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Association of serum interleukin-6 with mental health problems in children exposed to perinatal complications and social disadvantage

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ABSTRACT

There is consistent evidence that inflammation is involved in mental disorders pathogenesis. Herein, using data from the High Risk Cohort Study for Psychiatric Disorders, we investigated the relationship between parental mood disorders (PMD), environmental factors, serum interleukin-6 (IL6) and mental health problems in children aged 6–12. We measured the serum levels of IL6 in 567 children. Information related to socio-demographic characteristics, mental health problems and multiple risk factors, as well as parent's psychiatric diagnosis, was captured. We evaluated two groups of environmental risk factors (i.e. perinatal complications and social disadvantage) using a cumulative risk model. Results showed that higher serum levels of IL6 were associated with PMD (RR = 1.072, p = 0.001), perinatal complications (RR = 1.022, p = 0.013) and social disadvantage (RR = 1.024, p = 0.021). There was an interaction between PMD and social disadvantage (RR = 1.141, p = 0.021), as the effect of PMD on IL6 was significantly higher in children exposed to higher levels of social disadvantage. Moreover, there was a positive correlation between IL6 and mental health problems (RR = 1.099, p = 0.026), which was moderated by exposure to perinatal complications or social disadvantage (RR = 1.273, p = 0.015 and RR = 1.179, p = 0.048, respectively). In conclusions, there is evidence of a differential inflammatory activation in children with PMD and exposure to environmental risk factors, when compared to matched peers. Systemic inflammation may be involved in the pathway linking familial risk and mental health problems.

1. Introduction

Accumulating evidence indicates that mental disorders are highly prevalent among children and adolescents, with studies estimating a prevalence of 13–20% (Carter et al., 2010; Paula et al., 2014; Petresco et al., 2014). Mental health problems in childhood are associated with significant psychosocial impairment (Carter et al., 2010; Petresco et al., 2014) and often persist into adulthood (Reef et al., 2011, 2010). The high prevalence of mental disorders highlights the importance of early detection and illness pre-emption/prevention by identifying proximal and distal risk factors, as well as pathophysiological mechanisms (Insel, 2014). Low-grade inflammation has been proposed as a key component of mental health problems' pathogenesis (Dantzer et al., 2008; Glassman and Miller, 2007; Raison et al., 2006). Longitudinal studies have linked higher levels of circulating inflammatory markers such as interleukin 6 (IL-6) and C-reactive protein (CRP), with subsequent risk of depression and psychosis (Khandaker et al., 2014;

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Miller and Cole, 2012). There is also evidence of elevated markers of inflammation in pediatric populations with neuropsychiatric disorders (Mitchell and Goldstein, 2014; Slopen et al., 2013a,b).

One of the most replicated peripheral inflammatory markers in mental disorders is the IL6. IL6 is produced by macrophages and lymphocytes and released acutely in response to tissue aggressions and pathogens. Increased peripheral levels of IL6, have been observed across disparate mental disorders including, but not limited to major depressive disorder (Dowlati et al., 2010; Valkanova et al., 2013), bipolar disorder (Brietzke et al., 2009; Modabbernia et al., 2013; Rosenblat et al., 2014) and psychosis (Miller et al., 2011a; Upthegrove et al., 2014). However, findings on inflammation in mental disorders are remarkably heterogeneous (Glassman and Miller, 2007; Munkholm et al., 2013; Valkanova et al., 2013). As a result, it has been proposed that mental disorders and inflammation co-occur only in certain subgroups of individuals, specifically those who have been exposed to shared risk factors for psychopathology and inflammatory dysfunction (e.g. early life stress) (Danese et al., 2008; Miller and Cole, 2012). Evidence indicates that childhood adversity is associated with "clustering" of depression and inflammation, wherein the connection between depressive symptoms and increases in inflammatory markers is strengthened in, or restricted to, individuals exposed to childhood adversity (Danese et al., 2008; Miller and Cole, 2012). Childhood maltreatment has been the most widely studied form of early life adversity. However, other factors that possibly link increased IL6 and mental health problems, including genetic predisposition (Chase et al., 2015; Sun et al., 2008; Uddin et al., 2011), socio-economic disadvantage (Tabassum et al., 2008) and intra-uterine/maternal stress during pregnancy (Brietzke et al., 2011; Khan et al., 2014; Veru et al., 2015), have been relatively less explored and, to our knowledge, have not been previously evaluated. Moreover, recent evidence has indicated that susceptibility to mental health problems are influenced by the interaction between different risk and resilience factors with pre-existing vulnerabilities (Howes and Murray, 2014; Kofink et al., 2013; van Os et al., 2010). A greater impact of environmental risk factors on mental health problems has been reported in individuals with genetic risk (Clarke et al., 2009; Forsyth et al., 2013; Guloksuz et al., 2015; Vendlinski et al., 2011). Conversely, as genetic and environmental risk factors that have been associated with abnormal inflammatory activity frequently overlap (Derry et al., 2013; Gustafsson et al., 2015; van Nierop et al., 2013), it is also possible to hypothesize that their combination would similarly have an interactive/synergistic effect.

Using data from a large high-risk (i.e. enriched for individual and familial psychopathology) Brazilian cohort this study aimed to investigate the relationship between parental mental illness, environmental risk factors, serum IL6 levels and mental health problems in children aged 6–12. We assessed two groups of environmental risk factors (i.e. perinatal complications and social disadvantage) using an empirically supported cumulative risk model (Bannink et al., 2013; Chartier et al., 2010; Flouri and Kallis, 2007; Flouri et al., 2010; Gustafsson et al., 2015; Lahat et al., 2015; Raviv et al., 2010; