A Case of New Onset Psychosis in a Young Woman with Minimal Response to Risperidone, Ultimately Diagnosed with N-Methyl-D-Aspartate Receptor Encephalitis: A Review of this Under-Recognized Condition

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Abstract

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a severe, treatable and potentially reversible disorder presenting with memory deficits, psychiatric symptoms and seizures. Initially described in young patients with ovarian teratoma, the disease is meanwhile increasingly recognized also in women without tumors, in men and in children. The presence of anti-glutamate receptor (type NMDA) autoantibodies in serum or cerebrospinal fluid is specific for this novel and widely under-diagnosed disorder. We present a young women presenting with psychotic symptoms, initially treated psychiatrically, but was ultimately discovered to have anti-NMDAR encephalitis. We review this disease state with respect to epidemiology, phenomenology, pathogenesis, and treatment.

Key Words: Psychosis, Anti-N-Methyl-D-Aspartate Receptor Encephalitis, Teratoma

Introduction

Limbic encephalitis, whether paraneoplastic or auto-immune, has been referred to as an under-recognized neurological syndrome (1). Patients are often initially referred to psychiatrists because the initial clinical presentation of this disease mimics a primary thought or mood disorder. The classic syndrome of limbic encephalitis includes the rapid development of irritability, depression, sleep disturbances, seizures, hallucinations, and short-term memory loss. The subacute development, in days or weeks, of short-term memory deficits is considered the hallmark of the disorder (2).

The exact incidence of anti-NMDAR encephalitis is unknown, but on the basis of the rapid accrual of patients and increasing number of case reports, a relative frequency amongst causes of encephalitis is being established. For instance, in 2007, the California Encephalitis Project (CEP) was established to study the epidemiology of encephalitis. Between September 2007 and February 2011, 761 cases of encephalitis of uncertain etiology in individuals aged ≤30 years were referred to the CEP. Of the cases of identified etiology, anti-NMDAR encephalitis was the leading entity identified within the cohort of patients at 41% (as opposed to 9% for herpes simplex virus-1, 38% for enteroviral encephalitis, and 5% for West Nile virus and varicella-zoster virus). A conclusion from this study was that NMDAR encephalitis rivals—if not exceeds—viral etiologies as a cause

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of encephalitis within the CEP cohort (3). Additionally, in a multicenter, population-based prospective study of causes of encephalitis, at 4% of the studied population NMDAR encephalitis was the second most common immune-mediated cause after acute disseminated encephalomyelitis and before all antibody-associated encephalitis (4, 5). Finally, in one report, in subgroups of schizophrenia patients where autoimmune mechanisms could contribute to its pathogenesis, the occurrence rate of anti-NMDAR positive cases was 4/51 (5).

The neuropsychiatric presentation of anti-NMDAR encephalitis provides strong evidence for the NMDAR hypofunction hypothesis as one of the possible pathogenic pathways of schizophrenia. The relation between anti-NMDAR encephalitis and schizophrenia, year 2013/2014, is best described as two sets that intersect, resulting in a common subset. This common subset contains cases of schizophrenia that are attributable to anti-NMDAR encephalitis and, the other way around, cases of anti-NMDAR encephalitis that are indistinguishable from schizophrenia. In reference to the latter, it has been shown that prior autoimmune disease increases the risk of schizophrenia by 29%. Salient to the former, it has been retrospectively determined, NMDAR antibodies were positive in 6.5% of patients with first-episode psychosis that met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria of schizophrenia (6).

Since its identification in 2007, detection of NMDAR encephalitis has increased, at least in part, due to the development of clinical diagnostic criteria and identification of antibodies directed against two broad categories: 1) intracellular or classical paraneoplastic antigens and 2) extracellular target epitopes, including voltage-gated potassium channels and NMDAR. The disorders of the second category are linked with different tumors (thymoma, teratoma, Hodgkin's lymphoma vs. lung, testis), appear to be antibody-mediated (vs. cytotoxic T-cell responses) and respond better to immunotherapy than the former (4, 7).

Anti-NMDAR encephalitis has recently emerged in the literature with distinct clinical characteristics, including personality changes, anxiety, bizarre behavior, delusions, paranoia, and catatonia. In one study, greater than 90% of reported patients with anti-NMDA receptor encephalitis were female and were found to have an ovarian teratoma (8). Here, we report clinical features, extensive diagnostic investigations, and the treatment response to immunotherapy and oopherectomy in a young woman who presented with psychosis, but was later found to have many of the clinical characteristics of limbic encephalitis, ultimately diagnosed with anti-NMDAR encephalitis.

