

# Antineuronal autoimmunity and neuropsychiatric symptoms in HIV infection

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## Anti-N-Methyl-D-Aspartate Receptor Encephalitis (NMDAR-E)

- Immune-mediated encephalitis associated with antibodies in serum and cerebrospinal fluid (CSF) against the GluN1 subunit of the N-methyl-D-aspartate receptor (NMDAR).
- Antibodies bind to NMDARs and cause a decrease in NMDAR cluster density in post-synaptic neuronal membranes. (Dalmau et al., 2008; Le Guen et al., 2015; Moscato et al., 2014).
- The antibodies mediate internalization that is reverted using immunotherapy (Hughes et al., 2010; Masdeu, 2016).
- Up to 70% patients with NMDAR- E are initially evaluated by psychiatrists (Dalmau et al., 2008, 2011; Deakin et al., 2014; Vincent et al., 2011).

# Neuronal Surface Autoantibodies (NSAs) in psychotic patients populations

Authors	Cases studied	Isotype	Epitopes	Technique	Positive psychosis	Positive controls
Zandi et al., 2011	FPE	IgG	NMDAR NR1 and NR2B VGKC	CBA	3/46 (6.5%) anti-NMDAR 1/46 (2.2%) anti-VGKC	No controls
Tsutsui et al., 2012	SQZ SAD	IgG	NMDAR	Non specified	4/51 (7.8%)	No controls
Dickerson et al., 2012	Manic episodes	IgG	NMDAR: NR2A /2B	enzyme-linked immunosorbent assay (Elisa)	60 patients with elevated Ab	295 other psychiatric diagnosis 170 healthy controls
Steiner et al., 2013	Acute SQZ	IgG, IgM, IgA	NMDAR: NR1a; NR1a/NR2b AMPAR	CBA	12/121 (9.9%)	1/230 (0.4%)
Hammer et al., 2013	SQZ SAD	IgG, IgM, IgA	NMDAR: NR1; NR1/NR2b	CBA	93/1081 (8.6%) anti-NR1	143/1325 (10.8%) anti-NR1
Bergink et al., 2015	Postpartum psychosis	IgG	NMDAR: NR1 and NR2B	Immunohistochemistry CBA Nueronal cultures	2/96 (2.1%)	0/64
Pathmanandavel et al., 2015	FPE in children	IgG, IgM, IgA	D2R NMDAR: NR1	CBA Nueronal cultures	6/43 (13.9%); anti-NR1 (IgG, IgM, IgA) 3/43 (6.9%); anti-D2R (IgG, IgM)	0/43
Zandi et al., 2014	Acute psychosis	IgG	NMDAR	CBA	18/18	No controls
Lennox et al., 2017	FPE	IgG	NMDAR: NR1 y NR2B VGKC GABAR AMPAR	CBA Radioimmunoassay	20/228 (8.8%): all Ab 7/228 (3%) anti-NMDAR	0/105: anti-NMDAR 4/105 (3.8%): rest of Ab

FPE: First Psychotic Episode  
 SAD: Schizoaffective Disorder  
 CBA: Cell Based Assay

