Eur Arch Psychiatry Clin Neurosci (2010) 260:359–363
DOI 10.1007/s00406-009-0084-3

ORIGINAL PAPER

Association between intracellular infectious agents and Tourette's syndrome

Daniela Krause · Judith Matz · Elif Weidinger · Jenny Wagner · Agnes Wildenauer · Michael Obermeier · Michael Riedel · Norbert Müller

Received: 16 July 2009 / Accepted: 21 October 2009 / Published online: 5 November 2009

Abstract The underlying pathophysiological mechanisms in Tourette's syndrome (TS) are still unclear. Increasing evidence supports the involvement of infections, possibly on the basis of an altered immune status. Not only streptococci but also other infectious agents may be involved. This study investigates the association between the neurotrophic agents Chlamydia, Toxoplasma and TS. 32 patients with TS and 30 healthy matched controls were included. For each individual, IgA/IgG antibody titers against *Chlamydia trachomatis/pneumoniae* and *Toxoplasma gondii* were evaluated and analyzed with Fisher's exact test. We found a significantly higher rate of TS patients with elevated antibody titers against *Chlamydia trachomatis* ($P = 0.017$) as compared to controls. A trend toward a higher prevalence in the Tourette's group was shown for Toxoplasma ($P = 0.069$). In conclusion, within the TS patients a higher rate of antibody titers could be demonstrated, pointing to a possible role of Chlamydia and Toxoplasma in the pathogenesis of tic disorders. Because none of these agents has been linked with TS to date, a hypothesis is that infections could contribute to TS by triggering an immune response. It still remains unclear whether tic symptoms are partly due to the infection or to changes in the immune balance caused by an infection.

D. Krause (✉) · J. Matz · E. Weidinger · J. Wagner · A. Wildenauer · M. Obermeier · M. Riedel · N. Müller
Department of Psychiatry,
Ludwig-Maximilians University Munich,
Nußbaumstr. 7, 80336 Munich, Germany
e-mail: Daniela.Krause@med.uni-muenchen.de

Keywords *Chlamydia trachomatis* · Immune system · Infections · Tourette's syndrome · *Toxoplasma gondii*

Introduction

Gilles de la Tourette's syndrome (TS) is characterized by multiple motor and vocal tics which wax and wane over time [17]. The onset of this disease is usually at childhood or adolescence with the median age of 7 years [4]. Epidemiological studies have revealed that TS is relatively common (2.9–5.2 cases per 10,000) and more prevalent in boys [38]. A range of neuroimaging, biochemical, neurophysiological, and genetic studies support the concept that TS is an inherited, developmental disorder of synaptic neurotransmission. The involvement of the basal ganglia and the cortico-striato-thalamocortical circuits has been suggested [12, 20, 22] and biological therapy options such as deep brain stimulation are therefore being tested [1].

Recent studies revealed that group A β hemolytic streptococcal infections are an important contributing factor to neuropsychiatric and movement disorders. At present, the clinical phenotype of poststreptococcal tics and obsessive–compulsive disorders is termed as PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection) [24].

In addition to streptococci, several other infectious agents have been proposed to play an essential role in the pathogenesis of TS. Two case reports revealed that *Mycoplasma pneumoniae* might be associated with tic symptoms [10, 28]. This assumption was strengthened by a study that compared 29 Tourette patients to healthy controls regarding the Mycoplasma infection rates. The study found significantly more elevated antibody titers against *Mycoplasma pneumoniae* in TS patients as compared to

controls [27]. Furthermore, an association between herpes simplex virus 1 and the exacerbation of tics was stated [5]. Moreover, an acute infection with *Borrelia burgdorferi* presenting as TS was reported [32].

In addition to the infectious hypothesis for TS, it has been proposed that the involvement of the immune system could be a key component contributing to tic disorders. Beside others, increased levels of pro-inflammatory cytokines [21] and auto-antibodies against basal ganglia have been identified, but are discussed controversially [26, 36]. Also a neurotransmitter dysbalance involving dopaminergic [19] and serotonergic abnormalities has been reported in TS patients [37].

In this study, we investigated the prevalence of intracellular infectious agents that can establish an infection of the central nervous system for Tourette's syndrome patients. In particular, *Toxoplasma gondii*, *Chlamydia trachomatis* and pneumonia were measured.

Methods

Characterization of the patient and control population

For this study, 32 patients with TS (29.6 age ± 15.1 years; 81.0% male) fulfilled the pertinent diagnostic criteria, as defined by the IV edition of the Diagnostic and Statistical Manual (DSM-IV). TS patients reached on the Yale Global Tic Severity Scale (YGTSS) a median number of 40.8 (SD = 17.5). The disease onset of Tourette's syndrome was at mean age of 9.5 years (±6.98 years). Patients were recruited through the Department of Psychiatry of the Ludwig-Maximilians University Munich, Germany. Healthy control subjects were recruited via advertisement. The 30 people of the control population (age 33.7 ± 16.1 years; 58.0% male) were matched with the TS patients group considering ethnicity and age. Controls and TS patients were all Caucasians living in Bavaria, Germany. So patients and volunteers were recruited from the same rather homogenous region with regard to socioeconomic status. All study participants gave their informed consent prior to study inclusion. For this study, the responsible authorities (ethics committee) approved the procedure for sample collection and analysis, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. A concomitant organic disease or acute infections were exclusion criteria. Healthy controls underwent a psychiatric and clinical interview in order to exclude a history of psychiatric or neurologic disorders, autoimmune diseases, and acute medical illness. In the TS group, 70.2% were on antipsychotic treatment at the time of study inclusion. All individuals underwent a clinical and laboratory examination (blood analysis, C-reactive protein) for signs of inflammation or acute infections.

Measurement of antibodies

Serum blood samples were obtained from the participants by venipuncture. 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). Serum IgG and IgA antibodies were measured for *Toxoplasma gondii*, *Chlamydia trachomatis*, and *Chlamydia pneumoniae*.

Definition of cut-off values for positive antibody titers

Chlamydia pneumoniae IgG and IgA were counted as negative when the antibody titers were <10 U/ml. For *Chlamydia trachomatis* IgG and IgA values were classified as negative, when the index was <1. Values of *Toxoplasma gondii* IgA and IgG were evaluated as negative if <5 U/ml.

Data analysis

For the statistical analysis of categorical variables the Fisher's exact test was applied. Since we performed an exploratory study (no estimation of the role of Chlamydia or Toxoplasma was found) no correction for multiple testing was performed.

Results

Antibody titers of three different infectious agents were measured from 32 TS patients and 30 healthy controls.

Bacterial and protozoan antibody prevalence in TS and controls

In the group of TS patients, significantly more positive IgG antibody titers against *Chlamydia trachomatis* ($P = 0.017$) compared to healthy controls were found. For all tested antibodies against Chlamydia a higher prevalence was shown for the TS group, which reached significance in our sample only for *Chlamydia trachomatis* IgG. In addition, for *Toxoplasma gondii* IgG a trend towards a higher prevalence of positive antibody titers within the TS group was calculated ($P = 0.069$). For *Chlamydia pneumoniae* no statistically significant differences were evaluated, however, there was a higher rate of IgG and IgA in the Tourette's group. Also the prevalence of IgA for *Chlamydia trachomatis* and *Toxoplasma gondii* was elevated for TS patients. These results are shown in Table 1.

In order to evaluate to influence of gender on the distribution of antibodies, the antibody titers of male and female were calculated separately. There were no significant

Table 1 Percentage of positive bacterial and protozoan antibody titers in comparison of TS and controls

Bacteria/protozoan	Prevalence of positive antibodies in %		Fisher's exact test
	Tourette's patients	Healthy controls	
Chlamydia trachomatis IgG	19.2	0.0	$P = 0.017$
Chlamydia trachomatis IgA	19.2	10.0	Not sigificant
Chlamydia pneumoniae IgG	60.7	43.3	Not sigificant
Chlamydia pneumoniae IgA	42.8	36.7	Not sigificant
Toxoplasma gondii IgG	57.1	20.0	$P = 0.069$
Toxoplasma gondii IgA	14.3	0.0	Not sigificant

