Journal of Affective Disorders 135 (2011) 43–50

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

The load of short telomeres is increased and associated with lifetime number of depressive episodes in bipolar II disorder

Torbjørn Elvsåshagen [a,e,*], Elsa Vera [b], Erlend Bøen [a], Jorunn Bratlie [c], Ole A. Andreassen [d,e], Dag Josefsen [f], Ulrik F. Malt [a,e], Maria A. Blasco [b], Birgitte Boye [a]

[a] Department of Neuropsychiatry and Psychosomatic Medicine, Oslo University Hospital, Oslo, Norway
[b] Telomeres and Telomerase Group, Spanish National Cancer Center (CNIO), Madrid, Spain
[c] Research Institute of Internal Medicine, Oslo University Hospital, Oslo, Norway
[d] Section for Psychosis Research, Oslo University Hospital, Oslo, Norway
[e] Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[f] Department of Oncology, Oslo University Hospital, Oslo, Norway

ARTICLE INFO

Article history:
Received 27 April 2011
Received in revised form 1 August 2011
Accepted 1 August 2011
Available online 30 August 2011

Keywords:
Bipolar disorders
Aging
Load of short telomeres
Telomere length
Depressive episode

ABSTRACT

Background: It has recently been hypothesized that bipolar disorders are associated with accelerated aging. Telomere dysfunction, a biomarker of aging, is determined by the load of short telomeres, rather than by the mean telomere length. To our knowledge, the load of short telomeres has not been reported in any psychiatric disorder. The aims of the study were to examine the load of short telomeres and the mean telomere length and their relationships with illness duration and lifetime number of depressive episodes in bipolar II disorder (BD-II).
Methods: Twenty-eight patients (mean age = 34.8 ± 7.7) with a DSM-IV diagnosis of BD-II and 28 healthy control subjects (mean age = 34.8 ± 9.2) matched for age, sex, and education participated. The load of short telomeres (percentage of telomeres <3 kilobases) and mean telomere length in peripheral blood mononuclear cells were measured using high-throughput quantitative fluorescence in situ hybridization.
Results: The load of short telomeres was significantly increased in patients with BD-II relative to healthy controls and may represent 13 years of accelerated aging. The load of short telomeres and the mean telomere length were associated with lifetime number of depressive episodes, but not with illness duration.
Limitations: Modest sample size and cross-sectional design.
Conclusions: Our results suggest that BD-II is associated with an increased load of short telomeres. Depressive episode-related stress may accelerate telomere shortening and aging. However, longitudinal studies are needed to fully clarify telomere shortening and its relationship with clinical variables in BD-II.

1. Introduction

Bipolar I disorder (BD-I) and bipolar II disorder (BD-II) are among the leading causes of disability worldwide (Angst, 2007; Lopez and Murray, 1998). In recent years, associations have been found between bipolar disorders and elevated rates of cardiovascular disease, type 2 diabetes, and other diseases of aging (Kupfer, 2005; Osby et al., 2001). The excess morbidity may be related to indirect adverse effects of bipolar disorders, such as negative health behaviors (e.g., smoking, unhealthy diet, and sedentary lifestyle) and poor compliance with medical regimens (DiMatteo et al., 2000; Lasser et al., 2000; McElroy et al., 2002). In addition, it has been increasingly

* Corresponding author at: Department of Neuropsychiatry and Psychosomatic Medicine, Oslo University Hospital - Rikshospitalet, Pb 4950-Nydalen, 0424 Oslo, Norway. Tel.: +47 230 74920; fax: +47 230 74930.
E-mail address: telvsaha@ous-hf.no (T. Elvsåshagen).

0165-0327/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.jad.2011.08.006

recognized that the pathophysiological mechanisms underlying bipolar disorders may directly contribute to the excess risks (Evans et al., 2005; Kupfer, 2005). Although the assumed direct effects remain to be fully clarified, dysregulation of the hypothalamic–pituitary–adrenal axis, altered immune function, and oxidative stress may be involved (Kapczinski et al., 2008; Wolkowitz et al., 2010). It has recently been hypothesized that the indirect and direct adverse effects of bipolar disorders may cause accelerated aging (Simon et al., 2006; Wolkowitz et al., 2010).

Telomeres are DNA-protein structures at the ends of chromosomes that protect them from recombination and degradation (Aubert and Lansdorp, 2008; Blackburn, 2001). In human cells, telomeres are composed of tandem repeats of the TTAGGG sequence and average between 6 and 12 kilobases (kb) in length (Aubert and Lansdorp, 2008; Yamaguchi et al., 2005). Telomeres shorten with every cell division due to the incomplete replication of linear chromosomes (the so-called 'end-replication problem'). In most human tissues, the activity of telomerase, a reverse transcriptase that elongates telomeres, is insufficient to prevent telomere shortening (Collins and Mitchell, 2002; Harley et al., 1990). Accordingly, telomeres shorten with increasing age (Frenck et al., 1998; Yamaguchi et al., 2005). When telomeres become critically short, the risk of apoptosis is increased and proliferation is arrested, which eventually compromises tissue renewal capacity and function (Blasco, 2007; Hemann et al., 2001; Samper et al., 2001). Telomere length may therefore represent a 'molecular clock' that contributes to aging (Blackburn, 2001; Collins and Mitchell, 2002).

