

Solving the New Puzzle(s) 2014-2022: Flammer Syndrome Probably Represents a Mild Endophenotype of Raynaud's Phenomenon Mainly Associated with Ocular Disturbances and Also Due to Latent *T. gondii* Infection

Joseph Prandota, MD, PhD

Emeritus Professor of Pediatrics & Clinical Pharmacology

Former Senior Fulbright-Hays Program and The Kosciuszko Foundation (twice) fellow

Department of Periodontology, Faculty of Medicine and Dentistry, Wroclaw Medical University, 26 Krakowska Str., 50-425 Wroclaw, Poland

***Correspondence:** Joseph Prandota, MD, PhD, Emeritus Professor of Pediatrics & Clinical Pharmacology, Former Senior Fulbright-Hays Program and The Kosciuszko Foundation (twice) fellow, Department of Periodontology, Faculty of Medicine and Dentistry, Wroclaw Medical University, 26 Krakowska Str., 50-425 Wroclaw, Poland

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1. Flammer syndrome (FS)

The research on FS was initiated in the 1980s by Dr. Josef Flammer and his colleagues from the University of Basel Eye Clinic, Switzerland, following observation of abnormal long-lasting fluctuation of visual fields in patients with glaucoma [1-4]. The term FS has finally been established in 2014 [5]. It is a cluster of signs/symptoms which occur in a population of individuals usually regarded as healthy persons with primary vascular dysregulation (PVD, formerly "vasospasm"), and individuals with disease and secondary vascular dysregulation (SVD, vasospastic syndrome) [3, 6-8]. Most people with FS have predisposition to altered reaction to cold, stress, and hypoxia manifesting as vascular and/or nonvascular disturbances, and have an increased risk for development of several various ocular and other diseases. Although some progress in FS understanding has been made the cause(s) of the syndrome and its molecular background are poorly understood. It must be noted that there is a relationship between FS and Raynaud's phenomenon (RP) [4], and therefore the aim of the work was to establish associations between this entity and acute or chronic latent *T. gondii* infection because several authors reported potential similarities in genetic background, symptoms and signs, microvascular, biochemical and immune abnormalities, drug treatment, as well as concomitant diseases suggesting that the parasite is responsible for inducing and developing these abnormalities. Moreover, pathophysiology and pathomechanisms of many health disturbances and entities related to FS can be explained rationally basing on available clinical, epidemiologic, laboratory, immunologic and therapeutic data documented in animals and individuals with acute or chronic *T. gondii* infection.

A. FS in Europe and Asian countries. FS is more prevalent in Asians than Caucasians [5], and in Europe and Asian countries it occurs more frequently in women compared with men [4, 9-11]. In Korean patients, however, cold hypersensitivity in hands and feet (CHHF) has an independent

negative effect on quality of life [9]. The study of 334 healthy subjects aged 50 years or older in Japan showed that proportion of participants with increased sensitivity to cold widely ranged (6.1%-30.8% men, 14.3%-28.3% women) [12].

In Eastern Asian populations CHHF occurs in 20%-52% of subjects [13-15], and ratio of men to women is 2:3 [16]. In Japan, this condition called “hiesho” is quite common involving over 60% of females, and in the latter stage of pregnancy “hiesho” manifests in about 40% of women, particularly in the advanced maternal age [17, 18]. One study comparing Japanese with Brazilians reported that 57% of Brazilian pregnant women were aware of cold sensations [19, 20]. CHHF is associated also with RP, gastric disturbances [21], as well as gynecological disorders, such as infertility and dysmenorrhea [22, 23]. Nb. *T. gondii* infection causes ovarian dysfunction and disturbances in sperm motility, viability and concentration values, epididymis weight, and testicle inflammation [24-28]. The presence of “hiesho” was found to be risk factor which can also lead to abnormal delivery because of weak labor pains, prolonged labor and atonic bleeding, premature delivery, amnion membrane rupture [17, 29, 30]. In this context, it should be added that traditional Japanese fish dishes sushi and sashimi may, at least in part, play a role in development of these disorders [31], especially that wide distribution of *T. gondii* amongst sea fish and mammals may affect human health worldwide (e.g. the highest prevalence of the pathogen was found in otter (54.8%), and dolphin, whale and porpoise (30.92%) [32].

B. FS heritability. In Europe, most of FS symptoms appear in puberty and alleviate along with age, in women after menopause begun [33], albeit in the study of 3067 persons aged 65 years or older 23.6% men and 28.6% women had cold extremities [34]. Importantly, parents of FS subjects also had similar symptoms which may suggest a heritability of this clinical entity [3, 4]. Moreover, Konieczka & Erb [4] noted that there is a relationship between FS and RP, and suggested a genetic background of RP [35-38], but they believed that additional factor(s) may also play a role [4, 35]. Nb. genetic factors appeared to be important in the development of RP as has been demonstrated in one familial and twin study [39]. FS often occurs in individuals who are slender, have a low blood pressure, are active, but also have unusually cold extremities, increased pain sensitivity, altered circadian rhythm, and prolonged falling asleep time [40, 41].

C. Pathophysiological changes in FS. Individuals with FS have the autonomic nervous system imbalance with sympathetic predominance [4, 42], lymphocytes and leukocytes in the eye have altered gene expression, and

activated astrocytes in the retina also change their gene expression and morphology [2, 43-45], slightly increased plasma endothelin-1 (ET-1) levels, and increased systemic oxidative stress [5, 46]. They also have enhanced sensitivity to some drugs, such as for example calcium channel blockers or β -blockers [3]. FS subjects differently react to a number of stimuli, including coldness, emotional stress, hypoxia, starvation, together with additional signs and symptoms [40, 47]. These recurrent negative stimuli and exaggerated pathophysiological responses can induce development of several diseases and clinical entities involving one or more organs (tissues), particularly the eye diseases in younger patients [3, 40, 48].

D. FS and concomitant diseases. Patients with FS have increased risk for development of several ocular diseases, including normal-tension glaucoma (NTG), glaucomatous optic nerve neuropathy, the optic nerve compartment syndrome, artery and vein occlusions in the retina, and retinitis pigmentosa. They may also suffer from muscle cramps, tinnitus, sudden hearing loss, headaches and migraines, silent myocardial ischemic (Prinzmetal angina), and altitude sickness [3, 4]. On the other hand, FS patients with SVD may more frequently suffer from multiple sclerosis, rheumatoid arthritis, Sjögren syndrome, retrobulbar neuritis, fibromyalgia, giant cell arteritis, breast cancer and metastatic disease [3-5, 33, 49-51]. Other diseases like thyroid dysfunction, anorexia nervosa, heart diseases, whiplash trauma (an injury associated with car accidents), pancreatic cancer, and sudden hearing loss, are still under investigation [3, 4].

2. *T. gondii* infection

A. Global distribution of *T. gondii*. Infection with the pathogen is connected with higher mortality than in general population [52]. Worldwide more than six billion people have been infected, taking into account also ocular involvement [53-56]. Milne et al [57] argued that occult effects of parasite infection may outweigh the recognized overt morbidity caused by toxoplasmosis, especially that a relationship between nailfold microcirculation and retinal microcirculation abnormalities have also been found in apparently healthy subjects without systemic and ocular diseases [58], and in patients with non-rheumatic diseases [59]. Recently, Molan et al [60] determined anti-*Toxoplasma* IgG seroprevalence rate in apparently healthy general population (total 648,010 individuals; 166,255 seropositive) and found that an average global seroprevalence rate was 25.7%, and the overall range of seroprevalence was 0.5-87.7%, with African countries, Oceania, South America,

Europe, USA/Canada and Asia having 61.4%, 38.5%, 31.2%, 29.6%, 17.5%, and 16.4%, respectively. Toxoplasmosis in the USA is a neglected infection associated with high burden and low awareness [61-63], and its seroprevalence from 2011-2014 was estimated to be 11.14% [64], with approximately 40 million people infected [61, 62]. The parasite accrues economic losses of 3.6 billion dollars per year, and is second leading cause of foodborne illness responsible for mortality and death [65].

Human infection with *T. gondii* is acquired mainly via eating undercooked meat with cysts (bradyzoites), ingestion of not sufficiently cleaned vegetables, fruits, or drinking contaminated water (oocysts), vertical transmission (tachyzoites transplacental route from mother to fetus), organ transplantation or blood transfusion (tachyzoites), and via poor hand hygiene [66-68]. Presence of *T. gondii* has been confirmed in water, soil, air, food, fruits and vegetables in different regions of the world [69-74]. The largest outbreak of acquired ocular toxoplasmosis has been reported in south India in which the suspected source of infection was the common municipal drinking water [75]. Interestingly, experiments have demonstrated that oocysts persist on the surface of raspberry stored at 4°C for eight weeks [76].

B. Heritability and family household-related associations of *T. gondii* infection.

Contopoulos-Ioannidis et al [77] investigated members of 32 families of persons with *T. gondii* infection and found that multiple cases of acute toxoplasmosis may occur among family/household members (18/32; 56.25%), and families had more than one family member with acute infection.

Further study revealed high prevalence of *T. gondii* infection in the fathers of congenitally infected infants (29/81; 36%) relative to the average 9.8% seropositivity of boys and men aged 12-49 years estimated in USA between 1994 and 2004 ($p < 0.001$). It was suggested that there is clustering of the parasite infections within the families of infants with congenital toxoplasmosis [78]. Multiparas constitute a risk factor as in one study from Brazil prevalence of *T. gondii* was 45.8% with multiparas 2.6 times more often infected than primiparas (OR = 95% CI 1.25-5.39) [79].

In a case-control study with 170 enrolled family units divided into the family members seropositive for *T. gondii* IgM and/or IgG (group I) and the family members seronegative for IgM and IgG (group II) Yazdani et al [80] found that frequency of participants in group I was markedly higher than in group II (Table 1) [80].

Duffy et al [81] also demonstrated that of 2017 Old Order Amish participants (a homogenous community in USA with high prevalence of *T. gondii* seropositivity [82]) 1098 (54.4%) had positive serum IgG anti-*T. gondii* titers. The heritability for the parasite was found to be significant for both serointensity ($p = 1.7 \times 10^{-8}$) and seropositivity ($p = 1.9 \times 10^{-5}$), and there was a statistical trend for shared household environmental risk factors ($p = 0.06$) [81].

C. *T. gondii* main serotypes. In Europe, North America, and Africa are three main clonal lineages of *T. gondii*: type I (RH, GT1), type II (ME49), and type III (VEG), different in prevalence, virulence, migratory capacity, and ability to convert cyst phase to bradyzoite [82, 83]. Table 2 showed numbers of differentially expressed genes of the three types

Table 1. Frequency of *T. gondii* seropositivity in 170 household members of the studied patients (acc. to Yazdani et al [80]; with own modification).

| Parameters | <i>T. gondii</i> seropositive (IgM and/or IgG) patients (n = 85) | <i>T. gondii</i> seronegative (both IgM and IgG) patients (n = 85) | OR (CI 95%) | P |
|-----------------------|--|--|-------------|------|
| Age, yrs | 30.8 ± 6.6 | 32.9 ± 7.8 | 0.93 | 0.07 |
| Sex (male) (n, %) | 29 (34) | 25 (29.5) | 1.2 | 0.09 |
| Seropositivity (n, %) | 45 (53.9) | 29(34.1) | 2.17 | 0.01 |

Results are expressed as mean ± SD. $P < 0.05$ is statistically significant. OR, odds ratio.

Table 2. Differential effects of three canonical *T. gondii* strains on gene expression in human neuroepithelial cells (acc. to Xiao et al [84]; with own modification).

| Infection | No. of RefSeq | | No. of altered canonical pathways ^b | No. of altered networks ^c |
|-----------|---------------|---------------|--|--------------------------------------|
| | Upregulated | Downregulated | | |
| Type I | 396 | 726 | 34 | 25 |
| Type II | 54 | 24 | 4 | 2 |
| Type III | 197 | 147 | 16 | 15 |

^a $P < 0.01$; ^b> 1.2-fold change in expression. ^c $P < 0.05$. ^dIPA score, > 3; IPA, Ingenuity Pathways Analysis.

of the parasite [84]. Interestingly, a novel nonreactive (NR) and type II serotypes were found to prevail in German patients with ocular toxoplasmosis (OT), and NR serotype associated with development and recurrences of OT was detected markedly more often than in non-OT patients (OR 10.0, 95% CI: 3.4-40.8, $p < 0.001$) [85].

D. *T. gondii* infection of cells, their alterations, and immunological changes caused by the parasite. The pathogen infects and proliferates almost in all host cells increasing key host microRNAs levels [86]. The brain and retinal vascular endothelial cells are unusually susceptible to the infection [87-89]. Fetal astrocytes, microglial cells, and retinal pigment epithelial cells were associated with rapid division rates of tachyzoites (Table 3) [90]. It was demonstrated that in the endothelial cells the microbe induced alterations in gene expression, and several pathways of these genes were involved in inflammatory responses and signaling [91-94]. Recently, Bergersen et al [95] in mice showed a striking shift in earlier found novel gene expression related to neuropathology, inflammation and neuroinflammation when infection with the parasite progressed. Moreover, imbalanced reactive oxygen species (ROS) generation during infection contribute to driving immunosenescence, chronic inflammation, as well as autoimmunity [96]. This may further be supported by the finding of Kugler et al [97] that systemic

T. gondii infection triggered not only transient increase in the activated CD4 T lymphocytes + T_H1 cells but also persistent decrease in the size of naive CD4⁺ T lymphocyte pool. This immune weakness may be associated with a diminished resistance of individuals with autoimmune diseases (ADs) to a challenge with viral and/or bacterial pathogens, including CMV, EBV, measles virus, HBV, and *H. pylori* frequently detected in patients with ADs and toxoplasmosis [97, 98]. It must be noted that ocular disturbances often occur as early manifestations in several autoimmune rheumatic diseases, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren's syndrome (SS), and are associated with microvascular damage of retinal and choroidal vessels [99].

E. Diagnosis of toxoplasmosis. Sabin-Feldman test was recognized as the diagnostic gold standard for detection of toxoplasmosis, however its application was limited because of use of living tachyzoites [100]. Presence of m.w. 30 kDa band in combination with at least two other bands (m.w. 31, 33, 40, 45 kDa) in serum sample indicate parasite IgG [100, 101], although the range of molecular weights of protein antigens released from purified tachyzoites and antibodies in samples of human sera was greater [102]. Furthermore, in mice with acute phase of *T. gondii* infection cold stress caused an enhanced specific IgM concentrations of the 30, 42, 54, and

Table 3. Division rate of intracellular *T. gondii* tachyzoites in primary human cells in vitro (acc. to Channon et al. [90]; with own modification).

| Cell type | Parasite division rate | | Mechanism |
|---------------------------------|------------------------|----------------------|--------------------|
| | Unprimed | IFN- γ primed | |
| Hemopoietic | | | |
| Lymphocyte | S | | |
| Neutrophil | S | | |
| Adherent monocyte | S | | |
| Nonadherent monocyte | R | R | ROS; not TS |
| Dendritic cell | R | | |
| Alveolar macrophage | R | S | Partly TS |
| Peritoneal macrophage | R | S | |
| Monocyte-derived macrophage | R | S | ROS; not RNI |
| Nonhematopoietic | | | |
| Neuron | S | | |
| Foreskin fibroblast | R | S | TS |
| Umbilical vein endothelial cell | R | S | TS or ROS; not RNI |
| Retinal pigment epithelial cell | R | S | TS |
| Fetal astrocyte | R | S | RNI |
| Fetal microglial cell | R | R | |

R, rapid; S, slow; RNI, reactive nitrogen intermediates; ROS, reactive oxygen species; TS, tryptophan starvation.

60 kDa antigens compared with infected and non-stressed animals, while the level of IgG increased in both infected, and infected and stressed animals. Additionally, the 5-kDa antigen was detected in the mice with both acute and chronic toxoplasmosis exposed to cold [103].

F. Effects of cold stress on immunological and biochemical responses in humans. Even short exposure to cold temperatures leads to increased concentrations of norepinephrine and cortisol, lymphocytosis, diminished lymphoproliferative responses, decreased generation of proinflammatory T_H1 cytokines and salivary IgA [104]. The stimulation of sympathetic nervous system and hypothalamic-pituitary-adrenal axis also caused release of epinephrine, norepinephrine, cortisol, and aldosterone [104]. Moreover, in mice chronic cold stress triggered development of the regulatory phenotype of macrophages with diminished phagocytic ability, decreased TNF- α and IL-6, and increased IL-10 generation. Additionally, the resting macrophages from animals exposed to cold stress stimulated spleen cells production of regulatory interleukins, and lead to development of immunosuppressive state which impaired control of *Trypanosoma cruzi* replication. The regulatory effects correlated with increase in macrophage expression of 11β -hydroxysteroid dehydrogenase (HSD) changing inactive glucocorticoid to its active form [105]. These findings documented during short or chronic cold stress provide further support for a close relationship between pathophysiological alterations reported in individuals with FS and clinical and laboratory disturbances found in subjects with chronic latent *T. gondii* infection.

3. FS and perfectionism

Individuals with FS have a remarkable tendency toward perfectionism [4, 5, 106]. In the Flammer Syndrome Questionnaire this symptom amongst 7 (cold hands/feet, tendency to perfectionism, increased sensitivity to drugs, enhanced smell perception, skin blotches, tinnitus, and prolonged falling asleep time) of 15 signs and symptoms of FS was found markedly more often present in NTG patients than controls (OR = ~ 1.5 ; $p = 0.003$,) [40, 107].

A. Perfectionism is also reported in the subjects with latent *T. gondii* infection. Perfectionism is characterized by an individual need for high performance standards, doubting about actions and decisions, and worrying about making mistakes [108]. Latent toxoplasmosis may be associated with the changes in personality profile. Stock et al [109] demonstrated that healthy young adults with latent toxoplasmosis have been superior to *T. gondii*-free

participants with respect to response accuracy. Several authors suggested that one of the main factors driving these behavioral changes was a strongly increased dopaminergic signaling during acute and chronic infection [109-113]. The parasite manipulated behavior of its secondary host, and it was established that this is due to the increased dopamine synthesis and release [112-114].

Flegr and his group [115-117] studied changes of personality profiles using the Cattell's 16 PF questionnaire in 230 women with acute toxoplasmosis diagnosed during previous 14 years. They found positive correlation between the duration time of *T. gondii* infection and the levels of factors G (high superego strength) and Q3 (high strength of self-sentiment, i.e. perfectionism) [117].

B. Perfectionism in patients with some neuropsychiatric disorders is due to latent *T. gondii* infection. Several behavioral studies reported that perfectionism (especially its maladaptive form) has a close relationship with some mental vulnerabilities, such as, obsessive-compulsive disorder (OCD), eating disorders, suicidal behaviors, stress, anxiety, and depression [109, 118, 119].

Perfectionism is an essential trait in both women with anorexia nervosa (AN) and bulimia nervosa during acute illness [120, 121] and past recovery [121-123]. These rituals have been considered a transdiagnostic process within the OCD and AN [124, 125]. It was suggested that premonitory perfectionism may represent a risk factor for AN [123], and three genes associated with AN were found to be related with perfectionism [16]. In eating disorders, heritability estimates ranging between 22% and 42% suggested that perfectionism is a most likely endophenotype [118, 119]. In addition, dopamine is regarded as a critical factor in food intake [126].

Several authors reported that there is an association between the development of OCD and latent *T. gondii* infection [27, 127-130]. Recently, Chegeni et al [130] in their study of 9873 participants (389 with OCD, 25.96% *T. gondii*-positive) vs. 9484 with no OCD (17.12% *T. gondii*-positive) demonstrated that toxoplasmosis may be a risk factor for this clinical entity (OR = 1.96 [95% CI: 1.32-2.90]).

The parasite was also found to be associated with development of a number of other mental health disturbances, such as depression [131], suicide attempts [27, 132, 133], anxiety disorder [131, 134, 135], autism [136], schizophrenia [135, 137, 138], and headaches [139-141]. It should be emphasized that several drugs used in treatment of schizophrenia or other neuropsychiatric diseases inhibited replication of *T. gondii* tachyzoites [142].

C. Dopamine plays a key role in many pathophysiological processes in the brain leading to perfectionism. *In vitro* studies of Martin et al [112] and Prandovszky et al [113] showed that the infection of dopaminergic cells with *T. gondii* enhanced K⁺-induced release of dopamine several fold, with positive correlation between number of infected cells and quantity of the hormone. The parasite also increased dopamine metabolism in neural cells [113]. Unfortunately, this neurotransmitter caused a marked increase in tachyzoites counts in human fibroblast host cells compared to controls [143], which may affect severity of clinical entities associated with *T. gondii* infection.

Studies reported that dopamine significantly decreased the release of cytokines IL-2, IFN- γ , and IL-4 from the activated human T lymphocytes [144, 145], and increased TNF- α and IL-10 secretion by the resting T-cells [146]. The hormone also inhibited ROS production by leukocytes [147]. Chronic stimulation of dopamine receptor enhanced migratory activity of rodent microglial cells and attenuated release of lipopolysaccharide-induced NO [148]. These findings strongly support key role of dopamine in the changes of personality profiles resulting in perfectionism.

4. FS and high altitude sickness

The altitude sickness is more expressive in individuals with FS compared with healthy persons [3, 149-151]. This term includes large spectrum of health disturbances which occur in people spending time in mountains, especially in high mountain climbers. The main cause of this entity is low oxygen concentration at high altitudes leading to the increased levels of hypoxia-inducible factor 1 α (HIF1 α) and hypoxia. These changes augment expression of cytokines, growth factors, enzymes, ET-1 and erythropoietin. The individuals with FS have both increased ET-1 plasma concentrations and enhanced susceptibility of vessels to this neuropeptide [151]. At high altitude, Flammer et al [40] observed increased retinal venous pressure, and suggested that this may be associated with the rise of ET-1 levels [152].

A. Possible association between high altitude climbing, frequently unexplained health state disturbances and latent *T. gondii* infection. Many neurological, psychiatric, and/or ocular manifestations, and coagulation disorders reported during high altitude trekking may be explained by hypoxia and associated with hitherto undiagnosed latent *T. gondii* infection because hypoxia may trigger reactivation of latent toxoplasmosis and amplify preexisting central nervous system and ocular disturbances. Few famous Himalayan climbers recalled anecdotal serious general

and mental health disturbances affecting high altitude traveling, such as headaches, subfebrile states (Jerzy Kukuczka), brain damage, madness (Reinhold Messner), and increased personal conflicts, bizarre behavior (Tadeusz Piotrowski) [153]. Nb. also about 5% of people exploring Antarctic circle have been reported to meet criteria for psychiatric disturbances [153A-153C]. Moreover, several investigators suggested a potential impact of high altitude exposure on preexisting neurological conditions, and some of these disturbances falling outside the umbrella of altitude sickness have been documented in both case reports and reviews. These abnormalities included: migraine and other headaches, epileptic seizures, MS, permanent/transient ischemia of the brain, intracranial hemorrhage and vascular malformations, occlusive cerebral artery disease, cerebral venous thrombosis, intracranial space-occupying lesions, dementia, extrapyramidal disorders [154], cervical artery dissection, nystagmus, third and fifth cranial nerve palsies, eyelid ptosis, nystagmus [155], sixth nerve palsy, epilepsy [156], various ocular disturbances [157], retinopathy in otherwise healthy individuals [158], visual blurring, tinnitus, dysarthria, speech arrest, facial dysesthesia, generalized seizure, right-sided hemiparesis, ataxia, dizziness [159], and even meningioma [160]. Moreover, there was also reported a positive family history on epileptic disorders in father, brother, and daughter of the high altitude patient who had no preceding symptoms of acute mountain sickness [156], and a personal and familial vascular history in a 34-year old woman with neurological symptoms [159]. In this context, it must be added that similar familial heritability has also been recorded in the patients with RP [94, 161, 162], and the individuals with *T. gondii* infection [76, 81, 163-168]

B. Hypoxia and *T. gondii* infection. Persistent hypoxia creates tissue environment beneficial for *T. gondii* intracellular multiplication by increasing production of HIF1 required for the parasite growth and survival, even at physiological oxygen concentrations [169-172]. HIF1 α stimulates the synthesis and release of several interleukins such as IL-1, IL-6, IL-8, and NO, as well as different growth factors (e.g. TGF- β), by vascular endothelial cells (Table 4) [171-173], thus intensifying subclinical inflammatory reactions [171].

Astrocytes increase expression of heme oxygenase-1 (HO-1) in microglia, which has protective anti-inflammatory, antioxidant, and antiapoptotic properties [174]. Nb. TGF- β also induced HO-1 expression in microglia [175], and in epithelial cells [176]. Interestingly, the vascular smooth muscle cells (VSMCs) generate CO through heme degradation by HO-1, and treatment of VSMCs with the platelet-derived

Table 4. Effects of increased hypoxia inducible gene expression^a (acc. to Prandota [171-173]).

| |
|--|
| Erythropoietin |
| TNF- α , IL-1 β , IL-6, IL-8 |
| Nitric oxide synthase-2 |
| Heme oxygenase-1 (HO-1) |
| Ornithine decarboxylase; hexokinase 2 |
| Phosphofructokinase L; phosphoglycerate kinase-1 |
| Pyruvate kinase M; glucose transporter-1, -3 |
| Lactate dehydrogenase A |
| Glyceraldehyde-3-phosphate dehydrogenase |
| Insulin-like growth factor-2; enolase 1 |
| Aldolase A, C; adenylate kinase 3 |
| Pituitary adenylate cyclase-activating polypeptide |
| Transforming growth factor β_3 |
| Vascular endothelial growth factor |
| Endothelin-1 (ET-1) ^b |

^a*T. gondii* activates hypoxia-inducible factor 1 (HIF1) already at physiologically relevant oxygen levels and requires HIF1 for growth and survival [169]. ^bPlasma ET-1 level was found to be increased in normal individuals exposed to high altitude [152].

growth factor also stimulated HO-1 expression and CO synthesis [177]. High altitude generate thrombocytosis [178], and human platelets caused inhibition *T. gondii* growth [179]. The adherence of platelets to tachyzoites, disruption of their surface membranes, and cytoplasmic content release from microbes [180], may reinforce host defense against latent *T. gondii* infection in some high mountain climbers.

C. High altitude and development of thrombocytosis, increased capillary fragility, endothelial cell damage, and blood coagulation disturbances. Several studies showed that the acute exposure to hypobaric hypoxia was associated with blood coagulation abnormalities, such as decreased mean partial thromboplastin time, fibrinogen, and factor VII [154, 178, 181, 182]. Other blood components affecting thrombotic state, including thrombocytosis [178] and increased capillary fragility [183], as well as endothelial cell damage [181], have also been demonstrated. Some authors, however, have doubts that the altitude *per se* induces the prothrombotic state or development of severe health problems in mountaineers, especially that there were no signs of acute mountain sickness or cerebral edema [154-156, 159, 160, 184-192]. In this context, it should be emphasized that hypoxia enhances production of the plasminogen activator inhibitor-1 (PAI-1) which suppresses fibrinolysis, and this process may be associated with decreased expression of plasminogen activators [172, 193, 195], finally leading to development of microthrombi and embolization. In addition, it was reported that the subjects with migraine have blood hypercoagulability [196], including the increased von Willebrand factor levels

generated in endothelial cells and necessary for the adhesion of platelets to damaged vessel walls [197, 198].

D. The effects of *T. gondii* infection on the blood coagulation and fibrinolysis. Johnson et al [199] found in animals that the infection with the pathogen lead to disturbances in the blood coagulation system associated with a critical protective function. They demonstrated significantly increased fibrin concentrations in *T. gondii*-infected animals and biomarkers of T_H1 immunity [199]. Mullarky and his group [200] emphasized that two proinflammatory cytokines IFN- γ and TNF- α exerted dominant and opposite regulatory roles: IFN- γ diminished fibrin deposition in tissues, while TNF- α inhibited this process, especially through stimulation of PAI-1 production and decreased blood fibrinolytic activity [201, 202]. Thus, the changes in pro- and anti-inflammatory cytokine constellations status in the host tissues during *T. gondii* infection may also markedly affect blood coagulation and fibrinolysis [94].

The impaired function of the CO₂ gas channels (aquaporin-1, and aquaporin-4) associated with chronic *T. gondii* infection also caused hypoxia enhancing neuroinflammation [173]. In addition, hypoxia may participate in development of paradoxical microembolism because arterial oxygen desaturation increases expression of PAI-1, and this effect may be further amplified by a diminished expression of plasminogen activators, finally leading to blood hypercoagulability [172]. Thus, all the above mentioned disturbances can be responsible for the development various biochemical changes, clinical manifestations, and neuropsychiatric diseases observed in many individuals with health disturbances probably due to latent *T. gondii* infection, including recurrent headaches and migraines, cryptogenic epilepsy, and central nervous system and mental health disorders (multiple sclerosis, schizophrenia, anxiety, antisocial personality and attention deficit hyperactivity disorders, OCD, facial nerve palsy, brain tumors such as meningioma, glioma, and ependymoma, aseptic meningitis, tics, and posttraumatic stress disorder [27, 136, 138, 139, 171, 203-206].

5. FS and anorexia nervosa

Several authors reported that FS signs and symptoms often occur in the patients with anorexia nervosa [3, 4, 207], and individuals with FS are slim [208]. It should be noted that fasting intensified symptoms in persons with FS, which may be in agreement with their reduced responses of retinal vessels to flickering light [209]. Interestingly, the newborns of the mothers with FS phenotype had markedly low

weight and height, while mothers had significantly shorter gestational age, and augmented vascular stiffness compared with controls [210]. In one preliminary study [211] it was found that newborns from mothers with signs of FS ($n = 26$, mean age 27.2 ± 2.5 yrs) were significantly more often hypotrophic than babies born by healthy pregnant women ($n = 24$) (35.2% vs. 20.4%, $p = 0.031$), and hypertrophic - less often 13.5 % vs. 22.5%, $p = 0.059$). In addition, 25% of hypotrophic newborns weighted less than 2500 g compared with 6.25% of control babies. Moreover, at the beginning of pregnancy, body mass index (BMI) of women with FS was significantly lower compared with controls (20.9 ± 0.17 kg/m² vs. 23.2 ± 0.22 kg/m², $p = 0.046$) [211].