Case Report

Over the span of approximately one month, a previously healthy 18-year-old girl developed bizarre behavior and inappropriate laughter. At times, her family also noticed that she had auditory and visual hallucinations (A/VH) and delusions, believing that she was acting on camera when in front of bright lights. When she developed a persistent headache, they brought her to a local emergency department (ED). She was not found to have any focal neurological deficits, denies alcohol and illicit drugs, had a negative urine drug screen/blood alcohol level, no family psychiatric history and, after psychiatric consultation, was felt to be "suffering from a psychotic break."

Upon admission to a psychiatric facility, she had unsuccessful trials of fluphenazine and olanzapine, ultimately being discharged on risperidone 2 mg BID, with reportedly minimal changes in her symptoms. Both prior to and after antipsychotic administration, our patient did not demonstrate any dyskinetic movements. One week after discharge, she became unresponsive, then developed a seizure, for which she returned to the ED.

In the ED, her maximum temperature was 100.3° F; while the patient appeared at times uncooperative and unaware of her surroundings, the remainder of the general examination, other vital signs, routine blood studies, urinalysis and urine toxicology screening were normal. A head computed tomography (CT) scan was unremarkable; cerebrospinal fluid (CSF) analysis showed a white blood cell count of 12 cells/mL (98% lymphocytes, 2 monocytes) (normal=0–5 white blood cells [all mononuclear]), red blood cell count of 1 cells/mL (normal=0 cells/mL), CSF glucose 73 mg/dL (normal=50–80 mg/100 mL), and protein 42 mg/dL (normal=15–60 mg/dL) (9).

She was admitted to the hospital for further evaluation. An electroencephalogram (EEG) showed diffuse 6–7 Hz slowing, left greater than right, without epileptiform activity. An additional two EEG's during this hospital stay did not reveal any ictal events and she was not observed to have any further seizures. Acyclovir 800 mg IV every eight hours was started for possible herpes simplex virus (HSV) encephalitis, but discontinued when HSV polymerase chain reaction was negative. Non-contrast head magnetic resonance imaging (MRI) was also normal. Additionally, she was found to have normal thyroid function tests, normal microsomal antibodies, normal C3/C4 levels, negative antinuclear antibody, and a negative reactive plasma reagin. Despite a battery of negative tests and serial neurological exams that did not reveal any focal deficits, the patient continued to have intermittent episodes of agitation requiring restraints, occasionally pulling her IV line out with her teeth. She also continued to endorse VH and paranoid delusions despite continuation of risperidone 2 mg BID.

Table 1 Typical Course of Anti-N-Methyl-D-Aspartate Receptor (NMDAR) Encephalitis (Ref. #5, 15–18)

Stage	(Median) Time of Onset from Early Symptoms	Symptoms	Comments
1/Flu-Like Prodrome	-3 days	**Subfebrile temperature, headache, fatigue**	Unknown if caused by a general activation of the innate immune system as autoimmunity develops or this represents a true infection that triggers autoimmunity
2/Psychotic	0→8 days	**Bizarre behavior; disorientation; confusion;** paranoid thoughts; catatonia; **visual or auditory hallucinations; memory deficits**	NMDAR are highly expressed in the forebrain, limbic system, and hypothalamus, possibly accounting for these symptoms
3/Decreased Consciousness & Hypoventilation	10→20 days	**Decreased consciousness;** hypoventilation/mechanical ventilation; **lethargy; seizures; autonomic instability;** dyskinesias (often, oro-facial) develop	Affected individuals must often undergo treatment in intensive care units for long periods of time
4A/Recovery	160 days (range: 16–850 days) Relapse: 3 months–6 years (after improvement from a previous episode)	**There is amnesia for the duration of the illness** Risk of **relapses,** especially when the tumor is removed too late or not at all or if no tumor could be found	In around 75% of cases, a substantial regression of symptoms can be achieved Relapse rate=20–25%. Prognosis of patients depends on early diagnosis, implementation of appropriate immunomodulatory therapy and, in paraneoplastic cases, complete tumor removal
4B/Mortality	3–5 months	May be preceded by coma, status epilepticus, and cardiac dysrhythmias	25% of patients suffer from severe neurological deficits or die

Bold Type: Our patient's symptoms.

