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SPECIAL ISSUE

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Antibodies to infectious agents in individuals with recent onset schizophrenia

Abstract We investigated the levels of antibodies to infectious agents in the serum and cerebral spinal fluids (CSFs) of individuals with recent onset schizophrenia and compared these levels to those of controls without psychiatric disease. We found that untreated individuals with recent onset schizophrenia had significantly increased levels of serum and CSF IgG antibody to cytomegalovirus and *Toxoplasma gondii* as compared to controls. The levels of serum IgM class antibodies to these agents were not increased. Untreated individuals with recent onset schizophrenia also had significantly lower levels of serum antibody to human herpesvirus type 6 and varicella zoster virus as compared to controls. Levels of antibodies to herpes simplex virus type 1, herpes simplex virus type 2, and Epstein Barr virus, and did not differ from cases and controls.

We also found that treatment status had a major effect on the levels of antibodies in this population. Individuals who were receiving treatment had lower levels of antibodies to cytomegalovirus and *Toxoplasma gondii*, and higher levels of serum antibodies to human herpesvirus type 6 as compared to untreated individuals. The level of antibodies to Toxoplasma and human herpesvirus type 6 measured in treated individuals did not differ from the levels measured in controls. In the case of cytomegalovirus, the levels of CSF antibodies in treated individuals did not differ from those of controls, while the level of serum IgG antibodies to CMV remained slightly greater than controls in this population.

Our studies indicate that untreated individuals with recent onset schizophrenia have altered levels of antibodies to cytomegalovirus, *Toxoplasma gondii*, and human herpesvirus type 6 while the levels of these antibodies in treated individuals with recent onset schizophrenia are similar to those of controls. These findings indicate that infectious agents may play a role in the etiopathogenesis of some cases of schizophrenia.

Key words schizophrenia · antibodies · herpesviruses · Toxoplasma gondii

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Introduction

Schizophrenia is a pervasive neuropsychiatric disease of uncertain etiology. Family and twin studies suggest that there is a genetic component to schizophrenia; however, extensive genetic research has failed to identify genes of major effects which are operant in different populations. Epidemiological studies have also suggested a role for environmental factors, such as infections, in the etiology of some cases of schizophrenia. While many microbial agents have been proposed as risk factors for schizophrenia, many recent studies have focused on members of the viral family *Herpesviridae* as well as the protozoan organism *Toxoplasma gondii*. Reasons for the focus on these agents include their ability to establish persistent infection within the central nervous system [22, 25] as well as the occurrence of neurological and psychiatric symptoms in some individuals infected with these agents [11, 15, 17, 26, 30, 32, 33].

Immunological methods making use of the measurement of specific antibodies in the blood and other body fluids of affected individuals and controls are the principal analytic tools employed for the investigation of the role of specific infectious agents in a disease process. However, these methods can be difficult to apply accu-

rately to the investigation of the role of infectious agents in a protracted psychiatric disease such as schizophrenia. Individuals with schizophrenia are often exposed to infectious agents at a rate greater than control populations as a result of hospitalization or altered life style. These adventitious exposures can make it difficult to determine the etiological significance of antibodies to infectious agents measured in individuals with established cases of schizophrenia. Furthermore, it is possible that the medications administered to individuals with schizophrenia or the propensity for cigarette smoking in these individuals might alter their immune response to infectious agents [10, 19]. These limitations can be potentially overcome by the measurement of antibodies to infectious agents in individuals with a recent onset of schizophrenia who had not been previously hospitalized and who were not receiving anti-psychotic medication. We tested antibodies to human herpesviruses and *Toxoplasma gondii* in such individuals and compared the levels of antibodies to individuals with schizophrenia who were receiving medication as well as controls individuals without psychiatric diseases.

Materials and methods

Patient population

All study participants gave their informed consent and responsible authorities approved the procedures for sample collection and analysis. Schizophrenic and non-schizophrenic patients fulfilled pertinent diagnostic criteria, as defined by the IV edition of the Diagnostic and Statistical Manual (DSM-IV). 15–20 ml of cerebrospinal fluids (CSF) samples and serum were collected approximately around 12:00 PM using a non-traumatic lumbar puncture procedure. Routine CSF analyses included total cell count, total protein, CSF/serum albumin and IgG quotients, and determination of oligoclonal bands by isoelectric focusing and silver staining. All CSF samples revealed normal cell counts, normal CSF/serum albumin ratios and no oligoclonal bands, indicating healthy blood-brain barrier function and lack of a general increase in the synthesis of intrathecal immunoglobulin G.

