

## Solving the Old Puzzle 1862-2021: Pathophysiology and Pathomechanisms of Raynaud's Phenomenon. Key Role of Acute and Chronic Latent *T. gondii* Infection in these Clinical Events and their Potential Link with COVID-19 Pandemic

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### ABSTRACT

Almost 160 years ago dr Maurice Raynaud described a clinical entity usually called Raynaud's phenomenon (RP) manifesting as recurrent episodes of vasoconstriction involving peripheral small vessels of the fingers and toes exposed to cold, estimated at 3-5% of the world's population and associated with increased mortality. *T. gondii* is a widespread intracellular parasite able to attack and proliferate in virtually all nucleated cells, and infecting approximately 30-50% of the world's human population, but quite rarely manifesting clinically in immunocompetent individuals. The aim of this work was to present literature data linking development of primary and secondary RP with acute or chronic latent *T. gondii* infection, describe associated diseases and/or clinical events, biochemical abnormalities, and

explain several pathomechanisms involved in these processes. Vascular endothelial cells are particularly susceptible to infection with the parasite, which is associated with oxidative stress and endothelial dysfunction. *T. gondii* exerts significant pathophysiologic role in altering actin cytoskeleton of endothelial cells, dysregulating vascular wall barrier function and changing microvascular and macrovascular wall morphology observed in patients with primary and secondary RP. Development of RP has been associated with administration of several drugs and biological agents, and may be linked with *T. gondii* infection because these medications also have antitoxoplasmic activity, and in some cases specific toxoplasmosis treatment alleviated underlying disease manifestations. Acute or chronic latent infections with the pathogen may be responsible for the increased blood viscosity and cryoglobulinemia in RP. The parasite probably also participates in the formation of large von Willebrand factor multimers and development of acquired von Willebrand syndrome. Blood volume expander hydroxyethyl starch administration, as well as the intravenous fundus fluorescein angiography probably induce RP specifically in the patients with latent *T. gondii* infection. Similarly, low weight, involuntary weight loss, and anorexia nervosa associated with RP may be caused by latent infection with that microbe in such individuals. Furthermore, these infections may also be responsible for the hearing disturbances reported in the workers with hand-arm vibration syndrome and RP. Moreover, it must be noted that the health improvements in both primary and secondary RP observed after treatment with vitamin D may be, at least in part, associated with its antitoxoplasmic activity. Finally, based on the available literature data it is suspected that SARS-CoV-2 reactivates latent *T. gondii* infection in the vascular endothelial cells and this coinfection may be responsible for worsening of clinical course and increased mortality in some patients during the 2020/2021 COVID-19 pandemic.

**Key words:** Raynaud's phenomenon; *Toxoplasma gondii*; pathophysiology; Pathomechanisms; Drugs; Interferons; Blood viscosity; Cryoglobulinemia; Acquired von Willebrand syndrome; Hydroxyethyl starch; Fundus fluorescein angiography; Anorexia nervosa; Hand-arm vibration syndrome; Hearing disturbances; Vitamin D; COVID-19 pandemic

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## I. INTRODUCTION

### A. Raynaud's phenomenon (RP)

In 1862, Maurice Raynaud as a medical student in Paris described a phenomenon of "local asphyxia and symmetrical gangrene of the extremities" in 20 women and 5 men, being a part of his doctoral thesis<sup>[1-5]</sup>. At present, RP is defined as recurrent, reversible episodes of vasoconstriction involving peripheral small vessels of the fingers and toes, and sometimes also nose, ears, lips, tongue, oral mucosa, or nipples<sup>[6,7]</sup>, and associated with ischemia of tricolor pattern (white to blue to red) when exposed to cold environment and/or emotional stress<sup>[8,9]</sup>. These abnormalities are manifested clinically by transient attacks of distal swelling, pain, burning, numbness, and/or paresthesia<sup>[10,11]</sup>. RP is divided into primary RP (PRP) (Raynaud's disease; idiopathic RP) (80-90%)<sup>[12]</sup> with a relatively mild course, and secondary RP (SRP) (Raynaud's syndrome), which is quite often associated with several autoimmune diseases, broad range of medical conditions, physical-, chemical-, and drug-related causes, and with development of vascular structure and function abnormalities<sup>[8-10,13-16]</sup>.

A prevalence of RP is estimated at 3-5% of the general population and may be higher in those living in cold climates geographic regions<sup>[17,18]</sup>. The highest median prevalence was found in the USA (7.8% in women, 5.8% in men)<sup>[19]</sup>, and the lowest worldwide prevalence was reported in Japanese population (2.1% in women, 1.1% in men)<sup>[20]</sup>. RP is frequently observed in the so called "healthy population"<sup>[21-23]</sup>. This clinical entity was described in newborns, infants, older children, and adolescents<sup>[24-32]</sup>. In young women (15-30 years old) with low blood pressure RP is diagnosed earlier and more frequently<sup>[33,34]</sup>. Low body weight and unintended weight loss may be associated with RP<sup>[35]</sup>, while people with obesity were positively correlated only with secondary RP<sup>[36,37]</sup>. Nb. the vasoconstriction threshold was found to be increased in obese individuals<sup>[38]</sup>. Risk factors and associations for RP included female gender (9:1 female-to-male ratio), family history, smoking, manual occupation, migraine (in one study migraine was detected in 37.9% of 58 children with RP<sup>[31]</sup>), cardiovascular disease, and marital status<sup>[18]</sup>. It is believed that genetic predisposition play a role in development of RP because familial and twin studies demonstrated that 30-50% of patients with primary RP have a first-degree relative suffering from the entity<sup>[16,18,39-42]</sup>. Munir et al<sup>[43]</sup> reported that RP was connected with variation in gene nitric oxide synthase 1 (NOS1), and otherwise it is known<sup>[44]</sup> that inducible NOS (iNOS) is an important host factor for *T. gondii*-dependent disruption of the IFN- $\gamma$ -induced antiparasitic response in humans.

RP was found to be associated with increased mortality, especially among older adults, and in whites specifically the condition was linked with increased cardiovascular disease-related death<sup>[45]</sup>. Mortality was higher in men than in women ( $p < 0.0001$ ), and highest mortality rates were observed in patients with a concomitant presence of abnormal nailfold capillaries and antinuclear antibodies<sup>[46]</sup>. Chronic inflammatory state associated with a markedly decreased hemoglobin concentration appeared to be most strongly related to mortality in patients with RP<sup>[47]</sup>.

### B. *T. gondii* infection

This intracellular pathogen believed to be a global threat<sup>[48-50]</sup> infects approximately 30-50% of the human population, and ophthalmologists suggested that even some six billion people are chronically infected with *T. gondii*<sup>[49,51]</sup>. IgG seroprevalence against the parasite varied from 6.7% in Korea<sup>[52]</sup>, 47-50% in France and Germany<sup>[53,54]</sup>, to 98% in some regions<sup>[55]</sup>. In the US, *T. gondii* is responsible for approximately million infections each year, and the overall antibody seroprevalence among individuals  $\geq 6$  yrs of age in 2011-2014 was 13.3%<sup>[56,57]</sup>. The global annual incidence of congenital toxoplasmosis was estimated to be 190 100 cases (95% CI: 179 300-206 300)<sup>[58]</sup>, sometimes causing epidemics<sup>[59]</sup>. In general population toxoplasmosis was the second most common foodborne parasitic disease (10.3 million cases, 95% uncertainty intervals 7.40-14.9 million)<sup>[60]</sup>. The frequency of *T. gondii* infection was found to increase significantly with age in persons aged 66-75 years<sup>[51,57,61]</sup>.

Toxoplasmosis is an opportunistic disease and the intracellular parasite is highly pathogenic especially for immunocompromised individuals<sup>[62-64]</sup>. In immunocompetent persons *T. gondii* infection is believed to be asymptomatic<sup>[63,64]</sup>, but an increasing body of literature data strongly suggests that the pathogen is emerging as a neglected global health threat<sup>[48,50,62]</sup>. The parasite is omnipresent, and exposure to kittens and raw or uncooked foods are the main risk factors for *T. gondii* infection in the United States<sup>[65]</sup>. Contamination of drinking water with the parasite oocysts contributes to their widespread dissemination<sup>[66]</sup>. In North America, Europe, and Africa, there are three dominant lineages of *T. gondii* called type I (e.g. RH and GT1), type II (ME49), and type III (VEG), which differ in prevalence, virulence, migratory capacity within the host, and ability to convert to the bradyzoite cyst phase<sup>[67,68]</sup>.

Several authors documented that *T. gondii* infection was associated with weight loss, hypermetabolism, cachexia, and anorexia nervosa<sup>[69-71]</sup>, and low-grade immune-activation with elevation of circulating IL-6 has been observed in certain diseases states, as well as in several healthy elderly individuals<sup>[72-77]</sup>. For example, anorexia nervosa was reported in autistic women<sup>[78,79]</sup>, and in children and adolescents with systemic lupus erythematosus (SLE)<sup>[80]</sup>. On the other hand, the parasite has also been linked with overweight and obesity<sup>[73,81,82]</sup>.

Studies showed that the seroprevalence of toxoplasmosis correlated with various specific disease burden and therefore may be regarded as a neglected triggering factor responsible for development of many clinical entities<sup>[50,73,83]</sup>. Carter<sup>[84]</sup> related the parasite interaction with approximately 3000 host genes or proteins with several neurodegenerative diseases, including schizophrenia<sup>[85,86]</sup>, and interestingly, the contribution of NOS1 gene polymorphism to the development of this entity has been shown<sup>[87,88]</sup>. It must be noted that particularly IFN- $\gamma$ <sup>[89-94]</sup> and NO<sup>[94-99]</sup> play critical roles in the host defense during latent acute and chronic *T. gondii* infection.

The aim of the present study was to determine whether *T. gondii* infection is associated with development of primary and secondary RP in general healthy population of infants, older children and adults, as well as in patients with various diseases since this is a common pathogen with worldwide distribution, usually transmitted to humans by ingestion of food and water contaminated with oocysts shed by cats, and in pregnant women its vertical transmission to fetus may lead to congenital disease. In addition, in immunocompetent individuals toxoplasmosis is usually asymptomatic or difficult to establish proper diagnosis, and so far available laboratory tests are not fully specific and/or sensitive<sup>[100]</sup>.

Finally, an important potential link between *T. gondii* infection and COVID19 pandemic has also been shortly presented because human

vascular endothelial cells are particularly susceptible to persistent infection with these two pathogens, and such comorbidity may result in reactivation of the parasite in some individuals leading to worsening of clinical course and increased mortality of the host.

## II. VASCULAR ENDOTHELIAL CELLS (VECs) PARTICULAR SUSCEPTIBILITY TO *T. GONDII* INFECTION IS ASSOCIATED WITH OXIDATIVE STRESS AND ENDOTHELIAL DYSFUNCTION

### A. *T. gondii* infection of VECs

The endothelial cells are critically important for the delivery of nutrients and oxygen throughout the body, but they also contribute to pathology including triggering and persistence of inflammation<sup>[101]</sup>. Tropism of different pathogens for particular cell types and/or specific tissue sites was a long-recognized biological phenomenon<sup>[102]</sup>. *T. gondii* is disseminating in the body in a Trojan horse-manner in various eukaryotic cells, including endothelial cells and macrophages, and division rate of intracellular unprimed tachyzoites in endothelial cells, monocyte-derived macrophages, peritoneal, or alveolar cells is rapid (Table 1)<sup>[103]</sup>.

Human retinal endothelial cells are more susceptible to infection with tachyzoites than other subpopulations of endothelial cells<sup>[102,119]</sup>. Smith et al<sup>[102]</sup> found that retinal VECs have enhanced susceptibility to infection with *T. gondii* tachyzoites in comparison with aorta (55% more), umbilical vein (33%), and dermal endothelial cells (34%). The parasite adhesion to vascular endothelium was observed even during disturbed blood flow characteristic for atherosclerosis<sup>[120-122]</sup>. The analysis of invasion kinetics of two *T. gondii* strains, RH (virulent) and ME49 (nonvirulent) in two human vascular endothelial cell types, HMEC-1 (skin microvasculature) and HUVEC (umbilical cord vein vasculature) established that surprisingly the less virulent strain invaded a greater proportion of cells than the more aggressive RH strain<sup>[123]</sup>. These observations were in line with the earlier findings of other authors<sup>[124]</sup> who showed *in vitro* that RH tachyzoites invaded lower proportion of rat brain microvascular endothelial cells than those of ME49 strain. It appeared that an intracellular environment low in reactive oxygen species (ROS) or reactive nitrogen intermediates (RNI) and/or high in iron or tryptophan facilitated tachyzoite proliferation<sup>[114,117,125]</sup>.

*T. gondii* tachyzoites translocate across polarized monolayers of mouse brain endothelial cells and human intestinal CaCo2 cells without significantly perturbing barrier impermeability and with minimal change in transcellular electrical resistance. In contrast, challenge with parasite lysate or lipopolysaccharide (LPS) increased barrier permeability by destabilizing intercellular tight junctions and accentuated transmigration of the pathogen<sup>[126]</sup>. Kondradt et al<sup>[121]</sup> demonstrated that replication in and lysis of endothelial cells are required for parasites to invade the central nervous system (CNS). Analysis of acutely infected mice revealed significant numbers of free parasites in the blood and the presence of infected endothelial cells in the brain vasculature. It was documented that many of the infected ECs were present in smaller blood vessels, and it was found that over 80% of the infected ECs were in vessels with a diameter of less than 10  $\mu\text{m}$ <sup>[121]</sup>. Foci of *T. gondii* were observed surrounding microvessels in mice during acute infection<sup>[121]</sup> and reactivation of latent infection<sup>[127]</sup>, indicating that the parasite enters the brain through the vascular endothelial cells, by breaching the blood-brain barrier<sup>[128]</sup>.

**Table 1** Division rate of intracellular *T. gondii* tachyzoites in primary human cells *in vitro* (acc. to Channon et al [103]; with own modification).

Cell type	Parasite division rate	IFN- $\gamma$ primed	Mechanism	Refs
<b>Hemopoietic</b>				
Lymphocyte	S			[103]
Neutrophil	S			[103-105]
Adherent monocyte	S			[105-110]
Nonadherent monocyte	R	R	ROS; not TS	[103, 107]
Dendritic cell	R			[103]
Alveolar macrophage	R	S	Partly TS	[110]
Peritoneal macrophage	R	S		[111]
Monocyte-derived macrophage	R	S	ROS; not RNI	[109-112]
<b>Nonhemopoietic</b>				
Neuron	S			[113]
Foreskin fibroblast	R	S	TS	[114, 115]
Umbilical vein endothelial cell	R	S	TS or ROS; not RNI	[93, 109]
Retinal pigment epithelial cell	R	S	TS	[116]
Fetal astrocyte	R	S	RNI	[113, 117]
Fetal microglial cell	R	R		[118]

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

### B. *T. gondii* infection of VECs causes oxidative stress and endothelial dysfunction

Estateo et al<sup>[129]</sup> showed that mice infected with *T. gondii* had enhanced leukocyte adhesion to the endothelial cells leading to endothelial dysfunction. In acute toxoplasmosis treatment with sulfadiazine improved endothelial dysfunction through reduction of parasitic load and a decrease of endothelial inflammation. In patients with acute toxoplasmosis statins also exerted beneficial effects because they inhibit the adhesion, replication and proliferation of the parasite in HeLa cells<sup>[130]</sup>. Moreover, it was reported that verapamil (a calcium ion antagonist) ameliorated *in vitro* structural, functional, and metabolic alterations in human cerebrovascular endothelial cells during *T. gondii* infection<sup>[131]</sup>. This is not surprising because the discharge of micronemes (adhesive proteins of *T. gondii*) is stimulated by contact with host cells and this process is regulated by increases in intracellular calcium within the parasite<sup>[132]</sup>, due to phosphatidic acid-mediated signaling<sup>[133]</sup>. In addition, gliding motility of the parasite is controlled by secretion of microneme proteins and factors that alter calcium fluctuation in the cytosol, while chelation of intracellular calcium blocked parasite motility<sup>[134]</sup>.

Several authors reported that toxoplasmosis causes oxidative stress and endothelial dysfunction, and markedly increased serum malondialdehyde (MDA), endothelin-1 (ET-1), IL-6, NO, as well as decreased glutathione levels are characteristic for *T. gondii* seropositive patients<sup>[135-137]</sup>. Oxidation of low density lipoproteins results in the formation of reactive aldehyde products, such as MDA, which is the most abundant molecule arising from lipid peroxidation<sup>[138,139]</sup>. A significant increase in serum ET-1 (a potent vasoconstrictor produced by VECs) concentrations reflects endothelial dysfunction in various chronic infections<sup>[140]</sup>. IL-6 is regarded as a biomarker of endothelial dysfunction<sup>[141]</sup> because it causes increased intracellular replication of the parasite<sup>[76]</sup>. Finally, NO is a source of RNI generation<sup>[142,143]</sup>, and inhibits *T. gondii*

multiplication<sup>[94,144]</sup>. Recently Al-Kuraishy et al<sup>[135]</sup> reported that patients with acute toxoplasmosis had markedly increased serum ET-1, IL-6 and MDA levels compared with controls (Table 2). It appeared that serum IgM level concentrations significantly correlated with IgG ( $r = 0.55, p < 0.001$ ) and other analyzed bioparameters (ET-1,  $r = 0.51, p = 0.003$ ; IL-6,  $r = 0.45, p < 0.01$ ; MDA,  $r = 0.85, p < 0.0001$ )<sup>[135]</sup>. Similar results have been reported by Karaman et al<sup>[136]</sup>, and Al-Azzaay et al<sup>[137]</sup> (Tables 3 and 4).

It must be noted that free *T. gondii* tachyzoites cross endothelial cells via intercellular adhesion molecule-1. In addition, monocytes and dendritic cells (DCs) are highly permissive for the parasite due to different susceptibility for binding to tachyzoites. These changes stimulate monocyte adhesion to the vascular endothelium resulting in marked endothelial dysfunction<sup>[135,145]</sup>. In addition, the pathogen causes the subversion of the migratory functions of parasitized DCs and monocytes, because DCs adopt a hypermigratory phenotype to promote infection-related dissemination<sup>[146,147]</sup>. Recent reports showed that the activated signaling pathways converge on the small GTPase Ras to activate the mitogen-activated protein kinase (MAPK) and extracellular signal regulated kinase (Erk) signaling cascade, a central regulator of cell motility, and three known so far *T. gondii*-derived proteins have been linked to hypermigration: Tg14-3-3, TgWIP and ROP17<sup>[147]</sup>.

### C. Increased frequency of SRP and endothelial dysfunction among hemodialysis (HD) patients is associated with a high prevalence of *T. gondii* infection

Interestingly, small vessel dysfunction diagnosed as positive RP is a frequent finding in HD patients. Czupryniak et al<sup>[148]</sup> reported that RP diagnosed with cold stress test and thermography was found significantly more often in HD patients than in controls (11/21 vs. 1/10,  $p = 0.04$ ). This abnormality occurred in both hands in 7/11 patients, and plasma total homocysteine and von Willebrand factor (vWF) antigen were markedly higher in the RP-positive than RP-negative patients or controls<sup>[148]</sup>. Of note, hyperhomocysteinemia is regarded as an independent risk factor for vascular disease<sup>[149]</sup>, and plasma homocysteine levels were found to be higher in patients with SRP than patients with PRP and healthy controls<sup>[150]</sup>.

Several authors reported that patients with end-stage renal disease on HD have a high prevalence of *T. gondii* infection and therefore they are a group at risk for toxoplasmosis<sup>[148-153]</sup>. In such patients, Saki et al<sup>[152]</sup> found the parasite also in the whole blood, indicating disseminated infection probably due to reactivation of chronic toxoplasmosis.

## IIIA. IMPORTANT ROLE OF THE Rho FAMILY OF SMALL GTPases IN CHANGES OF ACTIN CYTOSKELETON AND CELLULAR FUNCTIONS LEADING TO DISTURBANCES IN VASCULAR ENDOTHELIAL BARRIER MORPHOLOGY AND FUNCTION IN PATIENTS WITH PRP AND SRP. EFFECTS OF THESE MOLECULAR SPECIES ON DEVELOPMENT OF MICROCIRCULATION ABNORMALITIES OBSERVED IN CONNECTIVE TISSUE DISEASES (CTDs). SIGNIFICANT PATHOPHYSIOLOGIC ROLE OF *T. GONDII* INFECTION IN THE GENERATION OF THESE IRREGULARITIES

**Table 2** Serum IgM, IgG and IgA, and some proinflammatory and oxidative stress biomarker levels in patients with acute toxoplasmosis and healthy controls (acc. to Kuraishy et al [135]; with own modifications)

Parameters	Patients (n = 31)	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	0.000
IgA, g/L	4.72 ± 2.54	1.99 ± 0.51	0.000
IL-6, pg/mL	3.22 ± 1.01	1.88 ± 0.51	0.001
ET-1, pg/mL	7.29 ± 4.59	3.11 ± 1.69	0.000
MDA, nM/mL	9.34 ± 4.17	2.87 ± 1.13	0.000

Values are expressed as mean ± SD. ET-1, endothelin-1; MDA, malondialdehyde. Results statistically significant at  $p < 0.05$ .

**Table 3** Serum glutathione (GSH), malondialdehyde (MDA), and nitric oxide (NO) concentrations in *T. gondii*-seropositive patients and healthy controls (acc. to Karaman et al. [136]; with own modification)

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

Values are means ± SD. Results statistically significant at  $p < 0.05$ . Serum GSH and NO levels are expressed as  $\mu\text{mol/L}$ , and MDA concentrations represent  $\text{nmol/L}$ .

**Table 4** Erythrocyte malondialdehyde (MDA), glutathione (GSH) nitric oxide (NO) concentrations in patients with *T. gondii* infection and healthy controls (acc. to Al-Azzaay et al [137]; with own modification)

Group	Erythrocyte MDA (nM/g Hb)	Erythrocyte GSH (nM/g Hb)	Serum NO ( $\mu\text{M/L}$ )
Patients with <i>T. gondii</i> infection (n = 50)	20.75 ± 2.06	2.10 ± 0.10	48.47 ± 0.30
Controls (n = 30)	4.43 ± 1.65	6.95 ± 1.21	42.38 ± 0.30
P	< 0.001	< 0.001	< 0.001

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

### A. General remarks.

Cell migration is an essential feature of eukaryotic life, necessary for various processes including feeding, phagocytosis, development, immunity, and tissue healing. Migration requires the actin cytoskeleton, specifically the localized polymerization of actin filaments near the plasma membrane<sup>[154]</sup>.

Actin is the most abundant protein in mammalian cells and constitutes about 10% of total protein in endothelial cells<sup>[155,156]</sup>. The actin cytoskeleton is a major determinant of cell morphology and polarity and the assembly and disassembly of filamentous actin structures, providing a driving force for several processes including cell motility, phagocytosis, growth cone guidance, and cytokinesis<sup>[157]</sup>.

Polymerization of actin is a common response of highly motile cells to chemoattractants<sup>[158-160]</sup>, and this ability in a directional way is important for motility and regulation of cell shape<sup>[161]</sup>. The majority of cells use a combination of actin-myosin-based contraction and actin polymerization-based protrusion to control their shape and motility<sup>[161]</sup>.

Actin assembly contributes a major force for cell movement, especially by driving the protrusions such as lamellipods and filopods that propel the leading edge. Actin powers protrusions by polymerizing just under the plasma membrane. The cell has two main choices of filament geometry, *i.e.* branched filaments leading to sheet-like protrusions, or long parallel or bundled filaments leading to generation of spikes<sup>[154]</sup>.



Polymerized actin is spatially organized in all eukaryotic cells into a variety of structures, including cytoplasmic stress fibers or cables, the cortical actin network at the plasma membrane, surface protrusions (lamellipodia and microspikes) or the contractile ring formed during cell division. In addition to maintaining cell shape, the actin networks can specify cell polarity, drive cell movement and cell division<sup>[162,163]</sup>.

It must be noted that the ability to reorganize actin filaments is also a key property of embryonic cells during development, and for example, the cell shape changes associated with gastrulation and dorsal closure are dependent on the plasticity of the actin cytoskeleton, while the ability of cells or axons (cell extensions) to migrate within the developing embryo requires quick and spatially organized changes to the actin cytoskeleton in response to many external environment factors<sup>[157]</sup>.

### B. The Rho family of small GTPases

These proteins control cell motility and morphology in response to extracellular stimuli. The organization of the actin cytoskeleton can be regulated by soluble factors that trigger signal transduction events involving the Rho family of GTPases (guanosine triphosphate (GTP) hydrolase enzymes (GTPases) - small signaling G proteins with m.w. ~ 21 kDa)<sup>[164-166]</sup>. Most Rho GTPases are subgrouped to various Rho families depending on their degree of homology: Rho (Ras homolog gene family), Rac (Ras-related C3 botulinum toxin substrate), and Cdc42 (cell division control protein 42 homolog)<sup>[166,167]</sup>. The approximately 20 Rho proteins can be divided into 5 groups: the Rho-like, Rac-like, Cdc42-like, Rnd, and RhoBTB subfamilies. The Rho-like subfamily are all very similar in sequence and when overexpressed as activated proteins they contribute to contractility and formation of stress fibers and focal adhesions<sup>[167]</sup>.

The Rho GTPases have been identified as eukaryotic master molecular switches taking part in many signal transduction pathways, mainly in regulation of the actin cytoskeleton<sup>[162,168]</sup>. It was established that Rho and Rac act on different pools of actin to trigger cytoskeletal changes. Because adhesive interactions are capable of organizing the actin-based cytoskeleton, Clark et al<sup>[164]</sup> examined the role of Cdc42, Rac-, and Rho-dependent signaling pathways in regulating the cytoskeleton during integrin-mediated adhesion and cell spreading, and found Rho dependence of the assembly of large focal adhesions from which actin stress fibers radiate. Initial adhesion to fibronectin also stimulated membrane ruffling which is dependent on both Cdc42 and Rac. In addition, it was reported that Cdc42 controls the integrin-dependent activation of extracellular signal-regulated serine/threonine kinase Erk2 or Akt (a kinase whose activity is dependent on phosphatidylinositol (PI) 3-kinase)<sup>[164,169]</sup>.

Activated RhoA is capable of stimulating microfilament bundling in serum-starved fibroblasts that are already adherent<sup>[170]</sup>, Rho is also essential for the formation of focal complexes<sup>[171]</sup>. The Rho-family member Rac controls growth factor-stimulated membrane ruffling and formation of lamellipodia<sup>[170]</sup>, while Cdc42 activation triggers the extension of filopodia<sup>[161,172,173]</sup>. Rac-induced lamellipodia are generated through localized actin polymerization at the cell periphery, which is independent of integrin complex assembly, while Rho-induced stress fibers are produced by integrin-independent bundling of actin filaments and integrin-dependent reorganization into parallel contractile bundles<sup>[161]</sup>. In contrast to cell adhesion, it was found that the process of cell spreading is dependent on Cdc42, Rac, and Rho<sup>[164]</sup>.

Rho proteins have been reported to regulate many cellular activities besides the cytoskeleton and cell adhesion, such as cell

polarity, endocytosis, vesicle trafficking, progression through the cell cycle, differentiation, oncogenesis and gene transcription<sup>[167,174]</sup>. In addition, Rho GTPases have many regulatory roles in host-pathogen interactions and host defense, including maintaining epithelial barriers, leukocyte migration, phagocytosis, T cell-APC (antigen presenting cell) interaction, and NF- $\kappa$ B (nuclear factor kappa-light-chain-enhancer of activated B cells) regulation<sup>[169]</sup>.

Finally, it must be noted that rapid ROS mitochondrial generation in smooth muscle cells may contribute to cold-induced vasospasm occurring in RP because cold causes translocation of  $\alpha_2$ C-adrenoceptors from the trans-Golgi to the plasma membrane, mediated by cold-induced activation of RhoA and Rho kinase signaling<sup>[175]</sup>.

### C. Important role of vascular endothelial cadherin (VE-cadherin) in ensuring microvascular wall integrity

Vascular wall leakage is observed in many pathological states and diseases and the endothelium forms a selective semi-permeable barrier controlling bidirectional transfer between blood vessel and the surrounding tissues. Endothelial permeability is regulated by the dynamic opening and closure of cell to cell adherens junctions (AJs). In endothelial cells, AJs are largely composed of VE-cadherin<sup>[176,177]</sup>. These biomolecules recruits catenins (mainly  $\beta$ - and p120-catenins) and bridge VE-cadherin multimers to the actin cytoskeleton via actin binding proteins<sup>[178-180]</sup>.  $\beta$ -catenin dephosphorylation, together with VE-cadherin mobility, contribute to endothelial cell-cell junction stabilization<sup>[177,181]</sup>.

The small GTPases Rho and Rac are required for the establishment of VE-cadherin-dependent cell-cell contacts<sup>[182]</sup>. Actin, VE-cadherin, and associated binding proteins form a mechanosensing complex in endothelial cells<sup>[183]</sup>. The vascular endothelium is exposed to diverse mechanical signals that regulate vascular endothelial barrier morphology and function. In addition to rigidity sensing through integrin adhesions, mechanical perturbations such as changes in blood flow shear stress can also activate intercellular force transduction signals. It was demonstrated that specifically perturbing VE-cadherin receptors activated these signals that increased integrin-dependent cell contractility and disrupted cell-cell and cell-matrix adhesions<sup>[184]</sup>. These processes may finally lead to development of abnormalities in vascular wall morphology.

### D. Effects of the Rho family of small GTPases on development of the microcirculation morphological abnormalities in CTDs

1. Clinical manifestation of peripheral microcirculation disorders is RP which may precede autoimmune CTDs many years, or accompany them<sup>[185,186]</sup>. Gorski et al<sup>[187]</sup> studied 66 pediatric and adolescent patients (42 girls) aged 6-19 years (mean age 14.5  $\pm$  4.52 SD; 34 with undifferentiated RP and 32 with SRP). Analysis of capillary parameters in patients with RP showed a significantly more frequent presence of irregular arrangement, tortuous and/or meandering capillaries, and giant capillaries in the group of adolescents older than 15 years. The authors suggested that these abnormalities are associated with subclinical vasculitis<sup>[187]</sup>.

In nailfold videocapillaroscopy, Gorski et al<sup>[187]</sup> in their patients with RP frequently observed "scleroderma pattern" images. They found a markedly more frequent occurrence of giant capillaries ( $p = 0.008$ ), microhemorrhages ( $p = 0.031$ ), and a significantly reduced number of capillaries in patients with RP compared to healthy controls ( $p = 0.015$ ). Scleroderma-type or nonspecific abnormalities, such as lack of morphological homogeneity of capillaries, tortuous or enlarged capillaries, local hemorrhages, or capillary loss have been also reported in patients with RP and several other CTDs

including systemic sclerosis, rheumatic disease, SLE, Sjögren's syndrome, dermatomyositis, CREST calcinosis, and mixed or undifferentiated CTDs<sup>[9,34,186]</sup>. Various authors postulated evolution of these abnormalities to CTDs because 15-20% of the patients with "scleroderma pattern" developed CTD in 2-10 years<sup>[187-189]</sup>.

2. Common features at the onset of pediatric SSc are RP (70%) and skin changes of hands (60%) including edema, sclerodactyly and induration of hands proximal to the metacarpals<sup>[190,191]</sup>. Throughout the course of the disease, almost all pediatric patients will have RP and skin changes of the hands (96-97%)<sup>[192]</sup>. The prevalence of nailfold capillary changes in pediatric SSc was reported to be 50%<sup>[190,192]</sup>, and the capillaroscopic abnormalities included dilatation, tortuosity, hemorrhage, avascularization and later arborization of the capillaries<sup>[193]</sup>. Arterioles were more narrow and stiff due to marked intimal hyperplasia and fibrosis caused by endothelial dysfunction<sup>[191,194]</sup>.

3. Cutolo et al<sup>[195]</sup> analyzed results of 40 microcirculation studies in patients with SLE using nailfold capillaroscopy and found that tortuous capillaries, abnormal morphology and hemorrhages were markedly more prevalent in SLE participants compared to controls, while hairpin-shaped capillaries were less often found. It was also revealed that frequency of RP attacks and digital gangrene significantly correlated with dilated capillaries.

### IIIB. SIGNIFICANT PATHOPHYSIOLOGIC ROLE OF *T. GONDII* INFECTION IN ALTERING ENDOTHELIAL CELLS, DYSREGULATING BARRIER FUNCTION AND CHANGING MICROVASCULAR WALL MORPHOLOGY

#### A. Induction of gene expression changes in *T. gondii* infected endothelial cells causes many biochemical and other pathophysiologic abnormalities

*T. gondii* infects and replicates in vascular endothelial cells and induces gene expression changes leading to an altered transcriptional profile of infected endothelial cells. Several of the genes in these pathways are involved in inflammatory responses and signaling, as has been previously reported during *T. gondii* infection of other cell types<sup>[196-198]</sup>. Recent RNA sequencing studies comparing genome-wide transcriptional profiles of the infected to uninfected endothelial cells demonstrated changes in gene expression associated with cell-cell adhesion, extracellular matrix reorganization, and cytokine-mediated signaling<sup>[199]</sup>. Studies of Franklin-Murray et al<sup>[199]</sup> showed that *T. gondii* infection of human umbilical vein endothelial cells altered cell morphology and dysregulated barrier function, increasing permeability to low-molecular weight polymers. The pathogen disrupted vascular endothelial VE-cadherin and  $\beta$ -catenin localization to the cell periphery and reduced VE-cadherin protein expression. Infection with the microbe led to reorganization of the host cytoskeleton by reducing filamentous actin stress fiber abundance under shear stress conditions and by decreasing cell polarity<sup>[199]</sup>. It must be noted that lysophosphatidic acid (LPA) and sphingosine-1-phosphate (S1P) - two molecular products of *T. gondii*<sup>[200,201]</sup> induce stress fiber formation through activation of Rho<sup>[161,202,203]</sup>. Nb. S1P regulates many cellular processes important for inflammation and immune responses that include cell growth, differentiation, lymphocyte trafficking, vascular integrity and cytokine/chemokine production<sup>[204]</sup>. Lastly, *T. gondii* infection renders cells resistant to multiple proapoptotic signals, and both PI 3-kinase pathway and the immediate downstream effector protein kinase B (PKB/Akt) play

important roles in cell survival and apoptosis inhibition<sup>[205,206]</sup>.

#### B. Biogenesis of parasite endomembranes and PV

Charron et al<sup>[207]</sup> demonstrated the ability of *T. gondii* to divert and use lipid resources from its host that may contribute incorporated into the surrounding vacuolar membrane<sup>[207]</sup>. The apicoplast-localized fatty acid synthesis (FAS) has the capacity to utilize FAS type II pathway and form LPA to the biogenesis of parasite membranes<sup>[207]</sup>. Lipids were found to be compartmentalized into parasite endomembranes and some of them, including phosphatidic acid (PA) and small molecular weight fatty acids, are key precursors used for bulk membrane biogenesis and parasite survival<sup>[208-212]</sup>. Intracellular PA is produced through the reversible reaction of diacylglycerol kinase 1 (DGK1) and PA phosphatases<sup>[200]</sup>. It was also demonstrated that *T. gondii* possesses a single cytosolic acetyl-CoA synthetase, which is involved in providing acetyl-CoA for the essential fatty acid elongation pathway to generate FAs used for membrane biogenesis<sup>[210]</sup>.

#### C. *T. gondii* invasion and egress from host cells

The pathogen host cell entry and egress are main steps in the lytic cycle of the parasite, making sure its survival and dissemination. *T. gondii* invades the host cells using its ability to move by gliding motility, which depends on the endocytic-secretory cycle<sup>[213]</sup>. It is noteworthy that the rapid onset of hypermotility in the parasite infected DCs (a hypermigratory phenotype) associated with migratory activation has been reported in connection with cytoskeletal rearrangement in a metastatic breast cancer cell line<sup>[214,215]</sup>. The actin-myosin-system of the parasite plays a key role in the formation and release of attachment sites during this process. Pezzella-Alessandro et al<sup>[216]</sup> in their 3D reconstruction model showed that the myosin distribution overlapped that of actin, and calmodulin was concentrated at the center of the apical pole of the *T. gondii* tachyzoite. The secretory-endocytic cycle leads to recycling of receptors (integrins), required to form such attachment sites, regulation of surface area during motility and generation of retrograde membrane flow. Gras et al<sup>[213]</sup> demonstrated that endocytosis functions during gliding motility in *T. gondii* and appears to be pivotal for the establishment of retrograde membrane flow. The authors recognized LPA as a potent stimulator of endocytosis, and showed that extracellular pathogens can efficiently incorporate exogenous materials. Moreover, they revealed that surface proteins of the parasite are recycled during this process, and the endocytic and secretory pathways of the microbe converge, with endocytosed material subsequently secreted<sup>[213]</sup>.

*T. gondii* egress is associated with the exocytosis of secretory organelles termed micronemes (apical organelles). Usually parasites egress from infected cells after five to six cycles of endodyogeny multiplication but harmful environmental changes such as the loss of host cell integrity can trigger earlier egress. Bisio et al<sup>[200]</sup> showed that DGK2 secreted into the PV produces PA, which acts as an intrinsic signal that elicits natural egress. This signaling platform responds to PA (an intrinsic lipid mediator) and extrinsic signals to control programmed and induced egress of the parasite from infected cells<sup>[200]</sup>.

#### D. Important role of PA generation at *T. gondii* plasma membrane in controlling microneme release

Membrane PA regulation is linked to the parasite's micronemes secretion<sup>[133,217]</sup>. *T. gondii* tachyzoites have few micronemes, sporozoites have an intermediate number, and bradyzoites have many<sup>[218]</sup>. Microneme proteins play important roles in multiple

stages of the parasite life cycle, including parasite motility, invasion, intracellular survival, and egress from host cells<sup>[219]</sup>. In *T. gondii*, extracellular potassium levels and other stimuli trigger a signaling cascade culminating in phosphoinositide-phospholipase C activation, which generates diacylglycerol (DAG) and inositol 1,4,5-triphosphate, and finally results in microneme secretion<sup>[217]</sup>. Bullen et al<sup>[217]</sup> showed that a fine equilibrium between DAG and its downstream product PA, is essential for controlling microneme exocytosis. This balance is supervised by the parasite-specific DGK1, which interconverts PA and DAG, and whose depletion impairs parasite egress and causes its death<sup>[217]</sup>.

#### IV. DRUG-INDUCED DEVELOPMENT OF RP AND ITS ASSOCIATION WITH *T. GONDII* INFECTION

Khouri et al<sup>[220]</sup> identified several classes of drugs responsible for development of primary and secondary RP, with various underlying pathomechanisms, such as enhancing vasoconstriction, endothelial dysfunction, increasing blood viscosity, neurotoxicity or decreased red blood cell deformability. All these medicines, including tyrosine kinase inhibitors (TKIs) and calcium channel blockers (CCBs), may be associated with acute or latent chronic *T. gondii* infections (Table 5).

##### A. TKIs and *T. gondii* infection.

Furspan et al<sup>[336]</sup> showed that the increased tyrosine phosphorylation by tyrosine kinase mediated enhanced vasoconstriction in response to cold, characteristic for RP. In patients with secondary RP associated with autoimmune diseases (SSc, scleroderma) or lung cancer, who were receiving treatment with some TKIs, such as imatinib, nilotinib, or erlotinib, both beneficial and harmful effects have been reported<sup>[305,337-339]</sup>.

Maintaining an optimal balance between pro- and anti-inflammatory cytokine responses is key to the success of *T. gondii* as an intracellular parasite in the host cells. Several TKIs exerted inhibiting effects *in vitro* on *T. gondii* and were effective in animals with toxoplasmosis (Table 5). Protein kinases have been shown to play a key role in the parasite motility, invasion, replication, and egress processes, and to promote parasite survival within the host by down-regulating host defense mechanisms<sup>[340-344]</sup>. It should be noted that active *T. gondii* kinome among several other kinases includes 20 calcium/calmodulin (a calcium binding protein) regulated kinases and 8 tyrosine kinase-like proteins (TKLs) which are responsible for tachyzoite fitness and alter host responses<sup>[344,345]</sup>. TKLs localize to several compartments in the parasite, including nucleus, cytosol, Golgi apparatus, and inner membrane complex<sup>[11]</sup>. Of note, TKL1 to TKL6 share sequence homology with tyrosine kinase but are catalytically serine-threonine kinases<sup>[346,347]</sup>. TKL1 plays a key role in acute toxoplasmosis<sup>[344]</sup>. Studies *in vitro* showed that TgTKL1 knockout parasites exhibited a severe defect in host cell attachment due to impaired microneme (*T. gondii* apical storage organelle) secretion and processing<sup>[344,348]</sup>. It was demonstrated that signal transducer and activator of transcription (STAT)3 and STAT6 serve as direct substrates for the pathogen microneme roptry protein 16 (ROP16) tyrosine kinase activity<sup>[349-351]</sup>. The active kinase ROP16 is secreted into the infected cells and subverts host function by direct tyrosine phosphorylation of STAT3/6, and dampening the generation of IL-12, IL-1 $\beta$  and IL-6<sup>[77,349,352]</sup>.

Infection by *T. gondii* down-regulates the host innate immune responses, such as proinflammatory cytokine production, in a STAT3-

dependent manner. It was demonstrated that the parasite type II strain fails to suppress immune responses because of a potential defect in ROP16, a highly polymorphic parasite-derived kinase<sup>[350]</sup> (Table 6).

Yamamoto et al<sup>[350]</sup> generated ROP16-deficient type I pathogens and showed a severe defect in parasite-induced STAT3 activation, finally resulting in enhanced generation of IL-6 and IL-12 p40 in the infected macrophages. Comparison of type I and type II ROP16 established that a single amino acid substitution in the kinase domain determined the strain difference in terms of STAT3 activation. Treatment with a tyrosine kinase inhibitor K-252a severely impaired the kinase activity of ROP16 for STAT3 Tyr705 phosphorylation in both *in vitro* and *in vivo* assays<sup>[350]</sup>.

Butcher et al<sup>[351]</sup> confirmed the above findings using infected mouse bone marrow-derived macrophages with rop16-deleted parasites. ROP16 mediated the suppressive actions of the pathogen on LPS-induced cytokine synthesis in macrophages and on IFN- $\gamma$ -induced NO generation by microglial cells and astrocytes. The roptry kinase was involved in activation of STAT3 and STAT6 transcription factors, and its lack resulted in enhanced IL-12 production and defective ability to inhibit production of proinflammatory mediators, while replication and dissemination of tachyzoites were found to be increased<sup>[351]</sup>.

##### B. CCBs and *T. gondii* infection.

CCBs affect the way calcium passes into vascular smooth muscle cells in the walls of arteries<sup>[354]</sup>, and calcium channel blockade was found to be very important in the pharmacologic management of RP<sup>[355]</sup>. Several clinical trials reported that oral CCBs, especially the dihydropyridine group (nifedipine, nicardipine, amlodipine, felodipine), were more effective than benzodiazepine (diltiazem), phenylalkylamine (verapamil), and others in reducing the frequency and severity of attacks associated with both primary and secondary RP, albeit some authors estimated CCBs as minimally or modestly effective medications in primary RP<sup>[354,356-360]</sup>.

