in the learning, memory, and other behavioral deficits observed in patients with anti-NMDAR encephalitis. Synaptic plasticity is thought to underlie mechanisms of memory, learning, and cognition. Central to these neurological functions is the proper synaptic

localization and trafficking of the excitatory glutamate NMDA and AMPA receptors, NMDA-type glutamate receptors provides an alternative model to understanding the pathogenesis of schizophrenia, the role of these receptors in memory, learning, cognition, and psychosis comes from more indirect approaches, such as pharmacological trials e.g: NMDA receptor (NMDAR) antagonists causing psychosis, and analysis of brain tissue from patients with Alzheimer's disease or schizophrenia in which several molecular pathways causing a downstream alteration of glutamate receptors are affected. there was a strong female predominance (ratio, 8.5:1.5) and the median age of the patients was 19 years (23 months to 75 years; 40% children). In 55% of the adults (less frequently in children), the disorder appears to be triggered by the presence of a tumor, mostly an ovarian teratoma that contains nervous system tissue and expresses NMDARs. Despite the severity of the symptoms, 75% of patients recover after receiving immunotherapy and, when appropriate, tumor removal and 25% are left with memory, cognitive, and motor deficits or rarely die of the disorder. The autoantibodies are present in patients serum and CSF the latter usually showing intrathecal synthesis and high antibody concentration.[7]

Conclusion

Anti-N-methyl D-aspartate (NMDA) receptor (anti-NMDAR) encephalitis is among one of the most common autoimmune encephalitides. However, variations in clinical presentation and nonsequential multiphasic course often lead to delays in diagnosis. The mild encephalitis (ME) hypothesis suggests a pathogenetic mechanism of low-level neuroinflammation sharing symptom overlap between anti-NMDAR encephalitis and other psychiatric disorders including schizophrenia. Clinical symptoms of anti-NMDAR encephalitis may mimic schizophrenia and psychotic spectrum disorders or substance-induced psychosis. Although initially described in association with ovarian teratomas in women, anti-NMDAR encephalitis has been reported in individuals without paraneoplastic association, as well as in males. It can affect all age groups but is usually lower in prevalence in individuals greater than 50 years old, and it affects females more than males. Clinical evaluation is supported by laboratory workup, which includes cerebrospinal fluid (CSF) assays. The latter often reveals lymphocytic pleocytosis or oligoclonal bands with normal to elevated CSF protein. CSF testing for anti-NMDAR antibodies facilitates diagnostic confirmation.

Serum anti-NMDAR antibody assays are not as sensitive as CSF assays. Management includes symptomatic treatment and immunotherapy.

References

1. Venkatesan, A., & Adatia, K. (2017). Anti-NMDA-receptor encephalitis: from bench to clinic. ACS chemical neuroscience, 8(12), 2586-2595.

2.Hansen, K., Yi, F., Perszyk, R., Furukawa, H., Wollmuth, L., Gibb, A. and Traynelis, S. (2018). Structure, function, and allosteric modulation of NMDA receptors. The Journal of General Physiology, 150(8), pp.1081-1105.

3.Barry, H., Byrne, S., Barrett, E., Murphy, K. and Cotter, D. (2019). Anti-N-methyl-d-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment.

4.Prüss, H., Dalmau, J., Harms, L., Höltje, M., Ahnert-Hilger, G., Borowski, K., ... & Wandinger, K. P. (2010). Retrospective analysis of NMDA receptor antibodies in encephalitis of unknown origin. *Neurology*, *75*(19), 1735-1739.

5. Newcomer, J. W., Farber, N. B., & Olney, J. W. (2000). NMDA receptor function, memory, and brain aging. Dialogues in clinical neuroscience, 2(3), 219.

6. Rong, X., Xiong, Z., Cao, B., Chen, J., Li, M. and Li, Z. (2017). Case report of anti-N-methyl-D-aspartate receptor encephalitis in a middle-aged woman with a long history of major depressive disorder. BMC Psychiatry, 17(1).

7. Hughes, E. G., Peng, X., Gleichman, A. J., Lai, M., Zhou, L., Tsou, R., ... & Balice-Gordon, R. J. (2010). Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. Journal of Neuroscience, 30(17), 5866-5875.