

Title: Metabolic Syndrome and Childhood Trauma: Also Comorbidity and Complication in Mood Disorder

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer 2440657

-1. Childhood trauma and relation of childhood trauma with medical disease has been emphasized on a wider plan in conclusion.

“Individuals reporting a history of any childhood adversity had higher systolic and diastolic blood pressure^[44]. Among subjects with a history of sexual abuse, a significant proportion met criteria for obesity, a trend toward overweight was found for subjects with a history of physical abuse, although this relationship did not remain significant after adjusting for potential confounders. There was no statistically significant difference in the overall rate of dyslipidemia and/or metabolic syndrome between subjects with and without childhood adversity. The results herein provide preliminary evidence suggesting that childhood adversity is associated with metabolic syndrome components in individuals with mood disorders. An association between stressful events and episode recurrences has repeatedly been found in bipolar patients^[45].

Psychological stress also may activate inflammatory responses in the brain^[46]. The theoretical model frames the depressive episode as being a repair response to stress induced neuronal microdamage that can grade into a chronic neuroinflammatory condition. Cardiovascular damage and atherogenic changes could be a by-product of this process. One of the mechanisms whereby psychosocial stress influences both peripheral and central inflammatory cascade, is coordinated by autonomic nervous system. Thus, the release of noradrenaline and adrenaline follows the activation of the sympathetic system and induces the activation of both alpha and beta adrenoreceptors on immune cells thereby initiating the release of pro-inflammatory cytokines via the nuclear factor-kappa-beta (NF-kB) cascade^[47]. The brain is now known to be directly influenced by peripherally derived cytokines and gluco-corticoids as well as immune cells, which can access the brain through leaky blood-brain barrier and/ or by activation of endothelial cells that line the cerebral vasculature, or bind to cytokine receptors^[48].

A public health paradox is implicit in these observations. One sees that certain common public health problems, while being often also unconscious attempted solutions to major life problems, harken back to the developmental years. The idea of the problem being a solution, while understandably disturbing to many, is certainly in keeping with the fact that opposing forces routinely coexist in biological systems. Clinical evidence suggests that metabolism and emotion homeostasis might share common mechanisms.”

44 McIntyre RS, Soczynska JK, Liauw SS, Woldeyohannes HO, Brietzke E, Nathanson J, Alsuwaidan M, Muzina DJ, Taylor VH, Cha DS, Kennedy SH. The association between childhood

adversity and components of metabolic syndrome in adults with mood disorders: results from the international mood disorders collaborative project. *Int J Psychiatry Med.* 2012; 43:165-77. PMID: 22849038

45 Etain B, Heny C, Bellivier F, Mathieu F, Leboyer M. Beyond genetics: childhood affective trauma in bipolar disorder. *Bipolar Disord.* 2008; 10:867–876. PubMed: 19594502

46 Wager-Smith K, Markou A. Depression: a repair response to stress-induced neuronal microdamage that can grade into a chronic neuroinflammatory condition? *Neurosci Biobehav Rev.* 2011; 35:742–764. PubMed: 20883718

47 Leonard BE. The concept of depression as a dysfunction of the immune system. *Curr Immunol Rev.* 2010; 3:205–212. PubMed: 21170282

48 Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol.* 2006; 27:24–31. PubMed: 16316783

-2. Hypertension has been emphasized on a wider plan.

“Increasing number of evidence shows that there is a bidirectional connection between mood disorders and some medical diseases ^[30]. Glucocorticoid/insulin signal mechanisms and immunoenflammatory effector systems are junction points that show pathophysiology between bipolar disorder and general medical situations susceptible to stress ^[7]. In BD, the changes in brain energy metabolism and brain glucose metabolism may be important in BD pathophysiology ^[31]. Noradrenalin (NA), a signal molecule in the central nervous system, which has etiologic importance for many diseases is an important neurotransmitter in BD etiology ^[32]. High noradrenergic tonus, which is determined mostly genetically, may develop susceptibility for more than one medical and mental diseases in a wide spectrum for many people. So that, hypertension, progressive weight gaining, diabetes and mania are all conditions in which noradrenergic tonus increases. Since 1987, the prevalence of hypertension has been reported to be elevated (14%) in bipolar patients, compared to normal population (5.6%) and to unipolar depression (5%) ^[5]. This was replicated in several studies in USA and in Europe. While the largest study involving 25,339 bipolar patients and 113,698 controls found an increased rate of new-onset cases of hypertension among bipolar patients compared to general population and to schizophrenic cases.”

5 Leboyer M, Soreca I, Scott J, Frye M, Henry C, Tamouza R, Kupfer DJ. Can bipolar disorder be viewed as a multi-system inflammatory disease? *J Affect Disord.* 2012; 141(1):1-10. doi: 10.1016/j.jad.2011.12.049. PMID: 22497876

-3. Metabolic syndrome has been emphasized on a wider plan in introduction.

