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Case Report

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Case Reports on 2 Patients of Anti Nmda Receptor Encephalitis

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Abstract

Anti-NMDA receptor encephalitis is an autoimmune disorder. Antibodies attack NMDA (N-methyl-D-aspartate)-type glutamate receptors at central neuronal synapses. This ailment occurs when antibodies generated by the body's defense system attack NMDA receptors in the brain. NMDA receptors are nitrogenous organic compounds that regulate electrical impulses in the brain. Their roles are important for assessment, perception, human interaction, formation and retrieval of memory, and activities such as breathing, swallowing, etc. Antibodies play a big role in the human immune system. Humans produce antibodies against viruses and bacteria. Under normal circumstances, the body prohibits the production of antibodies against its tissues. However, in some individuals, antibodies that prey on the host may be produced. This is what is known as "autoimmune" disease. In anti-NMDA receptor encephalitis immune serum globulin are generated against NMDA receptors and go on to raid these receptors in the brain where they are mostly found. Anti-NMDA receptor encephalitis may be associated with a tumor; the most common tumor type is a teratoma.

Unlike other tumors, it may contain many types of body tissues. Other types of tumors that correlate with anti-NMDA receptor encephalitis include but are not limited to breast cancer, cancer of the colon and lung cancer. The majority of tumors associated with anti-NMDA receptor encephalitis contain neural tissue that is identical to the brains and NMDA receptors. It is assumed that immune serum globulin is firstly formed against NMDA receptors found inside tumors, and then prey on similar-looking receptors in the brain producing clinical manifestation associated with anti-NMDA receptor encephalitis.

Patients suspected of suffering from anti-NMDA receptor encephalitis are checked for the presence of tumors. This diagnosis is done by use of computerized tomography and also magnetic resonance imaging of the chest, abdomen and pelvis. Women should also get an ultrasound of the ovaries while men receive an ultrasound of the testes. People suffering from anti-NMDA receptor encephalitis should be checked periodically for the presence of a tumor. A tumor is mostly negative when people suffering from anti NMDA are screened. This may be because the tumor is too minute to be detected with imaging techniques, or because it has been eradicated by the body's defense system or the analysis for the tumor is negative.

Abbreviations

CSF	Cerebrospinal fluid
CT	Computerized tomography
EEG	Electroencephalogram
MRI	Magnetic resonance imaging
USG	Ultrasonography
NMDA	N-methyl-D-aspartate receptor
EGFP	Enhanced green fluorescent protein
DMEM	Dulbecco's modified eagle medium
CDNA	Complementary DNA
PSDP 95	Postsynaptic density protein 95

Materials and Methods

Clinical data

The serum and CSF portion is sent on for testing by clinicians. The Standardized clinical questionnaire is given to the Patient with information sheets and consent forms are given .to the clinicians. Reference is made for the first 50 NMDAR immune serum globulin positive batch from a total of 450. Clinicians are asked to record in detail the timing of specific features such as high cognitive dysfunction, psychiatric, seizures and movement disorders. The categorizations are maintained as provided by the clinicians. All data collected is analyzed using Graph PadPris5.Thirty-two questionnaires were returned, and five were completed from clinic letters, emails.

Cell-based assay for Immune serum globulin binding human NMDAR

Human embryonic kidneys are used for cell-based assay. The kidney cells are plated on glass coverslips in highly concentrated components of amino acid, vitamins and supplementary components together with ten percent fetal calf serum, penicillin, streptomycin, and amphotericin. After one day the cells were transfected, using polyethylene amine and glucose, with untagged-NR1 and NR2B cDNA at a ratio of 3:1. An enhanced green fluorescent protein vector expression vector is co-transfected to visualize cells taking up complementary deoxyribonucleic acid. To stop cytotoxicity due to glutamate in the medium activating the NMDARs, cells are added with 500-μM ketamine sixteen hours post-transfection. Live cells are procreated with patient sera (1:20) or undiluted cerebrospinal fluid for one hour before fixation (3% formaldehyde) followed by 35 min incubation with Alexa Fluor 568 anti-human immunoglobulin G (IgG).

