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OBSERVATIONAL STUDY

# Recurrent headaches may be caused by cerebral toxoplasmosis

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## Abstract

**AIM:** To establish seroprevalence and provide characteristics of Toxoplasma gondii (TG) infection in children with recurrent headaches.

**METHODS:** The study was performed in 178 children aged 7-17 years admitted consecutively to the Department of Pediatric Neurology from November 2009 to July 2011. The children were surveyed with a questionnaire with the help and assistance of their parents and blood samples taken on admission were studied for the presence of specific anti-TG IgM, IgG antibodies and IgG avidity using enzyme immunoassay Platelia Toxo IgM, IgG.

**RESULTS:** The study showed that 19 children (8 boys, 11 girls; 8-17 years old, mean age 14.36 years) had high serum anti-TG IgG antibody levels (range: 32.2 > 240 UI/mL, mean 120.18 UI/mL; positive value for IgG was ⩾ 9 UI/mL). The avidity index (AI) ranged from 0.202 to 0.925 (scale: ⩾ 0.5 high AI). The results for IgM antibodies were all negative and the obtained results ranged from 0.113 to 0.25 U/mL (mean = 0.191 IU/mL) and all values below 0.8 IU/mL were considered negative. The most frequent complaints found in the seropositive patients were headaches that affected the frontal (13 children), occipital (4) and parietal areas (5). Headaches usually had a pulsating (in 7 patients) and squeezing (6) character and rarely were piercing, dull or expanding. Interestingly, 8 children did not feel discomfort during the headaches, probably because they did not have sufficiently increased intracranial pressure yet. The headaches usually appeared 1-2 times/mo, lasted for 2-6 h, and had a mean intensity of 5.5 points in a 10 point subjective scale. The comorbidities included epilepsy (5 patients), various infections in 3 children (chronic eustachitis, chronic rhinitis, chronic purulent tonsillitis, streptococcal pharyngitis, meningitis, allergic diseases), disturbances of behavior, deficits of attention, and ocular and motor concentration disorders in 1 child. The electroencephalographic and neuroimaging studies performed in our patients had a very limited value in establishing cerebral toxoplasmosis.

**CONCLUSION:** Ten point six seven percent of the studied children had markedly increased serum anti-TG IgG antibodies and high AI indicated chronic infestation. It is suggested that tests for TG infection should be introduced to routine diagnostics in patients with recurrent headaches.



**Key words:** Recurrent headaches; Children; Seroprevalence of anti-Toxoplasma gondii IgG antibodies; IgG avidity; Chronic Toxoplasma gondii infection; Cerebral

toxoplasmosis

**Core tip:** This work estimated the seroprevalence and characteristics of Toxoplasma gondii (TG) infection in 178 children admitted consecutively to the Pediatric Neurology Department because of recurrent headaches. Nineteen children had significantly increased serum anti-TG IgG antibody levels and high avidity index which indicated chronic infection. It is suggested to treat these patients specifically for 5-7 d and eventually be aware of the Jarisch-Herxheimer reaction.

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## INTRODUCTION

Migraine and/or other types of headaches are a common concern affecting 5% and 10% of children and adolescents, respectively, as well as nearly 30% of reproductive-age women[1,2]. Studies have shown that children with recurrent headaches are subjected to an ever-increasing risk of such diseases in adulthood as well as many physical symptoms and psychiatric disturbances, such as depression disorders[3]. According to the National Headache Foundation, each year up to 45 million United States citizens suffer from chronic and recurrent headaches with productivity loss amounts each year as much as 50 billion dollars due to work absence and health care costs generated by headache attacks[4]. From 1989-1990, the Australian National Health Survey conducted an analysis of 57000 people, concluding that about 12.2% of them had reported headaches in the past two weeks. As many as 280000 people had typical migraine attacks, while 2 million people reported more subtle forms of headaches during the same 2 wk period[5,6].

