

Anti-N-Methyl-D-Aspartate Receptor Antibody Testing in First-Episode Psychosis: Universal or Targeted Testing

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Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is an immune-mediated disorder that typically presents with rapid development of neuropsychiatric symptoms. As a potentially reversible cause of psychosis, there have been calls internationally for routine serological screening for anti-NMDAR antibodies in patients presenting with first-episode psychosis (FEP). Increased serological testing has, however, exposed several limitations of universal screening and rekindled debate as to which patients should be tested.

Screening criteria have been proposed for high-risk clinical features in FEP in which antineuronal antibody testing is indicated. The authors present a clinical vignette and a service audit as well as discuss the limitations of universal screening advocating instead for targeted testing for antineuronal antibodies in patients diagnosed as having FEP.

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CLINICAL VIGNETTE

“Sally,” a 38-year-old Caucasian woman, was brought to a tertiary hospital’s accident and emergency department by her husband with increasingly bizarre behavior. Sally, a mother of two young daughters, worked part-time as a high school teacher. Over the preceding 2 weeks, she had become preoccupied with the belief that several of her pupils had been replaced by members of the Secret Service. She reported hearing whispering about her in class and crackling noises when home alone, leading her to suspect that the secret agents had infiltrated the family home and planted monitoring devices within the air conditioning ducts. After she confided these concerns to her husband, they sought a general practitioner, who had advised her to take stress leave 1 week prior to her presentation. Over the subsequent 3 days, she became increasingly agitated and restless with significant insomnia. Her husband reported that she had complained of a headache but no other systemic symptoms. On the day of presentation, Sally had broken through plaster-board walls in her home to expose the air conditioning ducts to find the hidden monitoring devices, which alarmed her family. She had no prior psychiatric history and had never taken any illicit substances. Her medical history was significant for Hashimoto’s thyroiditis 6 years ago, which had since been well controlled with levothyroxine. She took no other regular medication.

Examination revealed Sally was an alert but agitated middle-aged woman who was tachycardic, hypertensive, and apyrexial. She paced back and forth in the interview room, continually clapping her hands together in a

stereotypical manner and intermittently trying to take off her clothes. She made poor eye contact with occasional grimacing and repeated the phrase, “in the ducts, in the ducts.” Neurological examination revealed increased, rigid tone in her upper limbs with negativism and gegenhalten. There was no mitgehen, ambitendency, or waxy flexibility. There was normal power and positive grasp reflex. The Bush-Francis Catatonia Rating Scale score was 21. Bedside cognitive testing revealed severe inattention and disorientation. She had normal cardiopulmonary; ear, nose, and throat; and abdominal examinations.

Baseline blood tests were unremarkable, including a full blood count; electrolytes; renal, liver, and thyroid function tests; C-reactive protein; and venous blood gas. Her urine drug screen was negative. An EEG was completed showing frontotemporal slowing with no epileptiform activity. MRI of the brain was unremarkable. A lumbar puncture was completed showing pleocytosis with 12 white cells, zero red cells, zero polymorphs, five mononuclears, no organisms on culture growth, normal glucose, and raised protein levels.

Given the abrupt onset and rapid progression of her psychotic symptoms, including numerous red flags for autoimmune encephalitis and associated EEG and cerebrospinal fluid (CSF) abnormalities, Sally was admitted to the neurology ward and CSF antineuronal antibody testing was ordered. CSF immunoglobulin G anti-N-methyl-D-aspartate (NMDAR) antibodies were detected, confirming the suspected diagnosis of autoimmune encephalitis. Sally was treated with a course of intravenous methylprednisolone and immunoglobulin, which led to rapid improvement in her mental state and behavior. She was discharged into her

husband's care 5 weeks later. She made a full recovery over the next 4 weeks and successfully returned to work.

