DIFFERENCES IN LEUKOCYTE TELOMERE LENGTH BETWEEN BIPOLAR DISORDER PATIENTS AND NON-PSYCHIATRIC CONTROLS ARE INFLUENCED BY LITHIUM TREATMENT

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Introduction: Bipolar disorder (BD) is associated with premature mortality and higher incidence of age-related disorders compared to the general populations. Several studies reported premature cell senescence in BD, as shown by reduced telomere length in affected subjects. Recent findings have also shown that antidepressants and lithium (Li) may have a protective effect against telomere shortening. In our previous work (PMID: 27084304) we showed that duration of Li treatment is inversely correlated with leukocyte telomere length (LTL) in BD patients. In the current study, we compared LTL between BD patients and non-psychiatric controls and tested if Li treatment may affect LTL in BD in a larger sample compared to our previous work.

Material and methods: The sample comprised 313BD patients and 316non-psychiatric controls of Sardinian ancestry. Diagnosis of BD was done according to DSM-IV and SADS-L criteria. Patients were characterized for Li response using the "Retrospective Criteria of Long-Term Treatment Response in Research Subjects with Bipolar Disorder" (Alda scale). Correlation between LTL and age at onset, number of manic and depressive episodes, years of illness before start of Li treatment and duration of Li treatment was also assessed. DNA was extracted from leukocytes and relative LTL measured using SYBR Green real-time PCR as previously described. Correlation between LTL and age was assessed using nonparametric Spearman's correlation test. Correlation between LTL and quantitative variables was determined using the partial correlation and linear regression tests controlled for age. Differences in LTL between cases and controls and between BD patients stratified for Li-exposure and controls were tested using Man-Whitney test and linear regression models.

Results: LTL correlated negatively with age ($P < 0.001$, Spearman's rho = -0.16) and was independent of sex ($p > 0.05$). Partial correlation test corrected for age confirmed the positive correlation between LTL and Li treatment duration in patients with at least 24months of treatment also in the extended sample ($n = 173$, beta = 0.17, $p = 0.03$), while there was no effect of the other variables tested. BD patients had longer LTL compared to healthy controls (beta = -0.16, $p=0.00002$). To test if Li treatment influenced the observed difference in LTL between affected and non-affected individuals, we divided the BD sample into two groups according to Li exposure. BD patients treated with Li for at least one year ($n=234$) had longer LTL compared to patients never exposed to Li ($n=62$; $p=1.5x10^{-8}$). The latter group showed reduced LTL compared to controls (mean LTL 1.11vs 1.37respectively), though this was not statistically significant ($p>0.05$).

Discussion and conclusions: Our data show that BD patients have longer LTL compared to controls, a finding that is apparently in contrast with the hypothesis of accelerated aging and cell senescence in BD. However, this difference was exclusively driven by Li treatment, as BD patients exposed to Li had longer LTL compared to both never-exposed patients and healthy controls, while BD subjects never exposed to Li had shorter though not significant telomere length compared to controls. Our data farther support previous findings showing that long-term Li treatment has a protective effect against telomere shortening in BD. Further analyses are ongoing to validate our findings in an independent replication cohort of around 100 patients with BD recruited in Greece, for which information on treatments as well as other clinical characteristics previously suggested to affect telomere length (e.g. smoking, alcohol intake and physical activity) have been collected.