As her exhaustive medical work-up continued to be unremarkable, she was transferred to pediatric neurology for further monitoring and treatment. Shortly after this time, the patient began to stop taking food by mouth and a nasogastric tube was placed. Routine imaging for placement of the nasogastric tube revealed an incidental left ovarian mass, ultimately diagnosed as a dermoid cyst. Repeat lumbar puncture was performed and, after three weeks, the presence of autoantibodies against the N1/N2 NMDA receptor subunits was demonstrated. Intravenous immune globulin (IVIg) treatment was initiated at 1,000 mg/day for five days status post left oophorectomy. While she never regained her memories surrounding this 2–3 month episode of illness, her psychotic symptoms gradually attenuated within ten days of initiating IVIg treatment, although a more robust diminution of her neuropsychiatric symptoms did not occur until about two months after initiating IVIg treatment. Despite lack of complete resolution of her symptoms, risperidone was discontinued seven days after stopping IVIg treatment.

Unfortunately, the patient's behavioral symptoms, including delusions and inappropriate affect, have recurred twice: initially four months status post the left oophorectomy, both times portending newly developed right dermoid cysts and treated with surgical cyst removal. We are currently monitoring the patient's behavioral and psychotic symptoms, each time marked resolution of her psychoses developed after excision of the dermoid cysts. She now awaits surgery for her third cyst removal in four years, as she again relapsed with inappropriate affect and AH with delusions. Her Brief Psychiatric Rating Scale (BPRS) (10) score was 51. We restarted the patient on risperidone (titrated) 2 mg BID, and her BPRS decreased to 40 after two weeks of risperidone therapy.

Discussion

NMDAR encephalitis is a new category of treatment-responsive encephalitis associated with "anti-NMDAR antibodies," which are antibodies to the NR1/NR2 heteromers of NMDAR. The antibodies disappear with clinical improvement, suggesting their pathogenic role (11). This autoimmune encephalitis predominantly affects children and young adults (about 80% of patients are women), occurs

Table 2 Diagnostic Evaluation of Paraneoplastic Syndrome (i.e., Anti-NMDAR Encephalitis) (20)

Stage Number	Work-Up	Our Patient's Findings (Reported Positive Findings in NMDAR Encephalitis)
1/Recognition of characteristic symptoms	**Symptoms of subacute encephalopathy**, including acute change in behavior or mental status, atypical symptoms or demographic features, progressive course with conventional therapies	
2/Diagnostic evaluation	**Brain MRI with and without contrast**: can demonstrate hyperintensity in medial temporal lobe(s) **Consider EEG:** may show epileptic foci in temporal lobe(s); focal or generalized slow activity **Lumbar puncture (LP):** screen for well-characterized paraneoplastic (onconeural) antibodies; also assess for inflammatory/autoimmune CSF markers, lymphocytic pleocytosis, high IgG index, oligoclonal bands with or without elevated protein **Alternative Diagnoses:** *Drugs of abuse, infections* (herpes simplex virus encephalitis, neurosyphilis, human herpes virus 6 [after bone marrow transplantation]), primary angiitis of the CNS; *Autoimmune disorder* (lupus erythematosus, Hashimoto's thyroiditis, Sjögren's syndrome, antiphospholipid syndrome); *Toxic-metabolic encephalopathy*	**MRI:** unremarkable (60%) **EEG:** generalized slow activity (80%); did not show epileptiform discharges (50%) **LP:** lymphocytic pleocytosis (70–90%), elevated protein (35%), oligoclonal bands (60–65%), N1/N2 NMDA receptor antibodies (~100%)
3/Search for hidden malignancy	Especially **ovarian** (teratoma), **testicular** (germ cell), and **lung cancer** (small cell) NB: Tests for paraneoplastic antibodies are often negative and do not rule out the diagnosis of a paraneoplastic syndrome Paraneoplastic syndromes can be associated with no known antibody (i.e., seronegative limbic encephalitis). Many cases are associated with a neoplasm	
4/Confirm diagnostic criteria for paraneoplastic limbic encephalitis	**Subacute onset** (days or up to 12 weeks) of short-term memory loss, seizures, confusion, and psychiatric symptoms suggesting involvement of the limbic system; **Neuroradiological evidence** (MRI SPECT, PET) of involvement of the limbic system demonstrating increased metabolism in temporal lobe(s) **Demonstration of cancer** within 5 years of the diagnostic neurological symptoms or the detection of well-characterized antibodies **CSF evidence of inflammation** is reported in 80% of limbic encephalitis and may be used to support the clinical diagnosis **Exclusion** of other possible etiologies of limbic dysfunction	