It must be noted that several CCBs are known to exert antiparasitic effects<sup>[361-366]</sup>. An important role for calcium ion (Ca<sup>2+</sup>) in the action of drugs used against various parasites, including *Leishmania*, *Trypanosoma*, and *Plasmodium* has long been recognized, and many of them have effects on calcium signaling in both parasites and mammalian cells<sup>[363,367]</sup>. For example, nimodipine<sup>[362]</sup>, amiodarone<sup>[368]</sup>, and several other dihydropyridines<sup>[369]</sup>, as well as a number of calcium channel and calmodulin antagonists<sup>[370]</sup> may exert anti-parasitic effects *via* disruption of calcium homeostasis in parasites. Johnson et al<sup>[38]</sup> developed also calcium-dependent protein kinase 1 (TgCDPK1) inhibitors with strong antitoxoplasmic activity. Interestingly, curcumin also affect calcium ion homeostasis in parasites<sup>[363,372]</sup>, and recently this vegetable product was found to be effective in the treatment of acute and chronic toxoplasmosis in mice<sup>[373,374]</sup>. It must be added that CCBs suppress cytokine-induced activation of human neutrophils<sup>[375]</sup>. Moreover, nifedipine and nitrendipine inhibit iNOS<sup>[376]</sup>, and nifedipine enhances endothelial CYP2C protein expression and generation of 11,12-epoxyeicosatrienoic acid which have vasodilation and anti-inflammatory properties<sup>[377]</sup>. Amlodipine also inhibits iNOS, as well as TNF- $\alpha$ , and IL-1 $\beta$  formation in a dose-dependent manner, and free radical generation<sup>[378]</sup>.

*T. gondii* is exposed to the ionic fluctuations of the host cytoplasm, such as increases in host cytosolic Ca<sup>2+</sup> during calcium ion signaling events. Several key steps of the lytic cycle of the parasite, such as egress, motility, attachment, and invasion, are regulated by fluctuations in cytosolic calcium levels<sup>[365,379-382]</sup>. It was also demonstrated that calcium entry is critical for *T. gondii* virulence<sup>[364]</sup>.



**Table 5** Drugs associated with the occurrence of RP and their pathomechanisms that may be involved in possible undiagnosed concomitant *T. gondii* infections.

Drugs and RP	Pathomechanisms of drugs used in RP cases during possible undiagnosed concomitant <i>T. gondii</i> infections
$\alpha$ 1- and $\alpha$ 2-Adrenoceptor blockers: phentolamine [221], prazosin [222], yohimbine [223], labetalol (a dual $\alpha$ 1- and $\beta$ 1/ $\beta$ 2-adrenoceptors blocker) [224, 225]	$\alpha$ 2-Adrenergics and $\beta$ -adrenergics have antitoxoplasmatic activity [226,227]. Moreover, <i>T. gondii</i> infection increases generation and accumulation of ROS and causes oxidative cellular damage[175,228-230], which stimulates RhoA/Rho kinase signaling and subsequent mobilization of $\alpha$ 2-adrenoceptors to the cell surface, finally contributing to cold-induced vasospasm occurring in RP [229]. The blockade of the $\alpha$ -adrenoceptors by phentolamine resulted in a favorable effect in patients with RP [221]. Prazosin, a quinazoline-based $\alpha$ 1-adrenoceptor antagonist, displayed antiproliferative activity superior to that of another $\alpha$ 1-blocker, phentolamine [231]. Moreover, triptanthrin (a quinazoline analog) derivatives were found to act as <i>T. gondii</i> inhibitors [231-234]. Finally, $\beta$ 2-adrenoceptors are critical for the anti-inflammatory effects of NE and ACh [235, 236].
Clonidine ( $\alpha$ 2-adrenergic agonist) [237]	Clonidine significantly decreased <i>in vitro</i> the number of <i>T. gondii</i> -infected macrophages. This effect was blocked by yohimbine (a specific $\alpha$ 2-adrenergic antagonist) [227]
Dopamine (DA) [238]	DA activates both $\alpha$ - and $\beta$ -adrenoceptors [239]. Intravenous infusion of even low doses of DA may cause vasospasm and extravasation [240]. Administration of DA to healthy individuals increased intra-platelet cAMP concentration [241]. The effect of DA has been prevented by pre-incubation of platelets with propranolol ( $\beta$ -adrenoceptor antagonist) whereas pre-incubation with phentolamine ( $\alpha$ -adrenoceptor antagonist) did not modify the platelet response to DA. Domperidone (DA receptor antagonist) directly increased cAMP levels and enhanced the effects of DA. In human fibroblast host cells DA caused a significant rise in tachyzoites counts compared to controls [242]. Nb. propranolol has antitoxoplasmatic activity [19]. <i>T. gondii</i> infection increased total DA amounts in PC12 cells 2-3-fold of the uninfected controls, and enhanced DA metabolism [244, 245]
Cocaine (dopaminergic agonist) [246, 247]	Cocaine (crystal form-crack) decreased /increased cytokine formation, decreased antibody production, CD4+: CD8+ ratio, lymphocyte proliferation, NK cell activity, cellular hypersensitivity, increased viral load and HIV progression [248]. It must be noted that the main mechanism of <i>T. gondii</i> elimination is augmented host Th1 immune response, including generation of cytokines such as IL-2, IFN- $\gamma$ , TNF- $\alpha$ , IL-12 [249], and IL-17-expressing CD4+ and CD8+ T lymphocytes, thus contributing to the control of parasite invasion and replication [250]. On the other hand, cocaine exposure caused platelet activation, $\alpha$ granule release, and platelet containing microaggregate formation [251, 252]. Otherwise it is known that human platelets cause inhibition of <i>T. gondii</i> growth [253], and adherence of platelets to tachyzoites together with disruption of the surface membranes and cytoplasmic contents of the organisms [254]. It must be noted that toxoplasmosis seropositivity was found to be markedly higher among substance abusers ( $p < 0.0001$ ) irrespective of the class of drugs used [255]
Serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitors (fluoxetine) [256, 257]	5-HT can modulate several immunological events, such as chemotaxis, leukocyte activation, proliferation, cytokine secretion, energy, and apoptosis [258]. In sheep, <i>T. gondii</i> infection significantly increased plasma 5-HT levels compared to controls [259]. The hormone in intracellular physiological concentrations may enhance IL-6 and TNF- $\alpha$ generation, while increased extracellular 5-HT levels may suppress the production of these cytokines [260, 261]. It must be noted that treatment with fluoxetine reduced IL-6 serum levels in depressive patients compared to those of healthy controls [262], and otherwise it is known that IL-6 may exert both beneficial and harmful effects on <i>T. gondii</i> intracellular replication through interaction with IFN- $\gamma$ and TNF- $\alpha$ [76, 263]. In addition, chronic intake of fluoxetine increased atherosclerotic lesion formation [264], and <i>T. gondii</i> probably plays an important role in this process [122]
Ergot alkaloids [265, 266]	Ergot alkaloids are highly biologically active compounds known to interact with serotonergic, dopaminergic, and adrenergic receptors as agonists or antagonists [267]. These biomolecules have diverse therapeutic properties, including antibacterial, antiproliferative, and antioxidant activities [268-270]
Methylphenidate (MPH), dextroamphetamine (AMPH) are ADHD stimulants [271-276]	In 3 boys, MPH induced a marked hypersensitivity to mitogen-induced proliferation of lymphocytes, a hypergammaglobulinemia, and increased IgE levels [277]. (Nb. the increased IgE as well as IgG concentrations may reflect defense against <i>T. gondii</i> in these patients [278]). In mice, MPH reduced by up to 63% numbers of T-helper/inducer cells and also IgG+ cells in the spleen and increased up to 400-fold the serum levels of IgG, both in a dose-dependent pattern [277]. Use of AMPH may be associated with idiopathic leukocytosis [279], which favors <i>T. gondii</i> dissemination in the host as a "Trojan horse" [103]. AMPH also enhanced NK cytotoxic activity <i>via b</i> -adrenergic mechanism [280]. Interestingly, MPH, lisAMPH and atomoxetine are current ADHD medications, and <i>T. gondii</i> seropositivity was found to be associated with 2.8-fold increase in the odds ratio of ADHD, and multiple linear regression analysis revealed a significant relationship with the parasite seropositivity, elevated IgG titers (serointensity), and enhancement of IgG avidity (chronic infection) [281].
Cyclosporine [282-285]	Cyclosporin A inhibited NOS induction in vascular smooth muscle cells [286]. In mice treated with cyclosporine synthesis of IgG and IgM antibody titers was significantly depressed, and the drug had anti- <i>Toxoplasma</i> activity <i>in vitro</i> and perhaps <i>in vivo</i> [287]. There was a possible reactivation of latent <i>T. gondii</i> infection secondary to cyclosporine-induced immunosuppression in two cats [288]. The drug had antitoxoplasmatic activity <i>in vitro</i> and perhaps <i>in vivo</i> because cats receiving the drug orally shed fewer oocysts for a shorter time than did control animals [289]. Finally, cyclosporine act as a strong inhibitor of <i>T. gondii</i> enzyme DHOD <sup>s</sup> , similarly like leflunomide [290]
Leflunomide [291]	Inhibitors of DHOD have proven efficacy for the treatment of rheumatoid arthritis, psoriasis, autoimmune diseases, and cancer [292]. It was reported that A77-1726, the active derivative of the human DHOD inhibitor leflunomid (an immunosuppressive drug), was found to exert strong antitoxoplasmatic activity against the enzyme TgDHOD associated with <i>T. gondii</i> mitochondrion because this organelle is the site of orotate production [292-295]
Sulfasalazine [296, 297]	Various genotypic strains of <i>T. gondii</i> are susceptible to sulfonamides, including sulfasalazine [298-302], and this pathogen plays an important pathophysiological role in triggering and development of several autoimmune diseases [73, 303]. Interestingly, the drug inhibited the NF- $\kappa$ B and I $\kappa$ B kinase pathway to regulate the release of proinflammatory cytokines from human adipose tissue and skeletal muscle <i>in vitro</i> [304]
Tyrosine kinase inhibitors (TKIs), e.g. nilotinib [305]	Gefitinib use (group II TKIs, host cells not destroyed) and afatinib (group III, host cells destroyed) inhibited intracellular growth of <i>T. gondii</i> in a dose-dependent manner through the inhibition of the direct phosphorylation of STAT6 [306-308]. This effect suggested that tyrosine kinases of EGFR family of the parasite itself may be the target because the pathogen induced sustained host cell EGFR phosphorylation to prevent its killing [306-308]. Administration of gefitinib to animals with ocular and cerebral toxoplasmosis resulted in disease control that was dependent on antiapoptotic Bcl-1 proteins [309]. Incubation of <i>T. gondii</i> tachyzoites with another tyrosine kinase-specific inhibitor, genistein, significantly impaired their attachment to and penetration into the macrophages [310]; nb. the drug also inhibited the egress of parasites from host cells [311]



Secukinumab [312]	Secukinumab was found to be effective in the treatment of psoriasis and psoriatic arthritis targeting the IL-23/T <sub>H</sub> 17/IL-17 axis [313, 314]. It was demonstrated that psoriatic patients have significantly higher anti- <i>Toxoplasma</i> IgG and IgM antibodies compared with controls [315, 316]. It must be noted that T <sub>H</sub> 17 level was superexpressed and underexpressed in the course of chronic <i>T. gondii</i> infection [317]. In mice, oral <i>T. gondii</i> infection increased IL-17 expression and contributed to the inflammatory response, while neutralization of this cytokine exerted a partial protective effect against fatal <i>T. gondii</i> -associated inflammation [318]. Moreover, IL-6 promoted NK cell production of IL-17 during toxoplasmosis [319]. In contrast, it appeared that IL-17A-deficient mice were found to be very susceptible to <i>T. gondii</i> infection due to excessively induced HSP70 and IFN- $\gamma$ generation [320]
Vinyl chloride (VC) [321]	Latent cryoglobulinemia (chiefly composed of IgA and IgG) found in the VC worker with scleroderma-like skin abnormalities [322] may eventually reflect impaired immune defense against concomitant toxoplasmosis. Cryoglobulinemia has also been reported in several other autoimmune diseases [83, 323, 324] frequently associated with <i>T. gondii</i> infection [73, 325]. It must be noted that vinyl sulfone inhibitor K11777b was found to inhibit two key <i>T. gondii</i> cathepsine proteases TgCPB and TgCPL that play key roles in the pathogenesis of toxoplasmosis [326, 327]
Arsenic [247, 328]	The trivalent metabolites of arsenate ( <i>e.g.</i> arsenite) are toxic at concentrations below 1 mg/L. Arsenite triggers cell apoptosis, and leads to an increase in intracellular calcium levels and generation of ROS [329]. Apoptosis induced by arsenic trioxide was found to be inhibited in <i>T. gondii</i> -infected THP-1 cells, but not in uninfected cells. <i>T. gondii</i> infection inhibited apoptosis through overproduction of antiapoptotic proteins, such as Bcl-2 family, and downregulation of proapoptotic Bax molecules [330, 331]. In addition, intracellular calcium stores in the parasite were responsible for the parasite invasion of host cells [332], and the infection has been associated with increased production of ROS and RNI [333, 334]. Lastly, arsenic increased the expression of VCAM-1, P-selectine, MCP-1, IL-8, and IL-6 at the RNA and protein levels in rabbit aorta [329], and therefore it may play an important role in the pathogenesis of atherosclerosis [122, 335]

ACH, acetylcholine; ADHD, attention deficit hyperactivity disorder; cAMP, adenosine 3',5'-cyclic monophosphate; <sup>a</sup>DHOD, dihydroorotate dehydrogenase (*T. gondii* enzyme); <sup>b</sup>K11777, (N-methyl-piperazine-PhehomoPhe-vinylsulfone-phenyl); Bcl-1 and Bcl-2, beclin-1 and -2, antiapoptotic proteins; EGFR, epidermal growth factor receptor; HSP70, heat shock protein 70; MCP-1, monocyte chemotactic protein-1; NE, norepinephrine; NF- $\kappa$ B, nuclear factor- $\kappa$ B; NK, natural killer cell; NOS, nitric oxide synthase; RNI, reactive nitrogen intermediates; ROS, reactive oxygen species; RP, Raynaud's phenomenon; SSRI, serotonin reuptake inhibitors; STAT6, signal transducer and activator of transcription; VCAM, vascular cell adhesion molecule-1.

In *T. gondii* extracellular tachyzoites the ER and acidocalcisomes were identified as the largest Ca<sup>2+</sup> stores, and other sources are Golgi complex, apicoplast, inner membrane complex, and secretory organelles<sup>[383]</sup>. Host cell mitochondria and ER have an intimate relationship with *T. gondii* due to their recruitment to and association with the PV membrane<sup>[384]</sup>. Moreover, discharge of adhesive proteins *T. gondii* micronemes is stimulated by contact with host cells and this process is regulated by increases in intracellular calcium within the parasite<sup>[132]</sup>. In addition, gliding of the parasite is controlled by secretion of microneme proteins and factors that alter calcium fluctuation in the cytosol, while chelation of intracellular calcium blocked parasite motility<sup>[134,385]</sup>.

Calcium ion entry was blocked by nifedipine and stimulated by the increase in cytosolic calcium and by the specific calcium channel agonist Bay K-8644<sup>[364,382]</sup>. Vella et al<sup>[382]</sup> demonstrated that host calcium ion signaling affects intracellular calcium concentrations of the pathogen as tachyzoites are inside a PV surrounded by the host cell cytosol which contains calcium concentrations 50-100 nM, and the host calcium increases are able to reach the parasite cytosol through a calcium influx mechanism sensitive to nifedipine<sup>[365,382]</sup>.

The presence of extracellular calcium ion affected the rate of egress, which was blocked with nifedipine<sup>[365,386]</sup>. A role for a change in extracellular potassium concentration also was recommended to stimulate calcium signaling leading to egress<sup>[387]</sup>. Active egress of the parasite from host cells essential for its dissemination requires rupture of the PV membrane and the host cell membrane<sup>[365,388,389]</sup>.

Since both haloperidol and valproic acid are capable of inhibiting calcium transport through cellular ion channels, and risperidone was found to inhibit cellular potassium currents and a calcium-activated potassium channel, it was suggested that these drugs antitoxoplasmic activity was related to their calcium inhibitory properties<sup>[390-392]</sup>. This recommendation was in line with the finding that tachyzoites require calcium to invade host cells, and the invasion was inhibited by CCBs and calmodulin antagonists<sup>[361,390,393]</sup>. The interaction of tachyzoites with host cells was also inhibited by CCBs (verapamil) and calmodulin antagonists (trifluoperazine, calmidazolium). The calmodulin concentrated at the apical end of the tachyzoite may be involved in cytoskeleton movement and conoid extrusion. In contrast, increase host cell cytosolic calcium significantly decreased tachyzoite

**Table 6** *T. gondii* microneme roptry kinases (ROPK) virulence determinants in different types of the parasite (acc. to Kemp et al [353]; with own modification)

ROPK	<i>T. gondii</i> type I	Type II	Type III
ROP5	++	+	+
ROP16	++	-	++
ROP18	++	+	-

Presence of ROP5, ROP16 and ROP18 forms in the three *T. gondii* lineages: -, inactive; + minimally active; ++, highly active.

invasion<sup>[361]</sup>. Several medications successfully used in the treatment of various neurological and psychiatric disorders showed to have antitoxoplasmic activity in cell culture (**Table 7**)<sup>[390]</sup>.

Cytokines can alter intracellular calcium levels by depleting calcium from the endoplasmic reticulum (ER) and by increasing calcium influx from the extracellular space<sup>[400]</sup>. Of note, vitamin D dose-dependently inhibits LPS-induced cytokines production in peripheral blood monocyte cells modulating intracellular calcium<sup>[401]</sup>. In *T. gondii* extracellular tachyzoites the ER and acidocalcisomes were identified as the largest Ca<sup>2+</sup> stores, and other sources are Golgi complex, apicoplast, inner membrane complex, and secretory organelles<sup>[383]</sup>. Host cell mitochondria and ER have an intimate relationship with *T. gondii* due to their recruitment to and association with the PV membrane<sup>[384]</sup>. Moreover, discharge of adhesive proteins *T. gondii* apical storage organelles (micronemes) is stimulated by contact with host cells and this process is regulated by increases in intracellular calcium within the parasite<sup>[132]</sup>. In addition, gliding of the parasite is controlled by secretion of microneme proteins and factors that alter calcium fluctuation in the cytosol, while chelation of intracellular calcium blocked parasite motility<sup>[134,385]</sup>.

Moreover, the increased calcium concentrations in tachyzoites (nuclear and perinuclear areas) enhanced invasion of the parasite into host cells, and increased its intracellular replication<sup>[361,332]</sup>. The interaction of tachyzoites with host cells was also inhibited by verapamil and calmodulin antagonists (trifluoperazine, calmidazolium). The calmodulin concentrated at the apical end of the tachyzoite may be involved in cytoskeleton movement and conoid extrusion. In contrast, increase host cell cytosolic calcium significantly decreased tachyzoite invasion<sup>[361,385,402]</sup>.

Finally, treatment with CCBs is associated with several adverse skin reactions, including pemphigus, bullous pemphigoid, cutaneous small vessel vasculitis, lichenoid eruption, pseudolymphoma<sup>[403]</sup>, and affects approximately 48% of patients<sup>[404]</sup>. The most common side effects are ankle or foot edema (~30%), gingival hyperplasia (21%), and flushing (10%). Less common disturbances include facial or truncal telangiectasia, photosensitivity reactions, hyperpigmentation, development of new-onset psoriasis (and its exacerbation), idiopathic- or CREST (calcinosis, Raynaud's phenomenon, esophageal hypomotility, sclerodactyly, and telangiectasia)-related calcinosis cutis, purpuric exanthemas, subacute cutaneous lupus erythematosus, gynecomastia, erythromelalgia, chilblains, granuloma-like annular reactions, chronic anal fissures, keloids, and oral ulcers<sup>[403-407]</sup>. (Nb. recently several authors documented a link between psoriasis, treatment with novel antipsoriatic drugs, and *T. gondii* infection<sup>[312,408,409]</sup>). These wide spectrum of CCBs side effects are in line with many changes associated with disturbances in calcium homeostasis and reciprocal calcium-dependent signaling generated in the host cells and *T. gondii* tachyzoites, which may result in manipulation host cell responses and gene expression during intracellular infection of the pathogen<sup>[331,365,410-412]</sup>.

In summary, both TKIs and CCBs exert antitoxoplasmic effects and therefore play an important role in the treatment of primary and secondary RP.

## IVA. DEVELOPMENT OF RP AFTER ATOMOXETINE, FLUOXETINE, PAROXETINE, AND RISPERIDONE, AND THEIR LINK WITH *T. GONDII* INFECTION. IMPORTANT ROLE OF HYPERPROLACTINEMIA IN THE HOST DEFENSE AGAINST THE PATHOGEN

### A. RP associated with therapeutic use of atomoxetine, fluoxetine, paroxetine, and risperidone

Several studies reported that development of RP was related to the treatment with atomoxetine<sup>[413-415]</sup>, fluoxetine<sup>[257,416,417]</sup>, and risperidone<sup>[418]</sup>. In the case of atomoxetine and fluoxetine, the RP event appeared to be dose-dependent<sup>[257,413,414,419]</sup>. Interestingly, Taner et al<sup>[419]</sup> described a 10-years-old boy with attention-deficit/hyperactivity disorder (ADHD) who manifested a unilateral ear redness (sometimes accompanied by a headache) as a secondary RP one hour after starting treatment with atomoxetine and lasted in 4 hours; the red ear and headache disappeared after ceasing the treatment.