Toxoplasma gondii (TG) is a ubiquitous protozoan parasite, infecting up to 30 species of birds and mammals, including the population of humans. Chronic asymptomatic infestation affects 30%-50% of the world population with hosts of parasite cysts located mainly in the central nervous system[7,8]. It is estimated that in continental Europe, around 50%-80% of the entire human population has a latent TG infection. In Paris, 84% of pregnant women had serum antibodies against the parasite[7], while in Poznań (Poland), the number reaches 60%[9]. In Poland, the majority of pigs, cattle and sheep (approximately 80%) have positive serological tests for TG infection[9,10]. It is known that domestic pets may be a source of TG infection because it was reported that, for example, even turtles were susceptible to the RH strain of TG and harbored the parasite for at least a month[7,11,12]. Studies involving immune-competent patients with acquired toxoplasmosis revealed that the most common symptoms of acquired cerebral toxoplasmosis were headaches and peripheral lymphadenopathy (88% and 77% of patients, respectively)[13]. Unfortunately, cerebral toxoplasmosis is not mentioned in textbooks or scientific papers as a cause of various types of headaches. Prandota[14-16] reported that pediatric and adult patients who suffered from headaches severe enough to undergo hospitalization had lumbar punctures and several other diagnostic tests performed but were finally found to have TG infection. The complaints disappeared after repeated anti-parasite treatment regimens. It must be noted that at present patients with migraine and other types of headaches usually receive only symptomatic drugs. The recurrent character of the headaches and frequently applied expensive diagnostic procedures may suggest that children and adolescents suffering from the condition should have serological tests for TG infestation commonly performed.

The purpose of this study was: (1) to estimate the seroprevalence of TG infection in the population of children hospitalized with recurrent headaches and symptoms and/or signs of the central nervous system abnormalities; (2) to establish whether it was an acute or chronic infection; (3) to summarize patients' complaints and describe clinical symptoms with special attention to their duration, intensity, frequency and abnormalities in laboratory data, including electroencephalographic (EEG) and neuroimaging procedures; and (4) to assess associated comorbidities.

## MATERIALS AND METHODS

The study was performed in 178 children aged 7-17 admitted consecutively from November 2009 to July 2011 to the Department of Pediatric Neurology in Wroclaw. All of them reported headaches as a major complaint and the reason for hospitalization but also as a secondary condition.

The children were surveyed with a questionnaire with the help and assistance of their parents and blood samples were taken on admission in order to do necessary laboratory tests and study the presence of specific anti-TG IgG, IgM and the index of IgG avidity.

To collect demographic, social and medical data, a specially prepared questionnaire was used. It consisted of three parts: (1) the general part included questions concerning the place of living and contact with domestic pets; (2) the family history with a special regard to occurrence of neurological disturbances, including headaches, in first-blood family members; and (3) the epidemiological part dealing with frequency, intensity and character of headaches, affected part of the head, concomitant symptoms and circumstances correlated with the onset of pain, as well as the degree of discomfort.

After the informed consent of parents was obtained, fasting blood samples were collected from children with headaches. Each sample was centrifuged for 10 min with 3000 rpm and then serum was extracted and kept in

**Table 1 Demographic data and positive serum anti-Toxoplasma gondii IgG concentrations in 19 of 178 children hospitalized because of recurrent headaches**

| Pt | Age/sex | Living place | Contact with animals[1] | Serum anti-Toxo IgG concn ($n \leq 9$ IU/mL) | Avidity index[2] |
|---|---|---|---|---|---|
| 1 | 8/M | Town | Yes[1] | 205.5 | 0.750 |
| 2 | 9/M | Town | Yes[1] | 59.5 | 0.754 |
| 3 | 9/F | Town | Cat | 59.0 | 0.202 |
| 4 | 12/F | Town | Cat | 94.1 | 0.666 |
| 5 | 13/F | Town | No | 168.0 | 0.782 |
| 6 | 13/F | Town | Yes[1] | 83.0 | 0.800 |
| 7 | 13/F | Town | No | 123.9 | 0.861 |
| 8 | 14/F | Village | Yes[1] | 151.2 | 0.740 |
| 9 | 15/M | Town | Yes[1] | 231.4 | 0.670 |
| 10 | 16/F | Town | Yes[1] | 81.0 | 0.859 |
| 11 | 16/F | Town | Dog | 74.7 | 0.767 |
| 12 | 16/M | Town | Ferret | 165.7 | 0.778 |
| 13 | 17/M | Village | Yes[1] | 175.03 | 0.788 |
| 14 | 17/F | Town | Yes[1] | 145.0 | 0.772 |
| 15 | 17/F | Town | Yes[1] | 40.5 | 0.687 |
| 16 | 17/M | Town | Yes[1] | > 240.0 | 0.843 |
| 17 | 17/F | Village | Yes[1] | 71.7 | 0.925 |
| 18 | 17/M | Town | Dog, parrot | 32.2 | 0.796 |
| 19 | 17/M | Village | Dog, cat, hens, ducks, cows | 82.0 | 0.894 |

