Brain, Behavior, and Immunity 28 (2013) 63–71

Contents lists available at SciVerse ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Childhood adversity and cell-mediated immunity in young adulthood: Does type and timing matter?

Natalie Slopen [a,*], Katie A. McLaughlin [b], Erin C. Dunn [c], Karestan C. Koenen [d]

[a] Center on the Developing Child, 50 Church St, 4th Floor, Cambridge, MA 02138
[b] Harvard Medical School, 21 Autumn Street, Boston MA 02115
[c] Psychiatric and Neurodevelopmental Genetics Unit, Center for Human Genetic Research, Massachusetts General Hospital, 185 Cambridge Street, Boston, MA 02114
[d] Mailman School of Public Health, Columbia University, 722 West 168th Street, 720G New York, New York 10032-3727

ARTICLE INFO

Article history:
Received 28 August 2012
Received in revised form 17 October 2012
Accepted 18 October 2012
Available online 26 October 2012

Keywords:
Cell-mediated immune response
Epstein–Barr Virus (EBV) antibody titers
Childhood adversity
Child abuse
Socioeconomic status
National Longitudinal Study of Adolescent Health (Add Health)

ABSTRACT

Childhood adversity can have powerful effects on health over the life course. Persistent changes in cell-mediated immune function may be one pathway linking adverse childhood experiences with later disease risk. However, limited research has examined childhood adversity in relation to cell-mediated immune function, and in particular, immune response to latent viruses in adulthood. The present study investigated the association of two types of childhood adversity, socioeconomic disadvantage during adolescence and abuse prior to age 18, with Epstein–Barr Virus (EBV) antibody titers in a large nationally representative sample of young adults aged 24–32 years. Data were drawn from the National Longitudinal Study on Adolescent Health, Wave 4 (n = 13,162). We examined the associations of three indicators of adolescent SES (parental education, household income, and occupational status) and frequency and timing of physical and sexual abuse with EBV antibodies, controlling for age, sex, race/ethnicity, and presence of a smoker in the household during adolescence. Lower parental occupational status and some categories of lower education were associated with elevated EBV antibodies ($p < .05$), and individuals who reported sexual abuse that occurred more than 10 times had elevated EBV antibodies relative to individuals who were not sexually abused ($p = 0.03$). Among individuals exposed to physical abuse, those who were first abused at age 3–5 years had heightened EBV antibodies relative to those first abused during adolescence ($p = 0.004$). This study extends prior research linking early adversity and immune function, and provides initial evidence that childhood adversity has a persistent influence on immune responses to latent infection in adulthood.

Adverse experiences in childhood, such as poverty and maltreatment, are associated with poor health over the life course (Shonkoff, 2011; Shonkoff et al., 2009). Research on the mechanisms that link adverse experiences in childhood to poor health outcomes is critical to identifying targets for intervention (Miller et al., 2011; Taylor, 2010; Taylor et al., 2011). Animal models and human correlational studies suggest cell-mediated immune function as a potential pathway by which early adverse experiences impact adult health (Danese and McEwen, 2012). Socioeconomic disadvantage (Dowd et al., 2009, 2010, 2012), maltreatment and neglect (Shirtcliff et al., 2009), and stressful life events (Caserta et al., 2008; Wyman et al., 2007) in childhood are associated with altered cell-mediated immune functioning during childhood, including immune responses to latent viruses. Childhood adversity is also associated with adult health conditions that indicate dysregulated immune function, including gastrointestinal disorders (Wegman and Stetler, 2009), rheumatoid arthritis (Dube et al., 2009; Von Korff et al., 2009), and heightened pro-inflammatory biomarkers (Danese et al., 2007). Persistent changes in cell-mediated immune function could be one pathway linking adverse childhood experiences to health conditions later in life; however, limited research has examined whether different types of childhood adversity differentially impact cell-mediated immune function and whether this effect is apparent in young adulthood. Furthermore, almost nothing is known about whether there are specific developmental periods during childhood when exposure to adversity may have particularly pronounced effects on long-term immune function relative to other periods of development. It is important to characterize changes in immune function in relation to various types and/or timing of childhood adversity in order to clarify the mechanisms that engender disease vulnerability in adulthood. In the present study, we investigated the association between two types of childhood adversity, socioeconomic disadvantage and abuse (with consideration of both frequency

* Corresponding author at: Center on the Developing Child, Harvard University, 50 Church Street, 4th Floor, Cambridge, MA 02138, United States. Tel.: +1 617 733 0309; fax: +1 617 496 1229.
E-mail address: nslopen@hsph.harvard.edu (N. Slopen).

0889-1591/$ - see front matter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.bbi.2012.10.018

and timing), on cell-mediated immunity in young adulthood, as indicated by elevated Epstein–Barr Virus (EBV) antibody titers.

Cell-mediated immune functioning has an important role in defending against autoimmune diseases, destroying intracellular bacteria and tumor cells, eliminating viral infections, and other immune reactions (Deepe, 1990; Marshall, 2011). It is estimated that 80–90% of Americans are infected with EBV by age 40, and it asymptomatically remains in the body for life (Glaser et al., 1991; Jones and Straus, 1987). Adequate cell-mediated immune function is required to maintain EBV in a latent state. Immunosuppression can cause EBV to reactivate and release antigens of the virus, which produces an antibody response (Glaser et al., 1991). Therefore, higher levels of EBV antibodies provide an indirect measure of one aspect of cell-mediated immune function, because elevated EBV antibodies reflect a failure of cellular immune processes to impede reactivation of the latent virus (Glaser et al., 1991; Segerstrom and Miller, 2004). Evidence suggests that psychosocially-induced immunological alterations can have implications for infectious illnesses, wound healing, progression of human immunodeficiency virus and cancers, and other diseases of aging (Godbout and Glaser, 2006; Kiecolt-Glaser and Glaser, 1995).

