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Metabolic syndrome and childhood trauma: Also comorbidity and complication in mood disorder

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Abstract

Studies for prevalence and causal relationship established that addressing comorbidities of mental illnesses with medical disease will be another revolution in psychiatry. Increasing number of evidence shows that there is a bidirectional connection between mood disorders and some medical diseases. Glucocorticoid/insulin signal mechanisms and immunoenflammatory effector systems are junction points that show pathophysiology between bipolar disorder and general medical situations susceptible to stress. A subgroup of mood disorder patients are under risk of developing obesity and diabetes. Their habits and life styles, genetic predisposition and treatment options are parameters that define this subgroup. Medical disease in adults had a significant relationship to adverse life experiences in childhood. This illustrates that adverse experiences in childhood are related to adult disease by two basic etiologic mechanisms: (1) conventional risk factors that actually are compensatory behaviors, attempts at self-help through the use of agents and foods; and (2) the effects of chronic stress.

Key words: Obesity; Dyslipidemia; Hypertension; Diabetes; Childhood trauma; Mood disorder

Core tip: 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.

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INTRODUCTION

Studies for prevalence and causal relationship established that addressing comorbidities of mental illnesses with medical disease will be another revolution in psychiatry[1]. There is a bidirectional relationship between psyche and soma, each influencing the other. Plausible biological explanations are appearing at an astonishing rate. Psychiatric comorbidity with many chronic physical disorders has remained neglected. Evidence base of prevalence and causal relationship of psychiatric comorbidities in these disorders has been highlighted and strategies to meet the challenge of comorbidity have been indicated.

In our study on 2000 outpatient population, prevalence of medical diseases in mental illnesses, temporal relationship between appearance of medical diseases and mental illnesses and, whether treatment of mental illness is suitable for medical condition were cross-sectionally analysed, the rate of calculated of third axis co-diagnosis were as follows; 56% for mood disorders (MD), 42.3% for anxiety disorders (AD), and 38.3% for schizophrenia (S)[2]. The rate of calculated of third axis co-diagnosis

were different between MD, AD and S as follows; hypertension 34.4%, diabetes 23.6%, thyroid disease 18.5%, coronary arteria disease 13% in MD, hypertension 42.4%, respiratory disease 30.7%, gastrointestinal disease 25%, autoimmune disease 7% in AD, hypertension 65.3%, diabetes 14%, respiratory disease 12%, gastrointestinal disease 8% in S. The time interval between the beginning of disease to from now was detected as follows 6.19 ± 7.55/7.12 ± 8.15, similar in mood disorders (r = 0.912). Coefficient of correlation (r) were 0.265 and 0.425 for AD and S respectively (3.21 ± 3.15/8.34 ± 5.71 and 13.82 ± 11.36/8.21 ± 8.55). Our results revealed that MD and medical disease appeared simultaneously. The pharmacologically treatment of MD, AD and, S insuitable to the Ⅲ. Axis diagnosis and, found as high valuable mean in.

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 susceptibility 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 cardiovascular disease (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.

OBESITY

Obesity is a leading cause of preventable death and the prevalence of overweight and obesity is increasing. A survey of 4.115 adult conducted in 1999 and 2000 as part of the National Health and Nutrition Examination Survey found that 64.5% of the population is overweight and 30.5% is obese[7]. A separate, smaller study of 50 bipolar patients, found an obesity rate that was only slightly higher (32%)[8]. In this study, most of the weight gain occurred during acute rather than maintenance treatment, and the increase in body mass index (BMI) was related to severity of depressive episode. Although several studies have found significant obesity in bipolar patients[9]. It is difficult to ascertain the degree to which the obesity is secondary to medications used to treat bipolar disorder or to the illness perse[10]. In our study rate of overweight was 62% and obesity 8% of the first episode manic patients[11]. Longitudinal studies of children and adolescents have found a positive association of major depressive disorder with adult BMI. This association persisted even after controlling for age, gender, substance abuse, socioeconomic level and medication exposure[12].

Atypical antipsychotic medications are associated specifically with central obesity, which occurs when the main deposits of body fat are localized around abdomen. Accumulating evidence suggests that central deposition of body fat is a risk factor independent of overall obesity for mortality due to cardiovascular disease and type Ⅱ diabetes[13]. In our study BMI was predictive variable of the diabetes in first episode mania[11]. Other medications used the treatment affective disorders, including lithium, valproate, and some antidepressants, have also associated with weight gain. Thus far, there has been less concern regarding the development of metabolic syndrome with this drugs than with the atypical antipsychotics.

