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Pain exposure associates with telomere length erosion in very preterm infants

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ABSTRACT

Very preterm (VPT) infants (gestational age < 32 weeks) require long-lasting hospitalization in the Neonatal Intensive Care Unit (NICU), even in absence of severe morbidities. During NICU stay, life-saving interventions occur and include invasive and painful skin-breaking procedures (NICU-related stress), which constitute a major early adverse experience for VPT infants. Telomeres are repeat-sequence at the end of chromosomes, which shorten with age and are highly susceptible to life adversities: the exposure to early adverse experiences is associated with shorter telomere length (TL). Nonetheless, previous research did not assess longitudinally the association between NICU-related stress and TL in VPT infants. In the present study, leukocyte TL was assessed from cord blood at birth in 46 VPT infants and in a group of 31 full-term (FT) infants, as well as at NICU discharge in VPTs only. NICU-related stress was measured as the number of skin-breaking procedures occurring throughout the NICU stay. A significant difference emerged for TL between VPT infants and FT counterparts at birth. TL decreased from birth to discharge in VPT infants, although the change was not significant in the group as a whole. The amount of NICU-related stress emerged as the primary predictor of TL erosion in VPT infants, even controlling for neonatal and clinical confounders. Furthermore, VPT infants exposed to high NICU-related stress exhibited a marked and significant decrease in TL, whereas VPT exposed to low NICU-related stress exhibited a non-significant increase. The present study confirms previous evidence of longer telomeres in VPT infants at birth compared to FT controls. Moreover, NICU-related stress emerged as a key regulator of TL erosion from birth to discharge in VPT infants. Future research is warranted to further explore TL erosion in VPT infants and the factors associated with individual differences in NICU-related stress susceptibility at the epigenetic level.

1. Introduction

1.1. Very preterm birth as an early adverse condition

Very preterm birth (gestational age < 32 weeks) ranges from 9.6 to 15.7 every 1000 live births worldwide (Delnord et al., 2016) and constitutes one of the major concerns for neonatal healthcare services. Even in absence of severe morbidities and clinical conditions, infants born very preterm (VPT) are at heightened risk for neurobehavioral (Zeitlin et al., 2008) and socio-emotional (Montagna and Nosarti, 2016) impairment later in life. Due to the neonatal profile of neurobehavioral immaturity, VPT infants need specialized and intensive care through long-lasting hospitalization in the Neonatal Intensive Care Unit (NICU).

Despite the NICU was developed to grant survival and adequate care for at-risk newborns, it is not a surrogate of the maternal womb. The highly technological and medicalized NICU environment includes the exposure to different sources of stress to which the immature brain of VPT infants might be especially susceptible (Ranger and Grunau, 2014). Life-saving procedures may be highly stressful, invasive and elicit pain-related stress in preterm infants (Grunau, 2013). NICU-related stress exposure has been found to associate with detrimental developmental outcomes including blunted reactivity to stress during infancy

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(Provenzi et al., 2016), increased risk for behavioral problems during childhood (Grunau et al., 2009), and reduced brain volumes (Ranger et al., 2015) in VPT infants.

1.2. Telomere erosion as a biomarker of early adversity exposure

Telomere length regulation is emerging as a promising epigenetic marker of early stress exposure (Blaze et al., 2015). Telomeres are TTAGGG nucleotide repeats that cap the ends of DNA that protect genomic DNA from damage during cell replications. With each cell division, telomeres shorten until they reach a critical senescence endpoint (Blackburn, 1991). Although the progressive erosion of telomeres depends on cell replication rate which is set at birth (Blackburn and Epel, 2012), the cumulative exposure to agents that produce DNA damage (Aviv et al., 2008) as well as environmental stressful conditions (Price et al., 2013) might increase telomere erosion rate. The study of telomere regulation in association with life adversities in humans is relatively recent (Shalev, 2012). Available retrospective studies documented that adults who reported to be exposed to childhood trauma and neglect exhibited shorter telomeres in peripheral blood compared to controls (Kiecolt-Glaser et al., 2011; Tyrka et al., 2010). The association between the degree of early adversity exposure (e.g., number of adverse events) and telomere erosion appears to be dose-dependent (Kananen et al., 2010). Notably, shortened telomeres due to early stress exposure is also associated with mental-health disorders in adulthood (O'Donovan et al., 2011).

