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Review Article

Metals Explain the Relationship Between *Toxoplasma gondii*, Influenza Virus, and COVID-19: A Hypothesis

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Abstract

Toxic metals such as zinc (Zn) have numerous biological roles in a man's body, and these tasks are upsetted upon a change in these vital metals. These metals induce various pathological disorders in addition to these positive functions. The current manuscript focuses on the responsibility of *Toxoplasma gondii* as a host for the influenza virus offering an appropriate environment to the virus to escape the immune system. Consistent with the mentioned hypothesis indicating that COVID-19 is the mutant form of the influenza virus, the slow spread of the pandemic between populations with a high prevalence of toxoplasmosis is attributed to the role of Zn in the regulation of immunity through the protection of host cells from the virus and the guard of parasites that hold viral colonies and stop its spread. It is recommended that experimental studies be performed to prove this hypothesis.

Keywords: Essential metals, Toxic metals, *Toxoplasma gondii*, Influenza virus, COVID-19

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Introduction

Toxoplasma gondii is one of the most widespread human zoonosis, infecting about one-third of the world's people. Toxoplasmosis is normally benign and often goes unobserved in immunocompetent persons. Nonetheless, non-specific flu-like symptoms, lymphadenopathy, and some uncommon consequences might be linked with the primary infection (1).

In late December 2019, a sequence of acute atypical respiratory pneumonia was raised in Wuhan, China and quickly spread throughout the world. It was soon recognized that a novel coronavirus was responsible for this pandemic. The novel coronavirus was named the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2, 2019-nCoV) owing to its high homology (~80%) to SARS-CoV, which induced acute respiratory distress syndrome and high death during 2002-2003 (2).

A few persons with the *T. gondii* infection may sense as if they have the "flu" with muscle aches or inflamed lymph glands and aches that exist for a month or more (3).

In my opinion, *T. gondii* is parasitized by the influenza virus, and this symbiotic association reduces the pathogenesis of *T. gondii* while enhancing the survival of the influenza virus, and then patients experience the flu for longer than a normal revival duration.

Metals ions are the essential fraction of several viral proteins and take part in a significant function in their endurance and pathogenesis. Magnesium (Mg), copper (Cu), and zinc (Zn) are the commonest metal ions that are connected with viral proteins. Metal ions contribute to the maturation of genomic RNA, stimulation and catalytic mechanisms, reverse transcription, initial integration process, protection of newly synthesized DNA, and the inhibition of proton translocation (M2 protein). In addition, they have a role in minus- and plus-strand transfer, promotion of nucleic acid annealing, activation of transcription, and integration of viral DNA into specific positions, and function as a chaperone of nucleic acid. Metal ions are also necessary for nucleocapsid protein-transactivation response-RNA interactions. In the influenza virus, Cu, Ni, Pt, and Zn, as well as Zn, Mg, Mn, and Co bind to M2 protein and M1 peptide linker, respectively. Further, as in the coronavirus, Zn connects to peptide CCHH motif and has three connecting positions, namely, NS, p66 HEL, and NS13 (4). Based on reports, Mg levels obviously reduced in patients with chronic toxoplasmosis, while no alteration was noticed in Zn levels (5).

Xiao et al found that Mg-dependent RNA connects to the PA endonuclease domain of the avian influenza polymerase (6), and we suggest a clear decline in the Mg level in chronic toxoplasmosis cases.

Zn is vital for the regular development and task of cells mediating innate immunity, neutrophils, and *natural killer* cells. Macrophages are also influenced by Zn insufficiency. Cytokines production, intracellular killing, and phagocytosis are affected by Zn insufficiency as well. Zn shortage unfavorably involves the growth and function

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of T and B cells. The capability of Zn for functioning as an anti-oxidant and stabilizing membranes indicates that it has a task in the avoidance of free radical-induced injury throughout inflammatory processes (7).

Normal levels of Zn in toxoplasmosis cause mild symptoms or even asymptomatic characteristics of this opportunistic infection.

Overall, Mg and vitamin D are equally essential for the immune system and may be helpful in the COVID-19 infection as Mg is needed for vitamin D activation (8). Zn helps vitamin D to work inside the cells (9). According to one study (10), COVID-19 patients had significantly low Zn concentrations compared to healthy controls, and Zn lacking patients developed more complications (70.4% vs. 30.0%, P=0.009).

We hypothesized that lead and cadmium mutate the influenza virus and lead to SARS-CoV-2 (11), which contradicts with the findings of Martinez et al. It was found that the *T. gondii* infection may be causal to the high indices of behavioral alterations, and a probable interface was suggested between the chronic *T. gondii* infection and elevated blood lead levels on children's neurobehavior (12). We propose that only high lead levels are accountable for their neurobehavior.

The recent data demonstrate that contact with As, Cd, Hg, and Pb is linked with respiratory dysfunction and respiratory diseases such as chronic obstructive pulmonary disease and bronchitis (13), and these toxic metals may increase viral replication.

The spread of COVID-19 is slower in communities where more people suffer from toxoplasmosis (14), and this supports our hypothesis about the source of COVID-19 (11) and hosting of *T. gondii* to the influenza virus.

In their studies, Gharadaghi et al and de Carvalho et al (15, 16) concluded that vital metal ($ZnCl_2$) saved the host cells and parasites against the toxic effects of non-essential metals ($HgCl_2$ and $CdCl_2$), highlighting the low spread of COVID-19 in societies with a high number of *T. gondii* cases.

Conclusion

In general, As the virus is inhibited by the parasite, its spread decreases. Moreover, normal concentrations of Zn in toxoplasmosis help to diminish the sequels of COVID-19. Thus, it is suggested that experimental studies be conducted to prove this hypothesis.

Competing Interests

None.

Ethical Approval

Ethical considerations were fully observed in this research.

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