[1]Dog, cat and/or turtle. [2]Avidity index: < 0.4-low avidity, 0.4 to 0.5-moderate, and ⩾ 0.5-high avidity. In Pt 13 control serum anti-Toxo IgG concentration examined 9 mo later was 552.7 IU/mL. It must be noted that Toxoplasma gondii IgG and IgA, but not IgM, antibody titers were also found to be increased in sera of immunocompetent mice in association with proliferation of tachyzoites in the brain during the chronic stage of infection[17].

-20 ℃ until assayed. The serum samples were analyzed for the presence of specific anti-TG IgM and IgG antibodies using the enzyme-linked immunosorbent assay (ELISA) technique (Euroimmun) and the index of avidity (Platelia, Toxo™ IgG Avidity). The study was approved by the Bioethics Committee of the Medical School.

## RESULTS

Among the studied group of 178 children admitted consecutively to the Department of Pediatric Neurology because of recurrent headaches, sometimes with various other accompanying neurological disturbances, and investigated for the presence of TG infection, serum tests of 19 children (11 girls, 8 boys) detected a marked increase of specific serum anti-TG IgG antibody concentrations (Table 1). The results ranged from 32.2 to over 240 IU/mL, with the mean value of 122.2 IU/mL, and the positive cut-off value for serum anti-TG IgG level was ⩾ 9 IU/mL. The results for IgM antibodies were all negative and the obtained results ranged from 0.113 to 0.25 U/mL (mean = 0.191 IU/mL), all values below 0.8 IU/mL were considered negative. It can be assumed that almost all children with positive IgG tests had chronic TG infection because in 18 children (except Pt 3) the index of avidity ranged between 0.67 and 0.925 and the value AI ⩾ 0.5 was considered high (Table 1).

In 19 children that were TG IgG-seropositive, the most common complaints were headaches reported by all patients. In 13/19 children, headaches affected mostly the frontal region, in 5/19 the temple and in 4/19 the occipital area. The headaches were bilateral in half of the children, while the other part reported headaches of changing, unilateral or bilateral character. The frequency of reoccurrence was about once a month in 7 children, 6 children had more frequent headache attacks, and two of them more rarely (Table 2).

Five out of 19 TG IgG-seropositive patients considered headaches a serious discomfort and 2 children confirmed that they were afraid of pain or anxious about its reoccurrence. Headaches usually were pulsating (in 7 patients) and squeezing (6), and rarely had a piercing, dull or expanding character. Interestingly, 8 children did not feel discomfort during the headaches. The mean duration of headaches was 2-6 h and the average gravity assessed according to 10 grade arbitrary scale was 5.5 (range 2-10) (Table 2). Comorbidities were assessed as well and the most frequent were epilepsy (5 patients), various infections in 3 children (including chronic eustachitis, chronic rhinitis, chronic purulent tonsillitis, streptococcal pharyngitis, meningitis and allergic diseases), disturbances of behavior, deficits of attention, and ocular and motor concentration disorders in one child (Table 3).

The most common disorder detected in accessory diagnostic tests was an abnormal EEG record, observed in 10 out of 15 TG-seropositive patients. It should be noted that 5 of these children were on antiepileptic therapy (Table 4). In 2 patients, X-ray of the paranasal sinuses revealed thickened sinus mucosa probably due to the chronic maxillary sinusitis. On magnetic resonance imaging (MRI), one 17-year-old girl (Pt 15) was suspected of having a cerebellar venous angioma and Kimmerle anomaly, another 17-year-old boy (Pt 17) was monitored concerning the demyelinating process, and 13-year-old girl (Pt 6) had a pia mater cyst, differentiated with atresia of a Turkish saddle diaphragm (Table 4).

