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Short communication

Anti-NMDA receptor antibody positivity in acute psychotic states: An exploratory study

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ABSTRACT

The glutamatergic theory of schizophrenia postulates N-methyl-D-aspartate receptor (NMDA-R) dysfunction. Anti-NMDA receptor antibodies may be present in some patients with psychosis. Fifteen patients presenting with acute psychotic states having one additional clinical feature suggestive of autoimmune etiology were recruited. Serum antibodies against NMDA-receptor were tested at baseline and at follow-up using Indirect Immunofluorescence Technique. None of the 15 patients had positive anti-NMDA antibody at baseline or at follow-up. The study failed to detect anti-NMDA antibodies in patients with acute psychotic states with clinical suspicion of autoimmunity. This does not rule out other mechanisms of NMDA receptor dysfunction in these patients. The glutamatergic theory of schizophrenia postulates N-methyl-D-aspartate receptor (NMDA-R) dysfunction. Anti-NMDA receptor antibodies may be present in some patients with psychosis. Fifteen patients presenting with acute psychotic states having one additional clinical feature suggestive of autoimmune etiology were recruited. Serum antibodies against NMDA-receptor were tested at baseline and at follow-up using Indirect Immunofluorescence Technique. None of the 15 patients had positive anti-NMDA antibody at baseline or at follow-up. The study failed to detect anti-NMDA antibodies in patients with acute psychotic states with clinical suspicion of autoimmunity. This does not rule out other mechanisms of NMDA receptor dysfunction in these patients.

1. Introduction

Psychotic disorders are a heterogenous group of disorders of which schizophrenia is a prototype. Schizophrenia has been postulated to be a severe mental disorder with complex aetiology (Harrison and Weinberger, 2005). The dopaminergic theory of schizophrenia was prominent initially, however recent evidence points to N-methyl-D-aspartate receptor (NMDA-R) dysfunction as the proximal cause of dopaminergic dysregulation in schizophrenia through complex interactions between glutamatergic and dopaminergic pathways (Schwartz et al., 2012).

Anti-*N*-methyl-D-aspartate receptor (NMDA-R) encephalitis has been recognized recently. Anti-NMDA-R encephalitis often presents as a diagnostic challenge with protean neuropsychiatric manifestations. Psychotic symptoms have been described among patients with anti-NMDA-R encephalitis (Dalmau et al., 2008; Irani et al., 2010). These psychotic symptoms are similar to those seen in schizophrenia such as delusions, hallucinations and catatonic features (Zandi et al., 2011). Case reports from India have reported anti-NMDA receptor antibody encephalitis presenting as catatonia or psychosis in which cognitive deterioration was also noted (Chatterjee et al., 2017; Palakkuzhiyil et al., 2018).

Literature for the role of anti-NMDA-R antibody in psychiatric disorders is sparse. These studies were done in a mixed group of patients with varied psychiatric disorders. These studies have found a frequency of anti-NMDA-R positivity to be between 0% (Masopust et al., 2015) to about 10% (Steiner et al., 2013). It was hypothesised that there may be a greater proportion of anti-NMDA receptor positivity among patients with acute psychotic state having associated clinical features such as high-grade fever, altered sensorium and seizures or display atypical psychotic features such as bizarre behaviour, cognitive impairment, progressive speech and language deficits, catatonia like state, confusion and dyskinetic movements.

The frequency of anti-NMDA antibodies among patients having acute psychosis along with one or more of pre-specified clinical features that are likely to indicate a potential immunological etiology was studied. Since previous studies have reported the presence of anti-NMDA antibodies even in healthy controls, the potential etiological role for a positive antibody test remains doubtful. Thus, the serum anti-NMDA antibody of patients was assessed at baseline and after about 4 weeks of follow-up using a semi-quantitative assay. A rise in titer between baseline and follow-up may be a stronger indicator for the role of anti-NMDA antibodies in the etiopathogenesis of acute psychotic states.

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Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
(1) Age between 13 to 40 years	(1) Presence of a co-morbid psychiatric diagnosis (except nicotine dependence syndrome)
(2) Can read and write Tamil or English	(2) history suggestive of mental retardation (ICD-10; F71, F72, F73)
(3) Present within 8 weeks of onset of acute psychotic state of acute or abrupt onset (as defined in ICD-10)	(3) Connective tissue disorders including Systematic Lupus Erythematosus (SLE) or on any immunosuppressive drugs were excluded based on available records and clinical evaluation
(4) One of the following criteria: (i) presence of a viral-like prodrome within 6 weeks before onset (ii) one sign of cognitive impairment such as memory deficits, inattention, disorientation, or speech and language impairment (iii) one of the following neurological symptoms such as catatonia, neuroleptic malignant syndrome (NMS), seizures, recent onset severe headache, abnormal involuntary movements (dyskinesias, chorea or gait disturbances) (iv) any sign of autonomic instability such as hypotension or hypertension, bradycardia or tachycardia, hyperthermia, hypoventilation or urinary incontinence	(4) Suspected acute infective encephalitis

2. Materials and methods

This was a prospective study conducted at a tertiary care medical institute in India. The patients were recruited as per the inclusion and exclusion criteria listed in Table 1. All patients and their caregivers provided written informed consent prior to recruitment into the study. In case of patients under 18 years of age their assent and caregiver consent were taken. The study was approved by the Ethics Committee of our institute.

