

Infectious agents are associated with psychiatric diseases

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Abstract

There are several infectious agents in the environment that can cause persistent infections in the host. They usually cause their symptoms shortly after first infection and later persist as silent viruses and bacteria within the body. However, these chronic infections may play an important role in the pathogenesis of schizophrenia and Tourette's syndrome (TS). We investigated the distribution of different neurotrophic infectious agents in TS, schizophrenia and controls. A total of 93 individuals were included (schizophrenic patients, Tourette patients and controls). We evaluated antibodies against cytomegalovirus (CMV), herpes-simplex virus (HSV), Epstein-Barr virus, Toxoplasma, Mycoplasma and Chlamydia trachomatis/pneumoniae. By comparing schizophrenia and TS, we found a higher prevalence of HSV ($P=0.017$) and CMV ($P=0.017$) antibodies in schizophrenic patients. Considering the relationship between schizophrenia, TS and healthy controls, we showed that there are associations for Chlamydia trachomatis ($P=0.007$), HSV ($P=0.027$) and CMV ($P=0.029$). When all measured viruses, bacteria and protozoa were combined, schizophrenic patients had a higher rate of antibodies to infectious agents than TS patients ($P=0.049$). Tourette and schizophrenic patients show a different vulnerability to infectious agents. Schizophrenic patients were found to have a higher susceptibility to viral infections than individuals with TS. This finding might point to a modification in special immune parameters in these diseases.

Introduction

In some psychiatric disorders environmental factors are involved in the pathophysiology of the diseases. Especially in schizophrenia and Gilles de la Tourette's syndrome (TS) the precise underlying pathophysiology is yet

unknown, however epidemiological studies have revealed different environmental factors in the pathogenesis such as winter and spring birth, birth in an urban area and complications during pregnancy.^{1,2} Moreover it has been suggested that infections might also be involved in the aetiology of some cases of schizophrenia.³ While until now different microbial agents have been proposed as risk factors for schizophrenia, many recent studies have focused on members of the viral family of Herpesviridae,⁴ Borna virus,⁵ intracellular bacteria like Chlamydia as well as the protozoan organism Toxoplasma gondii.^{6,7} Reasons for focusing on these agents include their ability to establish persistent infections within the central nervous system as well as the occurrence of neurological and psychiatric symptoms in individuals infected with these agents.⁸

Many pathophysiological parallels have been identified between schizophrenia and TS, which is characterized by multiple motor and vocal tics.⁹ Both disorders overlap in the clinical symptomatology and treatment strategies.¹⁰ Also some genetic parallels between the two diseases were identified: three out of five copy number variants were found to be implicated in TS and schizophrenia.¹¹ However, these findings represent just a subgroup of patients and with the current literature the genetic association between TS and schizophrenia is far from generally proven. From a biological point of view, especially dysbalanced neurotransmitter systems seem to be a major cause of psychiatric diseases. For schizophrenia and TS many similarities have been found in these systems: Imaging studies favour an important role of the dopaminergic system in TS pathophysiology.¹² Also in schizophrenia, dysregulations in various neurotransmitter systems - including dopamine, glutamate and acetylcholine - have been described.¹³⁻¹⁵ Serotonergic abnormalities have also been reported in TS and schizophrenia,^{16,17} possibly reflecting a disturbance within the tryptophan catabolism and the immune system in both diseases.^{18,19}

As well as in schizophrenia, recent studies have revealed that infections could also contribute to a subtype of tic disorders. Group A β hemolytic streptococcal infections are a possible contributing factor of neuropsychiatric and movement disorders. At present, the clinical syndrome of post-streptococcal tics and obsessive-compulsive disorders in children is termed PANDAS (paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection).²⁰ In addition to streptococci, several other infectious agents have been proposed to play a role in the pathogenesis of TS: two case reports revealed that Mycoplasma pneumoniae might be associated with tic symptoms.^{21,22} This assumption was strengthened

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ened in a study that compared 29 Tourette patients to healthy controls regarding the Mycoplasma infection rate and found significantly elevated antibody titers against Mycoplasma pneumoniae in TS patients.²³ Also viruses were investigated and an association between herpes simplex virus 1 and the exacerbation of tics was stated.²⁴ Moreover, Riedel *et al.* reported about a case where Lyme disease presented as Tourette's syndrome.²⁵

Considering all these findings, it still remains controversial, which of the neurotrophic infectious agents are involved in the pathogenesis of schizophrenia and TS and which ones are just present ubiquitously. In order to investigate this issue we searched for overlapping infection rates in both diseases that might help to identify relevant infectious agents that are associated with schizophrenia and TS. However, with the present study design conclusions in regard to the pathophysiology of these diseases cannot be made. In this study we investigated whether there are differences in the distribution of antibodies to infectious agents that establish a persistent central nervous system infection in healthy controls, schizophrenic and Tourette patients.