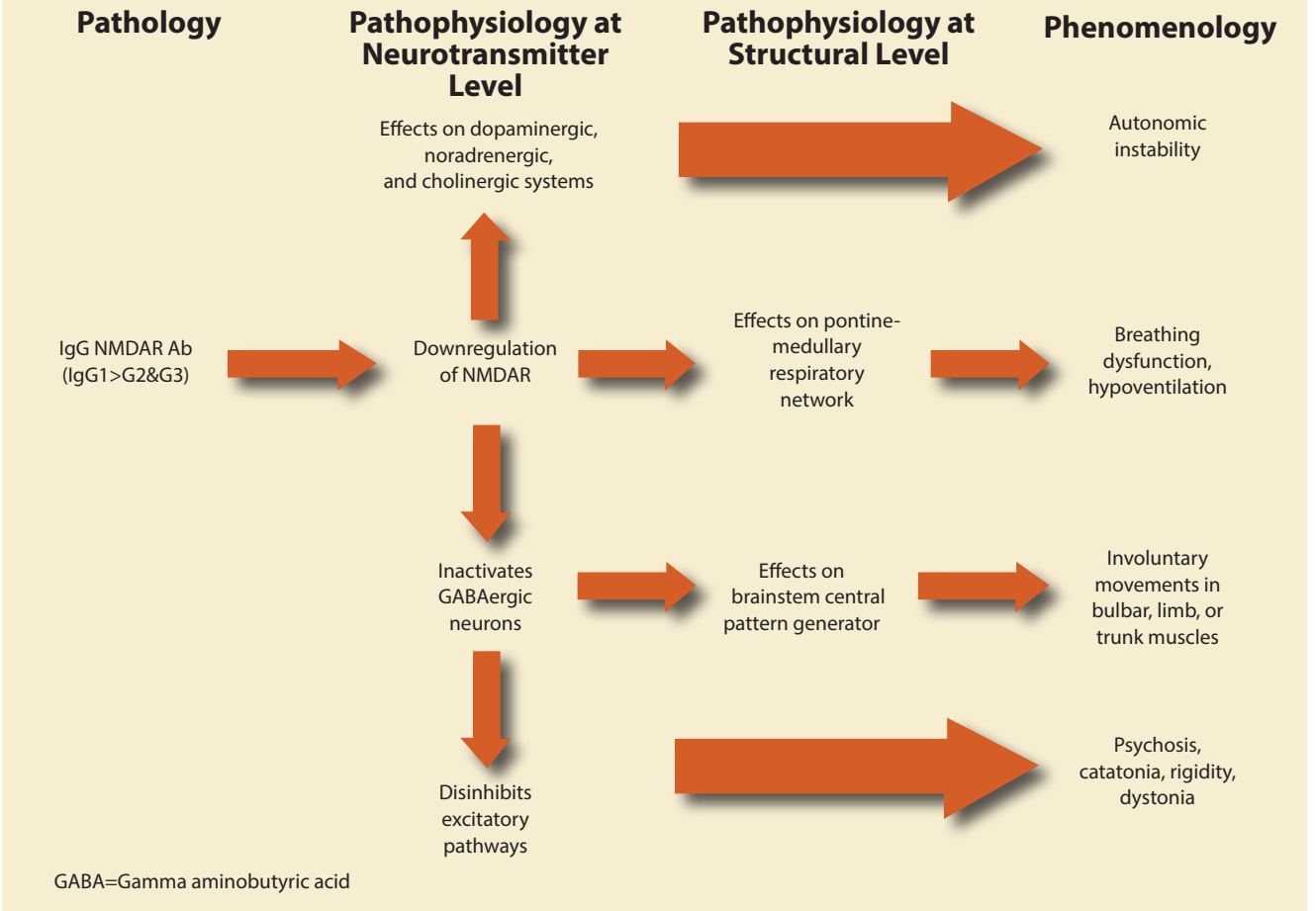
MRI=Magnetic Resonance Imaging; EEG=Electroencephalogram; SPECT=Single Photon Emission Computed Tomography; PET=Positron Emission Tomography; CSF=Cerebrospinal Fluid

with or without tumor association, and responds to treatment but can relapse. The presence of a tumor (usually an ovarian teratoma) is dependent on age, sex, and ethnicity, being more frequent in women older than eighteen years, and slightly more predominant in black women than in white women (5). Recent studies show, however, that this disorder can occur even in the absence of teratoma in up to 35% of patients, and boys/adult men have been affected (11).

NMDAR encephalitis may be suspected with the following phenomenological progression: flu-like prodromal symptoms, a psychotic stage, unresponsiveness with hypoventilation, autonomic instability and dyskinesia, and eventually death or recovery (see Table 1) (5, 12-15). Similar to our patient's history, patients with NMDAR encephalitis can present with prominent psychotic behavior including delusions, paranoia, hallucinations, and a catatonic-like state. These symptoms are not surprising given that NMDARs are highly expressed in the forebrain, limbic system, and hypothalamus (11, 15, 16).

