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Review Article

NMDAR Encephalitis: Navigating the Complexities of Diagnosis, Treatment, and Recovery

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Abstract

NMDAR encephalitis is an extremely uncommon form of autoimmune disease that manifests itself in the brain and is distinguished by the production of antibodies directed against the N-methyl-D-aspartate receptor (NMDAR). The primary purpose of this investigation was to carry out a review study on various points of view pertaining to NMDAR encephalitis. NMDAR encephalitis is an uncommon form of autoimmune disease that primarily affects young adult females. It manifests itself with a wide variety of neurological symptoms, and testing for anti-NMDAR antibodies is required in order to diagnose it. Recognizance and treatment at an early stage, which typically involves immunotherapy, are both absolutely necessary for a successful outcome. There is a wide range of potential long-term outcomes, with the majority of patients making a full recovery but others experiencing residual deficits or relapses.

Keywords: *NMDAR Encephalitis; Anti-NMDA Receptor Encephalitis; Autoimmune Encephalitis; Neurological Symptoms; Immunotherapy*

An overview of NMDAR encephalitis

The production of antibodies directed against the N-methyl-D-aspartate receptor (NMDAR) is the defining feature of the extremely rare autoimmune disease known as NMDAR encephalitis, which manifests itself as inflammation of the brain [1]. The central nervous system contains this receptor, which plays a critical role in the processes of learning and memory. Dr. Josep Dalmau and his colleagues were the ones who first described the disease in 2007, and ever since then, it has been gaining increasing recognition among neurologists and psychiatrists all over the world. In the following paragraphs, we will go over the epidemiology of NMDAR encephalitis, as well as its clinical manifestations, diagnosis, treatment, and prognosis [1].

Epidemiology of NMDAR encephalitis

NMDAR encephalitis is an autoimmune disorder of the central nervous system that can cause a wide variety of symptoms. These symptoms can include psychiatric symptoms, seizures, problems with memory, movement disorders, and autonomic dysfunction. NMDAR

encephalitis is relatively uncommon. The exact prevalence of the disease is unknown; however, based on data from case reports and small case series, it is estimated that it affects about one in 200,000 people [2].

The disease can strike people of any age, but it strikes young adults at a rate significantly higher than other age groups, with a median age of onset of 21 years. According to the findings of a large cohort study that included 577 patients diagnosed with NMDAR encephalitis, the disease was discovered to be most prevalent in patients between the ages of 10 and 30, with a female to male ratio of approximately 4:1 [3]. The presence of tumors, and more specifically ovarian teratomas, is one of the most significant clinical associations with NMDAR encephalitis. 58% of the cases of NMDAR encephalitis in female patients were found to have ovarian teratomas, according to a study that involved 100 patients [4]. Tumors were found to be present in 38 percent of cases of NMDAR encephalitis, with ovarian teratomas being the most common type of tumor found in the study of 571 patients who had the condition [5]. It is essential to keep in mind, however, that tumors are not always associated with NMDAR encephalitis cases, and that the disease can also manifest themselves in patients who do not have a discernible tumor. As a result, a comprehensive diagnostic evaluation is required in order to determine whether or not there is an underlying malignancy and to direct appropriate treatment. IgG autoantibodies that are directed against the GluN1 subunit of NMDARs are the cause of the most common form of autoimmune encephalitis, which is called NMDAR encephalitis [6]. Ovarian teratoma is frequently connected to this disease, which affects women more often than men (8:2 ratio of females to males) and has a high incidence rate. The age of 21 is considered to be the median age at presentation (range 1 - 85 years). Following abnormal behavior is cognitive dysfunction, seizures, movement disorders (oral, facial, and lingual dyskinesias, chorea, athetosis, and dystonia), autonomic dysfunction, and central hypoventilation. The most common symptom of schizophrenia is abnormal behavior, which can include visual or auditory hallucinations, acute schizoaffective disorder, depression, and mania. The presence of NMDAR IgG antibodies in the cerebrospinal fluid is diagnostic evidence that verifies the condition. B cells, CD4+ T cells, and IgG deposits are found in infiltrates of B cells, CD4+ T cells, and IgG deposits in the brain; however, there is little or no neuronal damage, which helps to explain the considerable recovery that can be accomplished following early immunotherapy. According to numerous pieces of evidence, the presence of NMDAR antibodies in the serum of patients is detrimental [7]. Antibodies cause NMDARs in cultured neurons to crosslink with one another, which results in the internalization of the receptors and an impairment of synaptic plasticity [7]. When patient CSF or IgG isolated from patient CSF was infused into the ventricular space in rats using intraventricular catheters, the rats exhibited memory impairments, anhedonia, and seizures. These effects were seen in both groups [8]. In addition to this, mice that are given an active immunization with GluN1/GluN2B heteromers develop a severe form of encephalitis [9]. In neurons that have been cultured, the NMDAR antibodies cause a reduction in the amount of NMDAR and NMDAR currents. There is also a transplacental transfer of NMDAR antibodies from pregnant patients to embryos, which results in neurological abnormalities in the children born to these mothers [10]. In general, these results lend credence to Witbesky's hypotheses, which state that NMDAR autoantibodies play a part in the development of disease. In contrast to NMOSD, where antibodies are significantly more easily detectable in serum than in CSF, anti-NMDAR antibodies are more likely to be found in the cerebrospinal fluid (CSF) of patients with this condition (both should be tested). Patients who have NMDAR encephalitis also have clonally increased levels of NMDAR-specific plasma cells in their cerebrospinal fluid (CSF), and the B cells in their CSF are able to produce anti-NR1 antibodies. In contrast to myasthenia gravis and NMOSD, in which antibody production takes place in the periphery, our findings show that the anti-NMDAR encephalitis NMDAR specific B cell response is compartmentalized in the central nervous system (CNS). This is shown by the fact that the NMDAR specific B cells are found in the brain and the spinal cord [11,12].

