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Anti-neuronal anti-bodies in patients with early psychosis

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ABSTRACT

It may be challenging to distinguish autoimmune encephalitis associated with anti-neuronal autoantibodies from primary psychiatric disorders. Here, serum was drawn from patients with a first-episode psychosis ($n = 70$) or a clinical high-risk for psychosis ($n = 6$) and controls ($n = 34$). We investigated the serum prevalence of 24 anti-neuronal autoantibodies: IgG antibodies for *anti-N*-methyl-D-aspartate-type glutamate receptor (*anti*-NMDAR), glutamate and γ-aminobutyric acid alpha and beta receptors (GABA-a, GABA-b), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), glycine receptor (GlyR), metabotropic glutamate receptor 1 and 5 (mGluR1, mGluR5), *anti*-Tr/Delta/notch-like epidermal growth factor-related receptor (DNER), contactin-associated protein-like 2 (CASPR2), myelin oligodendrocyte glycoprotein (MOG), glutamic acid decarboxylase-65 (GAD65), collapsin response mediator protein 5/crossveinless-2 (CV2), aquaporin-4 (AQP4), *anti*-dipeptidyl-peptidase-like protein-6 (DPPX), type 1 anti-neuronal nuclear antibody (ANNA-1, Hu), Ri, Yo, IgLON5, Ma2, zinc finger protein 4 (ZIC4), Rho GTPase-activating protein 26, amphiphysin, and recoverin, as well as IgA and IgM for dopamine-2-receptor (DRD2). *Anti*-NMDA IgG antibodies were positive with serum titer 1:320 in one patient with a clinical high risk for psychosis. He did not receive a diagnosis of encephalitis after comprehensive neurological evaluation. All other antineuronal autoantibodies were negative and there were no additional findings with immunohistochemistry of brain issues.

1. Introduction

Anti-N-methyl-D-aspartate-type glutamate receptor (*anti*-NMDAR) encephalitis was originally identified in young women with ovarian teratoma who had simultaneous prominent psychiatric manifestations. Later, it was noted that *anti*-NMDAR encephalitis can manifest without cancer (Dalmau et al., 2008), and some cases present with prominent psychotic symptoms (Kayser and Dalmau, 2016; Pollak et al., 2016). Clinically, patients with psychosis and IgG *anti*-NMDAR antibodies are characterized by acute or subacute onset, catatonic symptoms, epilepsy and movement disorders including stereotypies, perseveration, and dystonia, or fever. Several other anti-neuronal antibodies targeting important ion channels, receptor-associated or regulatory molecules have been reported in some patients with psychosis and in patients with encephalitis presenting psychotic symptoms (Armangue et al., 2014; Heine et al., 2015; Leypoldt et al., 2015; Pollak et al., 2016). The prevalence of these antibodies in patients with an early psychosis remains open. The identification of encephalitis in patients with early psychosis is crucial, as over 75% of patients with classic *anti*-NMDAR encephalitis have substantial recovery with specific treatments, while antipsychotic treatment is not effective in these patients (Kayser and Dalmau, 2016).

In a sample of patients with a first-episode psychosis (FEP) or a clinical high-risk for psychosis (CHR) and controls, we investigated the prevalence of 24 anti-neuronal antibodies that have been associated with autoimmune encephalitis.

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2. Methods

2.1. Clinical study protocol and assessment

The study started in November 2010. FEP and CHR patients (age 18 to 40 years) were recruited from the catchment area of the Helsinki University Hospital, city of Hyvinkää, and City of Helsinki, Finland. The inclusion criteria for the FEP patients were a score of at least 4 in Unusual thought content or Hallucinations in the Brief Psychiatric Rating Scale — Extended (BPRS-E) (Ventura et al., 1993) and being fluent in Finnish. Patients with substance-induced psychotic disorders and psychotic disorders due to a general medical condition were excluded. Baseline assessment was conducted as soon as the patient had entered treatment and was able to give informed consent according to the treating personnel. Follow-ups included structured diagnostic interviews and a review of patient charts and were conducted at two and 12 months. CHR was assessed with the Structured Interview for Prodromal Syndromes (Miller et al., 2003), and the Criteria of Prodromal Syndromes (COPS) was used to define CHR status.

Controls, matched by age, sex and region of residence, were identified from the Population Register Center and assessed at baseline and 12 months with the same protocol as the patients. The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The study protocol was approved by the Ethics Committee of the Helsinki University Hospital and by the institutional review boards of the National Institute for Health and Welfare, Helsinki, Finland. Research permissions were obtained from the Helsinki University Hospital and the Department of Psychiatry, and the Helsinki City Health Department. All participants gave a written informed consent.

2.2. Laboratory analytical methods

2.2.1. Blood sampling

A fasting blood sample was collected between 8 am and 10 am. Serum and plasma samples were immediately aliquoted and stored at −80 °C with a maximal storage of 4 years. The frozen samples were all sent at the same time for analysis.

