Seroprevalence survey of selective anti-neuronal autoantibodies in patients with first-episode schizophrenia and chronic schizophrenia

Chia-Hsiang Chen a,b,⁎, Min-Chih Cheng c, Chih-Min Liu d,e, Chen-Chung Liu d, Ko-Huan Lin f, Hai-Gwo Hwu d

a Department of Psychiatry, Chang Gung Memorial Hospital, Linkou, Taoyuan, Taiwan
b Department and Graduate Institute of Biomedical Sciences, Chang Gung University, Taoyuan, Taiwan
c Department of Psychiatry, Yuli Mental Health Research Center, Yuli Branch, Taipei Veterans General Hospital, Hualien, Taiwan
d Department of Psychiatry, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan
e Graduate Institute of Brain and Mind Sciences, College of Medicine, National Taiwan University, Taipei, Taiwan
f Department of Psychiatry, Hualien Armed Forces General Hospital, Hualien, Taiwan

ARTICLE INFO

Article history:
Received 8 January 2017
Received in revised form 1 March 2017
Accepted 5 March 2017
Available online xxxx

Keywords:
Autoimmune encephalopathy
Anti-neuronal autoantibodies
Anti-NMDA receptor encephalitis
First-episode schizophrenia
Chronic schizophrenia
Differential diagnosis

ABSTRACT

Autoimmune encephalopathy caused by autoantibodies against neuronal cell-surface proteins in the brain is a newly discovered disease category associated with psychiatric disorders. Correct diagnosis of this condition relies on the detection of specific autoantibodies in the blood or cerebral spinal fluid in addition to the clinical presentations. The study aimed to understand the seroprevalence of selective anti-neuronal autoantibodies in our patients with schizophrenia. First, we screened for six anti-neuronal autoantibodies in an archived blood sample collected from patients with the first-episode schizophrenia. The six autoantibodies including antibodies against N-methyl-D-aspartate (NMDA) receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors 1 and 2, and γ-butyric acid receptor type B1 (GABARB1), leucine-rich glioma inactivated-1 (LGII) protein, and contactin-associated protein-like 2 (CASPR2) protein. A total of 78 plasma samples (46 males and 32 females) were investigated; however, no positive case was identified. In this second study, we screened anti-NMDA receptor autoantibodies in a blood sample of 234 patients with chronic schizophrenia (133 females and 101 males) including 48 patients defined as treatment resistance. None of this sample was detected as positive. The negative findings in this study suggest that the seroprevalence of autoantibodies against neuronal surface proteins might be low in patients diagnosed with schizophrenia.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

Schizophrenia is a devastating chronic mental disorder that affects approximately 1% of the general population. It is also a complex disorder with high clinical and etiological heterogeneity. Immune system dysfunction is an important factor associated with the pathogenesis of schizophrenia. Several epidemiological studies have demonstrated that patients with autoimmune diseases had increased the risk of schizophrenia and other psychiatric diagnoses, and patients with schizophrenia had a higher prevalence of autoimmune diseases (Benros et al. 2014; Chen et al. 2012). Furthermore, increased prevalence of multiple autoantibodies was reported in a systematic and quantitative review of blood autoantibodies in schizophrenia (Ezeoke et al. 2013). Together, these data suggest autoimmune diseases are associated with the pathogenesis of schizophrenia and its related disorders.

Recently, several new autoantibodies against neuronal cell-surface proteins and synaptic proteins were detected in patients presenting with a range of acute neuropsychiatric features, representing a new type of autoimmune encephalitis associated with psychiatric disorders (Lancaster 2016; Linnoila et al. 2014). The correct diagnosis of this condition relies on the serological tests to detect the autoantibodies against neuronal surface proteins, which are only available recently. We were interested to know whether some of our first-episode schizophrenia might be due to this condition. Hence, we conducted a serological screening of autoantibodies against six neuronal cell-surface proteins in a sample of archived plasma from 78 patients diagnosed with first-episode schizophrenia using a commercially available indirect immunofluorescence assay. The six autoantibodies including antibodies against N-methyl-D-aspartate (NMDA) receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors 1 and 2, and γ-butyric acid receptor type B1 (GABARB1), leucine-rich glioma inactivated-1 (LGII) protein, and contactin-associated protein-like 2 (CASPR2) protein.

Among these autoimmune encephalopathies associated with psychiatric condition, anti-NMDA receptor encephalitis is the most well-studied in recent years. It is characterized by the presence of IgG

http://dx.doi.org/10.1016/j.schres.2017.03.012
0920-9964/© 2017 Elsevier B.V. All rights reserved.

Please cite this article as: Chen, C.-H., et al., Seroprevalence survey of selective anti-neuronal autoantibodies in patients with first-episode schizophrenia and chronic schizophrenia, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.03.012
antibody against the NR1 subunit of NMDA receptor in the affected patients. Several studies reported the detection of anti-NMDA receptor autoantibodies in patients with acute psychosis and schizophrenia-related diagnoses (Wandinger et al. 2011). The disease can occur in patients of all ages, and more predominantly in female patients. Patients with anti-NMDA receptor encephalitis usually have prodromal symptoms of a headache or fever, followed by the quick development of consciousness level change and a wide spectrum of psychiatric symptoms such as agitation, irritability, anxiety, insomnia, hallucinations, delusions, aggression, and bizarre behaviors. A wide range of neurological symptoms may concur with or follow the appearance of psychiatric symptoms, including movement abnormalities, autonomic dysregulation, seizure attacks, and loss of consciousness (Dalmau et al. 2011; Leyboldt et al. 2015). It is suggested that anti-NMDA receptor encephalitis should be considered as an important differential diagnosis of patients with a primary psychiatric diagnosis (Barry et al. 2015; Barry et al. 2011; Chapman and Vause 2011). Early recognition of this condition and timely treatment with immunotherapy will have a better outcome and even recovery in affected patients (Titulaer et al. 2013).

We were interested to know whether some of the patients diagnosed with chronic schizophrenia or even those who were refractory to psychopharmacotherapy might be associated with anti-NMDA receptor encephalopathy. Hence, in the second study, we conducted a seroprevalence survey of anti-NMDA receptor autoantibodies in patients with chronic schizophrenia, including some who were refractory to antipsychotic treatment.

2. Methods

2.1. Subjects

For the first-episode schizophrenia study, the patients came from two research projects of the early course of schizophrenia (Liu et al. 2013; Liu et al. 2011). Both projects have been approved by the institutional review board of the study hospital. All adult participants voluntarily provided their written informed consents and minors gave written assent with informed consent from their parents after full explanation of the study procedures to them. We recruited the patients between 16 and 45 years old, who newly developed the first episode of full-blown psychosis which met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for schizophrenia or schizophreniform disorder. Excluded from the study were those who had mood episodes, current use of the psychoactive substance, a history of central nervous system illness or traumatic brain injury, and an intelligent quotient (IQ) below 70. A total of 78 patients were recruited, and they received blood withdrawal and plasma extraction during acute phase of illness. The plasmas were stored at the −80 °C refrigerator. There were 32 male and 46 female subjects. The mean age was 24.1 ± 6.5 years old, and the mean age at onset was 23.2 ± 6.8 years old. The mean duration of illness was 1.1 ± 1.5 years. The mean storage years of plasma were 7.1 ± 2.1 years.

