

## CHAPTER 36

### THE AUTOIMMUNE ENCEPHALOPATHIES

The autoimmune encephalopathies are an exciting new chapter in neurology and psychiatry. These are newly recognized conditions. With this new awareness we are better able to help patients whom we had little to offer in the past. As importantly, study of these new conditions will advance our understanding of the 'old' conditions, which have been with us for centuries.

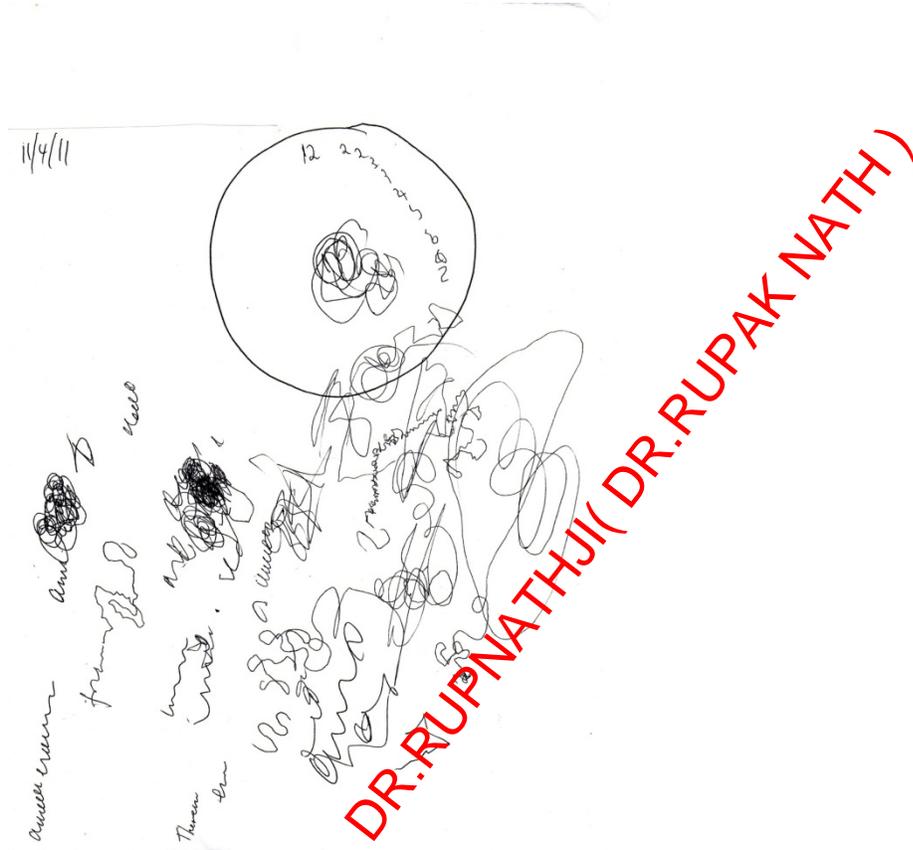


Illustration. A young Indian woman was admitted to hospital, behaving in a bizarre manner. Some of our staff thought she had schizophrenia. The current author was even wider of the mark, thinking she had conversion disorder. When she was asked to write she 'wrote' in a manner we did not recognize. However, when she was asked to draw a clock-face, it looked very 'organic', exactly in the style of a person with dementia/head injury. She had, of course, and autoimmune encephalopathy (with anti-NMDAR antibodies).

#### **Limbic encephalitis (Classical paraneoplastic encephalitis)**

Limbic encephalitis, featuring amnesia, disorientation and seizures, often associated with distant cancer, has been described over recent decades. Antibodies have been described, usually with intracellular targets.

### **Recently described encephalidies**

Very recently, a number of antibodies have been discovered which target extracellular neural proteins of receptors. These antibodies are sometimes associated with teratomas and other neoplasms (which express the target neural antigen). When neoplasm is not present, other unknown immunological triggers may be involved. Cross reactivity of antibodies against different antigens can occur (Irani and Vincent, 2012).