Patients and volunteers were recruited from the same rather homogenous region regarding socioeconomic characteristics and showed no relevant differences in this respect. Healthy volunteers were found through a word of mouth campaign and represented typical healthy inhabitants of their respective geographic areas. The control sample was also matched with respect to their history of cannabis use compared to the patients suffering from schizophrenia, where about one third reported frequent cannabis consumption of more than 20 times lifetime.

Serum samples were available from 73 healthy volunteers with no family history of schizophrenia (71.2 % male; age 28.0 ± 5.8 yrs); 36 drug-free schizophrenic in-patients undergoing their first-recognized psychotic episode (77.8 % male; age 29.1 ± 9.2 yrs); 10 drug-free schizophrenia patients who had received anti-psychotic treatment in the past, 80 % male; age 33.7 ± 8.3 yrs) and 39 acute schizophrenic in-patients treated with antipsychotic medications (76.9 % male; age 30.5 ± 10.7 yrs). Adequate samples for CSF testing were available from all of these individuals except for 2 of the drug-free schizophrenic in-patients.

Measurement of antibodies

Serum IgG class antibodies were measured to herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), cytomegalovirus (CMV), Epstein Barr virus (EBV, varicella-zoster virus (VZV), human herpesvirus type 6 (HHV-6) and *Toxoplasma gondii* (Toxo) using previously described immunoassay methods [2]. Briefly, these methods consist of the reaction of diluted serum to antigens immobilized on the wells of microtiter plates and the subsequent quantification of bound antibody by means of reaction with enzyme labeled anti-human IgG and enzyme substrate. Serum IgM class antibodies to CMV and Toxo were measured by similar methods except that enzyme labeled antibody to human IgM was substituted for enzyme labeled IgG. The levels of IgG antibodies in the CSF were measured to HSV-1, CMV, and Toxo using methods identical to those employed for serum except that the CSF was diluted 1:40 prior to addition to the solid phase antigens. Reagents and assay kits for HSV-1 and HSV-2 were obtained from Focus Laboratories, Cypress, CA. Reagents for HHV-6 were obtained from Advanced Biotechnologies Incorporated, Columbia, MD. Reagents for CMV, EBV, VZV, and *Toxoplasma gondii* were obtained from IBL Laboratories, Hamburg, Germany.

For each determination the amount of antibody in the serum specimen was quantified by the measurement of colorimetric substrate by means of a microplate colorimeter and converted into a ratio by dividing the amount of color generated in the sample wells by the amount of color generated from reaction with a weakly positive sample provided by the assay manufacturer. For comparison of quantitative results among the different antibody assays, this ratio was standardized to a value of 1.0 on each microtiter plate. Statistical analyses were performed by means of the STATA statistical package, College Station, Texas.

Results

We determined the levels of IgG class antibodies to 7 infectious agents in the sera of 38 individuals with recent onset schizophrenia who had never received antipsychotic medications and 73 controls without psychiatric diseases. As depicted in Fig. 1, we found that serum IgG antibodies to cytomegalovirus ($F = 17.2$, $p < 0.001$) and *Toxoplasma gondii* ($F = 4.4$, $p = 0.039$) were significantly increased in this population as compared to the con-