Clinical features

The NMDAR encephalitis is a complicated disease that can manifest itself with a diverse set of clinical characteristics. As was stated earlier, the disease frequently manifests itself with psychiatric symptoms, such as anxiety, depression, psychosis, or changes in behavioral patterns. These symptoms can appear prior to the manifestation of neurological symptoms. On the other hand, the neurological symptoms are the most distinctive feature of the condition, and they can be broken down into three stages: prodromal, hyperkinetic, and hypokinetic [13].

In the prodromal stage, symptoms such as headache, fever, and fatigue are present. These symptoms are not specific to the condition. Patients might also experience symptoms similar to the flu, problems with their gastrointestinal systems, or respiratory problems [14]. Because of this, these symptoms are frequently misdiagnosed as a viral infection or some other non-specific illness, which can cause a delay in the disease's diagnosis.

Involuntary movements, such as orofacial dyskinesias, chorea, dystonia, and limbic encephalitis, are a hallmark of the hyperkinetic stage of NMDAR encephalitis, which is the phase that best exemplifies the disease. Limbic encephalitis is a particularly important clinical feature of the disease because it can cause changes in behavior, as well as problems with memory [14]. Patients who have reached the hyperkinetic stage of the illness may also exhibit psychotic symptoms such as delusions, hallucinations, or other symptoms.

The hypokinetic stage is the most severe phase of the disease and is characterized by a decreased level of consciousness, catatonia, and autonomic instability. It is also the stage in which the disease is most likely to be fatal. Patients may sometimes experience seizures, respiratory failure, or cardiac arrest as a result of their condition [13]. Patients typically require the support of intensive care during this stage because it can be potentially fatal. It is essential to keep in mind that not all patients diagnosed with NMDAR encephalitis go through all three stages of the disease. Furthermore, the severity of each stage as well as the length it lasts can differ from patient to patient. Therefore, in order to identify the disease and determine the most appropriate course of treatment, a comprehensive clinical evaluation and diagnostic workup are required.

Diagnosis

Clinical, laboratory, and radiological findings are all taken into consideration when making a determination as to whether or not a patient has NMDAR encephalitis. Patients typically present with psychiatric symptoms, movement disorders, seizures, and autonomic instability, as was mentioned earlier. However, these symptoms are not specific to one particular neurological or psychiatric disorder; rather, they are shared by a number of conditions in these categories. Therefore, testing in a laboratory is essential in order to validate the diagnosis.

The examination of cerebrospinal fluid, also known as CSF, is an essential part of the diagnostic process for NMDAR encephalitis. In most cases, the analysis of the cerebrospinal fluid (CSF) reveals pleocytosis, which refers to an increase in the number of white blood cells, as well as elevated protein levels and oligoclonal bands [14]. The presence of these abnormalities lends credence to the possibility of an autoimmune encephalitis being the underlying condition.

In order to correctly diagnose NMDAR encephalitis, testing the patient's serum for anti-NMDAR antibodies is also essential. The detection of these antibodies in the serum is a highly sensitive and specific method for diagnosing the disease, with reported sensitivities ranging from 85 - 100% and specificities from 99 - 100% respectively [15]. Because treatment may cause a gradual decline in antibody levels over time, the testing for these antibodies should be done on the very first serum sample obtained from the patient.

Imaging studies of the brain, such as magnetic resonance imaging (MRI) and computed tomography (CT), can be helpful in the diagnosis of NMDAR encephalitis. These studies are typically performed in addition to laboratory testing. Imaging studies like these might reveal abnormalities in the limbic system, the basal ganglia, or some other parts of the brain [14].