2.2.2. Selection and testing of the antibodies

We screened for anti-brain antibodies that had been described in either sporadic primary psychosis or in primary encephalitis with psychotic symptoms. We took into account anti-brain antibodies that were of potential interest based on genetic association studies in psychosis (Gatt et al., 2015; Nie et al., 2015). Based on a literature review (OM, JS, BT), we selected isotype IgG antibodies for NMDAR, glutamate and γ-aminobutyric acid alpha and beta receptors (GABA-a, GABA-b), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA), glycine receptor (GlyR), metabotropic glutamate receptor 1 and 5 (mGluR1, mGluR5), *anti*-Tr/Delta/notch-like epidermal growth factor-related receptor (DNER), contactin-associated protein-like 2 (CASPR2), myelin oligodendrocyte glycoprotein (MOG), glutamic acid decarboxylase-65 (GAD65), collapsin Response Mediator Protein 5/Crossveinless-2 (CV2), aquaporin-4 (AQP4), *anti*-dipeptidyl-peptidase-like protein-6 (DPPX), type 1 anti-neuronal nuclear antibody (ANNA-1, Hu), Ri, Yo, IgLON5, Ma2, zinc finger protein 4 (ZIC4), Rho GTPase-activating protein 26, amphiphysin, and recoverin, as well as IgA and IgM antibodies for dopamine-2-receptor (DRD2).

Antibody analysis was performed blind to case/control status with an indirect immunofluorescence test of the immunoglobulin (Ig) IgG isotype, and additionally, IgA and IgM for DRD2. Sera were tested for the presence of antibodies using biochip mosaics of frozen brain sections (rat, monkey) and transfected HEK293 cells expressing the respective recombinant target antigens (Euroimmun, Germany) as previously described (Probst et al., 2014). Samples were classified as positive or negative based on fluorescence intensity of the transfected cells in direct comparison with non-transfected cells and control samples. Endpoint titers refer to the last dilution showing a detectable degree of fluorescence, with 1:10 being the cut-off for positivity. We report immunohistochemistry findings without corresponding positivity in the fixed cell-based assays, as these could have clinical relevance.

2.3. Statistical analysis

We calculated descriptive statistics for sociodemographic and clinical measures using SPSS Statistics for Windows, Version 22.0.

3. Results

The sociodemographic and clinical characteristics of the sample are described in Table 1. The only *anti*-NMDAR positive patient (serum titer 1:320) was a CHR patient with a major depressive disorder. At one year, he had not converted to psychosis (See Table 2) but still had *anti*-NMDAR autoantibodies (serum titer 1:100) in his blood. After a thorough evaluation, clinical treatment of encephalitis was not indicated. All other cell-based assays were negative and there were also no additional findings with immunohistochemistry of brain tissues. Additionally, one patient with a brief psychotic episode was sent for neurological evaluation due to a clinical suspicion of encephalitis. In the clinical laboratory testing, he was found to have marginally elevated serum anti-glycine receptor antibodies (titer 1:10). Antibodies were not found in his cerebrospinal fluid and encephalitis and neurological diseases were excluded. At the follow-up of 12 months, the patient was in full remission (Table 2).

4. Discussion

This is the first study to report a person with a CHR for psychosis having an increased level of *anti*-NMDAR antibodies. All other mainly FEP patients showed a negative finding in the tested 24 anti-neuronal antibodies.

Our results further strengthen the previous view that if brain autoantibodies are systematically screened in patients primarily treated for a psychiatric diagnosis, sporadic cases screen antibody NMDAR positive (Kayser and Dalmau, 2016). Some samples including FEP patients have not detected NMDAR antibodies (Masdeu et al., 2012; Masopust et al., 2015), but others report individuals with positive findings (Lennox et al., 2017; Pathmanandavel et al., 2015; Steiner et al., 2013; Zandi et al., 2011). In the largest study so far (228 cases and 105 healthy controls) seven (3%) patients but no controls had NMDAR antibodies (Lennox et al., 2017) However, the clinical relevance of the positive findings has to be confirmed by a thorough examination, and in this sample, none of the patients had a clinical diagnosis of an encephalitis. Other than *anti*-NMDAR antibodies, autoantibodies detected in autoimmune encephalitis seem to remain negative in patients with isolated early psychotic symptoms. Approximately 80% of adults with *anti*-NMDAR antibody encephalitis initially manifest behavioral and psychiatric symptoms (Kayser and Dalmau, 2016). The interest in *anti*-NMDAR antibodies has been strengthened by increased knowledge about the role of NMDAR in producing psychosis-like behavior and being involved in brain processes of etiological importance in psychosis (Carvajal et al., 2016; Pollak et al., 2016; Rosenthal-Simons et al., 2013). At the same time, isolated psychiatric symptoms, i.e. psychiatric symptoms without neurological symptoms, have been present in some patients with *anti*-NMDAR encephalitis (Kayser et al., 2013). It is concluded that diagnostic evaluation in FEP can be focused to those presenting specific neurological symptoms (Kayser and Dalmau, 2016).

