Auto-immune encephalitis as differential diagnosis of infectious encephalitis

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Abstract

Purpose of review—To describe the main types of autoimmune encephalitis with special emphasis on those associated with antibodies against neuronal cell surface or synaptic proteins, and the differential diagnosis with infectious encephalitis.

Recent findings—There is a continuous expansion of the number of cell surface or synaptic proteins that are targets of autoimmunity. The most recently identified include the mGluR5, DPPX, and the GABA_A receptor. In these and previously known autoimmune encephalitis (NMDAR, AMPAR, GABA_B receptor, LGI1, CASPR2), the prodromal symptoms or types of presentations often suggest a viral encephalitis. We review here clues that help in the differential diagnosis with infectious encephalitis. Moreover, recent investigations indicate that viral encephalitis (e.g., herpes simplex) can trigger synaptic autoimmunity. In all these disorders immunotherapy is usually effective.

Summary—Autoimmune encephalitis comprises an expanding group of potentially treatable disorders that should be included in the differential diagnosis of any type of encephalitis.

Keywords

autoimmune encephalitis; immunotherapy; herpes simplex encephalitis; viral encephalitis; neuronal surface antibodies

Introduction

Encephalitis is a significant cause of morbidity and mortality worldwide. In order to find the etiology of the disorder patients frequently undergo extensive testing but despite this, the cause remains unknown in about 60% of the cases.¹–³ The discovery that several forms of

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Conflict of interest:
Dr. Dalmau holds patents for the use of Ma2 and NMDAR as autoantibody tests, and has filed patents for the use of GABA_A and GABA_B as diagnostic tests.
encephalitis result from antibodies against neuronal cell surface or synaptic proteins, and that they are potentially treatable has led to a paradigm shift in the diagnostic approach of encephalitis. A recent multicenter population-based prospective study found that in 42 of 203 patients (21%) the etiology was immune-mediated and 38% of them occurred with neuronal antibodies. Another study by the California Encephalitis Project, a center focused in the epidemiology of encephalitis found that the frequency of anti-N-methyl-D-Aspartate receptor (NMDAR) encephalitis surpassed that of any individual viral etiology in young individuals. Moreover, recent studies show that some forms of autoimmune encephalitis can be triggered by herpes simplex encephalitis (HSE). This review focuses on the diagnosis and treatment of autoimmune encephalitis, mainly those associated with antibodies to cell surface or synaptic proteins (Table 1), with emphasis on the differential diagnosis with infectious etiologies.

Comparison between autoimmune and infectious encephalitis

Autoimmune encephalitis occurs more frequently in immunocompetent than immunocompromised patients (22% versus 3%). Most patients with antibody-associated encephalitis and HSE have seizures. In contrast, patients with encephalitis associated to varicella zoster virus (VZV) or Mycobacterium tuberculosis infrequently develop seizures. Psychosis, language dysfunction, autonomic instability and abnormal movements are a hallmark of anti-NMDAR encephalitis. Most patients with infectious encephalitis have fever, but approximately 50% of cases with autoimmune encephalitis present or develop fever during the course of the disease. Prodromal symptoms such as headache or flu-like symptoms occur frequently in autoimmune encephalitis and may lead to the suspicion of an infectious etiology. Skin lesions can assist in the recognition of VZV, however, CNS VZV reactivation may occur in the absence of rash.

Most autoimmune encephalitis associate with cerebrospinal fluid (CSF) lymphocytic pleocytosis that is usually milder than that found in viral etiologies. Patients with viral and autoimmune encephalitis have normal glucose levels and normal or mildly increased protein concentration, while patients with bacterial infections or Mycobacterium tuberculosis have a decrease of CSF glucose concentration.

Magnetic resonance imaging (MRI) of the brain can be useful in the differential diagnosis of encephalitis, particularly in patients with limbic encephalitis. Most patients with autoimmune or paraneoplastic limbic encephalitis have uni- or bilateral increased T2/FLAIR signal in the medial temporal lobes without contrast enhancement or abnormal diffusion-weighted images; an exception is the paraneoplastic encephalitis with antibodies against the intracellular protein Ma2, in which MRI often shows contrast enhancement. The syndromes with classical findings of limbic encephalitis include those associated with antibodies against the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), the gamma-aminobutyric acid-B receptor (GABA\textsubscript{B}R), leucine-rich glioma inactivated protein 1 (LGI1), and less frequently the metabotropic glutamate receptor 5 (mGluR5). In patients with anti-NMDAR encephalitis the brain MRI is normal in approximately 60% of the patients and shows nonspecific findings in the rest including, cortical-subcortical FLAIR changes in brain or posterior fossa, transient meningeal
The brain MRI in other autoimmune encephalitis, such as those associated with antibodies against contactin-associated protein-like 2 (CASPR2) or dipeptidyl-peptidase-like protein-6 (DPPX) is frequently abnormal but rarely suggestive of focal limbic encephalitis.\textsuperscript{21,22} Patients with high titer serum and CSF GABA\textsubscript{A}R antibodies may develop extensive cortical and subcortical T2-FLAIR changes during the course of the disease.\textsuperscript{23}

Only a few infectious encephalitis associate with MRI findings similar to those occurring in autoimmune limbic encephalitis; they include, post-transplant acute limbic encephalitis related to human herpesvirus 6 (HHV6), exceptional cases of neuro-syphilis, and HSE. Of note, HSE typically shows asymmetric medial temporal lobe necrosis along with involvement of cingulate and insular regions. Some patients, usually children, may develop more extensive MRI abnormalities in frontal, occipital or parietal lobes.\textsuperscript{24} The polymerase chain reaction (PCR) for herpes simplex virus (HSV) can be false-negative during the first 48 hours of HSE.\textsuperscript{24}

### Autoimmune encephalitis with antibodies against intracellular antigens

Most of the antibodies to intracellular proteins considered here are paraneoplastic and therefore, they occur in middle aged or elder patients who sometimes have a previous history of cancer. They include antibodies to Hu, Ma2, Ri, CRMP5, and amphipisin.\textsuperscript{25} In approximately 70% of the cases the development of neurological symptoms precedes the cancer diagnosis.\textsuperscript{25,26} Patients with any of these antibodies can develop limbic encephalitis, usually in the context of encephalomyelitis. Some patients with Hu antibodies develop focal cortical encephalitis and \textit{epilepsia partialis continua} suggesting a focal infectious process.\textsuperscript{27}

Patients with Ma2 antibodies may develop prominent brainstem dysfunction with abnormal gaze and facial movements which frequently suggest Whipple’s disease. In a series of 38 patients with anti-Ma2 encephalitis, 16% underwent duodenal biopsy for suspected Whipple’s disease before the final diagnosis was made.\textsuperscript{28}

A subset of patients with limbic or non-focal encephalitis with or without seizures has antibodies against GAD65.\textsuperscript{29} These antibodies rarely associate with cancer, and also occur in patients with cerebellar degeneration, stiff-person syndrome, and non-neurological disorders such as type I diabetes mellitus, vitiligo, or pernicious anemia. Moreover, GAD65 antibodies may associate with encephalitis related to other more relevant antibodies, such as AMPAR, GABA\textsubscript{B}R or GABA\textsubscript{A}R.\textsuperscript{18,23} All patients with encephalitis or seizures with GAD65 antibodies should be assessed for the co-occurrence of other antibodies against cell surface proteins.

### Autoimmune encephalitis with antibodies to cell surface or synaptic proteins

#### Anti-NMDAR encephalitis

This disorder predominates in young women and children although it can affect males and people of all ages (the youngest and the oldest patient described were 2 month and 85 year-old).\textsuperscript{12,20} The presence of a tumor (mostly an ovarian teratoma) is age dependent, and rarely...
encountered in patients younger than 12 years.\textsuperscript{20} The antibodies target the GluN1 subunit of the NMDAR receptor.\textsuperscript{30} The neuropsychiatric symptoms are often preceded by prodromal headache, fever or other features that may suggest an infection. In teenagers and young women, the onset is characterized by prominent psychiatric manifestations (delusional thoughts, bizarre behavior, psychosis, catatonia), followed by a decrease of consciousness, seizures, orofacial or limb dyskinesias, and autonomic instability.\textsuperscript{30} In children and adult male patients, the first symptom can be seizures or movement disorders.\textsuperscript{31–34} The differential diagnosis often includes a primary psychiatric disorder, drug abuse, neuroleptic malignant syndrome, or infectious encephalitis.\textsuperscript{5} In some instances the diagnosis of rabies has been considered due to the presence of extreme agitation, prominent sialorrhea, and abnormal movements.\textsuperscript{5} In contrast to anti-NMDAR encephalitis in which the brain MRI is frequently normal,\textsuperscript{30} the MRI of patients with rabies often shows symmetric involvement of the grey matter of dorsal brainstem, thalamus, basal ganglia, or central region of the spinal cord.\textsuperscript{35}