Fluorescent immune precipitation assay for antibodies to NMDAR

Cells are solubilized utilizing a buffer containing 1% digitonin. A protease inhibitor cocktail is affixed to this buffer immediately before use. The precipitate is analyzed using immune serum globulin to NR1 NR2and PSD95, and analysis of EGFP fluorescence infractions coming after sedimentation on a fixed sucrose gradient. For serological studies, 25 μl of serum is incubated with 250 μl of supernatant squeeze overnight at 4°C, as described previously Protein-the beads is rotated with the antigen-antibody mixture for two hours at room temperature. The beads are washed, and the captured fluorescence is measured using a fluorescent plate reader. Results are manifested as relative fluorescent units precipitated by 25-μl serums.

Results

Demodulation of NMDAR antibodies

Previously three assays were used for the diagnosis of NMDAR antibodies. To affirm the neuronal cell surface specificity of the immune serum globulin and, thus, their likely clinical importance, primary cultures of hippocampal neurons with sera and CSF are incubated to check binding to the surface of live neurons immune fluorescent cell-based assay is established to find NMDAR antibodies, Specifically The ratio 3:1 of NR1:NR2B cDNA as this gave better results the NR1 subunit is thought to contain the main antigen molecule in which antibody attaches itself. To detect protein binding only to the extracellular domain of the NR1/NR2B, cells are not permeabilized and applied serum is undiluted. Using a semi-quantitative approach similar to that employed for binding of antibodies to other cell surface antigens the binding was scored visually from 0 to 4. All positive outcomes are retested, and also examined for non-specific binding to the cells using human embryonic kidney cells transfected with other antigens scores

A quantitative assay for antibodies against the NR1 subunit

To measure NMDAR-antibody levels more quantitatively, a fluorescent immune precipitation assay was established similar to that reported for AQP4 antibodies. The best expression of EGFP-NR1 occurs when it was co-expressed with NR2B and PSD95. The cells are solubilized in a buffer containing 1% digitonin, and the EGFP-NR1 could be immune precipitated by anti-NR1 antibodies but not by anti-NR2B, or anti-PSD95 antibodies. The main enhanced green fluorescent-tagged material was sediment on a sucrose gradient with a peak corresponding to 280. Suggests that the important component is a dimer of NR1-EGFP rather than a tetramer containing both.

Patients with positive NMDAR antibodies

In general 50 of the 450 referred sera were positive for NMDAR immune serum globulin with scores between 1 and 4. Of the 44 patients who participated in the research ten were identified retrospectively from sera sent over the preceding three years for other antibody tests. Using assays in routine clinical use, all NMDAR-antibody-positive sera were negative for immune serum globulin against glutamic acid decarboxylase, amphiphysin and voltage-gated calcium channels. Two patients had low levels of voltage-gated potassium channel immune serum globulin

Key Words: Encephalitis, Anti-N-methyl-D-aspartate receptor antibodies, enhanced green fluorescent protein cerebrospinal fluid

Introduction

Anti-NMDA receptor encephalitis is an autoimmune disorder .its symptoms are similar to some other many types of diseases easily be misdiagnosed leading to wrong treatment, which may be fatal in the long- run. This ailment occurs when immune serum globulin generated by the body's defense system attack NMDA receptors in the brain. NMDA receptors are nitrogenous organic compounds that regulate electrical impulses in the brain. Their roles are important for assessment, perception, human interaction, formation and retrieval of memory, and activities such as breathing, and swallowing. Antibodies play a big role in the human immune system. Humans produce antibodies against viruses and bacteria [[i]]. The following three cases show different patients who all suffer from anti-NMDA receptor encephalitis. We are going to look at the patient's history and how the disorder was tested and found in the patients, the test that the physicians carried out to get positive results. Management of the disorder is also going to be looked at to ensure the patients fully recover. The main clinical manifestation of the disease will also be looked so that one can easily differentiate it from other ailments. This will give us insight and concrete conclusions about this disorder, its treatment, and management. Cells are then washed three times in phosphate-buffered isotonic solution and mounted on slides in the fluorescent mounting medium [[ii]]. They are then scrutinized using a fluorescence microscope with a MacProbe v4.3 digital imaging system. The binding is scored on a scale from 0–4. Positive samples are retested on tyrosine kinase or glycine α1 receptor transfected cells to exclude non-specific binding to the human embryonic kidney cells. For subclass experiments, cells are incubated with isotype-specific mouse antibodies and then with an Alexa Fluor 568 anti-mouse IgG. For immune absorption, the sera (1:20 dilution) are pre-incubated with 5 million trypsinized enhanced with green fluorescent protein-expressing human embryonic kidney cells for thirty minutes at 4°C before testing for binding. For detection of deposited complement on transfected cells, the live cells are incubated with heat-inactivated sera and fresh human plasma, as an additive [[iii]].

