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Research report

Analysis of telomere attrition in bipolar disorder

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ABSTRACT

Background: Telomeres can be considered a marker of biological aging. Studies have suggested that telomere shortening may be associated with aging related diseases and also psychiatric disorders.
Objectives: Investigate whether bipolar disorder (BD) and its clinical specificities are associated with telomere shortening.
Methods: Eighty-five BD patients and 95 healthy controls were paired for age, sex and educational level. Volunteers were submitted to a psychiatric interview and clinical evaluation. Patients and controls were compared as a whole sample and within specific telomere range (short and long telomeres). Intrapatients group comparison involved type of BD and comorbidities. A Real Time Quantitative PCR was performed in order to verify leukocytes telomere length.
Results: Bipolar disorder patients presented shorter telomeres when compared to controls ($p < 0.001$). However, there was no significant difference in telomere length between different BD subtypes. When two groups of patients (long and short telomeres) were compared, only panic disorder showed an association with telomere categories ($\chi^2 = 6.91$; $p = 0.009$; OR = 4.27).
Limitations: It was not possible to collect information about time since diagnosis, which limited conclusions regarding BD chronicity and telomere length. Furthermore, medication interference upon telomere length was not controlled.
Conclusions: Results suggest that BD is associated with reduced telomere length. Also, panic comorbidity may represent an additive risk factor. Understanding aspects that contribute to determination of telomere size in bipolar patients allows us to understand what the impact on telomeres size is, which is a health vulnerability marker.

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1. Introduction

Telomeres are tandem TTAGGG repeats of DNA located at the end of linear chromosomes (Blackburn, 2000). They are crucial for maintaining chromosomal integrity and to protect them from loss of genetic material and from end-to-end recombination (Blackburn, 2005). Due to its unique features, the enzyme named telomerase is responsible for replicating telomeric regions. However, in most human somatic tissues, telomerase activity is not enough to avoid telomere erosion over time (Chan and Blackburn, 2004). Consequently, telomeres shorten after each cell division and may be used as biological aging marker (Blackburn, 2005). For instance, some studies have suggested that telomere shortening may be associated with aging related diseases such as cardiovascular diseases and diabetes (Salpea et al., 2010; Wong et al., 2010)

Telomere length and telomerase activity can be influenced by several factors including body mass index range and smoking (Babizhayev et al., 2011; Valdes et al., 2005). Hypothetically, these factors added to oxidative and inflammatory stress states may trigger cellular responses that ultimately lead to senescence and telomere shortening (Valdes et al., 2005). Therefore, it has been suggested that telomere length may be a response to cellular stress.

Stress is defined as a threat to homeostasis. An organism responds to it by making efforts to return to its previous state (McEwen and Stellar, 1993). However, chronic stress exposure and persistent cellular response to stress may be dysfunctional (McEwen, 2003). Although depression is traditionally associated with increased cortisol level, long term exposure to stress has been

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related to a initial stage of hyperactive HPA axis evolving to a hypocortisolemic state, which is related to shorter telomeres (Wikgren et al., 2012). Moreover, studies have shown that high levels of pro-inflammatory cytokines during a depressive episode are associated with telomere shortening (Damjanovic et al., 2007). Therefore, a putative association between psychological stress and accelerated telomere attrition has been suggested.

Bipolar disorder (BD) is a mood disorder that affects from 2% up to 4% of general population (Merikangas et al., 2007). It has been categorized into two main subtypes. Type I BD is defined by the presence of at least one manic episode, regardless of the occurrence of depressive episodes. Type II BD is distinctive by the presence of hippomanic and depressive episodes (Goodwin and Jamison, 2007). BD is associated with poor quality of life (Judd et al., 2005), family disturbances (Judd and Akiskal, 2003) and high mortality rate, greater than average population rates (Angst et al., 2012). Bipolar disorder patients suffer more from cardiovascular diseases which account for one third of their deaths (Westman et al., 2013). Therefore, studies have suggested higher health vulnerability within this clinical group. Bipolar disorder can be hypothesized as presenting cumulative stress to the extent that mood episodes, drug abuse, and other conditions progressively occur (Kapczinski et al., 2008). An important issue is that higher concentrations of corticotrophin (ACTH) dysfunction persist in patients when compared to controls even during remission of symptoms, indicating prolonged consequences of stress response (Vieta et al., 1997). Furthermore, patients with HPA dysfunction seem to be more vulnerable to relapse (Vieta et al., 1997). These findings highlight the importance of clarifying stress response dynamics to improve both clinical and psychiatric prognosis.

Considering bipolar disorder evaluation of telomere length, although one study (Mansour et al., 2011) did not find any differences between groups, there is some evidence of shorter telomere length in bipolar patients in contrast with controls (Rizzo et al., 2013; Simon et al., 2006). Furthermore, one study has found a greater proportion of short telomeres within the bipolar group (Elvsåshagen et al., 2011). These authors suggested that the number of previous depressive episodes might be related to telomere attrition in bipolar disorder. Considering that only a few studies have investigated telomere attrition and even fewer have analyzed clinical features related to it, it becomes relevant to target these aspects in order to clarify stress dynamics and health vulnerability in BD.

In this study, the aim was to verify whether bipolar disorder and its clinical specificities are associated with telomere shortening. Apart from medication, the clinical aspects considered were those reported to be involved in BD patient prognosis, including history of suicide attempts, comorbidities and disorder subtype (Dalton et al., 2003; Vieta et al., 1997). The investigation is based on the hypothesis that these factors could provide additional stress, thus exacerbating telomere shortening.

2. Methods

2.1. Sample

The sample comprised 85 patients and 95 control subjects matched by age, gender and sex. All patients were diagnosed with bipolar disorder and classified by a senior psychiatrist according to their BD subtype (I or II) and the following comorbidities: Generalized Anxiety Disorder, panic, alcoholism, drug Abuse, eating and obsessive compulsive disorder. Classification was performed after a structured interview—MINI Plus 5.0 (Sheehan et al., 1998) which follows DSM-IV criteria for Axis I psychiatric disorders. Data for the presence of Borderline Personality Disorder was collected according to DSM-IV criteria. Volunteers were outpatients of a specialized bipolar clinic (Belo Horizonte, Brazil). Exclusion criteria among patients group were based on the presence of neurological conditions, poor insight that would preclude interview comprehension and present BD subtypes other than type I or II. The control group was selected using the structured interview cited above (Amorim, 2000; Sheehan et al., 1998) and subjects included were those who had no past or present history of psychiatric disorders.

Although mood status and medication were not inclusion criteria, it was previously investigated for sample description. Depressive mood status was assessed by a Brazilian version of Beck Depression Inventory—BDI II (Gorenstein and Andrade, 1998) and manic symptoms were screened by Brazilian version of Young Mania Rating Scale (Young et al., 1978). Medication prescription was also recorded.

The interview, scale and inventory, DNA extraction and analyses procedures were explained to all subjects, who previously provided informed consent. This study was approved by the local ethics committee (CAAE: 21185713.2.00005149) COEP and procedures were conducted according to the principles expressed in the Helsinki Declaration.

2.2. Telomere length assay

Peripheral blood samples were collected in tubes containing EDTA, followed by DNA extraction with a high salt method (Lahiri and Schnabel, 1993). DNA was quantified using a NanoDrop Spectrophotometer Thermo Scientific, Nanodrop 200 model, and diluted to 75 ng in 96 well plates.

Telomere length was measured using a relative quantification method that has been previously used and described (Cawthon, 2002). Briefly, two master mixes were prepared using the following primer pairs: for telomeres GGTTTTT-GAGGGTGAGGGTGAGG-GTGAGGGTGAGGGT and TCCCGACTATCCCTATCCCTATCCCTATCCCTA-TCCCTA, for control gene 36B4 CAGCAAGTGGGAAGGTGTAATCC and

Table 1
Sample characteristics.

	Patients ($N=85$)	Control ($N=96$)	p-value
Age (mean ± SD) years	39.46 (± 10.63)	38.33 (± 11.02)	0.48
Sex, woman, *n* (%)	21 (24.7%)	35 (36.5%)	0.08
Educational level			
Primary school, *n* (%)	17 (20.0%)	26 (27. 4%)	0.47
Secondary school, *n* (%)	39 (45.9%)	42 (44.2%)	
Undergraduation, *n* (%)	29 (34.1%)	27 (28.4%)	

BD patients had shorter mean telomere length compared to control subjects (Fig. 1) —with a moderate effect size (0.36).

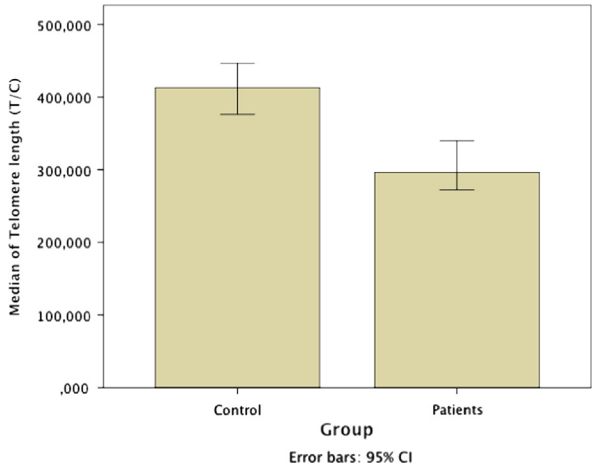

Fig. 1. Comparison between patients and controls.

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