Beyond weight gain caused medications, symptoms of depressive episode itself can lead to obesity. Depressed mood leads to lower levels of activity. Depressive episodes with atypical features such as hyperphagia, hypersomnia, leaden paralysis and carbohydrate craving are more liable to lead to weight gain. In the majority of bipolar patients, however, depressive symptoms are far more frequent than manic symptoms[14]. Depression is often accompanied by hypercortisolemia, which is also associated with central obesity. Even in the context of normal body weight, hypercortisolemia has been associated with excess visceral fat deposition as measured by computed tomography scan[15]. A national survey of 40.086 adults examined the relationship between body weight was associated with major depression and suicidal ideation and suicide attempts[16].

DIABETES

Because overweight and obesity are associated with diabetes, many risk factors that have been linked to weight gain apply also to the development of diabetes. The prevalence of reported diabetes mellitus was found to be approximately three times higher in a sample of 345 hospitalized bipolar patients than in the general population (3.4%)[17]. Patients in this sample also had a more severe

course of their mood disorders such as rapid cycling and chronic course[18]. In a recent work which takes its sampling from the society, the ratio of present diabetes diagnosis among bipolar diagnosed cases is found to be higher than healthy individuals (10.8%)[19].

A subgroup of bipolar disorder patients are under risk of developing diabetes[9]. Their habits and life styles, genetic predisposition and treatment options are parameters that define this sub-group[12]. Metabolic syndrome and glucose abnormalities are reported between 18% and 30% in bipolar cases[18]. Among these, 7% are diabetes, while 23 % are pre-diabetes abnormalities.

Besides, the level of HbA1c in nonmedicated bipolar cases was found to be higher than the healthy controls[20]. In another similar study, hyperglycemia was found to be 43.5% in bipolar patients evaluated at the beginning of acute episode treatment[21]. According to the same study, 4.3% of the patients are under antidiabetic treatment. In a study of cases that exhibit violent (homicidal) behavior conducted by Langevin *et al*[22], it was reported that diabetes prevalence was found higher in the sampling group, and more importantly, diabetes diagnosis was missed out in more than 25% of the cases[22]. In the same group it was stated that manic and psychotic findings were found often and especially among the younger cases, injury crime was not rare.

In our study, DM diagnosis was determined as 18% among first manic episode bipolar cases. When evaluated with glucose metabolism abnormalities, this ratio becomes 64%[11]. In late onset bipolar cases evaluating cases aged over 50, 42% of cases have manic episode diagnosis related to general medical condition. In general medical conditions, the ratio of diabetes is 50%[12].

Dysregulation of the hypothalamic-pituitary-adrenocortical axis occurs frequently in patients with mood disorders. Hypercortisolemia associated with depressive states can lead to insulin resistance. Elevated levels of cortisol can lead to decreased insulin receptor sensitivity through currently unknown mechanisms[14].

A more hypothetical link between bipolar disorder and diabetes relates to intracellular signal transduction involving the enzyme glycogen synthase kinase-3-beta (GSK-3β). Glycogen synthetase kinase (GSK3) is a serine/threonine kinase that is a responsible enzyme from the cyclic mechanisms of the cell, gene expression, oncogenesis and neuronal protection[23]. Hippocampal volume and BDNF level decrease in diabetes[7]. Animal studies show that in diabetes-related depression, neurogenesis is inhibited in dentate gyrus[24].

Alterations in GSK-3β functioning play role in insulin resistance. Insulin inhibits GSK-3β which result enhanced glucose transport into skeletal muscle. Insulin mediated inhibition of GSK-3β leads as well to increased glucose utilization and the production of glycogen[25]. GSK-3β is also one of targets for lithium action. Lithium significantly inhibits brain GSK-3β at concentrations relevant fort he treatment bipolar disorder. Disturbances in the GSK-3β signal transduction pathway associated with diabetes may affect the viability of neurons that play a role in mood stabilisation. Diminished insulin mediated inhibition of GSK-3β may have an effect opposite to that of lithium and may ultimately lead to an accentuation of psychiatric symptoms related to bipolar disorder. Besides, in a clinical study intranasal insulin was found to be more effective than placebo on cognitive distortion in unipolar and bipolar euthymic cases[26].

When patients with diabetes are being treated, lithium should be used with care. Patients with juvenil onset insulin dependent diabetes are susceptible to diabetic nephropathy, and the risk is increased by the presence of hypertension. On the other hand, there is evidence that when lithium is combined with an oral antidiabetics or insulin, it has an assisting hypoglycemic effect in diabetic patients[27]. Lithium increases the sensitivity of glucose transport and metabolism in skeletal muscle and adiposytes. This effects similar to the effects of exercise.