When a neoplasm is absent – it is possible that the immune response has eliminated that tumor.

More common in some ethnic groups: African, Asian, Latinos.

Antibodies mainly affect the limbic system (medial temporal lobes, amygdala, hippocampus and orbitofrontal cortex, leading to short-term memory deficits, emotional and behavioral disturbances such as confusion, irritability, depression, sleep disturbances, seizures and sometimes dementia.

Antibodies lead to rapid removal (reversible) of neurotransmitter receptors from synaptic sites, leading to changes in synaptic and circuit function.

Symptoms improve after immunotherapy or tumor resection [when present].

### **Anti-NMDA receptor encephalitis**

(a glutamate receptor; Dalmau et al, 2007)

1. Often follows prodrome of viral-like illness, hyperthermia, headache
2. Followed by personality changes which may take them to the psychiatrist
3. Followed by seizures, dyskinesia, decreased level of consciousness, autonomic instability, hypoventilation.

Usually women

MRI is usually normal, however, in 40% there is transient inflammation of the hippocampus, cerebral or cerebellar cortex, subcortical structures.

75% have a good recovery with treatment. 6% of patients have died (it is anticipated the survival rate will improve with greater awareness and earlier appropriate treatments).

Evidence suggests the NR1 subunit of NMDA receptor as the target autoantigen. (NMDA receptors are composed of 2 NR1 subunits and 2 NR2 subunits. NR1 antibodies are more common in the hippocampus.)

Antibodies cause a selective decrease in NMDA receptor density. However, this is reversible, consistent with frequent recovery.

### **Anti-AMPA receptor encephalitis**

(another type of glutamate receptor; Lai et al, 2009)

The most common presentation is as above, with personality changes followed by seizures, variation in consciousness and autonomic lability. Sometimes, however, patients present with rapidly progressive abnormal behavior resembling psychosis.

Usually women, 50 years plus. 70% have an underlying tumor – usually lung or breast, that expresses AMPA receptors.

The antigens is the GluR1 and/or GluR2 subunit of the AMPA receptors (GluR1 & 2 levels are high in the hippocampus and other limbic regions)

Treatment is by immunotherapy and tumor removal (when present).

### **Anti-GABA<sub>B</sub> Receptor Encephalitis**

(an inhibitory receptor; Lancaster et al, 2009)

Older people, both male and female.

47% small cell lung cancer (SCLC)

The autoantigen is the B1 subunit of GABA<sub>B</sub> receptor

Treated with immunotherapy and cancer therapy [when present]

### **Anti-Voltage-gated potassium channel disorders**

(peripheral and CNS types; Kleopa et al, 2006)

May or may not be paraneoplastic

Psychiatric and neurological symptoms, including seizure.

### **Effects of maternal antibodies on fetal development**

Studies of mothers of autistic children also raise the possibility that maternal antibodies may impact on fetal development. Asymptomatic mothers may have circulating neuronal antibodies that have access to the fetal brain and may affect brain development.

### **Schizophrenia**

Naturally, as some people have been found with an encephalitis (which may include some psychotic symptoms) and have no evidence of neoplasm, there is interest to discover whether some of those who have psychotic symptoms, but none of the other encephalitic symptoms (seizure, memory deficits and variation in conscious level) carry a receptor antibody.

It is too early to make firm conclusions, but some evidence suggests that some people with schizophrenia may carry receptor antibodies. Zandi et al (2011) examined 46 cases of schizophrenia and found 3 people with anti-NMDAR antibodies. Tsutsui et al (2012) studied 51 cases of schizophrenia and schizoaffective disorder and found 4 people with anti-NMDAR antibodies. All had failed to respond to standard treatment, but had responded to ECT. All were female, 2 had ovarian tumors.

Thus, it is possible that some people with schizophrenia carry antibodies. The next step may be to determine whether immunosuppression and tumor treatment have anything to offer such patients (Zehry et al, 2011).

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