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### Short Communication

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



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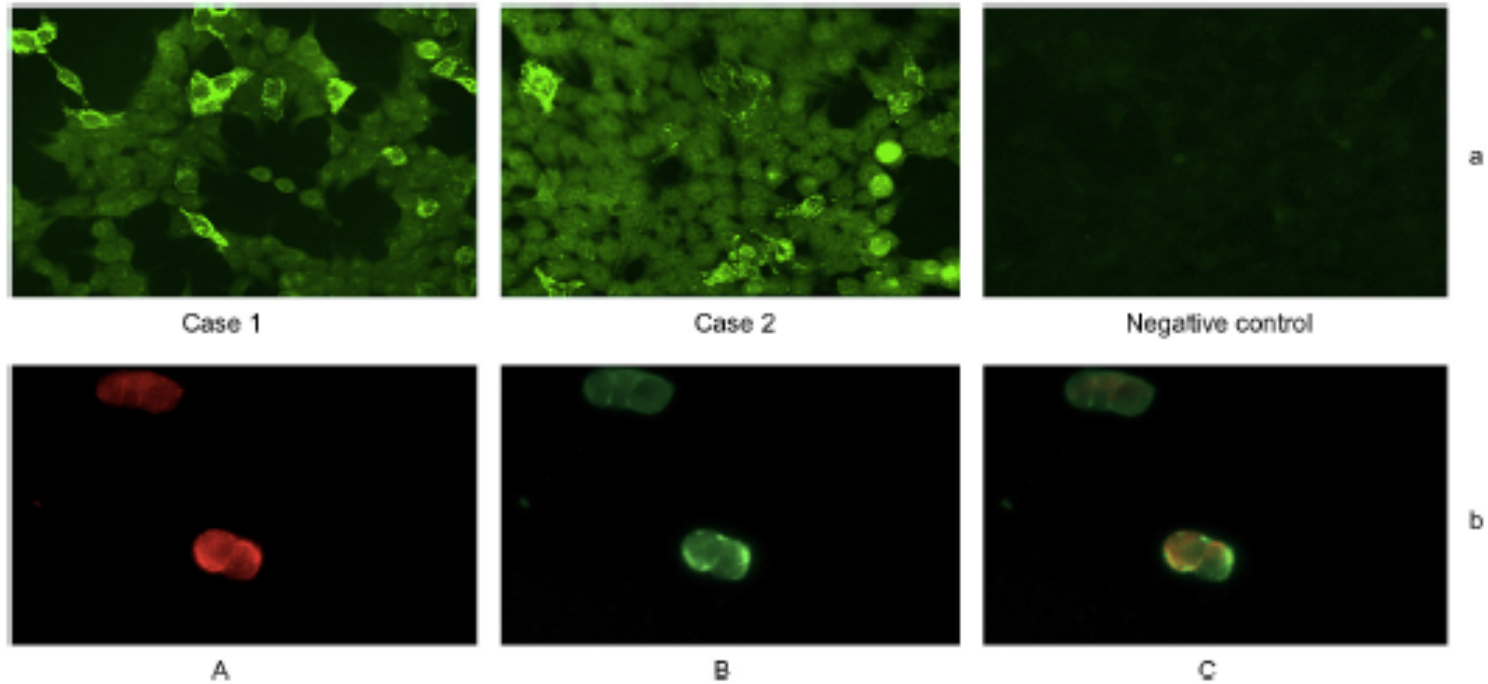
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# Hypothesis and Objectives

- To evaluate if a percentage of acute psychotic cases have autoimmune reactions against the NMDAR, as previous investigations have reported (Steiner et al., 2013; Zandi et al., 2011).
- The main goal of our study was to evaluate the prevalence of NSAs in first psychotic episode patients.
- Specifically, we analyzed antibodies against:
  - NMDAR (NR1),
  - $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) type 1 or 2,
  - gamma-aminobutyric acid receptor (GABAR) type B
  - proteins associated with the Voltage-gated potassium channels (VGKC):
    - leucine-rich glioma-inactivated 1 (LGI1)
    - contactin associated protein 2 (CASPR2).

# Results



**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).

# Clinical features of the 2 anti-NMDAR positive cases

G	Age	Psychotic Symptoms	Ancillary tests	NMDAR antibodies	Comorbidity	Psychiatric familial history	Diagnosis	Treatment	Prognosis
M	22	Hyperkinetic behaviour Insomnia Accelerated and Disorganized thinking Verbosity Delusions Auditory hallucinations	Blood tests Brain CT Brain MRI Testicular sonography Thorax, abdomen and pelvis CT	1/20 Serum	HIV Cannabis	Nes	Bipolar I Disorder	Olanzapine Valproic acid Clonazepam  lopinavir and ritonavir etravirine	Cronic course with relapses
F	30	<i>Déjà-vu</i> phenomenon Auditory hallucinations Disorientation Mystic delusional thinking Thought blockade Bradifrenia Catatonic and disorganized behavior Inappropriate mood Memory alterations	Analítica Brain CT EEG Brain MRI CSF tests	1/320 Serum CSF	Ovarian teratoma Cannabis	No	Schizophreniform disorder misdiagnosis  NMDAR-encephalitis	Levitracetam Aripiprazol Valproic acid  Prednisone Surgery	Remission and recovery

# Discussion

- An organ specific autoimmune response cannot be ruled out in some incipient psychotic patients (Kaneko et al, 2018).
  - 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).
- Future studies are needed to ascertain the role of NSAs in the neuropsychiatric involvement of HIV infection.