## DISCUSSION

The results of our study showed that monitoring of anti-

**Table 2 Characteristic features of headaches in the seropositive anti-Toxoplasma gondii IgG children**

| Pt | Frequency of headaches | Pain localization | Duration (h) | Pain intensity[1] | Pain character | Discomfort for patient |
|---|---|---|---|---|---|---|
| 1 | Once a month | Temples | < 2 | 6 | Squeezing | No |
| 2 | Once a month | Forehead | 2-6 | 4 | Squeezing | N/A |
| 3 | Once a month | Back | < 2 | 5 | Pulsating | No |
| 4 | Daily | Whole head | 2-6 | 5 | Squeezing | Yes |
| 5 | Once a month | Temples, forehead | 2-6 | 5 | Squeezing | Yes |
| 6 | Once a month | Forehead, occiput | < 2 | 3 | Pulsating, paroxysmal | N/A |
| 7 | More than once a month | Forehead | < 2 | 6 | Expanding | Manageable |
| 8 | Rarer than once a month | Stomach | < 2 | 2 | Squeezing | No |
| 9 | More than once a month | Forehead, occiput | 2-6 | 8 | Expanding, piercing | Yes |
| 10 | More than once a month | Forehead, temples | 2-6 | 5 | Pulsating | Small |
| 11 | More than once a month | Forehead (left side) | 2-6 | 10 | Expanding | Yes |
| 12 | More than once a month | Temples, orbitae (left side) | 2-6 | 7-8 | Pulsating, squeezing | Yes |
| 13 | Rarer than once a month | Forehead | < 2 | 5 | Pulsating | No |
| 14 | Once a month | Forehead, temples | 2-6 | 4 | Squeezing, pulsating | Yes |
| 15 | Once a month | Forehead, occiput | 0.5-24 | 2 | Dull | No |
| 16 | More than once a month | Forehead, temples | 6-12 | 5 | Pulsating | No |
| 17 | N/A | N/A | N/A | N/A | N/A | N/A |
| 18 | Once every 3 mo | Forehead, calvaria | < 2 | 4 | Piercing | No |
| 19 | Once every 6 mo | Forehead, orbitae | < 2 | 8 | Squeezing | No |

[1]Headache intensity was measured in a subjective 1-10 point scale. N/A: Data not available.

**Table 3 Concomitant symptoms and comorbidities in the seropositive anti-Toxoplasma gondii IgG children with recurrent headaches**

| Pt | Concomitant symptoms | Comorbidities |
|---|---|---|
| 1 | Fatigue | Epilepsy, attention and concentration disturbances |
| 2 | Autoaggression | Epilepsy, behavior disturbances, psychomotor development delay |
| 3 | Vertigo, nausea and vomiting, discrete balance disturbances, photophobia | Infection of upper airways, right eustachitis, suspected allergic rhinitis |
| 4 | Nausea, vomiting, abdominal pain, photophobia | Allergic lesions of nasal mucosa and paranasal sinuses, heart systolic murmur (2/6), overweight, aggression and autoaggression behavioral disturbances, attention and concentration deficits, myoclonus during sleep |
| 5 | Nausea, vomiting, abdominal pain | Allergy to dust and mites, serous rhinitis |
| 6 | Vertigo, changes of mood and behavior, fatigue | Frequent upper airway infections |
| 7 | Psychomotor slowdown, episodes of awareness (switch-offs) | Bronchial asthma, paranasal sinusitis, allergic rhinitis, obliteration of right optical nerve disc |
| 8 | Impairment of cognitive abilities, psychomotor hyperactivity, clumsy gait | Metachromatic leukodystrophy, significant peripheral nerve lesions-sensorial-motor axonal-demyelinating polyneuropathy |
| 9 | Nausea, photophobia, abdominal pain | Bronchial asthma, chronic eustachitis and rhinitis, allergy to dust |
| 10 | Photophobia, fatigue, hyperacusis, faintings, syncope | Eye refractive error, serous cerebrospinal meningitis at the age of 6 |
| 11 | Vertigo, hot flushes, weakness | Traffic accident injury of head and right thigh, diagnosed cerebral commotion, incisive wounds of forehead, nose and over upper lip, positive tetany tests-elevated plasma calcium levels |
| 12 | Aphasia, dysphasia, paresthesia of hands and forearms | Bronchial asthma |
| 13 | | Chronic purulent tonsillitis, streptococcal infection, epilepsy (observation), sclerosis multiplex (observation) |
| 14 | Fatigue | Epilepsy |
| 15 | Hyperacusis, drowsiness | Epilepsy, attention and concentration disturbances, impaired perception skill, eye-motor concentration disturbances, allergic rhinitis |
| 16 | Photophobia | |
| 17 | Individual incident of vertigo and limb numbness without loss of consciousness | Vision disorders and ventricular arrhythmia in anamnesis, left-eye divergent strabismus |
| 18 | Systemic vertigo, balance disturbances, nausea | Frequent upper airways infections, enlarged submandibular lymph nodes, right palpebral narrowing and discrete right-sided ptosis since early childhood |
| 19 | Nausea, vomiting, photophobia, numbness of tongue and right arm | Bronchial asthma, atopic dermatitis, mitral valve insufficiency |