Due to the frequent presence of prodromal symptoms (hyperthermia, headache, and other), most patients with anti-NMDAR encephalitis are investigated for an infectious etiology. In a few cases (overall less than 5\% of the cases) positive serologies for \textit{Mycoplasma pneumoniae}, HHV6, or enterovirus have been described; the significance of these findings is currently unclear.\textsuperscript{30,32} Detection of HHV6 or 7 in the CSF by PCR may represent detection of a latent rather than an active viral infection.\textsuperscript{36} A link between HSE and anti-NMDAR encephalitis (and other types of synaptic autoimmunity) was recently identified (discussed later).

The antibodies of patients with anti-NMDAR encephalitis cause a specific internalization of these receptors, and alter the NMDAR synaptic currents.\textsuperscript{30} A similar antibody mediated internalization of receptors was observed after infusing patients’ antibodies into the hippocampus of rats. Autopsies of patients with these antibodies show a decrease of NMDAR in areas of deposits of antibodies along with absence of cytotoxic T-cell infiltrates or deposits of complement.\textsuperscript{37}

**Encephalitis with predominant limbic involvement**—The term limbic encephalitis refers to an inflammatory process of the limbic system including, the medial temporal lobes, amygdala, and cingulate gyri, resulting in severe memory deficits, behavioral changes, psychiatric symptoms and temporal lobe seizures.\textsuperscript{38} The most frequent cell surface target antigen of limbic encephalitis is LGI1. The median age of patients with these antibodies is 60 years, and the neurological symptoms are often accompanied by hyponatremia.\textsuperscript{17,39} Patients rarely have an underlying tumor, and if so, it is usually a thymoma. Some patients develop myoclonic-like movements, also described as facio-brachial dystonic seizures, but with EEG features of tonic seizures.\textsuperscript{40,41} These seizures can precede or occur simultaneously with symptoms of limbic dysfunction and may lead to an early recognition of the disorder. Approximately 70\% of the patients with LGI1 antibodies improve with immunotherapy although residual memory deficits are frequent (unpublished observation). There is evidence that LGI1 antibodies may disrupt the normal interaction of LGI1 with the synaptic proteins ADAM22 and ADAM23, resulting in a decrease of post-synaptic AMPAR.\textsuperscript{42}
Other cell surface antigens related to limbic encephalitis include AMPA and GABA\textsubscript{B} receptors.\textsuperscript{16,18} More than half of the patients with these antibodies have cancer; the type of tumor varies with the antibodies (small cell lung carcinoma, SCLC, predominantly with GABA\textsubscript{B} receptor, and breast cancer and thymomas with AMPAR). Patients with SCLC may have other antibodies suggesting the presence of this tumor, such as SOX1 or N-type voltage-gated calcium channel (VGCC). Patients’ antibodies against AMPAR cause internalization of receptors and decrease of AMPAR mediated currents strongly suggesting a pathogenic role of these antibodies.\textsuperscript{16}

**Other autoimmune encephalitis**—A subset of patients with autoimmune encephalitis harbor antibodies to DPPX,\textsuperscript{22} a critical regulatory subunit of the Kv4.2 potassium channel. These patients develop agitation, confusion, psychiatric symptoms, seizures, tremor, myoclonus, and less frequently hyperekplexia.\textsuperscript{22,43} Characteristically, most of these patients have diarrhea or other gastrointestinal symptoms leading to profound weight loss. The etiology of these gastrointestinal symptoms is unclear, but may be related to the expression of DPPX in the myenteric plexus.\textsuperscript{22} This clinical presentation often leads to extensive gastrointestinal studies for a malignancy or infectious etiology, which in all cases has been negative.

