Journal of Psychosomatic Research xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Journal of Psychosomatic Research

Cardiovascular and psychiatric characteristics associated with oxidative stress markers among adolescents with bipolar disorder

Jessica Hatch [a,b], Ana Andreazza [c,d], Omodele Olowoyeye [e], Gislane Tezza Rezin [c], Alan Moody [f], Benjamin I. Goldstein [a,b,*]

[a] Sunnybrook Health Sciences Centre, Psychiatry, Toronto, ON, Canada
[b] University of Toronto, Pharmacology & Toxicology, Toronto, ON, Canada
[c] University of Toronto, Psychiatry, Toronto, ON, Canada
[d] Centre for Addiction and Mental Health, Toronto, ON, Canada
[e] University of Toronto, Institute of Medical Science, Toronto, ON, Canada
[f] Sunnybrook Health Sciences Centre, Medical Imaging, Toronto, ON, Canada

ARTICLE INFO

Article history:
Received 7 November 2014
Received in revised form 8 April 2015
Accepted 15 April 2015
Available online xxxx

Keywords:
Adolescent
Atherosclerosis
Bipolar disorder
Cardiovascular
Oxidative stress

ABSTRACT

Introduction: In the field of bipolar disorder (BD) research there is an absence of validated biomarkers and limited understanding of the biology underlying excessive and premature cardiovascular disease (CVD). Oxidative stress is a potential biomarker in both BD and CVD.
Objective: To examine psychiatric and cardiovascular characteristics associated with peripheral oxidative stress markers among adolescents with BD, who are at high risk for CVD.
Methods: Participants were 30 adolescents, 13–19 years old, with BD and without CVD. Ultrasonography was used to evaluate vascular function and structure. Traditional CVD risk factors were also measured. Psychiatric assessments were conducted via semi-structured interview. Serum levels of oxidative stress (lipid hydroperoxides (LPH) and protein carbonylation (PC)) were assayed.
Results: Compared to published data on adults with BD, adolescents had significantly lower levels of LPH and PC ($t_{52}(11.34)$, $p < 0.0001$; $t_{58}(29.68)$, $p < 0.0001$, respectively). Thicker mean and maximum carotid intima media thickness was associated with greater levels of LPH ($r = .455$, $p = .015$; $r = .620$, $p < 0.0001$, respectively). LPH was associated with diastolic blood pressure ($r = -.488$, $p = 0.008$) and pulse pressure ($r = .543$, $p = 0.003$). Mood symptoms and medication were not significantly associated with oxidative stress.
Conclusion: Adolescents with BD have lower levels of oxidative stress compared to adults with BD, supporting prevailing illness staging theories for BD. Oxidative stress is robustly associated with a proxy measure of atherosclerosis and may explain in part the increased risk of CVD in BD.

Introduction

Bipolar disorder (BD), prevalent in 2–5% of the general population, is characterized by states of depression and mania and/or hypomania (states of extreme elation and/or irritability, among other symptoms) [1]. To date, there are no definitive biomarkers despite a pressing need for objective markers that can be employed in assessment, prognosis, treatment selection, and determination of treatment response [2].

Oxidative stress has been implicated as a leading putative biomarker in BD [2–5]. Oxidative stress comprises a disruption in oxidant and anti-oxidant balance, in which increased oxidant levels may lead to physiological damage [6]. Reactive oxygen species (ROS) generation is ongoing in normal physiological conditions; however the imbalance in the redox regulation can lead to irreversible cellular damage [7].

It has been demonstrated that patients with BD have significantly different levels of antioxidant enzymes, lipid peroxidation and nitric oxide (NO) levels [8], compared to patients without BD [3,9,10]. Aberrant oxidative stress levels may therefore contribute to the pathophysiology of BD [10]. Notably, oxidative stress levels may comprise state markers of disease activity among adults with BD [10,11]. Recent meta-analyses on oxidative stress in adults with BD have highlighted the alterations in oxidative stress and antioxidant enzymes in BD, compared to psychiatrically healthy adults [9,10]. Brown and colleagues reported a meta-analysis on 971 participants with BD and 886 healthy controls, concluding that there is a clear role of oxidative stress in BD pathology, with a particularly robust association with elevated levels of lipid peroxidation [9].

* Corresponding author. Tel.: +1 416 480 6100x87572; fax: +1 416 480 6878.
E-mail address: benjamin.goldstein@sunnybrook.ca (B.I. Goldstein).

http://dx.doi.org/10.1016/j.jpsychores.2015.04.005
0022-3999/

Previous literature has also noted that BD can be described in terms of stages of disease course based not only on psychiatric symptomatology, but also via white matter integrity, inflammation and oxidative stress [4,6,12,13]. It has been highlighted that in the early stages of BD major antioxidant systems are not elevated compared to control patients; however, in the later stages in the course of BD, there is a significant increase in antioxidant levels [6]. It may therefore be the case that in the earlier stages in the course of BD, there has not yet been a mechanism to compensate for the higher levels of oxidative stress, and that this compensatory action may take place too late in the course of illness [6]. Oxidative stress has therefore been postulated to be a marker of neuroprogression for those with BD, which would provide much needed information for staging purposes, and perhaps better prevention strategies and personalized care [4].

BD pathology comprises not only aberrant mood patterns, but has been associated with increased risk of cardiovascular disease (CVD) [14]. CVD is excessive and premature in adults with BD suggesting that adolescents with BD are at a high risk for future CVD [15]. Likewise, oxidative stress has also been shown to be involved in the ageing of vasculature and the development and progression of endothelial dysfunction, atherosclerosis, and CVD [16–19]. In CVD, oxidative stress is potentially increased in multiple pathways, including but not limited to: shear stress on vasculature, NO impairment, apoptosis and cellular senescence [16]. Oxidative stress contributes to endothelial dysfunction, whereby vascular endothelial damage can result from interactions between ROS and vascular endothelial produced NO [20].

