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Association of Bipolar Disorder on Cardiovascular Disorders: And Mechanisms Included

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ABSTRACT

Bipolar disorder is one of several mental and physical health conditions associated with an increased risk of developing atherosclerosis (hardening of the arteries) and cardiovascular heart disease. And according to the American Heart Association, that increased risk may be evident early in life. Studies have found that young people with bipolar disorder have above-average rates of elevated triglycerides (blood fats), cholesterol, and blood pressure. Other risk factors for heart disease, such as overweight, obesity, diabetes, metabolic syndrome, smoking tobacco and other substance use, are more common in those with bipolar disorder than the general population.This review aims in analysing the association with bipolar disorders and cardiovascular disorders by assessing the mechanisms involved in the same which includes inflammation, oxidative stress and brain derived neurotrophic factor.

KEYWORDS: Bipolar disorder, Cardiovascular disorder, Inflammation, Oxidative stress, Brain derived neurotrophic factor, Reactive oxygen species, Atherosclerosis, Hypertension

I. INTRODUCTION

Bipolar disorder (BD) is adisorder associated with episodes of mood swings ranging from depressive lows to manic highs. 46 million people around the world, including 2.8% of the U.S. population, have bipolar disorder. The exact cause of bipolar disorder isn't known, but a combination of genetics, environment and altered brain structure and chemistry may play a role.There are 2 types of BD: BD-I, BD II.Depressive episodes have symptoms of a depressive disorder, causing a person to feel a strong sense of sadness with low energy and motivation. Manic episodes are the opposite-one can feel energetic, optimistic, and even euphoric-which can lead to irrational, impulsive decision-making. The type and intensity of symptoms of bipolar disorder vary from person to person. Several medicines are available to help stabilise mood swings. These are commonly called mood stabilisers and include: Lithium, Anticonvulsant medicines, Antipsychotic medicines. Counselling, cognitive behavioural therapy, psychotherapy are also included in treatment.

Persons with mental disorders are disproportionately burdened by medical comorbidity compared to age-matched controls, notably from cardiovascular disease (CVD) and hypertension (HTN).Although many psychotropic medications clearly exacerbate medical risk, bipolar disorder itself appears to confer risk for cardiovascular disease independent of treatments used to manage the disorder. Several cardiovascular risk factors are more common in individuals with bipolar disorder than in the general population, which may help to explain the elevated risk of cardiovascular morbidity and mortality. These risk factors include: obesity, hypertension, diabetes, and hyperlipidemia. Each could contribute to excess cardiovascular mortality. Adolescents with BD tend to develop CVD earlier than people in the general population.BD onset occurs before CVD, so clinicians have an opportunity to slow CVD progression. Because adults with BD have 5 times the risk of CVD, clinicians should recognize that young patients with BD show signs of CVD 17 years earlier than those who do not have BD.

MECHANISMS

Among persons with BD, there is a higher prevalence of unhealthy behaviours and known CVD risk factors, such as smoking, alcohol misuse, obesity, sedentary lifestyle, hypertension, diabetes, poor diet and poor treatment compliance. Individuals with mental illness are generally less likely to seek help and once help is sought, less likely to obtain adequate treatment for medical conditions. Several mechanisms underlie the BD-CVD connection: inflammation, oxidative stress,

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and brain-derived neurotrophic factor (BDNF). The proinflammatory markers C-reactive protein, interleukin 6, and tumor necrosis factor-alpha are increased in the presence of BD symptoms and are also implicated in atherosclerosis. Oxidative stress, also present during BD symptoms, causes dysfunction in the endothelium.During the symptomatic phase of BD, BDNF levels decrease, thereby damaging the endothelial cells, which increases the risk for CV events. BD is also linked genetically to coronary artery disease, hypertension, and diabetes.

Epidemiological evidence shows BD is associated with increased rates of inflammatory comorbidities including numerous autoimmune conditions, hypersensitivity reactions (asthma, seasonal allergies), and cardiometabolic diseases . Though causality in this regard has yet to be established, recent research indicates that the relationship is likely bidirectional . Patients with BD demonstrate both central and peripheral elevations in proinflammatory elements (cytokines, chemokines, prostaglandins, acute-phase reactants, oxidative/nitrosive species), increased inflammatory gene expression, as well as aberrant cellular (T-cell, monocyte, microglial) and complement activation. Despite some variation across studies, overall, patients with BD seem to consistently demonstrate higher serum concentrations of TNF soluble TNF-receptor 1 (sTNF-R1), IL-1β, IL-4, soluble IL-2 receptor (sIL-2R), and soluble IL-6 receptor (sIL-6R) compared to healthy individuals. Inflammation is also a key factor in all aspects of coronary disease including the initiation and progression of atherosclerotic plaque, plaque rupture, and thrombosis (atherothrombosis), especially in recurrent thrombosis where oxidative stress is known to play a significant role , including in those with normal cholesterol levels and in those being treated with “statins” and antiplatelet agents. Inflammation can affect the lining of your heart or valves, the heart muscle, or the tissue around the heart. Inflammation in the heart can lead to other serious health problems, including an irregular heartbeat called an arrhythmia, heart failure, and coronary heart disease.