### B. Relationship between antidepressant drugs and *T. gondii* infection

#### 1. Atomoxetine.

This is a selective norepinephrine (NE) reuptake inhibitor and one of the main agents and the first nonstimulant used in the treatment of ADHD, which occurs at a prevalence of 5.9-7.1% in children and adolescents<sup>[420]</sup>. More than 50% of those diagnosed with ADHD can experience part of the symptoms also in adulthood<sup>[421,422]</sup>. Monotherapy with the drug was found to be effective for treating ADHD in pediatric patients with depressive and anxiety symptoms<sup>[423,424]</sup>. Atomoxetine improved hyperactivity and inattention in children with autism spectrum disorders (ASD) and ADHD, because about a third of children with ASD also have ADHD<sup>[425]</sup>. This is not surprising because it was demonstrated that the drug reduced cortical gene expression

**Table 7** Drugs tested for *in vitro* activity against *T. gondii* (acc. to Jones-Brando et al. [390]; with own modification).

Drug	Solvent	ID <sub>50</sub> <sup>a</sup> (µg/mL)	TD <sub>50</sub> <sup>b</sup> (µg/mL)	TI <sup>c</sup>
Valproic acid	ethanol	4.5	62.4	13.9
Sodium valproate	ethanol	4.1	52	12.7
Carbamazepine	ethanol	72	100	1.3
Lithium carbonate	1 N HCl	> 100	> 100	
Haloperidol	ethanol	5.6	103	18.4
9-OH-Risperidone	tartaric acid	20.1	134	6.7
Risperidone	tartaric acid	74	129	1.7
Fluphenazine HCl	Toxo CGM	3.5	17.9	5.1
Clozapine	ethanol	5.8	20	3.4
Olanzapine	DMSO	33.2	100	3
Chlorpromazine HCl	DMSO	2.6	6	2.3
Quetiapine fumarate	DMSO	18.6	33	1.8
Trimethoprim	DMSO	5.3	63.8	12.1

<sup>a</sup>Median inhibitory dose, a measure of tachyzoite inhibition. <sup>b</sup>Median toxicity dose, a measure of cytotoxicity. <sup>c</sup>Therapeutic index, a measure of efficacy determined by TD<sub>50</sub>/ID<sub>50</sub> 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 µg/mL produced 2% inhibition, but the combination of these two compounds at those concentrations resulted in a potentiating effect inhibiting 55% of the tachyzoites. Fond et al [394] 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 (IC<sub>50</sub>) for the last preparation was 8 ± 1.8 µM while its serum levels varied from 0.01-0.12 µM [395], but antipsychotic drugs usually achieve much higher and persistent concentrations in the brain tissue [396]. In human fibroblast cell cultures, IC<sub>50</sub> for fluphenazine, thioridazine, and trifluoperazine against developing tachyzoites of the parasite RH strain was 1.7, 1.2 and 3.8 µM, respectively [397]. Recently, Murata et al [398] found that *in vitro* hydroxyzine (an antihistamine and anxiolytic compound) reduced parasite replication (IC<sub>50</sub> 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 [398], and it should be noted that bradyzoites within mature tissue cysts are dynamic and replicating entities *in vivo* [399].

of proinflammatory mediators, including TNF-α, IL-1β, iNOS, as well as CD40 and CD11b, markers of microglial cells activity<sup>[426,427]</sup>. These changes were associated with reduced activation of NF-κB, the main regulator of inflammation in the CNS<sup>[427]</sup>. In addition, the drug suppressed expression of chemokines (RANTES, CCL-5) and vascular and intercellular cell adhesion molecules (VCAM-1, ICAM-1) in rat brain following a systemic challenge with bacterial LPS, and thus supported the theory that NE has anti-inflammatory properties and CAMs facilitate leukocyte influx into the CNS<sup>[427,428]</sup>.

It must be noted that combined treatment with atomoxetine and fluoxetine was well tolerated<sup>[423]</sup>. Fluoxetine (Prozac) (t<sub>1/2</sub> = 53 ± 41 hrs, active metabolite -norfluoxetine, t<sub>1/2</sub> = 6.4 ± 2.5 days) metabolized by CYP2D6<sup>[429]</sup> may however cause markedly increased plasma atomoxetine levels and development of side effects in patients who are poor CYP2D6 metabolizers<sup>[430]</sup>. This may be supported by the finding that multiple-dose of paroxetine intake significantly changed pharmacokinetics of atomoxetine and its active glucuronide metabolite, resulting in a 5.8-fold increased area under the curve and 1.7-fold higher maximal drug concentration values after combined treatment, thus emphasizing the need to monitor possible unwanted cardiovascular effects during such link therapy<sup>[423,431]</sup>; nb. these adverse effects may result from chronic fluoxetine treatment, which involve increased eNOS activity, NO generation, and calcium-sensitive potassium channels activation<sup>[432]</sup>.

## 2. Fluoxetine.

Recently, Osimo et al<sup>[433]</sup> published the meta-analysis study of immune markers confirming that the levels of CRP, IL-3, IL-6, IL-12, IL-18, sIL-2R, and TNF- $\alpha$  were markedly higher in patients with depression compared with controls. Experiments in rats and depressed adult patients showed that fluoxetine exerted potent anti-inflammatory effects in the periphery and brain, and vagal pathways participated in these actions because vagotomy confirmed attenuated anti-inflammatory effect of the drug<sup>[434,435]</sup>. In one study of 41 children and adolescents aged  $14.12 \pm 2.30$  yrs treated for anxiety and/or depression with fluoxetine for 8 weeks, the overall positive response rate was 56%, and the medication significantly reduced TNF- $\alpha$  levels ( $p = 0.037$ ), with no effects in the concentrations of IL-6 and IL-1 $\beta$ <sup>[436]</sup>. In another study of 22 adolescents with major depression, fluoxetine treatment for 8 weeks showed that proinflammatory cytokines IFN- $\gamma$ , IL-1 $\beta$ , TNF- $\alpha$ , IL-6, IL-12, and IL-15 were significantly decreased only at week 4 compared to baseline, and there were no significant correlations between cytokine levels and symptomatic improvement in the Hamilton Depression Rating Scale (HDRS)<sup>[437]</sup>. Several other antidepressant drugs also had such anti-inflammatory properties (Table 8)<sup>[438]</sup>, indicating that their beneficial therapeutic effects may at least in part be associated with down-regulating inflammatory processes in the brain and periphery.

Recently, Eskelund<sup>[442]</sup> demonstrated reduced levels of the excitotoxin quinolinic acid and 5-hydroxyindoleacetic acid in various brain regions in rats with genetic model of depression, following administration of fluoxetine. These findings may therefore suggest that fluoxetine also exerts its antidepressant effects through down-regulation of tryptophane/kynurenine pathway associated with *T. gondii* infection in patients with depression and mood disorders. Moreover, the drug increased prolactin levels via serotonergic pathways leading to hyperprolactinemia<sup>[443,444]</sup>, which also exerts antitoxoplasmic activity<sup>[445]</sup>.

Antidepressants not only alleviate depressive symptoms but have other beneficial function, such as regulation of the inflammatory cytokine imbalance<sup>[446,447]</sup>. A strong *in vivo* links between proinflammatory cytokines and disrupted glutamate homeostasis in the brain has also been demonstrated since activated N-methyl-D-aspartate receptors may activate microglia and cause further release of inflammatory mediators<sup>[448]</sup>. It must be noted that glutamate release in the CNS decreased with chronic fluoxetine, desipramine, or reboxetine treatment<sup>[449-451]</sup>. However, in a 14-years-old girl suffering from depression, therapy with sertraline and then fluoxetine failed to

improve her mood, but after positive *T. gondii* serologic testing and administration of specific treatment she had less complaints and no symptoms with evident amelioration in depression scores<sup>[452]</sup>. Effects of the infection with the pathogen on the cytokines and other biomolecules secreted by various neural cells are presented in Table 9<sup>[543]</sup>.

It must be noted that approximately 30% of patients with depression fail to respond to selective serotonin reuptake inhibitors (SSRI), and it was found that patients with SSRI-resistant depression had significantly higher production of the pro-inflammatory cytokines IL-6 ( $p = 0.01$ ) and TNF- $\alpha$  ( $p = 0.004$ ) compared to controls<sup>[458]</sup>. IL-6 levels are known to be commonly elevated in patients with depression and psychosis, as well as in people who are at risk of developing these disorders<sup>[262,459,460]</sup>. In one study, plasma IL-6 levels in patients with major depressive disorder (MDD) were markedly higher than in controls, and a positive correlation was found between the cytokine concentration and HDRS<sup>[461]</sup>. These detrimental IL-6 effects may at least in part be explained by the enhancement of intracellular replication of *T. gondii* in the host by this cytokine and its interactions with IFN- $\gamma$  and TNF- $\alpha$ <sup>[76]</sup>. The fact that IL-6 levels decreased after treatment with SSRI antidepressants in patients with MDD<sup>[462]</sup> may support involvement of the pathogen in the development of depressive symptoms. Recent studies performed in the population-based birth cohort provided further evidence that IL-6/IL6R pathways are implicated in pathogenesis of severe depression and psychosis<sup>[463]</sup>.

## 3. Risperidone.

This is an atypical antipsychotic drug with high affinity to dopamine D<sub>2</sub> and serotonin 5HT<sub>2</sub> receptors<sup>[464]</sup>. In children and adolescents, risperidone is used for treatment of schizophrenia, conduct disorder, bipolar disorder, tic disorder, obsessive-compulsive disorder and behavioral problems associated with ASD or mental retardation<sup>[464-467]</sup>. Importantly, the agent was found to have antitoxoplasmic properties<sup>[390]</sup>. It must however be noted that risperidone worsened vascular endothelial function via upregulation of adhesion molecules VCAM-1, ICAM-1, and E-selectin in diabetic rats<sup>[468]</sup>, which may be consistent with the theory that *T. gondii* may be implicated in development of type 1 and 2 diabetes mellitus<sup>[469]</sup>. Similarly, it was reported that chronic intake of fluoxetine enhanced atherosclerosis<sup>[264]</sup>, and this is in line with the suggestion that the pathogen may also play a role in the pathogenesis of this clinical entity<sup>[73]</sup>. In both cases, the antitoxoplasmic activity of these drugs may serve as an explanation of these harmful actions.

**Table 8** Antidepressant effects on the host immune system (acc. to Antonioli et al [438]; with own modification).

Antidepressant	Source and type of effector cells	Neuroendocrine alterations
Reboxetine, fluvoxamine, imipramine	Murine glia cells	↓NO levels after IFN- $\gamma$ stimulation
Amitypyline, nortriptyline	Rat glia cells	↓IL-1 and TNF- $\alpha$ after LPS stimulation
Venlafaxine	Rat encephalogenic T cell clones, splenocytes, peritoneal macrophages	↓IL-12, TNF- $\alpha$ , and IFN- $\gamma$
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- $\alpha$ , CRP and leukocyte count
Paroxetine, bupropion, mirtazapine, citalopram, venlafaxine	Depressed patients	↓IL-6, TGF- $\beta$
Sertraline	Depressed patients	↓IL-12, ↑IL-4 <sup>a</sup> , TGF- $\beta$
Fluoxetine, desipramine	Rats	↓IDO activity, NO <sup>b</sup>

CRP, C-reactive protein; IDO, indoleamine 2,3-dioxygenase; NO, nitric oxide; TGF- $\beta$ , transforming growth factor- $\beta$ ; LPS, lipopolysaccharide. <sup>a</sup> Long-term effects of IL-4 may be detrimental, possibly because of the ability of this cytokine to inhibit proinflammatory antiparasitic IFN- $\gamma$  production [439].

<sup>b</sup> Fluoxetine increased the NO production via NF- $\kappa$ B-mediated pathway in BV2 murine microglial cells [440]. The anti-inflammatory cytokines TGF- $\beta$  and IL-4 suppress IDO activity in human monocytes and fibroblasts [114], which is consistent with IDO metabolic pathway being a marked contributor to the proinflammatory system [441]

### B. Important role of tryptophan/kynurenine metabolic pathway in inflammation, affective disturbances, and *T. gondii* infection

There is a strong evidence that tryptophan/kynurenine pathway plays a key role in the link between inflammation and affective disorders [470-473]. Laugeray et al [470] showed in mice that both fluoxetine and 1-methyl-D-tryptophan (an indoleamine 2,3-dioxygenase 1 (IDO) inhibitor) robustly reduced peripheral levels of proinflammatory cytokines in a model of stress-induced depression. On the other hand, it must be emphasized that toxoplasmosis has an accelerating effect on the tryptophan/kynurenine pathway [474-478]. *T. gondii* infection induces the expression and activation of IDO which causes tryptophan depletion and is responsible for the production of kynurenines, which occurs at the first steps of the enzymatic pathway. This is associated with persistent (life-long) neuroinflammation and increased production of glutamate, mitochondrial damage, and oxidative stress [453]. Metabolites of tryptophan, L-kynurenine, picolinic acid and quinolinic acid, were found to inhibit proliferation of CD4<sup>+</sup>, CD8<sup>+</sup> T lymphocytes and NK cells, thus affecting immune response of the host to the parasite [479]. In addition, quinolinic acid, 3-hydroxykynurenine, and 3-hydroxyanthranilic acid, are known to have the ability to generate free radicals, which may exert antitoxoplasmic effects [480]. IDO is expressed in various immune cells, including monocytes, macrophages and microglia [481-483]. The activity of IDO can be enhanced by interferons and LPS, and IFN- $\gamma$  (the main IDO activator) is produced during *T. gondii* infection and has important anti-toxoplasmic activity [89,114] thereby strongly supporting a link between the infection and development of depression and mood disorders.

The above-presented data related to antidepressant agents are consistent with several reports linking ADHD, ASD, schizophrenia, generalized anxiety disorder, and obsessive-compulsive disorder, with acute and latent chronic *T. gondii* infection [94,281,390,484,485,486-490].

### C. Hyperprolactinemia (HPRL) associated with *T. gondii* infection reflects defense against the pathogen and therefore its treatment should be carefully considered. Medications and HPRL

Prolactin (PRL) is a hormone that plays an important role in the immune system enhancing production of several proinflammatory and anti-inflammatory cytokines, including IL-1 $\beta$ , IL-3, IL-6, IL-12, IL-10, IFN- $\gamma$ , and perhaps TNF- $\alpha$  [263,491]. In toxoplasmosis, one major function of IFN- $\gamma$  is the induction of TNF, NO, and production of IDO that contribute to the intracellular control of *T. gondii* [492,493]. PRL was found to bind to tachyzoites and this process impairs their adhesion and penetration into the host cells [445]. HPRL demonstrated in patients with different autoimmune diseases may thus reflect host defense against *T. gondii* infection [73]. PRL was capable of inhibiting multiplication of *T. gondii* in murine microglial cell cultures [263], and restricted intracellular growth of the parasite in mice and human cell lines [445,494]. Dzitko et al [445] demonstrated that *in vitro* preincubation of *T. gondii* BK strain (type I) tachyzoites with recombinant human PRL (rhPRL) caused a significant decrease in the replication of tachyzoites in one murine (L929) and two human (HeLa and Hs27) cell lines. Moreover, it was reported that serum human PRL was bound to live RH tachyzoites (type I) and ME49 (type II) strains in a specific way and the binding was concentration-dependent [495]. Inhibitory effect of the hormone on the parasite proliferation has been found in the peripheral blood mononuclear cells from patients with HPRL [494]. It was also demonstrated that women with HPRL had lower *T. gondii* seroprevalence, and high PRL levels could be related to *Toxoplasma* seronegativity [496,497].

**Table 9** Possible consequences on neurons of cytokines and biomolecules secreted upon *T. gondii* infection (acc. to Fagard et al [453]; with own modification)

Cell type	Secreted biomolecules	Neurotic
Astrocyte	IL-6	-
	GM-CSF	-
	TNF- $\alpha$	$\pm$
	IL-1 $\beta$	-
	Arachidonic acid	+
Macrophage	IL-12	-
	NO	$\pm$
Microglial cells	RNI	+
	NO	$\pm$
	H <sub>2</sub> O <sub>2</sub>	+
	IFN- $\gamma$	-
	Glutamate	+
Neuron	NO	$\pm$
	TNF- $\alpha$	$\pm$
	Glutamate	+
Natural killer cell	IFN- $\gamma$	-
T cell	PAF	+
	IL-4	-
	IFN- $\gamma$	-
	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 [245]. Dopamine concentrations were 14% higher in the brain of mice with chronic *T. gondii* infection than in controls [454]. 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 [455]. Moreover, dopamine stimulated tachyzoite proliferation in human fibroblast and primary neonatal rat astrocyte cell cultures [242], 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 [456, 457].

### 1. Medication-induced HPRL and *T. gondii* infection.

Several drugs may cause HPRL, including antipsychotics, antidepressants, opiates and cocaine, antihypertensive preparations (verapamil, methyl dopa, reserpine), gastrointestinal agents (metoclopramide, domperidone, cimetidine, ranitidine), and estrogens [498,499] (Table 10).

Perkins [500] demonstrated that risperidone (mean dose 4-7.6 mg/day) was associated with the greatest elevation of plasma PRL levels after 4-8 weeks of treatment as compared with haloperidol (5-12.9 mg/day; almost 100 ng/mL end point PRL concentration). It must be noted that some of these drugs, such as chlorpromazine, risperidone, clozapine, olanzapine, quetiapine, verapamil, and haloperidol have antitoxoplasmic activity [73,131,390,501]. Of note, many women with schizophrenia treated with antipsychotic drugs suffer from PRL- and endocrine-associated disorders such as galactorrhoea and/or amenorrhoea [502-504]. These abnormalities may be due to latent *T. gondii* infections because there are several studies documenting important role of the parasite in development of both schizophrenia [484,490,505] and infertility [506-509].

Interestingly, HPRL is associated with a high prevalence of serum autoantibodies and high concentrations of proinflammatory cytokines [510], and in one study [511], the use of 1,25-dihydroxyvitamin D<sub>3</sub> for 7 days caused serum PRL levels to double in five healthy men.



This may not be surprising because vitamin D exerts antitoxoplasmic effects<sup>[512,513]</sup> and enhances mice sensitivity to toxoplasmosis<sup>[514]</sup>, and therefore these “healthy” individuals probably suffered from subclinical latent *T. gondii* infection. Several authors demonstrated antinuclear and other autoantibodies in healthy people and in general community<sup>[515-522]</sup>, which is in line with approximately 30-50% of world's human population infected with the parasite. On the other hand, lithium carbonate (a drug used in schizophrenia and schizoaffective disorders) appeared to decrease PRL levels by about 40%<sup>[523]</sup>. This finding may be explained by the facts that lithium has antitoxoplasmic activity<sup>[390]</sup>, and the long-term treatment of such patients with this medication<sup>[523]</sup> probably exerted beneficial effect on latent toxoplasmosis undiagnosed in those participants.

## V. DEVELOPMENT OF RP DURING THERAPY WITH VARIOUS INTERFERONS (IFNs) AND THE INCREASED IFN LEVELS OBSERVED DURING CLINICAL COURSE OF SEVERAL AUTOIMMUNE DISEASES MAY BE CAUSED BY CHRONIC LATENT *T. GONDII* INFECTION

### A. Treatment with IFNs and development of RP

In humans, there are three main types of IFNs: type I IFNs include 13 forms of IFN- $\alpha$  and one form of IFN- $\beta$  (source: plasmacytoid DCs (pDCs), fibroblasts), one type II IFN named IFN- $\gamma$  (NK cells, CD4 and CD8 cells, DCs, macrophages, B cells), and three members of type III IFNs: IFN- $\lambda$ 1 (IL-29), IFN-12 (IL-28A), IFN-13 (IL-28B), and IFN-14 (pDCs) have been identified<sup>[524-527]</sup>. The existence of these three types of IFNs, using three different receptors suggest that they play different roles in host defense against pathogens<sup>[528]</sup>, and are associated with different clinical entities.

RP has been frequently observed during treatment with various IFNs<sup>[220,529]</sup>. A meta-analysis with six eligible studies and 183 patients performed by Mohokum et al<sup>[530]</sup> calculated that the prevalence of RP in patients taking IFNs was 13.6% (95% CI 0.026, 0.313). Shapira et al<sup>[531]</sup> analyzed 24 case reports of RP associated with IFN therapy and found that IFN- $\alpha$  was the most common medication implicated (n = 14), followed by IFN- $\gamma$  (n = 5) and IFN- $\beta$  (n = 3), and the treatment time lasted from 0.5 to 49 months (mean 15.5 months). It is noteworthy that spontaneous recovery occurred for 50% of the patients after withdrawal of the cytokine<sup>[220,531]</sup>. Moreover, it should be emphasized that RP was also reported in the so called “healthy general population”<sup>[532]</sup>, but a long-term follow up of such individuals frequently revealed SSc and various mixed connective tissue diseases (MCTD)<sup>[186,533]</sup>, and this may be in agreement with the worldwide distribution and easy transmission of *T. gondii*, especially observed in developing countries.