The diagnosis of NMDAR encephalitis can be ascer-

Figure 1 Pathogenesis of Anti-N-Methyl-D-Receptor (NMDAR) Encephalitis (Ref. #2, 5, 11)



tained vis-à-vis a four-step process (see Table 2) (2, 16-19): 1) recognition of symptoms of subacute encephalopathy, including limbic dysfunction; 2) diagnostic work-up/rule out other diagnoses, especially HSV encephalitis; 3) search for an underlying malignancy; and, 4) establish the diagnosis by reviewing its diagnostic criteria.

Our patient's MRI of the head was unremarkable, while EEG did demonstrate generalized slow wave activity, and her CSF was remarkable for a lymphocytic pleocytosis, elevated protein, and oligoclonal bands. Comparing our patient to a case series analysis of patients with anti-NMDA-receptor encephalitis, abnormal MRI findings occurred in 60% of the patients studied, CSF abnormalities occurred in almost all of the 100 patients evaluated, with lymphocytic pleocytosis in >90% of these patients and oligoclonal bands in two-third of these patients, with almost 80% having slow wave activity on EEG (20). See Table 2 for a comparison of our patient's diagnostic tests vs. conventional norms for anti-NMDAR encephalitis (20). Interestingly, while not the first time reported (21), it was the incidental finding of the dermoid cyst in our patient that triggered the search for the autoantibody to the NMDA receptor, leading to the correct diagnosis and treatment.

Beyond treatment of the underlying tumor, immunotherapy—such as corticosteroids, IVIg, or plasma exchange—is a key treatment component of anti-NMDAR encephalitis. If an inadequate response is encountered or relapse, treatment can also include rituximab, azathioprine, or cyclophosphamide (22). Resolution of psychiatric and behavioral symptoms tends to follow suppression of the immune response in anti-NMDAR encephalitis. While our patient's acute neuropsychiatric symptoms significantly improved after combined oopherectomy and IVIg, her relative quick relapse (after four months status/post combined treatment) has still precluded us from determining if our patient ever returned to her premorbid state (13).

Some (8), but not all studies (15), intimate a psychiatrist as the initial point of contact in the evaluative process of anti-NMDAR encephalitis. Therefore, it is not uncommon for patients to be treated at sometime during the course of their illness with psychotropic medications, including conventional/atypical antipsychotics. The evidence base utiliz-

ing the latter to treat anti-NMDAR encephalitis is limited and with mixed results (23, 24). Our patient's result would seem to support a limited response (BPRS from 51→40) to risperidone.

One proposed theory of the pathogenesis of anti-NMDAR encephalitis postulates that an antibody-mediated decrease of NMDAR predominantly inactivates GABAergic neurons (which are rich in NMDAR), leading to disinhibition of excitatory pathways and increase of extracellular glutamate. As a result, patients develop a frontostriatal syndrome (FSS), which is characteristic of anti-NMDAR encephalitis. Psychiatric symptoms of psychoses and catatonia could occur either directly due to this FSS and/or downstream excitatory transmission in the mesolimbic pathway. The complexity of orofacial and limb movements in patients with this disorder is probably explained by disinhibition of a brainstem central pattern generator, which under normal conditions, is tonically inhibited by the GABAergic system. Because genetic disruption of NR1 causes hypoventilation, a direct effect of the antibodies on the medullary-pontine respiratory network might result in breathing dysfunction. The presence of NMDAR in dopaminergic, cholinergic, and noradrenergic systems probably explains the autonomic manifestations (hypersalivation, hypertension, hyperthermia, cardiac dysrhythmia) that are also typical of NMDAR antagonists (see Figure 1) (2, 5, 11).

In closing, patients with the rapid progression of a combination of symptoms, which usually include alteration of cognition/short-term memory impairment, changes in behavior (delusions, psychosis, catatonia), abnormal movements (orofacial dyskinesias, choreoathetosis) and seizures, should raise the suspicion of the psychiatrist to seek further diagnostic testing, such as antibodies against the GluN1 subunit of the NMDAR (especially in young people), which could herald NMDAR encephalitis (25). Additionally, perhaps harnessing identified autoantibodies to explore how NMDA receptor signaling and trafficking relate to psychoses might result in improved treatments of schizophrenia despite mixed results (26, 27) from the adjunctive use of small molecules (glycine, D-serine) that enhance NMDA neurotransmission to antipsychotics.

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