Table 1. Characteristics of the study population.

	Schizophrenic patients n=31	Mean (SD)	Tourette patients n=32	Mean (SD)	Healthy controls, n=31	Mean (SD)
Sex						
Female	13 (41.9%)		6 (18.8%)		13 (41.9%)	
Male	18 (58.1%)		26 (81.2%)		18 (58.1%)	
Age		36.5 (13.4)		29.6 (15.1)		33.7 (16.1)
Age of disease onset		31.9 (12.9)		9.48 (6.48)		
Positive and negative symptoms scale		92.1 (20.3)				
Yale global tic severity scale				40.8 (17.5)		

Materials and Methods

Characterization of the patient and control population:

In total 93 individuals were included: 31 patients with schizophrenia (age 36.5 ± 13.4 yrs; 18 male, 13 female) were diagnosed by two experienced psychiatrists fulfilled the diagnostic criteria, as defined by the IV edition of the Diagnostic and Statistical Manual (DSM-IV).²⁶ In addition, 32 patients with Tourette's syndrome ($29.6 \text{ age} \pm 15.1$ years; 26 male, 6 female) diagnosed by two experienced psychiatrists according to the IV edition of the DSM-IV were selected. The disease onset of Tourette's syndrome was at mean age of 9.48 years (± 6.98 years). Patients were recruited through the Department of Psychiatry of the Ludwig-Maximilians University Munich. At the time of study inclusion schizophrenic patients were rated with the positive and negative symptoms scale (PANSS) and showed a mean value of 92.1 ($SD=20.3$). TS patients reached on the Yale Global Tic Severity Scale (YGTSS) a median number of 40.8 ($SD = 17.5$). Healthy control subjects were recruited via advertisement. The 30 people of the control population (age 33.7 ± 16.1 years; 18 male, 12 female) were matched to the schizophrenic and Tourette group. All study participants gave their written informed consent prior to study inclusion. The responsible ethics committee approved the procedure for sample collection and analysis. A concomitant organic disease or acute general or genitor-urinary infections were exclusion criteria. Blood counts were performed (differential blood count, urea and electrolytes, CK, renal-, pancreatic-, liver- and thyroid-parameters, CRP and Haptoglobin as an indicator for infections) in order to exclude patients and controls with organic diseases. In addition, the control group did not meet the criteria for DSM-IV diagnosis of mental illness, this issue was evaluated by an experienced psychiatrist. In the schizophrenic group,

Table 2. Distribution of antibodies to herpes virus and cytomegalovirus between schizophrenic and Tourette patients.

Infectious agents	Prevalence of seropositivity in % Tourette	Prevalence of seropositivity in % Schizophrenia	Fisher's exact test *
Herpes simplex virus IgG	50.0	80.6	P=0.017
Cytomegalovirus IgG	18.8	48.4	P=0.017

IgG, immunoglobulin G. *Corrections for multiple testing revealed for both Herpes simplex virus IgG and Cytomegalovirus IgG P=0.051.

antipsychotic treatment had to be stopped at least four weeks prior to study inclusion. In the TS group 70.2% were on antipsychotic treatment at the time of study inclusion. Patients and volunteers were recruited from Munich, Germany. Table 1 summarizes the study population characteristics.

Measurement of antibodies

Serum blood samples were obtained from the participants by venipuncture with one 8.5 mL CPDA-Monovette (Sarstedt, Nümbrecht, Germany) in the morning. The samples were stored at -80°C and tested for antibodies using enzyme-linked immunosorbent assay (ELISA) at Max von Pettenkofer-Institute for hygiene and microbiology (Immunoassay systems from Siemens Medical Solution, Diasorin). Immunglobulin G (IgG) and IgM antibody seropositivity was measured of cytomegalovirus (CMV), herpes simplex virus type 1 and 2 (HSV), Epstein-Barr virus (EBV), Toxoplasma gondii (Toxo) and Mycoplasma. In addition IgG and IgA antibodies were evaluated for Chlamydia trachomatis and pneumoniae.

Data analysis

For statistical analysis of categorical variables the Fisher's exact test was applied. Since we did an exploratory study, correction for multiple testing was performed, but is only mentioned in the figure legends as an orientation. In order to test a not normally distributed population the Wilcoxon test was used.