Case Report

Case 1

A woman who did not have any pre-existing illness is admitted to the hospital with the sub-acute onset of personality change, anxiety, and psychotic-hallucinatory perception. A cranial MRI and abdominal computed tomography were done and the results were not conclusive. Examination appears to be normal in the electroencephalography and continuous slow activity with an intermittent right temporal focus was observed after two days of admission. She developed orofacial dyskinesia, and acute focal and generalized seizures. For these, she was given high doses of phenobarbital. The patient eventually

developed central hypoventilation with respiratory insufficiency and required ventilation. The outcome of a fludeoxyglucose composition emission tomography analysis was inconclusive regarding tumor screening; however, an abdominal ultrasound revealed a suspicious lesion in the right ovary. Surgery was conducted nine days after the patient was admitted and it showed teratomas **[**4-5**]**. Cerebrospinal fluid test analysis reveals oligoclonal bands without pleocytosis, and anti-NMDA receptor immune serum globulin was found in the CSF. The patient was in the intensive care unit for two weeks after admission; Therapy was started with immune absorption and followed by methylprednisolone **[**6**]**. However, the patient was also diagnosed with acute autonomic dysfunction, with cardiac arrhythmia, blood pressure issues, disturbed thermoregulation, and hypersalivation. The cardiorespiratory issue worsened to a serious condition within the next month. An additional surgery on her left ovary was undertaken to show no teratoma, and the second cycle of immune absorption followed by four cycles of cyclophosphamide was given in monthly intervals. Towards the fourth cycle of treatment, the patient started to boost steadily. The immunosuppressive therapy was reduced to immunoglobulin. Continuous analysis of CSF and serum NMDA receptor antibodies showed reducing antibody titers Thoracic and abdominal Computed tomography was repeated after six months, in addition to MRI of the pelvis. After seven months in the ICU, the patient was released for rehabilitation. At this juncture, the patient was oriented only to herself and could not even recall time and space, and she had mood swings. The patient was followed up for three years and her state gradually improved. On the last visit, the patient was fully orientated, cooperative.