A. Similarities between FS and RP

Some studies reported a relationship between these two clinical entities [4, 36, 37]. Recently, in 93 935 participants estimated by a self-administered connective tissue questionnaire, Abdulle et al [212] found that the low body weight and weight loss were frequently overlooked risk factors in individuals with RP. The prevalence of RP in these participants was 4.2% [95% CI: 4.1-4.4%], and has been almost three-fold higher in women than in men (5.7% vs. 2.1%, $p < 0.001$). It was established that the low body weight (BMI < 18.5 kg/m²) and prior involuntary weight loss were markedly associated with RP in both women and men. In addition, the individuals with RP had a significantly lower daily caloric intake than those without RP, and in women low-fat diet was also combined with RP [212].

B. Strong association between toxoplasmosis and development of low body weight in both animals and humans. Arsenijevic et al [213-215] reported that the mice with acute toxoplasmosis and unaltered food intake had energy expenditure markedly increased, and this hypermetabolic state and subsequent anorexia were associated with an increase of several interleukins, including TNF- α , IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-10, and IFN- γ [213]. In chronic phase of the infection animals had either partial gain recovery or no weight regain. Hypermetabolism was connected with high lipid oxidation, and the authors suggested that it was associated with accumulation of macrophage-type cells detected particularly in serum, lung, spleen and liver [214]. Nb. monocyte/macrophages and other cells infected with *T. gondii* disseminate in various organs as "Trojan horses" [216-218].

Flegr et al [219] reported that *T. gondii*-positive pregnant women had a lower body weight in the 16th week of gravity ($p = 0.02$) than *Toxoplasma*-negative pregnant women. Also, a marked negative correlation was found between the weight

and duration toxoplasmosis in a subset of *T. gondii*-infected women ($n = 174$, $p = 0.04$), which suggested cumulative effects of latent disease. In addition, the authors established a significant positive correlation between body weight and antibody titer, which was explained as a negative correlation between body weight and duration time of toxoplasmosis (Kendal Tau = 0.103, $Z = 2.02$, $p = 0.043$, two-tailed test) [219]. According to these authors, the changes in body weight of pregnant women could be, at least in part, explained by their increased activity because studies in rodents showed higher activity of *T. gondii*-infected animals [220-222]. It seems, however, that the above-mentioned changes in biomolecular parameters in mice reported by Arsenijevic et al [213] on cytokine abnormalities leading to hypermetabolic state and increased energy expenditure characteristic for acute and chronic toxoplasmosis also play an important role in these processes.

Finally, concerning the above-presented data on the newborns of mothers with FS phenotype [211] it must be emphasized that the pregnant women with latent toxoplasmosis had less developed fetuses during the 16th week of pregnancy [219, 223]. This may be supported by the preliminary information of Sergeeva et al [211] that the babies and their mothers with FS had several connective tissue abnormalities, *i.e.* changes in auricles, curve little finger, arachnodactyly, and/or joint hypermobility. All these findings may be supported by the data of Hurt et al [224] showing that toxoplasmosis had an impact on prematurity and low birth weight in human babies.

6. Relationship between FS, multiple sclerosis (MS) and other ADs, and *T. gondii* infection

A. FS and ADs. FS quite frequently occurs in patients with several ADs, including MS [225, 226], SS [33], thyroid dysfunctions, *e.g.* hypothyroidism, Hashimoto thyroiditis [3, 4, 40], and fibromyalgia syndrome [40, 227, 228]. It was reported that individuals with MS have six [225] to nine [226] of the 15 signs and symptoms characteristic for FS (cold extremities, dizziness, reduced thirst, decreased body mass index, perfectionism, long-sleep onset time, skin blotches, drug side effects, headaches) indicating that this clinical entity may be associated with MS. It should be noted that pathological eye involvement reflecting immune response to retinal and choroidal vessel damage is a quite common finding in autoimmune rheumatic diseases, and ocular abnormalities, frequently detectable accidentally, are observed as early manifestations of these clinical entities. Microvascular damage and ocular symptoms have also been reported in SLE, RA, and SS [99].

It was suggested that FS may serve as a protective factor in such individuals being responsible for their good life expectancy eventually explained by the low incidence of cardiovascular diseases, and probably associated with an increased adiponectin level [4, 229]. This cytokine, a key regulator of innate immunity [230], exerted also many anti-atherosclerotic effects by increasing cholesterol efflux from the macrophages (deficiency of cholesterol in these cells impairs *T. gondii* proliferation), and downregulating acyl-CoA: cholesterol acyltransferase 1 and 2 expression in cells infected with the microbe important for development of foamy macrophages and atherosclerosis [231-233]. These actions may be, at least in part, responsible for a relatively good health status of individuals with FS and potential *T. gondii* infection.

B. *T. gondii* infection and ADs. Several authors reported that toxoplasmosis may be responsible for development many autoimmune diseases (Table 5) [27, 98].

It is noteworthy that MS was reported in association (sequentially or simultaneously) with other ADs, such as systemic sclerosis (nb. one year after diagnosis of MS this patient developed RP [270]), SLE [271], RA [272], or scleroderma [273]. There is also a coexistence of several connective tissue diseases including RA, ankylosing spondylitis, SLE, SS, and antiphospholipid syndrome in the same patient [274]. Patients with ADs also often have ocular manifestations [275]. Moreover, there was an increased rate of ADs among family members of pediatric MS cases with first-degree, as well as second-degree relatives compared with controls (OR = 2.27, 95% CI: 1.71-3.01, $p = 0.001$; OR = 3.47, 95% CI: 1.36-8.86, $p = 0.009$, respectively),

and the ORs for maternal and paternal relatives were 2.64 and 6.37, respectively [276]. These data strongly suggest a shared pathogenetic mechanism caused by *T. gondii* responsible for molecular autoimmune processes taking place in these clinical entities [98, 235, 238] probably related with host/pathogen antigen(s) homology [277-279], because during its life cycle the pathogen interacts with approximately 3000 host genes and/or proteins [279]. Cytokines generated during infection play critical role in triggering, persistence, regulation and treatment of ADs [280]. Moreover, since *T. gondii* infection induces both positive and negative immunomodulatory effects, it may according to the 'hygiene hypothesis' [281, 282] also exert beneficial actions and protect against development of some ADs [283]. In this context, it was suggested [284] that *T. gondii* infection was negatively associated with MS [285, 286], thyroid dysfunction [284], and atopy [287, 288], also eventually exerting protective effects. Recently, however, it was suggested [27] that these "protective" effects of *T. gondii* infection may develop when the host is unable to fully clear the microbe (impaired cleaning function) resulting in immune dysfunction or immune evasion by the pathogen or both [289]. These progressive declines in T cell activity and survival lead to deficiencies in pathogen control by the host [290]. Thus, CD4 and/or CD8 T-cell exhaustion is associated with impaired clearance of chronic parasite burden, driven both by persistence of foreign antigen(s) and lack of accessory "help" signals, especially during concomitant viral infections [291-293]. (Nb. increased levels of IgE and/or IgG can also reflect host defense against *T. gondii* infection [94, 294, 295]). In addition, it must be emphasized that statins and alemtuzumab/natalizumab exerted beneficial effects in

Table 5. Autoimmune diseases associated with *T. gondii* infection (acc. to Flegr, Prandota et al [27] and Prandota [98]; with own modification).

| Clinical entity | Refs |
|---|----------------------------|
| Multiple sclerosis | 234 |
| Systemic sclerosis | 235-238 |
| Diabetes mellitus types 1 and 2 | 239-241 |
| Hashimoto thyroiditis, Graves' disease; other thyroid autoimmune diseases | 235, 238, 242-244 |
| Rheumatoid arthritis, Still's disease | 235, 245-249 |
| Myocarditis, chronic heart failure, rheumatic fever/myocarditis | 250, 251 |
| Scleroderma, psoriasis | 237, 252, 253 ^a |
| Systemic lupus erythematosus | 254-256 |
| Ocular toxoplasmosis (retinochoroiditis, uveitis, retinitis pigmentosa) | 257-260 |
| Polymyositis, dermatomyositis | 251, 261-267 |
| Polyarteritis nodosa | 268 |
| Wegener's granulomatosis; other vasculitides | 235, 238, 260 |
| Kawasaki disease (?) | 268 |

^aIt must be noted that psoriasis and atherosclerosis, two plaques suspected to be one syndrome [269], were associated with latent *T. gondii* infection [233].

patients with MS [296-300], and otherwise it is known that some agents of this group were found to be effective in ADs associated with *T. gondii* infection [252, 253, 301-303].

7. FS, heart diseases and *T. gondii* infection

Individuals with FS often suffer from silent myocardial ischemia, and its association with Prinzmetal angina, a vasospasms of the epicardial arteries [304], also cannot be excluded [40]. Recently, Salacki et al [305] described a patient with several RP attacks and the angiography of coronary vessels showed a spasm in left descending artery that disappeared following nitroglycerin administration. Moreover, pain in the chest was always preceded by paroxysmal arterial spasm in fingers turning pale [305]. Interestingly, vasospastic angina is a common clinical entity in Asians [306], the pattern similar to both primary vascular disease (PVD) and NTG [307]. Many patients or their relatives with glaucoma have also experienced nonocular diseases associated with FS, such as heart attacks, acute hearing loss, certain autoimmune diseases, and other health disturbances [4, 40, 308].

A. Increased retinal venous pressure and thromboembolism in patients with PVD and RP. Systemic hypoxia leads to infarction and an increase in HIF1 α , ET-1, vascular endothelial growth factor and other biomarkers that finally enhance blood-retina barrier permeability, cause neovascularization, and local vasoconstriction of veins. Venous dysregulation enhances retinal venous pressure that can lead to retinal venous thrombosis [40]. It appeared that the individuals with PVD have stiff and irregular retinal vessels, and reduced neurovascular coupling and autoregulation capacity [40]. Zuk et al [309] found that primary RP may be a risk factor for venous thromboembolism because it occurs relatively frequently among subjects with this clinical entity, with higher prevalence in women (OR 2.75, 95 CI: 1.31-5.78). It appeared that the RP patients formed denser plasma fibrin clots with impaired lysis and had increased endothelial damage [309].

B. Cold extremities in Asian countries and RP. CHHF is a common symptom in Korea and Japan, and the patients complain of cold extremities in environment not considered cold by healthy people [9, 11]. These individuals frequently suffer from anemia, hypotension, reflux esophagitis, chronic gastritis, chronic rhinitis, gastroduodenal ulcer, degenerative arthritis, hypothyroidism, peripheral neuropathy, and dysmenorrhea [10, 310-312], and cold extremities are believed to be a trigger for development of these disturbances [9, 313]. Several of the above-mentioned abnormalities may

be linked with *T. gondii* infection, such as degenerative arthritis, hypothyroidism, peripheral neuropathy, gastrointestinal disturbances, anemia, and dysmenorrhea [94, 98, 314-316]. Nb. in women with toxoplasmosis dysmenorrhea was associated with markedly increased testosterone concentrations [311, 312, 317, 318].

Although people with FS in Western countries are usually regarded as apparently healthy individuals [4], persons with PVD have increased risk for development of NTG, optic nerve syndrome, retinal vein and artery occlusions and anterior ischemic neuropathy, central serous choroidopathy, dysfunction of autonomic nervous system, higher prevalence of hemorrhages in optic nerve, and activated astrocytes [40]. The subjects with SVD have tendency to suffer more frequently because of muscle cramps, migraine with aura, silent myocardial ischemia, tinnitus, altitude sickness, retrobulbar neuritis, MS, RA, fibromyalgia, and giant cell arteritis [40]. Several of these health disturbances probably were also due to latent *T. gondii* infection, as it is presented in this work.

C. Sympathetic nervous system predominance in patients with PVD. In healthy PVD participants with sympathetic predominance analysis of the heart rate variability revealed imbalance of autonomic nervous system (ANS) [42], and shift of sympathicovagal balance of NTG patients to sympathetic activity [40, 319]. Moreover, dysfunction of ANS in individuals with NTG [320] was related to the rise in ET-1 concentrations [321]. Interestingly, silent myocardial ischemia was reported in patients with glaucoma and cataract [322, 323]. Additionally, Saladieh et al [324] found that increased heart rate and reduced heart-rate variability (HRV) were associated with the subclinical inflammation in middle-aged and elderly subjects with no apparent heart disease. Other studies also emphasized a relationship between indices of HRV and inflammation [325, 326]. Recent investigations performed by Thayer et al [327] in apparently healthy people supported the hypothesis that a clinically relevant endogenous cholinergic anti-inflammatory pathway controlled sympathetic nervous system predominance affecting these participants. Given that latent *T. gondii* infection has a global distribution and lifelong persistence in human body all these data may suggest an undiagnosed subclinical coronary heart inflammation/disease in these subjects caused by the parasite reflecting defense of the host. The cardiac autonomic dysfunction observed in NTG patients [319], and the link between the HRV and increased ET-1 levels in such individuals [321] may support this explanation.

Autonomic system dysfunctions (lower vagal and higher sympathetic tone) have been documented in chronic inflammatory diseases and aging associated with increased systemic inflammation [98, 328-331]. The cholinergic modalities acting through vagus nerve and involving $\alpha 7$ subunit-containing nicotinic acetylcholine (ACh) receptor-mediated mechanisms have been shown to suppress excessive inflammation in many experimental models of diseases [98, 328-331]. ACh binds with nicotinic receptors on lymphocyte surface and inhibits production of proinflammatory cytokines, serotonin, histamine, NO, prostaglandins, and leukotrienes during the inflammatory process [328, 330, 332, 333]. Of note, nicotine administration increased ACh concentration in rabbits [334], and T and B cells, macrophages and dendritic cells were necessary for the proper function of cholinergic system [98, 335].

The above-presented reasoning may be confirmed by several studies of the ACh-provocation test widely used in assessment of coronary spasm or dysfunction [336-338]. For example, Ong et al [337] analyzed 62 patients (26 men) with chest pain in spite of unobstructed coronary arteries who underwent ACh testing for diagnosis of coronary artery spasm. They found the test positive in 48 patients (27 of them had epicardial spasm, 21 microvascular spasm (the epicardial spasm was diffuse in 26 patients, 1 patient had focal spasm)). The ACh-positive patients had markedly elevated high sensitivity CRP, e-selectin (adhesion molecule), and sCD40 ligand levels associated with positive ACh-test response, which suggested concomitant subclinical inflammation (hs-CRP: OR 1.54, 95% CI: 1.02-2.33, $p = 0.04$, sCD40 ligand OR 1.001, 95% CI: 1.00-1.001, $p = 0.003$). Nb. the CD40/CD40 ligand interaction is involved in IL-12 production by macrophages, and IFN- γ generation by T-cells required for resistance to *T. gondii* encephalitis [339]. Moreover, Estato et al [338] showed that mice infected with the parasite (ME49 strain) had sustained neuroinflammation and decreased cerebral blood flow. Microscopic examination demonstrated significant brain capillary rarefaction, increased number of leukocytes rolling and adherent to the wall of cerebral capillaries, and neuroinflammation with microglial activation. The infection reduced angiogenesis, decreased number of blood vessels and length and branching of the laminin-stained capillaries [338]. Calcium antagonists regarded as the cornerstone of medical treatment in coronary artery spasm [340], and Ca^{2+} ion crucial for *T. gondii* host cell invasion [94], are in line with these findings.

D. *T. gondii* infection and the heart, muscle cramps, and low back pain. At present, cardiovascular involvement

in toxoplasmosis is regarded as rare and often asymptomatic or obscured by neurological deterioration [341-343]. Myocarditis, arrhythmias, pericardial effusion, constrictive pericarditis, and congestive heart failure have been reported in the patients infected by the parasite [344, 345]. The pathogen is driven by the actin-myosin-dependent motility mechanism forming intracellular vacuole made from the plasma membrane of cardiomyocytes [342, 346], and residing intracellularly in the phagosomes of macrophages and myocardial cells [342]. Toxoplasmic myocarditis is often subclinical and usually silent therefore diagnosis is frequently made postmortem [343, 344].

Individuals suffering from PVD have more frequently silent myocardial ischemia or muscle cramps than other health disturbances [40]. Toxoplasmosis may affect muscles during either primary infection or reactivation manifesting as myositis or polymyositis [251, 264, 345, 347]. Interestingly, Gomes et al [348] found that the infection of skeletal muscle cells with *T. gondii* increased the number of lipid droplets and damaged area in the time course-dependent manner. They also demonstrated an increase in proinflammatory cytokines IL-12 and IFN- γ , enhancement COX-2 mRNA, and PGE₂ synthesis, that may lead to development chronic infection in muscle cells [348]. Moreover, it was found that during chronic infection the parasite caused not resolving myositis with prolonged tissue damage associated with accumulation of proinflammatory macrophages, and regulatory T cells promoted this process [349]. These findings may therefore support a possible relationship between development of muscle cramps reported in people with PVD [40] and infection with the parasite.

It must be noted that “muscle cramps/myositis”, and “low back pain (LBP)” symptoms have been reported in several ADs, including MS, RA, SLE, SS, and diabetes [350-360] with documented chronic latent *T. gondii* infection [98, 235, 238, 239]. Nb. LBP symptoms have been described in Japanese patients with CHHF [11]. Interestingly, “takotsubo” syndrome, a transient ventricular dysfunction due to spasm of coronary vessels [361], may also be associated with latent infection with the parasite because: a) this clinical entity is prevalent in females elder than 50 years (mean age ~70) [362, 363], b) may be caused by coronary and peripheral endothelial dysfunction associated with enhanced ROS and RNI production, increased levels of H₂O₂ and malondialdehyde, and reduced glutathione concentrations [364] and c) is characterized to be secondary to excessive sympathetic stimulation [365]. It must be added that LBP, a major public health issue globally [366], is associated

with frequent comorbidities, including migraine/headache, irritable bowel syndrome and other diseases of the digestive system, and also with poorer mental health [367-371], *i.e.* the entities having a relationship with chronic latent *T. gondii* infection [98, 139, 140, 238, 314, 372]. Some changes of these biochemical parameters in patients infected with the pathogen are presented in Tables 6 and 7 [373, 374].

E. *T. gondii* infection and adipocardiovascular axis. Leptin and adiponectin: patients with CHHF induce increased serum adiponectin levels. Baltaci & Mogulkoc [375] showed that the rats infected with *T. gondii* have

markedly increased leptin levels (Table 8). Other investigators demonstrated significant positive association between the parasite seropositivity and obesity [376]. Van Dielen et al [377] established that in morbidly obese individuals leptin concentrations correlated with increased levels of inflammatory markers. Similarly, Aygun et al [378] reported that obese prepubertal children had markedly elevated leptin concentrations, as well as TNF- α , IL-1 β and IL-6 levels (Table 9) [378, 379]. Of note, leptin (a 16 kDa protein) is released locally within the intestinal mucosa, has chemical structure similar to IL-2, and activates immune system shifting it

Table 6. Serum glutathione (GSH), malondialdehyde (MDA), and NO concentrations in *T. gondii*-seropositive patients and healthy controls (acc. to Karaman et al [373]; with own modification).

| Bioparameter | Group | No of participants | Serum levels (mean \pm SD) | P |
|--------------|----------|--------------------|------------------------------|-------|
| GSH | Patients | 37 | 3.96 \pm 0.10 | 0.001 |
| | Controls | 40 | 10.37 \pm 0.13 | |
| MDA | Patients | 37 | 41.32 \pm 2.05 | 0.001 |
| | Controls | 40 | 9.18 \pm 1.21 | |
| NO | Patients | 37 | 47.47 \pm 1.00 | 0.001 |
| | Controls | 40 | 39.18 \pm 1.29 | |

Serum GSH and NO levels are expressed as μ mol/L, and MDA concentrations represent nM/L. Results statistically significant at $p < 0.05$.

Table 7. Erythrocyte MDA, GSH, and serum NO concentrations in patients with *T. gondii* infection and healthy controls (acc. to Al-Azzaay et al [374]; with own modification).

| Group | Erythrocyte MDA (nM/g Hb) | Erythrocyte GSH (nM/g Hb) | Serum NO (μ M/L) |
|---|---------------------------|---------------------------|-----------------------|
| Patients with <i>T. gondii</i> infection (n = 50) | 20.75 2.06 | 2.10 \pm 0.10 | 48.47 \pm 0.30 |
| Controls (n = 30) | 4.43 1.65 | 6.95 \pm 1.21 | 42.38 \pm 0.30 |
| P values | < 0.001 | < 0.001 | < 0.001 |

Values are means \pm SD. Results statistically significant at $p < 0.05$.

Table 8. Body weight and plasma leptin concentrations in rats intraperitoneally infected with *T. gondii* (acc. to Baltaci & Mogulkoc [375], with own modification).

| Study group | Body weight before the study (g) | Body weight after four weeks (g) | Plasma leptin levels (ng/mL) |
|------------------------|----------------------------------|----------------------------------|------------------------------|
| Control rats (n = 10) | 266.00 \pm 32.81 | 270.50 \pm 33.70 | 4.09 \pm 1.15 |
| Infected rats (n = 10) | 263.50 \pm 44.16 | 269.50 \pm 42.78 | 7.53 \pm 1.55* |

Results are means \pm SD. *Statistically significant result ($p < 0.01$).

Table 9. Serum proinflammatory cytokines and leptin concentrations in obese children at prepubertal age compared with healthy children of the same age (acc. to Aygun et al. [378]; with own modification).

| Parameters | Obese children | Controls | P |
|---------------------|-----------------|----------------|---------|
| Leptin (ng/mL) | 19.9 \pm 7.4 | 7.9 \pm 5.1 | < 0.001 |
| IL-1 (pg/mL) | 33 \pm 8.9 | 3.6 \pm 1 | < 0.001 |
| IL-2 (U/L) | 0.4 \pm 0.1 | 0.9 \pm 0.1 | < 0.01 |
| IL-6 (pg/mL) | 45.2 \pm 11.8 | 13.1 \pm 3.9 | < 0.001 |
| TNF- (pg/mL) | 9.2 \pm 2.3 | 3.9 \pm 1 | < 0.001 |
| E-selectine (ng/mL) | 78 \pm 38 | 59 \pm 29 | < 0.01 |
| hsCRP (mg/L) | 4.1 \pm 4.8 | 0.9 \pm 1.5 | < 0.001 |

Results are mean \pm SD; CRP, C-reactive protein; hs, high-sensitivity. Statistically significant results at $p < 0.05$.

to predominance T_H1 T cell population and decreased regulatory T_H2 phenotype [380]. In addition, in beta-less mice leptin administration was associated with increased energy expenditure (oxygen consumption) [381].

By contrast, adiponectin (a 30 kDa protein) is produced in adipose tissue, has structure similar to collagen VIII, X, and complement C1q, and exerts multiple beneficial effects in prevention of cardiovascular diseases because of its pleiotropic actions on heart and blood vessels [382, 383]. Moreover, the hormone exerts favorable actions on insulin resistance and metabolic disorders through stimulation of fatty acid oxidation in muscle cells [384]. Importantly, in the context of cold extremities, Park et al [229] demonstrated that serum adiponectin levels were positively associated with CHHF (particularly in women), irrespective of BMI ($\beta = 1.23$ $\mu\text{g/mL}$, 95% CI: 1.04-1.45), and therefore it may reduce risk of cardiovascular disease in such patients [229]. The increase in the hormone concentration also reflects their body self-defense against cold stress.

8. FS, RP, hypothyroidism and latent *T. gondii* infection

A. Hypothyroidism can be associated with vascular dysfunction such as impaired endothelial- and nonendothelial-mediated vasodilation [4, 385]. Thyroid diseases with vascular dysfunction are frequently observed in NTG patients [4, 40, 386]. Konieczka et al [3, 4] often demonstrated antibodies against thyroid gland in euthyroid patients with concomitant NTG with FS, and glaucoma patients with FS also may have Hashimoto thyroiditis (HT) [40]. Moreover, an association of RP with hypothyroidism has also been reported [94, 387-390].

B. *T. gondii* infection and hypothyroidism. *T. gondii* infection of thyroid gland leading to impaired thyroid function was found in animals [391, 392] and humans [242, 244, 393]. Anti-*T. gondii* antibodies have been documented in autoimmune thyroid diseases [98, 235, 243, 394]. Prior infection with the parasite was associated with marked elevation of autoantibodies against thyroid peroxidase

(TPOaAb) [243, 244]. In pregnancy, toxoplasmosis was linked with a decrease of serum thyroid stimulating hormone concentrations ($p = 0.049$) and a significant elevation of TPOaAb [244]. Kivity et al [395] showed that the prevalence of vitamin D deficiency was markedly higher in patients with autoimmune thyroid diseases (AITDs) compared with healthy individuals (72% vs. 30.6%, $p < 0.001$), as well as in patients with HT compared to participants with non-AITDs (79% vs. 52%, $p < 0.05$). Vitamin D deficiency also correlated to the presence of antithyroid antibodies ($p = 0.01$) and abnormal thyroid function tests ($p < 0.059$). In patients with HT and Graves' disease (GD) the prevalence of IgG against *T. gondii* appeared to be markedly higher than in controls (56.5% vs 38.0%, $p < 0.02$), suggesting that the parasite may be a trigger of autoimmune thyroid diseases [242]. Also sera obtained from the patients with hypothyroidism had significantly increased TPOaAb levels (Table 10) [243]. (Nb. in HT, T cells help in the destruction of the thyroid epithelial cells and thyroid epithelial structure leading to hypothyroidism, while GD is primarily a humoral disease where autoantibodies are produced against the thyroid stimulating hormone receptor leading to hyperthyroidism [394]).

Interestingly, thyroid-associated ophthalmopathy (exophthalmus, eye muscle dysfunction, optic nerve involvement, corneal involvement) was found to be associated with GD [396]. Hyperthyroidism has also been linked with coronary artery spasm (the entity characterized by PVD) [40, 397, 398], and treatment with L-thyroxine may induce coronary vasoconstriction [399].

C. Decreased synthesis of IgG and IgM by B lymphocytes associated with vitamin D deficiency might be responsible for lack of a link between *T. gondii* infection and some diseases/entities/ professional occupations which usually have been reported as connected with the parasite

In the case-control study on *T. gondii* seroprevalence Alvarado-Esquivel et al [284] suggested that thyroid dysfunction was not associated with seropositivity to the parasite and even demonstrated in their ≤ 50 years old patients a negative relationship between infection and

Table 10. Association of *T. gondii* with the elevation of (log) continuous TPOaAb concentrations (1807 sera, 482 positive for the pathogen), adjusted for age, and treatment for clinical hypothyroidism; Baltimore CPP, 2004-2008 (acc. to Wasserman et al [243]; with own modification).

| Parameters | β Coefficient | CI | Z (p) |
|----------------------------|---------------------|------------|--------------|
| <i>T. gondii</i> | 0.60 | 0.31, 0.88 | 4.10 (0.000) |
| Year increase in age | 0.02 | 0.00, 0.04 | 2.22 (0.03) |
| Treatment with L-thyroxine | 1.02 | 0.27, 1.76 | 2.68 (0.01) |

Generalized linear model estimates for γ distribution, with robust standard error for multiple samples. In the final sera analyses of independent association of viral pathogens with the elevation of TPOaAb, there was none significant for cytomegalovirus, Epstein-Barr virus, and herpes simplex viruses 1 and 2 [243].

thyroid dysfunction and hypothyroidism. However, a critical assessment of this finding suggests that the authors did not take into consideration some other factor(s) probably affecting the obtained results, such as that Mexico is a “sunny” country and otherwise it is known that vitamin D contributed to health improvement in both the subjects with primary RP and secondary RP because exerts beneficial immune effects and has a significant antitoxoplasmic activity [94, 400-403]. In addition, vitamin D causes decreased proliferation, differentiation, and IgG and IgM synthesis by B lymphocytes [404-406]. Bizzaro & Shoenfeld [407] emphasized that low levels of vitamin D were found to be associated with antithyroid antibodies presence, abnormal thyroid function, increased thyroid volume, elevated TSH levels in women with autoimmune thyroid disease, and that hypovitaminosis D is increasingly represented among healthy individuals. Interestingly, Alvarado-Esquivel et al [408] themselves admitted in their paper on the association between *T. gondii* infection and heart disease that the patients born out of Durango state had a significantly higher seroprevalence of *T. gondii* infection than participants born in Durango State ($p = 0.008$). Several other similar findings have also been reported by this group, including lack of statistically significant links between *T. gondii* infection and pregnancy [409, 410], epilepsy [411], suicide [412], bipolar disorder [413], healthy blood donors [414], and in workers occupationally exposed to unwashed raw fruits and vegetables and their respective controls [415]. In this context, it must be noted that the authors quite precisely described very favorable local climate conditions in their research zone called the “Lagunera” region of Durango State in the northwest area of Mexico [410]. Moreover, in the earlier case-control work (400 patients with heart diseases and 400 age- and gender-matched controls) they admitted that the *T. gondii* infection was significantly associated with the heart disease, and that exposure to the parasite was positively related with being born out of Durango State (OR = 2.93, 95% CI: 1.40-6.13, $p = 0.04$) [408].

9. FS may be associated with tinnitus and hearing loss in individuals exposed to vibrations or whiplash trauma. Possible key role of toxoplasmosis in development these disorders

A. Tinnitus, hearing loss and FS. It was suggested that FS is often associated with tinnitus and hearing loss [4, 40]. Subjects with PVD and NTG frequently have tinnitus and sudden (usually reversible) hearing loss [40, 416]. Hearing disturbances during migraine infarction have also been reported [417], and the presence of endothelin receptors in the spiral modiolary

artery may support this relationship [418]. Several patients with ophthalmologic abnormalities and sudden hearing loss have signs of disturbed eye microcirculation, despite apparent good state of health [419]. In addition, auditory processing deficits often occur in patients with primary open-angle glaucoma (POAG) [420], thus supporting a holistic approach of sick eye in sick body [421]. This avenue can be reinforced by the finding of associations between tinnitus and glaucoma suggesting a common pathomechanism(s) operating in these two clinical entities [422, 423]. Moreover, patients with sensorineural hearing loss (SNHL) showed a markedly higher incidence of glaucoma development than those non-SNHL counterparts with a higher adjusted hazard ratio and cumulative probability [422]. In this context, for the population-based study [423, 423A], glaucoma patients had a 19% increase in odds for tinnitus (OR 1.19, 95% CI: 1.02-1.40), suggesting that those with glaucoma were more likely to have tinnitus than those without glaucoma. Finally, it should be noted that ischemia and hypoxia (each of these disturbances is characteristic for FS and *T. gondii* infection, respectively) result in the loss of outer hair cells and damage of neural units, leading to inner ear disorders, including tinnitus [424, 425].

B. Vibrations, whiplash trauma and FS. Patients with FS are more sensitive to vibrations [40, 308, 426, 427], and they tend to have more, longer-lasting and stronger whiplash trauma symptoms, such as headaches, sleep disturbances, and dizziness (whiplash is a sudden acceleration and deceleration of the thorax independent of head movement during, for example, car collision) [3, 4, 40]. Workers with hand-arm vibration syndrome also suffer from cold-induced finger and feet vasospasms [428, 429]. Based on practical experience, Flammer et al [40] suggested that patients with FS may have an underlying body predisposition to develop such reactions to vibrations.

C. Hearing loss, tinnitus, vibrations, whiplash trauma and *T. gondii* infection. There are several reports documenting a marked association between *T. gondii* infection and SNHL in adults [430-432], children [433-435], including infants with congenital toxoplasmosis [433, 436, 437]. It must be noted that Zanetti et al [438] in a study of 413 patients with inner ear disorders of unknown etiology tested for anti-laminin antibodies showed that 68% of patients had SNHL, and otherwise it was documented that there was a potential relationship between the increased serum autoantibodies against laminin in patients with autoimmune diseases [439] and latent *T. gondii* infection [98]. A positive family history found in patients with SNHL [440] may support an infectious origin of this disorder.

Chien et al [422] established that age was a risk factor of glaucoma and adjusted odds ratio of the patients aged 60 to 79 years had a significantly higher values than younger participants, and this finding was consistent with the results obtained in earlier studies [441]. Nb. it must be noted that the increased incidents of *T. gondii* infection in nonpsychiatrically affected control individuals also were depending on age (Table 11) [442].

Tinnitus and cataracts also were reported to have a significant relationship with the parasite infection [443, 444], and Hsieh et al [445] found that patients with cataract had higher hazard ratio developing tinnitus than controls (OR = 1.53, 95% CI: 1.17-2.01, $p < 0.01$). In addition, the number of individuals with comorbidities (anxiety, hearing loss, vertigo, insomnia) was significantly higher among the patients with cataract than in controls [445]. Furthermore, other studies showed that hearing loss, insomnia and anxiety were highly relevant to tinnitus severity [445-448]. Interestingly, Neri et al [449] showed that the levels of oxidative damage markers (malondialdehyde, myeloperoxidase, 4-hydroxynonenal) were significantly higher in patients with tinnitus than in controls, whereas glutathione peroxidase (an antioxidant) had lower activity, thus probably sharing similar pathogenesis with development of cataract. The oxidative stress and endothelial dysfunction disturbances, as well as the similarity of pathogenesis are in a good agreement with comparable biochemical abnormalities reported in patients with *T. gondii* infection [373, 374, 450, 451].

The use of hand-held vibration tools may not only be associated with development white fingers and RP but also with difficulties in hearing [416, 424, 425, 452], and recently a robust documentation has been presented that latent *T. gondii* infection perhaps was critical risk factor responsible for these disorders [94]. These data may be supported by a markedly higher parasite seroprevalence in persons participating in traffic accidents compared with controls [453-456].

D. Possible relationship between tinnitus, stroke, and infection with *T. gondii*. Huang et al [457] reported that tinnitus was significantly associated with a higher risk of ischemic cerebrovascular disease (ICVD) incident among young and middle-aged patients. They suggested that tinnitus and ICVD may share a common pathophysiological mechanisms, such as for example arterial stiffening, which leads to impairment cochlear microcirculation [457]. In addition, it was reported that a higher common carotid artery stiffness index was markedly linked with the formation and severity of tinnitus [458], and the carotid artery abnormality was associated with higher incidence of stroke [457, 459]. The link between tinnitus and stroke could also be supported by involvement of some other pathophysiological factors, such as hypoxia [460], oxidative stress [461, 462], and increased sympathetic activity [463].

Recent studies of Pearce et al [464] performed in 13,904 respondents from the National Health and Nutrition Examination Survey III supported a link between serological evidence of prior infection to *T. gondii* (a parasitic, viral and bacterial burden) and stroke among subjects aged 20-59 (OR = 2, $p = 0.005$). Moreover, cerebral toxoplasmosis in patients with HIV also have stroke-like presentation [465, 466].

The vascular endothelium is exposed to diverse mechanical signals that regulate vascular endothelial barrier morphology and function. Franklin Murray et al [93] demonstrated that *T. gondii* infection of human umbilical vein endothelial cells altered cell morphology and dysregulated vessel wall barrier function leading to increased vascular wall permeability regulated by opening and closure cell to cell adherent junctions (AJs). In endothelial cells, AJs are largely composed of VE-cadherin [466A, 467]. The pathogen disrupted vascular endothelial VE-cadherin and β -catenin localization to the cell periphery and reduced VE-cadherin protein expression. The infection lead to

Table 11. Percentage of *T. gondii* positive individuals among 214 nonpsychiatrically affected controls depending on age analyzed during a large epidemiologic study of 869 psychiatric patients (Hinze-Selch et al [442]).

| <i>T. gondii</i> positive (%) | Age (yrs) | | | | | | | | | | | |
|-------------------------------|-----------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| | 18-20 | 21-25 | 26-30 | 31-35 | 36-40 | 41-45 | 46-50 | 51-55 | 56-60 | 61-65 | 66-70 | 71-75 |
| 100 | | | | | | | | | | | | 100 |
| 80 | | | | | | | | | 80 | | 80 | |
| 60 | | | | | | | 58 | 58 | | 60 | | |
| 40 | | 35 | 32 | 40 | 39 | 38 | | | | | | |
| 20 | 19 | | | | | | | | | | | |
| 0 | | | | | | | | | | | | |

In the control participants 45 yrs or younger recruited from the same geographical region as the psychiatric patients admitted to the hospital, serofrequency of *T. gondii* infection ranged between 20 and 40% without any systematic age effect, whereas in the individuals older than 45 yrs serofrequency systematically increased with age from about 40% to almost 100% [442].

reorganization of the host cell cytoskeleton by reducing filamentous actin (F-actin) stress fiber abundance under shear stress conditions, and planar cells polarity. Moreover, infection with *T. gondii* induced changes in gene expression in endothelial cells associated with cytokine-mediated signaling, extracellular matrix reorganization, and cell to cell adhesion [93]. Nb. in these cells actin represents about 10% of total protein [468, 469]. F-actin interacts with catenins to anchor interendothelial cell junctions and stabilize endothelial barrier integrity [470]. Actin, VE-cadherin, and binding proteins form mechanosensing complex in endothelial cells [471], and as a result, various external/internal mechanical forces (e.g. transient or steady-state shear stress) [472, 473] are transduced through the actin cytoskeleton into cellular responses [93, 474], finally leading to development of abnormalities in vascular wall morphology. More details related to these molecular processes that probably are also taking place in RP have been presented earlier [94].

10. FS, breast cancer (BC) and *T. gondii* infection

A. FS and BC. BC causes more than half million deaths each year [475, 476]. Importantly, the brain is one of most predominant sites of metastatic spread recorded in more than 20% of BC patients in several individuals subgroups [476-478]. It was reported that 1 in 8 of the U.S. women will have invasive BC during their lifetime. In 2018, there were 3.1 million women with BC, and about 2500 invasive BC cases have been expected in men [479]. Zubor et al [49] demonstrated the tendency of BC patients to the increased prevalence of FS symptoms than disease-free participants. They prognosed that approximately 90% of patients create unpredicted subpopulations taking into account disease predisposition, development and progression [49], and this is in line with various serotypes and antigens of *T. gondii* affecting the host, as well as with its current immune status [102].

It seems that FS is involved in the BC pathology and may predispose to metastatic disease, and a spectrum of other concomitant diseases [40, 49-51]. Smokovsky et al [51] demonstrated that several symptoms present in FS individuals are also highly prevalent particularly in the postmenopausal BC patients (Table 12).

B. Changes in blood morphology and biochemical parameters in BC patients.

Mishra et al [480] analyzed 102 cases of BC with and without metastasis and 25 healthy non-pregnant females. They found a significant increase in lactate dehydrogenase (LDH), reduced glutathione (GSH), and ferritin blood concentrations, as well as decreased hemoglobin levels in cancer patients without metastasis compared with controls. Patients with metastases also had a marked rise in alkaline phosphatase (ALP), LDH, γ -glutamyl transpeptidase (GGTP) and ferritin levels, and anemia in comparison to healthy controls (Table 13).

C. FS, BC and *T. gondii* infection. Several authors reported a markedly higher serum ferritin level in BC patients with metastases [481-484]. The increase in serum ferritin has been attributed to the iron requirement for cell growth and malignant cells need for modulation of transferrin receptors present on proliferating abnormal cells [485]. This deficiency in the iron body stores of BC patients [480] may be, at least in part, associated with chronic latent toxoplasmosis because intracellular replication of *T. gondii* is iron-dependent [486], and the parasite is an auxotroph for iron, iodine and folic acid [98, 486, 487]. In this context, the persistent rise in ferritin and LDH levels with response to therapy observed in few BC cases by Kher et al [484] attributed to recurrence of metastasis is not surprising. Also NO intercepts iron before its incorporation into ferritin, and also indirectly mobilizes iron from ferritin in a glutathione-dependent manner [488].

Table 12. Significant symptoms of the FS recorded in postmenopausal BC patients vs BC-free participants (acc. to Smokovski et al [51]; with own modification).

| FS symptoms | Postmenopausal BC (n = 67) | patients | BC-free individuals (n = 73) |
|------------------------------------|----------------------------|---------------|------------------------------|
| | Prevalence | | Prevalence |
| Feeling cold | + | 0.001 | - |
| Headache | + | 0.008 | - |
| Drug sensitivity | + | 0.001 | - |
| Smell perception | + | 0.001 | - |
| Low body weight in early adulthood | + | 0.001 | + |
| Σ criteria | | 5 significant | |

P value < 0.05 is considered statistically significant. The following system was employed: “+” means higher prevalence of the corresponding symptom (above the lowest average of the groups of comparison); “-” means lower prevalence of the corresponding symptom (lowest average and below it).

Table 13. Serum levels of various enzymes, GSH, ferritin and hemoglobin (Hb) in BC patients without and with metastasis as compared with controls (acc. to Mishra et al [480]; with own modification).

| Group | ALP (U/L) | LDH (U/L) | GGTP (U/L) | GSH (mg%) | Ferritin (ng/mL) | Hb (gm%) |
|--------------------------------|------------------------------|------------------------------|---------------------------|-------------------------|-----------------------------|------------------------|
| Controls (n = 25) | 130.0 ± 15.2 (110-146) | 228.8 ± 54.5 (195-270) | 20.1 ± 7.0 (10-250) | 30.2 ± 3.0 (25-36) | 98.0 ± 35.2 (68-102) | 13.1 ± 2.7 (11-15) |
| BC without metastasis (n = 58) | 157.0 ± 32.6 (120-190) | 433 ± 99.6** (350-505) | 23.9 ± 4.9 (17-29) | 49.0 ± 6.5** (41-57) | 214.0 ± 36.2** (180-250) | 10.0 ± 1.9** (7-12) |
| BC with metastasis (n = 44) | 750.3 ± 102.6** (610-850) | 730.0 ± 136.7** (565-950) | 92.3 ± 16.9** (75-126) | 67.4 ± 12.2* (55-82) | 647.5 ± 58.2** (590-705) | 9.1 ± 2.4 (7-12) |

Values are mean ± SD. +, $p < 0.05$; **, $p < 0.001$. ALP, alkaline phosphatase; GGTP, γ -glutamyl-transpeptidase; GSH, reduced glutathione; Hb, hemoglobin; LDH, lactate dehydrogenase.

The marked anemia found in BC patients by Mishra et al [480] was probably due to a concomitant latent *T. gondii* infection and IFN- γ -dependent, signal transducer and activator of transcription 1-independent red blood cell loss [315, 489, 490]. This may be supported by the findings that the parasite activates HIF 1 α [169, 170], and LDH A gene promoters contain essential binding site for HIF 1, as well as is a key player in carcinogenesis (increased body lactic acidosis), a key player in carcinogenesis [491-493], thus creating hypoxic environment critical for BC development and metastasis [494, 495]. In addition, hypoxia inhibited production of NO in the rat smooth muscle cells treated with both lipopolysaccharide and IFN- γ [496], and vasospasm is closely related to FS [40, 497, 498]. Importantly, hypoxia is a crucial contributor to the development of aggressive metastatic disease [499, 500]. Finally, anemia was reported in animals and humans with toxoplasmosis [501-504].

Gradascevic et al [505] found that serum oxidative stress marker malondialdehyde (MDA) levels in the invasive BC patients (n = 43) were markedly higher than in the patients with benign breast disease (n = 39) (Mann-Whitney U = 619.00; $p = 0.042$), thus indicating its importance in carcinogenesis of the entity. In addition, a statistically significant correlation between serum MDA levels and ages of BC patients with lymph node metastases was found ($p = 0.006$). It must be noted that in subjects with acute toxoplasmosis Al-Kuraishy

et al [450, 506] documented significantly higher MDA, ET-1 and IL-6 concentrations compared with controls (Table 14). It appeared that serum IgM level markedly correlated with IgG ($r = 0.55$, $p < 0.001$), and other analyzed bioparameters (MDA, $r = 0.85$, $p < 0.0001$; ET-1, $r = 0.51$, $p = 0.003$; IL-6, $r = 0.45$, $p < 0.01$) [450, 506]. Nb. IL-6 enhances intracellular replication of the parasite [507, 508]. Karaman et al [373] also found significantly increased serum MDA, GSH and NO levels in *T. gondii* seropositive patients. All these data strongly suggest that more BC patients suffer from latent toxoplasmosis than officially diagnosed, especially that endothelial dysfunction has also been reported in this clinical entity [450, 506].

