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Review

A systematic, quantitative review of blood autoantibodies in schizophrenia

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ABSTRACT

Objective: Schizophrenia is associated with immune system dysfunction, including an increased prevalence of autoimmune disorders and autoantibodies. We performed a systematic, quantitative review of self-reacting blood antibodies in patients with schizophrenia.
Method: We identified articles by searching PubMed, PsychInfo, and ISI, and the reference lists of identified studies.
Results: Eighty-one of 111 studies identified met the inclusion criteria. There was a significant increased prevalence of positive titers for 20 different autoantibodies in patients with schizophrenia compared to controls. The prevalence of positive anti-cardiolipin IgG and NMDA receptor titers was also significantly increased in subjects with first-episode psychosis versus controls ($p < 0.01$). Absolute titers for anti-cardiolipin IgG and IgM, and nerve growth factor were significantly increased in patients with schizophrenia compared to controls ($p < 0.02$ for each).
Conclusion: Schizophrenia is associated with an increased prevalence of multiple autoantibodies, although there is marked study heterogeneity, and correlations between autoantibodies and clinical features are inconsistent. This area merits more research evaluation, especially controlling for potential confounding factors such as clinical status, age, genetic background, psychotropic medications, BMI, and smoking.

1. Introduction

Schizophrenia is a heterogeneous disorder, including symptomatology, clinical course, and outcome (Messias et al., 2007). An association between immune system abnormalities in schizophrenia has been an enduring finding in the field. One of the most replicated associations is the inverse relationship between schizophrenia and rheumatoid arthritis (RA; Oken and Schulzer, 1999; Chen et al., 2012). By contrast, the literature on self-reacting antibodies in schizophrenia is fraught with inconsistent and incongruent findings, including negative studies. Why are these findings so contradictory with respect to the long-standing negative association between schizophrenia and RA? Many factors likely contribute to between-study heterogeneity and negative findings, including potential effects of assay methodology, genetic background, environmental exposures, age, gender, race, BMI, smoking, medications, sampling at different stages of disease progression, and different clinical courses of illness.

Now, in the context of other areas of research, findings of self-reacting antibodies in schizophrenia are making more sense. Several lines of evidence provide further support for an association between immune system abnormalities in the pathophysiology of some patients with schizophrenia. Serologic studies have found associations between maternal antibodies to a variety of infectious agents and risk of schizophrenia in the offspring (Brown and Derkits, 2010).

There is an increased prevalence of multiple different autoimmune diseases in both patients with schizophrenia (Eaton et al., 2006; Benros et al., 2011; Chen et al., 2012) and nonaffective (Eaton et al., 2010) and affective (Gilvarry et al., 1996) psychoses, as well as their first-degree relatives (Gilvarry et al., 1996; Eaton et al., 2006, 2010) compared to controls. Both a personal (Eaton et al., 2006) as well as a family history (Eaton et al., 2010) of any autoimmune disease are also associated with a significant increased risk of schizophrenia. Adjunctive non-steroidal anti-inflammatory drugs (NSAIDs), which are used in the treatment of autoimmune disorders, have also been efficacious in improving psychopathology in some patients with schizophrenia (Muller et al., 2002; Akhondzadeh et al., 2007; Laan et al., 2010; Muller et al., 2010). Furthermore, single nucleotide polymorphisms in genes in the major histocompatibility complex (MHC) on chromosome 6p, which are critical to immune system function and associated with autoimmune disorders, are also risk factors for schizophrenia (International Schizophrenia Consortium et al., 2009; Shi et al., 2009; Stefannson,

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2009). Several studies have reported abnormal absolute levels of antibody-producing B-lymphocytes in patients with schizophrenia (McAllister et al., 1989; Printz et al., 1999; Steiner et al., 2010). There are, however, failures to replicate these findings (Ganguli and Rabin, 1993; Arolt et al., 1997; Bilici et al., 2003; Redolf et al., 2004). Several recent studies have found that a subset of patients presenting with first-episode psychosis (FEP) have evidence of autoantibodies associated with either limbic encephalitis (Zandi et al., 2011; Steiner et al., 2013) or neuropsychiatric systemic lupus erythematosus (Mantovani et al., 2012) in the absence of overt signs of encephalitis or rheumatologic disease, respectively. An important aspect of these findings is that self-reacting antibodies detectable in the peripheral blood are able to cross the blood–brain barrier and contribute to CNS pathophysiology.

Many studies have examined the prevalence of self-reacting antibodies to a myriad of antigens in patients with schizophrenia compared to control subjects. However, to date a systematic, quantitative review of these findings has not been performed. Although this is a heterogeneous area of research, such a review is an important next step towards increased understanding of potential mechanisms whereby immune system dysfunction might contribute to the pathophysiology of schizophrenia. Based upon a systematic, quantitative review of literature, we evaluated the prevalence of positive self-reacting antibodies in the blood of patients with schizophrenia. The primary aims were to evaluate the prevalence and specificity of various autoantibodies in patients with schizophrenia, and in doing so, to integrate these findings with data on other immune abnormalities in schizophrenia.

2. Material and methods

2.1. Study selection

Studies of autoantibodies in schizophrenia were systematically searched using Medline (PubMed, National Center for Biotechnology Information, US National Library of Medicine, Bethesda, Maryland), PsycInfo (via Ovid, American Psychological Association, Washington, DC), and Thomson Reuters (formerly ISI) Web of Knowledge (Science Citation Index and Social Sciences Citation Index, Thomson Reuters, Charlottesville, Virginia) in May 2012. The primary search strategy was "autoantibodies and (schizophrenia or psychosis)." Limiting results to studies in English identified 441 articles from PubMed, 20 for PsycInfo, and 50 for ISI. From these sources, plus a manual review of reference lists from identified studies, we found a total of 111 potential studies for inclusion, which are described in Supplementary Table 1.

The inclusion criteria were: 1) cross-sectional studies of blood autoantibodies (either absolute titers or the proportion positive titers) in patients with schizophrenia or related psychotic disorders, including schizophreniform disorder, brief psychotic disorder, psychotic disorder not otherwise specified, delusional disorder, and schizoaffective disorder, 2) longitudinal studies that measured blood autoantibodies in patients with schizophrenia at multiple time points, and 3) studies published in English.

The exclusion criteria were: 1) studies that did not report the proportion of subjects with positive titers, 2) studies that did not report the mean and standard deviations for absolute titers, after attempting to contact the study authors, 3) significant overlap in study population, 4) genetic studies related to autoantibodies or autoimmunity, 5) studies of the prevalence of autoimmune disorders in subjects with schizophrenia and related disorders, and 6) child or adolescent patient population.

After independent searches, review of study methods by two authors (BJM and AE), and attempts to contact the authors, 81 studies met the inclusion criteria. There was universal agreement on the included studies. Thirty studies were excluded due to: proportions or means for autoantibody titers not available ($n = 28$), no control group ($n = 2$), and child or adolescent patient population ($n = 2$). A flow chart summarizing the study selection process is presented in Supplementary material.

2.2. Data extraction and analysis

Data were extracted on the sample size and the proportion of either positive titers or absolute titers for subjects with schizophrenia and controls for all autoantibodies were assessed in each study. One author (AE) extracted all data, which was independently verified by another author (BJM). For studies with categorically defined antibody titers (i.e., positive or negative), we calculated the overall proportion of positive titers, which were compared using a Chi-squared test. The main statistical hypotheses were that there will be no differences in the proportion of positive titers between a) patients and controls, and b) pre- and post-antipsychotic treatments for illness relapse. In a planned secondary analysis, we repeated this procedure for studies of patients with FEP versus controls to study potential effects of antipsychotic medications on these parameters. For each autoantibody, we also calculated the ratio of patients to controls with positive titers.

For data on absolute titers, we calculated effect size estimates (Hedges' g) for each autoantibody in each study. Random effects pooled effect size estimates and 95% confidence intervals were calculated using the method of DerSimonian and Laird. The random effects model is more conservative than the fixed effects model, as it yields a lower Type I error rate and wider confidence intervals (Hunter and Schmidt, 2000). Meta-analysis could not be performed for autoantibodies that were assessed in only a single study. The main statistical hypothesis was that the effect size for the difference in titers between a) patients and controls, and b) pre- and post-antipsychotic treatments for illness relapse for each autoantibody will equal to zero. All tests were two-sided p-values, and they were considered statistically significant at the $\alpha = 0.05$ level. The statistical analyses were performed in Stata 10.0 (StataCorp LP, College Station, TX). The meta-analysis procedure also calculates a χ^2 value for the heterogeneity in ES estimates, which is based on Cochran's Q-statistic (Cochran, 1950). Between-study heterogeneity χ^2 was considered significant for $p < 0.10$ (Song et al., 2001).

For descriptive purposes, we also extracted correlational data for self-reacting antibodies and patient clinical features, including age, age of onset of illness, duration of illness, and psychopathology scores. We recorded the direction, magnitude, and statistical significance (yes/no) of each correlation. A quantitative analysis of correlative data was not possible. We examined these data qualitatively for replicated, significant findings.

3. Results

The 81 included studies measured autoantibodies against more than 50 different antigens, of which 31 antibodies were assessed in more than one study. Table 1a presents the quantitative analysis of the prevalence of positive titers. In cross-sectional studies, there was a significant increased prevalence of positive titers for 20 of the 31 different autoantibodies among all patients with schizophrenia compared to controls ($p < 0.05$). In subjects with FEP, there was a significant increased prevalence of positive titers for cardiolipin IgG and NMDA receptor ($p < 0.01$), but not ANA ($p = 0.79$), cardiolipin IgM ($p = 0.33$), and anti-histone IgG ($p = 1.00$) versus controls.

Absolute titers for anti-cardiolipin IgG ($p = 0.02$), anti-cardiolipin IgM ($p < 0.01$), and nerve growth factor ($p = 0.02$) antibodies were also significantly increased in patients with schizophrenia compared to controls (see Table 1b). There was no significant difference in absolute anti-hippocampal IgG titers between patients with schizophrenia and controls ($p = 0.50$). In FEP, absolute titers for anti-cardiolipin IgG were significantly decreased versus controls ($p < 0.01$). Data were not available to compare absolute titers for any other antibodies.

Two longitudinal studies measured the change in the proportion of positive titers for anti-cardiolipin IgG and IgM among subjects at baseline (at the time of an acute illness exacerbation) and again following a period of antipsychotic treatment. There was a non-significant increase in the proportion of subjects with positive titers for both anti-

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