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Short Communication

Anti-NMDAR antibodies in new-onset psychosis. Positive results in an HIV-infected patient

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ABSTRACT

The role of neuronal surface autoantibodies (NSAs) in non-encephalitic psychosis is of recent and controversial interest. Most of the studies relating NSAs with psychosis are retrospective and only focused on the N-methyl-D-aspartate glutamate receptor (NMDAR). Our goal was to evaluate the prevalence of IgG antibodies against the NMDAR NR1 subunit (NMDAR-Abs) along with five additional NSAs in 61 first psychotic episode patients and 47 matched controls. We found two patients positive for NMDAR-Abs (3.3%). One of them was eventually considered to have been misdiagnosed and reclassified as encephalitis. The other met the criteria for bipolar I disorder, presented no neurological symptoms and had a comorbid HIV infection of vertical transmission. This is the first reported case of an HIV-infected patient with psychosis associated with NSAs. This study shows that patients presenting with clinically incomplete forms of anti-NMDAR encephalitis, with predominant or isolated psychiatric symptoms, can remain undetected if no ancillary tests are performed.

To improve patient diagnosis and treatment of individuals with a first psychotic episode, more detailed neurological examinations might be needed. Further studies are required to better clarify the role of NSAs in the neuropsychiatric effects of HIV infection.

1. Introduction

N-methyl-D-aspartate glutamate receptor (NMDAR) dysfunction has been associated with schizophrenia (Elert, 2014; Schwartz et al., 2012; Stephan et al., 2009; Timms et al., 2013).

The search for an autoimmune mechanism in schizophrenia or psychosis has been especially intense since anti-NMDAR encephalitis (NMDAR-E) was described as a novel autoimmune neuropsychiatric entity, diagnosed by the presence of IgG antibodies against the NMDAR NR1 subunit (NMDAR-Abs) (Dalmau and Bataller, 2007). Up to 70% of patients with NMDAR-E are initially evaluated by psychiatrists, and NMDAR-Abs positive cases with isolated psychotic symptoms have also been described (Dalmau et al., 2008, 2011; Lebon et al., 2012; Steiner et al., 2013). Recent studies have described a spectrum of phenotypes associated with NMDAR autoimmunity and suggest a pathophysiological overlap between some cases of psychosis and NMDAR-E (Maneta and Garcia, 2014).

Rates of NSAs seropositivity among psychotic patients have been reported to be up to 6.5–10% (Steiner et al., 2013; Tsutsui et al., 2012; Zandi et al., 2011), but results have not been conclusive. There is a need to prospectively analyze the presence of NSAs in patients with new-onset psychosis without encephalitis (Deakin et al., 2014; Kayser et al., 2013).

The main goal of our study was to evaluate the prevalence of NSAs in first psychotic episode patients (FPEP). Specifically, we analyzed antibodies against NMDAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR) type 1 or 2, gamma-aminobutyric acid receptor (GABAR) type B and the proteins associated with the Voltage-gated potassium channels

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(VGKC): leucine-rich glioma-inactivated 1 (LGI1) or contactin-associated protein 2 (CASPR2). A secondary goal of the study was to evaluate the presence of onconeural, systemic and thyroid autoantibodies in FPEP.

2. Materials and methods

2.1. Patients and controls

We included 61 FPEPs admitted from May 2010 to January 2013 to the new-onset psychosis treatment program. Control subjects were 45 healthy volunteers (sex, age and ethnicity matched with patients) recruited from the general population after answering a brief questionnaire to rule out a mental disorder diagnosis.

The median time of follow-up for patients recruited in the study was 11 (SD 9) months. The duration of untreated psychosis (DUP) ranged from less than 1 week to more than 1 year, with a median of 3 and mean (SD) of 9 (13.1) weeks. Serum was obtained when patients signed the informed consent, and the mean time from symptoms onset until serum obtainment was 2.4 months (SD 4.4).

2.2. Clinical variables

Full clinical assessment and ancillary tests were performed to rule out medical conditions that could explain the psychotic symptoms. The diagnosis was performed independently by two clinicians according to DSM-IV TR criteria (Table 1).

The project was approved by the Ethics Committee of Majorca. All patients, and their legal tutors for those younger than 18 years-old, signed an informed consent.

2.3. Autoantibodies testing

2.3.1. Blood sampling

A venous blood sample was obtained after overnight fasting and centrifuged immediately after sampling; serum was stored frozen at −80 °C until analysis. Antibodies were analyzed within a month of sample extraction and samples had only undergone one freeze/thaw cycle when the analyses were performed.

Only one of the patients positive for NMDAR-Abs was tested for NSAs in the cerebrospinal fluid (CSF).

