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ORIGINAL ARTICLE

Telomere length and childhood trauma in Colombians with depressive symptoms

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Objective: Childhood trauma and telomere length (TL) are important risk factors for major depressive disorder. We examined whether there was an association between childhood trauma and TL in a sample of Colombians who were assessed for depressive symptoms.
Methods: We applied the Center for Epidemiologic Studies Depression scale, the Patient Health Questionnaire-9, the Hospital Anxiety and Depression scale and the Childhood Trauma Questionnaire to 92 Colombian subjects (mean age = 21). TL was measured with quantitative PCR. Spearman's correlation coefficient (r_s) was used to analyze the relationship between childhood trauma scores and TL.
Results: We found a significant correlation between TL and sexual abuse scores (r_s = 0.428, p = 0.002) in individuals with higher depressive symptom scores.
Conclusion: This is the first report of a significant association between TL and sexual abuse in a Latin American sample and provides additional evidence about the role of childhood trauma and TL in neuropsychiatric disorders.

Keywords: Childhood trauma; depression; Latin America; sexual abuse; telomere length

Introduction

Major depressive disorder (MDD) is among the main public health problems worldwide, with an estimated prevalence of around 4.7%, and is a leading cause of disability in individuals from 15 to 44 years of age.[1] Colombia has one of the highest MDD rates in South America, with an estimated prevalence of 6.3%.[2] Excess medical morbidity and mortality have been associated with MDD, including elevated rates of cardiovascular disease and cancer.[3]

Epidemiological studies have provided strong evidence for the finding that adverse experiences during childhood, such as neglect or abuse, are associated with significant increases in the risk of developing depression.[4] In addition, childhood traumas increase the risk of attempted suicide in childhood, adolescence or adulthood two- to five-fold.[5] A number of studies have reported associations between telomere length and high levels of psychosocial stress[6] or stress biomarkers,[7] and there is additional evidence of an association between exposure to adverse conditions in childhood and subsequent differences in telomere length (TL).[8]

Telomeres are specialized nucleoprotein structures at the ends of linear chromosomes that protect the chromosome ends from degradation.[9] They are composed of repetitive DNA and DNA-binding proteins that are critical for maintaining chromosome integrity and cellular function.[9] TL declines with each cell division and has been associated with cellular aging.[9] Telomere shortening can be influenced by factors such as inflammation, cellular stress and genetic and epigenetic regulation.[9] It is known that telomere shortening in non-proliferative cells, such as adult neurons, is associated with oxidative stress and may be related to exposure to chronic psychosocial stress.[9]

Previous studies have analyzed the correlation between TL and childhood adversity in different populations, mainly from the United States and Europe, finding contrasting results.[10-14] To date, no reports have been published about the association between TL, stressful life events and depressive symptomatology in Latin American populations. The aim of the present study was to investigate the possible association between TL and childhood trauma in a sample of young Colombians who were assessed for frequency and severity of depressive symptoms.

Methods

Participants

A total of 92 healthy subjects participated in this study. The mean age was 21 years (standard deviation [SD] = 3.0) and 76% of the sample were women. The socioeconomic status (SES) of the sample was generally

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low (32.6%) or medium (45.6%), defined according to mean socioeconomic strata for Colombian cities (ranging from 1 = very low to 6 = very high). The participants' marital status was mainly single (93.4%) and their education level was mainly secondary (78.2%).

One inclusion criterion was that participants could not have a self-reported history of major psychiatric or neurological disorders, which was assessed during a medical history evaluation carried out by health science professionals.

Participants with clinically significant scores for depressive symptoms (according to the recommended cutoff points) on at least two of the depression assessment scales were compared with participants who had no depressive symptoms.

This study was conducted in accordance with Declaration of Helsinki principles. The Universidad Antonio Nariño institutional ethics committee approved the study (protocol number: 07062015-1) and all participants gave written informed consent.

