Psychiatry Research 259 (2018) 460–462

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

No neuronal autoantibodies detected in plasma of patients with a bipolar I disorder

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ARTICLE INFO

Keywords:
Bipolar disorder
Autoimmune
Mania
Antibodies
Encephalitis
Immunology

ABSTRACT

A subpopulation of patients with bipolar disorder type I (BD-I) might suffer from undiagnosed autoimmune encephalitis. We tested plasma of 104 BD-I patients with a current or recent manic episode in the past 2 years for the presence of neuronal autoantibodies using immunohistochemistry, immunocytochemistry and cell-based assay (CBA). Neuronal antibodies were not detected in any of the BD type I. This finding suggests that the frequency of an undiagnosed autoimmune encephalitis in patients with BD I is less than 1%. However, these findings need to be confirmed in cerebrospinal fluid and/or blood of acutely ill manic patients.

1. Introduction

Accumulating evidence suggests a role for the immune system in the pathogenesis of bipolar disorder (BD). A potential mechanism of this relationship is autoimmunity caused by autoantibodies against neuronal antigens resulting in autoimmune encephalitis. Depending on the neuronal antigen that is targeted by these antibodies a specific syndrome can develop that can include prominent psychiatric symptoms. The best example is anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis. Patients with this disease usually develop severe psychiatric symptoms in the first stage after onset. These symptoms can resemble a bipolar like manic-psychotic episode or schizophrenia-like psychotic disorder (Titulaer et al., 2013). Most patients develop additional overt neurologic symptoms, including movement disorders, seizures and autonomic dysfunction. However, a minority of patients presents with isolated psychiatric symptoms (Höftberger et al., 2015; Kayser et al., 2013). It has therefore been suggested that a proportion of patients with an autoimmune encephalitis may have been misdiagnosed with having a bipolar disorder type I (BD-I) or schizophrenia, which is supported by various case reports (Parrat et al., 2009 Choe et al., 2013 Kuo et al., 2012 Mierlo et al., 2015). How frequently this occurs and whether testing for neuronal antibodies should be added to the routine diagnostic work-up of psychiatric patients are therefore clinically relevant questions. To answer these questions, several cohorts of patients with psychiatric disorders have been tested for the presence of neuronal autoantibodies. For schizophrenia the results are inconsistent, but overall the seroprevalence of pathogenic neuronal autoantibodies seems rare (0–1.5%) when the test results are validated by multiple techniques (Pearlman and Najjar, 2014; de Witte et al., 2015). In postpartum affective psychosis 4% of the patients are positive for neuronal auto-antibodies (Bergink et al., 2015). The seroprevalence of neuronal auto-antibodies in BD is unclear still, despite the fact that mood disturbances are frequently reported in autoimmune encephalitis (Pearlman and Najjar, 2014; León-Caballero et al., 2015). Two studies included 'affective disorder patients' in their sample and reported an increased seroprevalence of neuronal autoantibodies (Hammer et al., 2014; Zandi et al., 2011). However, these studies did not specify the results for patients with BD-I and did not include validation steps of the test results which increase the specificity of antibody testing (de Witte et al., 2015; Gresa-Arribas et al., 2014). In addition, Dickerson et al., described increased levels of serum antibodies to the NR2 peptide in mania. The specificity for the NMDA receptor and the pathogenicity of these antibodies in this assay are not clear. We therefore set out to analyse the frequency of neuronal autoantibodies in a cohort of 104 patients with BD type I.

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https://doi.org/10.1016/j.psychres.2017.10.043
Received 6 June 2017; Received in revised form 25 October 2017; Accepted 31 October 2017
Available online 02 November 2017
0165-1781/