2.3.2. NSAs detection

Neuronal surface antibodies of the IgG isotype were studied using a cell-based assay. Sera were tested at a starting dilution of 1:10 by an indirect immunofluorescence immunoassay (IFI) using biochips containing rat cerebellum, hippocampus sections and transfected HEK293 cells expressing one of the following antigens: NMDAR (subunit NR1), AMPAR type 1 or 2, GABAR type B, LGI1 or CASPR2 (EUROIMMUN AG., Lübeck, Germany).

Double immunolabeling of NMDAR-transfected HEK293 cells, using patient's serum and a rabbit monoclonal antibody against NR1 (1:1000, AB9864, Chemicon, Temecula, CA, USA) followed by secondary antibodies [1:400, Alexa Fluor conjugated anti-rabbit IgG, Jackson Immunoresearch, West Grove, PA, USA and fluorescein-labeled anti-human IgG (FITC) (EUROIMMUN AG)] was performed to demonstrate co-localization with the NR1 subunit.

Positive results for NMDAR-Abs were cross-validated by immunohistochemistry on rat brain sections (Gresa-Arribas et al., 2014) and immunofluorescence on cultured neurons at the Dr. F. Graus Laboratory of Clinical and Experimental Neuroimmunology, Institut D'Investigacions Biomèdiques August Pi i Sunyer, Hospital Clinic, University of Barcelona, Spain.

2.3.3. Intracellular and intracellular synaptic neuronal (onconeural) antibodies detection

Onconeural antibodies were screened at a 1:10 titer on biochips containing rat cerebellum or primate cerebellum sections (EUROIMMUN AG). Antibodies to amphiphysin, GAD65, Hu, Yo, CV2, Ri, Ma1, Ma2 and SOX-1 were also tested by line immunoblot assay (ravo Diagnostika, Freiburg, Germany).

2.3.4. Screening of autoantibodies associated with systemic autoimmune diseases

Antinuclear antibodies (ANAs) were determined by IFI on Hep2 lines (INOVA, San Diego, USA). We screened Anti-ENA and anti-ribosomal P antibodies by line immunoblot assay (Innogenetics, Ghent, Belgium), and reactive sera were studied by ELISA for specific antigens (INOVA) or a fluorescence enzyme immunoassay (Elia) (Thermo Fisher Scientific-Phadia, Waltham, MA USA). We tested anti-DNA (dsDNA) antibodies by IFI on *Crithidia luciliae* (INOVA) and by Elia (Thermo Fisher Scientific-Phadia).

2.3.5. Thyroid autoantibodies detection

Antibodies to thyroperoxidase were measured by a chemiluminescence technique (Abbott, Wiesbaden. Germany).

2.4. Statistical analysis

Statistical analysis was performed with SPSS (Released 2009. PASW Statistics for Windows, Version 18.0. Chicago: SPSS Inc.). Fisher's exact tests were used to test statistical significance.

Table 1
Characteristics of FPEP.

	Gender		Age	Diagnosis of FPEP								
	N	%	Mean sd	SD N %	ME N %	DE N %	BPD N %	PS N %	DS N %	SP N %	PNOS N %	PM N %
Females	25	41.0	29.48	13	5	2	2	0	1	0	0	2
			12.80	52	20	8	8	0	4	0	0	8
Males	36	59.0	20.48	22	7	0	2	2	0	1	2	0
			5.25	61	19.4	0	5.6	5.6	0	2.8	5.6	0
Total	61	100	24.5	35	12	2	4	2	1	1	2	2
			10.35	57.4	19.6	3.3	6.6	3.3	1.6	1.6	3.3	3.3

SD: Schizophreniform disorder, ME: Manic episode, DE: Major depressive episode, BPD: Brief psychotic disorder, PS: Paranoid schizophrenia, DS: Disorganized schizophrenia, SP: Substance-induced psychotic disorder, PNOS: Psychotic disorder not otherwise specified, PM: Psychotic disorder due to a medical condition.

