

## TOWARD APPLICATION OF MACROMINERALS AND TRACE ELEMENTS FOR TREATMENT OF PSYCHIATRIC DISEASES

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Dear editor,

Macrominerals (MM) and trace elements (TE) are found in living organisms that are essential for human life. Calcium and magnesium (MM) and trace elements such as chromium (Cr), cobalt (Co), copper (Cu), fluorine (F), iodine (I), iron (Fe), manganese (Mn), molybdenum (Mo), selenium (Se), zinc (Zn), and to less extent the boron (B) and vanadium (V) have various functions in living organisms.

Psychiatric diseases encompass a wide range of symptoms and signs that debilitate the human organism. Several recent pieces of evidence suggest MM and TE play an important function in psychiatric diseases. The important role of MMs and TEs in psychiatric diseases has been well shown in various studies. They are important in depression, schizophrenia, dementia, mental retardation, eating disorders, dysphoria, autism, and attention deficit hyperactivity disorder. Also previously it has been documented excess amount of these elements in genetic disorders also has a role in the appearance of psychiatric diseases (Islam et al. 2018).

MM elements have an important role in brain pathologies. MMs facilitate nerve transmission and neuromuscular conduction. From his standpoint, it can cause various neurologic symptoms. MMs are mainly found in bones. Calcium has some important functions in the brain such as neurotransmitter synthesis and release, neuronal excitability, phosphorylation, brain aging, the elevation of glucocorticoids. In familial disorders such as Primary familial *brain* calcification, there is widespread deposition of calcium in brain vessels. Calcium imbalance triggers Alzheimer's disease. Magnesium also has similar effects (Botturi et al. 2020).

TEs abnormalities are also associated with some important brain pathologies. Iron (Fe) has a relation to psychiatric diseases. Iron deficiency results in poor brain myelination and impaired monoamine metabolism. Iron deficiency anemia subjects had an increased risk of psychiatric disorders including mood disorders, autism spectrum disorder, attention deficit hyperactivity disorder, and developmental disorders. Also, it causes emotional disorders such as anxiety through different mechanisms such as neurotransmitter release, energy metabolism, and oxidative stress (Lee et al. 2020). Chromium (Cr) deposition has been observed in post-stroke blood vessels. Cr improves post-stroke recovery. Chronic exposure to cobalt and chromium was associated with subtle changes in brain structure. A study on developing brains revealed the toxic effect

of fluoride (F) impaires fetal brain development. Previous studies revealed a high concentration of F harms memory and learning (Li et al. 2019). Copper (Cu) dyshomeostasis in the brain also causes disease. Cu reduction and also Cu accumulation both have been observed in psychiatric diseases (Shohag et al. 2012). Iodine (I) is important for brain development and also in later life, in deficiency states brain damage (Błażewicz et al. 2016). Manganese (Mn) accumulation causes toxicity in the brain. Mn requires as a cofactor for many enzymes and also Mn is necessary for the metabolism of proteins, lipids, and carbohydrates. Molybdenum (Mo), as an essential micronutrient is directly involved in the metabolism of other elements including carbon, sulfur, and nitrogen. Mo alone is not biologically active unless it binds to specific cofactors. Acute elevation of Mo is associated with acute psychosis with visual and auditory hallucinations, a series of petit mal seizures, and one life-threatening grand mal attack. Selenium (Se) is important for cognitive function through the improvement of oxidative stress. 25 selenoproteins neutralize oxidative stress. Se is important for GABAergic (GABA,  $\gamma$ -aminobutyric acid) parvalbumin-positive interneurons of the cerebral cortex and hippocampus. It is also important for dopaminergic function (Tippairote et al. 2017). Zinc (Zn) deficiency reduces levels of BDNF, neurogenesis, synaptic plasticity-related proteins, and dendritic spine density *in vivo*. Also, Zn accumulation causes neurotoxicity and neurodegeneration. Boron (B) and vanadium (V) are also important for brain function and recently some shreds of evidence have been identified (Gutiérrez-Ravelo et al. 2020).

As it was said, both deficiency and accumulation cause disease. Different elements cause various symptoms and therefore therapy is not the same for all symptoms. It is reasonable to use trace elements as conjunctive therapy along with other drugs, especially in high-risk individuals. Human studies in this regard are rare but animal studies confirm the stated proposal. Also, psychiatric symptoms as co morbid symptoms in other disorders will well benefit from such treatments. Deficiency can be treated by the application of supplements and excess can be treated by chelators as there are different types for different elements. In most cases there are reversible damages and would benefit upon on-time diagnosis of the disease. Consideration of this etiology for psychiatric diseases may be of great value for applying the true treatment.

**Acknowledgments:** None.

**Conflict of interest:** None to declare.

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