



## Psychotic Symptoms Related Anti NMDA Receptor in Ovarian Teratoma

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### ABSTRACT

Psychotic symptoms related ovarian teratoma are uncommon but has been well known in previous medical literature. Psychotic problems experienced by patients are often mistaken for psychological causes without organic causes, because commonly patients do not show symptoms associated with teratomas. Diagnosis of teratoma-related psychotic illnesses is often delayed due to the nature of the symptoms, that is leading to delayed treatment and worsen long-term neurological outcomes. Neuropsychiatric symptoms in teratoma can occur if it contains brain tissue inside and antibody anti-NMDA (N-methyl-D-Aspartate) receptor. The occurrence of psychotic symptoms in ovarian teratomas is based on cellular mechanisms. Antibodies bind to the NMDA receptor, which leads to the internalization of the cell surface and the relative state of the NMDA receptor hypofunction. While the impact of specific regions and circuit circuits of anti-NMDA receptor antibodies remains to be explored, the mechanism of anti-NMDA receptor encephalitis strengthens the hypothesis that NMDA receptor hypofunction may have a role in schizophrenia and psychosis.

### 1. Introduction

Teratomas are a rare type of tumor that contains tissues and organs that develop mature or immature, including hair, teeth, muscles, neuron cells, and bones. Teratomas are most common in the spine, ovaries and testes, but can occur elsewhere in the body.<sup>1</sup>

Ovarian teratomas are characterized by pelvic problems. However, neuropsychiatric symptoms in teratoma can occur if it contains brain tissue inside. Psychotic problems experienced by patients are often mistaken for psychological causes without organic causes, because commonly patients do not show symptoms associated with teratomas. Often, diagnosis of teratoma-related psychotic illnesses is delayed due to the nature of the symptoms, that is leading to delayed treatment and worsen long-term neurological

outcomes.<sup>2</sup>

Teratomas with encephalitis and psychotic symptoms are uncommon but has been well explained in the psychiatric and medical literature. This disease is more experienced by young women without a history of mental disturbance before. More than 500 cases have been published, which affect both sexes but the majority are women (80%), with ages ranging from childhood to the 90s. Most patients with a diagnosis of anti-NMDA receptor encephalitis are related between 18.5 and 24 years, with teratomas associated in 60% of those who are women.<sup>1,2</sup>

### Anti NMDA Receptor in Teratoma

Encephalitis and psychotic-related anti-NMDA receptors are autoimmune disorders in which

antibodies attack NMDA (N-methyl-D-aspartate) -type of glutamate receptors in synapses of central neurons. Symptoms include neurological deficits and prominent psychiatric manifestations that often involve mental health professionals into treatment. Neuropsychiatric manifestations begin with psychotic symptoms early in the course of the disease followed by more severe fluctuations in consciousness with neurological involvement, and finally cognitive disturbance and behavioral deficits.<sup>3-5</sup>

N-Methyl-d-aspartate receptors are a class of glutamate receptors which, when activated, mediate neurotransmission through non-selective cation pathways, including  $\text{Ca}^{2+}$ , through channels. NMDA

receptors are spread throughout the brain and are understood to play a key role in synaptic plasticity and memory function. They are activated by binding to glutamate and glycine co-agonists, in addition to exposure to positive changes in membrane potential throughout cells. The functional NMDA receptor heterotetramer is generally formed by a "dimer of dimer" mechanism and conventionally consists of two glycine-binding NR1 subunits and two glutamate-binding NR2 subunits (Figure 1). While the NR1 subunit is considered important for complex formation, data shows that the NR2 subunit can be exchanged for one or two NR3 subunits.<sup>6</sup>

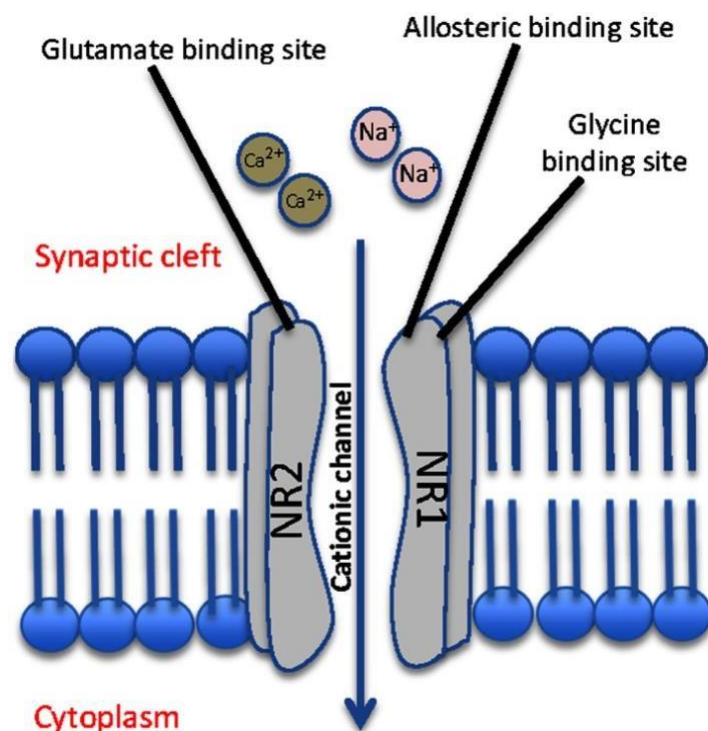


Figure 1. Schematic representation of typical NMDA receptors. NMDA contains four subunits, two glycine-binding NR1 subunits and two glutamate-binding NR2 subunits, and allows cationic entry from the synaptic cleft into the cell. (Image source: Lakhan S, 2013)<sup>3</sup>

Glutamate is the main excitatory neurotransmitter in the brain. Glutamate is involved in synaptic plasticity during brain development, memory, learning, and motor activity. The learning and memory substrate is believed to be encoded in long-term potentiation (LTP), which is an excitatory current that

causes changes in synaptic plasticity [10]. The main glutamatergic circuit connects the prefrontal cortex with the Nucleus Accumbens (NAc) and the Ventral Tegmental Area. NAc also receives glutamatergic stimulation from the hippocampus and amygdala, two limbic brain structures involved in long-term memory,

especially spatial memory and emotional reaction memory. Attention to the glutamatergic neurotransmitter system in psychosis comes from observations on the PCP substrate, which is a glutamatergic N-methyl-D-aspartate (NMDA) receptor antagonist, can induce psychotic symptoms in humans and behavior such as addiction in animals. Other studies have shown psychotic glutamate hypofunction accompanied by reports of low cerebrospinal fluid glutamate levels in patients with psychotic symptoms.<sup>3,7</sup>

### **Pathophysiology of psychotic symptoms in ovarian teratoma**

The occurrence of psychotic symptoms in ovarian teratomas is based on cellular mechanisms. Antibodies bind to the NMDA receptor, which leads to the internalization of the cell surface and the relative state of the NMDA receptor hypofunction. Synaptic proteins and other synaptic structures are not affected. CSF titers of anti-NMDA receptor antibodies correlate with clinical disease, and both the synaptic effect and the severity of symptoms can be reversed by antibody clearance. So as with other synaptic encephalitides, auto-antibodies themselves appear to be pathogenic, in contrast to syndromes related to antibodies against intracellular targets where cytotoxic T cell mechanisms seem to be the cause. In addition, NMDA receptor antagonists and mouse models reduce the expression of NMDA receptors mimicking several aspects of this disorder. While the impact of specific regions and circuit circuits of anti-NMDA receptor antibodies remains to be explored, the mechanism of anti- NMDA receptor encephalitis strengthens the hypothesis that NMDA receptor hypofunction may have a role in schizophrenia and psychosis.<sup>8-9</sup>

Teratomas with anti-NMDA receptors are associated with immune cell infiltrates in the brain; which is characterized by the presence of antibody deposits in the brain at autopsy. This disease usually shows lymphocytic pleocytosis in the evaluation of cerebrospinal fluid (CSF) at the onset of the disease

and oligoclonal bands in advanced stages. The neuronal component in teratomas usually triggers immunological reactions, especially in ovarian teratomas. This disease can be diagnosed with antibody titers, the highest with definite malignancy and can be tested in blood, CSF, or tumor specimens. Normal antibody titers have levels less than 1:10 in serum and less than 1: 1 in CSF. Levels of antibody titers should be monitored for treatment.<sup>10-13</sup>