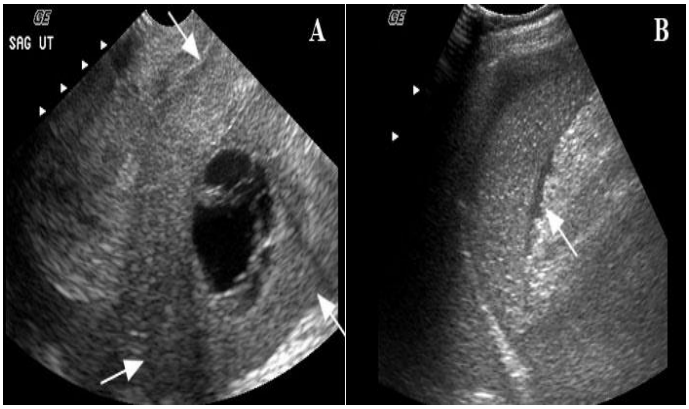

Figure 1

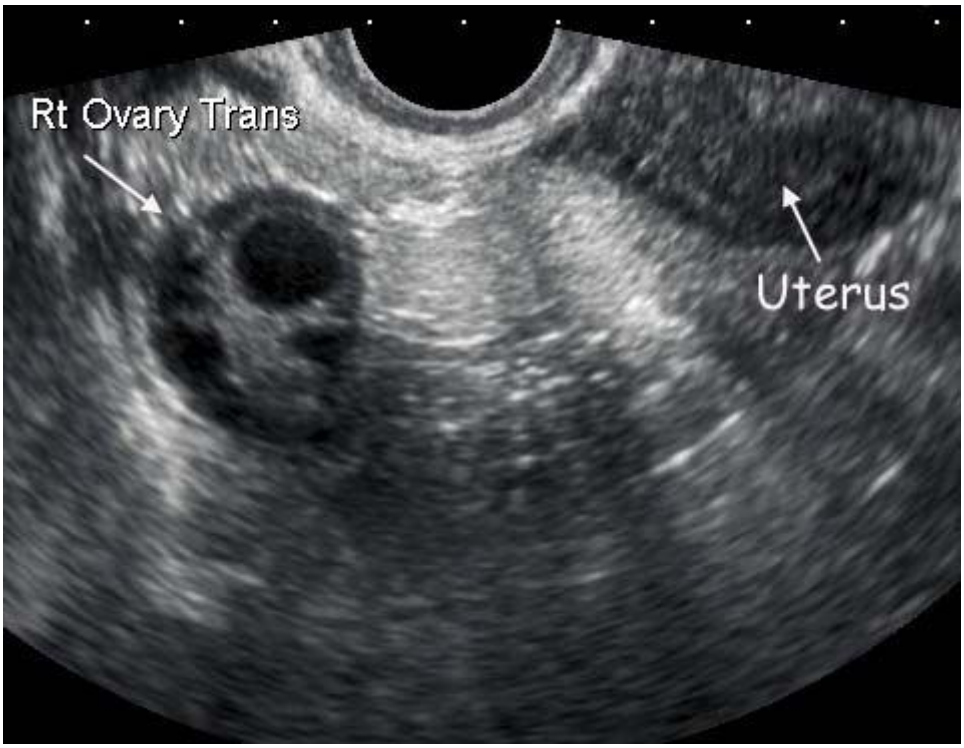

Figure 2

USG abdomen report

Case 2

Another woman was referred to the hospital for confirmation of a diagnosis of anti-NMDA receptor encephalitis. She had been admitted to a different hospital previously with the following symptoms; mild generalized headache and mood changes with latent aggressive behavior. Alpha activity with an indication of varying vigilance was described in the screening. Within a week, the patient had contracted aphasia with semantic paraphrases, anxiety severe apraxia, and hallucinations and reduced orientation to person, time, place and situation **[**7**]**. Cranial MRI was done but the examinations were unremarkable. A cerebrospinal fluid test was carried out and showed 156 cells/µl, positive oligoclonal bands, a positive Epstein-Barr virus polymerase chain reaction (PCR) analysis and an elevated 14-3-3 protein concentrations. The doctors suspected it was Infectious meningoencephalitis thus antiviral and antibiotic therapy was started. In weeks, the patient started to get orofacial dyskinesia. Previous results from the CSF test found NMDA receptor-IgG antibodies in the cerebrospinal fluid and serum and the patient was given haloperidol (2×2.5 mg) and prednisolone (100 mg, orally), but subsequently began a neuroleptic malignant syndrome. The haloperidol was instantly stopped, and the rigor signs eased; however, the patient developed respiratory issues and required ventilation. The patient's state worsened

and after two weeks she then got a trismus-like spasm of the jaw, fracturing several maxillary teeth, and complex focal seizures. She was taken for scan CT scan and the results were normal regarding neoplasia; however, due to age and the vigorous clinical symptoms, prophylactic surgery was undertaken but showed no teratomas. Cyclophosphamide was better after five cycles of plasmapheresis followed the patient. The patient was released for rehabilitation after two months in the hospital.