AUTOIMMUNE PSYCHOSIS

Autoimmune encephalitis is a syndrome in which antibodies to synaptic, glial, and neuronal cell surface (neural surface antibodies) disrupt cortical and subcortical network activity, causing severe neurological and psychiatric signs and autonomic dysregulation (1). Autoimmune psychosis is the diagnostic term for the disorder experienced by a subgroup of these individuals who present with clinical features of severe psychosis, most commonly mediated by antibodies to NMDAR (2). Red flag clinical features suggestive of autoimmune psychosis broadly include an infectious prodrome, accompanying neurological signs and symptoms, rapid onset of severe illness that is treatment refractory, and significant impairment of cognition and language (3). As demonstrated in this case, routine blood investigations and MRI are often normal, and changes in EEG are common although non-specific (4). The definitive diagnosis is made by the presence of neural surface antibodies (NSabs) in the CSF (2). Management of autoimmune psychosis involves immunotherapy and tumor resection where indicated. Delays in appropriate management are associated with poor outcomes (5, 6); therefore, early detection is critical.

THE DILEMMA WITH UNIVERSAL ANTI-NMDAR ANTIBODY TESTING

There is debate as to which patients should be tested for NSabs. About 7% of patients experiencing psychosis are seropositive for NSabs (7). Some of these have a true autoimmune psychosis, as evidenced by antibodies and inflammation in the central nervous system (CNS) that is responsive to immunotherapy (8, 9). In the United States, it has been demonstrated that routine antibody testing in patients diagnosed with first-episode psychosis (FEP) is cost effective (10). Clinical guidelines from Australia (11) and Germany (12) have recommended routine serological screening for NSabs in patients with FEP.

However, with increased testing for anti-NMDAR antibodies in individuals experiencing psychosis, the limitations of universal testing have come to light. There is currently no international gold-standard diagnostic test for anti-NMDAR antibodies, and there is variability in the validity of tests used by different laboratories. False positives can result from weak staining with indirect immunofluorescence, and false negatives from antibody titers too low for detection. The use of serum samples as opposed to CSF has limitations regardless of the type of assay used. Studies have demonstrated that seropositive patients without evidence of CNS involvement have the same clinical outcomes as seronegative patients (13–15).

Without due attention to the type of specimen and assay, and to the clinical presentation, serum testing for NSabs is of

TABLE 1. Demographic and clinical characteristics of subjects tested for *N*-methyl-D-aspartate antibodies and matched untested sample

Characteristic	Tested subjects	Untested subjects
Gender (male:female)	19:8	19:8
Mean age (years)	21.3	21.4
Age range (years)	13–26	15–26
Median duration of psychosis (weeks)	4.5	6.0
Range of duration of psychosis (weeks)	0–52	1–32

limited validity and clinical utility. Further, there is a risk of iatrogenic harm from unwarranted immunosuppressive therapy (16). The low prevalence of autoimmune psychosis in patients with FEP leads to low pretest probability (17), inflating the rate of false positives. Consistent with these concerns, and in contrast to guidelines recommending universal testing, the recently published international consensus approach to the diagnosis and management of autoimmune psychosis recommended targeted testing for NSabs (2).

ANTI-NMDAR ANTIBODY TESTING IN CLINICAL PRACTICE

Our group conducted an audit of anti-NMDAR antibody testing undertaken at the Bondi Early Psychosis Program in Sydney in order to establish current practice benchmarked against local guidelines that recommend universal testing in patients with FEP (11). Medical records for all individuals referred to the service over the 2-year period from November 1, 2017, to October 31, 2019, were retrospectively audited. Each medical record was reviewed to determine whether NMDAR antibody testing had been completed. The medical records of tested subjects were audited to determine whether high-risk clinical features of autoimmune psychosis were documented as either absent or present. This was compared with documentation for an age- and gender-matched group of untested subjects.

Only 27 of the 136 (20%) patients diagnosed with FEP were tested for anti-NMDAR antibodies at or before the time of entry to the program; none of them tested positive. Two of the subjects were tested from CSF samples; the remaining tests were completed from serum samples. Table 1 shows the gender, mean age, and median duration of psychotic symptoms (including treated and untreated psychosis) for the 27 tested subjects and matched untested sample. The eight most commonly documented high-risk features are shown in Table 2, although documentation of each feature (as either absent or present) was infrequent. Severe cognitive dysfunction and speech changes were the most commonly documented features as part of the mental state examination. The remaining high-risk features (headache, adverse response to antipsychotic, insufficient response to antipsychotic, movement disorder, seizure, tumor, autoimmune disorder, and paresthesia) were not documented as either

TABLE 2. Documentation of high-risk features of autoimmune psychosis in the medical record of subjects tested for *N*-methyl-D-aspartate antibodies and matched untested sample

High-risk feature	Tested subjects			Untested subjects		
	Documented as present	Documented as absent	Not documented	Documented as present	Documented as absent	Not documented
Rapid progression	5	0	22	0	0	27
Severe cognitive dysfunction	2	8	17	0	19	8
Speech changes	2	8	17	0	17	10
Infectious prodrome	1	4	22	1	3	23
Autonomic disturbance	1	3	23	0	3	24
Focal neurological disease	0	7	20	0	2	25
Hyponatremia	0	6	21	0	3	24
Decreased consciousness	0	1	26	0	4	23

absent or present in over 90% (25 of 27) of subjects in both tested and untested groups. Only 11% (3 of 27) of tested subjects met proposed diagnostic criteria for possible autoimmune psychosis (2) based on documentation. No subjects in the untested sample met proposed criteria.

DISCUSSION

The increasing recognition that some patients with psychosis have an autoimmune illness mediated by anti-NMDAR antibodies (2) offers hope for a reversible mechanism underlying presentations of FEP. Enthusiastic adoption of screening for anti-NMDAR antibodies has occurred in many services around the world. As evidenced by our service audit, however, there is an ad hoc approach to anti-NMDAR antibody testing in clinical services. Despite local guidelines endorsing universal testing, a minority of patients with FEP were tested for antibodies. There was limited documentation of high-risk clinical features, which did not reflect considered clinical reasoning to inform targeted testing.

Implementation of targeted testing for NSabs would enable rational use of scarce health resources. There have been two sets of screening criteria proposed for high-risk clinical features in FEP where anti-NMDAR antibody testing is indicated. Herken and Prüss (3) proposed 10 “yellow flag” criteria that should raise suspicion of an autoimmune etiology. These include decreased levels of consciousness, abnormal postures or movements, autonomic instability, focal neurological deficits, aphasia or dysarthria, rapid progression of psychosis, hyponatremia, catatonia, headache, and other autoimmune diseases. Scott et al. (18) proposed screening criteria that require rapid onset of psychotic illness and one or more of the following: concurrent neurological signs, evidence of severe cognitive impairment, catatonia, or the need for management with electroconvulsive therapy because of illness severity. Warren et al. (19) retrospectively assessed these criteria in a sample of 258 anti-NMDAR encephalitis cases and

103 control cases. They demonstrated high performance of both criteria, which remained accurate when neurological variables were excluded (19). These screening criteria support targeted testing for NSabs, although further research is needed to prospectively assess the criteria in larger cohorts.

The service audit has a number of limitations. As a single-site audit, the results are representative of current practice at one FEP program in Sydney and may not be generalizable to national or international practice. The results are further limited by a small sample size and the reliance on medical record documentation. The absence of documentation of high-risk features may have underestimated the degree to which testing was based on clinical phenotype. Furthermore, the clinical notes focused on the onset of psychotic symptoms and lacked detail of prodromal features, making it difficult to ascertain how long after illness onset the samples were obtained. Nonetheless, the audit highlights that even in a subspecialized early psychosis program, NMDAR testing is not being conducted in a systematic way. In real-world practice, testing is neither universal nor targeted, with a need for greater attention to and documentation of high-risk features that would warrant testing.

CONCLUSIONS

We suggest that targeted, rather than universal, testing for antineuronal antibodies in people with FEP should be implemented. This would ensure that patients like the one described in our clinical vignette are investigated so that the correct diagnosis and appropriate management can be delivered in a timely manner. Validation of clinical criteria to date has only been conducted retrospectively. Further research is needed to prospectively assess and refine the criteria for testing of NSabs in larger FEP cohorts. Clinician education is needed to ensure that targeted testing of NSabs, with considered clinical rationale and documentation, occurs in services treating people with early psychosis.

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