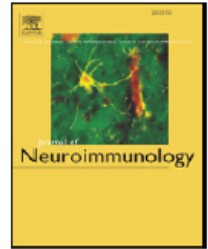




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Short communication

# Neuronal surface antibodies in HIV-infected patients with isolated psychosis



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## Background

- HIV infected macrophages generate neurotoxic factors that cause apoptosis – exhibition of neuronal antigens (Aksenova et al., 2009; Eugenin et al., 2011; O'Donnell et al., 2006).
- Activated B Lymphocytes in HIV (Louboutin y Strayer, 2012).
- Increased BBB permeability in HIV (Louboutin y Strayer, 2012).
- Recent descriptions of NSA-related autoimmune relapses in encephalitis caused by herpes virus simplex (HVS) (Armangue et al., 2014).
- GABAR type A antibody-associated encephalitis-HIV (VHS) (Spatola et al., 2017).

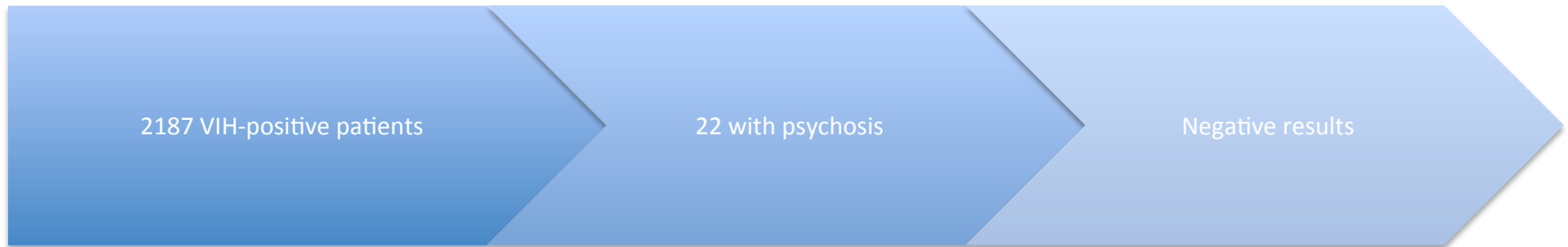
## **Hypothesis and Objectives**

- HIV infection might enable an altered immune response and lead to autoimmunity, as happens with HVS.
- Psychosis could be an autoimmune mediated neuropsychiatric manifestation in some HIV-infected patients.