“In bipolar disorder (BD), metabolic syndrome is more prevalent than general population. A subgroup of bipolar patients have higher risk of developing metabolic syndrome. Their habits, life styles, genetic suscpetibility and choices of treatment are variables determining this subgroup, childhood trauma may be another variable. Metabolic syndrome has been reported at the rate of 35-40% in bipolar patients. Metabolic syndrome encompasses obesity, diabetes, hypertension and dyslipidemia as cardiovascular risk factors. Although they are not among diagnostic criteria of

metabolic syndrome, proinflammatory and prothrombotic state are considered in the framework of metabolic syndrome^[3]. In our study, ICAM and VCAM levels measured at first manic episode were found to be higher than those found in subsequent remission period and healthy individuals. As our study group included only patients at first manic episode, there was no chronic effect of psychotropics use on these results. According to these results, probable CVD risk, reflected by increased ICAM and VCAM levels, is already present at the onset of the disease in bipolar patients^[4].

Exploring the biological pathways that could account for the observed link show that dysregulated inflammatory background could be a common factor underlying metabolic syndrome and MD. Comorbid medical illnesses in bipolar disorder might be viewed not only as the consequence of health behaviors and of psychotropic medications, but rather as an early manifestation of a multi-systemic disorder^[5]. It is also necessary to look for subgroups of MD based on their rates of comorbid disorders.

Psychiatric and medical diseases have a two-way relationship, and may have some effects on each other's clinical appearance and clinical course, treatment options and choices as they affect the possibility of keeping links to carry the etiologic causes. The lifespan of people with serious and chronic disorders, such as mood disorder, decrease by 30% because of untreated medical diseases^[6]. Obesity and diabetes are most common metabolic disease, related hypertension, dyslipidemia and cardiovascular disease.”

3 Vancampfort D, Vansteelandt K, Correll CU, Mitchell AJ, De Herdt A, Sienaert P, Probst M, De Hert M. Metabolic syndrome and metabolic abnormalities in bipolar disorder: a meta-analysis of prevalence rates and moderators. *Am J Psychiatry*. 2013; 170:265-74. doi: 10.1176/appi.ajp.2012.12050620. PMID: 23361837

4 Turan Ç, Kesebir S, Süner Ö. Are ICAM, VCAM and E-selectin levels different in first manic episode and subsequent remission? *J Affect Disord* 2014; 163: 76-80. Doi: 10.1016/j.jad.2014.03.052.

3 Revision has been made according to the suggestions of the reviewer 58872

As recommended by the reviewer, I added the references.

“Hepatic steatosis, is more frequent among people with diabetes and obesity, and is almost universally present amongst morbidly obese diabetic patients. the links between hypercortisolism and obesity/metabolic syndrome, they hypothesize that this low prevalence of fat accumulation in the liver of patients with Cushing's syndrome could result from the inhibition of the so-called low-grade chronic-inflammation, mainly mediated by Interleukin 6, due to an excess of cortisol, a hormone characterized by an anti-inflammatory effect^[35]. Moreover, insulin resistance is associated with lower serotonin levels. Visceral obesity, strictly linked to hepatic steatosis is specifically associated with mild to severe somatic affective-depressive symptom clusters. Previous data support the view that depression involves serotonergic systems, reflecting low levels of urinary 5-hydroxy-3-indoleacetic acid (5-HIAA). In Tarantino et al.'s study, among metabolic indices, cholesterol, HDL-cholesterol, triglycerides and uric acid were not able to predict urinary concentrations of 5-HIAA, which were not associated with hepatic steatosis; vice versa, ferritin levels, and mainly HOMA values, were independent predictors of the urinary excretion of 5-HIAA^[36]. Dystimia/depression severity was negatively predicted by urinary 5-HIAA levels in the sense

that the highest BDI values were forecast by the lowest values of urinary 5-HIAA. The importance of measuring the 24-h urinary excretion of 5-HIAA in follow-ups could rely on a method simultaneously mirroring the well-being status, the adherence to physical activity, which leads to improved insulin sensitivity, and the eating habits acquired by dystimic/depressed overweight/obese patients. In contrast, the significance of the urinary 5-HIAA is reduced in evaluating the severity of hepatic steatosis, likely because it is a structured process.”

35 Tarantino G, Finelli C. Pathogenesis of hepatic steatosis: the link between hypercortisolism and non-alcoholic fatty liver disease. *World J Gastroenterol.* 2013; 19:6735-43. doi: 10.3748/wjg.v19.i40.6735. PMID: 24187449

36 Tarantino G, Savastano S, Colao A, Polichetti G, Capone D. Urinary excretion of 5-hydroxy-3-indoleacetic acid in dystimic/depressed, adult obese women: what correlations to hepatic steatosis? *Int J Immunopathol Pharmacol.* 2011; 24:769-79. PMID: 21978708

Thank you for your re-consideration of our work. Hope to hear from you soon.
With kind regards;

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