D. Headache/migraine in BC patients may be associated with latent *T. gondii* infection. Golubnitschaja et al [509] emphasized that some migraineurs in general demonstrated a reduced risk in development of BC [510-512], while particularly migraineurs without aura suffered from aggressive and metastatic triple negative BC phenotypes [499, 500, 509, 513]. Gramer et al [514] reported that of 2027 patients with glaucoma or ocular hypertension the significantly higher frequency of migraine and vasospasm had participants with NTG (n = 140), and family history of glaucoma (FHG). Patients with FHG had markedly higher frequency of migraine than patients without FHG ($p = 0.02$). Moreover, migraine was significantly more often present in

Table 14. Serum levels of immunoglobulins, IL-6, ET-1, and MDA in patients with acute toxoplasmosis compared with controls (acc. to Al-Kuraishy et al [450, 506]; with own modification).

| Parameters | Patients (n = 21) | Controls (n = 20) | P |
|--------------|-------------------|-------------------|--------|
| IgM (g/L) | 3.6 ± 2.99 | 1.2 ± 0.8 | 0.001 |
| IgG (g/L) | 22.96 ± 9.57 | 4.31 ± 2.95 | 0.0001 |
| IgA (g/L) | 4.72 ± 2.54 | 1.99 ± 1.34 | 0.0001 |
| IL-6 (pg/mL) | 3.22 ± 1.61 | 1.88 ± 0.51 | 0.0007 |
| ET-1 (pg/mL) | 7.29 ± 4.59 | 3.11 ± 1.69 | 0.01 |
| MDA (nM/mL) | 9.34 ± 4.17 | 2.87 ± 1.13 | 0.01 |

Results are expressed as mean ± SD. The unpaired Student's *t*-test was used to determine the differences. Results statistically significant at $p < 0.05$. ET-1, endothelin-1; MDA, malondialdehyde.

NTG (21.4%) than POAG (n = 1233) (13.1%, $p = 0.01$), and the age-corrected probability for migraine was also 63.5% higher in NTG individuals ($p = 0.007$) [514]. These findings may be due to latent *T. gondii* infection in these subjects because several studies reported that headaches/migraine were associated with reactivation of cerebral toxoplasmosis [139, 140, 172, 372, 515]. Furthermore, this may support the earlier reasoning on heritability and family household-related associations of the parasite, and therefore the parasite may be a strong environmental risk factor for NTG development, especially that migraine and vasospasm were significantly more frequent in females [514].

E. FS, BC, diabetes mellitus (DM), atherosclerosis and latent *T. gondii* infection. It must be noted that endothelial dysfunction and microvascular complications characteristic for FS have been also demonstrated in type 1 and 2 DM [516, 517]. The nailfold capillaroscopy documented alterations in patients with DM [518, 519]. In 792 women with various breast diseases Muck et al [520] found that the frequency of DM was twice to three times higher in women with BC (n = 326) than females with breast fibroadenoma (n = 101), papilloma (n = 80), fibrocystic disease (n = 107), lipoma, granuloma, fibrosis (n = 88), and other BC-like entities.

Kankova et al [521] found that pregnant women with latent toxoplasmosis had significantly higher glucose concentrations in oral glucose tolerance test (n = 191, $p = 0.01$), the level of fasting plasma glucose and higher DM prevalence in 24-28th gestation weeks than *T. gondii*-free women (n = 532, 19.5 vs. 12.0 %, OR = 1.78, $p = 0.033$). In pregnant rats, Xu et al [522] demonstrated that the brain glucose metabolism was markedly increased in *T. gondii* infected animals than in control rats in the initial stage of pregnancy. Other studies reported anti-*T. gondii* antibodies in both type 1 and 2 DM [239-241, 523-525]. Moreover, in acutely infected mice with *T. gondii* Me49 strain infection Beshay et al [524] revealed the presence of the pathogen tachyzoites adjacent to Langerhans islets and in pancreatic parenchyma. In animals with chronic infection, there was a significant decrease of islet number and sizes associated with development of insulinitis. In addition, there was a marked infiltration of the islets by CD8⁺ and CD45⁺ immune cells, a significant reduction of insulin expression in the islets, and a marked rise in serum glucose levels [524]. Nb. Konieczka et al [3] suggested that there is a link between pancreatic cancer and FS. Interestingly, attenuated *T. gondii* vaccine strain has been beneficial in pancreatic tumor-bearing mice through immunity stimulation [526]. Moreover, inoculation of mice with a uracil auxotroph *T. gondii* RH strain inhibited

through immunomodulation BC growth and metastasis [527]. Of note, BC has also been reported in children [528, 529].

It was suggested that individuals with FS suffer from atherosclerosis less frequently than the FS-free persons, but retinal arterial and vein occlusions such as thrombi or emboli due to atherosclerosis can occur in FS subjects, especially under psychological stress or strong cold exposure [3, 5]. Postmenopausal BC women appeared to have a higher risk developing atherosclerosis associated with an increased frequency of cardiovascular risk factors, such as DM and metabolic syndrome, compared with females without BC. Atheromatous plaques were markedly more frequent in the BC women than controls ($p = 0.013$) [530]. Moreover, It was reported that the low heart rate variability (HRV) indices were observed in postmenopausal women with BC compared to postmenopausal women without BC, and in these females the reduction in HRV indices were inversely correlated with triglyceride concentrations [531, 532]. The autonomic dysfunction may reduce vasodilation, promote oxidative stress, increase chronic inflammation, and accelerate atherosclerosis progression [532]. This may be at least partly related to the diminished cholinergic anti-inflammatory pathway in the host involving $\alpha 7$ subunit-containing nicotinic ACh receptor mechanisms expressed on endothelial cells, macrophages, lymphocytes, and keratinocytes, which also release ACh and express other markers of the vagal system [533]. Both atherosclerosis and autonomic system dystonia (associated with reduced parasympathetic efficacy and enhanced sympathetic tone) may be due to latent *T. gondii* infection [233, 333, 534-536] because in rats infected with the parasite Tonin et al [333] found significantly increased acetylcholinesterase (AChE) activity in blood and lymphocytes, which diminished ACh concentration through hydrolysis of the neurotransmitter [536]. This may reflect a defense reaction of the animals against the pathogen because ACh probably promotes *T. gondii* proliferation and migration, like it was revealed for the brain-eating amoeba [534]. In addition, AChE inhibited activation of macrophages and release of proinflammatory cytokines, including IL-6, TNF- α , IL-1, and IL-18 [537], necessary for destroying the microbe. Concerning the vegetative dystonia and a loss of normal HRV in FS individuals [5] and in postmenopausal women with BC [531], Thayer et al [327] presented evidence supporting associations between inflammatory markers, cholinergic anti-inflammatory pathway, and sympathetic nervous system overdrive in healthy human adults manifesting as alterations in HRV.

F. BC and latent *T. gondii* infection. The intracellular parasite lacks the ability to synthesize cholesterol and depends upon acquisition of low density lipoprotein (LDL)-derived cholesterol from host cell *via* endocytosis mediated by LDL receptor [538], to multiply [539]. *T. gondii* transforms many lipid precursors from host cytoplasm to complex lipids [540]. Cholesterol is a risk factor for BC and it was found that 27-hydroxycholesterol (27-HC) (primary cholesterol metabolite) may function as an estrogen, increasing the proliferation of estrogen receptor positive BC cells [541, 542]. In postmenopausal women excessive dietary cholesterol consumption was found to be associated with increased BC risk [543]. Nelson et al [542] found that the cholesterol effects on tumor pathology required its conversion to 27-HC by CYP27A1 oxidase, which expression degree in human BC samples correlated with tumor grade (i.e. in high-grade tumors, both tumor cells and tumor-associated macrophages exhibited high expression levels of the enzyme) [542]. Moreover, Zhang et al [544] revealed that in mice estradiol promoted Pru (type II) and VEG (type III) *T. gondii* infection *in vitro* and *in vivo*, thus significantly contributed then to the pathogenicity of the parasite. They found that estradiol can enter tachyzoites and a residual estradiol metabolism-related gene hydroxysteroid dehydrogenase (*Tg*-HSD) can efficiently transform estrone into estradiol markedly increasing its level in animals [544]. On the other hand, however, it must be noted that tamoxifen (a selective estrogen receptor modulator and one of the most successful drugs in the endocrine long-lasting BC treatment) administered in rats was found to significantly increase both anti-*T. gondii* IgM and IgG titers after 14 and 24 days of treatment [545]. These findings strongly support the above-presented reasoning that latent *T. gondii* infection play an important role in individuals with FS and BC patients.

11. Potential relationship between FS, RP, glaucoma and *T. gondii* infection

Glaucoma is the most common cause of irreversible blindness worldwide [546, 547], and it was predicted that by 2020, 79.6 million people will have this clinical entity, and 74% will suffer from POAG [548]. This disease is associated with progressive loss of retinal ganglion cells [549, 550]. FS contributes to development of NTG [5, 40, 551-554], and patients with this disease have an increased frequency of ocular abnormalities and disturbances, including increased retinal venous pressure, the activated retinal astrocytes, optic nerve compartmentalization, optic disc hemorrhages, diffuse visual field defects fluctuating, and enhanced oxidative stress [5, 40, 555]. Also, a number of patients with either FS or NTG

have optic nerve head (ONH) retinal vessels less shifted to nasal side [7]. It was demonstrated that cold provocation induced transient visual field deterioration in the glaucoma patients with FS [556]. Finally, vasospasm and increased ET-1 level found in NTG subjects [557, 558], and the fact that transgenic mice with ET-1 overexpression in vascular endothelial cells progressively lose retinal ganglion cells, are consistent with NTG development [559, 560].

Current studies emphasized important role of immune factors in NTG pathophysiology [561-563]. Monocytes and activated T-cells were found to be accumulated in the ONH at the site of damage. In inherited mouse glaucoma model it was demonstrated that monocytes migrate through vascular endothelium to ONH prior retinal ganglion cells degeneration, and this suggested that monocyte infiltration may be a cause of this entity [563]. The infiltration may be stopped by the X-ray radiation of the eye [564] indicating that cessation of this process acted as neuroprotection preventing glaucoma development [563]. The activated retinal T-cells participated in the autoimmune response to the damage, probably functioning as regulatory T-cells. It appeared that plasma CD4⁺ T cells found in glaucoma patients presented increased stimulation, proliferation and proinflammatory cytokine secretion [563, 565].

It was demonstrated that the optic disc hemorrhage frequently found in NTG patients was often associated with the “nonphysiologic” nocturnal blood pressure dips known as overdips [566, 567]. Patients with NTG were classified among two subgroups: low-teen IOP (IOP ≤ 15 mmHg) and high-teen IOP (15 mmHg < IOP ≤ 21 mmHg), and interestingly, a higher of the RP was found in the low-teen IOP patients than in high-teen IOP patients [562, 568]. These findings are in line with the decreased both systolic and diastolic blood pressure in adults with *T. gondii* infection [569], and a potential key role of the parasite in RP development, especially that vascular dysregulation, hypercoagulability and increased blood viscosity are contributing factors in RP and NTG etiology [94, 570]. Erickson et al [569] in a study based on multiple regression modeling (n = 12,010) demonstrated that toxoplasmosis was associated with lower systolic/diastolic blood pressure, lowered probability of elevated blood pressure, and stages 1 or 2 hypertension. Other studies reported that the parasite elicited IFN- γ -mediated NO production [571, 572], and increased NO levels reduced arterial stiffness after maximal exercise, whereas down-regulated expression of inducible NO synthase may contribute to rises in blood pressure after submaximal exercise [573]. Moreover, *T. gondii* infection

reduced brain noradrenergic activity by decreasing dopamine beta hydroxylase gene expression [574], and lowered concentration of norepinephrine important for maintaining blood pressure [575], finally leading to decreased systolic and diastolic blood pressure [569].

A. Increased calcium and/or iron intake was significantly associated with glaucoma. Possible relationship between increased levels of these ions and latent toxoplasmosis in pathogenesis of glaucoma, as well as Alzheimer, and Parkinson diseases. Wang et al [576] reported that participants (3833 individuals, ≥ 40 years old) who consumed supplementary calcium (≥ 800 mg/day) or iron (≥ 18 mg/day) had markedly higher odds having been diagnosed with glaucoma than did those who had not consumed these ions (OR 2.44, 95% CI: 1.25-4.76 for calcium; OR 3.80, 95% CI: 1.79-8.06 for iron). Concurrent consumption of both calcium and iron above these quantities resulted in evidently greater odds glaucoma diagnosis (OR 7.24, 95% CI: 2.42-21.62) [576].

Studies *in vitro* suggested that iron plays an important role in glaucoma's pathogenesis both in retinal ganglion and trabecular meshwork (TM) cells [577, 578]. Interestingly, *T. gondii* is auxotrophic for iron [486, 487, 579-581], and anemia often observed in individuals with toxoplasmosis is a good source of the ion necessary for growth, metabolism and proliferation of the pathogen. It must be added that iron seems to play key role in Parkinson's disease (PD) pathogenesis [582-584]. Dysregulation of calcium homeostasis has also been implicated in the pathogenesis of glaucoma [585] and some neurodegenerative diseases [586]. Calcium overload and impaired calcium regulation were found in lamina cribrosa cells of donors with glaucoma [587], and it was suggested that treatment of glaucoma patients with calcium channel blocker may be beneficial in slowing loss of visual fields [588]. Nb. the lamina cribrosa is the most vulnerable part of the retinal ganglion cell, and dopamine, serotonin and glutamate have the potential to drive retinal glial cells into programmed cell death [589], while oxidative stress stimulated antigen presentation by the retina and optic nerve head glia [590]. Moreover, He et al [591] found that TM cells from donors with glaucoma were defective in mitochondrial function, resulting in abnormal sensitivity to calcium-induced stress. It must be noted that *T. gondii* tethers host cell mitochondria to its vacuole to promote its growth [592]. On the other hand, however, infection with the parasite is associated also with mitochondrial dysfunction [593], and otherwise it is known that mitochondria restricted pathogen growth by limiting its uptake of fatty acids [594, 595]. Nb. cytokine IL-6, regarded

as endothelial cell dysfunction biomarker [596], causes increased intracellular replication of *T. gondii* tachyzoites [507]. Serum levels of this proinflammatory interleukin were borderline higher in NTG patients than in controls, and it was suggested that IL-6 might be associated with the severity of NTG [597]. Moreover, during toxoplasmosis IL-6 promotes NK cell generation IL-17 [598], the cytokine important for development of chronic inflammatory neurological and autoimmune diseases [599].

Diffuse brain damage has been reported in subjects with NTG [600]. Conformational study performed by Boucard et al [601] in Japanese patients with this entity showed many structural changes in the white matter indicating that this disease may be included to neurodegenerative disorders. Moon et al [602] estimated the risk developing AD in 1,469 Koreans with OAG and found that this ocular abnormality was markedly associated with an increased incidence of AD (hazard ratio = 1.403, 95% CI: 1.180-1.669, $p < 0.001$) but not PD ($p = 0.983$). Participants with OAG aged ≥ 65 years were more likely to develop AD than those aged < 65 years, and females had a greater risk of developing AD than males [602]. Several investigations have focused on the relationship between glaucoma and cognitive impairment due to AD and PD [603-605], and a population-based research showed that dementia is associated with OAG [606]. Sivak [606A] emphasized similarities between cell and molecular biology mechanisms in AD and POAG pathology. Even large population studies showed an association between dementia and anemia [607, 608], which may suggest a link with chronic latent *T. gondii* infection.