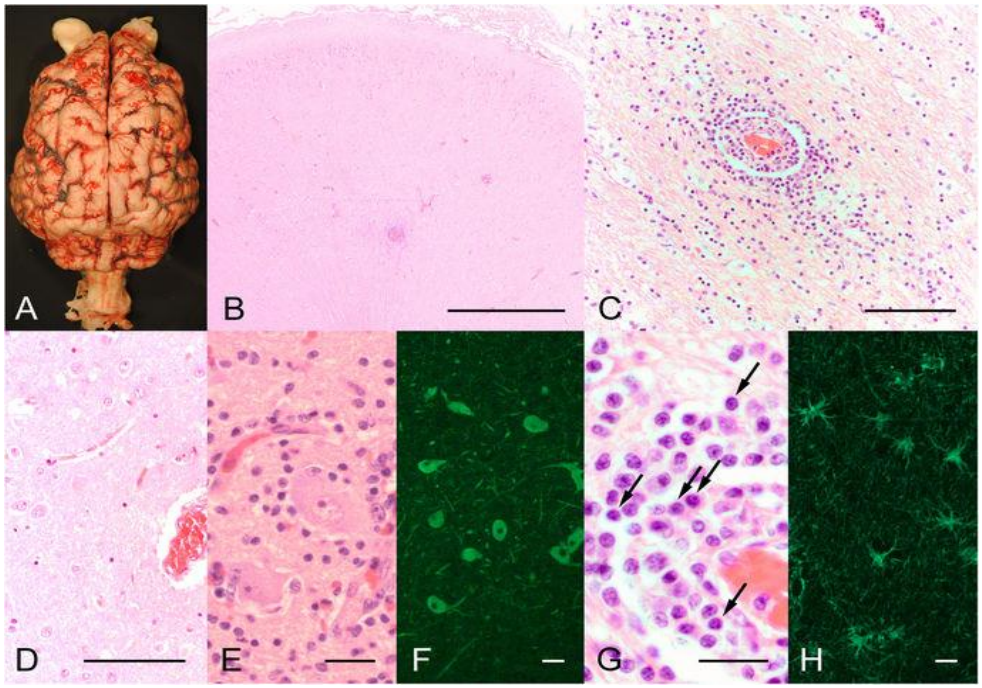

Figure 3

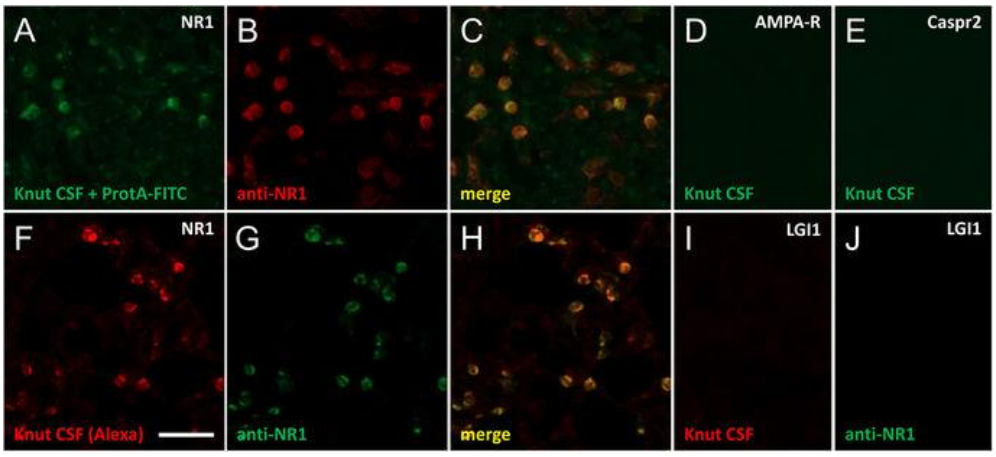

Figure 4

CSF test found NMDA receptor-IgG antibodies in the cerebrospinal fluid and serum and the patient was

given haloperidol (2×2.5 mg) and prednisolone (100 mg, orally), but subsequently began a neuroleptic malignant syndrome

Assessment

As a defining state, anti-NMDA receptor-IgG antibodies were got in the CSF and serum in all patients. Same serum and CSF samples were analyzed in the two patients. CSF and serum were analyzed for NMDA receptor antibodies. This was followed by end-point titration on transfected HEK 293 cells. In some patients, NMDA receptor antibodies are only found in the CSF, which is rare but not unusual as serum antibodies are negative in patients using detection techniques such as rat brain slice and transfected HEK cells. Calculation of the antibody-specific index showed an intrathecal synthesis of antibodies. The same CSF and serum potion were found at the beginning of the disease; however, no antibodies were found in the CSF following repeated analysis. This observation is rare, as antibodies in the central nervous system appear to mediate the clinical symptoms, The NMDA receptor seropositivity alone has been seen in patients with the herpes simplex virus. The highest CSF and serum titers were detected in patient 1 screening. He was one of the patients that showed the least clinical improvement. Worth noting is the contrast in which clinical symptoms declined between months 10 and 11. During immunosuppressive treatment, however, simultaneously CSF and serum protein concentrations reduced significantly this shows that the protein levels to determine the CSF titer/CSF protein and serum titer/serum ratios adjusted the antibody titer.

