Psychiatry Research 230 (2015) 704–708

Contents lists available at ScienceDirect

Psychiatry Research

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

Circulating anti-brain autoantibodies in schizophrenia and mood disorders

Francesco Margari [a], Maria Giuseppina Petruzzelli [a,*], Rossana Mianulli [a], Maria Gloria Campa [a], Adriana Pastore [a], Marilina Tampoia [b]

[a] Department of Basic Medical Sciences, Neuroscience and Sense Organ, University of Bari "Aldo Moro", Azienda Policlinico, P.zza Giulio Cesare 11, 70124 Bari, Italy

[b] Laboratory of Clinical Pathology, University of Bari "Aldo Moro", Azienda Policlinico, P.zza Giulio Cesare 11, 70124 Bari, Italy

ARTICLE INFO

Article history:
Received 23 February 2015
Received in revised form
31 July 2015
Accepted 27 October 2015
Available online 30 October 2015

Keywords:
Autoimmunity
ANA
Hippocampus
Hypothalamus
Cerebellum
Psychiatric disorders

ABSTRACT

In recent years, an inflammatory autoimmune process, autoantibodies mediated, has been porposed as having a role in the development of different psychiatric disorders. The aim of this study was to assay organ-specific and non organ-specific circulating autoantibodies in schizophrenia, mood disorders and healthy controls; among organ-specific autoantibodies we focused on different fluorescence patterns of anti-brain autoantibodies against rat and monkey's sections of hippocampus, hypothalamus and cerebellum. Serum samples from 50 acutelly ill patients (30 schizophrenia and 20 mood disorders) and from 20 healthy controls were collected. Autoantibodies were assayed by indirect immunofluorescence, enzyme linked immunosorbent assay and chemiluminescence immunoassay. We found a significant difference for circulating autoantibodies to hypothalamus, hippocampus and cerebellum and for anti-nuclear autoantibodies in both schizophrenia and mood disorders when compared to the control group. Referring to the two groups of patients only, circulating antibodies anti-hypothalamus were found significant higher in mood disorders rather than in schizophrenia, with specific regard to nuclear and cytoplasmic staining of the neurons. These data suggest an aspecific diffuse brain involvement of anti-brain autoantibodies in acute phases of schizophrenia and mood disorders. The greater involvement of the hypothalamus in mood disorders highlights the close relationship between autoimmunity, hypothalamic-pituitary-adrenal axis and affective disorders.

© 2015 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Schizophrenia and mood disorders are the most sever mental illnesses, with heterogeneous kinds of symptomatology, clinical course and outcome. Several factors, with a gene-environment interaction, have been suggested to explain the complex and multifactorial etiopathology of both diseases, but to date their causes remain not fully understood (Rivollier et al., 2014; Uher, 2014; Pearlson, 2015).

For a long time the brain was considered to be an immunologically privileged site, as under normal physiological condition, the blood brain barrier limits the access of antibodies, immune mediator and immune cells from the systemic circulation into the brain (Carter et al., 2014). However it is now accepted that this immune privilege is relative rather than absolute and can be disturbed under specific disease conditions (Coutinho et al., 2014; Severance et al., 2014). A large number of publications over the past 20 years have indicated as the immune system function is altered in schizophrenia, mood disorders and other psychiatric illness, as summarized in some recent reviews (Drexhage et al., 2011; Najjar et al., 2013; Smyth and Lawrie, 2013). One of the argument in favor of an autoimmune hypothesis of psychosis has been the circumstantial evidence of high serum levels of self reacting antibodies in patient's sera. Findings of various systemic and organ-specific autoantibodies have already been reported in major depression, bipolar disorders and schizophrenia (Padmos et al., 2004; Jones et al., 2005; Laske et al., 2008; Ezeoke et al., 2013; Margari et al., 2013), but the screening of patients for autoantibodies known to be present in other autoimmune conditions has not validated any particular hypothesis (Sidhom et al., 2012; Pathmanandavel et al., 2013). Autoantibodies with cross reactivity against brain antigens have been described in the sera and cerebrospinal fluid of patients with schizophrenia, but consistency in the findings has not been high and the correlation with disease

* Corresponding author. Fax: +39 080 5595260.
E-mail addresses: maria.petruzzelli@uniba.it, francesco.margari@uniba.it, mtampoia@libero.it (M.G. Petruzzelli).

http://dx.doi.org/10.1016/j.psychres.2015.10.029
0165-1781/© 2015 Elsevier Ireland Ltd. All rights reserved.

activity has been ambiguous (Pathmanandavel et al., 2013). Recent developments in the study of antibodies associated to central nervous system autoantigens, provided findings implicating autoantibodies against ligand-activated receptor channels and potassium channels in psychiatric and neurological disorders (Martinez-Martinez et al., 2013). But they were found in a small number of patients and seem to be rarely involved in the pathophysiology of schizophrenia and other psychotic disorders (Rhoads et al., 2011; Haussleiter et al., 2012). Despite heterogeneous results these studies point towards the existence of an antibody reactivity in at least a subgroup of patients with mood disorders and schizophrenia.

Based on the hypothesis that an autoimmune mechanism, autoantibodies mediated, may be involved in the pathogenesis of psychiatric disorders we compared circulating anti-brain autoantibodies against hippocampus, hypothalamus and cerebellum between a group of patients with schizophrenia and related disorders, a group of patients with mood disorders and a group of healthy controls; different fluorescence patterns, corresponding to nuclear and cytoplasmic staining of the neurons, neuroendothelium of blood vessels and neurofilaments were examined for each brain areas studied. In addition we compared a wide range of others organ specific and non-organ specific autoantibodies to verify a broader antibody reactivity in the sera of all study groups.