Non-invasive imaging measures of vascular structure and function have been previously validated among non-BD adolescents, as demonstrated by the association of these measures with standard cardiovascular risk factors [21–25]. We recently demonstrated that, despite multiple potential confounds such as variation in medications and other clinical characteristics, non-invasive vascular imaging measures are associated with traditional cardiovascular risk factors among adolescents with BD as well [25].

While oxidative stress has been established as a leading candidate biomarker in BD pathology among adults, there is a paucity of data on this topic among adolescents with BD. A recent magnetic resonance spectroscopy study found that adolescents and young adults with BD do not differ significantly from controls with regard to brain glutathione [26,27]. However, no prior study has examined serum oxidative stress markers in this population. Similarly, no previous study of any age group has examined whether oxidative stress is associated with vascular function and structure in BD. We therefore set out to conduct a preliminary study examining the psychiatric and cardiovascular characteristics that may be associated with peripheral oxidative stress among adolescents with BD.

Methods

All procedures were approved by the Research Ethics Board (REB), and are in accordance with the Helsinki Declaration of 1975. Written informed consent was obtained from all participants (parents and/or guardians and adolescents) prior to study procedures.

Sample

English-speaking adolescents (N = 30, 13–19 years old) were recruited from the Centre for Youth Bipolar Disorder, Sunnybrook Health Sciences Centre (Toronto, Ontario). Participants were excluded if they had an infectious illness within the past 14 days, or were unable to provide informed consent (i.e. due to developmental delay or psychosis). Participants were free from any cardiac condition, autoimmune, infectious, or inflammatory illness, and were not taking medication for any of the noted conditions.

Assessment

Interviews

The Schedule for Affective Disorders and Schizophrenia for School-Aged Children, Present and Lifetime version (K-SADS-PL), a semi-structured diagnostic interview, was utilized for diagnostic purposes [28]. DSM-IV criteria were confirmed for bipolar subtype (BD type I (BD-I) and BD type II (BD-II)), and BD not otherwise specified (BD-NOS) was defined using operationalized criteria from the Course and Outcome of Bipolar Youth (COBY) study [29]. Participants were interviewed directly, and parents/guardians were separately interviewed about the participant. A child-adolescent psychiatrist confirmed diagnoses.

Ultrasound and physical assessments

Participants completed study procedures starting with diagnostic interviews on visit one. Visit two began with ultrasound, followed by blood-draw and symptom assessments, with appointments starting between eight and ten a.m. Participants fasted ten hours prior to appointment start time (no food or drink, except for water). All participants were also instructed not to use illicit drugs, smoke tobacco or consume alcohol for 24 h prior to the appointment. Adherence to fasting and abstinence from drugs was assessed via interview.

A sonographer carried out ultrasound (Phillips, iU22) procedures to measure flow mediated dilation (FMD) and carotid intima media thickness (cIMT). FMD assesses macrovascular function, while cIMT assesses macrovascular structure. Imaging procedures utilized two-dimensional doppler imaging, with a high-frequency (10 MHz) linear-array transducer, with duplicate scans performed for reliability. Blood pressure and electrodes were placed for a three-lead electrocardiogram (ECG), prior to FMD and cIMT measurement. Procedures began with participants reclining and rested for at least ten minutes. cIMT was measured with the subject recumbent, neck extended and head at a 45-degree angle, contralateral to the side being examined. The common cIMT, bulb IMT, and internal common cIMT (regions as described in Urbina et al., 2009) [21] for right and left sides, were investigated [21,30]. Blood pressure was measured using a stethoscope, sphygmomanometer and adjustable cuff, as per standard procedures. Pulse pressure (PP) was calculated as the difference between systolic blood pressure and diastolic blood pressure.

Participants remained recumbent with their right arm adjacent to the sonographer for FMD assessment. A stand was used to hold the transducer steady during FMD measurement, which was taken concurrently with an ECG recording. Lower-arm placement of the blood pressure cuff was used, with the cuff inflated to 50 mmHg above systolic for five minutes. Following cuff deflation, FMD was recorded for five minutes, and analyzed at 30-second intervals. As in previous studies, FMD was calculated as a percentage-change in brachial artery diameter compared with baseline measurements. A second blood-pressure reading was taken on the contralateral arm following ultrasound procedures.

Blood-draw was carried out between nine and eleven a.m. (exact time was recorded). Fasting glucose, triglycerides, total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were assessed. Anthropomorphic measurements were assessed next. Subject weight and height were recorded (to the nearest 0.5 cm and 0.1 kg, respectively), with duplicate measures taken for reliability purposes. To account for clothing, adjusted body mass index (BMI) was calculated (subtracting from measured weight: 1.4 kg for long pants and long-sleeves/sweatshirt, 1.1 kg for short pants or short-sleeves, and 0.9 kg for short pants and short sleeves) and waist circumference was measured using a flexible tape measure (to the nearest 0.5 cm).

Assays

Commercial enzyme linked immunosorbant assay (ELISA) kits, were used to quantitatively assess lipid hydroperoxides (LPH) (Cayman

Please cite this article as: Hatch J, et al, Cardiovascular and psychiatric characteristics associated with oxidative stress markers among adolescents with bipolar disorder, J Psychosom Res (2015), http://dx.doi.org/10.1016/j.jpsychores.2015.04.005