

ORIGINAL ARTICLE

Neuropsychiatric symptoms are common in immunocompetent adult patients with *Toxoplasma gondii* acute lymphadenitis

WENG KIT WONG¹, ARLO UPTON² & MARK G. THOMAS¹

From the ¹Department of Molecular Medicine and Pathology, Faculty of Medical and Health Sciences, The University of Auckland, and ²Microbiology Department, Labtests, Auckland, New Zealand

Abstract

Background: Chronic toxoplasmosis has been shown to be strongly associated with a range of neuropsychiatric effects including schizophrenia and suicide. However there have not been any prospective, community-based studies of the neuropsychiatric effects of acute toxoplasmosis in adult immunocompetent patients. **Methods:** Adult patients with a positive serum IgM anti-*Toxoplasma gondii* test result, in the context of an acute illness with lymphadenopathy, were invited to complete a questionnaire seeking information relating to the nature, severity, and duration of symptoms in the months following the diagnosis of acute toxoplasmosis. **Results:** Laboratory testing identified a total of 187 adults who had a positive serum IgM anti-*T. gondii* test result between 1 January and 30 November 2011. Consent to contact 108/187 (58%) patients was provided by their family doctor; 37 (34%) of these 108 patients completed and returned the questionnaire. Questionnaires from the 31/108 (29%) patients who reported swollen lymph nodes during their illness were included in the study. Fatigue (90%), headache (74%), difficulty concentrating (52%), and muscle aches (52%) were the most commonly reported symptoms. These symptoms commonly persisted for at least 4 weeks. Twenty-seven of 31 (87%) subjects reported a moderate or severe reduction in their overall physical and mental health during the first 2 months of illness. **Conclusions:** Acute toxoplasmosis in immunocompetent adults commonly causes moderately severe neuropsychiatric symptoms that might result from replication of the organism in the central nervous system with consequent effects on brain function. Patients should be advised that such symptoms are common and reassured that they usually resolve completely within a few months.

Keywords: *Acute toxoplasmosis, neuropsychiatric symptoms, fatigue, headache, impaired concentration*

Introduction

Toxoplasmosis is a common human infection worldwide. Most descriptions of acute *Toxoplasma gondii* infection state that it is either asymptomatic or the cause of a relatively benign, self-limited illness in the overwhelming majority of immunocompetent patients [1]. However there is a large body of evidence that chronic *T. gondii* infection is associated with significant neuropsychiatric effects. For example, serological evidence of chronic *T. gondii* infection is strongly associated with schizophrenia, self-directed violence in women, and with more subtle effects in a variety of neuropsychiatric tests [2–4]. Investigations in experimentally infected rodents have consistently shown effects of chronic *T. gondii* infection on rodent

behaviour [5,6], which may be due to excessive synthesis and secretion of dopamine by *T. gondii*-infected cells [7].

Previous studies of immunocompetent patients with acute toxoplasmosis have found that ‘asthenia’ and ‘cephalea’ [8], ‘fatigue’ [9], ‘malaise’ [10], and ‘confusion’ [11] are commonly reported symptoms. However the prevalence and duration of these symptoms, and the magnitude and duration of their effect on quality of life have not been adequately investigated in a population-based study. We surveyed adults with a recent serologically confirmed diagnosis of acute toxoplasmosis associated with lymphadenitis to determine the prevalence and duration of neuropsychiatric symptoms and their impact on the patient’s quality of life.

Correspondence: M. G. Thomas, Department of Molecular Medicine and Pathology, Faculty of Medical and Health Sciences, The University of Auckland, Private Bag 92019, Auckland, New Zealand. Tel: +64 9 373 7599. Fax: +64 9 373 7492. E-mail: mg.thomas@auckland.ac.nz

(Received 19 July 2012; accepted 27 September 2012)

Methods

Adults resident in the greater Auckland area with a positive serum IgM anti-*T. gondii* test result (ADVIA Centaur® and ADVIA Centaur XP® systems, Siemens Healthcare Diagnostics Inc., NY, USA) in a blood sample tested between 1 January and 30 November 2011 by Labtests NZ Ltd, the sole medical laboratory funded to perform diagnostic testing of samples collected from outpatients at the request of their family doctor, were identified from the computerized laboratory database. These potential subjects were sent a questionnaire in December 2011 seeking information about the symptoms that they experienced during and after their illness. Consent to contact these patients was sought and received from their family doctors, and written informed consent was sought and received from the patients.

Acute toxoplasmosis was diagnosed in subjects who had a serum IgM titre ≥ 1.0 and who reported symptoms of lymphadenopathy at the time of laboratory testing. The questionnaire sought basic demographic information, information about past medical history, the features of the acute illness, and the duration and severity of any effects of the illness on the subject's overall physical and mental health. Subjects were asked to score their overall physical and mental health for each month, from 2 months before the onset of acute toxoplasmosis to 6 months after the start of the illness, using a numeric score of: 1 ("the worst physical and mental health I can imagine"), 2 ("severe reduction in physical and mental health"), 3 ("moderate reduction in physical and mental health"), 4 ("minor reduction in physical and mental health"), or 5 ("best ever physical and mental health"). The questionnaire was developed for this study, based on reports of symptoms by patients previously cared for by one of the authors (MGT) and was piloted on 2 patients with acute toxoplasmosis who consulted one of the authors (MGT) during 2010. Patients were also invited to provide any further written information about the illness that they thought might be of interest to the researchers.

The study was approved by the New Zealand Ministry of Health Northern X Regional Ethics Committee.

Results

Between 1 January and 30 November 2011, Labtests tested 1929 samples from 1817 adult patients for IgM and IgG antibodies to *T. gondii*. Two hundred and eighty-three samples from 187 adult patients had a positive IgM result. The IgM anti-*T. gondii* titre was 1.0–2.0 in 76 patients, 2.01–10.0 in 33

patients, and 10.01–100 in 78 patients. Consent to contact 108 patients who had a positive IgM anti-*T. gondii* result in a sample submitted to Labtests was provided by their family doctors. Questionnaires were sent to these 108 patients and were returned by 37 patients. The study group comprised 31 patients who reported lymphadenopathy and had a serum anti-*T. gondii* IgM titre ≥ 1.0 .

The median age of the subjects was 34 y (range 10–66 y). Twenty-six of 31 (84%) subjects were female. The median IgM anti-*T. gondii* titre was 15.31 (range 1.21–40). The median duration between the onset of symptoms of acute toxoplasmosis and completion of the questionnaire was 8 months (range 1–15 months). Apart from 1 subject who had previously undergone a splenectomy, no subjects reported suffering from an immunosuppressing illness. None were being treated with immunosuppressive medications. Two subjects were pregnant at the onset of the toxoplasmosis illness. Sixteen described contact with cats or cat faeces, and 4 reported gardening with bare hands at least once a week. One subject was briefly admitted to hospital because of fever (38.7°C), drenching sweats, muscle aches, and tachycardia (heart rate 115/min). Table I shows the clinical features of the 31 subjects with acute toxoplasmosis.

Lymphadenopathy, a requirement for inclusion in the study, was reported by all subjects. The median duration of lymphadenopathy was 8 weeks (range 1–65 weeks). Fatigue (90%), headache (74%), and difficulty concentrating (52%) were commonly reported symptoms. Fatigue persisted for a median duration of 6 weeks, while headache and difficulty concentrating persisted for median durations of 5 weeks and 11 weeks, respectively.

In the 2 months before the onset of acute toxoplasmosis, 19 subjects gave their overall physical and mental health a score of 5 (best ever physical and mental health), 11 subjects a score of 4 (minor

Table I. Prevalence and duration of symptoms in immunocompetent adults with acute toxoplasmosis.

Symptom	Prevalence (%)	Median and range of duration (n)
Swollen lymph nodes	31/31 (100)	8; 1–65 (30)
Fever	12/31 (39)	3; 1–12 (11)
Headache	23/31 (74)	5; 1–26 (19)
Fatigue	28/31 (90)	6; 1–47 (23)
Difficulty concentrating	16/31 (52)	11; 1–47 (12)
Change in vision	4/31 (13)	4; 4–22 (3)
Muscle aches	16/31 (52)	4; 1–20 (14)

Note. Data are presented as the number of subjects who reported the symptom, with the percentage in parenthesis, and as the median and range of duration of the symptom in weeks, with the number who reported the duration of the symptom in parenthesis.

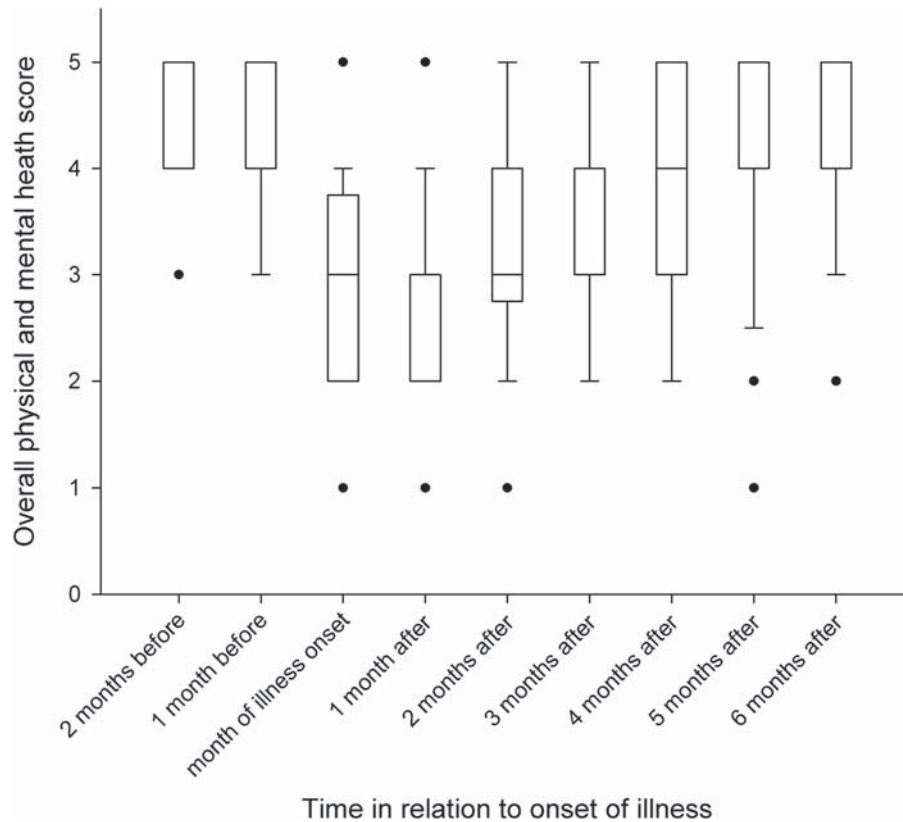


Figure 1. Box and whisker plot of scores of overall physical and mental health from 2 months before the onset of acute toxoplasmosis to 6 months after the onset of illness.

reduction in physical and mental health), and 1 subject a score of 3. However, in the 2 months after the onset of acute toxoplasmosis 2 subjects gave their overall physical and mental health a score of 1 (the worst physical and mental health I can imagine), 14 subjects a score of 2 (severe reduction in physical and mental health), 11 subjects a score of 3 (moderate reduction in physical and mental health) and only 4 subjects a score of 4 or 5. At 4 months after the onset of illness, 7/26 subjects (27%) gave their overall physical and mental health a score that was less than that in the 2 months before the onset of illness. Figure 1 illustrates the mean scores of overall physical and mental health from 2 months before the onset of acute toxoplasmosis to 6 months after the illness began. The scores of overall physical and mental health in the month illness began (mean 2.93, standard deviation (SD) 0.96), at 1 month after illness began (mean 2.96, SD 0.96), and at 2 months after illness began (mean 3.31, SD 1.09) were all significantly less than the score of overall physical and mental health at 2 months before the onset of illness (mean 4.61, SD 0.57) ($p < 0.001$).

Twenty-four subjects provided further comments about the effects of their illness on their quality of life. A common theme among these comments was

an increased feeling of fatigue. Several subjects reported not having fully recovered from this fatigue several months after the onset of illness. Two subjects who reported high levels of physical fitness prior to the onset of toxoplasmosis, described marked reductions in exercise performance during their illness. One subject reported feeling “the most depressed that I have ever felt in my life”. Another reported severe dizziness and vertigo during the first 2 weeks after the onset of illness, which then gradually resolved over the subsequent 6 months.

Discussion

We found that fatigue, headache, and difficulty concentrating were common symptoms in patients with acute *Toxoplasma lymphadenitis* and that these and other symptoms caused a significant deterioration in patients’ overall mental and physical health, which frequently persisted for 2 to 3 months. Previous descriptions of acute toxoplasmosis in the immunocompetent adult have characterized it as a “benign, self-limited, non-specific illness that rarely needs treatment” [1]. It is widely accepted that a significant proportion of immunocompetent people who acquire *T. gondii* infection in adult life remain asymptomatic

or experience very mild symptoms. We chose to study adult patients who had lymphadenopathy in the context of an illness that led their family doctor to suspect acute toxoplasmosis. Our findings demonstrate that such patients may suffer several weeks of symptoms with significant distress. Perhaps because acute toxoplasmosis is commonly perceived as a minor illness, there have not been any randomized controlled trials of treatment with agents active against *T. gondii* in immunocompetent adults with acute toxoplasmosis. Our results indicate that in patients with lymphadenitis as a component of their acute infection, the symptoms of acute toxoplasmosis are sufficiently common, severe, and prolonged to warrant trials of such treatment. In the absence of any evidence for benefit from treatments active against *T. gondii*, patients with acute *Toxoplasma* lymphadenitis should at least be advised of the commonly expected symptoms and reassured that while such symptoms may be relatively severe, they will usually resolve within a few months.

Our study has a number of weaknesses. A relatively small proportion of potential subjects completed the questionnaire, and there was a marked female bias in the respondents. We relied on self-reported symptoms and did not have access to any clinical information other than the anti-*T. gondii* antibody titres. We did not include a control group, and relied on patients' subjective assessment of their symptoms, reported some months after the onset of illness, which may have resulted in recall bias. However the strengths of our study include the fact that we attempted to recruit all adult patients with a diagnosis of acute *Toxoplasma* lymphadenitis made by their family doctor, rather than accumulate patients referred to a hospital or specialist practice which inevitably would have resulted in the selection of a biased cohort of patients. We obtained data concerning the duration of symptoms and the duration of the effects of the illness on the patient's overall health, information that is not available from previous articles that have reported only the symptoms present in patients at the time of diagnosis. We consider it likely that of the 108 subjects sent the questionnaire those with the most severe symptoms would have been more likely to complete and return the questionnaire. However, even if the 76 subjects who did not respond to our questionnaire had no significant neuropsychiatric symptoms associated with their episode of acute toxoplasmosis, our results still indicate that relatively severe and prolonged symptoms occur in at least 15–20% of patients.

Accumulating evidence suggests that infection of the central nervous system by *T. gondii* is common in immunocompetent experimentally infected animals and results in profound effects on their behaviour. Rodents with chronic *T. gondii* infection appear

normal in all other respects but have a reversal of their normal aversion to the smell of domestic cats and other felines [5,6]. This alteration in rodent behaviour is believed to enhance predation of infected rodents by felines in the wild and thus facilitate the *T. gondii* lifecycle. There is strong evidence that increased secretion of dopamine by neural cells infected with *T. gondii* may be responsible for this alteration in the behaviour of chronically infected rodents [7].

The high incidence of toxoplasmic encephalitis in patients with severe immunosuppression suggests that chronic infection of the central nervous system is a very common consequence of acute *T. gondii* infection in humans. It is possible that persistent infection of the central nervous system is responsible for the strong association between schizophrenia and self harm and chronic *T. gondii* infection [2,3], and for the more subtle alterations in behaviour seen when various population groups with serologic evidence of chronic *T. gondii* infection are compared with uninfected controls [4]. Our findings raise the possibility that infection of the central nervous system may be the cause of the moderately severe neuropsychiatric symptoms that we found occurring relatively commonly in patients with acute toxoplasmosis. Future prospective studies of acute toxoplasmosis may help to more precisely determine the prevalence, severity, and duration of these symptoms and elucidate the underlying pathological processes. We hope that the findings of this study will result in a more widespread appreciation that for many patients acute toxoplasmosis is a moderately disabling illness with relatively severe and prolonged neuropsychiatric effects.

Acknowledgements

We are grateful to the subjects who participated in the study and to their family doctors for assistance with enrolment.

Declaration of interest: WKW was supported by a grant from the University of Auckland during the period of the study.

References

- [1] Montoya JG, Liesenfeld O. Toxoplasmosis. *Lancet* 2004;363:1965–76.
- [2] Torrey EF, Yolken RH. *Toxoplasma gondii* and schizophrenia. *Emerg Infect Dis* 2003;9:1375–80.
- [3] Pedersen MG, Mortensen PB, Norgaard-Pedersen B, Postolache TT. *Toxoplasma gondii* infection and self-directed violence in mothers. *Arch Gen Psychiatry* 2012; Jul 2:1–8. [Epub ahead of print]

- [4] Lafferty KD. Can the common brain parasite, *Toxoplasma gondii*, influence human culture? *Proc Biol Sci* 2006;273:2749–55.
- [5] Vyas A, Kim SK, Giacomini N, Boothroyd JC, Sapolsky RM. Behavioural changes induced by *Toxoplasma* infection of rodents are highly specific to aversion of cat odors. *Proc Natl Acad Sci USA* 2007;104:6442–7.
- [6] Webster JP, Lamberton PH, Donnelly CA, Torrey EF. Parasites as causative agents of human affective disorders? The impact of anti-psychotic, mood-stabilizer, and anti-parasite medication on *Toxoplasma gondii*'s ability to alter host behaviour. *Proc Biol Sci* 2006;273:1023–30.
- [7] Prandovszky E, Gaskell E, Martin H, Dubey JP, Webster JP, McConkey GA. The neurotropic parasite *Toxoplasma gondii* increases dopamine metabolism. *PLoS One* 2011;6:e23866
- [8] Durlach RA, Kaufer F, Carral L, Hirt J. Toxoplasmic lymphadenitis—clinical and serological profile. *Clin Microbiol Infect* 2003;9:625–31.
- [9] Beverley JK, Beattie CP. Glandular toxoplasmosis. A survey of 30 cases. *Lancet* 1958;2:379–84.
- [10] McCabe RE, Brooks RG, Dorfman RF, Remington JS. Clinical spectrum in 107 cases of toxoplasmic lymphadenopathy. *Rev Infect Dis* 1987;9:754–74.
- [11] Teutsch SM, Juranek DD, Sulzer A, Dubey JP, Sikes RK. Epidemic toxoplasmosis associated with infected cats. *N Engl J Med* 1979;300:695–9.