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cause various metabolic disorders while their high levels are toxic. Non-essential elements like aluminium, lead and cadmium are highly toxic even in trace amounts and reported to be associated with neurological disorders. Studies have shown that trace elements are involved in neuropsychiatric illness. Studies have shown that copper, zinc and cesium deficiencies are seen in women affected by chronic depression. It has been found that the levels of magnesium and zinc are decreased in serum samples of schizophrenia and dementia patients. Although pivotal biochemical alterations underlying the neuropsychiatric disorders are unknown, changes in trace elements play an important role in bipolar disorders. Recently, essential elements like vanadium have been implicated as a causative factor for bipolar mood disorder while the elevation of vanadium and molybdenum levels has been reported in serum samples of bipolar mood disorder patients. Christiansen et al. have shown that lithium alters the levels of elements such as calcium and magnesium in serum samples during treatment. This data is only part of the limited data set available on the concentration of trace elements in the serum of individuals with bipolar mood disorders while there are no interelemental complexity studies in the literature pertaining to trace elemental levels in serum samples of patients suffering from three types of bipolar disorder. Furthermore, while the above-mentioned studies have focused on individual elements, no attempt has been made to understand the interelemental relationships and trace elemental homeostasis in bipolar disorder.

We assessed the serum levels of eleven elements in bipolar disorders types I, II and V and attempted to understand the complexity of trace elemental interrelationships in bipolar disorders as compared to the control group. Trace elements, namely, Na, K, S, Ca, Mg, P, Cu, Fe, Zn, Mn and Al were analyzed in serum samples of Bipolar I (n = 40), Bipolar II hypomania (n = 25), Bipolar II depression (n = 25), Bipolar V depressives (n = 25) and control (n = 25) using Inductively Coupled Plasma-Atomic Emission Spectrometry (ICP-AES). The patients were assessed as per the standard diagnostic criteria of DSM IV and classified into types I, II and V by a psychiatrist using the concept of Young and Klerman. The significant results were a) in Bipolar I (Mania), Na, K, P, Cu, Al and Mn were elevated significantly (P < 0.001); b) in Bipolar II hypomania, Na, S, Al and Mn were increased significantly (P < 0.02) while in Bipolar II depression, Na, K, Cu and Al were increased significantly (P < 0.001); c) in Bipolar V, Na, Mg, P, Cu and Al were increased significantly (P < 0.002) but S (P < 0.000001) (Comment: but this was increased in b), Fe (P < 0.002) and Zn (P < 0.004) were decreased in all three bipolar groups. The data revealed disturbance in the charge distribution and interelemental interdependency in bipolar group serum compared to that of the control group. These results suggest that there is definite imbalance in trace elemental homeostasis as evidenced by trace elemental interrelationships in serum samples of bipolar groups compared to those of the control group.

Based on our new and others’ findings and Dr. Zecca’s highly significant contributions, we developed a hypothetical model explaining the possible relevance of trace elemental homeostatic imbalance in the serum of bipolar disorder to their effects in brain.

With these findings, the following two pathways can be deduced. In pathway 1, increased Al levels in the serum of bipolar disorder patients is likely to alter the trace elemental homeostasis pool. Irrespective of whether elements are primary risk factors or consequences of disease processes, a change in an individual metal ion will upset the elemental homeostasis pool resulting in significant imbalance in elemental levels and charge distribution pattern in the body system. The element-to-element mole ratios of Al / Fe and Al / Zn increased because of high concentrations of Al present, which alters other elemental levels. This is evidenced by the existence of an inverse relationship between Al and S.

The elevated Al levels may disturb the metal homeostasis in the serum by increasing the levels of paramagnetic oxidant elements like Cu and Mn and decrease the levels of Zn, which is an antioxidant metal (required for the production of Cu Zn-SOD and Zn-thionein) essential to prevent oxidative damage. Elevated Al level is found to increase superoxide dismutase (SOD) activity to protect the cell from oxidative damage. Recently, Kolugulu et al. showed SOD activity levels are higher in bipolar disorder patients’ serum and also reported the presence of lipid peroxidation. Increased Al levels may be one of the reasons for high SOD activity in bipolar disorder. Elevated levels of paramagnetic elements Cu and Mn in serum may catalyze the conversion of H2O2 to potent hydroxyl radicals, which could lead to oxidative damage.

In pathway 2, the elements in the serum possibly reflect the brain elemental homeostasis. Previous studies demonstrated that Al and Fe levels decreased in cerebrospinal fluid (CSF) while they are elevated in the brain. Al is known to be cotransported with the Fe-Transferrin complex in neurological disorders. In the normal brain, Fe and Al compete for transport across the blood brain barrier and Al can cross the blood brain barrier with the help of ferritin. Al can promote Fe-mediated oxidative stress by inhibiting catalase activity in the brain and also by causing mitochondrial dysfunction leading to oxidative stress and neuron dysfunction. These pathways highlight the fact that trace elemental imbalances in bipolar disorder patients’ serum may cause imbalances in trace elemental levels in the brain which may lead to oxidative stress and damage the biomolecules like DNA, lipids and proteins. This may be the reason for alteration in the neurotransmitter receptors and the levels of secondary messengers in bipolar disorder patients’ brain. It can be inferred that
elemental homeostatic imbalance results in the imbalance of biochemical events and oxidative stress in bipolar disorder, which may later manifest as neurodegeneration. There are few studies supporting our hypothesis. PET scan study by Bier et al.[30] reported that depression might cause neurodegeneration. Another study by Buhl et al.[31] demonstrated the presence of neuritic pathology in bipolar mood disorder. On the contrary, Damadzic et al.[32] reported that neuritic pathology is lacking in the entorhinal cortex, subiculum and hippocampus in middle-aged adults with schizophrenia, bipolar disorder or unipolar depression. We believe that neuritic pathology may be the final onset phase of neurodegeneration with initial phases probably being neuropsychiatric phenomena with biochemical and brain function alteration. Our findings illustrate that more studies are required to link neuropsychiatry to neurodegeneration.

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