### **Diagnosing Psychotic Symptoms Related Teratoma**

Neuropsychiatric symptoms in ovarian teratomas begin with nonspecific prodromes, such as mucocutaneous blisters, headaches, or fatigue. The patient is afebrile and presents within a few weeks with neuropsychiatric symptoms. About 77% were initially evaluated by a psychiatrist and received a diagnosis of bipolar disorder or schizophrenia. Symptoms include hallucinations, psychosis, memory disorders, disinhibition, dyskinesias, autonomic dysfunction with flushing, tachycardia, arrhythmias, arrhythmias, hypersalivation, catatonia, central hypoventilation, diaphoresis. These symptoms occur on average 5 days (no more than 2 weeks) before the onset of behavior change. Psychiatric manifestations of anti-NMDA receptor encephalitis are broad and varied; given the frequent absence of neurological symptoms during this period, patients are often first seen by a psychiatrist. Psychotic symptoms predominate, including hallucinations, delusions, perception disorders, and irregular thoughts and behavior. Specifically, patients usually show anxiety or fear and agitation, along with paranoid ideas, mood lability, and strange behavior with personality changes. Many patients can become aggressive and aggressive, although asociality and blunt effects are also common. Interestingly, while psychotic symptoms are common in adults, the pediatric population often manifests with manic symptoms such as irritability and explosive behavior, sleep dysfunction, hyperactivity, and hypersexuality.<sup>9,14</sup>

In addition to behavioral changes, cognitive decline and abnormal speech often develop. Short-term

memory deficits and confusion often occur (although difficult to detect given the severity of psychiatric symptoms), as well as difficulties in normal activities of daily life. In some cases, cognitive changes may be more protracted in the early phases of the disease, and may be subsyndromal, for example, causing role dysfunction. Patients of all ages often experience progressive decline in speech and language, including alogia, echolalia, perseveration, mumbling, and mutism. These changes in speech often persist throughout other stages of the disease. In short, the initial psychiatric phase of this syndrome seems to last for 1-3 weeks, although some cases increase the likelihood of changes in behavior and personality that last longer at a weakened level before presentation of symptoms.

Early psychiatric changes were followed by more global changes in awareness and decreased responses, sometimes developing into catatonic conditions with mutism and open eyes, while other times showing increased agitation. This stage is accompanied by abnormal movements, such as orofacial dyskinesias, dystonic postures, and leg movements such as choreography, as well as autonomic instability (hyperthermia, notches or bradycardia, hypo- or hypertension). In children, abnormal movements often become part of the presentation rather than occur later in the disease process. Other common complications at this stage are hypoventilation, especially in adults, and often of central origin; one large study described an average of 2 months of ventilatory support needed.

After diagnosis, treatment focuses on immunotherapy and appropriate tumor treatment. Corticosteroids and intravenous immunoglobulin (IVIg) or plasma exchange are recommended in managing the immune response; This therapy seems to work best in situation where the underlying tumor has been removed. The use of plasma exchange is challenging in anxious patients or cases with autonomic instability, and IVIg is often preferred. About 75% of patients experience full recovery or mild deficits, while 25% remain severely deformed or die;

death is estimated at 4%. In patients without an underlying tumor, first-line immunotherapy is often not enough, and treatment with rituximab or cyclophosphamide may be needed. Current recommendations suggest using one or both second-line immunotherapy if no improvement is observed with corticosteroids and IVIg.<sup>10,11</sup>

While consensus has begun to emerge in the management of neurological symptoms, the control of psychiatric manifestations is sometimes more difficult to understand. Although not systematically studied, various interventions have been tried throughout the course of the disease, ranging from high-dose neuroleptics to ECT. The literature review shows that in many cases of teratoma-related NMDA receptor encephalitis, high-dose dopamine blockade worsens diskietic and dystonic movements when used in anxious patients. The use of typical antipsychotics such as haloperidol can further complicate the clinician's analysis, whether the symptoms are due to anti-NMDA receptor encephalitis or due to the malignant neuroleptic syndrome. Sedatives such as anticholinergics, benzodiazepines and valproic acid have been shown to be beneficial in many cases. Treatment with quetiapine is recommended to overcome agitation and anxiety in ovarian teratoma patients with psychotic symptoms.

Encephalitis and psychotic symptoms related to NMDA receptors in ovary teratomas are the first and best syndromes described in a new class of autoimmune encephalitis over the past 5 years. These complex disorders require ongoing management and coordination of care between various medical specialties. The involvement of psychiatrists in many phases of the disease shows that familiarity with the syndrome is important, especially early when a proper diagnosis can help anticipate neurological decompensation. Several cases that were evaluated retrospectively have been described with apparently mild forms of disorder that are purely psychiatric, suggesting that anti-NMDA receptor encephalitis can sometimes be misdiagnosed as a primary psychiatric disease. As an illustration, patients who are referred

to pure psychiatric symptoms usually have subtle neurological findings, representing a milder or "frustrated form" of the disorder.

## 2. Conclusion

Ovarian teratomas are generally accompanied by neuropsychiatric symptoms, especially psychotic symptoms and encephalitis, because this type of teratoma has a component of neuron cells in the tumor. Therefore this diagnosis needs to be considered every organic cause of mental status changes, including gynecological causes, especially in young female patients with encephalopathy or acute psychosis.

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