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

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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
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.

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References

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


**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.**


- 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.


- 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.


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