### B. Increased IFN- $\gamma$ production during acute and chronic latent *T. gondii* infection

The parasite can successfully infect a wide range of different nucleated host cells<sup>[534,535]</sup>. IFN- $\gamma$  has been shown to be critical both for the early control of *T. gondii* tachyzoites expansion and for preventing reactivation of dormant parasite stages, and the induction of NO and RNI have been identified as important effector molecules which restrict pathogen growth in infected host cells<sup>[95,142]</sup>. Nb. an association of RP with a polymorphism in the NO synthase 1 gene in the general population<sup>[43,536]</sup> documented that the early production of the proinflammatory cytokine IL-12, which stimulates natural killer (NK) and CD4<sup>+</sup> and CD8<sup>+</sup> T cells to release IFN- $\gamma$ , is important for

**Table 10** Effects of psychotropic drugs on serum PRL levels (acc. to Molitch [498]; with own modification)

Medications	Increase in PRL <sup>a</sup>
Antipsychotics	
Typical	
Phenothiazines (chlorpromazine, fluphenazine, thioridazine)	+++
Butyrophenones (haloperidol)	+++
Thioxanthenes (thiothixene)	+++
Atypical	
Risperidone	+++
Molindone	++
Quetiapine	+
Olanzapine	+
Antidepressants	
Tricyclics	
Amitriptyline	+
Desipramine	+
Clomipramine	+++
Monoamine oxidase inhibitors	
Pargyline	+++
Clorgyline	+++

<sup>a</sup> +, PRL increase to abnormal levels in small percentage of patients; ++, increase to abnormal levels in 25-50% of patients; +++, increase to abnormal levels in > 50% of patients.

effective control of the parasite<sup>[92,537,538]</sup>. Although lysis of pathogen-infected cells by cytotoxic lymphocytes contributes to host resistance, the primary role of these cells is in the production of IFN- $\gamma$ , which upregulates antimicrobial effector mechanisms<sup>[539]</sup>. The importance of IL-12 induction in early phase of *T. gondii* infection is supported by the reports that monocytes<sup>[540]</sup>, CD8a<sup>+</sup> DCs<sup>[541]</sup>, pDCs<sup>[542]</sup> and neutrophils<sup>[543]</sup> all contribute to the generation of this activation signal<sup>[536]</sup>. CD8a<sup>+</sup> DCs produce large amounts of IL-12 but not other proinflammatory cytokines, such as TNF and IL-1 $\beta$ <sup>[544]</sup>. Neutrophils are the dominant cell type responsible for early IFN- $\gamma$  responses<sup>[545]</sup>, however the level of IFN- $\gamma$  observed in each neutrophil is low compared to that of activated NK or T cells<sup>[545]</sup>. On the other hand, neutrophils accumulate in large quantities at the site of inflammation due to acute *T. gondii* infection and therefore markedly enhance their antitoxoplasmic effects<sup>[92,546]</sup>. It must be added that IFN- $\gamma$  alters host cell metabolism, which can lead to tryptophan (in fibroblasts)<sup>[114]</sup> and iron starvation (in enterocytes)<sup>[125]</sup> because *T. gondii* is a tryptophan auxotroph. Moreover, IFN- $\gamma$  induces IDO, an enzyme that degrades cellular tryptophan and inhibits pathogen growth in human cells<sup>[114,547]</sup>. This cytokine also stimulates phagocytes to produce ROS and RNI, which can lead to parasite damage and impede its growth in macrophages<sup>[548,549]</sup>. Activated macrophages kill tachyzoites *in vitro*<sup>[144,550]</sup>, and IFN- $\gamma$  is important for immunity acting as the “macrophage activating factor”<sup>[524]</sup>. Moreover, it has also been demonstrated that IFN- $\gamma$  stimulated the expression of IDO1 in human retinal pigment epithelial cells, which inhibited the growth of *T. gondii* and *S. aureus*<sup>[116]</sup>, and contributed to the host defense against the parasite in macrophages<sup>[111,551,552]</sup>.

**C. Patients with several autoimmune diseases (ADs) frequently have secondary RP and increased various types of IFNs, including IFN- $\lambda$ , associated with chronic latent *T. gondii* infection** ADs are the third most common category of disease in the United States after cancer and cardiovascular disease, affecting approximately 14.7-23.5 million people (5-8% of the population)

with at least one autoimmune condition<sup>[553]</sup>. *T. gondii* infection seems to play a critical role in triggering, development and persistence of several ADs<sup>[73,83,554]</sup>.

### 1. SLE patients (involved types I-III IFNs).

IFNs are believed to be key molecules in the pathogenesis of SLE<sup>[555-557]</sup>. Oke et al<sup>[556]</sup> estimated levels of type I, II and III IFNs in a large group of such patients and found that all IFNs were higher in SLE individuals than in controls. They suggested that these cytokines contribute to the tissue specific pathology and heterogeneity of clinical manifestations in this clinical entity with high IFN- $\gamma$  as well as high functional type I IFN activity characteristic of severe SLE, elevated levels of IFN- $\alpha$  associated with active mucocutaneous inflammation and a more benign cardiovascular profile, while IFN- $\lambda$  1 in isolation linked with milder disease<sup>[556]</sup>. In a model TLR7-induced lupus, IFN- $\lambda$  promoted immune cell recruitment and tissue-specific inflammation (skin and kidney cells)<sup>[558]</sup>.

It must be noted that RP is a frequent manifestation in patients with primary Sjögren's syndrome<sup>[559-562]</sup>, and a pathogenic role of IFN- $\gamma$  has been suggested in such individuals because 36 of 108 patients analyzed by Willeke et al<sup>[561]</sup> had a markedly increased number of IFN- $\gamma$ -secreting peripheral blood mononuclear cells compared with patients without RP or controls.

### 2. SSc patients (IFN- $\gamma$ , IFN- $\lambda$ ).

RP is the earliest and most common manifestation of SSc, affecting almost 96% patients<sup>[533,557,563]</sup>, and its independent markers may predict progression to full development of SSc by years or decades<sup>[563,564]</sup>. Koenig et al<sup>[565]</sup> reported that amongst 586 patients with RP who were followed up for 3,197 person-years, 74 (12.6%) developed the definite disease with a characteristic microvascular damage established by nailfold capillary microscopy.

Molteni et al<sup>[566]</sup> found that patients with SSc affected by RP had markedly higher concentrations of IFN- $\gamma$  cells than healthy individuals (Table 11).

It was suggested that a population of CD4<sup>+</sup> T lymphocytes might play a protective role in RP patients and in established scleroderma<sup>[566]</sup>. In one study, development of circumscribed scleroderma (*morphea*) was associated with *T. gondii* infection and the evolution of lesions was correlated with antibodies titre specific for the parasite<sup>[567]</sup>. This finding may be in line with the possible involvement of the kynurenine pathway in scleroderma<sup>[568]</sup>.

IFN- $\lambda$  (IL-29) has immune-regulatory function and plays an important role in the pathogenesis of several autoimmune diseases, including SSc<sup>[569]</sup>. This novel IFN family interact through the IFN- $\lambda$  receptor whose expression is mainly restricted to cells of epithelial origin<sup>[570,571]</sup>. Table 12 summarizes IFN- $\lambda$  -responsive cell types in humans<sup>[572]</sup>.

IFN- $\lambda$  orchestrates innate and adaptive mucosal immune responses<sup>[572]</sup>. It was reported that this cytokine protected intestinal epithelial cells from protozoal oral infection with *Cryptosporidium parvum*<sup>[574]</sup>, and therefore may also be effective in common oral infections with *T. gondii*, because IFN- $\gamma$ -activated primary enterocytes inhibit pathogen replication by limiting the availability of intracellular iron to this microbe<sup>[575]</sup>.

In patients with SSc, Taveras Dantas et al<sup>[569]</sup> found that IFN- $\lambda$  1 and IFN- $\gamma$  concentrations were markedly higher than in controls, and demonstrated a significant positive correlation between IFN- $\lambda$  1 and IFN- $\gamma$  levels ( $p = 0.0103$ ,  $r = 0.3526$ ). It appeared also that IFN- $\gamma$  elevations were associated with development of muscle involvement (myositis) ( $p = 0.0483$ ). Other authors<sup>[576,577]</sup> showed that IFN- $\lambda$  1

**Table 11** *In vitro* proliferation and IFN- $\gamma$  production by alloactivated PBMCs from SSc and RP patients compared to healthy controls (acc. to Molteni et al [566]; with own modification).

Participants	Cell proliferation (ct/min)	P	IFN- $\gamma$ production (pg/mL) <sup>a</sup>	P
Healthy controls	15212 $\pm$ 1149 (n=60)		308 $\pm$ 34 (n=60)	
SSc pts (total group)	30084 $\pm$ 2940 (n=48)	< 0.001	474 $\pm$ 56 (n=49)	0.01
SSc stable disease	31919 $\pm$ 4109 (n=26)	< 0.001	576 $\pm$ 76 (n=27)	< 0.001
SSc active disease	27916 $\pm$ 4228 (n=22)	< 0.001	348 $\pm$ 78 (n=22)	NS
RP pts (total group)	17791 $\pm$ 2881 (n=26)	NS	608 $\pm$ 78 (n=26)	< 0.0001
Idiopathic RP pts	15627 $\pm$ 1873 (n= 6)	NS	609 $\pm$ 97 (n=16)	< 0.001
Seropositive RP pts	21254 $\pm$ 6959 (n=10)	NS	605 $\pm$ 134 (n=10)	< 0.001

<sup>a</sup> The mean level of IFN- $\gamma$  produced by total clones after stimulation (ct/min, corrected by dividing the amount of IFN- $\gamma$  produced by each clone by its proliferation). PBMCs, peripheral blood mononuclear cells; pts, patients; RP, Raynaud's phenomenon; SSc, systemic sclerosis.

**Table 12** IFN- $\lambda$ -responsive cell types in humans (acc. to Ye et al [572]; with own modification).

Cell type	Response to IFN- $\lambda$
Epithelial cells	Yes
Hepatocytes <i>ex vivo</i>	Yes
Hepatocytes <i>in vivo</i>	ND
B cells	Yes
Neutrophils	Unclear <sup>a</sup>
pDCs	Yes
cDCs	ND
BMDCs	ND
moDCs	Yes/No
T cells	No
NK cells	No
Macrophages	Yes

BMDCs, bone marrow-derived dendritic cells; cDCs, conventional DCs; moDCs, monocyte-derived DCs; NK, natural killer; ND, not determined; pDCs, plasmacytoid DCs. <sup>a</sup> Unclear whether the response is direct or indirect. It must be noted that in children IFN- $\lambda$  1 (IL-29) was identified as a specifically decreased intraocular biomarker for juvenile idiopathic arthritis-associated uveitis as compared to those with idiopathic uveitis ( $p < 0.001$ ) [573].

inhibited human TH2 cell responses by diminishing secretion of cytokines IL-4, IL-5 and IL-13 in T cells. This cytokine also enhanced IL-6, IL-8 and IL-10 production by monocytes in a dose-dependent manner<sup>[576,578]</sup>.

### 3. RA patients (IFN- $\gamma$ , INF- $\alpha$ ).

RA may traditionally be included among the diseases associated with development of Raynaud's syndrome. A meta-analysis of 28 studies contributing data on 3,730 participants with RA, a pooled prevalence of 12.3% and 95% CI 0.093-0.157 were obtained<sup>[579]</sup>. IFN- $\gamma$  may activate both antigen presenting cells and CD4<sup>+</sup> T cells, and thereby contributes to the autoimmunity in RA<sup>[580]</sup>. Anti-IFN- $\gamma$  and anti-TNF- $\alpha$  antibodies showed similar efficacy in patients with active RA<sup>[580,581]</sup>. This is not surprising because toxoplasmosis has been considered as a potential risk factor for rheumatoid patients<sup>[73,582,583]</sup>. A meta-analysis of data from eight articles encompassing 1244 patients with RA (46% with toxoplasmosis) and 2799 controls (21%) showed OR 3.30 (95% CI 2.05-5.30,  $p < 0.0001$ )<sup>[582]</sup>.

### 4. Other diseases.

Some other ADs, including migraine<sup>[584-589]</sup>, diabetes mellitus<sup>[590,591]</sup>, and Leśniowski-Crohn disease<sup>[592]</sup> also had a significantly increased

prevalence of RP compared with controls. The authors suggested that the microvascular disturbances associated with RP may play a role in the pathophysiology of these clinical entities. This notion is in line with well documented important role of *T. gondii* infection in these disorders<sup>[73,74,469,593,594]</sup>.

## VI. INCREASED BLOOD VISCOSITY IN BOTH RAYNAUD'S DISEASE AND ACUTE/CHRONIC LATENT *T. GONDII* INFECTION

### RP

#### A. Patients with PRP and SRP have significantly decreased blood pressure in hands compared with controls

Studies showed that both patients with PRP and SRP had a markedly lower blood pressure in fingertips ( $p < 0.0001$ ), periungual ( $p < 0.0001$ ), palmar side of 3rd finger ( $p < 0.0001$ ), and palm areas ( $p < 0.0001$ ), than controls. Moreover, blood pressure was significantly lower in PRP than in SRP and SSc patients in the above areas as ( $p < 0.04$ )<sup>[595]</sup>. At 10°C patients with PRP also had finger systolic blood pressure markedly lower compared to controls<sup>[596]</sup>.

#### B. RP and changes in blood platelets: gender differences and effect of cold exposure

Butkiewicz et al<sup>[597]</sup> reported gender-dependent differences in the distribution of normal platelet counts in healthy blood donors with markedly higher counts being observed in females than in males ( $p = 0.0002$ ). In addition, Ali et al<sup>[598]</sup> analyzed 2376 blood samples (791 males, 1565 females, age range 16-91 yrs) and found that sex-divided ranges for mean platelet volume, platelet large cell ratio, and plateletcrit were significantly higher in women than in men ( $p = 0.007$ ,  $p = 0.015$ , and  $p < 0.001$ , respectively). It must be noted that cytokine thrombopoietin (TPO) concentrations have also been sex-dependent but they were markedly lower in women than in men ( $p = 0.03$ )<sup>[3]</sup>. Otherwise it is known that TPO may augment platelet P-selectin expression stimulating platelet-leukocyte interactions<sup>[599-601]</sup>, and primes platelet aggregation in response to shear stress and several agonists<sup>[602]</sup>.

In healthy young volunteers Neri Serneri et al<sup>[603]</sup> investigated the effects of cold application on platelet aggregation ratio,  $\beta$ -thromboglobulin ( $\beta$ -TG) release and plasma thromboxane B<sub>2</sub> (TxB<sub>2</sub>) levels and demonstrated a prompt and marked increase in platelet aggregates and plasma  $\beta$ -TG and TxB<sub>2</sub> concentrations. It must be added that platelet-derived  $\beta$ -TGs increased the rate of thrombin generation, and modulated coagulation through an interaction with Factor X<sup>[604]</sup>.

#### C. RP and an increased whole blood and/or plasma viscosity

In PRP and SRP patients elevated whole blood and/or plasma viscosity, fibrinogen and erythrocyte aggregation are the main findings after exposure to cold<sup>[605-609]</sup>. For example, Goyle et al<sup>[609]</sup> measured whole blood viscosity in 10 patients with RP and in 10 healthy controls at 27°C and 37°C. The viscosity was markedly higher ( $p < 0.05$ ) at 27°C than that of the controls when measured at a low shear-rate (0.77 s<sup>-1</sup>); (nb. low shear rates occur in veins and in arteries in areas of flow separation caused by changing arterial geometry such as dilatations, branches, and curves<sup>[610]</sup>).

Whole blood viscosity (WBV) is determined by hematocrit, plasma viscosity, red blood cell aggregation, deformability, shear stress, and other factors. Plasma viscosity depends on plasma protein concentrations, predominantly fibrinogen, especially in SRP<sup>[611,612]</sup>. Moreover, in inflammation blood viscosity is increased by elevated

concentrations of acute phase reactants and hypergammaglobulinemia<sup>[610]</sup>. Vaya et al<sup>[608]</sup> found that age was markedly higher in patients with SRP than in those with PRP, and that serum IgA, IgG, and plasma viscosity were higher in SRP than in healthy controls ( $p < 0.05$ ). Patients with digital ulcers had significantly higher serum IgA levels ( $p = 0.012$ ), lower erythrocyte aggregation time ( $p = 0.008$ ), and a trend for higher plasma fibrinogen concentrations ( $p = 0.064$ ) and plasma viscosity ( $p = 0.069$ )<sup>[608]</sup>. The authors suggested that immunoglobulin levels seemed to aggravate the rheological changes in these subjects<sup>[608]</sup>, and this proposition is in line with the increased serum IgG, IgM and IgA concentrations observed in patients during the course of toxoplasmosis<sup>[135,613]</sup>.

Interestingly, Ho et al<sup>[614]</sup> in 113 participants with different hemoglobin, white blood cells (WBC) and platelet count showed that hematocrit, hemoglobin, red blood cells, as well as the increased WBC and platelet counts may impair whole blood viscosity (WBC,  $r = 0.261$ ,  $p = 0.005$ ; platelets,  $r = 0.227$ ,  $p = 0.016$ ) but not plasma viscosity. Other authors<sup>[615]</sup> also reported that platelets were hyper-reactive to fluid shear stress at temperatures of 24, 32, and 35°C as compared to 37°C, and these changes lead to the platelet enhanced aggregation and increased whole blood viscosity. Thus, more blood components in RP than reported to date participate in development of whole blood and/or plasma viscosity, especially in cold environment.

#### D. RP and increased blood viscosity as well as blood coagulation disturbances in the patients with venous thromboembolism (VTE)

Increased blood viscosity contributes to the association of acute infections with VTE, venous thrombosis, and myocardial infarction<sup>[610]</sup>. VTE is a quite common condition and its incidence increases with age<sup>[616]</sup>. Žuk et al<sup>[617]</sup> studied 360 patients with VTE with no autoimmune disease and found that PRP occurred in 17% participants, with almost 4-fold higher prevalence among women than in men, acting as a potential risk factor for this clinical entity. Individuals with PRP tended to form more dense plasma fibrin clots displaying impaired lysability and had increased endothelial damage. Patients with PRP had higher fibrinogen and vWF levels, lower plasma clot permeability, and longer clot lysis time (CLT) (all  $p < 0.05$ ). CLT showed positive associations with PAI-1 ( $r = 0.33$ ,  $p = 0.012$ ) and vWF ( $r = 0.35$ ,  $p = 0.0072$ ). PRP appeared to be a predictor of prolonged CLT in the whole analyzed group (OR 3.46, 95% CI 1.92-6.24) and in women following VTE (OR 2.75, 95% CI 1.31-5.78)<sup>[617]</sup>. Interestingly, there is some evidence of venodilation in the patients with PRP<sup>[618]</sup>.

#### E. Beneficial effects of piracetam on the whole blood viscosity and platelets, and red and white blood cells deformability in PRP and SRP. A possible strong link with *T. gondii* infection

Piracetam, a  $\gamma$ -aminobutyric acid (GABA) derivative, was found to reduce erythrocyte adhesion to vascular endothelium, hinder vasospasm, and improve microcirculation<sup>[619-623]</sup>. In patients with PRP and SRP the drug in a dose-dependent manner caused a significant reduction in blood and plasma viscosity and 30-40% decrease in plasma fibrinogen and vWF levels, as well as an increase in red and white blood cells and platelets deformability. Pharmacological effects of piracetam has been attributed to inhibition of platelet function by inhibition of thromboxane A<sub>2</sub> synthetase or antagonism of thromboxane A<sub>2</sub> activity, and a direct stimulant effect on prostacyclin synthesis in endothelium, which has both vasodilator and platelet aggregation inhibitory properties. Importantly, the drug had no evident side effects<sup>[624,625]</sup>. It must



be noted that the endothelial production of prostacyclin and NO molecules that increase erythrocyte deformability and decrease erythrocyte and platelet aggregability, is shear rate-dependent<sup>[626-628]</sup>, and NO/RNI play an important role in the host defense against *T. gondii* infection<sup>[95,98,117,629]</sup>.

Finally, it must be emphasized that GABA receptor-associated protein-like 2 (GABARAPL2) plays a pivotal role in the growth restriction of *T. gondii* in HeLa cells treated with IFN- $\gamma$ , and this protein is recruited to membrane structures surrounding PV<sup>[630]</sup>. GABA is synthesized and released by the endothelium<sup>[631]</sup>. The drug receptors have been found in DCs, macrophages and T lymphocytes, and all these cells are capable to produce GABA<sup>[632]</sup>. GABA was demonstrated to be a potent regulator of both T<sub>H</sub>1- and T<sub>H</sub>2-types cytokine secretion from human peripheral blood mononuclear cells and CD4<sup>+</sup> T cells where this aminoacid generally decreases these processes in a concentration-dependent manner<sup>[633]</sup>. It was demonstrated that GABA agonists decreased TNF, IL-6, and IL-12 production and inhibited T lymphocyte proliferation indicating that this aminoacid have potential anti-inflammatory activity, especially in autoimmune diseases<sup>[634,635]</sup>. Thus, piracetam may also play an important role in defense against *T. gondii* infection through modulation of host immunity, beneficial effects on inflammation processes, and a direct antiparasitic action.

### *T. gondii* infection

#### A. Infection with *T. gondii* increases P-selectin, mean platelet volume and oxidized stress in the host

Hamdy et al<sup>[636]</sup> found that in patients with acute and chronic *T. gondii* infection mean platelet volume (MPV), serum malondialdehyde (MDA, a lipid peroxidation marker), oxidized glutathione (GSSG), and soluble P-selectin (an inflammatory biomarker) concentrations were significantly higher than in healthy controls. On the other hand, serum total glutathione (tGSH) and reduced glutathione (GSH, an antioxidant) levels in the patients were markedly lower compared with controls (Tables 13 and 14). In all analyzed *T. gondii* patients sP-selectin concentrations showed a significant positive correlation with mean platelet volume and platelet count ( $p = 0.000$  and  $p = 0.014$ , respectively)<sup>[636]</sup>. Similar abnormalities in GSH and MDA levels have also been reported by other authors<sup>[136,637]</sup>.

#### B. Effects of *T. gondii* infection on blood coagulation and fibrinolysis

In animals, Johnson et al<sup>[638]</sup> found that *T. gondii* infection caused disturbances in blood coagulation and at the same time was associated with a critical protective function. It was demonstrated that after peroral infection with avirulent strain ME49 *T. gondii*, C57BL/6 mice build up a strong T<sub>H</sub>1 type immune response, characterized by robust IFN- $\gamma$  generation, which quickly included parasite replication. The infection prompted a transient coagulative response, and the authors<sup>[638]</sup> detected markedly elevated fibrin levels in *T. gondii*-infected animals, including fibrin deposition within hepatic and intestinal tissues which kinetically correlated with peaks in both parasite burdens and hallmarks of T<sub>H</sub>1 type immunity. Moreover, IFN- $\gamma$  stimulated also expression of genes in macrophages that favors and/or stabilize fibrin deposition<sup>[639-641]</sup>.