TG IgG antibody levels and estimation of the avidity index are an important part of the diagnostic and therapeutic process in children and adolescents with recurrent headaches and associated comorbidities seeking neurological help. Despite the evidence concerning a correlation between acquired toxoplasmosis and increased incidence of neuropsychiatric symptoms, including headaches, vertigo, attention deficits and educational difficulties[14,16,18], there is still lack of broader information regarding acquired toxoplasmosis as one of the impor-

**Table 4 Results of laboratory tests and head X-ray/neuroimaging studies in the seropositive anti-Toxoplasma gondii IgG children with recurrent headaches**

| Pt | ESR (mm/h) | WBC ($10^3$/mL) | CRP (mg/L) | EEG | Head X-ray/CT/MRI |
|---|---|---|---|---|---|
| 1 | | 6.4 | | Increased percent of slow waves | CT normal |
| 2 | 10 | 14.9 | 0.10 | Abnormal | CT normal |
| 3 | | 4.0; 6.5 | 20.25; 1.92 | Normal | MRI-brain and fluid spaces normal, massive lesions of paranasal sinuses, total obliteration of the right maxillary sinus, thickened ethmoid mucosa |
| 4 | | 5.4 | 0.57 | Paroxysmal parietal and temporal alterations without paroxysmal activity | MRI-arachnoidal cyst at the right frontal-parietal border |
| 5 | 22 | 6.9 | | Normal | CT normal; X-ray-thickened right sphenoid mucosa |
| 6 | | 6.9 | | Discrete bilateral alterations in frontal regions | MRI-arachnoidal cyst, underdevelopment of Turkish saddle diaphragm; X-ray-thickened right maxillary sinus mucosa |
| 7 | | 6.5 | 0.27 | Discrete bilateral alterations in temporal regions-increased slow waves | MRI-brain and fluid spaces normal, small and hypoplastic frontal sinuses with thickened mucosa, moderate thickening of ethmoid mucosa and moderate inflammatory or post-inflammatory lesions of maxillary sinuses |
| 8 | 16 | 5.7 | 0.30 | Generalized alterations | MRI-extensive lesions (differentiation between metabolic and demyelinating disorder) |
| 9 | | 7.1 | | Generalized alterations: many dispersed theta waves; biparietal paroxysmal alterations during HV | CT and sinus X-ray normal |
| 10 | 12 | 8.4 | 0.60 | Normal | CT normal |
| 11 | | 4.7 | 0.86 | Readout unavailable-pending | Head CT and X-ray of cervical spine normal; MRI-modest lateral ventricle asymmetry, some minute fluid foci adjacent to pineal gland |
| 12 | | 7.5 | | Normal | MRI normal |
| 13a | 8 | 4.5 | 0.41 | Increased percent of slow waves; increased number of theta waves during HV | MRI demyelinating foci (June 2009); partial regression of these abnormalities (February 2010) |
| 14 | | 6.9 | 0.39 | Slowed down basal function, biparietal alterations | MRI normal |
| 15 | 24 | 9.2 | 1.45 | Paroxysmal bioccipital alterations | MRI-venous angioma suspected in right cerebellar hemisphere; X-ray-Kimmerle foramen in C1 of cervical spine |
| 16 | 9 | 6.59 | | | CT normal |
| 17 | | 10.6 | | Normal | MRI-discrete lesions in the vicinity of dorsal parts of lateral ventricle corpora, paraventricular foci of demyelination? |
| 18 | | | 0.24 | Normal | CT-isolated tiny hypodense foci in midbrain and pons |
| 19 | N/A | 7.9 | N/A | Normal | MRI-choroid plexus cysts |

[1]In Pt 13, the anti-streptolysin titer was 530 U ($n \leqslant 200$ U). WBC: White blood cells; CRP: C-reactive protein ($n \leqslant 5$ mg/mL); HV: Hyperventilation; N/A: Data not available; CT: Computed tomography; MRI: Magnetic resonance imaging; ESR: Erythrocyte sedimentation rate; EEG: Electroencephalography.

tant causes of headaches.