It is essential to point out that a high index of suspicion is required for the diagnosis of NMDAR encephalitis, and patients should be evaluated by a specialist who is well-versed in autoimmune encephalitis. This is because NMDAR encephalitis is a rare condition. Imaging techniques for the brain, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), can supply supplementary data that bolsters the diagnosis of NMDAR encephalitis. Because of its ability to detect signal abnormalities in a variety of regions of the brain, including the medial temporal lobes, basal ganglia, and cortex, magnetic resonance imaging (MRI) is the imaging technique

of choice for diagnosing NMDAR encephalitis [14]. In particular, T2-weighted and FLAIR (fluid-attenuated inversion recovery) sequences may show abnormalities in the medial temporal lobes that are hyperintense signal abnormalities. These abnormalities are characteristic of the disease. Positron emission tomography, also known as PET, is another diagnostic tool that may be useful in NMDAR encephalitis cases. PET may show hypometabolism in the affected areas of the brain, which can be seen as reduced glucose uptake on fluorodeoxyglucose (FDG)-PET imaging. This is because hypometabolism results in less glucose being taken up by the body [16].

As was mentioned earlier, approximately fifty percent of female patients diagnosed with NMDAR encephalitis are found to have ovarian teratomas. Therefore, a pelvic ultrasound or computed tomography (CT) scan might be helpful in detecting the presence of a teratoma, which might then prompt further evaluation for NMDAR encephalitis. Imaging studies such as MRI and PET can provide additional information that helps to support the diagnosis of NMDAR encephalitis. In conclusion, the diagnosis of NMDAR encephalitis requires a combination of findings from the clinical setting, the laboratory, and imaging studies.

Treatment

Immunotherapy and other forms of supportive care are utilized in the treatment of NMDAR encephalitis. The primary objective of immunotherapy is to suppress the autoimmune response and lower the levels of antibodies that target NMDAR receptors. The treatment of seizures, assistance with breathing, and monitoring and upkeep of vital functions are all components of supportive care. Corticosteroids, intravenous immunoglobulin (IVIg), or plasma exchange (PLEX) are the immunotherapies that are considered to be the first-line treatments for NMDAR encephalitis [17]. Because of their anti-inflammatory and immunosuppressive properties, corticosteroids, like methylprednisolone, are frequently utilized in the first-line treatment of a variety of conditions. IVIg is another treatment that is frequently used as a first-line option. It is thought to be effective because it prevents autoantibodies from binding to the NMDAR [13]. PLEX is effective in lowering antibody levels and improving clinical symptoms, and it can remove circulating antibodies from the bloodstream very quickly [13]. If the patient does not respond to the first-line therapy or has a relapse, the second-line immunotherapy could be an option. Rituximab, cyclophosphamide, or mycophenolate mofetil (MMF) are examples of potential treatments for use in the second line of treatment [17]. The monoclonal antibody rituximab is directed against B cells, which are the cells in the body that are in charge of producing antibodies. Cyclophosphamide is an alkylating agent that is used as an immunosuppressant. It also works by inhibiting the process of DNA synthesis. MMF is an immunosuppressant that works by preventing the multiplication of T and B cells. The severity of the disease, the presence or absence of a tumor, and the patient's response to any previous treatments all factor into the decision of which immunotherapy to use. Decisions regarding treatment ought to be arrived at after discussion with a neurologist or an immunologist who has prior expertise in the administration of treatment for autoimmune encephalitis. In a nutshell, immunotherapy and care that is supportive are the two main components of the treatment for NMDAR encephalitis. Patients who do not respond to first-line treatment or who have experienced a relapse may be candidates for second-line therapy, which may include rituximab, cyclophosphamide, or MMF. Corticosteroids, IVIg, and PLEX are the most common treatments that are used for first-line therapy.

Summary

NMDAR encephalitis is an uncommon form of autoimmune disease that manifests itself in the brain. Young adults and females are more likely to be affected by this condition than men. The disease manifests itself with a wide variety of clinical features, some of which are movement disorders, seizures, psychiatric symptoms, and autonomic instability. The clinical, laboratory, and radiological findings, including the presence of anti-NMDAR antibodies in serum and cerebrospinal fluid, are used to make a diagnosis of NMDAR encephalitis. This diagnosis is made based on a combination of these findings. Depending on the extent of the disease, immunotherapy may be administered in the form of corticosteroids, IVIg, PLEX, rituximab, cyclophosphamide, or MMF. In addition to curative treatment, supportive care is an essential component of disease management. A better prognosis can be achieved through early detection and prompt treatment of the condition.

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