1.3. Evidence for altered telomere length in preterm infants

Limited research has investigated telomere length in preterm infants. Recently, Vasu and colleagues (Vasu et al., 2017) provided an account of available evidence, showing that previous studies were mainly cross-sectional and with little sample size. Longer telomeres have been observed in very low birth weight preterm infants (birth weight < 1500 g) compared to low birth weight and full-term counterparts at birth (Friedrich et al., 2001). TL erosion is also documented to advance with increasing gestational age at birth (Menon et al., 2012; Turner et al., 2014). Unfortunately, to the best of our knowledge, the longitudinal relationship between NICU-related stress exposure and telomere length has not been assessed in VPT infants. This is surprising since research evidence suggests that: (a) epigenetic mechanisms are involved in the long-term setting of heightened risk of developmental impairments in VPT infants (Provenzi et al., 2015) and (b) early adversity exposure might increase the rate of telomere erosion with critical consequence for health and disease (Blaze et al., 2015).

1.4. The present study: studying telomere erosion in VPT infants in association with NICU-related stress exposure

In sum, the application of telomere length research to the study of early VPT infants' development appears to hold potentials to further increase our knowledge of the biochemical pathways through which NICU-related stress might contribute to setting the risk of altered developmental trajectories in at-risk infants. In the present prospective micro-longitudinal study, telomere length (TL) has been compared between VPT infants and full-term (FT) counterparts at birth and at term-equivalent age (TEA). The main aim of this study was to assess the association between NICU-related stress (i.e., number of skin-breaking procedures) and the progressive erosion of telomere length (TL) from birth to NICU discharge in VPT infants. Based on previous retrospective literature on humans (Price et al., 2013), we hypothesized that greater exposure to skin-breaking procedures during the NICU stay would predict greater TL erosion, even controlling for neonatal confounders.

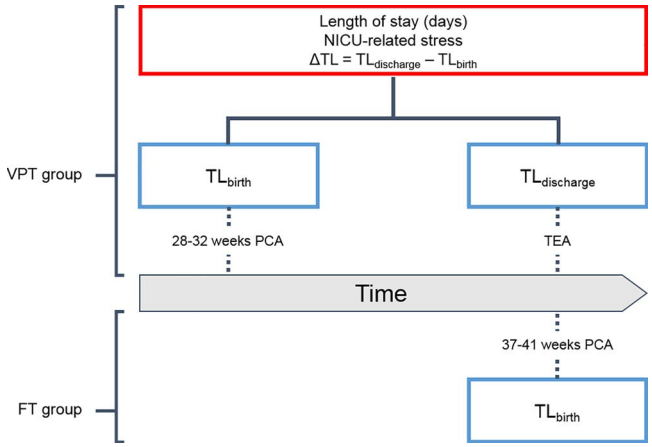

Fig. 1. Overview of the study design. Note: VPT, very preterm; FT, full-term; NICU, Neonatal Intensive Care Unit; TL, telomere length; ΔTL, birth-to-discharge change in TL; PCA, post-conception age; TEA, term-equivalent age.

2. Methods

2.1. Participants

The sample included 77 infants. Forty-six VPT infants (24 females, 52.2%) were recruited at the NICU, *XXXX* (insert after blind review). Thirty-one FT infants (15 females, 48.4%) were recruited at the Pediatric Unit of the *XXXX* (insert after blind review). Exclusion criteria for VPT infants included major brain lesions as documented by cerebral ultra-sound, neuro-sensorial deficits, genetic syndromes, and/or major malformations. All FT infants were healthy and had no neonatal morbidities or prenatal/perinatal-risk factors. Maternal exclusion criteria for both groups included age less than 18 years, psychotropic medication during pregnancy, prenatal depression/anxiety assessed by the NICU psychologist.

2.2. Procedures

The overview of the study design is reported in Fig. 1. The Ethic Committees of *XXXX* (insert after blind review) and the participating hospitals approved the study protocol. VPT infants' mothers were contacted during the day following delivery by nurses who were aware of the research aims and procedures. FT infants' mothers were approached during pre-partum classes by trained nurses and/or pediatricians. All the mothers received an information pack including a letter resuming the study protocols, aims and procedures as well as questionnaires (see below). They signed a written informed consent if they decided to participate into the study. As in previous research (Kantake et al., 2014; Provenzi et al., 2015), cord blood was collected at birth for both VPT and FT infants. Peripheral blood sample was collected at hospital discharge for VPT infants only, following routine clinical procedures. Blood samples were obtained by trained nurses to avoid hemolysis and immediately stored at −20 °C.

2.3. Measures

2.3.1. Socio-demographic data

Socio-demographic data (i.e., maternal age and occupational status of both parents) were obtained. According to Hollingshead's classification (Hollingshead, 1975), the more prestigious occupational level between parents was considered as family socio-economic status (SES) score ranging from 0 to 90. Lower scores reflected lower socio-economic conditions.