The strengths of the study include inclusion of FEP and high-risk patients, comprehensive selection of specific brain receptor antibodies, and a careful psychiatric evaluation. A limitation of the study was that no information about non-participants was available to evaluate the representativeness of the sample. Cerebrospinal fluid analysis, which

Table 1
Characteristics of the sample with 76 cases and 34 controls.

Characteristic	Patients, n = 70	Clinical high risk, n = 6	Controls, n = 34
Age, mean ± standard deviation	26.3 ± 5.8	25.4 ± 3.5	28.8 ± 6.5
Male, n (%)	46 (65.7%)	5 (83.3%)	19 (55.9%)
Main lifetime diagnosis, n (%)			
Schizophrenia	42 (60.0%)	0	0
Schizoaffective disorder	2 (2.9%)	0	0
Bipolar disorder	6 (8.6%)	0	0
Major depressive disorder	2 (2.9%)	1 (16.7%)	6 (17.6%)
Psychosis NOS	13 (18.6%)	1 (16.7%)	0
Other psychotic disorder	5 (7.1%)	0	0
Other psychiatric diagnosis	0	4 (66.7%)	5 (14.7%)
Brief Psychiatric Rating Scale score at baseline, mean ± standard deviation	44.5 ± 10.4	49.0 ± 6.7	25.5 ± 2.9
Social and occupational functioning assessment scale score (Goldman et al., 1992) at baseline, mean ± standard deviation	39.3 ± 9.2	50.3 ± 7.1	87.1 ± 6.4
Duration of antipsychotic treatment, median, days	27	28	NA

would confirm a pathologic process (Kreye et al., 2016), was not available for patients who did not have antibodies in peripheral blood, and therefore, false-negative findings are possible. The testing was performed using fixed cells; testing on living cells might be more sensitive (Gresa-Arribas et al., 2014) but is difficult to standardize and lacks suitability for large-scale analyses. The validation of these antibodies has been done only for neurological purposes. Future research should explore the possibility that there are other anti-neuronal autoantibodies that are specifically related to psychotic disorders.

Table 2
Case reports for the two patients where NMDA encephalitis was suspected.

Case 1
Case 1 was a 23-year old university student with a history of recurrent major depressive episodes. He was referred to the study from outpatient care as a clinical high-risk patient. He had experiences of paranoid fears and illusions, while the most difficult symptoms for the patient were depression, anxiety, insomnia, and a rapid onset of difficulties in thinking and concentrating. He was nonsmoking and had no history of alcohol or other substance abuse. He met the criteria for Attenuated Positive Prodromal Syndrome by receiving a score of 4 in suspiciousness and persecutory ideas. Baseline Social and occupational functioning assessment scale score was 45, and depressive symptoms were severe (Beck Depression Inventory score 42). The sample was positive for *anti*-NMDAR autoantibodies with serum titer 1:320. Based on this finding, we contacted the treating personnel and the patient was sent for neurological examination one year after the *anti*-NMDAR positive serum sample had been taken. Serum *anti*-NMDAR autoantibodies were still present with titer 1:100, but antibodies were not found in his cerebrospinal fluid and encephalitis and other neurological diseases were excluded in the examination. Any etiology for the presence of *anti*-NMDAR autoantibodies was not found. In the 1-year follow-up, he no longer met clinical high-risk criteria but had a diagnosis of major depressive disorder, with a severe major depressive episode without psychotic features. His level of functioning was low and he had not been able to continue his studies. He continued to have severe depressive and anxiety symptoms as well as insomnia despite adequate pharmacological and psychological treatment.
Case 2
Case 2 was a 34-year-old technician with no previous treatment contact for mental disorders. Psychotic symptoms, including delusions, disorganized behavior and marked variation between agitation and motor retardation developed within a few days. Low-grade fever and headache had preceded other symptoms a few days earlier. Treatment was started at a neurological department, where the patient was found to have marginally elevated serum anti-glycine receptor antibodies (titer 1:10). Antibodies were not found in his cerebrospinal fluid and thus, encephalitis and other neurological diseases were excluded. C-reactive protein, lipid, glucose and liver function tests were normal. Laboratory tests for drug use were negative, and the patient had no history of smoking or current alcohol use. Intensity of delusions at the most severe phase of the illness was 7 (extremely severe) and intensity of hallucinations 5 (moderately severe) based on baseline Brief Psychiatric Rating Scale interview. Treatment was continued at a psychiatric department, and psychotic symptoms resolved within a month. At the two-month follow-up, the following diagnoses were assigned: a brief psychotic disorder, with simultaneous social phobia (current) and previous alcohol abuse, in full remission. At one year, the patient had returned to work in full remission of psychotic symptoms.

Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

OM, JS, TR, TK, TM, ML, and ER contributed to design and sampling of the FEP and CHR samples and controls. OM, JS and MS designed the study and wrote the protocol concerning autoantibodies. BT and WS were responsible for the analysis of the antibodies. OM and JS managed the literature searches. OM undertook the statistical analysis, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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