Mullarky et al<sup>[642]</sup> demonstrated an important role for the signal transducer and activator of transducer-1 (STAT1) in the suppression of infection-stimulated fibrin deposition via a STAT1-dependent pathway operating in endothelial cells, and interestingly, expression of plasminogen activator inhibitor-1 (PAI-1), the main regulator of endogenous fibrinolytic enzyme system, is also STAT1 regulated

**Table 13** Platelet count and platelet volume in patients with acute and chronic *T. gondii* infection and controls (acc. to Hamdy et al [636]; with own modifications).

Parameters	Controls	<i>T. gondii</i> patients	
	(n = 10)	Acute infection (n = 10)	Chronic infection (n = 20)
Platelet count (x10 <sup>9</sup> /L)	243.5 ± 39.3 (194-341)	258.7 ± 25.6 (222-293)	264.3 ± 68.4 (151-387)
Platelet volume (fL)	7.67 ± 0.93 (6.5-10.0)	12.2 ± 1.4 <sup>a</sup> (10.3-14.9)	13.1 ± 1.5 <sup>a</sup> (10.9-15.2)

Results are means ± SD; values in parentheses denote range. <sup>a</sup> Results significantly higher compared with controls ( $p = 0.000$ ).

**Table 14** Serum MDA, tGSH, GSH, GSSG, and sP-selectin concentrations in patients with acute and chronic *T. gondii* infection and controls (acc. to Hamdy et al [636]; with own modifications).

Parameters	Controls	<i>T. gondii</i> patients	
	(n = 10)	Acute infection (n = 10)	Chronic infection (n = 20)
MDA (nmol/mL)	0.377 ± 0.12 (0.21-0.57)	7.2 ± 4.5 <sup>a</sup> (0.68-12.5)	4.6 ± 3.03 <sup>a</sup> (0.83-9.7)
tGSH (nmol/mL)	11.42 ± 0.414 (11.00-12.5)	8.9 ± 1.27 <sup>a</sup> (6.6-10.4)	9.3 ± 0.85 <sup>a</sup> (7.5-10.8)
GSH (nmol/mL)	11.01 ± 0.43 (10.56-12.10)	8.4 ± 1.37 <sup>a</sup> (5.8-9.9)	8.6 ± 0.89 <sup>a</sup> (6.8-10.2)
GSSG (nmol/mL)	0.38 ± 0.05 (0.26-0.44)	0.59 ± 0.14 <sup>a</sup> (0.48-0.88)	0.65 ± .15 <sup>a,b</sup> (0.48-0.96)
sP-selectin (ng/mL)	7.28 ± 1.85 (3.96-9.00)	13.2 ± 3.24 <sup>a</sup> (9.2-19.2)	15.5 ± 3.96 <sup>a</sup> (10.1-21.4)

<sup>a</sup> Values statistically significant compared with controls ( $p = 0.000$ ). Values in parentheses denote range. <sup>b</sup> The value was markedly higher compared with that in the patients with acute *T. gondii* infection ( $p < 0.038$ ).

<sup>[643]</sup>. IFN- $\gamma$  appeared to suppress expression of PAI-1 in endothelial cells<sup>[644]</sup>, and as PAI-1 antagonizes fibrin degradation, thereby promoting fibrin deposition, STAT1-mediated suppression of PAI-1 expression in endothelial cells. This may well account for the effects of IFN- $\gamma$  on fibrin deposition during infection<sup>[642]</sup>. In addition, a simultaneously increased IL-4 (an anti-inflammatory cytokine) during inflammation may suppress PAI-2 formation in stimulated human monocytes<sup>[641,645]</sup> suggesting that T<sub>H</sub>1 type immunity may locally up-regulate procoagulant activity, thereby protecting against its own destructive effects. Mullarky and his group<sup>[642]</sup> finally established that neither the pathogen burden nor hemorrhage was a primary regulator of fibrin levels. They emphasized that two T<sub>H</sub>1 type cytokines exerted dominant and opposite regulatory roles: IFN- $\gamma$  acting via STAT1 suppressed fibrin deposition, while TNF- $\alpha$  promoted fibrin deposition, especially through stimulation of PAI-1 production by endothelial cells and decreased blood fibrinolytic activity<sup>[646-648]</sup>. TNF- $\alpha$  also increased expression of procoagulant biomolecules and decreased expression of anticoagulant factors<sup>[649,650]</sup>, and/or suppressed fibrin degradation in human endothelial cells<sup>[647,648]</sup>. Moreover, studies showed that TNF- $\alpha$  may favor fibrin deposition by stimulating vascular wall permeability<sup>[651,652]</sup>, and it was reported that fibrin can upregulate expression of proinflammatory cytokines and chemokines in humans<sup>[653]</sup>. Thus, the vigorous activation of the host immune system can damage *T. gondii*-infected tissue while simultaneously limiting hemorrhage and promoting tissue repair through the deposition of protective fibrin<sup>[642]</sup>.

#### C. Infection with the parasite may be associated with RP and cryoglobulinemia

Several authors documented increasing blood viscosity by induction of serum cryoprecipitation, deposition of immune complexes, and arterial occlusion by thrombi caused by the procoagulant activity



of IFNs  $\alpha$ ,  $\beta$ , and  $\gamma$ <sup>[220,324,530,531,654]</sup>. It was suggested that clinical features of type I cryoglobulinemia (5-25% of cases with monoclonal immunoglobulin) are often related to blood hyperviscosity and thrombosis, and clinical symptoms, such as RP, digital ischemia, livedo reticularis, purpura, and various neurologic disturbances may be observed<sup>[324,655]</sup>.

It was reported that *T. gondii* infection associated with development of digital vasculitis, periarteritis nodosa, thromboangiitis obliterans (TO)<sup>[324]</sup>, and a number of autoimmune diseases manifesting with cryoglobulinemia<sup>[83]</sup>, had initially been presenting as PRP or SRP. For example, Mohokum et al<sup>[530]</sup> performed a meta-analysis of eight studies contributing data on 851 patients with SRP associated with TO and found a pooled prevalence of 28.1% (95% [CI] = 0.158, 0.423).

Shapira et al<sup>[83]</sup> studied the sera of 1514 patients with various autoimmune diseases for the prevalence of anti-*T. gondii* antibodies (ATA) IgG and IgM and serum autoantibodies. They found that serum IgG were positive in 42% of patients with autoimmune diseases vs. 29% of controls ( $p < 0.0001$ ). ATA IgG were associated with cryoglobulinemia ( $p < 0.0001$ ), antineutrophil cytoplasmic autoantibodies-associated vasculitides, SSc, and rheumatoid arthritis. ATA IgM were more prevalent in patients with SSc than in controls ( $p < 0.05$ )<sup>[83]</sup>. Cryoglobulinemia associated with *T. gondii* infection has also been reported in patients with SLE, Sjögren's syndrome, and vasculitis<sup>[324]</sup>. On the other hand, patients with hepatitis C and mixed cryoglobulinemia (IgG and IgM) were found to have markedly increased seroprevalence of anti-*T. gondii* IgG<sup>[324,656]</sup>. Although both these infections contribute to development of cryoglobulinemia these findings may well illustrate the puzzle of what was the first - chicken or the egg concerning the priority of infection, similarly like the concomitant *T. gondii* and viral infections reported in the children and adults manifesting with hand, foot and mouth disease in Henan province (China)<sup>[657,658]</sup>.

Finally, it should be noted that blood platelets provide important contribution to the thrombo-inflammatory response that affects hemostatic, immunomodulatory, and inflammatory activities in the host, because they adhere and aggregate to other platelets and to endothelial cells, leukocytes, and erythrocytes<sup>[659-662]</sup>. Endothelial activation biomarkers increased during infection are associated with a thrombotic state<sup>[662]</sup>. During activation, platelets can bind to the endothelium<sup>[661]</sup>, especially after damage due to microbial colonization<sup>[663]</sup>. Activated platelets can induce superoxide anion release by monocytes and neutrophils through P-selectin<sup>[664]</sup>. The interactions between platelets and innate immune cells promotes thrombosis, inflammation, and tissue damage, but they also regulate the resolution of inflammation, tissue repair, and wound healing<sup>[665]</sup>. It must however be emphasized that platelets play an important role in the host defense against *T. gondii* infection<sup>[253,254]</sup>.

## VII. PLASMA VOLUME EXPANDER HYDROXYETHYL STARCH (HES) IMPAIRS vWF RELEASE FROM ENDOTHELIAL CELLS. HES BINDING TO PLATELET SURFACE MAY DIMINISH HOST DEFENSE AGAINST *T. GONDII* INFECTION. DEGRADATION AND LYSIS OF TOXOPLASMA TACHYZOITES/PV<sub>s</sub> AND THE ACCUMULATED PROTEIN DEBRIS IN ENDOTHELIAL CELLS PROBABLY PARTICIPATE IN

## THE FORMATION OF LARGE vWF MULTIMERS AND DEVELOPMENT OF ACQUIRED vW SYNDROME

### A. HES (a colloidal synthetically modified polymer of amylopectin) administration may be associated with development of RP and reactivation of chronic latent *T. gondii* infection in the host

**A case history:** Bojinova et al<sup>[666]</sup> described a teenager who during the spine surgery lasting 8 hrs received several drugs routinely, and 0.5 L HES and 1 L Ringer's lactate infusions because of blood loss and negative fluid balance. The laboratory tests showed markedly decreased hematocrit and hemoglobin resulting in anemia. The plasma endothelin-1 (ET-1) concentration was increased (2.9 pg/mL, upper limit 2.5 pg/mL). Cold-provocation test showed blood flow cessation in one out of four left eye capillaries for 57 sec (norm = < 10 sec). Before admission, the patient complained of cold extremities, had migraine and headaches, low blood pressure, low body weight, and reversible skin blotches (red or white). After the operation he developed ocular hypoxia (reduced venous vasodilation in the disturbed left eye) and reduced arterial vasodilation in the uninvolved right eye). Eye fundus photograph performed 7 days after admission showed in the left eye disc pallor, constriction of the peripapillary arterial vessels, and hypopigmentation of the peripapillary choroids<sup>[666]</sup>. Careful analysis of the patient's past medical history and the obtained clinical and laboratory findings may suggest that the teenager suffered from undiagnosed reactivation of chronic latent toxoplasmosis: anemia<sup>[667,668]</sup>, increased ET-1<sup>[135]</sup>, spine surgery<sup>[669-671]</sup>, migraine and headaches<sup>[593,668,672,673]</sup>, low body weight<sup>[35,71,674]</sup>, skin blotches<sup>[675-677]</sup>, and ocular toxoplasmosis<sup>[678-680]</sup>. Moreover, it seems that the HES infusion probably triggered RP development (cold extremities and positive cold-provocation test of the eye capillaries). Moreover, the hypopigmentation in the teenager may be in line with the history of *incontinentia pigmenti* diagnosed shortly after birth in a 5-years-old girl with secondary RP<sup>[681]</sup>, and the harmful effects of *T. gondii* infection on retinal pigment epithelial cells<sup>[682,683]</sup>.

### B. HES accumulation in endothelial cells may affect their shape and function

HES solutions are widely used for hemodilution and plasma volume expansion. Nohe et al<sup>[18]</sup> documented accumulation of HES in human umbilical venous endothelial cells (HUVEC). They found that the fluorescein-conjugated HES 200/0.5 incubated with these cells was internalized in a dose- and time-dependent manner by pinocytosis into secondary lysosomes, and 50% of the formerly ingested HES molecules could not be eliminated. Interestingly, despite accumulation, HES did not attenuate the expression of E-selectin, ICAM-1 or VCAM-1 on TNF- $\alpha$ -activated HUVEC<sup>[684]</sup>. It must be noted that the treatment of human microvascular endothelial cells with HES resulted in a dose-dependent increase in 157-phosphorylated vasodilator-stimulated phosphoprotein, a protein responsible for controlling the geometry of actin-filaments<sup>[685]</sup>, and this can therefore affect shape and function of the host endothelial cells.

### C. HES increases endothelial binding of polymorphonuclear leukocytes (PMNs) which may enhance *T. gondii* dissemination in the host

Binding of activated PMNs to bovine aortic endothelial cells was found to be significantly increased by HES<sup>[686]</sup>. Inflammatory vascular injury has been shown to include an important role

for neutrophil-derived myeloperoxidase (MPO), which directly mediates biomolecule oxidation and catalytically biodegrades NO, thus impairing the vascular relaxation, eicosanoid-regulatory, cell adhesion, and anti-inflammatory actions of these reactive signaling species<sup>[687]</sup>. MPO from degranulation of activated PMNs avidly binds to the endothelium *in vitro* and *in vivo*. In the presence of HES, bovine aortic endothelial cells exposed to N-formyl-methionyl-leucyl-phenylalanine-activated PMNs showed significantly greater bound PMN and MPO activity (Table 15)<sup>[686]</sup>.

It must be emphasized that *T. gondii* can invade and multiply inside any nucleated cell type including epithelial cells and blood leukocytes<sup>[688,689]</sup>. Several studies indicated that DCs and monocyte/macrophages function as systemic parasite transporters during infection<sup>[74,689-691]</sup>. The parasite can be also transmitted from infected DC to NK cells<sup>[692]</sup>, and NK cells and T cells have been suggested to contribute to parasite dissemination via a sequestering mechanism<sup>[692,693]</sup>. Taking all these facts into consideration one cannot exclude that HES administration may, at least in part, favor infection with *T. gondii* and/or cause reinfection, especially in individuals with impaired innate and/or acquired immunity.

#### D. Binding of HES to platelet surface may diminish host defense during toxoplasmosis

Deusch et al<sup>[694]</sup> demonstrated extracellular binding of HES molecules to the platelet surface. The percentage of platelets binding fluorochrome-coupled HES was found to be increased in a concentration-dependent manner at clinically relevant levels of hemodilution<sup>[694,695]</sup>. It appeared that HES solutions impaired platelet function by reducing the availability of the fibrinogen glycoprotein IIb-IIIa receptor on the platelet surface<sup>[694-697]</sup>. Chemical properties of HES molecules such as the mean molecular weight and the extent of substitution<sup>[696,697]</sup> modulate their influence on platelets<sup>[695,698]</sup>. Nb. blood loss was found to be greater in cardiac surgical patients receiving high vs. middle molecular weight HES<sup>[699]</sup>. It was also suggested that the high concentration of calcium in the crystalloidal solvent in Hextend<sup>®</sup> may be responsible for the platelet-activating effect<sup>[695]</sup>. Although Gamsjager et al<sup>[700]</sup> excluded the interference of HES with calcium-dependent intracellular signal transduction pathways as a mechanism of HES-induced platelet dysfunction, it seems that this process may however take place because *T. gondii* tachyzoites increase their gliding motility and secretion of the micronemes in calcium-rich environment and drive host cell invasion and egress of the parasite<sup>[364,365,380]</sup>. This explanation may support the important role of calcium suggested by Deusch et al<sup>[695]</sup>, and the calculated by them approximately 16% degree of hemodilution after intravenous 10 ml/kg of 6% Hextend<sup>®</sup> (m.w. 670 kDa) administration in healthy volunteers probably also affected platelet-inhibiting and/or stimulating effects<sup>[695,701,702]</sup>.

Human platelets are cytotoxic to tachyzoites of *T. gondii* and adherence of these cells to the microbes and disruption of surface membranes, as well as cytoplasmic contents, were observed ultrastructurally<sup>[696]</sup>. Platelet to tachyzoites ratios as low as 1:3 were toxic to the pathogens with direct cell-cell contact critical for platelet-mediated cytotoxicity, and it appeared that release of thromboxane B<sub>2</sub> (TxB<sub>2</sub>) in stimulated platelets was responsible for this effect<sup>[696]</sup>. Toxoplasma-cidal activity was retained even in the TxB<sub>2</sub> synthetase-containing microsomal fractions of platelets disrupted by freezing and thawing<sup>[696]</sup>. In the Fischer rat model, a cytotoxic effect of tachyzoites mediated by platelets and IgE antibodies has been documented<sup>[278,703]</sup>. Moreover, platelet-derived growth factor (PDGF) impaired growth of the parasites within host cells and this action probably involved

**Table 15** Influence of human serum albumin (HSA) and HES on endothelial binding of MPO released by activated PMNs (acc. to Lang et al [686]; with own modifications).

Condition	MPO activity (nM x min <sup>-1</sup> x cell well <sup>-1</sup> )
Nonactivated PMNs	14.6 ± 3.2
Activated PMNs <sup>b</sup>	20.9 ± 4.7
HSA	19.3 ± 3.3
HES	34.6 ± 4.5 <sup>a,b</sup>

HES, hydroxyethyl starch; MPO, myeloperoxidase; PMNs, polymorphonuclear leukocytes. <sup>a</sup>  $p < 0.05$  vs. untreated controls. <sup>b</sup>  $p < 0.05$  vs. N-formyl-methionyl-leucyl-phenylalanine-activated PMNs.

the cyclooxygenase cycle and/or increased IL-6 generation<sup>[253]</sup>. In addition, it was demonstrated that PDGF modulated several responses of vascular smooth muscle cells, including a time- and concentration-dependent increase in the levels of heme oxygenase-1 mRNA and protein, CO synthesis, generation of ROS, and downregulated the induction of NO synthesis by IL-1 $\beta$  in these cells<sup>[704,705]</sup>.

#### E. HES impairs vWF release from endothelial cells. Protein debris resulting from degradation and lysis of *T. gondii* tachyzoites and PVs in endothelial cells probably participate in the formation of large vWF multimers and development of acquired vW syndrome (AvWS)

vWF was found to be adsorbed on HES macromolecules<sup>[706,707]</sup>, and cultured vascular endothelial cell exposure to HES showed dose-dependent inhibition of stimulated vWF release<sup>[708]</sup>, thus HES administration may accentuate von Willebrand disease (vWD).

AvWS is a rare bleeding disorder with laboratory findings similar to those for congenital vWD, but it occurs in 0.04-0.13% of the general population<sup>[709]</sup>. Interestingly, AvWS was observed usually in individuals with no personal or family history of bleeding diathesis<sup>[710,711]</sup>, and occurred regardless of age, most often in elderly people with some other underlying diseases<sup>[709]</sup>. It is a rare clinical entity in children with only 113 pediatric cases published in the literature between 1968 and 2009<sup>[712]</sup>, most frequently found in association with congenital or acquired heart defects<sup>[713,714]</sup>. AvWS was often reported in patients with lymphoproliferative, myeloproliferative and cardiovascular disorders, autoimmune disturbances (SLE, connective tissue diseases, hypothyroidism, diabetes), infections, uremia, and the use of various drugs, including HES solutions<sup>[710,711,715-717]</sup>. Several of these clinical entities have been associated with chronic latent *T. gondii* infection. It must be added that treatment with valproic acid in children was also connected with AvWS development and coagulation disturbances<sup>[718,719]</sup>, and otherwise it is known that the drug effectively inhibited *T. gondii* growth *in vitro*<sup>[390]</sup>.

It must be emphasized that *T. gondii* is a widespread pathogen which causes congenital and acquired toxoplasmosis<sup>[48,58]</sup> manifesting as a wide range of various diseases, including several of the abovementioned clinical entities<sup>[50,73,74,122,469]</sup>, and associated with development of AvWS. The frequency of infection with the parasite significantly increases in elderly subjects<sup>[51,61]</sup>. The pathogen secretory microneme proteins are essential for *T. gondii* tachyzoites motility and host cell invasion, and MIC2-M2AP (associated protein) is an abundant microneme complex critical for operating both these functions (MIC2 and M2AP are stored in micronemes as proforms)<sup>[720,721]</sup>. In addition, adhesion MIC is bridging the extracellular attachment of the host cells to the intracellular actin-myosin motor system responsible for cytoskeletal reorganization of the pathogen to drive invasion<sup>[720,721]</sup>. Importantly, with a vWF A domain and six thrombospondin repeat domains in its ectodomain, MIC2 connects to

the parasite actomyosin system through its cytoplasmic tail<sup>[720,722]</sup>.

These findings may at least in part explain the pathophysiological relationship between *T. gondii* infection and development of AvWS in the host, which leads to the transitory persistence of large vWF multimers. The heightened proteolysis of vWF in two patients with AvWS receiving ciprofloxacin or doxycyclin (the antibiotics with antitoxoplasmic and anti-inflammatory activity)<sup>[723-725]</sup> may support the presence of such link<sup>[726,727]</sup>. It must be noted that in mice infected with ME49 strain *T. gondii* the levels of ADAMTS13 (A Disintegrin-like And Metalloprotease with ThromboSpondin type 1 motif), caspase 3, 8, and 9, and TNFR1 expression were found to be increased significantly and kept enhanced for several days<sup>[728-730]</sup>. In addition, it was reported that *T. gondii* infection caused sustained neuroinflammation and microvascular dysfunction<sup>[129]</sup>. Endothelial cells can be stimulated to secrete long vWF strings by proinflammatory cytokines (TNF- $\alpha$ , IL-6, and IL-8)<sup>[731]</sup>. Otherwise it is known that vWF is synthesized in vascular endothelial cells and these cells also synthesize and release ADAMTS13<sup>[732,733]</sup>, which cleaves long vWF multimeric strings anchored to endothelial cells<sup>[734]</sup>. Acute or chronic latent *T. gondii* infections may therefore be associated with the increased consumption of ADAMTS13 and, for example, Mannucci et al<sup>[735]</sup> reported that patients with SLE had deficiency of the protease and increased level of IgG autoantibodies [83] that probably have been induced by the parasite<sup>[73]</sup>. Of note, it was found that inhibition of ADAMTS13 reduced vWF degradation also during high shear stress<sup>[733,736,737]</sup>, and otherwise it is known that shear forces enhance *T. gondii* tachyzoite motility on vascular endothelium<sup>[120]</sup>.