The term “oxidative stress” describes the imbalance between reactive oxygen species (ROS) production and the antioxidant system’s ability to eliminate them. Either overproduction of ROS or a decrease in antioxidative agents can cause oxidative imbalance. During cellular respiration in mitochondria, some electrons escape the electron transfer chain and produce ROS. Evidence suggests that BD is associated with mitochondrial dysfunction, probably due to a dysregulation in mitochondrial genes. Besides, in BD patients, dopamine and glutamate levels increase, which have a high tendency to produce excess ROS . Another source of ROS production isneuroinflammation in BD patients. Oxidative stress and inflammation are highly interdependent and aggravate each other.Oxidative stress has also been identified as critical in most of the key steps in the pathophysiology of atherosclerosis and acute thrombotic events, including dyslipidemia leading to atheroma formation, the oxidation of LDL, endothelial dysfunction, plaque rupture, myocardial ischemic injury, and recurrent thrombosis (i.e., the secondary, or subsequent clot that often occurs after initial thrombolysis). ROS negatively affect myocardial calcium handling, cause arrhythmias, and contribute to cardiac remodelling by inducing hypertrophic signalling, apoptosis, and necrosis. In pathological situations, particularly atherosclerosis or hypertension, the release of ROS exceeds endogenous antioxidant capacity, leading to cell death. At cardiovascular levels, oxidative stress is highly implicated in myocardial infarction, ischemia/reperfusion, or heart failure.

Brain-Derived Neurotrophic Factor (BDNF) is crucial for various aspects of neuronal development and function, including synaptic plasticity, neurotransmitter release, and supporting neuronal differentiation, growth, and survival. In contrast, BDNF antisense RNA (BDNF-AS) is linked to the regulation and control of BDNF, facilitating its suppression and contributing to neurotoxicity, apoptosis, and decreased cell viability. The BDNF transcript is translated into a pre-pro-BDNF precursor protein, which is further cleaved into the precursor form, pro-BDNF. Then, pro-BDNF is cleaved intracellularly into the mature form (m-BDNF), which is then released into the extracellular space and is simply called BDNF. The alteration of BDNF levels, as well as the imbalance between pro-BDNF and m-BDNF, and deficits in BDNF signalling are associated with the pathogenesis of various neurologic and psychiatric disorders, including depressive disorder, schizophrenia, and bipolar disorder. Research examining post-mortem brain tissue from individuals diagnosed with bipolar disorder (BD) revealed a decrease in BDNF levels in the hippocampus and prefrontal cortex.BDNF is synthesized and packaged in the alpha granules of megakaryocytes, the platelet precursor. Platelets

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circulate in blood, and following platelet aggregation, BDNF is released with other platelet granule contents. Thus, platelet adhesion to the injured vasculature, which can occur in regions of atherosclerosis or thrombosis, provides high local concentrations of BDNF to the vessel wall.BDNF plays a role in the progression of human cardiovascular disease. For example, this neurotrophin promotes atherogenesis and plaque instability via the activation of NAD(P)H oxidase. In patients after myocardial infarction BDNF is related to inflammation and platelet activation6. At the same time low plasma BDNF was associated with future coronary events and mortality in patients with angina pectoris.

II. CONCLUSION

Although bipolar BD and CVD are frequently comorbid, clinicians may not seize the opportunity to prevent CV events in patients with the comorbidities. Yet in people with BD, CVD is the leading cause of death. Several mechanisms are involved in association of BD with CVD: inflammation, oxidative stress, and BDNF. While the BD-CVD association appears incontrovertible, changes in diet, exercise, and weight could alter modifiable risk factors.5 Indeed, the earlier that clinicians recognize the comorbidities, the earlier they can slow the progression to CV events, even in adolescents recently diagnosed with BD.More research is needed to understand the link between BD and heart disease and develop treatment approaches to address both conditions.

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