Sixteen individuals with acute psychotic episode of not more than 8 weeks duration fulfilling the inclusion criteria were recruited after explaining the study details and taking written informed consent. Following this a trained clinician collected certain details like socio-demographic, illness parameters and applied certain scales like Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962), Bush-Francis Catatonia Rating Scale (BFCRS) (Bush et al., 1996), Abnormal Involuntary Movement Scale (AIMS)(Guy, 1976), Montreal Cognitive Assessment (MOCA) (Nasreddine et al., 2005) and Global Assessment of Functioning (GAF) (Hall, 1995) to assess the baseline severity of psychotic symptoms, catatonic symptoms, abnormal involuntary movements and cognitive functions respectively. Then, 5 ml of serum sample was collected under sterile aseptic condition. The samples were then preserved at -80^{0}C.

The same individual was followed up after a period of about 3–6 weeks. On follow-up, the clinician reapplied BPRS, BFCRS, AIMS, MOCA and GAF and again collected 5 ml of serum sample under sterile aseptic condition at the end of interview. The samples were preserved at -80^{0}C. Paired serum samples were treated with transfected cell line expressing NMDA receptor (Euroimmun Anti-NMDA IIFT). Using Anti-human IgG conjugate tagged with Fluorescein, auto-antibodies against NMDA type glutamate receptors was evaluated by Indirect Immunofluorescence Technique (IIFT).

3. Statistical analysis

Descriptive statistics such as mean and standard deviation was used to describe continuous variables. Frequency and percentage were used to describe categorical data. Wilcoxon-Signed Rank test was used to compare the mean and standard deviation of total BPRS, BFCRS, AIMS and MOCA between the index point and repeat assessment.

Table 2
Basic demographic and clinical details of the participants (N = 15).

Variables	Categories, Units	n (%), Mean (SD), Median (IQR)
Age	Years	27.87 (7.51)
Sex	Female	3 (20%)
	Male	12 (80%)
Education	Years	12.07 (4.59)
Socioeconomic Status	Upper middle	5 (33.3%)
	Lower middle	2 (13.3%)
	Upper lower	1 (6.7%)
	Lower	7 (46.7%)
Background	Rural	9 (60%)
	Semi-urban	3 (20%)
	Urban	3 (20%)
Occupation	Unemployed	2 (13.3%)
	Student	2 (13.3%)
	Semiskilled worker	3 (20%)
	Skilled worker	5 (33.4%)
	Professional	2 (13.3%)
	Housewife	1 (6.7%)
Marital Status	Single	9 (60%)
	Married	6 (40%)
Family History	Any psychiatric disorder	8 (53.3%)
	Psychotic disorder	3 (20%)
	Affective disorder	1 (6.7%)
	ADS	3 (20%)
	Intellectual disability	1 (6.7%)
Diagnosis	Schizophrenia (F20)	3 (20%)
	Acute Transient Psychotic Disorders (F23)	8 (53.4%)
	Other Psychotic disorders (F28)	2 (13.3%)
	Mania with psychotic symptoms (F31.2)	2 (13.3%)
Duration of episode at time of assessment	Days	30 (12,90)
Number of past episodes		1 (0,1) (Range = 0-3)
Time at follow-up assessment	Days since baseline assessment	40 (28,70)
Time of onset of associated symptom (in days)	One associated symptom (n = 15)	1 (1,12) (Range = 1-75)
	Two associated symptoms (n = 8)	7 (6,11.5) (Range = 5-20)
	Three associated symptoms (n = 1)	20

4. Results

Sixteen subjects were recruited in the study. One subject did not come for follow-up. Table 2 lists the socio-demographic characteristics of the fifteen subjects. The mean age of the participants was 27.87 years (S.D. −7.51). The participants had 12.07 years (S.D. −4.59) of education. Median duration of the current episode was 30 days (IQR: 12, 90) at the time of assessment and all subjects sought first medical consultation at our hospital. Median time to repeat assessment was 40 days (IQR: 28, 70) from the date of baseline assessment. A majority of the participants (80%) were men. The time of onset of the associated

Table 3
Comparison between the mean scores of various scales between index assessment and repeat assessment.