## VIII. INTRAVENOUS FUNDUS FLUORESCIN ANGIOGRAPHY (IFFA)-INDUCED RP MAY BE ASSOCIATED WITH *T. GONDII* INFECTION. LOW TEMPERATURE INCREASES BINDING OF FLUORESCIN TO HUMAN SERUM PROTEINS. THE FLUORESCIN-LABELED HORMONE PROLACTIN FORMS A MACROMOLECULE WITH SERUM ALBUMIN WHICH MAY DIMINISH HOST DEFENSE AGAINST THE PARASITE

### A. IFFA and development of RP

IFFA is a frequently performed and practically useful diagnostic procedure in ophthalmology clinic. In a recent review of literature adverse reactions to IFFA ranged from 0.083% to 21.69%, and were subdivided into mild (1.24-17.65%), moderate (0.2-6%), and severe (0.04-0.59%), including 1:100,000 to 1:220,000 deaths<sup>[738-740]</sup>. In one study, 9.72% of adverse reactions to IFFA were found in the patients who had this test performed for the first time<sup>[741]</sup>, and some risk factors associated with the occurrence of side effects with fluorescein included diabetes, arterial hypertension, and drug allergy history<sup>[741,742]</sup>.

In the literature, there are only few cases reported of RP which developed after IFFA<sup>[743-745]</sup>. Blaise et al<sup>[743]</sup> described a 71-yr-old man who was admitted because of decreased vision in the left eye, and one hour after IFA his nose and the two distal phalanges of each finger were found to be discolored. The patient was diagnosed as RP secondary to the stress associated with his visual problem, and his earlier history, clinical examination and laboratory results were

insignificant. However, one cannot exclude that this patients suffered from latent ocular toxoplasmosis because *T. gondii* serofrequency in persons older than 65 yrs was found to become systematically increased reaching almost 100%<sup>[61]</sup>. Recently, retinal RP was visualized in a 22-years-old woman with SLE retinopathy who had unaffected vision<sup>[745]</sup>. The fundus fluorescein angiogram following bolus injection of the dye showed a cyclical filling and emptying of the retinal vessels with no evident perfusion deficit<sup>[745]</sup>. In this case it must be noted that patients with SLE and other autoimmune diseases have significantly increased prevalence of anti-*Toxoplasma* antibodies compared with controls<sup>[73,554]</sup>.

### B. The dye and *T. gondii* infection

Results of the study by Rockey et al<sup>[746]</sup> may be in line with the commonly accepted opinion that RP attacks are precipitated in individuals exposed to cold and emotional stress because the binding of fluorescein to human serum proteins measured by equilibrium dialysis at 4°C showed that the association constant for the dye was almost twice higher than that obtained at 37°C (7.1  $\times$  10(3) vs. 3.7  $\times$  10(3)M<sup>-1</sup>, respectively). It was calculated that 93.5% of the total fluorescein would be bound by undiluted human serum proteins at 37°C<sup>[746]</sup>. This may favor formation of macromolecules with serum proteins, and for example Church et al<sup>[747]</sup> demonstrated that the fluorescein-labeled prolactin-bovine serum albumin complex was bridged through the fluorescein moiety and not the prolactin molecule. As a result, the hormone in this protein complex may not be effective in binding to *T. gondii* tachyzoites at least for a certain period of time, leading to its diminished antitoxoplasmic effect and/or increased pathogen reactivation in the host tissues<sup>[73,263,445]</sup>.

Norose et al<sup>[748]</sup> demonstrated that in tissues of WT C57BL/6 mice, *T. gondii* was detected in the following order: brain, retina, choroid, sclera, and optic nerve (ON) (the highest parasite load was found in the posterior retina). In IFN- $\gamma$  knockout (GKO) mice, the pathogen load was highest in the choroid and ON. It appeared that IFN- $\gamma$  regulated the *T. gondii* load and interconversion in the eye, and tachyzoites were present in GKO mice, whereas bradyzoites were observed in WT C57BL/6 mice. Interestingly, fluorescein showed dye leakage from the retinal capillaries of GKO mice, and therefore a toxoplasmic vasculitis model was established with these animals<sup>[745]</sup>. The conversion of tachyzoites into bradyzoites is a way for the parasite to establish a chronic and asymptomatic infection together with lifelong persistence in the host. The bradyzoites form tissue cysts in the retina, and Kim et al<sup>[749]</sup> reported that both ganglion cells (a type of retinal neurons) and Müller cells (predominant retinal glial cells) could harbor cysts and suggested that microglial cells play a role in chronic ocular toxoplasmosis.

## IX. LOW WEIGHT, PRIOR INVOLUNTARY WEIGHT LOSS, AND ANOREXIA NERVOSA (AN) ASSOCIATED WITH RP MAY BE CAUSED BY ACUTE AND CHRONIC *T. GONDII* INFECTION

### A. Development of RP and decreases of body weight

Approximately 95% of persons with an eating disorder are 12-25 years of age, and 90% are females. In the US, anorexia nervosa (AN) affects one out of 200 females (mild AN: BMI  $\geq$  17 kg/m<sup>2</sup>, moderate: 16-16.99, severe: 15-15.99, and extreme AN: < 15 kg/m<sup>2</sup>). This clinical entity is frequently accompanied by depression and/or other comorbid psychiatric disorders<sup>[750]</sup>.



In a population-based cohort study Abulle et al<sup>[35]</sup> analyzed the questionnaire completed by 93 935 participants and found that the prevalence of RP was 4.2%, being three-fold higher in women than in men (5.7% vs 2.1%,  $p < 0.001$ ). It appeared that low body weight and involuntary weight loss in both men and women were significantly associated with the presence of RP, and low-fat diet was linked with RP but only in women [OR 1.27 (1.15-1.44)], while low-calorie intake ( $< 1000$  kcal/day) was not found to be linked with RP<sup>[35]</sup>. Several case reports also showed that RP can concomitantly occur in various eating disorders<sup>[674,751]</sup>.

It is believed that in healthy individuals acrocyanosis is a rare, benign condition but in connection with AN the occurrence of this abnormality has been reported in up to 20-40% of unselected cases<sup>[751-753]</sup>. There is an increased cutaneous vasoreactivity to cold in AN<sup>[754]</sup>, and this entity can affect all organ systems, with gastrointestinal symptoms being frequently reported<sup>[755]</sup>. Interestingly, Deschner et al<sup>[756]</sup> described a 12-yrs-old girl diagnosed initially with an atypical eating disorder, which developed into AN over 2 years and celiac disease (CD). Her family history was positive for RP, vasculitis, and several autoimmune diseases, including hypothyroidism, celiac disease, depression, and ADHD in mother, father, brother, and other relatives. In a recent cohort based case-control study Marild et al<sup>[757]</sup> examined 18 000 Swedish women (median age 28 yrs) with a diagnosis of CD and found a higher incidence of AN in these participants as compared with matched controls. Importantly, they established that the incidence of AN was higher in patients with CD, but also that women diagnosed with CD were more likely to develop AN in the future<sup>[757]</sup>. Both diseases AN and CD can present with weight loss/growth issues, intentional nutritional restriction, and gastrointestinal and/or neurologic symptoms<sup>[758]</sup>. Moreover, children with CD may present initially with isolated anorexia and mood abnormalities<sup>[756,759]</sup>.

SLE, another autoimmune disease, frequently has neuropsychiatric involvement including affective disorders, psychosis, and cognitive dysfunction, and Toluany et al<sup>[80]</sup> suggested that development of AN in adolescents with SLE may be due to steroid-induced changes in weight and body shape. In six patients, the median age at onset of AN symptoms was 12.2 yrs and diagnosis of AN was established 1.4 yrs later. The median age at SLE diagnosis was 14.2 yrs with median time after onset of AN symptoms of 20 months (7.5-32 months). All patients had joint symptoms and a positive antinuclear antibody. The authors proposed that AN may be a novel presentation of neuropsychiatric SLE<sup>[80]</sup>. In other study<sup>[760]</sup>, it was well documented that the patients with early scleroderma and AN suffering from RP exhibited nailfold capillaroscopic findings typical of connective tissue diseases.

### B. AN/cachexia in animals and humans and *T. gondii* infection

Anorexia and depletion of fat stores are classic signatures of infection that play an important role in restricting systemic bacterial pathogen replication but can trigger a host-detrimental response during viral infection<sup>[761,762]</sup>. Cachexia, defined as the loss of 5% of lean body mass in six month, is distinct from starvation or malabsorption, and can be accompanied by anorexia, elevated proinflammatory cytokines (IL-1, IL-6 and TNF- $\alpha$ ), loss of fat and insulin resistance<sup>[763,764]</sup>. In industrialized countries (USA, Europe, and Japan) where the frequency of cachexia is well-documented, approximately 1% of the population are cachectic<sup>[765]</sup>.

Oral infection with *T. gondii* cause gastrointestinal tract TH1-type immunopathology in animals and humans<sup>[74,766,767]</sup>. Several studies documented that in mice per oral acute and chronic *T. gondii*

infection were associated with weight loss, hypermetabolism, chronic cachexia, progressive wasting syndrome, and sustained commensal gastrointestinal dysbiosis<sup>[69-71,74,764,768-770]</sup>. It was reported that *T. gondii* infection with Me49 strain was accompanied by hypermetabolism and weight loss in the acute phase lasting 2 weeks, and in the chronic phase of infection the animals showed either a resolution of hypermetabolism and partial weight recovery or persistent hypermetabolism, with stable weight loss. Hypermetabolism was associated with enhanced lipid oxidation dependent on IFN- $\gamma$ , and particularly linked with tissues rich in macrophages<sup>[69]</sup>. It was found that the hypermetabolic state persisted in animals during subsequent anorexia, whose onset coincided with elevated IL-2, and at the end of the acute phase of cachexia both anorexic and hypermetabolic states were associated with increased pro- and anti-inflammatory cytokine TNF- $\alpha$ , IL-1 $\beta$ , IL-2, IL-4, IL-5, IL-6, IL-10, and IFN- $\gamma$  levels<sup>[768]</sup>. In mice with chronic phase of *T. gondii* infection, a second immunological challenge with LPS (the major component of the outer membrane of Gram-negative bacteria) exacerbated hypermetabolic state associated with enhanced TNF- $\alpha$  and IL-10 (an anti-inflammatory cytokine) generation<sup>[769]</sup>.

Hatter et al<sup>[71]</sup> described a sustained cachexia phenotype in adult C57BL/6 mice following per oral *T. gondii* infection. *Toxoplasma* cachexia was characterized by a loss of 20% in body mass, including fat and muscle, transient anorexia and an acute elevation of proinflammatory cytokines IL-1, TNF- $\alpha$  and IL-6. They found that parasites replicates in the distal jejunum/proximal ileum throughout acute infection, inducing severe, regional inflammation. Small intestine pathology resolved few weeks post-infection but cachexia sustained<sup>[71]</sup>. This process was associated with loss of muscle mass and IL-1-dependent liver and skeletal muscle fibrosis. Animals deficient in the IL-1 receptor had more severe acute muscle wasting, adipocyte and hepatocyte necrosis, independent of parasite burden. A proinflammatory TH1-mediated immune response is necessary to restrict infection and eventually clear systemic parasitemia but the host remains infected for life with low titers of *T. gondii* predominantly in the bradyzoite cyst form in the brain, muscle and other tissues<sup>[764,771]</sup>. The innate immune cytokines TNF- $\alpha$ , IL-1 $\alpha$ , IL-6 and IFN- $\gamma$  also comprise an inflammatory signature frequently observed in cachectic patients<sup>[772]</sup>, and in rodent models, administration of this recombinant cytokine constellation was sufficient to induce muscle atrophy and/or cachexia<sup>[75,764]</sup>. It must be noticed that chronic, low-level inflammation with elevation of circulating IL-6 has been observed in certain disease states, as well as in many healthy elderly individuals, and Haddad et al<sup>[75]</sup> demonstrated that IL-6 infusion resulted in muscle atrophy characterized by a preferential loss of myofibrillar protein (-17%), probably due to the enhancement of *T. gondii* intracellular replication by IL-6 and interactions with IFN- $\gamma$  and TNF- $\alpha$ <sup>[76]</sup>.

It should be added that autistic women are overrepresented among patients with AN, and there has been an increasing interest in the overlap between autism and eating disorders, particularly AN, with some research on this issue being conducted especially in Europe<sup>[78,79,773,774]</sup>. Of note, *T. gondii* infection seems to play an important role in development of ASD<sup>[72,94,775-777]</sup>, and RP has been reported in a child with autism and ADHD, two entities significantly associated with the parasite<sup>[415,778]</sup>.

Lastly, Toluany et al<sup>[80]</sup> proposed that AN may be a novel presentation of neuropsychiatric SLE, and suggested that the development of AN in adolescents with SLE may be triggered by steroid treatment-induced changes in weight and body shape. This motion may be supported by the findings of Kang et al<sup>[779]</sup> because they established that in mice infected with *T. gondii*, two-weeks



treatment with dexamethasone induced a depression in T<sub>H1</sub> immune responses, that may be followed by an increment of parasites within the brain<sup>[780,781]</sup>. In addition, reactivation of cerebral toxoplasmosis was demonstrated after two weeks of the steroid administration, and this probably was associated with a promotion of type 2 cytokine generation<sup>[782-784]</sup>.

## X. HEARING DISTURBANCES IN INDIVIDUALS WITH RP AND HAND-ARM VIBRATION EXPOSURE MAY BE DUE TO *T. GONDII* INFECTION

### A. RP

Extensive and prolonged exposure to manual work involving the use of various vibrating power tools can lead to development of the hand-arm-vibration syndrome (HAVS, vibration white finger) associated with several vascular, neurological, and musculoskeletal disturbances frequently manifesting with RP triggered by cold<sup>[785-791]</sup>. HAVS was officially recognized as the most commonly prescribed industrial disease<sup>[792]</sup>.

The pathophysiological mechanisms underlying cold-induced RP reaction in general population have not been fully known so far<sup>[2]</sup>. It was believed that the response to vibration tools may represent an exaggerated vasoconstrictor  $\alpha_2$ -adrenoceptor reflex triggered by prolonged exposure to vibration, but abnormalities in the digital vessels, such as endothelial damage, thickening of the vascular wall, functional receptor changes, as well as generation of some vasoactive substances, including endothelins, thrombomodulin, thromboxane A<sub>2</sub>, immunologic factors, and changes in blood viscosity, also play a role in disease pathogenesis<sup>[791,793,794]</sup>.

Increased occurrence of RP, neurosensory injury and carpal tunnel syndrome (CTS) have been reported in workers with vibrating tools, including artists<sup>[794-796]</sup>. Basing on the 41 scientific articles published between 1978 and 2013, Nilsson et al<sup>[795]</sup> found that the prevalence of RP ranged from 0% to 53% in different studies, with an average of 22%, and the risk for RP was 4.56 (OR 95% CI 3.00 - 6.95). At equal exposures, neurosensory injury occurs with a 3-time factor shorter latency than RP. Workers who are exposed to hand-arm vibration have an increased risk of vascular and neurological diseases compared to non-vibration exposed individuals. The risk increase was approximately 4-5 fold. The corresponding risk of neurosensory injury was 7.4 and the equivalent of CTS - 2.9<sup>[795]</sup>. Guan et al<sup>[797]</sup> studied the risk factors of CTS in 1,512 Chinese outpatients aged 41-70 years with no other diseases which could cause numbness and 4,536 non-CTS outpatient controls. It was found that rheumatic disease, diabetes mellitus, hypothyroidism, and age were the main risk factors of this entity.

Musicians are also affected by HAVS and microvascular abnormalities may affect their health and performance ability. Three cases of RP have been reported so far in a slap bass player and two guitarists<sup>[796,798,799]</sup>. Sirufo et al<sup>[796]</sup> described a 30-year-old guitar player suffering of RP with cold-induced blanching and pain in his right hand fingers, which started from the middle and ring finger and spread to all the other fingers. The patient has been playing guitar for an average of 3 hrs a day since he was 10 years old. He was having problems in carrying out several everyday tasks, including a little impairment in his playing ability. Body cooling even in a warm environment and localized cold exposures were the main triggers for these symptoms. The disorder was unilateral for about 3 years, than it started involving the left hand too. Nailfold vascular capillaroscopic

images showed microvascular abnormalities characterized by lack of morphological homogeneity of capillaries, presence of enlarged and tortuous capillaries, ectasia of the efferent tract of the loops, local hemorrhages, and neoangiogenesis<sup>[796]</sup>. It should be noted that the resonant frequency of the human hand fingers is in the range of 150-300 Hz, and the vibration at frequencies above 100 Hz is better absorbed by the fingers and hands<sup>[796,799]</sup>.

The use of hand-held vibration tools may not only be associated with white fingers and RP but also with difficulties in hearing<sup>[787,790]</sup>. In a questionnaire sent to 12 606 participants aged 35-64 years Palmer et al<sup>[790]</sup> inquired about years of employment in noisy jobs, lifetime exposure to hand transmitted vibration (HTV), hearing difficulties and tinnitus, and a history of cold induced finger blanching. Among 8193 respondents were 1151 who reported finger blanching. It appeared that hearing difficulty was about twice as common in men and women who notified of finger blanching, including those who had never been importantly exposed to noise and in those never exposed to HTV<sup>[790]</sup>. On the other hand, Pettersson<sup>[787]</sup> analyzed 342 participants who had a confirmed noise-induced hearing loss formally accepted as the work-related disability. 84 men and 36 women specified if they had RP and also whether they used hand-held vibrating machines. Nearly 41% of them used such machines and 18% used them at least 2 hrs each workday. It was found that there were 23 men/6 women with RP, and 37% reported white fingers among those individuals who were exposed to HTV and 15% among those not exposed to such vibration<sup>[787]</sup>. This "discrepancy" is not surprised because the ubiquitous parasite *T. gondii* is widely distributed in general human population<sup>[50]</sup>.

### B. Auditory disorders and *T. gondii* infection

Toxoplasmosis has been associated with auditory disturbances when calcium deposits, similar to those found in the brains of children with congenital toxoplasmosis, were found in the spiral ligament and the cochlea<sup>[800]</sup>. Prenatal damage of the inner ear and hearing impairment in young children due to *T. gondii* infection is well documented<sup>[801-805]</sup>. Hearing loss was reported in about 20% of the congenital toxoplasmosis cases, especially in untreated children or those receiving two short treatments<sup>[801]</sup>. This clinical entity may cause sensorineural deficit and proper therapy of pregnant women and newborn babies improves prognosis<sup>[802,803,806]</sup>. Andrade et al<sup>[804]</sup> estimated hearing of the newborns with congenital toxoplasmosis (positive specific IgM) among 30 808 screened babies (97% of live births), 20 had the infection and 15 of them were asymptomatic at birth. Out of 19 children evaluated by hearing tests, 4 had sensorineural impairment<sup>[804]</sup>. In another two studies, Noorbakhsh and his group<sup>[802,803]</sup> analyzed the role of *T. gondii* infection in infants with sensorineural hearing loss (SNHL) because in various parts of Iran, the prevalence of antibodies against *T. gondii* ranged from 24 to 57.7%. They compared specific IgM and IgG antibodies measured by ELISA in 95 blood samples of infants with SNHL and 63 matched controls. It was found that IgM and IgG antibodies were present in 12 and 21.2% of SNHL children, respectively. Most children with increased IgG antibodies aged less than 1 year (maternal antibody), while IgM antibodies (acute infection) were more prevalent in the 3-5 years old group of children. Acute infection was significantly more frequent in the SNHL group, and IgG immunity was more common in the control group ( $p = 0.01$ ). Specific treatment administered during the first year of life resulted in a diminished occurrence of this complication<sup>[802,803]</sup>. Recently, Castro-Correa et al<sup>[805]</sup> in their review confirmed that there is an evidence of the association between hearing disorders and congenital toxoplasmosis characterized by

SNHL.

In older children and adults auditory disturbances may be also caused by *T. gondii* infection, e.g. Schlottmann et al<sup>[807]</sup> reported a 9-year-old boy who suffered from unilateral hearing loss and tinnitus. Microbial study showed a high toxoplasmosis titer of 1:102 400. The patient received treatment with pyrimethamine and sulphadiazine and although the antibody titer slightly decreased and the SNHL did not change markedly, the tinnitus disappeared. In another study, Katholm et al<sup>[808]</sup> described an 18-year-old woman with acute acquired toxoplasmosis who experienced sudden deafness and a loss of vestibular function first in the right ear and 3 months later also in the left. After specific treatment hearing was retrieved to a such degree that she was able to communicate with the help of hearing device and lip-reading. The authors believed that toxoplasmosis was the cause of the hearing disorders<sup>[808]</sup>.

In summary, it seems that *T. gondii* infection may be, at least in part, responsible for the hearing disturbances reported in HAVS. Rheumatic disease, diabetes mellitus, hypothyroidism, and age, the main risk factors of CTS<sup>[797]</sup>, have already been linked with the pathogen<sup>[73]</sup>. The association of autoimmune diseases and sudden SNHL was reported by Gross et al<sup>[809]</sup>. They found the prevalence of anti-heat shock protein-70, anticardiolipin, and anti-beta2-glycoprotein-1 autoantibodies in such patients, and otherwise it is known that these proteins are produced in infected animals<sup>[810]</sup> and in patients with autoimmune diseases and chronic latent *T. gondii* infection<sup>[73]</sup>.

## XI. VITAMIN D CONTRIBUTES TO HEALTH IMPROVEMENT IN BOTH PRP AND SRP BECAUSE IT EXERTS BENEFICIAL IMMUNE EFFECTS AND HAS ANTITOXOPLASMIC ACTIVITY

### A. Vitamin D levels and development of SRP

RP is frequently reported in patients with various autoimmune diseases, such as MCTD<sup>[186,812-814]</sup>, SSc<sup>[186,563,565]</sup>, Sjögren's syndrome<sup>[186,559,815]</sup>, migraine<sup>[586,587,815,816]</sup>, hypothyroidism<sup>[817-819]</sup>, and cardiovascular diseases<sup>[820,821]</sup>. RP in SSc is a typically the earliest clinical manifestation of this condition, with a lag period lasting several years or decades before skin and other manifestations emerge<sup>[812,822,823]</sup>.

Helou et al<sup>[824]</sup> studied if 8 weeks of oral vitamin D<sub>3</sub> supplementation (600,000 IU monthly, total 3 doses) contribute to self-judgment improvement in 53 patients with RP (42 patients were deficient in vitamin D). The participants answered on a visual analogue scale basis about their RP. After treatment, the authors found an increase of vitamin D blood concentration and RP self-estimated change for the better<sup>[824]</sup>.

Vitamin D exerts a pivotal role in infections due to its remarkable positive impact on both innate and adaptive immunity and on the suppression of the inflammatory processes. The link between systemic inflammation and vascular-specific inflammation from endothelial cells activation is well established<sup>[825]</sup>. Vitamin D may also prevent autoimmunity by stimulating naturally occurring regulatory T cells (Tregs)<sup>[826]</sup>. The active vitamin D hormone, 1,25(OH)<sub>2</sub>D<sub>3</sub>, can be produced in endothelial cells through activity of a specific endothelial  $\alpha$ -hydroxylase on circulating 25(OH)D<sub>3</sub>. Vitamin D acts through vitamin D receptor (VDR) present on the surface of antigen presenting cells, NK cells, as well as B and T lymphocytes exerting multiple immunomodulating effects<sup>[73,827-829]</sup>. A summary of

some immunoregulatory actions of vitamin D on immune system is presented in **Table 16**<sup>[827]</sup>.

Decreased VDRs expression leads to enhanced sensitivity of fibroblasts to TGF- $\beta$ , a central mediator of fibroblast activation, resulting in an enhanced production of extracellular matrix in SSc<sup>[847,848]</sup>. Nb. TGF- $\beta$  was reported to increase *in vitro* replication of *T. gondii* in retinal cells<sup>[849]</sup>, and elevated expression of TGF- $\beta$  in vitreous, retina and retinal pigment epithelium has been closely correlated with retinal fibrosis and choroidal neovascularization<sup>[846]</sup>. Low vitamin D status is associated with enhanced autoimmune response in healthy individuals, and increased risk of T<sub>H</sub>1 cytokines production-mediated development of both ADs and neurodegenerative disorders<sup>[850-853]</sup>.

Decreased vitamin D levels have been found in several ADs, including RA<sup>[854]</sup>, SLE<sup>[852,854-856]</sup>, SSc<sup>[823,857]</sup>, MCTD<sup>[813,858]</sup>, MS<sup>[859]</sup>, Sjögren's syndrome<sup>[860,861]</sup>, inflammatory bowel diseases<sup>[859]</sup>, diabetes mellitus<sup>[854]</sup>, autoimmune thyroid diseases<sup>[862-865]</sup>, migraine, and headache<sup>[866-868]</sup>. Vitamin D deficiency may also play a role in development of various clinical abnormalities (e.g. arterial stiffness, leukocytopenia) and perpetuation of these entities<sup>[813,823,856,861,869]</sup>. (Nb. arterial stiffness was improved by vitamin D supplementation in a dose-response manner in overweight African Americans with vitamin D deficiency<sup>[870]</sup>.) In addition, a single nucleotide polymorphism in the VDR region may have a role in the pathogenesis of some ADs, such as for example SSc, SLE, and diabetes<sup>[871,872]</sup>.

### B. Vitamin D and *T. gondii* infection

Vitamin D significantly decreased *in vitro* proliferation of *T. gondii* tachyzoites in macrophages (**Table 17**), increased NO production in these cells (**Table 18**), and diminished tissue pathology in animals infected with the pathogen (**Table 19**), probably by acting on tachyzoites in PV<sup>[513]</sup>. Interestingly, vitamin D may also be linked to the increased susceptibility and mortality of mice infected with the pathogen, probably because of downregulation of the T<sub>H</sub>1 type cytokine response<sup>[514]</sup>. Furthermore, the parasite inhibits NO production in different activated mouse macrophages cell lines by reduction of iNOS expression<sup>[873]</sup>.

In summary, these clinical and experimental data provide strong evidence that vitamin D exerts beneficial effects on innate and acquired immunity, as well as has antitoxoplasmic activity, and therefore it should find a firm place in the treatment of patients with PRP and SRP who frequently have vitamin D deficiency.

## XII. POTENTIAL COMORBIDITY OF CORONAVIRUS 19 (COVID-19; SARS-COV-2) PANDEMIC AND *T. GONDII* INFECTION MAY EVENTUALLY LEAD TO REACTIVATION OF CHRONIC LATENT TOXOPLASMOSIS, INVOLVEMENT OF INTERNAL ORGANS IN THE HOST, AND INCREASED PRODUCTION OF AUTOANTIBODIES EVEN WITHOUT SEVERE INITIAL DISEASE

The outbreak of COVID-19 severe acute respiratory syndrome was first identified in Wuhan, Hubei province, China, in December 2019<sup>[874]</sup>. Interestingly, similar abnormalities in the vWF production and secretion together with low ADAMTS-13 activity levels presented earlier in this work, have been also reported in the endothelial cells

exposed to COVID-19<sup>[875]</sup> and dengue virus NS1 infections<sup>[876,877]</sup>. The comorbidity of *T. gondii* infection with the hand, foot and mouth disease (HFMD) caused by Coxsackievirus A16 (CoxA16) and enterovirus 71 (EV71, one of the leading causes of child mortality in China) may be another good example<sup>[878,879]</sup>. Interestingly, the overall anti-*T. gondii* IgG antibody prevalence among HFMD patients was 12.46%, which was markedly higher than in control children without CoxA16, EV71 or other enterovirus infections (1.80%). In these children the highest seroprevalence of the pathogen was detected in critical patients (22.58 %), followed by severe cases (11.50%), and the lowest was found in children with mild manifestations (8.33%)<sup>[878]</sup>. On the other hand, the overall anti-*Toxoplasma* seropositivity studied by these authors four years later in primary school children aged 6 to 11 years, was 9.51% (233/2451), of which 7.59% (186/2451) had IgG positivity<sup>[879]</sup>. One cannot therefore exclude that a concomitant chronic latent *T. gondii* infection with viral infections may exacerbate their clinical course, especially that these three pathogens have special predilection to attack vascular endothelial cells.

COVID-19-infected patients often have neurologic, neurodegenerative and neuropsychiatric conditions<sup>[880-884]</sup>, (e.g. anosmia<sup>[881]</sup>), cardiovascular<sup>[885,886]</sup>, ocular<sup>[887-889]</sup> and neurological and musculoskeletal manifestations<sup>[890-892]</sup>. Similar clinical manifestations and clinical entities have been reported in *T. gondii*-infected individuals<sup>[50,51,61,73,484,893-900]</sup>. Frequently observed aging-related neuroinflammation complications during COVID-19 pandemic<sup>[901]</sup>

are in line with the markedly increased seroprevalence of *T. gondii* infection reported in persons aged 66-75 years<sup>[51,61]</sup>. Moreover, the cytokine storm diagnosed in some SARS-CoV2 patients<sup>[902]</sup> and/or multisystem inflammatory syndrome reported in the virus-infected children<sup>[903,904]</sup> may be enhanced by an overlapping inflammation associated with latent *T. gondii* infection. In children with this syndrome, serum cardiac and coagulation markers were considerably abnormal<sup>[642,648]</sup>. This suggestion is consistent with frequent heart diseases described during latent *T. gondii* infection<sup>[894,897,905]</sup>, and blood coagulation disorders due to the increased TNF- $\alpha$  and PAI-1 levels produced mainly in endothelial cells and probably associated with proinflammatory cytokine(s) produced during infection with that pathogen<sup>[617,642,646-648]</sup>. The above-presented reasoning may also serve as an explanation for the recent data that Oxford-AstraZeneca COVID-19 vaccine was linked to a number of thromboembolic events observed in vaccinated persons<sup>[906]</sup>. This is an important issue because COVID-19 infection was found to be associated with arterial and venous thrombotic complications<sup>[907]</sup> in both non-critically ill patients (2.5 % of 229 hospitalized individuals) and critically ill individuals (35.3% of 170 treated patients)<sup>[908]</sup>. Thus, all these individuals, especially elderly people with increased markers of blood clots (D-dimer), excessive inflammation (C-reactive protein), tissue damage (lactate dehydrogenase), and thrombocytopenia, perhaps should be carefully analyzed in this respect before administration of the vaccine against COVID-19<sup>[909,910]</sup>.

An increasing number of reports also identify obesity as a risk

**Table 16** Effects of 1,25-dihydroxyvitamin D<sub>3</sub> on innate immune system (acc. to Pelajo et al [827]; with own modification)

Vitamin D actions	Refs
Decreases the antigen-presenting activity of macrophages to lymphocytes	828, 830
Increases apoptosis induced by DCs and T lymphocytes - tolerance	831-833
Inhibits the maturation of monocytes into DCs	834, 835
Induces the activation of Tregs and NK T cells	836, 837
Inhibits Th1 type profile	783, 834, 835, 837
Decreases IL-2 and IFN- $\gamma$ synthesis	830, 834, 835, 838
Stimulates the Th2 type dominance	783, 834, 835, 837
Increases IL-4, IL-5, IL-10, and TGF- $\beta$ synthesis	830, 831, 834
Inhibits the synthesis of IL-12, IL-1, IL-6 and TNF- $\alpha$	828, 838-840
Inhibits B cell proliferation, plasma cell differentiation, and antibody production	830, 834, 835, 841, 842
Induces NOS in a human monocyte/macrophage cell line <sup>b</sup>	843

DCs, dendritic cells; NK, natural killer T cells; NOS, nitric oxide synthase; TGF- $\beta$ , transforming growth factor  $\beta$ ; Tregs, regulatory T cells; <sup>a</sup> This cytokine is well known for its immunosuppressive action on leukocyte cell lines [844], and may favor growth of *T. gondii* [845, 846]. <sup>b</sup> NO is an effector molecule of parasite killing [97].

**Table 17** Effect of vitamin D<sub>3</sub> and IFN- $\gamma$  on proliferation of *T. gondii* (RH strain) tachyzoites per infected peritoneal macrophage of BALB/c mice after incubation for 96 hrs in RPMI1640 cells culture (acc. to Ghaffarifar et al [512]; with own modification).

Experiment No.	Controls	Solvent <sup>a</sup>	Vit D <sub>3</sub> (1000 IU)	IFN- $\gamma$ (100 IU)	Vit D <sub>3</sub> (1000 IU) plus IFN- $\gamma$ (100 IU)
1	3.01±0.14	2.93±0.16	2.49±0.19 <sup>b</sup>	2.6±0.2 <sup>b</sup>	2.37±0.19 <sup>b</sup>
2	3.15±0.12	3.03±0.16	2.74±0.16	2.5±0.15 <sup>b</sup>	2.58±0.13 <sup>b</sup>
3	3.05±0.15	3.04±0.14	2.82±0.17	2.57±0.16 <sup>b</sup>	2.69±0.2 <sup>b</sup>
4	3.16±0.14	3.0±0.14	2.39±0.19 <sup>b</sup>	2.59±0.2 <sup>b</sup>	2.03±0.19 <sup>b</sup>

Numbers of tachyzoites are given as a mean±SD. <sup>a</sup> Ethanol 95. <sup>b</sup> Statistically significant differences compared with controls ( $p \leq 0.05$ ).

**Table 18** Effect of vitamin D<sub>3</sub> and IFN- $\gamma$  on NO production by peritoneal macrophages of BALB/c mice infected with *T. gondii* (RH strain) after incubation for 24 hrs in RPMI1640 cells culture (acc. to Ghaffarifar et al [512]; with own modification).

Experiment No.	Controls	Solvent <sup>a</sup>	Vit D <sub>3</sub> (1000 IU)	IFN- $\gamma$ (100 IU)	Vit D <sub>3</sub> (1000 IU) plus IFN- $\gamma$ (100 IU)
1	109±8.02	108.2±12.45	165±11.30 <sup>b</sup>	146±7.22 <sup>b</sup>	187.8±9.82 <sup>b</sup>
2	108±9.46	108.9±6.93	121.2±6.68	139.5±5.76 <sup>b</sup>	136.2±10.21 <sup>b</sup>
3	109.6±7.35	108.2±4.96	139±7.01 <sup>b</sup>	146±4.93 <sup>b</sup>	146.9±9.62 <sup>b</sup>
4	109±7.03	108.6±4.26	166±7.01 <sup>b</sup>	146.2±5.60 <sup>b</sup>	191.5±9.62 <sup>b</sup>

Values are given as mean±SD. <sup>a</sup> Ethanol 95. <sup>b</sup> Statistically significant results compared with controls ( $p \leq 0.05$ ). NO production was estimated as a nitrite release from infected macrophages ( $\mu$ M).

**Table 19** Effect of pretreatment with 1,25(OH)<sub>2</sub>D<sub>3</sub> (0.5  $\mu$ g/kg/2 days) on tissue pathology caused by *T. gondii* avirulent ME49 strain infection with 20 cysts administered intraperitoneally in BALB/c mice (acc. to Rajapakse et al[513]; with own modification).

Tissue	Pathology	No treatment	Treatment with Vit D <sub>3</sub>
Lung	Alveolar macrophages	1	0
	Inflammatory foci	2	1
Liver	Inflammatory foci	3	2
	Hemorrhage	2	0
	Mitosis	1	0
Small intestine	Inflammatory infiltrates	1	0
	Necrotic mucosal cells	2	1
Brain	Presence of the parasite	2	0
Spleen	Granulocytes	2	1

Histopathologic examination of the tissues was performed 7 days post inoculation. Numbers are based on severity of the lesions (0, no lesion; 1, mild; 2, slight; 3, moderate changes) and the total was divided the number of animals in the group. Also, *in vitro* studies with incubated intestinal epithelial cells showed a significant dose-dependent inhibition of intracellular *T. gondii* tachyzoites (RH strain, type I) proliferation at 10<sup>-7</sup> M of 1,25(OH)<sub>2</sub>D<sub>3</sub> concentration.



factor for COVID-19 related morbidity and mortality<sup>[911,912]</sup>, probably because despite impaired breathing efficiency in such individuals, they frequently have low-grade inflammation and immune activation due to the concomitant *T. gondii* infection<sup>[81,82]</sup>. It must be added that arterial blood oxygen desaturation characteristic for severely ill patients may trigger reactivation of cerebral toxoplasmosis (hypoxia-inducing factor 1 is important for the parasite's growth and survival), enhances expression of PAI-1, finally leading to blood hypercoagulability and paradoxical microembolism<sup>[913]</sup>.

Interestingly, there is an increasing evidence suggesting induction of immune responses to self-antigens generated during acute, severe SARS-CoV-2 infection with autoimmune prone B cell hyperactivation, as well as the preponderance and then persistence for few months of increased levels of several different IgG autoantibodies among convalescent individuals even without severe initial disease<sup>[914,915]</sup>. Importantly, autoantibodies against type I IFNs in patients with life-threatening COVID-19<sup>[916]</sup>, as well as prothrombotic autoantibodies have also been demonstrated in patients hospitalized from SARS-CoV-2<sup>[917]</sup>. Moreover, inborn errors of type I IFNs immunity were found in some patients with life-threatening infection<sup>[918]</sup>. All these findings are in a good agreement with the reports on possible critical role of *T. gondii* infection in patients with several autoimmune diseases<sup>[73,83]</sup>, abundance of antigens generated in the host after reactivation of the pathogen<sup>[100]</sup>, and the fact that approximately 30-50% of human global population is infected with the parasite<sup>[50]</sup>.

Several studies provided evidence that the use of CCBs, such as amlodipine and nifedipine, was associated with markedly lower case fatality rates (14.6% vs 50%,  $p < 0.01$ ), and lower rates of mechanical ventilation (4.2% vs 39%,  $p < 0.01$ ) during SARSCoV-2 infection<sup>[919-921]</sup>. It was found that amlodipine had significant antiviral effects against SARS-CoV-2 in Vero E6 green monkey cells<sup>[920]</sup>. Also Straus et al<sup>[922]</sup> demonstrated in Vero E6 cells and in epithelial kidney cells that amlodipine, nifedipine and felodipine limited the growth of SARS-CoV-2. Moreover, it was reported that amlodipine significantly reduced levels of viral transcription in stem cell-derived pancreatic organoids, and also caused selective differential expression of IFNs type 1 pathway signaling genes, which play central roles in coronavirus-host interactions<sup>[919,923]</sup>.

It must be noted that hypocalcemia was reported in 60% or more of patients at hospital admission<sup>[924-926]</sup>, and severe hypocalcemia has been strongly positively associated with COVID-19 infection severity and a worse outcome in such patients<sup>[924,925,927-930]</sup>. [Nb. earlier studies reported that  $Ca^{2+}$  played a central role also in other viral infectious and replicative mechanisms<sup>[919,924]</sup>. Individuals with hypocalcemia had significantly lower hemoglobin, hematocrit and red blood cell count (all  $p < 0.01$ )<sup>[927]</sup>, leukocytopenia and thrombocytopenia<sup>[929]</sup>, and higher circulating IL-6 levels<sup>[930]</sup>. Moreover, treatment with glucocorticoids increased the risk of progression from not severe to severe clinical state<sup>[929]</sup>. All these abnormalities are in line with similar disturbances observed in patients with acute and chronic latent *T. gondii* infection described in this work, as well as with hypocalcemia found in women with toxoplasmosis and repeated abortion<sup>[931,932]</sup>, and in children with autism<sup>[94,933]</sup>.

The effectiveness of amlodipine, nifedipine and other CCBs in SARSCoV-2 infection, and on the other hand, positive associations of marked hypocalcemia with mortality, have been sending opposing signals to clinicians, especially that a considerable evidence supports the idea of Crespi and Alcock<sup>[919]</sup> that hypocalcemia may reflect a host defense and therefore requires not too precise calcium supplementation in such patients. Interestingly, a significantly

decreased serum calcium level has also been found even in patients with non-severe SARS-CoV-2 infection, and Pal et al<sup>[934]</sup> suggested that this abnormality may be intrinsic to the disease. These two fine theories are well in line with my argumentation concerning the acute and chronic latent *T. gondii* infection in humans because the parasite requires a lot of  $Ca^{2+}$  for its many endogenous bioprocesses necessary to survive in the host, including microneme protein secretion during invasion of host cells (preferentially endothelial cells), gliding motility<sup>[132-134,332,342,361,379-382]</sup>, calcium signaling, intracellular growth, replication, and lytic cycle<sup>[217,365,366,383,385,386]</sup>.

SARS-CoV-2 infection may cause a various degree of liver damage in 14-53% of affected individuals, especially in those with gastrointestinal symptoms and underlying chronic hepatic disease<sup>[935-937]</sup>. In one study, Xu et al<sup>[938]</sup> reported that moderate microvesicular steatosis and mild lobular and portal activity were detected in the postmortem liver biopsy of a patient with COVID-19, and the authors suggested that either SARS-CoV-2 infection or other factor(s) may be responsible for the liver injury. In another study, hepatocyte degeneration, focal necrosis, and cholestasis of cholangioles have been found<sup>[939]</sup>. A meta-analysis of such patients described three main abnormal processes: hepatocellular injury, cholestasis, and hepatocellular dysfunction<sup>[940,941]</sup>. These findings may be in line with several histopathologic abnormalities reported in patients with acute and chronic latent *T. gondii* infection<sup>[942,943]</sup>. The most common pre-existing non-alcoholic fatty liver disease having more severe clinical course in patients with COVID-19 strongly supports these data<sup>[943a]</sup>.

Recently, several adjunctive treatment options for SARS-CoV-2-associated neuro-psychiatric manifestations have been suggested because many proinflammatory cytokines, such as IL-2, IL-6, IL-7, IL-10, IL-18, IFN- $\gamma$ , TNF- $\alpha$  were positively associated with symptom severity, with IL-6 and TNF- $\alpha$  levels acting as predictors of disease severity and survival rates of infected patients<sup>[944]</sup>. Moreover, various medications have been proposed to be included into such therapeutic anti-COVID-19 armamentarium, including antibiotics, antipsychotics, antidepressants (e.g. calcium channel blockers), tryptophan/kynurenine pathway modulators, and  $\alpha_2$ -adrenergic receptor modulators<sup>[944-946]</sup>, and many of them have antitoxoplasmic activity. Moreover, some authors administer orally or intravenously dexamethasone to reduce rapidly developing inflammation, especially during proinflammatory cytokine storm<sup>[935,947,948]</sup>. Despite many beneficial anti-inflammatory and immune modulating actions of corticosteroids it seems however that treatment with these preparations in COVID-19 patients should be carefully considered because they may increase growth rate of *T. gondii* tachyzoites and inhibit the expression of iNOS in macrophages<sup>[949,950]</sup>, impair phagocytosis and intracellular killing of different pathogens<sup>[951,952]</sup>, and augment parasite load in the brain, and/or cause reactivation of toxoplasmosis<sup>[953,954]</sup>.

It must be emphasized that COVID-19 infection has been also associated with development of RP<sup>[955-957]</sup>, and positive nailfold capillaroscopy findings in such patients documented microvascular involvement<sup>[958]</sup>. Moreover, some reports suggested that RP may develop in visceral organs involving heart, lung, and kidneys. For example, Yamashita et al<sup>[959]</sup> described a patient with changes similar to RP observed on colonoscopy and it was suggested that RP as a systemic disorder may affect also several body organs in addition to fingers and toes (e.g. pulmonary RP?<sup>[960]</sup>). Finally, severe acute respiratory syndrome reported in some individuals with coronavirus disease may be consistent with the airborne infections associated with environmental *T. gondii* oocysts burden in the soil, water and cat

feces<sup>[65,961-968]</sup>, probably intensified by changes in global climate (e.g. rising temperature, forest cutting, water shortage).

All these data strongly suggest that SARS-CoV-2 may activate acute and/or chronic latent *T. gondii* infection and lead to worsening of clinical course in some patients with this undiagnosed comorbidity.

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