Discussion

These cases illustrate the attributes of the different levels of clinical manifestation and the range of rigidity of anti-NMDA receptor encephalitis, in conditions with their anti-NMDA receptor antibodies. In patients with the classic signs of the sub-acute onset of psychic disruption, differences in character, memory loss, and seizures, the scope of differential diagnoses is limited. Clinical manifestation and verification of NMDA receptor antibodies clarify the diagnosis of anti-NMDA receptor encephalitis. . Infectious determinants of encephalitis, particularly HSV and less known Varicella-Zoster virus or cytomegalovirus, must be left via PCR and or antibody index using CSF analysis **[**8**]**. Metabolic roots, such as uremic and hepatic encephalopathy, may be assessed by standard laboratory tests. More often, diagnostic uncertainty transpires if signs are mild or negative signs, such as depression, influence psychic changes. Routinely anti-NMDA receptor encephalitis, the clinical manifestation passes through different stages. During the first period, the prodromal phase, which precedes the next stage by two weeks, more patients suffer from unspecific flu-like signs, such as fever, headache, nausea, and unrest.

In the second phase, neuropsychiatric signs are clear, and seizures occur. All the current patients showed psychological deficiency, ranging from unrest and disorientation to fear, affective interruptions and revealed psychosis and loss of short-term memory. Furthermore, all the current patients ailed from generalized seizures. Central hypoventilation is another common trait of the initial phases of anti-NMDA receptor encephalitis.

The third phase occurs between ten and twenty days and is characterized by dyskinesia and vegetative dysregulation. Patient one suffered from autonomic dysfunction with cardiac arrhythmia, blood pressure deregulation, disturbed thermoregulation and hypersalivation. The initial signs of anti-NMDA receptor encephalitis can be mistaken to be flu and usually begin the neuropsychiatric manifestations within two weeks. This indicates the rapid onset of antibody creation.

Conclusion

Ponto-medullary respiratory reflexes such as an NMDAR blockade may cause patients to have hypoventilation. The time-course of symptoms supports a primarily cortical mechanistic pathway, with secondary subcortical alteration and disturbance of corticostriatal and brainstem pathways. The NMDA receptor is expressed in hippocampal, cortical and cerebellar neurons, in addition to glial cells such as oligodendrocytes and astrocytes, in varying concentrations and subunit composition may be of further pathophysiological relevance to the clinical presentation and time course of the disease.the expression always changes under different pathophysiological conditions, such as ischemia. A typical feature of anti-NMDA receptor encephalitis may be elaborated more by the vigorous expression of the NMDA receptor in hippocampal neurons **[**9**]**.

Patients suspected of suffering from anti-NMDA receptor encephalitis are checked for the presence of tumors. This is done with imaging (CT or MRI) of the chest, abdomen, and pelvis. Women should also get an ultrasound of the ovaries while men receive an ultrasound of the testes. People with anti-NMDA receptor encephalitis should be checked periodically for the presence of a tumor. In many people with anti-NMDA receptor encephalitis a tumor is negative. This may be because the tumor is too minute to be detected with imaging techniques, or because it has been eradicated by the immune system, or there is no tumor.

It has been demonstrated that the titer of NMDA receptor antibodies correlates with clinical outcome and that high antibody titers are more common in patients with poor outcomes or tumors in the present cases, the highest antibody titer was found in a patient with mystic teratoma who failed to be analyzed by ultrasound, CT, MRI, and PET. High antibody titers may be a sign of an underlying tumor, more so if there is no reduction following immunosuppressive treatment.

NMDA receptor antibodies are part of the overall protein mix measured in the CSF or serum. Fewer antibody titers may therefore correlate with an overall cutback in protein concentration. This is of importance for patients with anti-NMDA receptor encephalitis. Significantly decrease in the protein mix in serum and this may be avoided by calculating the antibody/protein ratio as opposed to the antibody titers alone **[**10**]**. This also shows the significance of follow-up CSF analysis as a marker for disease actions, and forecast during this disease.

In patients with a new and not chronic onset of neuropsychiatric symptoms, the differential diagnosis of anti-NMDA receptor encephalitis should be considered and CSF analysis may aid the detection of anti-NMDA receptor antibodies. Although multistage clinical presentation is a standing out feature of the disease, the severity of symptoms is not fixed. Cranial MRI is usually paramount for differential diagnosis; however, in anti-NMDA receptor encephalitis outcomes are not certain. Depending on the signs, other diagnoses may be excluded if anti-NMDA receptor encephalitis is positive, an intensive search for tumors, more so teratomas, is needed. Immunosuppressive treatment is required immediately, as a good clinical outcome is associated with early therapy for reducing anti-NMDA receptor antibody mix.

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