B. *T. gondii* infection is associated with anemia/low hemoglobin levels caused by decrease in both erythropoiesis and survival time of red blood cells (RBC) in the circulation, and the inhibitory role of proinflammatory cytokine IFN- γ profusely generated by the pathogen. Potential link of chronic latent toxoplasmosis with anemia in patients with AD and PD. Several studies reported that acute and/or chronic toxoplasmosis are linked with development of anemia and decreased hemoglobin levels in animals and humans [503, 504, 609-611]. Importantly, in acute and chronic latent infection reactivation, tachyzoites were demonstrated in blood and can be located in each organ of the host, including kidney and liver, leading to impairment of their functions [27, 315, 612-614].

Tanabe et al [610] reported that *T. gondii* tachyzoites penetrated nucleated erythroblasts and macroreticulocytes from fetal mouse liver, and the circulating erythrocytes of fetal, neonatal or severely anemic adult mice. Electron

microscopy showed that the parasite more preferentially invaded immature reticulocytes than mature reticulocytes or erythrocytes, and biochemical experiments demonstrated that *T. gondii* closely interacted with the host cell membranes [615]. Wang et al [315] found that the pathogen-infected mice exhibited anemia due to both decreased erythropoiesis (reduced numbers of circulating reticulocytes) and survival time of (RBC) compared to control animals ($p < 0.02$). Moreover, infection-induced anemia was associated with fecal occult blood, which confirmed that the hemorrhage resulted from *T. gondii* infection in the animals. The authors demonstrated that the infection-stimulated anemia resulted primarily from IFN- γ -dependent and signal transducer and activator of transcription 1-independent loss of circulating RBC [315]. These findings are supported by increased IFN- γ production during *T. gondii* infection emphasizing significant role of proinflammatory cytokines IFN- γ and TNF- α in the onset of anemia [616-619]. Specifically, production of IFN- γ correlated with the onset of anemia during both autoimmune and infectious disease [620], and other researchers suggested inhibitory role of IFN- γ in the maturation of erythroid progenitors [621, 622].

Many neurodegenerative diseases, including AD and PD, are associated with preceding undiagnosed anemia or low hemoglobin levels probably caused by latent toxoplasmosis. Several studies demonstrated a link between anemia and risk of AD or PD development [623-626]. For example, Savica et al [625] reported that in patients with PD anemia or low hemoglobin levels were more common in the history of cases than of controls (OR 2.00, 95 % CI: 1.231-3.06, $p = 0.001$). Moreover, the analyses showed that anemia started 20 to 29 years before the onset of the entity [625]. These findings may also be in agreement with some studies suggesting that latent toxoplasmosis play an important role in the pathophysiology of AD and PD [27, 279, 627-631]. Interestingly, a significant association was demonstrated between PD and eating undercooked eggs ($p < 0.004$), as well as keeping cat ($p < 0.03$), two main risk factors responsible for *T. gondii* infection [632].

C. Pharmacologic treatment of glaucoma may be associated with serious and unexpected side-effects. This may be due to chronic latent *T. gondii* infection since many administered drugs had antitoxoplasmic activity and probably antigens released during tachyzoite damage/death lead to increased generation of antibodies/autoantigens, cytokines and other factors by the host. Several medications are risk factors for inducing OAG, especially corticosteroids [633-637] and non-steroidal anti-inflammatory drugs [634,

638]. The number of medications risky for acute angle-closure glaucoma is long and includes antidepressants and monoamine oxidase inhibitors, antipsychotic drugs with lithium and atypical antipsychotics [639], antihistaminic and antiparkinsonian agents, anticonvulsants (e.g. topiramate), sympathomimetic drops, mydriatic agents, antispasmodic drugs, and botulinum toxin vaccine [634, 640]. Several of these drugs, including citalopram, escitalopram, paroxetine, fluoxetine, duloxetine, venlafaxine, ziprasidone, sertraline, tricyclic antidepressants, and antipsychotics, are responsible for their harmful effects on intraocular pressure, pupil size, glaucoma risk involving pharmacological action of important endogenous substances, such as adrenaline, acetylcholine, dopamine, serotonin, and TNF [634]. However, there are also preparations that may decrease the risk of OAG, such as statins [296, 641] (nb. statins inhibit *T. gondii* multiplication in macrophages [642]), metformin (this drug exacerbates Ca^{2+} -induced permeability transition pore opening by decreasing the capacity of mitochondria to accumulate Ca^{2+} and increasing the oxidation of thiol groups [643]), bupropion (TNF- α antagonist), post-menopausal hormones, selective serotonin reuptake inhibitors, cannabinoids [633]. Studies also demonstrated down-regulation the WNT/ β -catenin pathway signaling responsible for oxidative stress, inflammation and glutamatergic processes in glaucoma, and otherwise it is known that *T. gondii* induces alterations of these molecular mechanisms that control neurogenesis during cortical development [644, 645].

Tables 15 and 16 present some drugs used in schizophrenia/bipolar disorder and their *in vitro* activity against *T. gondii*, and several antidepressants which induce neuroendocrine alterations in cytokine and other biomarker levels in human and animal effector cells that may interact with immune changes associated with latent *T. gondii* infection probably triggering development of glaucoma, as well as their neurotic consequences on neurons [Table 17].

FS individuals often show altered drug sensitivity due to differential expression of ABC transporter proteins [663, 664], and the sensitivity for certain drugs, such as calcium channel blockers (CCB) and systemic β -blockers, is increased, which require lower doses to achieve expected beneficial effects and to avoid side-effects [40, 664]. *Ex vivo* investigations [308, 665] showed that low doses of CCB nifedipine and amlodipine exerted beneficial effects in some FS as well as glaucoma patients. Recently, it was reported that magnesium intake for 6 weeks (12 mM daily) acting as a mild CCB significantly decreased retinal venous pressure in eyes 30 NTG and FS individuals (mean age 61.7 ± 13.5

Table 15. Drugs tested for *in vitro* activity against *T. gondii* (acc. to Jones-Brando et al [142]; with own modification).

| Drug | Solvent | ID ₅₀ ^a (µg/mL) | TD ₅₀ ^b (µg/mL) | TI ^c |
|---------------------|---------------|--|--|-----------------|
| 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 | 3.0 |
| Chlorpromazine HCl | DMSO | 2.6 | 6 | 2.3 |
| Quetiapine fumarate | DMSO | 18.6 | 33 | 1.8 |
| Trimethoprim | DMSO | 5.3 | 63.8 | 12.1 |

^aMedian inhibitory dose, a measure of tachyzoite inhibition. ^bMedian toxicity dose, a measure of cytotoxicity. ^cTherapeutic index, a measure of efficacy determined by TD₅₀/ID₅₀ ratio. DMSO, dimethylsulfoxide; Toxo CGM, *Toxoplasma* cell growth medium. Valproic acid at a concentration of 1 µg/mL inhibited 7% of the tachyzoites and trimethoprim at 3.2 g/mL produced 2% inhibition, but the combination of these two compounds at those concentrations resulted in a potentiating effect inhibiting 55% of the tachyzoites. Fond et al [646] reported that also other antipsychotic drugs, such as amisulpride, cyamemazine, levopromazine, loxapine, tiapride and zuclopenthixol *in vitro* exerted antitoxoplasmic activity in the range of 0.19 to 1 µM concentrations. The 50% inhibitory concentration (IC50) for the last preparation was 8 ± 1.8 µM while its serum levels varied from 0.01-0.12 µM [647], but antipsychotic drugs usually achieve much higher and persistent concentrations in the brain tissue [648]. In human fibroblast cell cultures, IC50 for fluphenazine, thioridazine, and trifluoperazine against developing tachyzoites of the parasite RH strain was 1.7, 1.2 and 3.8 µM, respectively [649]. Murata et al [650] found that *in vitro* hydroxyzine (an antihistamine and anxiolytic compound) reduced parasite replication (IC50 value for *T. gondii* tachyzoites was 1.0 mM) and had no effect on host cell viability. Importantly, the drug also reduced the number of *in vitro*-induced bradyzoites [650], and otherwise it should be noted that bradyzoites within mature tissue cysts are dynamic and replicating entities *in vivo* [651]. Recently, Enshaeieh et al [652] reported that in mice chronic treatment with valproic acid (a mood-stabilizing and antipsychotic drug) was comparable to the effects of trimethoprim-sulfamethoxazole (TMP-SMZ), *i.e.* the drug decreased brain TNF-α expression ($p < 0.0001$), and histological examination showed significant decrease in cysts, perivascular infiltration of lymphocytes, and glial nodules, similarly to the findings in the TMP-SMZ group of animals.

Table 16. Antidepressant effects on the host immune system (acc. to Antonioli et al [653]; with own modification).

| Antidepressant | Source and type of effector cells | Neuroendocrine alterations |
|---|---|--|
| Reboxetine, fluvoxamine, imipramine | Murine glia cells | ↓ NO levels after IFN-γ stimulation |
| Amitriptyline, nortriptyline | Rat glia cells | ↓ IL-1 and TNF-α after LPS stimulation |
| Venlafaxine | Rat encephalogenic T cell clones, splenocytes, peritoneal macrophages | ↓ IL-12, TNF-α, and IFN-γ |
| Imipramine, mianserin, clomipramine, sertraline, and citalopram | Human peripheral white blood cells | ↓ proinflammatory cytokines ↑ anti-inflammatory cytokines |
| Fluoxetine, imipramine, venlafaxine | Healthy human whole blood treatment resistant | ↓ IL-10 |
| Fluoxetine, paroxetine sertraline, citalopram, fluvoxamine | Depressed patients | ↓ TNF-α, CRP and leukocyte count |
| Paroxetine, bupropion, mirtazapine, citalopram, venlafaxine | Depressed patients | ↓ IL-6, TGF-β |
| Sertraline | Depressed patients | ↓ IL-12 ↑ IL-4 ^a , TGF-β |
| Fluoxetine, desipramine | Rats | ↓ IDO activity, ↑ NO ^b |

CRP, C-reactive protein; IDO, indoleamine 2,3-dioxygenase; NO, nitric oxide; TGF-β, transforming growth factor-β; LPS, lipopolysaccharide. ^aLong-term effects of IL-4 may be detrimental, possibly because of the ability of this cytokine to inhibit proinflammatory antiparasitic IFN-γ production [654]. ^bFluoxetine increased the NO production via NF-κB-mediated pathway in BV2 murine microglial cells [655]. The anti-inflammatory cytokines TGF-β and IL-4 suppress IDO activity in human monocytes and fibroblasts [656], which is consistent with IDO metabolic pathway being a marked contributor to the proinflammatory system [657]

Table 17. Possible consequences on neurons of cytokines and biomolecules secreted upon *T. gondii* infection (acc. to Fagard et al [658]; with own modification).

| Cell type | Secreted biomolecules | Neurotic |
|---------------------|-------------------------------|----------|
| Astrocyte | IL-6 | - |
| | GM-CSF | - |
| | TNF- α | \pm |
| | IL-1 β | - |
| | Arachidonic acid | + |
| Macrophage | IL-12 | - |
| | NO | \pm |
| Microglial cells | RNI | + |
| | NO | \pm |
| | H ₂ O ₂ | + |
| | IFN- γ | - |
| | Glutamate | + |
| Neuron | NO | \pm |
| | TNF- α , | \pm |
| | Glutamate | + |
| Natural killer cell | IFN- γ | - |
| T cell | PAF | + |
| | IL-4 | - |
| | IFN- γ | - |
| | IL-10 | - |

RNI, reactive oxygen intermediates; PAF, platelet-activating factor; GM-CSF, granulocyte-macrophage colony stimulating factor. It must be noted that *T. gondii* infection caused a significant increase in dopamine metabolism in neural cells, which may lead to psychobehavioral changes in toxoplasmosis-infected humans [113]. Dopamine concentrations were 14% higher in the brain of mice with chronic *T. gondii* infection than in controls [659]. In addition, induction of IDO expression and decreased levels of tryptophan and increased formation of kynurenine were found in the brain, lungs and serum of infected animals [660]. Moreover, dopamine stimulated tachyzoite proliferation in human fibroblast and primary neonatal rat astrocyte cell cultures [143], thus further enhancing harmful effects of the parasite on the brain function. Finally, chronic latent *T. gondii* infection is associated with various cytokines overproduction and it was postulated that cytokines may induce changes in mood and behavior leading to depressive illness in man [661, 662].

years) [665A]. It must be added that propranolol (a β -blocker and a weak CCB) administered at low doses also was found to be efficacious in FS [308], and otherwise it is known that low doses of this drug were effective against acute and latent murine toxoplasmosis, as well as increased therapeutic efficacy during its combination with pyrimethamine, a classic antitoxoplasmic medication [666]. Interestingly, similar dose-dependent RP developing after the use of antidepressant drugs atomoxetine [667] and fluoxetine (both drugs are selective norepinephrine reuptake inhibitors) used in attention-deficit hyperactivity disorder [668], and *T. gondii* seropositivity was found to be markedly increased in this clinical entity [94, 135, 279, 669].

Corticosteroids increase the risk of OAG [633] probably because they enhance growth rate of *T. gondii* tachyzoites and inhibit the expression of iNOS in macrophages [670, 671], impair phagocytosis and intracellular killing of various pathogens [672, 673], augment parasite load in the brain, and/or cause reactivation of toxoplasmosis [94, 674, 675]. Anticholinergics, cholinergics, adrenergics, and sulfonamides increase the risk of acute angle-closure glaucoma crisis [633], and these medications also have a link with *T. gondii* [676-680]. Regarding botulinum toxin, it was demonstrated that the botulinum toxin A vaccine exerted beneficial effects in

subjects with RP, and this may be due to the blocking of mast cells important for *T. gondii* cytotoxicity [681-683].

Finally, it must be emphasized that several drugs used in glaucoma treatment [633-635] have antitoxoplasmic activity, including statins [296, 642, 684-687], antihistaminic agents hydroxyzine, clemastine [650, 688], ketotifen [689], adrenergics [676, 677], sulfonamides (sulfadiazine, sulfamethoxazole, sulfadoxine) [678-680], antipsychiatric agents [646, 690] (nb. this group of drugs showed direct correlation between clinical potency and presynaptic influence on dopamine neurons [691]), immunosuppressants, immunomodulators, anticancer drugs [680]. It must be noted that effects of these drugs on the host with glaucoma may be either beneficial, neutral or harmful depending on the final proinflammatory and anti-inflammatory cytokines constellation in the host, its innate and/or adaptive immune status, antigen(s) released from damaged or killed *T. gondii* tachyzoites, bradyzoites or sporocysts, and the parasite strain type. Excretory/secretory antigens produced by the pathogen not only upregulated secretion of anti-inflammatory cytokines IL-10, TGF- β 1, but also inhibited secretion of proinflammatory interleukins TNF- α and IL-1 β [692].