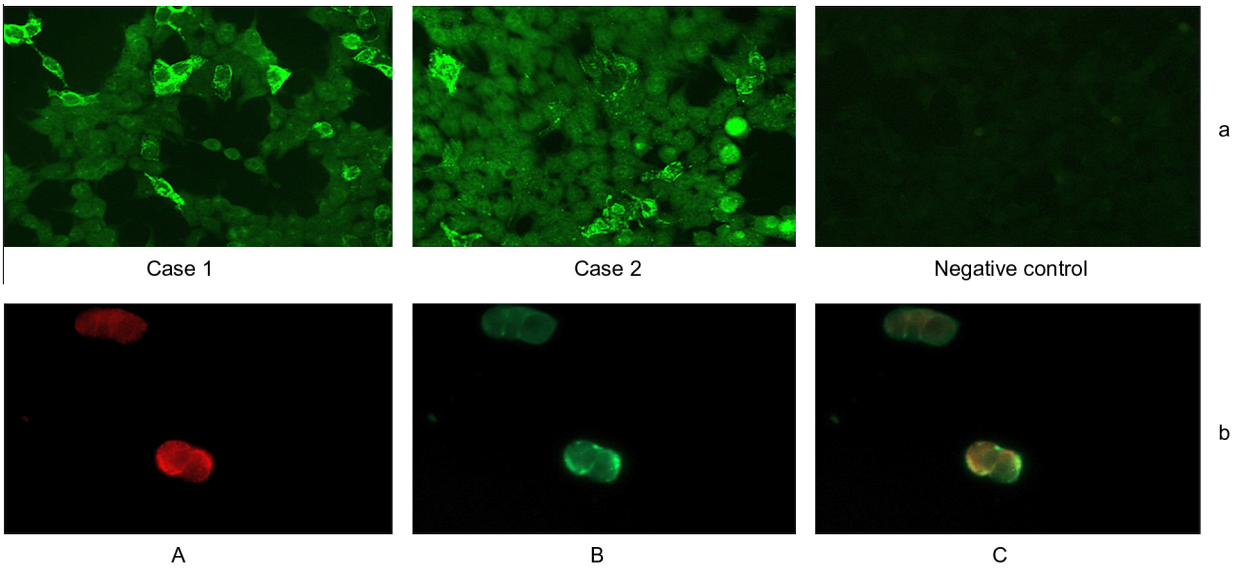

Fig. 1. Indirect immunofluorescence (IFI) on NMDAR-transfected HEK293 cells. a: IFI results of Case 1 and Case 2 positive patients and a negative control, by using FITC-conjugated anti-human IgG. b: IFI pattern obtained after Case 1 serum incubation along with a rabbit monoclonal antibody against the NR1 subunit, followed by Alexa fluor-conjugated anti-rabbit IgG (A), FITC-conjugated anti-human IgG (B) and merged reactivity (C).

3. Results

3.1. NSAs

We detected NMDAR-Abs in two FPEPs (3.28%) (Fig. 1). None of the healthy controls were positive. None of the samples showed positivity for other NSAs.

Case 1 was a 22-year-old male admitted in poor hygiene, with elevated tone of voice, accelerated and disorganized thought, loose associations, euphoric mood, insomnia, grandiose and paranoid delusions and auditory hallucinations. He had a co-morbid HIV infection of vertical transmission, with an undetectable viral load and unchanged antiretroviral treatment in the last 3 years. He was a chronic cannabis user. The patient's mother had a bipolar disorder diagnosis. Neurological examination, routine investigations and brain computed tomography (CT) scan were normal. He was diagnosed with bipolar I disorder, single manic episode. His treatment at discharge after 3 weeks was olanzapine and valproic acid. 18 months later, he presented with a second manic episode and consented to enter the study. The patient had stopped the treatment with olanzapine and valproic acid 6 months before the readmission. NMDAR-Abs were detected in his serum; the titer was low (1/20) but was confirmed by a co-localization technique and also in a second determination four months later. At time of serum collection the patient was under treatment with olanzapine, valproic acid and clonazepam. Neurological examination and electroencephalogram (EEG) were normal. Brain magnetic resonance imaging (MRI) with contrast showed insular brain atrophy. Ancillary tests ruled out the presence of neoplasm.

Case 2 was a 30-year-old woman who presented with pseudo-seizures and mystic delusional thinking, thought blockade, catatonic and disorganized behavior and auditory hallucinations. The initial diagnosis was a schizophreniform disorder, but NMDAR-Abs were found in her sera at a high titer (1/320), and they were confirmed in the CSF. A body CT scan revealed an ovarian teratoma, and the diagnosis was changed to NMDAR-E.

Both positive samples for NMDAR-Abs showed its characteristic pattern by immunohistochemistry on rat brain. Case 1 serum reactivity to a neuronal surface antigen was also confirmed by immunofluorescence on cultured neurons.

3.2. Intracellular and synaptic neuronal (onconeural) antibodies

We did not find any IFI pattern compatible with intracellular or synaptic antibodies neither in the FPEPs nor in the HCs. We ruled out, by line immunoblot, the presence of the most frequent onconeural antibodies in all sera.

3.3. Systemic autoantibodies

There was no significant difference between the percentage of ANA positive patients among FPEPs (4.92%) and HCs (4.26%). Autoantibodies to specific antigens were negative in all sera tested.