A form of non-focal encephalitis (although often referred as limbic encephalitis) associates with Hodgkin’s lymphoma, and is known as Ophelia syndrome.\textsuperscript{44} These patients usually have antibodies to mGluR5.\textsuperscript{19} Identification of this disorder is important because it is highly responsive to treatment of the tumor and immunotherapy.\textsuperscript{19,45} Autoantibodies to mGluR5 can also occur in patients with autoimmune encephalitis without Hodgkin’s lymphoma.

CASPR2 is the target antigen of antibodies of some patients with Morvan’s syndrome, encephalitis (sometimes focal limbic encephalitis), or a subset of cases with neuromyotonia. Autoantibodies against CASPR2, and those directed against LGI1 were previously reported as voltage-gated potassium channels (VGKC) antibodies. About 30\% of patients with CASPR2 antibodies have an underlying thymoma.\textsuperscript{21,39,46}

The most recently identified autoimmune encephalitis occurs with antibodies against the GABA\textsubscript{A} receptors.\textsuperscript{23} High titers of these antibodies in serum and CSF usually result in refractory seizures and status epilepticus, along with extensive MRI cortical/subcortical FLAIR changes. Approximately, 40\% of the patients are children. Low titers of serum antibodies associate with encephalitis and seizures, but also opsinclonus and stiff-person syndrome (with or without GAD65 antibodies). Patients with GABA\textsubscript{A}R receptor antibodies are often misdiagnosed as having anti-GAD65 associated encephalitis or Hashimoto’s encephalitis due to the frequent co-occurrence of GAD65 or thyroid-peroxidase (TPO) antibodies. Patient’s GABA\textsubscript{A}R antibodies cause a specific decrease of these receptors at synapses.\textsuperscript{23}

Several studies have indicated the presence of antibodies to dopamine receptor 2 (DR2) in some patients with basal ganglia encephalitis or Sydenham chorea.\textsuperscript{47,48} At this time, the frequency and pathogenic significance of these antibodies are unclear.
HSE triggers synaptic autoimmunity

There is recent evidence that HSE triggers synaptic autoimmunity. This finding likely explains cases with prolonged or atypical neurological symptoms after successful control of the viral infection, or patients who develop a syndrome described as “relapsing post-HSE” or “choreoathetosis post-HSE”. These disorders are important to recognize because the outcome without immunotherapy is usually poor. In contrast, aggressive immunotherapy appears to be beneficial, sometimes with substantial recoveries. Choreoathetosis post-HSE, usually develops a few weeks after patients have recovered from HSE; the main differences between true viral relapses and autoimmune encephalitis post-HSE are shown in Table 2. The clinical features of autoimmune encephalitis post-HSE are similar to those of anti-NMDAR encephalitis, although some patients develop fragments of this syndrome. A recent study showed that the novel synthesis of NMDAR antibodies occurred after the viral encephalitis. Some patients may develop antibodies to DR2 and other yet unknown cell surface neuronal proteins.

Diagnosis and treatment of encephalitis with antibodies to cell surface antigens

Current experience suggests that any rapidly progressive encephalopathy of unclear etiology, particularly if accompanied by lymphocytic CSF pleocytosis (although routine CSF studies can be normal), and multifocal symptoms with or without MRI changes should raise concern for an immune mediated process. FLAIR-T2 MRI abnormalities (without substantial enhancement) involving medial temporal lobes occur frequently in patients with typical limbic encephalitis, and should increase the suspicion of an immune mediated process, keeping in mind that the MRI findings could be the result of seizures or a viral infection.

