HYPOZINCEMIA IN BIPOLAR I DISORDER (BID) PATIENTS

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ABSTRACT: One-third of the world’s population is at risk of zinc deficiency. It has been hypothesized that low serum/plasma zinc may contribute to alteration of brain Zn homeostasis and thus lead to various psychological disorders. This study was designed to evaluate serum zinc (Zn) as well as copper (Cu) concentrations in patients with Bipolar I Disorder (BID) in our community to support the findings on the possible association of Zn in neuropsychological functions. Participants included 30 BID patients with different phases of mania and depression and 30 healthy controls. Results indicated the mean serum Zn level of the BID group was significantly lower than that of controls (P< 0.0001). Similar results were obtained for Cu. These findings suggest a possible association of Zn levels on neuropsychological dysfunction.

KEYWORDS: Bipolar I disorder, Hypozincemia, zinc

INTRODUCTION

In spite of the proven benefits of zinc (Zn), approximately one-third of the world’s population remains at risk of Zn deficiency (World Health Report, 2002). The earliest report on human Zn deficiency was described by Prasad from a rural Iranian adolescent with severe growth retardation and immune and neurological dysfunctions (Prasad, 1969).

Zn, the second most abundant trace-element in the body with an overall mean serum value of 85.6 ± 0.1mg/dl, plays a critical role in the functional and structural integrity of cells, DNA synthesis, cell membrane stabilization and is vital in a number of normal biological process in the brain (Hotz, 2003; Vallee and Falchuck, 1993; Sandstead et al, 2000).

Various scientific reports document that low serum/plasma Zn concentration may contribute to alteration of brain Zn homeostasis and hypothesize that this may lead to a wide range of psychological disorders including depression, anorexia nervosa, mood liability, dyslexia, impaired learning and attention-deficit/hyperactivity (Wojcik et al, 2006, MCLoughlin and Hodge, 1990; Maes et al, 1994; Bryce-Smith, 1984; Agett and Hariis, 1979; Arnold and Di Silverstro, 2005). The antidepressant activity of Zn in relation to human depression also has been suggested (Nowak and Szewczyk, 2002). The rise of social changes in our community has resulted in greater attention being given to such diseases as bipolar I disorder, a manic-depressive disorder with extreme mood changes and with no national statistics available on the number of sufferers. On the basis of the evidence mentioned above and the recent and on-going attention given to reports of Zn status from different populations on psychological impairment, the aim of this study was to evaluate serum Zn, as well as its antagonist ion, copper (Cu) concentrations in patients with Bipolar I Disorder (BID) in our community to support the findings on the possible association of Zn in neuropsychological functions.

SUBJECTS AND METHODS

A total of 60 subjects participated in the study. All patients (n=30) were outpatients with BID, identified as having different phases of mania and depression and mixed psychotic features. They were being treated at our psychiatric outpatient hospital and diagnosed by two psychiatric physicians according DSM-IV-TR criteria using semi-structured interview of the DSM-IV-TR. The mean age of patients was 33.86 ± 9.48 yrs., of whom, 57.7% were male (n=19) and 43.3% were female (n=11). Healthy volunteers (n=30) were selected as controls from non-first relatives of patients and who had no immediate family history of BID. Controls had a mean age of 36 ± 11.49 of whom 54.8% were male (n=17) and 45.2% were female (n=13) and a GHQ test within the normal range. Patients and controls were taking no vitamin or mineral supplement, anticonvulsant drugs or had any unconventional dietary habits. Both subjects and controls were given written consent forms and a questionnaire covering other variables such as marital status, education level and occupation. Our questionnaire included data on occupation in order to...
eliminate those who may be exposed to excessive amounts of Zn or Cu in the workplace. At this stage of our investigation, no other nutritional abnormalities or status of other trace elements are being considered.

Zn and Cu serum concentrations were analyzed by atomic absorption spectrophotometry (Unicam 929) at the Cellular Molecular Research Center according to established methods. Samples were carefully collected in acid-washed metal-free tubes to insure no contamination. The CV of repeated Zn and Cu analysis of pooled serum was approximately 4% and 3.87%, respectively.

Statistical analysis was performed by SPSS-11.5 for Windows. Comparison within two groups was determined using Student t-test. Results are expressed as mean ± SD and differences were considered to be significant at P<0.05.

RESULTS

The observations obtained (% or mean), clinical characteristics and serum Zn and Cu concentrations are given in Table 1. These results indicate that the mean serum concentration of Zn in all patients with BID (69.07 ±12.53 mg/dl (range 49.2-100)) was significantly lower than the mean Zn levels of healthy control group (90.45 ± 11.2 mg/dl, (range 70-116) P<0.0001), a possible implication for prediction of higher risk for BID in our patients as expected in other relevant psychiatric diseases.