3.4. Thyroid autoantibodies

We detected a high titer of thyroid autoantibodies only in one case, which was diagnosed with Graves-Basedow disease. This patient was negative for the rest antibodies studied.

4. Discussion and conclusions

In our cohort of 61 patients diagnosed with new-onset psychotic disorders, 2 cases (3.3%) were found to be positive for NMDAR-Abs. No cases with antibodies against other neuronal antigens were detected. One of the positive cases eventually met the criteria for NMDAR-E. The other met the DSM-IVR criteria for a bipolar I disorder and is the first reported case of an HIV-infected patient with psychosis associated with NSAs. The sample included another HIV-positive patient with a schizophreniform disorder diagnosis. We could not identify any clinical features which could distinguish the NMDAR-Abs positive bipolar patient from others without the antibodies (Hammer et al., 2013; Zandi et al., 2011).

To date, no NSAs-positive cases have been described among HIV-infected patients. In fact, NMDAR hyperactivation has been described in HIV infection (King et al., 2010). HIV-associated psychosis and "AIDS mania" are associated with depressed CD4 counts, a past positive psychiatric history, no antiretroviral therapy and dementia (de Ronchi et al., 2000; Harris et al., 1991; Nakimuli-Mpungu et al., 2006). The viral load of our NMDAR-Abs positive

HIV patient was undetectable, and CD4 counts were in the normal range at hospital admissions and one year later.

Autoimmune relapses associated with NSAs in post-herpes virus encephalitis indicate that infection might trigger NMDAR-E (Armangue et al., 2014). Our data do not allow us to rule out that HIV infection had compromised the BBB function (Louboutin and Strayer, 2012), leading to a pathologic effect of NMDAR-Abs (Hammer et al., 2013). Additionally, HIV could favor the activation of B lymphocytes and the production of autoantibodies.

Recent studies describe that the role of NMDAR-Abs in psychosis might be explained by epitope specificity and that subjects with psychosis and IgG against the NR1A subunit alone need to be reclassified as encephalitis (Steiner et al., 2013). In our study, the bipolar patient with anti-NR1 IgG did not meet the diagnostic criteria for encephalitis, suggesting that misdiagnosis might not be a consistent rule.

Recovery of non-encephalitic psychosis has been reported using immunotherapy (Zandi et al., 2011), electroconvulsive therapy (Maneta and Garcia, 2014; Tsutsui et al., 2012) and adjuvant D-serine (Heresco-Levy et al., 2015). In the current study, the HIV and NMDAR-Abs positive patient did not receive immunotherapy because it was not included in the clinical protocols as an evidence-based efficacious treatment.

The finding that a small percentage of acute psychotic cases might have autoimmune reactions against the NMDAR is consistent with other investigations (Steiner et al., 2013; Zandi et al., 2011). Tsutsui et al. (2012) found NMDAR-Abs in 3 out of 5 (60%) patients with a comorbid diagnosis of psychosis and narcolepsy, and considered a shared autoimmunity between these disorders. Our group could not validate these results (Canellas et al., 2014).

In contrast to previous studies with negative results (de Witte et al., 2015; Haussleiter et al., 2012; Masdeu et al., 2012; Rhoads et al., 2011), we analyzed the cases in early stages of psychosis to avoid NMDAR-Abs drop over time, a phenomena already suggested (Gresa-Arribas et al., 2014; Zandi et al., 2011). We also extended the number of NSAs analyzed in comparison with previous studies. Additionally, we did not exclude affective psychosis from our sample because mood changes are common psychiatric symptoms in NMDAR-E (Kayser et al. 2013) and because NMDAR-Abs seropositivity has also been reported in bipolar-spectrum disorders (Bergink et al., 2015).

Some limitations need to be taken into account when considering these results. First, we could not confirm NMDAR-Abs positivity in the CSF of the bipolar patient because he did not consent to perform the lumbar puncture. Nevertheless, cross-validation by immunohistochemistry and co-localization studies confirmed the presence in serum. Second, CSF was not sampled in any patient except in Case 2; therefore, we might have underestimated the frequency of positive sera (Gresa-Arribas et al., 2014). Finally, MRI studies were not performed systematically due to economic restrictions.

All of these results allow for a conclusion that an organ specific autoimmune response cannot be ruled out in some incipient psychotic patients. More intense neurological examination might be needed in these patients to identify the possible cases and perform the necessary ancillary tests to prevent misdiagnosis.

Future studies are needed to ascertain the role of NSAs in the neuropsychiatric involvement of HIV infection. Larger FPEP samples should be analyzed to define a risk phenotype for NSAs seropositivity, and NMDAR epitopes research might help us understand if psychosis and NMDAR-E belong to the same spectrum of disorders.

Conflict of interest statement

This was not an industry supported study.

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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