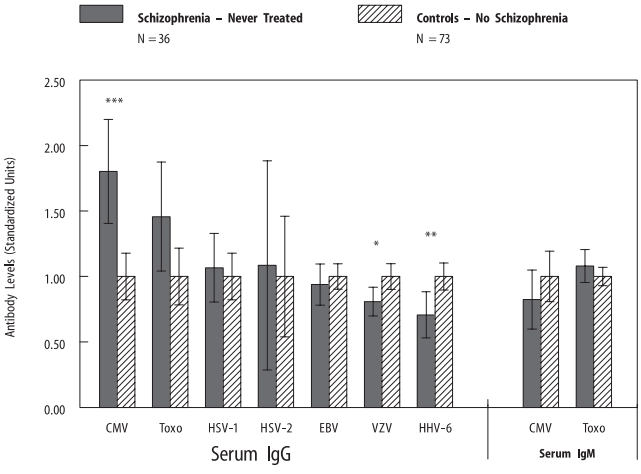

Fig. 1 Antibody levels measured in the sera of individuals with first episode schizophrenia and controls. IgG and IgM antibody levels were measured in the sera of 36 never-treated individuals with recent onset schizophrenia and 73 controls without psychiatric disease as described in the text. Bars represent the mean and 95 % confidence intervals of the antibodies expressed in standardized units. *CMV* Cytomegalovirus; *Toxo* Toxoplasma gondii; *HSV-1* Herpes simplex virus type1, *HSV-2* Herpes simplex virus type 2, *EBV* Epstein Barr virus, *VZV* Varicella Zoster virus, *HHV-6* Human herpes virus type 6; *** $p < 0.001$, ** $p < 0.004$, * $p < 0.04$

trols. Serum IgG antibodies to herpes simplex virus type 1, herpes simplex virus type 2, and Epstein Barr virus did not differ between cases and controls. The levels of serum IgG antibody to HHV-6 ($F = 8.8$, $p = 0.0037$) and VZV ($F = 5.5$, $p = 0.021$) were significantly lower in individuals with untreated schizophrenia as compared to controls. We also measured serum IgM class antibodies to CMV and Toxo in the untreated individuals with recent onset schizophrenia. As depicted in Fig. 1, the levels of these antibodies did not differ from the levels measured in the controls.

We also examined the effect of treatment status on the serum levels of antibodies to CMV, Toxo, and HHV-6 by the further analysis of the levels measured in individuals with recent onset schizophrenia who presented after receiving treatment in the past or who were receiving active treatment at the time of the entry in the study. As depicted in Fig. 2, previous treatment had little effect on the level of antibodies to these agents in individuals with recent onset schizophrenia who were not receiving medication at the time of presentation. On the other hand, individuals with recent onset schizophrenia who were receiving anti-psychotic medications at the time of entry into the study had levels of antibody which were significantly lower than those measured in the untreated individuals. In the case of antibodies to Toxo and HHV-6, the levels of antibodies were indistinguishable from those of controls, while in the case of CMV, the levels were somewhat greater than those of controls ($F = 5.7$, $p = 0.018$).

We also measured IgG class antibodies to CMV, Toxo, and HSV-1 in the CSFs of untreated individuals with recent onset schizophrenia. As depicted in Fig. 3, we found that the levels of CSF antibodies to CMV ($F = 9.1$, $p < 0.0033$) and Toxo ($F = 12.4$, $p < 0.001$) were significantly greater in these individuals as compared to the controls. The levels of CSF IgG antibodies to HSV-1 did not differ between cases and controls. As in the case with the serum antibodies, CSF antibody levels to CMV and Toxo were lower in individuals with recent onset schizophrenia who were receiving therapy at the time the sample was obtained; in both cases the levels in these individuals was indistinguishable from those of controls.

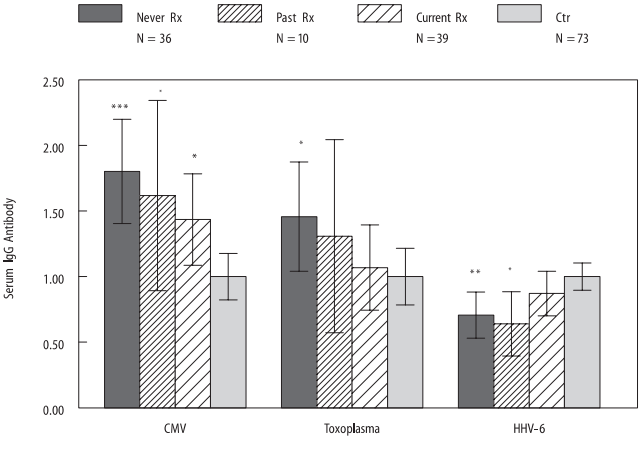

Fig. 2 Levels of Serum IgG antibodies in treated and untreated individuals. Levels of IgG antibodies to cytomegalovirus, Toxoplasma gondii and human herpes virus type 6 were measured in individuals with recent onset schizophrenia who had never received anti-psychotic medications (Never Rx), had received medication in the past (Past Rx) or who were receiving treatment at the time of their entry into the study (Current Rx) as well as in the sera of controls without psychiatric diseases (Ctr). Bars represent the mean and 95 % confidence intervals of the antibodies expressed in standardized units. *CMV* Cytomegalovirus; *Toxoplasma* Toxoplasma gondii; *HHV-6* Human herpes virus type 6. *** $p < 0.001$, ** $p < 0.004$, * $p < 0.04$