Results

Antibody prevalence in Tourette's syndrome and schizophrenia

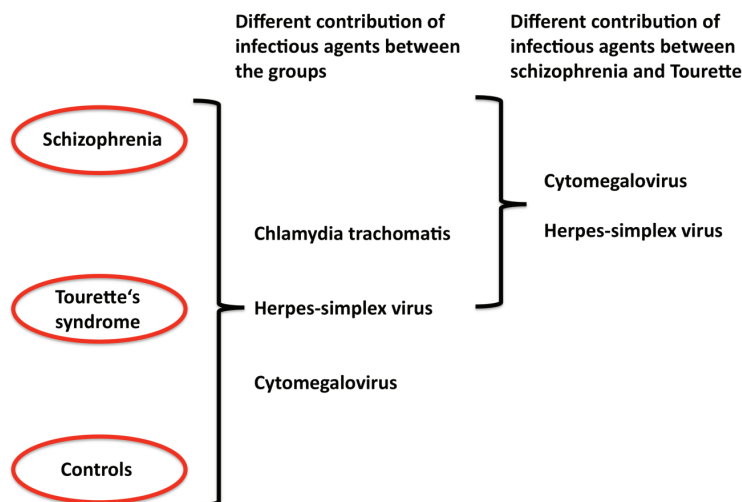
The presence of antibodies to specific infections was compared between schizophrenic and TS patients. We found that schizophrenic patients had significantly higher rates of seropositivity to herpes simplex virus IgG ($P=0.017$) and cytomegalovirus IgG ($P=0.017$) than Tourette patients. For the other investigated infectious agents no differences could be measured. Results are shown in Table 2.

Comparison of Tourette's syndrome, schizophrenia and healthy controls

For Chlamydia trachomatis IgG ($P=0.007$), herpes simplex virus IgG ($P=0.027$) and cytomegalovirus IgG ($P=0.029$) seropositivity differed significantly within the three groups. See Table 3 for results. When comparing only schizophrenia to healthy controls, a strong trend towards a higher rate of Chlamydia trachomatis IgG ($P=0.05$) and also herpes simplex virus IgG ($P=0.056$) could be shown for the schizophrenic group. The TS patients had a significantly higher number of positive antibodies against Chlamydia trachomatis IgG ($P=0.017$) as compared to healthy controls. See Table 4.

Comparison of all seropositivity levels for schizophrenic and Tourette patients

We evaluated the number of seropositivity per person. So the frequency of all viral, bacterial and protozoan antibodies (IgG, IgA and IgM) was counted for each study participant. An infectious index was created for the group of schizophrenic and TS patients. All measured IgG, IgA and IgM antibodies were included. The Wilcoxon test revealed that the group of schizophrenic patients had a significantly higher seropositivity of infectious agents as compared to TS ($P=0.049$). Results are shown in Table 5. Figure 1 shows the summary of the results.



Discussion

The present study revealed that the rate of positive antibodies against infectious agents differs between schizophrenic and TS patients. We showed that there is a higher prevalence of seropositivity for viral infections in the schizophrenic group as compared to TS, because antibodies against herpes simplex virus and cytomegalovirus were overrepresented in schizophrenia. In total, Tourette patients showed lower rates of different antibodies to infectious agents than schizophrenic patients. When the two diseases were compared to healthy controls a strong trend towards a higher rate of Chlamydia trachomatis was found in schizophrenia and TS. These findings are in line with previous studies that concluded that Chlamydia infection represents one risk factor for schizophrenia.²⁷

To our knowledge, so far no study has investigated the comparison of TS and schizophrenia regarding the antibody distribution. Even so, the two diseases TS and schizophrenia show parallels in the underlying pathophysiology their different, but in total elevated vulnerability to infectious agents, might be explained by alterations within the immune status. One possible explanation for the varying disposition of antibodies between the two groups is that there might be a shift within particular immune parameters. As the toll like receptor family plays a fundamental role in virus/ bacteria recognition and activation of innate immunity these TLR might qualify to be further investigated in TS and schizophrenia. The present study found some indications that could point to a disturbed immune system in these diseases: we have seen mainly IgG and not IgM or IgA antibodies to be elevated. IgG antibodies are involved in secondary immune responses and IgM antibodies appear already early in the course of an infection and usually reappear. This finding could indicate that the infections have progressed to dormant infec-

Figure 1. Graphical summary of the study results.

Table 3. Number of positive and negative antibodies to infectious agents for Tourette's syndrome, schizophrenia and controls. IgG: immunoglobulin G.

	Positive antibody titers	Negative antibody titers	Fisher's exact test
Chlamydia trachomatis IgG			
Healthy controls	0	30	P=0.007
Tourette's syndrome	5	21	
Schizophrenia	8	23	
Herpes simplex virus IgG			
Healthy controls	17	13	P = 0.027
Tourette's syndrome	16	16	
Schizophrenia	25	6	
Cytomegalovirus IgG			
Healthy controls	13	17	P = 0.029
Tourette's syndrome	6	26	
Schizophrenia	15	16	

Table 4. Percentage of positive antibodies in comparison of schizophrenic patients and controls and Tourette patients and controls.