In our study, free T4 levels have been found higher in diabetic first episode manic patients than nondiabetic first episode manic patients[11]. Thyroid Releasing Hormone (TRH -which is an endogen like antidepressant neuropeptide-) decreases the expression of GSK3-β[28]. GSK3-β activity, which increases in the manic phase of bipolar disorder, may be causing the reactive increase of free T4 by suppressing TRH.

In diabetic bipolar cases, triglyceride and cholesterol levels and BMI are determined as higher[11]. Triglyceride level and BMI are predictors in third and fourth order in regression analysis. When diabetes is in question, these findings are not a surprise, such that diabetes development is together with lipid metabolism abnormalities[10]. Also in our study, there is a correlation between triglyceride levels with fasting blood glucose and blood glucose level at the first hour of oral glucose tolerance test[11]. There is a stronger correlation between BMI with fasting blood glucose and HbA1c. In a recent work, the prevalence of obesity among bipolar cases was reported as 39.1%[29]. In the same study, high BMI, chronic course, longer disease period, lower functionality scores are shown to be comorbid with prevalent anxiety disorder, hypertension, diabetes and other diseases frequently. Additionally, in cases that show remission with lithium, BMI was found lower. In bipolar cases evaluated by Kim *et al*[21] at the beginning of acute period treatment, the ratio of hyperglycemia was determined as 43.5%. In the same study, 4.3% of the cases are under antidiabetic treatment, while 1.1 % of the cases are under anticholesterolemic treatment. There is hypercholesterolemia in 20.7% of the cases and obesity in 30.4% of the cases. All these findings should be considered as to question if the bipolar disorder itself acts like metabolic syndrome.

Increasing number of evidence shows that there is a bidirectional connection between mood disorders and some medical diseases[30]. Glucocorticoid/insulin signal mechanisms and immunoinflammatory 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 25339 bipolar patients and 113698 controls found an increased rate of new-onset cases of hypertension among bipolar patients compared to general population and to schizophrenic cases.

Impaired fatty acid and phospholipid metabolism may be a primary cause of depression in many patients and may explain the interactions with other diseases. Postmortem analysis of brains of bipolar patients revealed that in orbitofrontal cortex of those subjects reduced DHC levels were detected due to elevated saturated fatty acids and arachydonic acid metabolism[31]. In manic patients both DHA and arachydonic acids levels were increased[33]. The same fatty acids and phospholipid mediated disruption of secondary messaging systems in BD is also operative in diabetes and vascular disease[34].

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[36], 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. 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.

Recently, an increasing number of susceptibility variants have been identified for complex diseases. Somatic gene conversion and deletion were shown for BD, coronary arterial disease, rheumatoid arthritis, Chron's disease, hypertension and diabetes[37]. In a study of Lehne *et al*[38], comorbidity is mentioned between BD, Chron's disease and diabetes. At the same time, the concern of "missing heritability" has also emerged. There is however no unified way to assess the heritability explained by individual genetic variants for binary outcomes. A systemic and quantitative assessment of the degree of "missing heritability" for complex diseases is lacking. The diseases under evaluation included Alzheimer's disease, bipolar disorder, breast cancer, coronary artery disease, Crohn's disease, prostate cancer, schizophrenia, systemic lupus erythematosus (SLE), type 1 diabetes and type 2 diabetes[39]. The median total variance explained across the 10 diseases was 9.81%, while the median variance explained per associated SNP was around 0.25%. These results evaluated according to environmental impact assessment. This is because methylations and demethylations of DNA continue in primordial germ cells during of development within the terms of epigenetic principles. In fact, a substantial proportion of heritability remains unexplained for the diseases.

CONCLUSION

Medical disease in adults had a significant relationship to adverse life experiences in childhood (ACE). Examples of the links between childhood experience and adult biomedical disease are the relationship of ACE score to obesity, diabetes, coronary artery disease chronic obstructive pulmonary disease and autoimmune disease[40]. This illustrates that adverse experiences in childhood are related to adult disease by two basic etiologic mechanisms: (1) conventional risk factors that actually are compensatory behaviors, attempts at self-help through the use of agents and foods; (2) the effects of chronic stress as mediated through the mechanisms of chronic hypercortisolemia, proinflammatory cytokines and other stress responses on the developing brain and body systems, dysregulation of the stress response and pathophysiological mechanisms yet to be discovered. There is some biological correlates for adverse life experiences of childhood in bipolar patients. Early menarche and EEG abnormalities are some of them[41-43].

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 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.

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