In the United States, migraine is a common neurological disorder, with about 18% of women and 6% of men suffering from the disease[19]. In 1988, it was postulated that the neurogenic inflammation due to acquired TG infection might be the cause of different types of headaches[14-16]. Several studies showed that the parasite harbors molecules that induce synthesis of proinflammatory cytokines because investigations performed *in vitro* showed proliferation of TG tachyzoites in HeLa cells and increased secretion and expression of monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1α (MIP-1α) and MIP-1β, cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2) *via* mitogen-activated protein kinases[20-24]. The stimulation of human polymorphonuclear leukocytes by the TG antigen has been shown to upregulate MIP-1α and MIP-1β[22]. Cysteine-cysteine chemokines, MCP-1 and MIP-1α, may contribute to the recruitment of monocytes and lymphocytes[22], COX-2 catalyzes production of PGEs from arachidonic acid at inflammation sites[20], and $PGE_2$ may promote $T_H$ type 2 immune responses by impairing the ability of locally maturing dendritic cells to produce proinflammatory cytokine interleukin-12 (IL-12)[25,26]. $PGE_2$ is also a potent suppressor of both monocyte antigen presenting function and T-cell expression of IL-2[27].

Studies by Kaciński *et al*[28] and Gergont *et al*[29,30] performed in a large cohort of children with migraine and episodic tension headaches showed a significant increase of serum IL-1β, IL-6, tumor necrosis factors (TNF)

and soluble TNF type I receptor levels compared with controls. It should be emphasized that investigations performed in women with acute TG infection (peripheral lymphadenopathy, IgM index > 0.7, specific anti-TG IgG titer exceeding 300 IU/mL, low avidity) showed a highly significant increase in serum IL-5, IL-6 and IL-10, while TNF-α level was not changed, which indicated a proinflammatory process and simultaneous anti-inflammatory reactions of the organism (increased level of IL-4, IL-10, IL-13) trying to counterbalance the excess of systemic pro-inflammatory activity[31]. The anti-inflammatory cytokines IL-4, IL-10 and IL-13 have also been detected during the interictal period in plasma of children with migraine and tension-type headache[32]. These data are consistent with the findings of Koseoglu *et al*[18] who in the group of 104 patients with migraine showed significantly increased serum anti-TG antibodies levels in 46 of them using the ELISA test compared to 26 seropositive results in 50 healthy individuals and 12 positive values in the group of 50 patients with headaches due to sinusitis. Moreover, finding of markedly increased concentrations of proinflammatory cytokines in the cerebrospinal fluid [MCP-1, IL-1ra, transforming growth factor beta 1 (TGF-β1)] and plasma (TNF, IL-1β, sTNF type I receptor, IL-6, sICAM-1) of children and adolescents with migraine and other types of headaches[33-35] corroborates further the earlier suggestion of Prandota[16] that those disturbances have been, at least in part, caused by a neurogenic inflammatory process that enhances production of cerebrospinal fluid. This explanation is also in line with the feeling of no discomfort reported by our eight IgG seropositive children with headaches, probably because intracranial pressure had not yet reached a clinically significant limit.

The presented reasoning is in line with the reports highlighting a possible role of inflammation in migraine pathophysiology[34,36-38]. Recent studies in migraineurs showed an increased production of matrix metalloproteinase-9 (MMP-9)[33,37] and TGF-β1[34], a multifactorial proinflammatory cytokine, and it was reported that NO in a concentration-dependent manner regulated MMP-9 activity secreted from macrophages[38]. It must be emphasized that NO is a key molecule in migraine and other vascular headaches responsible for cerebral and extracerebral cranial blood flow and arterial diameters and nociceptive processing[39-41]. Moreover, triptans (including sumatriptan, the golden standard in the treatment of acute migraine) showed some anti-inflammatory and immunomodulatory potentials[42-44]. For example, these drugs were found to directly inhibit pMMP-9 secretion by neutrophils[44], reduce the influx of leukocytes into the site of inflammation, formation of brain edema, and inhibit neuropeptides calcitonin gene-related peptide and substance P release[42]. All these processes may affect the development of immune processes responsible for reactivation of cerebral toxoplasmosis. Although sumatriptan indirectly inhibited peripheral blood mononuclear cells' natural killer (NK) cell activity[44] important for production of interferon gamma (IFN-γ)[45], it is known that only NK1.1(+) T-like cells, but not NK cells, negatively regulate the protective immunity against TG infection, possibly by producing IL-4 and suppressing heat shock protein 65 expression in the host macrophages[46-48]. According to these premises, it seems that tests detecting TG infection should be introduced on a routine base to the diagnostic process of children, adolescents and adults with headaches. Moreover, taking into consideration our previous and present clinical experience[14-16,49,50], we suggest treating these patients for 5-7 d with co-trimoxazole, the drug successfully used in patients with acquired immunodeficiency syndrome and cerebral toxoplasmosis[51,52]. Doses of the drug should be at the lowest recommended range because of the possible development of the Jarisch-Herxheimer reaction due to massive killing of the parasite associated with influx of foreign proteins into the host systemic circulation[57,58]. This may manifest as a transient and markedly increased intensity of headache and sometimes as aseptic meningitis[50,59-62].

In our patients, epilepsy, bronchial asthma, allergic rhinitis, recurrent upper airways infections, eustachitis and paranasal or ethmoid sinusitis were frequent comorbidities. These clinical disturbances are similar to the findings of Lateef *et al*[63] who reported asthma, hay fever and frequent ear infections as more common in children with headache, with at least 1 of these occurring in 41.6% of children with headache *vs* 25.0% of children free of headache. Aamodt *et al*[64] even suggested that both migraine and nonmigrainous headache are related to asthma, hay fever and chronic bronchitis. These suggestions may be partly supported by the *in vitro* finding that betamethasone, a glucocorticoid anti-inflammatory and immunosuppressant sometimes used in these clinical entities, increases invasion of TG tachyzoites to the host cells *in vitro*[65] and atopic dermatitis was frequently diagnosed in the seropositive ant-TG IgG children with headaches[16]. Note that recently it was reported that the parasite actively inhibits neuronal function in chronically infected mice[66] and histamine, known to be produced in increased quantities in atopic dermatitis and asthma, exerts anti-inflammatory effects and modulates microglia function[67,68]. Histamine enhanced the secretion of $T_H2$ cytokines, such as IL-4, IL-5, IL-10 and IL-13, and inhibited the production of $T_H1$ cytokines IL-2 and IFN-γ, as well as modulated the cytokine network through up-regulation of prostaglandin $E_2$ and nitric oxide (NO)[68]. It must be added that two of our seropositive children had epilepsy and it was reported that chronic TG infection could be a cause of cryptogenic epilepsy[69-71] and several antiepileptic drugs have anti-toxoplasma activity (Table 5). Moreover, strabismus observed in Pt 17 also may be due to congenital toxoplasmosis[72].

The value of computed tomography in diagnosis of headaches was very limited in our patients, while MRI studies appeared to be useful in showing brain abnormalities in 7 out of 11 studied individuals. These findings are in agreement with the results of other authors[73,74]

**Table 5 Drugs tested for *in vitro* activity against Toxoplasma gondii (according to Jones-Brando *et al*[52]; with own modification)**

| Drug | Solvent | ID50[1] (μg/mL) | TD50[2] (μg/mL) | TI[3] |
|---|---|---|---|---|
| Valproic acid | Ethanol | 4.5 | 62.4 | 13.9 |
| Sodium valproate | Ethanol | 4.1 | 52 | 12.7 |
| Carbamazepine | Ethanol | 72 | 100 | 1.3 |
| Lithium carbonate | 1 N HCl | > 100 | > 100 | |
| Haloperidol | Ethanol | 5.6 | 103 | 18.4 |
| 9-OH-Risperidone | Tartaric acid | 20.1 | 134 | 6.7 |
| Risperidone | Tartaric acid | 74 | 129 | 1.7 |
| Fluphenazine HCl | Toxo CGM | 3.5 | 17.9 | 5.1 |
| Clozapine | Ethanol | 5.8 | 20 | 3.4 |
| Olanzapine | DMSO | 33.2 | 100 | 3 |
| Chlorpromazine HCl | DMSO | 2.6 | 6 | 2.3 |
| Quetiapine fumarate | DMSO | 18.6 | 33 | 1.8 |
| Trimethoprim | DMSO | 5.3 | 63.8 | 12.1 |