Assessment of depressive symptoms

For greater reliability, three validated and widely used scales were used to measure depressive symptoms.

The Center for Epidemiologic Studies Depression Scale (CES-D)

This self-report scale measures the current level of depressive symptoms. In Vazquez et al.'s Spanish validation study (non-psychiatric sample),[15] the scale showed good reliability and the suggested cut-off point was $\geqslant$ 26. In the present study, the Cronbach's alpha for the CES-D was 0.89.

The Patient Health Questionnaire-9 (PHQ-9)

This self-report scale was designed to measure depression symptoms according to DSM-IV criteria. The recommended cutoff point is $\geqslant$ 10, which is indicative of clinically significant depressive symptoms.[16] The scale has demonstrated good reliability and validity in different languages, included Spanish.[17] In the present study, the Cronbach's alpha for the PHQ-9 was 0.84.

The Hospital Anxiety and Depression Scale (HADS)

This self-report screening test was created to indicate the possible presence of anxiety and depression states. In the current study, we only used the depression subscale (HADS-D). The cutoff point indicative of clinically significant depressive symptoms is $\geqslant$ 6.[18] The scale has been validated in Colombia by Hinz et al.,[19] showing good psychometric properties. In the present study, the Cronbach's alpha for the HADS-D was 0.65.

Assessment of child abuse and neglect

The Childhood Trauma Questionnaire (CTQ)-brief version was used to measure the participants' history of childhood trauma. This self-administered inventory provides an assessment of child abuse and neglect with five clinical scales: physical abuse, sexual abuse, emotional abuse, physical neglect and emotional neglect. Each of these scales contains five items plus three additional items to control false-negative reports. The CTQ has been validated in Spanish with good reliability and validity.[20] On the physical abuse and neglect scales, the cut-off score is 9 for men and women, while on the sexual abuse scale, it is 5 and 7 in men and women, respectively.[20] In the present study, the Cronbach's alpha was 0.89 for the total score, 0.78 for physical abuse, 0.78 for emotional abuse, 0.90 for sexual abuse, 0.74 for emotional neglect and 0.52 for physical neglect (thus, physical neglect was not included in the final analyses).

Telomere length measurement

Genomic DNA was extracted from 400 μL of the participants' peripheral blood by a salting-out method. Genomic DNA extracted from peripheral blood corresponds to nucleic acids from leucocytes. The material was quantified in a Qubit 2.0 fluorometer (Thermo Fisher Scientific, MA, USA) using the Qubit dsDNA HS assay (Thermo Fisher Scientific) and then adjusted in TE^{-4} to working aliquots of 10 ng/μL.

Telomere length was measured using a Monochrome Multiplex Real-Time quantitative PCR (MMqPCR) assay, following the technique of Cawthon.[21] This method consists of quantifying, in a single reaction, the relative copy numbers of telomeres (T) and a single copy gene (S).[21] Materials for the MMqPCR reaction included 2 μL (20 ng) of genomic DNA, 0.8 μM of each of the four primers, 1X of Kapa SYBR FAST qPCR Kit Master Mix (Kapa Biosystems, MA, USA) and ultrapure water to complete a final volume of 20 μL. As a negative control, 2 μL of ultrapure water was used. The primer sequences for the telomeres were: F: ACA CTA AGG TTT GGG TTT GGG TTT GGG TTT GGG TTA GTG T and R: TGT TAG GTA TCC CTA TCC CTA TCC CTA TCC CTA TCC CTA ACA. The primers used for amplifying the albumin gene (single copy gene) were: F: CGG CGG CGG GCG GCG CGG GCT GGG CGG AAA TGC TGC ACA GAA TCC TTG and R: 5' GCC CGG CCC GCC GCG CCC GTC CCG CCG GAA AAG CAT GGT CGC CTG TT.[21] The MMqPCR assay was carried out in a CFX96 Touch Real-Time PCR system (BioRad, CA, USA), consisting of enzyme activation at 95 °C for 3 minutes, followed by two cycles of 95 °C for 15 seconds and 49 °C for 15 seconds, 32 cycles of 95 °C for 15 seconds, 62 °C for 10 seconds, 74 °C for 15 seconds (first signal acquisition), 84 °C for 10 seconds and 88 °C for 15 seconds (second signal acquisition).[22] TL measurement was performed in duplicate for each sample and was expressed by the T/S ratio. The T/S obtained from each sample was normalized with the T/S from the same reference DNA run in every experiment.