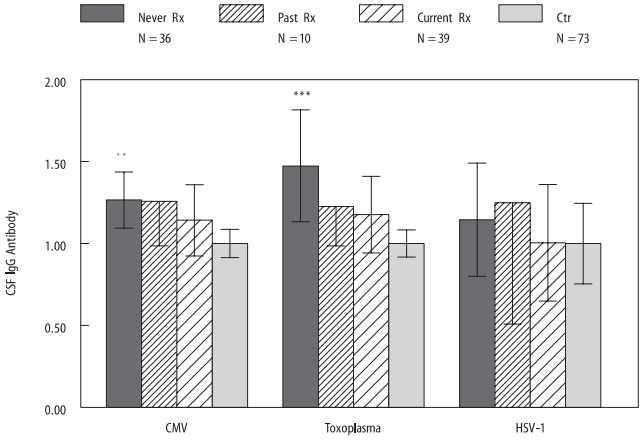

Fig.3 Levels of cerebrospinal fluid antibodies in treated and untreated individuals. Levels of IgG antibodies to cytomegalovirus, Toxoplasma gondii were measured in individuals with recent onset schizophrenia who had never received anti-psychotic medications (Never Rx), had received medication in the past (Past Rx) or who were receiving treatment at the time of their entry into the study (Current Rx) as well as in the sera of controls without psychiatric diseases (Ctr). Bars represent the mean and 95 % confidence intervals of the antibodies expressed in standardized units. *CMV* Cytomegalovirus; *Toxoplasma* Toxoplasma gondii; *HSV-1* Herpes simplex virus type 1; *** $p < 0.001$; ** $p < 0.004$

Discussion

Our studies document that individuals with first episode schizophrenia who had not received prior anti-psychotic treatment at the time of presentation had increased levels of serum and CSF IgG antibodies to the potentially neurotropic infectious agents cytomegalovirus and *Toxoplasma gondii*. CMV is a beta-herpesvirus which is transmitted by person-to-person contact. CMV can infect the central nervous system and establish a persistent infection, particularly in immunocompromised individuals or neonates who are infected transplacentally. Infection of the brain can lead to a number of long term cellular consequences, including apoptosis [5] and glial cell activation [18], processes which have been identified in some cases of schizophrenia [4, 23]. Furthermore, CMV infection of experimental animals can lead to a decrease in prepulse inhibition, a response similar to one found in many individuals with schizophrenia [24].

Toxoplasma gondii is a parasite of the family *Apicomplexa*. Felines are the main reservoir for Toxoplasma, but humans can become infected from the in-

halation of cysts from cat feces or the consumption of cysts from undercooked meat. Infection in humans can lead to persistent replication within the central nervous system. As in the case for CMV, central nervous system replication is most common following perinatal infection or in individuals who are rendered immunocompromised by HIV infection or immunosuppressive chemotherapy. The finding of increased antibodies to Toxoplasma gondii is consistent with previous studies documenting increased levels of antibodies to this agent in some populations of individuals with schizophrenia [32] as well as with epidemiological studies indicating that early contact with cats is a risk factor for the development of schizophrenia in later life [29].

On the other hand we did not find increased antibodies to other human herpesviruses. This finding indicates that the increase in antibodies to CMV and Toxoplasma were not simply a consequence of a non-specific increase in antibody levels due to immunological activation. The lack of increased levels of antibodies to these agents also renders it unlikely that the increased levels of antibodies to CMV and Toxo are related to differential rates of infectious exposures due to geographic or socioeconomic differences between the case and control populations. In fact, we found that untreated individuals with recent onset schizophrenia had lower levels of serum antibodies to VZV and HHV-6 than controls. The reason for these lower levels is not known with certainty, but may be related to either decreased exposure to these agents or to some degree of immune suppression in individuals with recent onset schizophrenia [10].

