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Review

Mental Health Disorders Associated with Bartonella spp. and Toxoplasma gondii

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ABSTRACT

Both *Bartonella* spp. and *Toxoplasma gondii* (*T. gondii*) can infect humans through vectors such as ticks, flies, and cats. Diseases caused by both microorganisms can be treated with combined antibiotics, but if not treated, situations that can reach fatal conditions. Recent studies have shown that these microorganisms can additionally affect the central nervous system, causing major depression to severe psychosis. What we generally observe is that although most patients do not have a direct psychiatric disorders in the first place, these pathogens are perceived as such since they were not initially taken into account, indicating that the effects of these microorganisms cannot be underestimated. In this review, we discussed mostly the psychiatric conditions caused by *Bartonella* spp. and *T. gondii*.

Keywords: *Bartonella* spp., prognosis, psychiatric disorders, *Toxoplasma gondii*

Bartonella spp. is a gram-negative, facultative intracellular parasite microorganism that is the only genus in the *Bartonellaceae* family.[1-3] They can be transmitted to humans by ticks, fleas, sand flies, mosquitoes, and cat-like mammalian.[4] *Bartonella* spp. is responsible for many infectious diseases occurring worldwide and most of the infections that can be transmitted to humans are caused by *Bartonella henselae*, *Bartonella quintana* and *Bartonella bacilliformis*. In addition, infections caused by *Bartonella* spp. bacteria can be fatal if untreated.[5]

Another microorganism, *Toxoplasma gondii* (*T. gondii*), is from the phylum Apicomplexa. It is an obligate intracellular parasite protozoan and its infection causes toxoplasmosis. Usually, they are using Felidae as a host.[6-8] Infection is often caused by oocysts shed by cats that are contaminated with food or water. Also, undercooked meat and which is contain cysts meats can cause infection.[9] Serological methods can detect infections caused by these two microorganisms and they can be treated with various antibiotics. However, in this review, we primarily focus on what kind of psychiatric phenomena these pathogens cause by affecting the central nervous system (CNS), rather than their known effects.

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Neurological Disorders and *Bartonella* spp.

Bartonella spp. has been reported to be associated with CNS symptoms. In a study investigating the association of *Bartonella* spp. bacteria with schizophrenia, rate of having *Bartonella* spp. infection among participants with schizophrenia was higher than in healthy subjects, and samples from volunteers were confirmed by polymerase chain reaction analysis.[10]

In a case report, a boy after showing some psychosis-like symptoms was investigated which diseases could cause the source of the condition. As mentioned in this report, the patient goes through various consultation phases, and mostly he is thought to have a psychiatric disorders and his treatment is continued for a long time with antipsychiatric drugs. Afterward, there was no progress despite repeated hospitalizations, and increasing conditions such as loss of consciousness, schizophrenia, delusions, and paranoia, after the situation it is analyzed in more detail and then as a result of the studies, he is diagnosed with Pediatric Acute-onset

Neuropsychiatric Syndrome.[11] However, a result of the serological and microbiological tests, revealed the patient has neurobartonellosis.

After bacterial strain-specific antimicrobial combinations and antibiotic drugs, the patient recovered, this research has shown that the *Bartonella* spp. how can affect the CNS.[11]

The point that should not be forgotten here is that such infections may not always have the same effect on every patient, the reason for this is the genetic structure of each patient and the physiological levels that may is not the same for becoming this cognitive state.[12-14] Variables such as familial predisposition, physiological parameters, and immune system can determine the rate of infection affecting the CNS.[15,16] This study shows that the conditions that are considered to be directly psychiatric cases might be also connected with microorganism origins, in addition, the microbiological examination should be done first to confirm the possibility of a pathogen origin and finally, if these tests are to be done, this will determine the outcome of the possible possibilities more quickly.[17]

In some studies, *Bartonella* spp. infection caused by cat scratches is associated with major depression and has been observed to cause neurosis.[18-20] In a study conducted on 250 subjects, the results of *Bartonella* spp. and *T. gondii* seropositivity were evaluated. The test resulted that these infections cause depression and the results shows differ by gender. This study also showed patients who were seropositive for both *Bartonella* spp. and *T. gondii*, had lower depression than subjects seropositive with just with *Bartonella* spp.[21]

As shown in another case report, a patient who was initially diagnosed with a direct psychiatric diagnosis actually had a *Bartonella* spp. infection. This situation did generate in the patient general anxiety disorder, social anxiety, and panic attack. The patient was then treated with combined antibiotics such as rifampicin, and trimethoprim-sulfamethoxazole, after all that, it was reported that all psychiatric findings disappeared.[22] In addition, as indicate in this study, the patient had a traffic accident and suffered from the same psychiatric conditions again. It is thought like a flashback effect from an originating previous infection. We can interpret from this case report, *Bartonella* spp. can hide in our CNS like some latent viruses, and if a patient's immune system is low, or maybe the patient can be disposed of some genetic diseases, it is also can affect this relapse situation.[22]

Also, it has been observed connection has a stronger psychiatric effect when the disease combines with Lyme disease. When Lyme disease co-infection with *Bartonella* species such as *B. henselae* mostly every time shows psychiatric syndromes.[23,24] As we mentioned previously, that co-infection situations do not compass every pathogen. For instance, *Bartonella* spp. infection alone causes more depression than both *Bartonella* spp. and *T. gondii* together.