Statistical analysis

Cronbach's alpha was used to determine the reliability of the CTQ instrument and depression scales. We examined skewness and kurtosis to explore the normal distribution

of the CTQ questionnaire scores, the depression scale (CES-D, PHQ-9 and HADS-D) scores and TL.[23] For the CTQ scale analysis, we created abused/non-abused groups. To investigate the associations between variables for the two groups of individuals (with or without clinically significant depressive symptoms), Spearman's rank-order correlation was performed for variables that did not show normality (CTQ scores, age and gender), and Student's *t*-test was performed for the SES and TL analysis between the two groups. For the association between TL and CTQ scores, $p < 0.0125$ (after a Bonferroni correction for multiple testing) was considered statistically significant. Finally, a moderation analysis was conducted to evaluate whether depression had a moderating role in the association between childhood trauma and TL; a chi-square test was conducted to assess whether participants reporting childhood trauma were at greater risk of depressive symptomatology. SPSS version 18 was used for all statistical analyses.

Results

The group of participants with clinically significant depressive symptoms included 40 individuals (mean age 21 years, SD = 3; 85% were women) and the group of subjects without depressive symptoms included 52 individuals (mean age of 21 years, SD = 3; 69% were women). It was found that 46, 40 and 48 subjects showed clinically significant depressive symptoms according to the HADS-D, CES-D and PHQ-9 cut-off points, respectively. A chi-square test showed that history of childhood trauma was significantly associated with depressive symptomatology ($\chi^2 = 23.9$, $p = 0.001$).

According to Spearman's analysis, there was no significant correlation between TL and gender ($p = 0.888$) or age ($p = 0.233$). Student's *t*-test revealed no significant differences in TL between groups ($p = 0.600$) or between the different SES ($p = 0.285$). For this reason, we did not carry out multivariate analyses to adjust for age, gender, and SES as possible confounders.

Spearman's analysis revealed a significant positive correlation in the clinically significant depressive symptoms group between TL and sexual abuse (Table 1), which remained significant after a Bonferroni correction for multiple testing. We found no significant correlations for other types of childhood trauma (such as physical or emotional abuse and neglect) in either the whole sample or separate groups.

In the moderation analysis, it was found that depressive symptoms did not have a significant moderating role in the relationship between childhood trauma and TL ($p > 0.05$).

Discussion

In a number of studies, mainly from the United States and Europe, it has been found that the TL of individuals who have suffered childhood abuse or trauma is different from those who have not.[10,11,14] In Latin America, the high levels of child abuse are an important public health problem.[24] Although there are few available reports on child maltreatment in Colombia, in 2004, the Colombian Institute of Legal Medicine and Forensic Sciences reported 59,770 cases of domestic violence, of which 9,847 involved the abuse of children and adolescents.[25]

Our study is the first to explore the association between TL, childhood trauma and depressive symptoms in a Latin American sample. The presence of adverse events during childhood has been associated with a higher prevalence of several mood disorders, including MDD, and adults who have experienced childhood abuse or neglect appear to have an enhanced emotional sensitivity to stress.[26] In addition, changes in the hypothalamic-pituitary-adrenal axis and autonomic stress responses have been found in