In contrast to our findings with IgG antibodies, we did not find increased levels of IgM class antibodies to CMV or Toxo in the serum of untreated patients with schizophrenia. This indicates that the patients had not undergone an increased rate of primary infection within 3 months prior to presentation, but rather had undergone either a more distant primary infection or reactivation of infection acquired earlier in life. Additional studies should be performed to more precisely define the time course of CMV and Toxo infections in this population. The finding that the increased levels of antibodies to these agents are the result of the reactivation of infection acquired during the perinatal infant period would be consistent with studies indicating that many cases of schizophrenia are associated with evidence of maternal infection and neurodevelopmental abnormalities [2, 16].

Both CMV and Toxo are common infections in many human populations. An association between infection with these agents and the development of schizophrenia might occur in only a small proportion of infected individuals, presumably ones who are rendered more susceptible to the effects of infection. Possible susceptibility factors include the timing of primary infection, co-infection with other microorganisms, or genetic susceptibility to the effects of infection. In terms of the latter possibility, it is of note that polymorphisms of a number of genes encoding cytokines and other immune reactive proteins have been recently identified which confer susceptibility on infection with cytomegalovirus and Toxoplasma gondii. Increased rates of polymorphisms in cytokine genes have also been found in some populations of individuals with schizophrenia. The association between cytokine polymorphisms and increased levels of antibodies to cytomegalovirus and Toxoplasma gondii in individuals with schizophrenia should be the subject of additional investigations. The identification of such interactions would be consistent with recent theories of schizophrenia positing that many cases of schizophrenia occur as a result of gene-environmental interactions occurring in genetically susceptible individuals.

It is of note that we found significantly lower levels of antibodies to CMV and Toxo in individuals with first episode schizophrenia who were receiving anti-psychotic medications as compared to either untreated individuals with first episode schizophrenia or individuals who had received some medication in the past but who were not receiving active treatment. Similarly, the decrease in antibodies to HHV-6 noted in untreated individuals with first episode schizophrenia as compared to controls was not found in treated individuals. The reasons for the effect of treatment on antibody levels is not known with certainty, but may be related to an increased period of time from exposure to the infectious agent or to the effect of the medication on microbial replication or the immune response to infection. It is of note in terms of the possible effect of medications that some of the therapeutic agents commonly employed for the treatment of schizophrenia and bipolar disorder have the ability to inhibit the in vitro replication of *Toxoplasma gondii* (13). Additional longitudinal studies should be performed to better define the time course of antibody levels during the course of schizophrenia treatment.

Our findings also have implications concerning the interpretation of serological studies investigating the role of infectious agents in schizophrenia. Previous studies of antibodies to infectious agents in individuals with schizophrenia have shown varying results with some studies showing significant associations [9, 21, 27] and others not finding differences between cases and controls [7]. Our study indicates that the timing of sampling and the medication status of the patient are crucial variables in terms of the levels of antibodies measured in individuals with schizophrenia. For example, had we only measured antibodies in treated individuals with recent onset schizophrenia we would have failed to detect differences between cases and controls in terms of serum or CSF antibodies to Toxo or CSF antibodies to CMV and would only have encountered small case-control differences in the levels of serum IgG antibody to CMV (Figs. 2–3). Differences in microbial expression during different stages of disease may also explain the discrepancies encountered with attempts as the direct identification of microbial nucleic acids in post-mortem brains obtained from individuals with schizophrenia [3,

19]. Our findings indicate that the analysis of relatively large sets of samples obtained from individuals in different stages of schizophrenia is required for the accurate assessment of the role of infectious agents in the overall disease process.

Our study provides immunological evidence that infections with common infectious agents such as cytomegalovirus and *Toxoplasma gondii* may contribute to the etiopathogenesis of some cases of schizophrenia. Additional studies should be directed at the further analysis of anti-cytomegalovirus and anti-Toxoplasma antibodies in the sera and CSFs of individuals with recent onset schizophrenia as well as at the direct detection of nucleic acids and proteins derived from these organisms in these samples. The identification of these organisms is of particular importance since antimicrobial agents are available which can inhibit the replication of these organisms within the CNS. It is of note in this regard that an initial study of the antiviral medication valacyclovir documented clinical improvement in some individuals with schizophrenia and IgG antibodies to CMV who were administered this medication for a 16 week period of time [6]. Furthermore, studies using antimicrobial agents in individuals with schizophrenia who have antibodies to *Toxoplasma gondii* are underway at several institutions. The identification of microbial pathogens associated with schizophrenia may result in the development of new modalities for the prevention and treatment of this disease in a variety of patient populations.

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