In another study, *Bartonella* spp. also causes diseases such as Leber's neuroretinitis, dementia, and bipolar disorder more easily in human immunodeficiency virus patients with immunodeficiency.[25] This may be due to the low immune system's inability to detect the pathogen adequately, and the increased rate of activity in the brain for the development of the pathogen, after all, it can settle in these chemical pathways more easily since there are not enough antibodies against it. In addition to these, chronic fatigue syndrome is also may be caused by *Bartonella* spp. there is have some findings about this.[26,27] One study observed that people who were exposed to a severe cat scratch or bite before age thirteen scored higher in schizotypic and schizophrenia-related conditions.[28] In this study, it has been suggested that exposure to such infections from cats or for any other reason at an early age causes chronic inflammation in the brain and increases the susceptibility to such psychosis in later ages, however, its relationship with psychosis is still not fully understood.[29,30]

Neurological Disorders and *Toxoplasma gondii*

Compared to *Bartonella* spp., more studies have been conducted on *T. gondii* and more information about *T. gondii* psychiatric connections. It is known that *T. gondii* is associated with many psychiatric disorders, including schizophrenia.[31] *T. gondii* infection has three infectious stages. The first is the tachyzoites stage that spread during acute infection, then tissue cysts called bradyzoites form and this leads to chronic infection, therefore, the sporozoites stage comes and they spread to the environment as structures called oocysts.[32] While research has generally limited the link of *T. gondii* to schizophrenia, it is not limited to this. *T. gondii* is also associated such as bipolar disorder, self-harm, suicidal thoughts, autism, depression, anxiety, and obsessive-compulsive disorder.[33-38]

Seropositivity of *T. gondii* can also lead to cognitive decline in the elderly. In addition, it causes a decrease in abilities such as reading and comprehension in school-aged children.[38-41]

In another study, in the experiment performed on mice, the cysts caused by *T. gondii* were found in the brain. While there were marked behavioral disorders in mice with cysts, and infected mice without cysts no change was observed. This result indicates that the presence of cysts is a provide psychiatric changes.[31]

In a study, 798 psychiatric patients and 681 healthy control groups were evaluated. The seropositivity of immunoglobulin (Ig) G and IgM antibodies for *T. gondii* was compared in both groups. According to the results, the IgG and IgM seropositivity of the psychiatric patient group was quite high compared to the healthy ones.[42] In another study, serological IgM, and IgG values of *T. gondii* antibodies were compared directly to bipolar disorder, schizophrenia, and obsessive-compulsive disorder. As seen in the results here, individuals who had a disorder had higher values. An interesting additional issue is that antipsychotics can lower IgM and IgG values.[43]

The infection of *T. gondii* causes various severe psychoses, but it is not known exactly which specific disease or why it causes various psychotic states that are not stable. The reason of this, infection is don't keep just one place in the brain. It can affect different places, and as a result, the diseases vary.

In another study conducted in Taiwan, patients with *T. gondii* had higher Charlson comorbidity index than those without. According to the results of the study, the rate of psychiatric disorders was higher in most of the patients with *T. gondii*.[44]

T. gondii has been shown to have a particularly negative impact on the CNS's astrocytes when its function in the pathogenesis of psychiatric disorders is examined. Usually, *T. gondii* crosses the blood-brain barrier one week after infection and can do so by lysing endothelial cells if necessary.[45] Once the pathogen reaches the CNS, it can initiate the activation of glial cells such as astrocytes. As a result, cytokines and free radicals are released by macrophages. There is beginning inflammation in the brain and cyst formation.[46] *T. gondii* can usually be randomly localized in the brain but is thought to be particularly prone to the prefrontal cortex and amygdala. Chronic *T. gondii* infection increases the aforementioned cytokines, factors such as tumor necrosis factor alpha and certain interleukins.

All these changes in brain chemistry can cause psychosis, self-harm, and depression.[46] In addition, evaluations in terms of IgG, and IgM seropositivity have been tried in many countries and the average results have been recorded the same.

In a study it was observed that *T. gondii* caused unconscious behavioral disorders by increasing dopamine and testosterone levels in male mice.[47]

T. gondii has been observed to alter dopaminergic pathways in the brain, including the tryptophan-kynurenine structure and GABAergic, AKT1, and Jak/STAT pathways. Irregular deterioration of these structures may also play a role in many psychiatric disorders.[48]

In another study, it was reported that *T. gondii* suppresses serotonin production by activating indoleamine-2,3-dioxygenase and consuming tryptophan. This may partly explain the depression caused by *T. gondii*.[49]

It is seen that *T. gondii* causes many psychiatric disorders, including schizophrenia. It does this by forming cysts in the brain tissue, altering dopamine-serotonin and other pathways, inducing inflammation, and using lines such as the gut-brain axis.[50]

Pathogens can be transported to the brain via the bloodstream after infection, contaminated during surgery, or transmitted directly from structures such as the sinus or middle ear.[51] The reason why microorganisms create psychiatric effects when they reach the brain is not fully understood, but it is generally thought that these psychiatric cases are caused by changing some dopamine pathways to consume resources in their favor, interacting gut-brain axis and creating inflammation with cysts on the neurochemical connections provide to this psychiatric conditions.[52] Moreover, there is a common view about microorganisms that can cause psychiatric disorders. The view is that exposure to the infection long before the onset of symptoms, and this pathogen could reach the brain. When a pathogen gets reached the brain and remains there for a long-time, it causes after a long time to psychiatric disorders.[53] The latent pathogen becomes active again after a long time and causes psychiatric disorders, exposure of the main pathogen usually acquired in childhood, to other common pathogens in adolescence may be associated with the re-activation of the old main pathogen. This situation may vary with the seasons, but the geographical variability is low.[54,55]

In conclusion, when microorganisms get access to the brain, they almost all accomplish the same thing: they damage biochemical neural pathways and feed on brain tissue. The purpose is the same; breed, develop and ensure the continuation of the generation. So all these psychiatric outcomes in the

body, are products of survival effort. However, for this subject, there are still some conflicts due to we don't know the whole mechanism yet.

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