For the chronic schizophrenia study, patients meeting the diagnostic criteria for chronic schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revision (DSM-IV-TR; American Psychiatric Association, 2000) were recruited into this study. They were from the Department of Psychiatry, Chang Gung Memorial Hospital-Linkou, Taoyuan, Taiwan, the Department of Psychiatry, Yuli Mental Health Research Center, Yuli Branch, Taipei Veterans General Hospital Hualien, Taiwan, and the Department of Psychiatry, Hualien Armed Forces General Hospital, Hualien, Taiwan. Patients met the proposed guidelines for determining treatment resistance in schizophrenia by Conley & Kelly were defined as treatment-resistance in this study (Conley and Kelly 2001). The study was approved by the Institutional Review Board of each hospital. Informed consent was obtained from each subject and their families after the study was fully explained to the patients and their families. A total of 234 patients with chronic schizophrenia were recruited into this study, including 133 female patients (mean age: 50.3 ± 8.4 years) and 101 male patients (mean age: 40.6 ± 7.0 years). Among these 234 chronic patients, 48 patients met the proposed guidance of treatment resistance. A total of 5 ml venous blood was collected from each subject with ethylenediaminetetraacetic acid (EDTA) as anti-coagulant. Plasma was collected and was frozen in −30 °C freezer until use.

2.2. Autoantibody screening assay

For the first-episode schizophrenia study, plasma autoantibodies from each subject were assessed using a commercially available indirect immunofluorescence test kit, IIFT: Autoimmune Encephalitis Mosaic 1 (FA 112d-1005-1, Euroimmun AG, Lübeck, Germany). This assay contained six wells of fixed HEK293 cells transfected with cDNA of NR1 subunit of NMDA receptor, AMPA1 and AMPA2 of AMPA receptor, GABARB1 of GABA receptor, leucine-rich glioma inactivated-1 (LG11), and contactin-associated protein-like 2 (CASPR2), respectively. The experimental procedures followed the instructions from the manufacturer with the initial 1:10 dilution of the plasma. The results were examined under a fluorescent microscope. Samples were classified as positive or negative based on the intensity and pattern of surface immunofluorescence of transfected cells following the recommendations from the manufacturer.

For chronic schizophrenia, the commercially available anti-glutamate receptor (type NMDA) IIFT kit (FA 112d-1005-51, Euroimmun AG, Lübeck, Germany) was used in the screening assay to detect the plasma anti-NMDA receptor IgG autoantibodies. The kit is an indirect immunofluorescence cell-based assay containing the fixed EU 90 cells that expressed the recombinant subunit 1 of NMDA receptor. Non-transfected cells were used as negative control. Testing was performed following the manufacturer instructions. In brief, slides were incubated with the plasma sample with the initial dilution of 1:10. Following the incubation, slides were washed and stained with fluorescein-labeled anti-human IgG antibodies and visualized using a fluorescence microscope. Positive or negative results were based on the comparison of the intensity of surface immunofluorescence between transfected cells and non-transfected cells following the manufacturer’s recommendations.

2.3. Verification assay

The immunohistochemistry on rat brain was used for verification purpose. The assay was performed using the commercially available indirect immunofluorescence test IIFT: Neurology Mosaics (FA 111 m−3, Euroimmun AG, Lübeck, Germany) which contains rat hippocampus and cerebellum tissue, EU90 cell transfected with glutamate receptor (type NMDA) and untransfected UE90 cells as negative control. The experimental procedures followed the manufacturer’s instructions. The results were examined under a fluorescent microscope, and the interpretation of the results followed the manufacturer’s recommendation.

3. Results

In the first-episode schizophrenia study, none of the 78 patients was positive in the screening of six neuronal autoantibodies using the indirect immunofluorescent cell-based assay. In the chronic schizophrenia study, also no positive case among 234 patients was detected in the survey of anti-NMDA receptor autoantibody. Two patients with ambiguous results in the initial screening were subjected to further verification test using rat brain immunohistochemistry assay; however, both of them were negative in the verification study.
دریافت فوری
متن کامل مقاله

امکان دانلود نسخه تمام متن مقالات انگلیسی
امکان دانلود نسخه ترجمه شده مقالات
پذیرش سفارش ترجمه تخصصی
امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
امکان دانلود رایگان ۲ صفحه اول هر مقاله
امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
دانلود فوری مقاله پس از پرداخت آنلاین
پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات