EXPERT REVIEW OF ANTI-INFECTIVE THERAPY, 2018
https://doi.org/10.1080/14787210.2018.1417838

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EDITORIAL

Is there a relation between the manipulative activity of *Toxoplasma* and personalized medicine?

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ARTICLE HISTORY Received 5 October 2017; accepted 12 December 2017

KEYWORDS Toxoplasmosis; Rhesus factor; blood group; personalized medicine; parasite; infection; allergy; immunity; manipulation hypothesis

The prevalence of infection with the protozoan parasite *Toxoplasma gondii* varies between 20% and 80% in different countries, depending on the climate, cooking and eating habits, hygienic standards, and demography of a given country [1]. After a short phase of acute infection, reminiscent of a common viral or bacterial disease and only rarely correctly diagnosed, the disease spontaneously proceeds into its latent phase in most immunocompetent subjects. The latent form of the *Toxoplasma* infection is probably lifelong and therefore its prevalence increases with age. Most likely, after the age of 65 more than 50% inhabitants of our planet are already infected. Latent *Toxoplasma* infection is characterized by the presence of anamnestic immunoglobulins class G(IgG) antibodies in blood and so-called tissue cysts in the brain, muscles, and other organs of infected hosts. In these cysts, a slowly dividing form of the parasites, the bradyzoites, waits for the transmission to the stomach of the definitive host of *Toxoplasma*, which is any species of feline predator. Only within cats can the parasite reproduce sexually and produce oocysts, which can stay viable in soil for years. After ingestion these oocysts can infect any species of warm-blooded animals, including humans [2]. To increase the chance of trophic transmission from the intermediate host into the intestine of cats, *Toxoplasma* manipulates the behavior of infected hosts. Infected mice and rats have prolonged reaction times [3], impaired ability to recognize novel stimuli [4], and express the so-called 'fatal attraction phenomenon' [5,6]. Noninfected rodents avoid places where they smell cats while after infection they prefer to stay in such places. The mechanisms of this manipulation activity probably include the increase of testosterone in infected males, the increased synthesis of dopamine and kynurenic acid, and the hypomethylation of regulation regions of certain genes in the medial amygdala [7]. Practically all changes described in the infected animals, including the analogy of the fatal attraction [8], have also been observed in infected humans. Certain physiological changes, for example the increased concentration of dopamine in specific regions of the brain, probably have serious clinical impacts, namely an increase in the risk of schizophrenia in genetically predisposed subjects, see [9]. The increased concentration of kynurenic acid (and decreased level of tryptophan) could be the reason for higher risk of suicides [10] and the prolongation of reaction times could explain the 2.6 times higher risk of traffic accidents in the infected subjects [11].

The *Toxoplasma* infection-associated behavioral changes have been widely studied in the course of the past 20 years. However, the spectrum of phenotypic changes induced by parasites, including *Toxoplasma*, in their hosts is much broader. The main battlefield of the parasite–host conflict is the immune system of hosts. The main interest of the host is to tune up its immune system in a way that either helps to eliminate the parasites or at least slows down the progress of the infection. The main interest of the parasite is to avoid all this by means of immunosuppression or, preferably, by specific immunomodulation (the parasite should keep its host resistant against other pathogens). Therefore, our phenotype, including the status of our immune system, is not just the product of activities of our genes but also of activities of our parasites' genes. These two groups of genes are coadapted for the never-ending struggle between host and parasites. This fact could have rather interesting impacts on our individual lives as well as on public health. By increasing our hygienic standards, we nearly eradicated helminth infections in a large part of developed world. However, our immune system is adapted to the presence of these symbionts in our intestine and on their immunomodulating activity, which downregulates the cellular arm of immunity and specifically modulates the humoral arm of immunity [12]. Absence of this immunomodulating activity in modern helminth-free humans causes a shifting balance between various components of cellular and humoral immunity from its optimum, and this is in turn probably the primary cause of a dramatic increase of the incidence of allergic disorders in the developed world [13]. Not only helminth but also *Toxoplasma* has been shown to express a protective effect against allergies [14]. Therefore, the current decrease of the prevalence of *Toxoplasma* infection in many European countries and in the USA (about 1% per year in the last 20 years) could have some undesirable side effects.

Toxoplasma has strong impacts on the activity of the immune system of its hosts. Infected mice in the latent phase infection exhibit temporarily increased production of

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interleukin (IL)-12 and decreased production of IL-10. They also exhibit a decreased production of IL-2 and nitric oxide and a decreased proliferation reaction (synthesis of DNA that reflects activity of T-lymphocytes) in the mixed lymphocyte culture [15]. Probably, some of these changes represent direct effects of parasite immunomodulating activities (e.g. the inhibition of the proliferation reaction) and some represent the (unsuccessful or only partly successful) reaction of the host organisms on these activities (e.g. the increase of IL-12). Differences in the status of the immune system can also be observed between humans with and without latent *Toxoplasma* infection. However, the nature of the changes differs between men and women [16]. Men with latent *Toxoplasma* infection had decreased while women increased leukocyte, natural killer (NK)-cell and monocyte counts when compared to controls. The B-cell counts were reduced in both *Toxoplasma*-positive men and women. It is not clear whether these differences are caused by the manipulation activity of *Toxoplasma* or whether they represent the result of various adaptive or maladaptive reactions of the human immune system on the chronic infection [17].

The physiological differences, including differences in the activity of various components of the immune system, between *Toxoplasma*-infected and *Toxoplasma*-free subjects probably have large practical consequences. The infected subjects have a different, mostly increased, incidence of many diseases. A WHO data-based ecological study performed on a set of 88 countries showed that the specific disease burden of 23 of 128 analyzed diseases and disease categories on the WHO list showed correlations (18 positive, 5 negative) with the prevalence of *Toxoplasma* infection in a particular country. Another 12 diseases showed positive trends ($p > 0.1$) [18]. Similarly, a cross-sectional study performed on the cohort of 1486 volunteers showed that 333 infected subjects scored significantly worse than 1153 controls in 28 of 29 health-related variables and they reported higher rates of 77 on the list of 134 disorders reported by at least 10 participants of the study [19]. *Toxoplasma*-infected and *Toxoplasma*-free subjects differ not only in the incidence of particular disorders but also in their form. For example, only *Toxoplasma*-infected schizophrenia patients express typical changes in brain morphology, namely a decrease of gray matter density in certain areas of the brain [20]. Also, *Toxoplasma*-infected schizophrenia patients have more serious positive symptoms of the disease (hallucinations and delusions) and are hospitalized for a longer time [21], and have a 17 times higher probability of having a continuous form of schizophrenia than the *Toxoplasma*-free patients [22]. Interestingly, the people with blood group Rh plus, especially the Rh-positive heterozygotes, are more resistant to negative effects of *Toxoplasma* infection [23]. Some of these effects can be observed only in Rh-negative subjects [24]. It is not yet clear whether the Rh-positivity plays a role only in the protection against negative effects of *Toxoplasma* infection or against other environmental and genetic factors too. However, empirical data seem to support the latter possibility [25].

The serendipitous discoveries achieved during the studies of the manipulative activity of *Toxoplasma* suggest that the Earth is currently populated by two types of humans who differ by the incidence and course of many diseases and disorders. About one-third of people are infected with *Toxoplasma* and express a different, mostly higher, probability of certain diseases and different prognoses of certain diseases than the other two-thirds of population. This fact should be taken into consideration not only when searching for diagnoses of certain disorders but also when searching for the optimal method of treatment. Currently, there are no official recommendations available. It has already been suggested that infected schizophrenia patients should preferentially be treated with such antipsychotic drugs that are known to also inhibit the growth of *T. gondii* infection [26]. Experienced clinicians know that, statistically, different methods of treatment of the same disorder work better in men than in women or in younger rather than older patients. Possibly, it is the time to begin also seeking the optimum treatment for *Toxoplasma*-infected and *Toxoplasma*-free subjects, for both Rh-negative and Rh-positive subjects and for subjects with different combinations of these (and other) traits. Personalized medicine has been knocking on the door for many years. It is not necessary to wait for some dramatic transformative headway in applied genomics. Medicine can be personalized step by step by using standard methods and already available knowledge.

Funding

The paper was not funded.

Declaration of interest

J Flegr was supported by a grant from Czech Science Foundation P407/16/20958. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Pappas G, Roussos N, Falagas ME. Toxoplasmosis snapshots: global status of *Toxoplasma gondii* seroprevalence and implications for pregnancy and congenital toxoplasmosis. Int J Parasitol. 2009;39:1385–1394.
2. Tenter AM, Heckeroth AR, Weiss LM. *Toxoplasma gondii*: from animals to humans. Int J Parasitol. 2000;30(12–13):1217–1258.
3. Hrdá S, Votýpka J, Kodym P, et al. Transient nature of *Toxoplasma gondii*-induced behavioral changes in mice. J Parasitol. 2000;86(4):657–663.
4. Hodková H, Kodym P, Flegr J. Poorer results of mice with latent toxoplasmosis in learning tests: impaired learning processes or the novelty discrimination mechanism? Parasitology. 2007;134:1329–1337.
5. Berdoy M, Webster JP, Macdonald DW. Fatal attraction in rats infected with *Toxoplasma gondii*. Proc R Soc Biol Sci Ser B. 2000;267(1452):1591–1594.
6. Vyas A, Kim S-K, Giacomini N, et al. Behavioral changes induced by *Toxoplasma* infection of rodents are highly specific to aversion of cat odors. Proc Natl Acad Sci USA. 2007;104:6442–6447.

7. Dass SAH, Vyas A. *Toxoplasma gondii* infection reduces predator aversion in rats through epigenetic modulation in the host medial amygdala. Mol Ecol. 2014;23(24):6114–6122.
8. Flegr J, Lenochová P, Hodný Z, et al. Fatal attraction phenomenon in humans: cat odour attractiveness increased for *Toxoplasma*-infected men while decreased for infected women. PLoS Neglect Trop D. 2011;5(11):e1389.
9. Flegr J. Schizophrenia and *Toxoplasma gondii*: an undervalued association? Expert Rev Anti Infect Ther. 2015;13(7):817–820.
10. Ling VJ, Lester D, Mortensen PB, et al. *Toxoplasma gondii* seropositivity and suicide rates in women. J Nerv Ment Dis. 2011;199:440–444.
11. Flegr J, Havlíček J, Kodym P, et al. Increased risk of traffic accidents in subjects with latent toxoplasmosis: a retrospective case-control study. BMC Infect Dis. 2002;2:art–11.
12. McSorley HJ, Maizels RM. Helminth infections and host immune regulation. Clin Microbiol Rev. 2012;25(4):585–608.
13. Bell RG. IgE, allergies and helminth parasites: a new perspective on an old conundrum. Immunol Cell Biol. 1996;74:337–345.
14. Fenoy IM, Chiurazzi R, Sánchez VR, et al. *Toxoplasma gondii* infection induces suppression in a mouse model of allergic airway inflammation. PLoS One. 2012;7(8). DOI:10.1371/journal.pone.0043420
15. Kaňková S, Holáň V, Zajícová A, et al. Modulation of immunity in mice with latent toxoplasmosis—the experimental support for the immunosuppression hypothesis of *Toxoplasma*-induced changes in reproduction of mice and humans. Parasitol Res. 2010;107:1421–1427.
16. Flegr J, Stříž I. Potential immunomodulatory effects of latent toxoplasmosis in humans. BMC Infect Dis. 2011;11:274.
17. Kamerkar S, Davis PH. *Toxoplasma* on the brain: understanding host-pathogen interactions in chronic CNS infection. J Parasitol Res. 2012;2012:1–10.
18. Flegr J, Prandota J, Sovickova M, et al. Toxoplasmosis – a global threat. Correlation of latent toxoplasmosis with specific disease burden in a set of 88 countries. PLoS One. 2014;9(3). DOI:10.1371/journal.pone.0090203

•• **An ecological study indicates that prevalence of *Toxoplasma* infection positively correlates with incidence and morbidity of many diseases, including cardiovascular diseases and some forms of cancer. The study shows that difference in prevalences of *Toxoplasma* infection between European countries can explain 23% between-countries variability in the total disease burden.**

19. Flegr J, Escudero DQ. Impaired health status and increased incidence of diseases in *Toxoplasma*-seropositive subjects – an explorative cross-sectional study. Parasitology. 2017;143:1974–1989.

• **A cross-sectional cohort study performed on 1500 volunteers indicates that *Toxoplasma* seropositivity positively correlates with incidence of many diseases and with significantly worse health statuses.**

20. Horacek J, Flegr J, Tintera J, et al. Latent toxoplasmosis reduces gray matter density in schizophrenia but not in controls: voxel-based-morphometry (VBM) study. World J Biol Psychiatry. 2012;13:501–509.
21. Holub D, Flegr J, Dragomirecká E, et al. Differences in onset of disease and severity of psychopathology between toxoplasmosis-related and toxoplasmosis-unrelated schizophrenia. Acta Psychiatr Scand. 2013;127:227–238.
22. Celik T, Kartalci S, Aytas O, et al. Association between latent toxoplasmosis and clinical course of schizophrenia – continuous course of the disease is characteristic for *Toxoplasma gondii*-infected patients. Folia Parasitol. 2015;62.
23. Novotná M, Havlíček J, Smith AP, et al. *Toxoplasma* and reaction time: role of toxoplasmosis in the origin, preservation and geographical distribution of Rh blood group polymorphism. Parasitology. 2008;135:1253–1261.

•• **The first study shows that Rh positive heterozygotes are resistant to certain negative effects of latent *Toxoplasma* infection. This demonstration of the heterozygote advantage provided the solution of an old enigma of coexistence of Rh-negative and Rh-positive subjects in human populations.**

24. Kaňková Š, Šulc J, Flegr J. Increased pregnancy weight gain in women with latent toxoplasmosis and RhD-positivity protection against this effect. Parasitology. 2010;137:1773–1779.
25. Flegr J, Preiss M, Klose J. Toxoplasmosis-associated difference in intelligence and personality in men depends on their Rhesus blood group but not ABO blood group. PLoS One. 2013;8(4):e61272.
26. Goodwin DG, Strobl JS, Lindsay DS. Evaluation of five antischizophrenic agents against *Toxoplasma gondii* in human cell cultures. J Parasitol. 2011;97:148–151.

• **The study suggests that different kinds of antipsychotic drugs should be used for treatment of schizophrenia in *Toxoplasma*-infected and *Toxoplasma*-free patients.**