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Accelerated telomere shortening: Tracking the lasting impact of early institutional care at the cellular level

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ABSTRACT

Studies examining the association between early adversity and longitudinal changes in telomere length within the same individual are rare, yet are likely to provide novel insight into the subsequent lasting effects of negative early experiences. We sought to examine the association between institutional care history and telomere shortening longitudinally across middle childhood and into adolescence. Buccal DNA was collected 2–4 times, between the ages of 6 and 15 years, in 79 children enrolled in the Bucharest Early Intervention Project (BEIP), a longitudinal study exploring the impact of early institutional rearing on child health and development. Children with a history of early institutional care ($n=50$) demonstrated significantly greater telomere shortening across middle childhood and adolescence compared to never institutionalized children ($n=29$). Among children with a history of institutional care, randomization to high quality foster care was not associated with differential telomere attrition across development. Cross-sectional analysis of children randomized to the care as usual group indicated shorter telomere length was associated with greater percent of the child's life spent in institutional care up to age 8. These results suggest that early adverse care from severe psychosocial deprivation may be embedded at the molecular genetic level through accelerated telomere shortening.

1. Introduction

Telomeres, found at the end of chromosomes, comprise repetitive DNA sequences, proteins, and non-coding RNAs that are conserved across evolution, found in organisms from yeast to humans. In addition to their role in cellular senescence and apoptosis, telomeres also serve as global epigenetic regulators, sensitive to cellular and physiological stressors (Ye et al., 2014). Telomere length (TL) has been proposed as a biological mediator between negative early experiences and later psychopathology and poor health (Blaze et al., 2015). Shorter TL has been associated with environmental stress exposure (e.g., neighborhood-level social environmental risk and prenatal tobacco exposure; Theall et al., 2013a, 2013b) and poor caregiving environments for the child (e.g., physical maltreatment, institutional care, poverty; Drury et al., 2012; Mitchell et al., 2014). High quality parental care may buffer the negative impact of adversity on TL (Asok et al., 2013; Enokido et al., 2014). In adults and adolescents, decreased TL has also been associated with cardiovascular disease (Saliques et al., 2010), diabetes (Willeit et al., 2014), and obesity (Müezzinler et al., 2014), all negative health outcomes linked with experiences of early adversity. Collectively, these findings suggest that TL may link early adversity to negative health outcomes, foreshadow increased health risk, and have salience across the life course.

Though there is mounting evidence that early adversity is associated with TL measured at a single time point, measuring TL trajectory over time may be a more meaningful metric for assessing cellular aging (Chen et al., 2011). A growing, but to date limited, number of studies have examined TL longitudinally. In adult women, greater telomere shortening was found among those who experienced a major life stressor during a one year follow-up period, suggesting a proximal link between stress and changes in TL (Puterman et al., 2015). Even fewer studies of the change in TL in children exist, and only one examined telomere shortening in children in relation to stress. In this study, Shalev et al. (2012) found greater TL attrition between ages 5 and 10 years in children who experienced maltreatment during that time period. While this study provides an important extension of cross-sectional results, additional longitudinal studies are needed.

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Using data from the Bucharest Early Intervention Project (BEIP), a longitudinal randomized controlled trial of foster-care for children who experienced early psychosocial deprivation, we examined the impact of early and cumulative exposure to institutional caregiving on TL change across middle childhood and into adolescence (age range 6–15 years). We predicted that children exposed to early institutional care (ever institutionalized group: EIG) would demonstrate accelerated telomere shortening compared to never institutionalized children (never institutionalized group: NIG). We further examined whether randomization to high-quality foster care at a mean age of 22 months, moderated TL change, hypothesizing that those randomized to the foster care intervention (foster care group; FCG) would have attenuated telomere attrition compared to the children assigned to the care as usual condition (care as usual group; CAUG). Given our previous cross-sectional findings only within the EIG where shorter TL was associated with increased percent of time in institutional care through 54 months of age (Drury et al., 2012), we examined whether a similar pattern persisted with exposure captured through 8 years of age.

