



AE IS REFRACTORY TO ANTIPSYCHOTICS

“Autoimmune Encephalitis is refractory to antipsychotics; indeed, antipsychotic agents make affected patients much worse, even to the point of developing something akin to neuroleptic malignant syndrome.” Reports Dr. Josep Dalmau who identified the first antibody, anti-NMDAr, in autoimmune encephalitis in 2007.

IAES has compiled a reference list of research that explains why clinicians should *not* give anti-psychotic dopamine antagonist medications, such as Risperdal (risperidone), Haldol, to Autoimmune Encephalitis Patients.

See quotes from these key papers and what researchers suggest should be prescribed when dealing with neuropsychiatric symptoms.

REPORTING FROM THE ECNP CONGRESS - January 15, 2019

BARCELONA – Consider the possibility of an autoantibody-related etiology in all cases of first-onset psychosis, Josep Dalmau, MD, PhD, urged at the annual congress of the European College of Neuropsychopharmacology.

“There are patients in our clinics all of us – neurologists and psychiatrists – are missing. These patients are believed to have psychiatric presentations, but they do not. They are autoimmune,” said Dr. Dalmau, professor of neurology at the University of Barcelona.

Dr. Dalmau urged psychiatrists to become familiar with the red flags suggestive of synaptic autoimmunity as the underlying cause of first-episode, out-of-the-blue psychosis.

“If you have a patient with a classical presentation of schizophrenia or bipolar disorder, you probably won’t find antibodies,” according to the neurologist.

It’s important to have a high index of suspicion, because anti-NMDA receptor encephalitis is treatable with immunotherapy. And firm evidence shows that earlier recognition and treatment lead to improved outcomes. Also, the disorder is refractory to antipsychotics; indeed, antipsychotic agents make affected patients much worse, even to the point of developing something akin to neuroleptic malignant syndrome.

FIRST-ONSET PSYCHOSIS

Red flags for synaptic autoimmune-mediated encephalitis

- 🚩 Rapidly progressive symptoms over days to weeks
- 🚩 No prior history of psychiatric disease
- 🚩 The presence of a benign teratoma, thymoma, or other tumor or a viral infection
- 🚩 Coexisting very mild neurologic symptoms, such as facial twitching
- 🚩 Symptoms are refractory to antipsychotic agents
- 🚩 Abnormal brain MRI or EEG findings
- 🚩 Cerebrospinal fluid pleocytosis

MDedge News

Source: Dr. Dalmau

References –

The Diagnosis and Treatment of Autoimmune Encephalitis

Eric Lancaster

<https://synapse.koreamed.org/search.php?where=aview&id=10.3988/jcn.2016.12.1.1&code=0145JCN&vmode=FULL>

“Intoxications such as neuroleptic malignant syndrome and serotonin syndrome may often present with similarities to autoimmune encephalitis. Conversely, patients with anti-NMDAR encephalitis may develop psychosis as an initial symptom and be treated with neuroleptics, then later show catatonia, rigidity, autonomic instability and altered level of consciousness; this pattern of findings may be mistaken for neuroleptic malignant syndrome. Autoimmune encephalitis therefore should enter into the differential diagnosis of any case of suspected neuroleptic malignant syndrome (Patients with anti-NMDAR encephalitis may be particularly sensitive to strong dopamine antagonists, and our group attempts to avoid using these medications).”

Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis

Prof Josep Dalmau, MD, Eric Lancaster, MD, Eugenia Martinez-Hernandez, MD, Prof Myrna R Rosenfeld, MD, and Prof Rita Balice-Gordon, PhD

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3158385/>

“Studies investigating the effects of phencyclidine and ketamine (non-competitive antagonists of NMDARs) in human beings show that these drugs induce behaviours that are much the same as the positive and negative symptoms of schizophrenia, along with repetitive orofacial and limb movements, autonomic instability, and seizures”

“The profile of symptoms caused by antagonists of NMDAR is dose dependent and varies in much the same way as the multistage clinical course of anti-NMDAR encephalitis does ([figure 5](#)). At low doses, NMDAR antagonists cause psychosis, agitation, memory disturbance, and decreased responsiveness to pain, and at higher doses they cause dissociative anesthesia, a state of profound unresponsiveness with catatonic features, and coma”

Anti-N-Methyl-D-Aspartate Receptor Encephalitis: A Review of Psychiatric Phenotypes and Management Considerations: A Report of the American Neuropsychiatric Association Committee on Research.

https://www.ncbi.nlm.nih.gov/pubmed/30561283/?fbclid=IwAR1kSieN61wFduhcr_p1DaXKxjV4Cej2oNKIXbl9GPQZRVrNVi4EjyaQtuE

Of the patients with documented exposure to antipsychotics, 33% were suspected to have an adverse drug reaction (notably, neuroleptic malignant syndrome in 22% of the cases).

CONCLUSIONS:

On the basis of these findings, it is important to consider anti-NMDAR encephalitis in the differential diagnosis of patients with an acute onset psychosis, especially in association with agitation, catatonia, or adverse response to antipsychotics.

Furthermore, it is important to use antipsychotics with caution in patients with suspected or confirmed anti-NMDAR encephalitis.