Antibody testing cannot replace the clinical evaluation. Determination of antibodies should be considered as a supportive test to confirm the etiology of a disorder clinically suspected to be immune mediated. In our experience the association of some syndromes with one or a restricted number of antibodies is so high that in many patients the type of syndrome directs the antibody testing. This high syndrome-antibody specificity is obtained when comprehensive testing for one or a specific subset of antibodies is applied, including immunohistochemistry with brain tissue and cell-based assays with patient’s serum and CSF. If studies are less comprehensive (e.g., serum only with cell-based assays only) the specificity decreases and the number of false positive or negative cases increases. The importance of a comprehensive evaluation including CSF and serum was recently demonstrated in a study on anti-NMDAR encephalitis. Comprehensive testing identifies also cases that might erroneously be considered variants of a syndrome or “widening” of the spectrum of symptoms, while in fact represent the overlap of two different syndromes with independent immune responses (e.g., myelitis or optic neuritis with aquaporin4 or myelin oligodendrocyte glycoprotein [MOG] in patients with anti-NMDAR encephalitis). Therefore, it is important to store aliquots of CSF when spinal taps for viral studies are done. Depending on the syndrome and degree of clinical suspicion,
the study for autoantibodies can be initiated at the same time that viral studies are conducted or wait until PCR or serological studies for the most common viruses are completed. However, it is important to keep in mind that some tests (e.g., HSV or Mycoplasma pneumoniae) can be positive and the patient still have an immune mediated process.

If studies for an infectious or autoimmune etiology are negative, but there is concern for an underlying autoimmune process, one should consider examining the CSF and serum in a research laboratory. The rate of novel autoantibodies described (approximately 1–2 per year) and the fact that for many of them the initial assessment of patient’s CSF was critical, emphasize the importance of banking or keeping aliquots of CSF.

The extent of tumor search depends on the type of antibody, age, and sex of the patient (as discussed above). Immunosuppression (steroids, IVIg or plasma exchange) can be effective, but patients often require more aggressive therapies (rituximab, cyclophosphamide). Although the follow-up of CSF and serum antibody titers may assist in some assessments (e.g., relapses or effects of treatment), clinical decisions about changing or discontinuing treatments should rely more on clinical assessment (e.g., antibody titers may remain detectable after neurological recovery).

**Conclusion**

Autoimmune encephalitis comprises an expanding group of potentially treatable disorders that should be in the differential diagnosis of any type of encephalitis. They can resemble infectious encephalitis, and sometimes are triggered by infectious disorders (e.g., HSE). Aggressive immunotherapy is often effective.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

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**Abbreviations**

- **ADC**: apparent diffusion coefficient
- **ADEM**: acute disseminated encephalomyelitis
- **AQP4**: aquaporin 4
- **AMPA**: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
References


autoimmune encephalitis and the main differences between those associated with antibodies to intracellular and cell surface antigens. It provides guidelines about the interpretation of antibody findings.


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Key points

1. A rapidly expanding subset of autoimmune encephalitis occurs in association with antibodies to neuronal cell surface or synaptic proteins.

2. Symptoms of autoimmune encephalitis are diverse and include psychiatric manifestations (psychosis, catatonia, abnormal behavior), seizures, abnormal movements, decrease of level of consciousness, or autonomic dysfunction.

3. Detection of antibodies to cell surface or synaptic proteins often associates with response to immunotherapy.

4. Autoimmune encephalitis can mimic infectious encephalitis. Comprehensive testing for autoantibodies should include CSF and serum.
### Table 1
Clinical features of encephalitis associated with well characterized antibodies to intracellular and neuronal cell surface antigens