EBV antibody titers are recognized as one of the strongest immune-related correlates of psychosocial stress (Herbert and Cohen, 1993b; McDade and Hayward, 2009; McDade et al., 2000). In adult samples, increased EBV antibody titers have been associated with a wide variety of stressors, including caregiving for family members with Alzheimer's disease (Kiecolt-Glaser et al., 1987b), poor quality marriages (Kiecolt-Glaser et al., 1987a), marital separation or divorce (Kiecolt-Glaser et al., 1987a), medical school exams (Glaser et al., 1985a, 1986), perceived stress (Borders et al., 2010), loneliness (Glaser et al., 1985b), and discrimination (McClure et al., 2010). However, the majority of prior studies of stress in relation to EBV antibodies focus on concurrent acute and chronic stressors or laboratory challenges, rather than experiences from early life (Segerstrom and Miller, 2004). In a meta-analysis of over 300 empirical articles describing the relationship between psychological stress and immune system function in humans, Segerstrom and Miller (2004) identified only nine studies examining the persistent effect of stressors that occurred years in advance of immune assessment (referred to as "distant stressors" with combat exposure the most common stressor assessed); none of these studies considered adversities in early life.

Several previous studies have examined childhood adversities in relation to indicators of cell-mediated immune response to latent viruses in children and adolescents (Caserta et al., 2008; Dowd et al., 2012; McDade et al., 2000; Shirtcliff et al., 2009; Wyman et al., 2007). Using data on U.S. children ages 6–16 drawn from the National Health and Nutrition Examination Survey, Dowd and colleagues (Dowd et al., 2012) found that family poverty was associated with heightened antibody response to cytomegalovirus (CMV). In another study, (Shirtcliff et al. (2009) found elevated levels of antibodies to herpes simplex virus-1 (HSV-1) among adolescents who experienced early adversity due to institutionalization or physical abuse relative to healthy control participants. This study provides some evidence for an enduring influence of early experiences on immune functioning, because the observed differences were present many years after the institutionalized children were adopted into improved child-rearing settings. Because data linking childhood adversities to markers of immune control in adulthood are lacking, the extent to which childhood adversity has an enduring influence on cell-mediated immune functioning is unknown.

Within prior research on childhood adversity and immune biomarkers, it is common for studies to examine only one form of adversity (e.g., maltreatment or socioeconomic status) (Slopen et al., 2011). Although consideration of a single exposure can provide valuable information, studies that examine multiple types of stressors are able to distinguish whether certain types of stressors (e.g., acute, chronic) are more strongly associated with changes in immune functioning, which has implications for prevention. Related, research is needed is needed to extend knowledge about how timing of childhood adversity affects later physiological consequences. Studies that have examined timing of childhood adversity in relation to other physical (Bosch et al., 2012; Flaherty et al., 2009; Jun et al., 2011; Tottenham and Sheridan, 2010; Wilkin et al., 2012; Ziol-Guest et al., 2009) and mental (Fisher et al., 2010; Kaplow and Widom, 2007; Keiley et al., 2001; Kotch et al., 2008; Thompson et al., 2012; Thornberry et al., 2001; Wilkin et al., 2012) health outcomes suggest that timing matters – however, across existing studies, there are no consistent patterns to suggest that earlier or later exposure is more detrimental. Earlier exposure to adversity may have larger health consequences relative to later exposure, because physiological plasticity may be greater during early development (Gluckman et al., 2007). Alternatively, younger children may be buffered from experiences that would result in distress among older children because of their limited cognitive skills (Kaplow and Widom, 2007; Keiley et al., 2001), resulting in more detrimental effects of stressors experienced later in childhood.

Using data from the National Longitudinal Study on Adolescent Health (Add Health), the present study examined adverse childhood and adolescent experiences in relation to cell-mediated immune function in young adulthood. Specifically, we examined the associations between three indicators of SES during adolescence as well as physical and sexual abuse prior to age 18 with EBV antibodies. Among respondents who were abused, we also examined if the timing and frequency of abuse was associated with immune control in young adulthood. We hypothesized that lower SES in adolescence and exposure to abuse prior to age 18 would be associated with elevated EBV antibodies in young adulthood, and that more frequent and earlier experiences of abuse would be associated with poorer immune control relative to later experiences of abuse. Finally, in light of research suggesting that cigarette smoking (Anda et al., 1999; Lee et al., 2012) or depression (Dunn et al., 2012; Herbert and Cohen, 1993a) may be pathways linking childhood adversity to compromised immune-related processes, we examined current smoking and depressive symptoms as potential mechanisms for observed associations.

1. Methods

1.1. Sample

Data for this study were drawn from Add Health, an ongoing nationally-representative school-based study of adolescents in grades 7 through 12 that began in 1994 and has followed respondents into young adulthood (Udry et al., 1997). Add Health was designed to examine predictors of health-related behaviors, and particularly the role of social context. To date, there have been four follow-up surveys. Details about Add Health have been described in other publications (Harris et al., 2003; Resnick et al., 1997; Udry et al., 1997), and can be found at http://www.cpc.unc.edu/projects/addhealth/design. The present study utilized data from Waves 1 and 4.

At Wave 1, a multi-stage sampling design was used to enroll students into the study. A systematic random sample of 80 high schools was selected from the 26,666 U.S. high schools that had at least an 11th grade and at least 30 students in the school. These 80 schools were selected proportional to enrollment size. Schools were stratified by region, urbanicity, school type, and percentage of White students prior to sampling. For each of these selected high