Neuronal surface autoantibodies, encephalitis, and psychosis: from neurology to psychiatry page 6-9

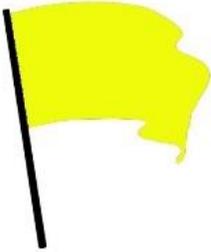
<http://www.acnr.co.uk/wp-content/uploads/2017/11/ACNR-N-J18-low-rez-2.pdf>

“In terms of psychiatric treatment, there is mounting evidence that patients with NMDAR antibody encephalitis may respond poorly to antipsychotic treatment, with high rates of rhabdomyolysis and even development of a neuroleptic malignant syndrome (NMS)-type picture.^{22,23} For this reason, benzodiazepines are preferred for initial

management of behavioral disturbance and catatonia. If antipsychotics are required, sedating atypical antipsychotics such as olanzapine may be preferable.”

Red Flags: Clinical Signs for Identifying Autoimmune Encephalitis in Psychiatric Patients
Julia Herken and Harald Prüss

Table 4 Warning signs pointing to an autoimmune etiology in new-onset psychosis.

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|---------------|---|---|
| Yellow Flags: |  | <ul style="list-style-type: none">• Decreased levels of consciousness• Abnormal postures or movements (orofacial, limb dyskinesia)• Autonomic instability• Focal neurological deficits• Aphasia or dysarthria• Rapid progression of psychosis (despite therapy)• Hyponatremia• Catatonia• Headache• Other autoimmune diseases (e.g., thyroiditis) |
| Red Flags: |  | <ul style="list-style-type: none">• Cerebrospinal fluid (CSF) lymphocytic pleocytosis or CSF-specific oligoclonal bands without evidence for infection• Epileptic seizures• Faciobrachial dystonic seizures• Suspected malignant neuroleptic syndrome• MRI abnormalities (mesiotemporal hyperintensities, atrophy pattern)• EEG abnormalities (slowing, epileptic activity or extreme delta brush) |

"Delayed recognition of the disease can also result in inadequate use of neuroleptics, which in patients with NMDAR encephalitis frequently worsens the symptoms, leading to the working diagnosis of a neuroleptic malignant syndrome. Indeed, a number of warning signs ("red flags") can help to facilitate the timely diagnosis of an autoimmune psychiatric disease, likely enabling earlier immunotherapy and better prognosis."

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5311041/>

The development of extrapyramidal symptoms (EPS) when placed on antipsychotics should alert the team to consider this diagnosis. Of course, EPS is a known side effect of antipsychotics, but is just another reminder to consider the possibility of Autoimmune Encephalitis.

Delayed recognition of the disease can result in inadequate use of neuroleptics. Patients who develop psychosis as an initial symptom may be treated with neuroleptics, then later show catatonia, rigidity, autonomic instability and altered level of consciousness and possible coma; this pattern of findings may be mistaken for neuroleptic malignant syndrome. Patients with anti-NMDAR encephalitis may be particularly sensitive to strong dopamine antagonist medications such as Risperdal (risperidone), Haldol and these should be avoided. For this reason, benzodiazepines are preferred for initial management of behavioral disturbance and catatonia in suspected autoimmune encephalitis.

Autoimmune encephalitis therefore should enter into the differential diagnosis of any case of suspected/new onset of possible Neuroleptic Malignant Syndrome (especially if the Creatine Kinase (CK) is normal, or CK normalizes after treatment, but without improvement.)

Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis Prof Josep Dalmau, MD, Eric Lancaster

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3158385/> “The profile of symptoms caused by antagonists of NMDAR is dose dependent and varies in much the same way as the multistage clinical course of anti-NMDAR encephalitis does. At low doses, NMDAR antagonists cause psychosis, agitation, memory disturbance, and decreased responsiveness to pain, and at higher doses they cause dissociative anaesthesia, a state of profound unresponsiveness with catatonic features, and coma”

Neuronal surface autoantibodies, encephalitis, and psychosis: from neurology to psychiatry

Starting on page 6

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<http://www.acnr.co.uk/wp-content/uploads/2017/11/ACNR-N-J18-low-rez-2.pdf>

This article discusses what to give an AE patient

Autoimmune encephalitis in psychiatric institutions: current perspectives

Treatments should not hide disease evolution neither worsen symptoms. They advised to choose atypical and more sedative antipsychotics rather than typical antipsychotics as dopamine antagonists that aggravate agitation, in order to treat psychotic symptoms. To treat mood symptoms, valproic acid was advised for sedation, sleep, and seizure benefits and thanks to the availability of an intravenous form. Uses of lithium and benzodiazepines are also reported in the literature but do not cause significant changes.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5089825/>

Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin by:

Thomas A Pollak, PhD, Belinda R. Lennox, DM, Sabine Muller, PhD, Michael E Benros, PhD, Harald Pruss, MD, Prof Ludger Tebartz van Elst. Et al

The pharmacological management of patients with psychosis in the acute phase typically involves the use of antipsychotics. However, their use in autoimmune

encephalitis-related psychosis can precipitate autonomic instability, often recognized in the mental health setting as suspected neuroleptic malignant syndrome. Antipsychotics should, therefore, be used with care in patients with suspected autoimmune psychosis; the general approach of starting low and going slow is recommended. There is no clear evidence to support any particular antipsychotic. Antipsychotics that allow optimal symptom control with minimal risk for extrapyramidal symptoms should be preferentially used, mainly the atypical or second-generation antipsychotics. Benzodiazepines are essential in the management of catatonia and in unclear cases of psychosis or aggression. Electroconvulsive therapy has been used in some cases for rapid symptom control, with significant efficacy reported.