2. Methods

2.1. Participants

Participants were children enrolled in the BEIP (Zeanah et al., 2003), a longitudinal randomized controlled trial of foster care compared to care as usual for children in Romanian institutions, described in detail elsewhere (Nelson et al., 2007; Zeanah et al., 2009). 136 children, between 6 and 31 months of age, residing in six institutions in Romania were initially enrolled, and following baseline assessments, randomly assigned to CAUG ($n=68$) or FCG ($n=68$) (Fig. 1, CONSORT). The foster care system was created for this project as an intentional alternative to institutional care. The related ethical considerations have been described in detail (Nelson et al., 2014; Zeanah et al., 2012). A reference group of children without any history of institutional rearing were recruited either from birth records from the same maternity hospitals in which the EIG were born or, for later recruitment, from area schools. Following randomization and placement of children in foster care, all subsequent decisions regarding placement were made by the child protection commissions in Romania.

As mandated by Romanian law, the Commission on Child Protection provided informed consent for each of the child participants. The Institutional Review Boards of Children's Hospital of Boston, University of Maryland, and Tulane University approved this study.

2.2. Measures

2.2.1. Full-Scale IQ

At the age 12 follow-up assessment, full-scale IQ was obtained via the Wechsler Intelligence Scale for Children (Wechsler, 2004) which was translated into Romanian and administered by trained and reliable Romanian psychologists.

2.2.2. Monochromic multiplex quantitative polymerase chain reaction (MMP-qPCR)

DNA was collected using Isohelix buccal swabs (Cell Projects, Kent, UK) with careful attention to the integrity, purity, and concentration of the DNA. Swabs were collected, air dried, and stored with a desiccator pellet to decrease potential for bacterial growth. Swabs were immediately frozen and stored frozen until extracted. Integrity of the genomic DNA and purity was assessed via 260/280 and 260/230 ratios from nanodrop, QuBit analyses for double stranded DNA concentration, and agarose gel electrophoresis. The average relative buccal-derived TL (bTL) was determined from the telomere repeat copy number to single gene (albumin) copy number (T/S) ratio using an adapted monochrome multiplex quantitative real-time PCR (MMP-qPCR) and a BioRad CFX96 as previously described (Drury et al., 2014a). All samples were performed in triplicate, with a 7-point standard curve (0.0313 ng to 2 ng) derived from a single pooled control buccal DNA sample, eliminating plate to plate variability as a result of differences in DNA standards. Triplicate plates were repeated with all samples in a different well position on the duplicate plate. All time points from each individual were run on the same plates to further decrease variance due to batch or plate effects.

PCR efficiency criteria for both reactions were 90–110%. Coefficients of variations (CV) were calculated within each triplicate (CV criteria $\leq 10\%$) and between plates (CV criteria $\leq 6\%$). Samples with unacceptably high CVs (10% intra- and 6% inter-assay CV) were removed from analysis or repeated ($N=6$), resulting in a final sample of 79 individuals with multiple time points that each passed quality control metrics on duplicate plates. bTL ratio was derived by the average of the triplicates from both plates. The CV for samples was 2.4%. bTL assays and quality checks were conducted blind to group status.

Individuals contributed anywhere from 2 to 4 data points.

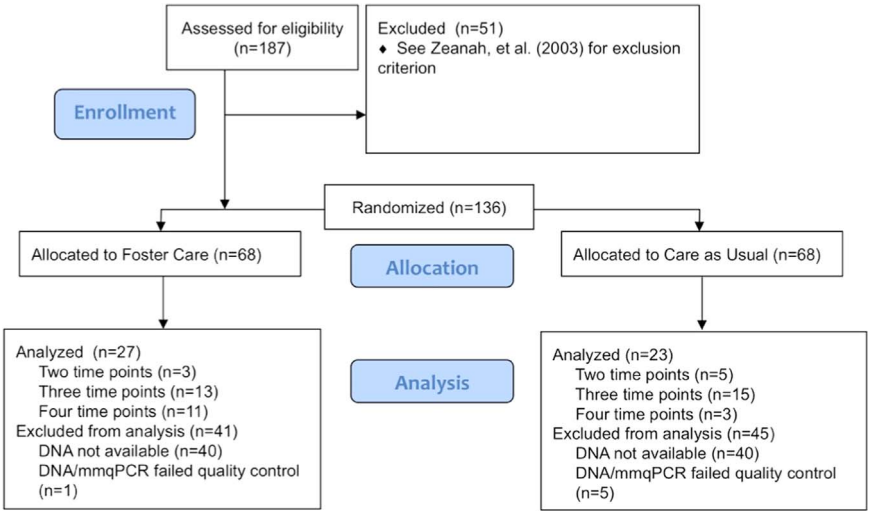

Fig. 1. CONSORT diagram.