Table 1 Association between childhood trauma and telomere length

Types of childhood abuse	Median (IQR)	% of sample with CT	Spearman's correlation*	p-value
Entire sample (n=92)[†]				
Physical abuse	7 (6-8)	25	-0.008	0.939
Emotional abuse	8 (6-10)	39	-0.017	0.874
Sexual abuse	5 (5-5)	13	0.011	0.918
Emotional neglect	6 (6-10)	42	0.042	0.689
Group without depressive symptoms (n=52, 57%)[‡]				
Physical abuse	6 (6-7)	12	-0.011	0.443
Emotional abuse	7 (6-8)	14	0.072	0.619
Sexual abuse	5 (5-5)	4	-0.054	0.736
Emotional neglect	7 (5-8)	22	-0.008	0.954
Group with depressive symptoms (n=40, 43%)[§]				
Physical abuse	8 (6-11)	40	0.166	0.293
Emotional abuse	10 (8-15)	69	0.102	0.520
Sexual abuse	5 (5-7)	24	0.428	0.002[†]
Emotional neglect	10 (7-13)	67	0.265	0.090

CT = childhood trauma; IQR = interquartile range.
* Bivariate correlations between types of childhood abuse and TL.
[†] Significant after Bonferroni correction for multiple testing.
[†] Mean age = 21 (standard deviation = 3), 76% women.
[‡] Mean age = 21 (standard deviation = 3), 69% women.
[§] Mean age = 21 (standard deviation = 3), 85% women.

adults who experienced childhood abuse.[27] Previous studies have shown that chronic psychological stress in women may lead to telomere shortening and lower levels telomerase function in peripheral blood mononuclear cells, possibly associated with oxidative stress.[6]

The results of this study indicate that in individuals with clinically significant depressive symptoms there is an association between longer leukocyte telomeres and a self-reported history of childhood emotional neglect. Previous studies have found shorter leukocyte telomeres in individuals who suffer depression[10,11,28,29] and in those exposed to stressful social environments.[30] One study, however, reported a trend toward longer telomeres in individuals with higher childhood trauma questionnaire scores who suffered from posttraumatic stress disorder.[14] Previously reported results in the literature are discordant: Mason et al.[29] observed that reduced TL was associated with physical abuse, but not sexual abuse. A study attempting to replicate these results in a larger UK twin cohort found no significant correlations between TL and physical and sexual abuse.[12] In addition, longitudinal studies by Hoen et al.[31] and Verhoeven et al.[32] found no relationship between depression and telomere shortening.

The discrepancies between these studies could be explained by the fact that they included neither depression assessment nor sample stratification according to the presence and severity of depressive symptoms. In Colombian samples, some studies have reported high levels of depressive and anxiety symptomatology.[33] Furthermore, large studies have reported high prevalence rates for common mental disorders in Colombia, higher than those reported in Mexico, Spain, and Nigeria.[34] This is very important, since Colombia has been exposed to a decades-long internal armed conflict, which could at least partially explain such high rates, given the well-known association between exposure to stress and the development of mental disorders.[35]

Moreover, it is important to consider that TL has been associated with a stressful social environment, including low income, low maternal education and family instability.[30] In Colombia, 68,585 cases of domestic violence were reported in 2000, of which 16.6% involved child maltreatment.[36] During the same year, 13,352 cases of sexual and physical abuse were reported, of which 86% involved children and adolescents.[36]

Our study is the first in a Latin American sample that reports a significant association between TL and sexual abuse in individuals with clinically significant depressive symptoms. We also found no significant correlation between age and TL; it is possible that this was due to the limited age range of our participants (mean age 21 years), since in young adulthood it is normal to observe a plateau phase in TL.[37]

Our findings add evidence to the existing literature about the role of TL in individuals with clinically relevant neuropsychiatric symptoms. One limitation of our study was the cross-sectional design, which makes it difficult to infer causality. We recommend that futures studies include larger samples in other populations known to have a larger burden of childhood and adult trauma and chronic stress, as well as the study of other genetic and epigenetic markers.

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Disclosure

The authors report no conflicts of interest.

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