Infectious agent	Prevalence of seropositivity in % Schizophrenia	Prevalence of seropositivity in % Healthy controls	Fisher's exact test*
Chlamydia trachomatis IgG	25.8	0.0	P=0.050 (a)
Herpes simplex virus IgG	80.6	54.8	P=0.056 (b)
	Tourette	Healthy controls	
Chlamydia trachomatis IgG	19.2	0.0	P=0.017 (c)
Cytomegalovirus IgG	18.8	43.3	P=0.054 (d)

*a: corrections for multiple testing $P=0.015$; * b: corrections for multiple testing $P=0.112$; * c: corrections for multiple testing $P=0.034$; *d: corrections for multiple testing $P=0.108$.

Table 5. Number of positive antibodies per person. The first column shows possible numbers of positive antibodies. Looking at the first row, there were no schizophrenic patients that had no positive titer, but there are two Tourette individuals that showed no positive titer.

Number of positive antibodies	Schizophrenia	Tourette's syndrome	Wilcoxon test
0	0	2	P= 0.049
1	0	0	
2	5	5	
3	7	9	
4	8	6	
5	6	3	
6	5	1	

tions with a persistent immune response.

Recently the involvement of the immune system in the pathophysiology of psychiatric diseases has gained broad attention: the international schizophrenia consortium has demonstrated an association between the major histocompatibility complex and schizophrenia, implicating aetiological mechanisms involving autoimmunity and infections.²⁸ Numerous studies have identified the important role of immunologic parameters in schizophrenic patients.²⁹ An immune disturbance in schizophrenia was suggested because of elevated levels of interleukin-1 β , tumour necrosis factor- α and a higher nuclear factor- κ B (regulates the cytokine system) activation.³⁰ Furthermore signs of inflammation were found in the brains of schizophrenic patients.³¹

Also for TS evidence for the important role of immune parameters in the disease's pathophysiology is emerging: support for this immunologically based hypothesis of TS comes from studies investigating the prevalence of different immunogenic cells: Kawikova et al. found that TS patients have a decreased number of CD4⁺CD25⁺ regulatory T cells and their number correlated with the severity of symptoms.³² On balance, these results suggest that both innate and adoptive cell mediated mechanisms may be overactive in TS.

A probable mechanism of how infections can influence the cerebral immune balance could be the activation of the tryptophan catabolism via infectious agents and elevated proinflammatory cytokines.³³ The essential amino acid tryptophan gets degraded either to serotonin or over the kynurenine pathway to other products,³⁴ which function either as a NMDA-receptor agonist or antagonist and control the neurotransmitter availability.³⁵ The activation of this kynurenine pathway has been shown to play an important role in the pathophysiology of schizophrenia.³⁶ Also for TS, Behen et al. have identified in an imaging study that TS patients have an abnormal tryptophan metabolism in the cortical and subcortical area.³⁷

There are also some limitations to our study: first, it is known that antipsychotic medication influences the immune system and therefore also the infectiousness might be affected.³⁸ In this study, only the schizophrenic patients were unmedicated considering antipsychotic drugs. The TS patients received in 70.2% antipsychotic treatment at the time of study inclusion. As TS patients usually get diagnosed during childhood, patients at our hospital have started treatment already several years before. A second limitation is that it was not possible to evaluate the rate of sexual activity in patients and controls. This seems important as Chlamydia trachomatis is a sexually transmitted disease. Though the groups were age matched, it is likely that their sexual activity

might resemble. However, there are studies showing that schizophrenic patients suffer from sexual dysfunction and of less social activity and have therefore an impaired sexual life.³⁹ Third, the sample size was rather small and therefore the statistical power might be slightly restricted.

In summary infectious agents might influence the cerebral neurotransmitter balance via activating on the tryptophan catabolism. The precise mechanism, how an altered metabolism of tryptophan might contribute to the pathogenesis of schizophrenic symptoms and tics is not yet fully understood. On the one hand it could reflect a state of immune activation; or on the other hand it might be possible that kynurenine and its neuroactive metabolites (e.g. quinolinic acid) cause directly a toxic effect in the basal ganglia and the CNS. So far the association of infections and the kynurenine pathway seems promising as this finding could have therapeutic implications: at present inhibitors or enhancers of certain metabolites of this pathway are available and being currently tested for different neuropsychiatric conditions.⁴⁰

Conclusions

The outcome of this study emphasizes on the association between infectious agents and psychiatric diseases (schizophrenia and TS). It highlights the differential distribution of seropositivity to these agents in both patient groups. Future studies with larger sample sizes are needed to investigate the precise role of infectious agents as possible contributing factors to psychiatric diseases.

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