Most previous telomere studies in humans have measured the mean telomere length. However, evidence suggests that it is not the mean telomere length, but rather the amount of short telomeres that determines telomere dysfunction and cell viability (Armanios et al., 2009; Blasco, 2007; Hao et al., 2005; Hemann et al., 2001; Rajaraman et al., 2007; Samper et al., 2001). Methods have been developed that allow the measurement of telomere length at individual chromosomes at the single-cell level, thereby enabling the quantification of short telomeres (Aubert and Lansdorp, 2008). With these methods, it has been shown that the load of short telomeres increases with age in peripheral blood mononuclear cells (PBMCs) (Canela et al., 2007) and correlates with cell senescence (Bendix et al., 2010). To our knowledge, the load of short telomeres has not been reported in any psychiatric disorder.

A few studies have measured the mean telomere length in PBMCs from subjects with mood disorders, and have found evidence for accelerated telomere shortening in bipolar disorder (Simon et al., 2006) and major depressive disorder (Hartmann et al., 2010; Lung et al., 2007; Simon et al., 2006). The exact mechanisms that may underlie telomere shortening in mood disorders are incompletely understood. It has been hypothesized that mood disorder-related chronic stress leads to accelerated telomere shortening and aging (Simon et al., 2006; Wolkowitz et al., 2010). This notion is supported by findings of significant associations between chronic stress and telomere shortening among healthy adult women (Epel et al., 2004) and caregivers of Alzheimer's disease patients (Damjanovic et al., 2007). However, in bipolar disorders, self-reported levels of psychological distress are higher during depressive episodes than during periods of euthymia (Goossens et al., 2008). In addition, a recent study found that a composite measure of systemic toxicity or stress, assessing peripheral neurotrophins, oxidative stress, and inflammatory markers, was elevated in depressive episodes, but not during euthymia among subjects with bipolar disorder (Kapczinski et al., 2010). Therefore, an alternative hypothesis is that episodic depressive episode-related stress, rather than chronic stress, accelerates telomere shortening and aging in bipolar disorders.

The main objective of the present study was to measure the load of short telomeres in BD-II. We hypothesized that BD-II patients would have increased load of short telomeres in PBMCs relative to age-matched healthy control subjects. In addition, the mean telomere length was measured. Based on previous findings (Hartmann et al., 2010; Lung et al., 2007; Simon et al., 2006), it was hypothesized that BD-II patients would have shorter mean telomere lengths in PBMCs than the control group. Moreover, the relationships between the two telomere measures and illness duration and lifetime number of depressive episodes were examined. A significant association between the telomere measures and illness duration would support the chronic stress hypothesis, while an association between the telomere measures and lifetime number of depressive episodes would support the depressive episode-related stress hypothesis of telomere shortening. Finally, in explorative analyses, we assessed the relationships between telomere shortening and clinical variables.

2. Methods

2.1. Participants

Twenty-eight patients with BD-II were recruited from psychiatric outpatient clinics in the Oslo area. Clinical examinations were carried out by three of the authors (E.B, B.B, and U.F.M), who are senior psychiatrists in a university department specializing in the evaluation and treatment of mood disorders. Axis I diagnoses and psychiatric comorbidities were determined using the Mini-International Neuropsychiatric Interview (MINI), DSM-IV criteria version 5.0 (Sheehan et al., 1998). Demographic and supplementary information, including illness duration (current age minus age at the onset of first symptoms of hypomania or depressive symptoms that affected functioning), and lifetime number of depressive (duration of at least 14 days) and hypomanic episodes (duration of at least 4 days) was obtained using the Stanley Foundation Network Entry Questionnaire (NEQ), formerly known as the Patient Questionnaire and the Clinician Questionnaire (Suppes et al., 2001). The NEQ was applied as a semi-structured interview. Alcohol and drug abuse were assessed with the Alcohol Use Scale and the Drug Use Scale (Drake et al., 1996), respectively. Mood state at the time of telomere measurement was determined by the Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and the Young Mania Rating Scale (YMRS) (Young et al., 1978).

Twenty-eight healthy control subjects matched with the patient group for sex, age, and education were recruited through local advertising and underwent a full examination similar to that of the BD-II patients. Healthy controls with previous or current psychiatric illness were excluded from