## **Hypothesis and Objectives**

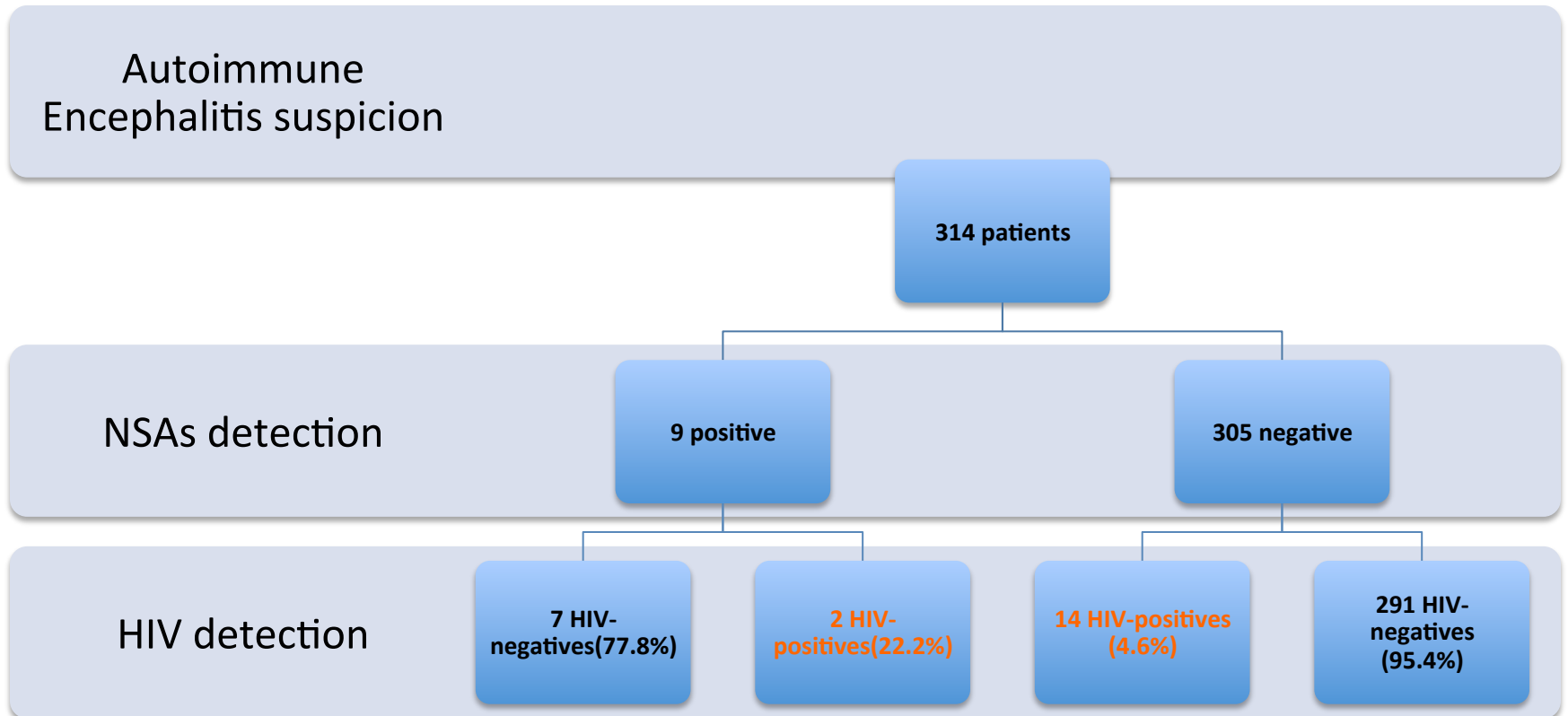
- The aim of the present work was to evaluate the prevalence of NSAs in HIV-infected patients whose only neurological manifestation was psychosis.
- We analyzed antibodies against:
  - NMDAR (NR1),
  - AMPAR type 1 or 2,
  - GABAR type B
  - Proteins associated with VGKC:
    - LGI1
    - CASPR2

## Results



Patients were recruited prospectively from January 2014 to June 2015, at the Infectious Diseases Unit or the Psychiatry Department of Hospital Universitari Son Espases.

# Results



Results of the retrospective cohort (november 2012 – june 2016)

## Results

- The overall percentage of HIV infection among NSA-positive patients was 22.22% versus 4.59% within NSA-negative samples. There is a trend towards significance in the association ( $p = 0.07$ ) (Fisher's exact test).

## Results

- In the retrospective cohort:
  - 2 patients HIV-positive presented antibodies against NMDAR:
    - Bipolar I disorder
    - Autoimmune cerebellar disease



## Discussion

- A limitation of our study is the lack of CSF samples, due to ethical reasons. These samples are more sensitive to NMDAR-Abs testing (Gresa-Arribas et al., 2014).
- Antibodies titers may spontaneously decrease over time whereas most patients were not recruited at an early course of psychosis and only three patients presented acute symptoms when blood was taken.

## Discussion

- In spite of our negative results the positivity for NMDAR-Abs found in CSF of a HIV-positive patient with a cerebellar disease and in serum of a psychotic HIV-infected non-encephalitic patient, might still suggest an association between HIV neuropsychiatric manifestations and NSA.
- Wider studies, including patients with other neurological diseases NSA-related, are needed in order to ascertain the role of NSA among HIV-positive patients.

*Gràcies*