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Leukocyte telomere length in patients with bipolar disorder: An updated meta-analysis and subgroup analysis by mood status

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ABSTRACT

The purpose of the present meta-analysis was to compare leukocyte telomere length (LTL), a proposed marker for cell aging, between patients with bipolar disorder (BD) and healthy controls and explore potential moderators for the LTL difference. We searched for the major research databases up to May 2018 for studies that examined LTL in patients with BD and healthy controls. The effect sizes (ESs) of LTL differences from the included studies were pooled using a random-effects model. Furthermore, we adopted subgroup analysis to investigate whether mood status of BD patients or methods for measuring telomere length may influence such differences. We included 10 studies, with a total of 579 patients and 551 controls, in the current meta-analysis and observed significantly shorter LTL in BD patients compared to control subjects. Such differences were found in studies with patients in all mood statuses and in studies using different methods for measuring telomere length. Late-stage BD patients demonstrated more significant LTL shortening than early-stage BD patients. Our current results support the hypothesis of accelerated aging in BD patients. In the future, further properly controlled longitudinal studies are warranted to determine whether LTL changes with disease status or medication use in BD patients.

1. Introduction

Bipolar disorder (BD) has been recognized as a serious public health issue (Akiskal et al., 2000). Although effective anti-manic agents are available, BD patients often manifest long-term cognitive function impairment, despite achieving a euthymic state with syndrome remission (Mur et al., 2008; Zarate et al., 2000). BD patients also possess an increased risk of age-related physical morbidities and mortality (Westman et al., 2013), including obesity, metabolic syndrome, type 2 diabetes mellitus, cardiovascular disorder, and dementia (Chen et al., 2015; SayuriYamagata et al., 2017; Westman et al., 2013). Hence, BD has been conceptualized as a disorder of accelerated aging (Rizzo et al., 2014; Vasconcelos-Moreno et al., 2017).

Previous researchers have hypothesized that telomere length is a cellular biomarker of aging (Bekaert et al., 2005) that can be associated with deteriorating integrity and physiological dysfunction of cells, and vulnerability to cell death (Lopez-Otin et al., 2013). Telomeres are composed of tandem repeated guanine-rich DNA and specified proteins and cap the ends of eukaryotic chromosomes. Telomeres help maintain genome stability by protecting DNA from potential damage during the cell division process (Blackburn, 2001, 2005). An RNA-dependent DNA polymerase, telomerase plays a vital role in the telomere length maintenance system (Blackburn, 2005). Telomerase is activated to synthesize telomeric repeat sequences, which cap the ends of chromosomal DNA, in order to increase telomere length during cell replication and maintain cells in a healthy status (Kim et al., 2003). Telomere length in normal human somatic cells is 5–15 kilobases and is shortened at an average rate of 30 base pairs per year (Bekaert et al., 2005; Muezzinler et al., 2013). Cells are more susceptible to senescence or apoptosis when telomere length is short, particularly when less than 2.8 kilobases (Allsopp and Harley, 1995; Blackburn, 2005). Telomere length potentially plays a role in monitoring health status (Hochstrasser et al., 2012) and predicting treatment response in both physical and psychiatric illnesses (Park et al., 2017; Rasgon et al., 2016).

During the past decade, clinical research has shown that BD patients have shortened leukocyte telomere length (LTL) and has proposed that

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LTL shortening may represent 10 years (Simon et al., 2006) to 13 years (Elvsashagen et al., 2011) of accelerated aging in subjects with BD, although some conflicting results were also found (Mansour et al., 2011; Martinsson et al., 2013). One meta-analysis (Colpo et al., 2015) included seven studies to examine telomere length in BD patients and observed no difference when compared to healthy controls. This result was replicated in a later meta-analysis (Darrow et al., 2016), which included six studies after excluding one study that examined telomere length in the gray matter of the cerebellum (Zhang et al., 2010). However, the generalization of these results to a broad group of patients may be limited due to the small number of studies and the heterogeneity among the included studies, which may result from patients' characteristics or methods for measuring telomere length. Furthermore, information about the impact of different mood status on LTL in BD patients is lacking. Therefore, the more precise implications of LTL changes in BD patients may be obscured in these meta-analyses. In addition, four original studies examining this particular issue (Barbé-Tuana et al., 2016; Fries et al., 2017; Kose Cinar, 2018; Vasconcelos-Moreno et al., 2017) were published in the past two years. A timely updated meta-analysis is needed to re-examine these important issues.

In light of the aforementioned reasons, we aimed to conduct an updated meta-analysis to pool relevant results strictly from all eligible case control studies that primarily focused on measuring telomere length from leukocytes in BD patients to avoid a potential bias from different sample selection (Dlouha et al., 2014; Wong et al., 2011) and would like to examine the total differences in LTL between BD patients and healthy controls, as well as the possible effects of mood status and other moderators that may account for such differences.

2. Methods

2.1. Literature search

To identify eligible studies, two independent reviewers (Y.-C. Huang and P.-Y. Lin) searched for studies available as of May 2018 in the electronic databases of PubMed at the National Library of Medicine, ScienceDirect, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science. This search was performed using the following search terms: telomere AND (bipolar disorder OR mania OR manic), without special language limitations. The references of relevant articles and review articles were also searched for citations not indexed in the aforementioned databases. The titles and abstracts of studies obtained using this search strategy were then screened to determine whether they potentially met the inclusion criteria of this meta-analysis and to exclude studies that were not eligible, such as review articles, non-human studies, and studies not mentioning telomere. In case of disagreement regarding eligibility, agreement was reached through consensus.

2.2. Inclusion criteria for studies in this meta-analysis

The manuscripts that passed the initial screening were then examined based on the inclusion criteria adopted for this meta-analysis, which consisted of the following: (1) included patients with bipolar disorder, (2) used samples from leukocyte DNA, (3) measured telomere length, (4) included case control comparison between subjects with bipolar disorder and control subjects, and (5) dataset did not overlap with other studies. When the datasets from two studies overlapped, we included only the one with the larger sample size.

2.3. Meta-analytic methods

The main outcome of this study was to compare LTL between BD patients and controls. Patients were diagnosed with BD based on the DSM-based diagnostic interviews carried out in individual studies.

For each identified study, the effect sizes (ESs) expressing the difference in telomere length between patients and controls were described as standardized mean differences (SMDs) based on Hedges' adjusted g, where values greater than 0 indicated that the patients' telomere was longer. The means and standard deviations of telomere length of both the patient group and the control group were used to determine the ES of each included study. When these data were not available in these articles, we either contacted the authors to acquire the data directly or derived the ES from other statistical parameters, such as sample size, t value, or p value. Based on the anticipatory assumption of heterogeneity of subject characteristics among the recruited studies, we synthesized the ESs of individual studies using a random-effects model (Shadish and Haddock, 1994). The significance of the pooled ES was determined by the z-test. We examined heterogeneity to determine whether the group of ESs came from a homogeneous source by using Q statistics and assessed their related p value and the I^2 statistic, which is the percentage of the variability in the estimate of effects due to heterogeneity rather than random error. A rejection of homogeneity suggests that the included studies may have a systemic difference. We carried out sensitivity analysis to determine whether any individual study was responsible for the significant result. Each study was individually removed, and the significance was retested for the remaining studies.

Furthermore, we used Egger's regression (Egger et al., 1997) to statistically examine evidence of a publication bias. If such bias was found, we adopted Duval and Tweedie's trim and fill method (Duval and Tweedie, 2000) to adjust the ESs. We performed meta-regression using the unrestricted maximum likelihood method to examine whether mean age, gender distribution (percentage of females), or duration of illness of the included subjects moderates the ES. We also examined the pooled effect in separate groups of studies based on (1) mood status (manic, euthymic, or depressed) of the included BD patients and (2) the methods for measuring telomere length (Southern blot, polymerase chain reaction (PCR), or fluorescent in situ hybridization (FISH)).

Statistics in meta-analyses were performed using Comprehensive Meta-Analysis software, version 3 (Biostat, Englewood, NJ, USA). Two-sided p values <0.05 were considered statistically significant. We reported the methods and results of the meta-analyses by following the MOOSE checklist (Supplementary Table 1) (Stroup et al., 2000).

3. Results

3.1. Selection of studies

Our literature search provided 116 results for initial consideration in the meta-analysis. After examining their titles and abstracts, we excluded 102 articles because they were review articles ($n = 38$), meta-analysis articles ($n = 2$), articles that did not measure telomere length ($n = 40$), articles that did not include patients with bipolar disorder ($n = 19$), or non-human studies ($n = 3$). Then we examined the text of the remaining 14 articles according to the inclusion criteria and excluded four more studies because they measured telomere length in brain ($n = 2$) or buccal cells ($n = 1$) or had no control subjects ($n = 1$). Ultimately, we included 10 articles in the current meta-analysis (Barbé-Tuana et al., 2016; Elvsashagen et al., 2011; Fries et al., 2017; Kose Cinar, 2018; Lima et al., 2014; Mansour et al., 2011; Martinsson et al., 2013; Rizzo et al., 2013; Simon et al., 2006; Vasconcelos-Moreno et al., 2017); the selection process is shown in Fig. 1. The characteristics of the included articles are described in Table 1. Two of these articles had two independent subgroups, patients with early-stage BD and those with late-stage BD, so we considered them as containing two independent studies (Barbé-Tuana et al., 2016; Kose Cinar, 2018).

3.2. Comparison of LTL between BD subjects and healthy controls

First, our analysis showed a significant decrease in LTL in BD