2. Methods

2.1. Subjects

Acutely ill patients of both sex, aged 18–65 years, were recruited from consecutive admission at the Psychiatric Unit, Department of Basic Medical Sciences, Neuroscience and Sense Organs of University “Aldo Moro” of Bari, over a six months period. Study samples included 30 inpatients with schizophrenia, and 20 inpatients with mood disorder. The diagnosis were made according to DSM-IV TR criteria, by trained psychiatrists in clinical and diagnostic assessments. The Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impression (CGI) were also performed. All patients were also subjected to clinical and instrumental assessment including medical histories, physical and neurological examination, laboratory investigation and electrocardiogram.

The control group was composed of 39 healthy, normal volunteers. They were screened for the absence of a current and lifetime major psychiatric disorder through clinical psychopathological assessment and an anamnestic interview.

Patients and controls with a previous history of a diagnosed autoimmune disease and/or with current immunomodulating treatment (corticosteroids, interferons, cancer immunotherapy, intravenous gammaglobulines, vaccinations) were excluded.

A written, informed consent was obtained after the study procedures had been fully explained by the research team. Ethical committee of the Hospital Consortium Policlinico of Bari–Italy approved the study (prot. n. 1040/C.E.01/10/2009).

2.2. Laboratory methods

Venous blood samples were collected between 8:00 and 9:00 a.m. after overnight fast. All sera was separated from peripheral blood samples and frozen at −70°C until assayed. All samples were analyzed in a single analytical session.

Organ-specific (including anti-brain) and non organ-specific autoantibodies were assayed by indirect immunofluorescence (IIF), enzyme linked immunosorbent assay (ELISA) and chemiluminescence immunoassay (CLIA), as explained below.

2.2.1. Organ-specific anti-brain autoantibodies

The detection of anti-brain autoantibodies was performed with the IIF method using kits provided free of charge by BioSystem (Barcellona, Spain).

In detail, each sample was analyzed at a serum dilution of 1:10 on two different substrates of rat’s brain (dentate gyrus of hippocampus and hypothalamus) and on two different sections of monkey cerebellum (vermis and floccule).

The slides were provided as frozen sections fixed with acetone, and without fixative.

Anti-human Ig conjugate was used.

Different fluorescence patterns can be observed in these sections:

a. a positive reaction with nuclear and cytoplasmic staining of neurons;
b. a positive reaction of the neuroendothelium of blood vessels;
c. a positive reaction of the neurofilaments.

A positive and a negative control serum were analyzed in each analytical session. The intensity of the fluorescence was determined by two different readers blind to subject characteristic and a scale from 0 to 3 was assigned (0 no reaction, 1 weak or uncertain fluorescence, 2 moderate fluorescence, 3 high fluorescence). Samples scored positive if a 2 or 3 fluorescence reaction was observed at 1:10 sample dilution.

2.2.2. Other organ-specific autoantibodies

Anti-mitochondrial autoantibodies (AMA), anti-smooth muscle autoantibodies (ASMA), anti-parietal cell autoantibodies (APCA) were assayed by the IIF method at a serum dilution of 1:40, using frozen sections of rat (liver, kidney and stomach) and an anti-human IgG conjugate (Euroimmun, Lubueck, Germany).

Samples scored positive if a fluorescence reaction was observed at 1:40 sample dilution.

Anti-thyroperoxidase (TPO) and anti-thyroglobulin (Tg) autoantibodies were assayed with the CLIA method with the LIASION analyser (DiaSorin, Saluggia, Italy).

Samples scored positive if autoantibody levels exceeded the cut-off value provided by the manufacturer (60 U/mL for anti-TPO and for anti-Tg).

Anti-tissue transglutaminase IgA (tTG-IgA) and IgG (tTG-IgG) autoantibodies were assayed using the ELISA method on the Impatto analyzer (Eurospital, Trieste, Italy).

Samples scored positive if autoantibody levels exceeded the cut-off value provided by the manufacturer (9 U/mL for anti-tTG IgA e 30 U/mL for anti-tTG IgG).

2.2.3. Non organ-specific autoantibodies

Anti-nuclear autoantibodies (ANA) were assayed with the IIF method at a serum dilution of 1:80, using human epithelial cells (HEp-2) as substrate and an anti-human IgG conjugate (Euroimmun).

Samples scored positive if a fluorescence reaction was observed at 1:160 dilution.

All ANA-positive samples were investigated for anti-dsDNA and anti-extractable nuclear antigen (ENA) autoantibodies, by the LIASION and ETIMAX analyzers (DiaSorin), respectively. Samples scored positive if autoantibodies levels exceeded the cut-off value provided by the manufacturer (25 U/mL for anti-dsDNA and index >1.1 for anti-ENA).

Anti-cardiolipin autoantibodies (aCL-IgG/IgM) were assayed with the EIA method with ETIMAX 3000 (DiaSorin). Samples scored positive if autoantibodies levels exceeded the cut-off value provided by the manufacturer (20 U/mL for aCL-IgG and 15 U/mL for aCL-IgM).

Download English Version:

https://daneshyari.com/en/article/10303649

Download Persian Version:

https://daneshyari.com/article/10303649

Daneshyari.com