[1]Median inhibitory dose, a measure of tachyzoite inhibition. [2]Median toxicity dose, a measure of cytotoxicity. [3]Therapeutic index, a measure of efficacy determined by $TD_{50}/ID_{50}$ ratio. Valproic acid at a concentration of 1 μg/mL inhibited 7% of the tachyzoites and trimethoprim at 3.2 μg/mL produced 2% inhibition, but the combination of these two compounds at those concentrations resulted in a potentiating effect inhibiting 55% of the tachyzoites. Recently, Fond *et al*[53] also reported that other antipsychotic drugs, such as amisulpride, cyamemazine, levopromazine, loxapine, tiapride and zuclopenthixol *in vitro* exerted anti-toxoplasmatic activity in the range of 0.19 to 1 μmol/L concentrations. The inhibitory concentration 50 ($IC_{50}$) for the last preparation was 8 ± 1.8 μmol/L while its serum levels varied from 0.01-0.12 μmol/L[54], but antipsychotic drugs usually achieve much higher and persistent concentrations in the brain tissue[55]. In human fibroblast cell cultures, $IC_{50}$ for fluphenazine, thioridazine and trifluoperazine against developing tachyzoites of the parasite RH strain was 1.7, 1.2 and 3.8 μmol/L, respectively[56]. DMSO: Dimethylsulfoxide; Toxo CGM: Toxoplasma cell growth medium; TI: Therapeutic index; TD: Median toxicity dose; ID: Median inhibitory dose.

who suggested that neuroimaging procedures should not be routinely ordered in the initial diagnosis of types of headaches, recent onset of severe headaches, neurological dysfunction and on demand by parents or physicians[74].

Twelve of 178 children with recurrent headaches had slightly increased but not significant serum anti-Toxo IgM concentrations ranging from 0.1 to 0.3 IU/mL. This may result in part from different proteins from various TG strains and subclinical amounts and of the parasite antigens responsible for the generation of the host antibodies[75]. It should be noted, however, that at present diagnostic tests used for estimation of TG IgG, IgM and IgA seropositivity are not fully sensitive and specific and various methods of serum sample preservation and elaboration[76], as well as a diseases state of the host (*e.g.*, oxidative stress and resulting protein oxidation), may also affect both these parameters[77,78]. One may therefore suggest that such patients should receive a 5-7 d pilot treatment to avoid costly diagnosis and hospitalization because it was found that in animals antiparasitic treatment suppressed production and avidity of TG-specific antibodies[79].

In summary, 19 (10.67%) out of 178 studied young children and adolescents had specific serum anti-TG IgG antibodies and high index of avidity suggesting chronic infection. In our patients, peripheral lymphadenopathy, which would be of help in the diagnosis of acquired toxoplasmosis, was only observed in one child. On admission, the main clinical symptoms were headaches affecting the frontal, parietal and occipital areas. Almost all of the children had pets that may have been the source of infestation. In order to maintain a successful school performance as well as relationship with family and peers, primary care physicians should be aware of the probability of cerebral toxoplasmosis and therefore tests for TG infection must be taken into consideration during a routine diagnostic process of patients suffering from recurrent headaches because it is an underestimated condition, even in neurology practice[80].

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## COMMENTS

### *Background*

Headaches in both children and adults are very frequent and diagnosis often requires hospitalization associated with very expensive diagnostics. At present, in immunocompetent individuals Toxoplasma gondii (TG) infection is believed to be asymptomatic and in pediatrics/neurology books there is no suggestion of performing tests to search for infection with this parasite.

### *Innovations and breakthroughs*

This work estimated the seroprevalence and characteristics of TG infection in 178 children admitted consecutively to the Pediatric Neurology Department because of recurrent headaches.

### *Applications*

This work will help pediatricians and family physicians to check such patients for TG infestation.

### *Peer review*

Prandota *et al* report an analysis of 178 patients admitted to the neurology service. Out of this cohort, 19 patients tested positive for TG infection. This is a well written article. It has high priority for publication in your esteemed journal.

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