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Neurological symptoms</th>
<th>Age, sex, presence of tumor, response to immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intracellular antigens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hu (ANNA I)</td>
<td>Encephalomyelitis, PCD, Brainstem encephalitis, focal cortical encephalitis</td>
<td>Mostly adults, 96–98% associated with cancer. Mostly SCLC (Hu, CV2, amphiphysin, Ri), thymoma (CRMP5), breast (amphiphysin, Ri, Yo), ovary (Yo, Ri), testes (Ma2) Limited response to immunotherapy, and treatment of the tumor</td>
</tr>
<tr>
<td>CRMP5</td>
<td>Encephalomyelitis, chorea, PCD, limbic encephalitis</td>
<td></td>
</tr>
<tr>
<td>Amphiphysin</td>
<td>Stiff-person syndrome, myelopathy and myoclonus, encephalomyelitis</td>
<td></td>
</tr>
<tr>
<td>Ri (ANNA 2)</td>
<td>Brainstem encephalitis, opsoclonus myoclonus</td>
<td></td>
</tr>
<tr>
<td>Ma2</td>
<td>Diencephalic, limbic encephalitis, brainstem encephalitis</td>
<td></td>
</tr>
<tr>
<td>GAD65</td>
<td>Ataxia, stiff person syndrome, epilepsy</td>
<td>Adults, &lt;10% tumors, limited response to immunotherapy</td>
</tr>
<tr>
<td><strong>Neuronal surface antigens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NMDAR receptor (NR1 subunit)</td>
<td>Psychiatric symptoms, language dysfunction, abnormal movements, seizures, decreased level of consciousness, autonomic instability</td>
<td>Children (40%) and young adults (median 19 y), 80% female. Presence of a tumor varies with age, sex, and race (9–55%), mostly ovarian teratomas 80% good recovery with immunotherapy</td>
</tr>
<tr>
<td>GABA(_B)R</td>
<td>High titers in serum and CSF: refractory seizures, or status epilepticus. Low titers in serum: more broad spectrum of symptoms including seizures, stiff person syndrome, opsoclonus myoclonus syndrome</td>
<td>Limited experience, 39% in children; no clear cancer association (some patients may have thymoma). Severe disorder (2/6 patients with high titres died, but the other 4 had substantial response to immunotherapy.</td>
</tr>
<tr>
<td>GABA(_B)R (B1 subunit)</td>
<td>Classic limbic encephalitis. Early and prominent seizures (GABA(_B)R), isolated psychiatric symptoms (AMPAR), hyponatremia and brief tonic-myoclonic seizures (LGI1)</td>
<td>Adults (median 62y, 50% female) 60% small-cell lung cancer Good response to immunotherapy</td>
</tr>
<tr>
<td>AMPAR (Glu R1/2 subunit)</td>
<td></td>
<td>Adults (median 80y, 90% female) 70% tumors (lung, breast, thymus) Good response to immunotherapy</td>
</tr>
<tr>
<td>LGI1</td>
<td>Morvan’s syndrome, encephalitis, peripheral nerve hyperexcitability</td>
<td>Adults (median 60y, 65% male) &lt;10% tumors (thymoma)</td>
</tr>
<tr>
<td>CASPR2</td>
<td></td>
<td>Adults (median 60y, male predominance) Limited experience, ~30% thymoma</td>
</tr>
<tr>
<td>DPPX</td>
<td>Diffuse encephalitis, prodromal severe diarrhea. Psychiatric symptoms, tremor, myoclonus, ataxia, nystagmus, hyperekplexia</td>
<td>Limited experience, no association with cancer, response to immunotherapy</td>
</tr>
</tbody>
</table>

Abbreviations: AMPAR: alpha-aminoo-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2: contactin-associated protein-like 2; CNS: central nervous system; CSF: cerebrospinal fluid; DPPX: dipeptidyl-peptidase-like protein-6; GABA\(_B\)R: gamma-aminobutyric acid-B or A receptor; GAD65: 65 kDa glutamic acid decarboxylase; LGI1: leucine-rich glioma inactivated protein 1; mGluR5: metabotropic glutamate receptor 5; NMDAR: N-methyl-D-aspartate receptor; PCD: Paraneoplastic cerebellar degeneration; SCLC: small cell lung carcinoma; y: years
<table>
<thead>
<tr>
<th>TIME HSE TO RELAPSE</th>
<th>VIRAL-RELATED POST-HSE ENCEPHALITIS</th>
<th>NON VIRAL RELATED POST-HSE OR &quot;CHOREATHETOSIS POST-HSE&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>4 – 6 weeks (also described so early as 7 days after onset of HSE)</td>
<td></td>
</tr>
<tr>
<td>NEUROLOGICAL SYMPTOMS</td>
<td>focal neurological signs, seizures, behavioral abnormalities, low frequency of abnormal movements</td>
<td>In children frequent abnormal movements (choreoathetosis, ballism), adults and adolescents (abnormal behavior)</td>
</tr>
<tr>
<td>HSV PCR IN CSF</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>NEW NECROTIC LESIONS ON MRI</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>RESPONSE TO ANTI-VIRAL THERAPY</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ETIOLOGY</td>
<td>Infectious</td>
<td>Suspected autoimmune. A substantial number of patients have NMDAR antibodies. Some patients may have antibodies to DR2 and against unknown cell surface antigens</td>
</tr>
</tbody>
</table>