As for serum Cu levels in patients with BID, the mean value of 89.28 ± 21.2 mg/dl, (range 56-149.2) was also lower than that of control subjects (105.42 ± 22.2mg/dl (range 74-154.8)) p< 0.001.

DISCUSSION

This study on BID patients, which to our knowledge is first such report, indicates that there was a significant difference in serum zinc concentration in persons with BID comparing to healthy controls.

Hypozincemia has previously been described in connection with a number of other psychiatric disorders. Wojcik, McLoughlin, Maes and Nowak found that depressed subjects had lower Zn concentration than that of controls (Wojcik et al, 2006; McLoughlin and Hodge, 1990; Maes et al, 1994; Nowak et al, 2005). Patients with minor depression (i.e. dysthymic disorder and adjustment disorder with depressed mood) showed intermediate values (Maes et al, 1994). Hansen reported a case of treatment resistance depression with low serum Zn concentration (Hansen et al, 1983). Similar results of significantly lower Zn levels were obtained in patients with paranoid schizophrenic and attention deficit/hyperactivity (Nechifor et al, 2004; Toren et al, 1996). A recent animal study showed rats deprived of Zn showed an increase in anxiety-like behavior (Takeda et al, 2007).

Several human experimental studies with Zn supplementation have improved clinical neuropsychological disorders. Feeding 50 mg/dl of Zn to subjects with anorexia nervosa lowered the level of depression and anxiety comparing to control group (Katz et al, 1987). Nowak showed the benefit of Zn supplementation along with antidepressant drug therapy in major depression when compared with placebo treatment (Nowak et al, 2003). Administration of Zn with other micronutrients demonstrated superior cognitive and psychomotor performance (Penland et al, 1997).

There is no clear suggestion on the relationship between lower serum Zn and psychopathological disorders, but several explanations have been proposed including poor appetite and reduced food intake in patients with such disorders. Other factors involve alteration of Zn homeostasis related with disorganized immunological system (increased CD4+/CD8+ T cell ratio, serum neopterin and interleukin-6) and impaired function of cell immunity (reduced T cell cytokin production) (Maes et al., 1999; Nowak et al, 2005). Poor nutrition was not observed in our subjects, but there is a possibility that similar disorganized immunological mechanisms may exist in our patients also. Excess level of Cu was found in some patients with psychological

| TABLE 1. Base line characteristics and serum Zn and Cu concentration of patients with BID and controls |
|-------------------------------------------------|-----------------|-----------------|
| Age (year)                                      | 33.86±9.48      | 36±11.49        |
| Gender M/F (%)                                  | 56.7/43.3       | 54.8/45.2       |
| Married (%)                                     | 50              | 64.5            |
| Education year (%)                              | 53.3            | 41.0            |
|       <12 yr                                      | 33.3            | 25.8            |
|       >12yr                                      | 13.3            | 32.3            |
| Occupation (%)                                  | 83.3            | 38.7            |
|       Temporary                                  | 13.3            | 38.7            |
|       Government                                 | 3.3             | 22.5            |
| Family History of BID (%)                       | 23.3            | None            |
|       Positive                                   | None            | None            |
|       Negative                                   | 76.3            | 0               |
| BMI (kg/m²)                                     | 25.54 ± 4.69    | 24.31 ± 3.20    |
| Serum Zn (mg/dl)                                | 69.07 ± 12.53   | 90.45 ± 11.23   |
|       (49.2-100)                                 | (70-116)*        | (p<0.0001)      |
| Serum Cu (mg/dl)                                | 89.28 ±12.21    | 105.42 ± 22.20  |
|       (56.00-149.2)                               | (74.00-154.80)**| (p<0.001)       |

Data are % or Mean ± SD
*p<0.0001
**p<0.001
improvement and accompanied by lower Zn serum levels (Nechifor, 2004). No excess level of Cu was found in our patients.

Zn concentration is well regulated within the specific brain regions and is about 10 fold higher than plasma concentration. About 90% of Zn is bound to Zn metalloenzymes and the rest is found in certain synaptic vesicles in specific neurons. (Takeda, 2001; Frederickson, 1983). During synaptic events, Zn plays a role in synaptic neurotransmission and acts as an endogenous neuromodulator of several receptors; Harrison and Gibbons, (1994). Chronic low levels of Zn may have adverse effect on brain homeostasis, which may in turn impair normal brain function (Takeda et al, 2001).

In conclusion, these initial findings indicating an imbalance in serum Zn in BID patients in our community is in agreement with previous findings. Whether or not levels of this ion can be considered as a sensitive marker in such disorders, or whether Zn supplementation is needed, requires further controlled studies with larger populations and accurate evaluation of dietary Zn intake.

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REFERENCES