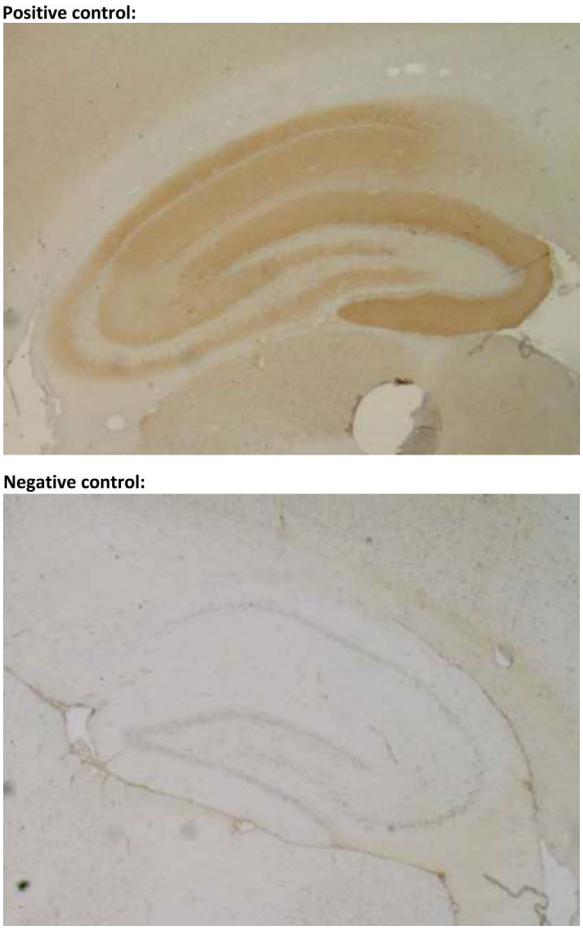

Fig. 1. Positive control: Negative control.

2. Methods

The subjects are all of Dutch ancestry and part of the Dutch Bipolar Cohort study described in Vreeker et al. (2016). This study was approved by the medical ethical committee and all participants gave written informed consent. The sample met the following criteria: diagnosis of bipolar disorder type I, confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I). Plasma was collected as part of the assessments of this study and stored at −80 Celsius until further analyses. From the cohort, we selected 104 patients with a current or recent manic episode in the past 2 years (n = 104). The sample size was based on the reported prevalence of 4% autoimmune encephalitis in postpartum psychosis (Bergink et al., 2015) and the preselection based on presumed likelihood of detecting undiagnosed encephalitis specifically in patients with a recent manic episode. The screening methods have been described in detail before (Bergink et al., 2015; Gresa-Arribas et al., 2014). In short, all samples were tested using immunohistochemistry on sagittal sections from rat brain fixed for 1 h in 4% PFA (1:200). When immunohistochemistry showed neuronal staining or the results were inconclusive, samples were analyzed by immunocytochemistry using live hippocampal neurons as well as cell-based assays (CBA) for NMDAR and AMPA receptor (AMPAR) (Bergink et al., 2015; Gresa-Arribas et al., 2014). At least one serum of a patient with definitive NMDA-receptor encephalitis was used as positive control in every batch (see Fig. 1).

3. Results

We analyzed 104 patients with the following demographics: 58% female; mean age 44.3 (SD = 11.6) years; mean duration of illness 15.4 (SD = 10.0) years; mean time since last manic episode 6.61 (SD = 7.64) months. Thirty-six percent had manic symptoms at the moment of drawing blood. Analysis for neuronal antibodies was negative in 99 patients. Plasma of one patient showed neuropil staining and the results of four patients were inconclusive. These five samples were tested by immunocytochemistry and CBA and tested negative.

4. Discussion

In this study we did not detect plasma neuronal autoantibodies in a cohort of 104 BD-I patients with a current or recent manic episode. This finding suggests that the frequency of an undiagnosed autoimmune encephalitis in patients with BD I with the currently available techniques, is less than 1% (95% CI 0.0–3.5%). Strengths of this study are the comprehensive characterization of the patients, an unbiased screening for neuronal autoantibodies using immunohistochemistry, and the use of several techniques to increase the specificity of antibody testing. Limitations of our study includes the modest sample size with lower bound detection level of roughly 1% and the chronicity of the illness. It is of note that we analyzed plasma whereas cerebrospinal fluid (CSF) samples are superior, because in some cases neuronal antibodies may be detectable in CSF only and not be present in blood (Gresa-Arribas et al., 2014). In addition, neuronal antibodies that specifically recognize human antigens might be missed since we performed our stainings on rat brain slices. However, previously unknown neuronal antibodies, such as NMDAR, AMPAR, Caspr2, DPPX and GABABR, have been identified this way and this discovery pathway is not exhausted yet, still leading to newly discovered antibodies. Furthermore, we cannot exclude that autoantibodies are only temporarily detectable in blood of (a subset of) acutely ill first episode BD patients, since antibodies titer can drop below detection limit after the acute phase of the disease (Gresa-Arribas et al., 2014). To fully address this, future research should be directed towards investigating neuronal autoantibodies in CSF and blood of acutely first episode manic patients. In addition, developing new techniques for detection of novel neuronal antibodies are warranted in future research.

Acknowledgments

We thank Mariska M. Nagtzaam and Esther S. Hulsenboom for their excellent technical assistance.

Formatting of funding sources

This project is supported by a 2014 NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation (grant no. 22979), and a Memorabel fellowship by the Netherlands Organisation for Scientific Research (NWO, Titulaer). The Dutch Bipolar Cohort study was funded by NIH/NIMH R01 MH090553 (Ophoff). These organizations had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. The authors have no financial relationships to disclose.

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