Variables	Index ASSESSMENT (Mean ± SD)	Repeat assessment (Mean ± SD)	Paired difference (Mean ± SD)	Z	p value
BPRS	52.93 ± 12.04	24.93 ± 11.98	28.00 ± 15.01	−3.412	**0.001***
AIMS	0.31 ± 1.11	0.23 ± 0.83	0.08 ± 1.44	−0.447	0.655
BFCRS	4.47 ± 4.26	1.00 ± 3.36	3.47 ± 4.75	−2.196	**0.028***
MOCA	12.73 ± 11.09	17.07 ± 11.57	−4.33 ± 16.91	−1.415	0.157
GAF	54.47 ± 12.76	76.33 ± 12.32	−21.87 ± 15.84	−3.182	**0.001***

clinical features ranged from day 1 to day 75 in the patients. More than half the patients had been diagnosed with acute and transient psychotic disorders (F23) as per the International Classification of Disease, 10th edition, Diagnostic Criteria for Research (ICD-10 DCR) (World Health Organization, 1993). The mean scores of the BPRS, AIMS, BFCRS, MOCA and GAF at two different time points and the comparison between baseline and follow-up visits is listed in Table 3. None of the serum samples were positive for anti-NMDA antibodies by IIFT although some non-specific organelle fluorescence patterns were observed both in transfected control cells (EU-90) and NMDA-R transfected cells.

5. Discussion

Anti-NMDA receptor is a ligand gated ionotropic glutamatergic receptors that is highly permeable to calcium. NMDARs are formed from four subunits which includes two GluN1 subunits in combination with two GluN2 or GluN3 subunits. GluN1 subunit is found as eight different splice variants (GluN1–1a through GluN1–4a and GluN1–1b through GluN1–4b), while GluN2 and GluN3 are made from four (A–D) and two (A–B) genes respectively (Regan et al., 2015; Traynelis et al., 2010; Zhu and Paoletti, 2015). These variations in NMDA-R peptides may confer differential susceptibility to autoimmunity to NMDA-R among different populations.

The anti-NMDA-R antibody positivity has been explored in several psychiatric disorders such as schizophrenia, schizoaffective disorder, mania and major depressive disorders with variable findings (Hammer et al., 2014; Haussleiter et al., 2012; Masopust et al., 2015; Rhoads et al., 2011; Tsutsui et al., 2012; Zandi et al., 2011). The methodologically sound study done by Steiner et al. noted a frequency of anti-NMDA-R antibodies to be more in schizophrenia (9.9%) than in major depression (2.8%), borderline personality disorder (0%) or healthy controls (0.4%). These antibodies (IgA and/or IgM) were against type 1 NMDA-Receptor (NR1a/NR2b subunit) (Steiner et al., 2013). Another study by Dickerson and colleagues, found that combined inflammation score of IgG class antibodies against type 2 NMDA-Receptor (NR2 peptide fragment) in individuals with mania differed significantly from that of the control group. When the same patients were followed up after six months, the inflammation score decreased significantly (Dickerson et al., 2012).

There are studies that have failed to detect anti-NMDA-R antibodies in various psychiatric disorders (Hammer et al., 2014; Masopust et al., 2015; Rhoads et al., 2011). These studies included all patients with a psychiatric disorder without any clinical suspicion towards autoimmunity. Since 65% of individuals with antibodies for NMDA-R have psychotic symptoms (Lennox et al., 2012) and only 7.6% of patients with acute psychotic disorder have NMDA-R antibodies (Schou et al., 2016), it has been suggested by few authors that the possibility of antibodies against NMDA-R should be considered in cases with “flu-like” prodromal symptoms, acute onset of psychosis, catatonia like features, seizures, neurocognitive dysfunction, severe autoimmune manifestations and/or deterioration during treatment with antipsychotics (Masopust et al., 2015). Similarly, a recently published study from Bangalore (Chandra et al., 2019) found that the triad of clinical symptoms of (i) Panic attacks, (ii) Sleepiness and (iii) either Seizures or Catatonia were strongly indicative of immune mediated aetiology for dementia. Even though we had additional inclusion criteria to raise the suspicion of autoimmune aetiology, we did not find any NMDA-R antibody positivity. However, the study was conducted in a Neurology clinic and our study was done in a Psychiatry clinic. The findings may have been different because of a selection bias as patients with significant neurological symptoms such as seizures and cognitive decline are less likely to present to a psychiatry clinic.

It could possibly be explained by (a) the lack of neurological features like dyskinetic movements or features of encephalitis in our study sample which is strongly associated with anti-NMDAR encephalitis, (b) older age (mean age 27 years) as opposed to the adolescent onset described for anti-NMDAR encephalitis, (c) predominantly male subjects (as previous reports have suggested that anti-NMDAR encephalitis may be more common in women), (d) taking only one associated symptom may not have sufficiently enhanced the pre-test probability of an autoimmune etiology. The yield would have been positive if at least 4 of the following groups of symptoms like psychiatric disturbance, cognitive dysfunction, speech dysfunction, seizure, movement disorders, decreased level of consciousness and autonomic dysfunction or central hypoventilation are considered to recruit the subjects (Graus et al., 2016).

A broader screen for antibodies against limbic system structures must be considered in future rather than specific antibodies against NMDA-R. It is possible that other etiopathogenetic mechanisms or downstream signaling molecules/NMDA receptor interacting proteins may be involved in causing NMDA-R pathway dysfunction among patients with acute psychosis (Kristiansen et al., 2007).

Conflicts of interest

None of the authors have any conflicts of interest to declare.

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Ethical statement

The study has been done after due approval from the Institute Ethics Committee (Ref:JIP/IEC/2017/0097).

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