Table 2 Analysis of positive antibody titers considering gender differences

	Male (%)	Female (%)	Odds ratio	*P* value
Chlamydia trach. IgG	20.0	5.4	0.24	0.14
Chlamydia trach. IgA	13.3	13.5	1.02	1
Toxoplasma IgG	30.8	30.0	0.97	1
Toxoplasma IgA	7.7	0	0	0.39

The table shows the percentage of positive antibody titers for male and female patients with regard to Chlamydia and Toxoplasma infection

Table 3 Analysis of the influence of medication status on antibody titers

	No medication (%)	On medication (%)	Odds ratio	*P* value
Chlamydia trach. IgG	3.0	20.0	7.68	0.06
Chlamydia trach. IgA	15.2	15.0	0.99	1
Toxoplasma IgG	24.1	60.0	4.46	0.19
Toxoplasma IgA	0	20.0	Inf.	0.18

The percentage of positive antibody titers to infectious agents is shown in comparison for patients on and off medication

differences between male and female patients. For results see Table 2.

In addition, as some of the TS patients were treated with medication, we measured whether the medication status has an impact on antibody distribution. For *Chlamydia trachomatis* IgG a trend towards more positive titers could be found in patients treated with medication ($P = 0.06$). No significant values could be shown for the other infectious agents. Results are provided in Table 3.

Also the effects of the symptom severity on the antibody prevalence were evaluated with the YGTSS scale. It revealed that higher scores for symptoms severity showed significantly more *Chlamydia trachomatis* infections. See Table 4.

Table 4 Values of YGTSS (scale for symptom severity) with regard to positive and negative antibody titers to infectious agents

YGTSS values per infectious agent			
	Antibodies positive	Antibodies negative	*P* value
Chlamydia trach. IgG	52.8	18.08	0.006
Chlamydia trach. IgA	20.88	21.44	0.85
Toxoplasma IgG	19.8	7.0	0.10
Toxoplasma IgA	44.0	22.48	0.11

The absolute scores of the YGTSS are shown for patients with either positive or negative antibodies to infectious agents

Discussion

The present study reveals that TS patients had a significantly higher rate of positive antibodies against infectious agents as compared to healthy controls. These results emphasize a role of infections in the pathogenesis of (a subtype of) TS patients.

To our knowledge, we are the first ones to demonstrate an association between *Chlamydia trachomatis* and TS. Previously, the involvement of mainly intracellular agents, like viruses (herpes) and intracellular bacteria (Mycoplasma and Borrelia) in the pathogenesis of tic disorders, has been described [5, 27, 32]. In this study, we have focused only on intracellular agents such as Chlamydia and Toxoplasma.

In addition to intracellular agents, another prominent finding regarding the infectious hypothesis of Tourette was the connection to streptococci infections (PANDAS) [24]. However, the causality has yet to be proven [34]. Considering the pathomechanism of this association, it has been suggested that antibodies in PANDAS react with the neuronal cell surface and caudate-putamen and induced calcium–calmodulin-dependent protein kinase II activity in neuronal cells. Therefore, the streptococci antibodies might influence neuronal cell signalling [18]. Furthermore, it was suggested that neurotrophic infections could provoke an abnormal developmental process that moderates or mediates the expression of the TS phenotype. This phenotype would be more susceptible to exacerbations by infectious agents or other unspecific factors [6]. In the case of TS, one possible factor could be that infectious agents do not directly cause psychiatric symptoms but influence the immune balance via the status of a chronic infection. We have seen in our study mainly IgG and not IgA antibodies were elevated in TS. This could indicate that the infections have progressed to dormant infections with a persistent immune response. For this study, we chose to investigate IgA antibodies instead of IgM, because they seem to be more sensitive for the detection of Toxoplasma and Chlamydia [3, 7]. As especially *Chlamydia trachomatis* seems

to be involved in autoimmune processes (for example reactive arthritis [9, 33]), this suggests that Chlamydia might trigger (auto-)immune responses also in TS. This assumption is further strengthened since TS has been discussed as an autoimmune disease [15]. The underlying pathophysiology of how Chlamydia might cause movement disorders remains elusive. An in vitro study investigated a microglia cell line that has been infected with Chlamydia and showed an enhanced production of proinflammatory cytokines after infection [16].

Another probable mechanism for the influence of infections on the cerebral immune balance could be the activation of the tryptophan catabolism via infectious agents and proinflammatory cytokines [8]. Especially in microglia, which are the resident innate immune cells of the brain, tryptophan gets degraded to serotonin and to other products of this metabolism [13], which function either as a NMDA-receptor agonist or antagonist and control the neurotransmitter availability [30]. So far, an imaging study of Behen et al. [2] has identified that in TS there is an abnormal tryptophan metabolism in the cortical and subcortical area. These results are in line with plasma kynurenine levels, that have been shown to be elevated in Tourette's syndrome [31]. However, these findings are still controversial in literature. Hoekstra et al. [14] observed an unaltered kynurenine pathway in patients with tic disorders. In summary, this indicates that infectious agents might influence the cerebral neurotransmitter balance via the tryptophan catabolism. The association of infections and the kynurenic pathway could have therapeutic implications, as at present inhibitors of certain metabolites of this pathway are available [8].

There are also some limitations to our study. The first one has to do with the age of the participants. The disease onset of Tourette's syndrome was at a mean age of 9.5 years and study participants showed a mean age of 29.6 years, it is difficult to draw conclusions whether the higher infection rates show a pathophysiologic cause or a secondary phenomenon. Chlamydia infection rates in early childhood are as low as 4.7% [35] and increase especially when sexual activity begins. In 2006, among youths aged 10–14 years, 12.364 cases of Chlamydia were reported in females and 1.238 in males according to the US 'Nationally Notifiable Disease Surveillance System' [11]. Therefore, further studies investigating the clinical amelioration of TS with regard to antibiotic treatment are needed.

The majority of our sample of TS patients was on antipsychotic treatment. It is known that antipsychotics can reduce infections and influence the immune balance [23, 29], so it would be import to conduct another study that investigates drug-naïve or unmedicated TS patients. In unmedicated patients, an even higher rate of positive antibody titers could be expected, as it has been shown in the cerebrospinal fluid in schizophrenic patients [23]. In this study no significant differences of the antibody distribution were found with regard to medication status, but there was a slight trend towards more positive antibodies to *Chlamydia trachomatis* IgG for medicated TS patients. A further limitation could be that there were more males in the Tourette's group (81%) than in the control group (58%). This is of importance because infection rates of Chlamydia differ between sexes. In 2007, the overall rate of reported chlamydial infection among women in United States (543.6 cases per 100,000 females) was almost three times higher than the rate among men (190.0 cases per 100,000 males). This could be explained by the fact that a greater number of women are screened for this infection and that many of the sexual partners of women with Chlamydia are not being diagnosed or reported as having Chlamydia [25]. The present study revealed no differences between the antibody distributions regarding gender. The antibody distribution showed only differences for symptoms severity. This demonstrates that TS patients who suffer from severe symptoms (high YGTSS score) had a significantly higher rate of positive titers against *Chlamydia trachomatis*: An indicator for the prominent role of Chlamydia in profoundly ill patients.

In conclusion, this exploratory study showed an increased prevalence of infections in TS patients, but further research is needed to clarify the involvement of infectious agents, the immune system, and the neurotransmitter balance on the pathogenesis of TS.

Acknowledgments This study has been financed by own resources of the Department of Psychiatry of the Ludwig-Maximilians University Munich, Germany and no research grants from other sources were involved.

Conflicts of interest statement All authors report no biomedical financial interest or potential conflicts of interest for the research covered in the article submitted

References

1. Anonymous (2007) Psychiatric challenges throughout the life span. In: Abstracts of the Second Meeting of West European Societies of Biological Psychiatry. December 13–15, 2007. Strasbourg, France. Eur Arch Psychiatry Clin Neurosci 257(Suppl 2):4–61
2. Behen M, Chugani HT, Juhasz C, Helder E, Ho A, Maqbool M, Rothermel RD, Perry J, Muzik O (2007) Abnormal brain tryptophan metabolism and clinical correlates in Tourette syndrome. Mov Disord 22(15):2256–2262
3. Bertozzi LC, Suzuki LA, Rossi CL (1999) Serological diagnosis of toxoplasmosis: usefulness of IgA detection and IgG avidity determination in a patient with a persistent IgM antibody response to *Toxoplasma gondii*. Rev Inst Med Trop Sao Paulo 41(3):175–177
4. Bruun RD, Budman CL (1997) The course and prognosis of Tourette syndrome. Neurol Clin 15(2):291–298

5. Budman CL, Kerjakovic M, Bruun RD (1997) Viral infection and tic exacerbation. J Am Acad Child Adolesc Psychiatry 36(2):162
6. Burd L, Li Q, Kerbeshian J, Klug MG, Freeman RD (2009) Tourette syndrome and comorbid pervasive developmental disorders. J Child Neurol 24(2):170–175
7. Cevenini R, Sarov I, Rumpianesi F, Donati M, Melega C, Varotti C, La PM (1984) Serum specific IgA antibody to *Chlamydia trachomatis* in patients with chlamydial infections detected by ELISA and an immunofluorescence test. J Clin Pathol 37(6):686–691
8. Costantino G (2009) New promises for manipulation of kynurenine pathway in cancer and neurological diseases. Expert Opin Ther Targets 13(2):247–258
9. Cragnolini JJ, Garcia-Medel N, de Castro JA (2009) Endogenous processing and presentation of T-cell epitopes from *Chlamydia trachomatis* with relevance in HLA-B27-associated reactive arthritis. Mol Cell Proteomics 8(8):1850–1859
10. Ercan TE, Ercan G, Severge B, Arpaozu M, Karasu G (2008) Mycoplasma pneumoniae infection and obsessive-compulsive disease: a case report. J Child Neurol 23(3):338–340
11. Gavin L, MacKay AP, Brown K, Harrier S, Ventura SJ, Kann L, Rangel M, Berman S, Dittus P, Liddon N, Markowitz L, Sternberg M, Weinstock H, vid-Ferdon C, Ryan G (2009) Sexual and reproductive health of persons aged 10–24 years—United States, 2002–2007. MMWR Surveill Summ 58(6):1–58
12. Grisham JR, Anderson TM, Sachdev PS (2008) Genetic and environmental influences on obsessive-compulsive disorder. Eur Arch Psychiatry Clin Neurosci 258(2):107–116
13. Heyes MP, Achim CL, Wiley CA, Major EO, Saito K, Markey SP (1996) Human microglia convert l-tryptophan into the neurotoxin quinolinic acid. Biochem J 320(Pt 2):595–597
14. Hoekstra PJ, Anderson GM, Troost PW, Kallenberg CG, Minderaa RB (2007) Plasma kynurenine and related measures in tic disorder patients. Eur Child Adolesc Psychiatry 16(Suppl 1): 71–77
15. Hoekstra PJ, Kallenberg CG, Korf J, Minderaa RB (2002) Is Tourette's syndrome an autoimmune disease? Mol Psychiatry 7(5):437–445
16. Ikejima H, Friedman H, Yamamoto Y (2006) *Chlamydia pneumoniae* infection of microglial cells in vitro: a model of microbial infection for neurological disease. J Med Microbiol 55 (Pt 7): 947–952
17. Jankovic J (2001) Tourette's syndrome. N Engl J Med 345(16): 1184–1192
18. Kirvan CA, Swedo SE, Snider LA, Cunningham MW (2006) Antibody-mediated neuronal cell signaling in behavior and movement disorders. J Neuroimmunol 179(1–2):173–179
19. Krause KH, Dresel S, Krause J, Kung HF, Tatsch K, Lochmuller H (2002) Elevated striatal dopamine transporter in a drug naive patient with Tourette syndrome and attention deficit/hyperactivity disorder: positive effect of methylphenidate. J Neurol 249(8): 1116–1118
20. Leckman JF, Cohen DJ, Goetz CG, Jankovic J (2001) Tourette syndrome: pieces of the puzzle. Adv Neurol 85:369–390
21. Leckman JF, Katsovich L, Kawikova I, Lin H, Zhang H, Kronig H, Morshed S, Parveen S, Grantz H, Lombroso PJ, King RA (2005) Increased serum levels of interleukin-12 and tumor necrosis factor-alpha in Tourette's syndrome. Biol Psychiatry 57(6):667–673
22. Leckman JF, Peterson BS, Anderson GM, Arnsten AF, Pauls DL, Cohen DJ (1997) Pathogenesis of Tourette's syndrome. J Child Psychol Psychiatry 38(1):119–142
23. Leweke FM, Gerth CW, Koethe D, Klosterkotter J, Ruslanova I, Krivogorsky B, Torrey EF, Yolken RH (2004) Antibodies to infectious agents in individuals with recent onset schizophrenia. Eur Arch Psychiatry Clin Neurosci 254(1):4–8
24. Mell LK, Davis RL, Owens D (2005) Association between streptococcal infection and obsessive-compulsive disorder, Tourette's syndrome, and tic disorder. Pediatrics 116(1):56–60
25. Miller WC, Ford CA, Morris M, Handcock MS, Schmitz JL, Hobbs MM, Cohen MS, Harris KM, Udry JR (2004) Prevalence of chlamydial and gonococcal infections among young adults in the United States. JAMA 291(18):2229–2236
26. Morris CM, Pardo-Villamizar C, Gause CD, Singer HS (2009) Serum autoantibodies measured by immunofluorescence confirm a failure to differentiate PANDAS and Tourette syndrome from controls. J Neurol Sci 276(1–2):45–48
27. Muller N, Riedel M, Blendinger C, Oberle K, Jacobs E, Abele-Horn M (2004) Mycoplasma pneumoniae infection and Tourette's syndrome. Psychiatry Res 129(2):119–125
28. Muller N, Riedel M, Forderreuther S, Blendinger C, Abele-Horn M (2000) Tourette's syndrome and Mycoplasma pneumoniae infection. Am J Psychiatry 157(3):481–482
29. Muller N, Riedel M, Hadjamu M, Schwarz MJ, Ackenheil M, Gruber R (1999) Increase in expression of adhesion molecule receptors on T helper cells during antipsychotic treatment and relationship to blood-brain barrier permeability in schizophrenia. Am J Psychiatry 156(4):634–636
30. Muller N, Schwarz M (2006) Schizophrenia as an inflammation-mediated dysbalance of glutamatergic neurotransmission. Neurotox Res 10(2):131–148
31. Rickards H, Dursun SM, Farrar G, Betts T, Corbett JA, Handley SL (1996) Increased plasma kynurenine and its relationship to neopterin and tryptophan in Tourette's syndrome. Psychol Med 26(4):857–862
32. Riedel M, Straube A, Schwarz MJ, Wilske B, Muller N (1998) Lyme disease presenting as Tourette's syndrome. Lancet 351(9100):418–419
33. Savolainen E, Kettunen A, Narvanen A, Kautiainen H, Karkkainen U, Luosujarvi R, Kaipiainen-Seppanen O (2009) Prevalence of antibodies against *Chlamydia trachomatis* and incidence of *C. trachomatis*-induced reactive arthritis in an early arthritis series in Finland in 2000. Scand J Rheumatol 18:1–4
34. Shulman ST (2009) Pediatric autoimmune neuropsychiatric disorders associated with streptococci (PANDAS): update. Curr Opin Pediatr 21(1):127–130
35. Silveira MF, Ghanem KG, Erbelding EJ, Burke AE, Johnson HL, Singh RH, Zenilman JM (2009) *Chlamydia trachomatis* infection during pregnancy and the risk of preterm birth: a case-control study. Int J STD AIDS 20(7):465–469
36. Snider LA, Swedo SE (2004) PANDAS: current status and directions for research. Mol Psychiatry 9(10):900–907
37. Steeves TD, Fox SH (2008) Neurobiological basis of serotonin-dopamine antagonists in the treatment of Gilles de la Tourette syndrome. Prog Brain Res 172:495–513
38. Tanner CM, Goldman SM (1997) Epidemiology of Tourette syndrome. Neurol Clin 15(2):395–402