Prostaglandin analogs of prostaglandin F_{2 α} , such aslatanoprost, travoprost and bimatoprost, increase uvo scleral

outflow and are the first choice treatment for POAG [634, 636, 693, 694]. Latanoprostene bunod is an NO-donating drug rapidly metabolized to latanoprost acid and butanediol mononitrate (an NO-donating moiety) [695, 696]. Potential side effects associated with use of these preparations include an increase in melanin pigmentation in the iris and periocular skin, blurred vision, cystoid macular edema, anterior uveitis, backache, and myalgia [697].

D. Potential relationship between glaucoma, serum lipid abnormalities and latent toxoplasmosis. Several studies demonstrated that hyperlipidemia is significantly associated with an increased risk of glaucoma [698-702]. Total cholesterol, triglycerides, and LDL were found to be markedly enhanced in patients with glaucoma compared with controls [700-702] (Table 18).

Wang et al [700] reported that both blood total cholesterol and LDL-cholesterol level had a significant association with IOP, the primary risk factor for development of glaucoma. However, it was observed that there are healthy people who have an IOP significantly elevated without ever developing glaucoma, many patients with IOP ≤ 21 mm Hg, as well as patients in spite of control IOP who progress to glaucoma, which suggested that there must be other independent risk factor(s) important for its pathogenesis [589, 701, 702].

E. Possible association between glaucoma, beneficial effects of statins, DM, and latent *T. gondii* infection. McCann et al [684] conducted the meta-analysis of three case-control studies and one cross-sectional investigation with 583,615 glaucoma participants to evaluate the effect of treatment with oral statins on IOP and the incidents and progression of the entity. Pooled ORs showed that there was a significant association between short term use of statins (< 2 years) and reduced incidence of the glaucoma (OR 0.96, 95% CI: 0.94-0.99). This is an important finding because several investigators showed that statins have antitoxoplasmic activity [296, 642, 686, 703, 704]. Moreover, recently Tiwari et al

[705] analyzed 100 patients with DM type 2, 100 participants with POAG plus diabetes, and 100 individuals with diabetes without POAG; 100 healthy subjects represented a control group. The authors found that the mean values of fasting blood sugar and glycated hemoglobin (HbA1c) were significantly increased ($p < 0.0001$) in DM type 2 plus POAG cases as compared to controls. The mean values of total cholesterol, triglycerides, and LDL markedly increased ($p < 0.0001$) in DM type 2 plus POAG patients as compared to controls, whereas HDL level was significantly decreased. It must be emphasized that several studies demonstrated an association between POAG and DM [705-710]. Importantly, many investigators showed that latent *T. gondii* infection may be responsible for development of both type 1 and 2 DM [168, 239, 523, 711]. Moreover, immunological pathomechanisms of glaucomatous degeneration may support involvement of the pathogen in these processes because monocytes and activated T-cells have been found to accumulate in the optic nerve at the site of damage, and oxidative stress and excitotoxicity contribute to cell death in glaucoma [563]. In a mouse model of glaucoma monocytes migrate through the endothelium to the optic nerve head prior to retinal ganglion cell degeneration, suggesting that monocyte infiltration may be a cause of this entity [563, 564]. Plasma CD4⁺ T cells found I glaucoma also showed greater stimulation, proliferation and proinflammatory secretion [565]. These findings are in line with many similarities of immunological and biochemical disturbances associated with *T. gondii* infection, including oxidative stress, endothelial dysfunction, increased production of ROS, RNI, proinflammatory cytokines IFN- γ , TNF- α , IL-1 β , and NO, enhanced glutamate (excitotoxic factor) generation by microglial cells, activation of toll-like receptor pathways, and trafficking of several parasitized cells (including monocytes, macrophages, leukocytes) as a "Trojan horse" [373, 658, 712, 725]. It must be added that NO (a regulator of blood flow through relaxation of the vascular smooth muscle) has been shown to have either neuroprotective

Table 18. Characteristic of participants and serum lipid levels in patients with POAG and controls (acc. to Gupta et al [702]; with own modification).

| Parameters | Patients (n = 100) | Controls (n = 100) | P |
|--------------------------|--------------------|--------------------|----------|
| Age (yrs) | 56.36 \pm 7.91 | 54.33 \pm 9.78 | 0.1081 |
| Gender (male : female) | 41 : 59 | 53 : 47 | 0.1192 |
| Locality (urban : rural) | 67 : 33 | 56 : 44 | 0.1463 |
| Cholesterol (mg/dL) | 217.15 \pm 6.29 | 174.95 \pm 5.23 | < 0.0001 |
| Triglycerides (mg/dL) | 156.05 \pm 7.91 | 112.70 \pm 8.67 | < 0.0001 |
| LDL (mg/dL) | 144.1 \pm 4.24 | 109.8 \pm 6.27 | < 0.0001 |
| HDL (mg/dL) | 37.28 \pm 4.43 | 38.46 \pm 4.18 | 0.0541 |

Values are expressed as mean \pm SE. $P < 0.05$ is considered significant. HDL, high density lipoproteins. LDL, low density lipoproteins.

or neurodegenerative effect on retinal ganglion cells in animal models [726-728]. High NO levels caused oxidative damage to the retinal ganglion cells [634, 729], as well as enhanced endothelial cells permeability [730], and was essential for host control of persistent *T. gondii* infection [731]. Nb. individuals with the increased serum cholesterol or triglyceride levels exhibited remarkably high serum NO levels [732]. It must be also noted that cytokine IL-6 generated in increased amounts during toxoplasmosis and regarded as the biomarker of endothelial dysfunction [506], causes enhanced intracellular replication of *T. gondii* tachyzoites [507]. Serum levels of this interleukin were borderline higher in NTG patients than controls, and it was suggested that it was suggested that IL-6 concentrations might be associated with the severity of NTG [597]. Moreover, during toxoplasmosis IL-6 promotes NK cell generation of IL-17 [598, 733], the cytokine important for development of autoimmune diseases. Finally, it must be added that experimentally the pathogen invaded the pancreas, caused the islet destruction, and significantly increased serum glucose concentrations during chronic toxoplasmosis [733]. Thus, all these data strongly suggest that there is a link between development of glaucoma, DM and latent toxoplasmosis.

F. Relationship between *T. gondii* infection and serum lipid metabolism disorders in animals and humans.

Several studies reported that acute and chronic infection with the pathogen cause lipid abnormalities and liver damage in experimental animals [734-739] and humans [536, 740, 741]. In infected mice Milanovic et al [734] found that a marked decrease in serum levels of HDL and total cholesterol (TC) was first noted in infected vs. control mice on day 14 and persisted to day 42 ($p = 0.043$). Conversely, LDL concentration was not changed until day 42, when it increased significantly. LDL levels at day 42 correlated only with cyst counts in the brain above 300 (found in 44% of animals), while the change in HDL concentration between days zero and 42 correlated with both the overall mean cyst count ($p = 0.041$) and cyst counts above 300 ($p = 0.044$). Moreover, Al-Kennany and his group [736-738] showed that the pathogen may be responsible for inducing oxidative stress, plasma lipid profile

abnormalities and triggering primary atherosclerotic lesions in chickens and cats (Table 19) [736].

Recently, Xu et al [740] in a case-control study of 1045 healthy participants showed that *T. gondii* seropositive persons had significantly higher serum LDL ($p = 0.0043$) and total cholesterol ($p = 0.0134$) levels compared to seronegative individuals. Also Babekir et al [741] studied the adult population of the U.S. from the NHANES 2009-2010 sample participants ($n = 5324$; age 47.2 ± 0.49 [mean \pm SE] years, 51.9% women, 48.1% men), and found that *T. gondii* IgG antibody-positive subjects had significantly increased systolic blood pressure ($p = 0.0022$), triglycerides ($p = 0.0399$), C-reactive protein ($p = 0.422$), γ -glutamyl transferase ($p = 0.0400$), and fasting glucose ($p = 0.0213$) than the negative individuals. In addition, the positive participants had markedly lower HDL cholesterol ($p = 0.0431$) than the negative individuals [741]. It must be noted that the biochemical abnormalities found in the studied population may also reflect undiagnosed liver damage and an early phase of DM during infection with the parasite [239, 536].

Host cells have mobilizable lipid resources for *T. gondii* [742], and the cholesterol esterification in both host and parasite is essential for proliferation of the microbe [743, 744]. Host cell lipids control cholesteryl ester synthesis and storage in intracellular tachyzoites [745]. The pathogen depends upon acquisition of LDL-derived cholesterol from the host cell via endocytosis mediated by the LDL receptor [538] or the LDL receptor-related protein [539]. LDL-derived cholesterol starvation induces tachyzoite to bradyzoite stage conversion in *T. gondii* [746]. The microbe resides within a parasitophorous vacuole (PV) and its membrane lipids can be: 1) scavenged by the pathogen from host cell; 2) synthesized in large quantities by *T. gondii* independently from host cell; and 3) produced de novo by the microbe but not in quantities sufficient for its needs [540, 747, 748]. Interestingly, various lipid substances with antiproliferative properties are avidly acquired by the pathogen eventually resulting in PV membrane defects, and death [540]. Nb. this may, at least partly, explain the lack of significant association between *T. gondii* infection and DM reported in some studies.

Table 19. Plasma lipid profile of broiler chickens infected intraperitoneally with 50 tissue cysts of *T. gondii* (acc. to Al-Kennany [736]; with own modification).

| Groups | Total cholesterol mg/dL | Triglycerides mg/dL | HDL-C mg/dL | LDL-C mg/dL | VLDL-C mg/dL | Atherogenic index |
|----------|-----------------------------|-------------------------------|-------------------------------|--------------------------------|-------------------------------|-------------------------------|
| Controls | 117 \pm 0.23 | 105.3 \pm 1.28 | 42.06 \pm 2.72 ^a | 53.88 \pm 1.25 | 21.06 \pm 0.02 | 2.78 \pm 0.12 |
| Infected | 478 \pm 0.30 ^a | 192.3 \pm 0.48 ^a | 33.36 \pm 1.04 | 406.81 \pm 1.04 ^a | 38.49 \pm 1.28 ^a | 14.17 \pm 0.81 ^a |

Results are means \pm SD of 10 broiler chickens per group. ^aSignificant differences at $p \leq 0.05$. HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; VLDL-C, very low density lipoprotein-cholesterol.

G. Important role of Rho family of small GTPases in development of glaucoma abnormalities is similar to that recently presented in RP pathogenesis [94]. Elevated IOP is a main risk factor for POAG, the most frequent form of glaucoma. Impairment of eye aqueous humour (AH) drainage through the conventional or TM pathway is considered to be a primary cause in glaucoma patients [749]. Rho A, Rho B and Rho C kinases (ROCKs) are small serine/threonine proteins (m.w. 160 kDa) that act through actin polymerization (e.g. cell migration, polarity, trafficking, phagocytosis, proliferation, differentiation, cell survival), and actomyosin assembly (cell adhesion, cell-to-cell junctions, cell contraction, permeability barrier, extracellular matrix proteins organization, mechanotransduction). ROCKs regulate cytoskeletal activities and calcium-dependent smooth muscle contraction, modulation of cell adhesion, and increasing cell stiffness [634, 749, 750]. They also have a role in other cellular responses, such as axonal growth and cytokinesis [751]. ROCKs are expressed in all cell tissues and organs, and Rho kinases expressed in eye tissues have been implicated in the pathology of many ocular diseases, including glaucoma, cataract, diabetic retinopathy, age-related macular degeneration, retinal detachment, macular degeneration, and corneal dysfunction [752]. ROCKs have also been identified as an important regulator of TM outflow altered in glaucomatous eyes [753]. Clinically, optical coherence tomography angiography studies have shown that glaucoma is associated with ocular microvasculature changes in the optic nerve head vessel density (VD), macular VD, superficial peripapillary VD, foveal avascular zone area, and the parapapillary choroidal microvascular dropout [754]. Moreover, in the patients with POAG/OAG nailfold capillary microscopy investigation revealed various types of microvascular abnormalities, such as the presence of dilated capillaries (OR = 2.9, 95% CI: 1.6-5.5), avascular zones (OR = 4.4, 95% CI: 1.7-11.3), and hemorrhages (OR = 12.2, 95% CI: 5.9-25.1) [755-757] that can play an important role in the pathogenesis of these clinical entities [757], thus being in line with *T. gondii* infection as a cause of these disturbances [94]. Other works found that vascular density was higher in normal eyes and decreased successively in glaucoma suspects, mild glaucoma, and moderate to severe glaucoma eyes [758, 759], and vessel changes preceded functional decline in normal visual field [760]. Glaucoma-suspect eyes had significantly greater asymmetry of peripapillary vascular density compared to normal eyes [761]. The association between retinal microvascular characteristics and eye disease have also been demonstrated [762]. In the context of the above data, it must be added that Rho and

Rac1 small GTPases from the host cell are involved in the establishment of the *T. gondii* parasitophorous vacuolar membrane, and their accumulation on the membrane surface after the pathogen invasion of the host cells, regardless of the virulence of the microbe strains, was dependent on their GTPase activity [763]. Host infection with the parasite programs monocytes to preferentially migrate through tissues by using the secreted kinase ROP17 to activate Rho/ROCK-dependent processes [764].

Rho kinase inhibitors (RKIs) have been used in several pathological conditions from ocular and central nervous system disorders to cardiovascular diseases [753, 765]. Inhibition Rho kinase lowers IOP via relaxation of the TM which enhances AH outflow, while activation of Rho GTPase/Rho kinase signaling in the trabecular outflow pathway increases IOP by altering the contractile, cell adhesive and permeability barrier features of the TM and Schlemm's canal tissues [749, 766]. RKIs Fasudil, Ripasudil and Netarsudil are used in glaucoma, cerebral vasospasm, hypercholesterolemia, atherosclerosis, Raynaud's syndrome, diabetic macular edema, diabetic retinopathy, and scleroderma [634, 750, 752, 767]; nb. *T. gondii* infection may be linked with scleroderma [235, 237, 768-771]. RKIs have recently been also used in treatment of patients with FS [772].

More detailed data on the important role of the Rho family small GTPases and their relationship with *T. gondii* infection, including changes of actin cytoskeleton and cellular functions leading to disturbances vascular endothelial barrier morphology and function in patients with autoimmune connective tissue diseases eventually preceded by primary and secondary RP many years or accompany them, as well as development of microvascular disorders, have been discussed in my recent review [94]. Several authors also documented important role of latent toxoplasmosis in development of chronic inflammation and vascular injury [773-775].

In summary, all available literature data strongly suggest that FS is due to *T. gondii* infection since many signs and symptoms, pathophysiology and pathomechanisms, as well as ocular abnormalities and concomitant ADs and other clinical entities reported in FS are similar to these found in subjects with toxoplasmosis. This knowledge is important especially in not fully diagnosed and/or difficult to treat cases, and in patients with serious side effects observed during their clinical or ambulatory pharmacotherapy because many medications have antitoxoplasmic activity [680].

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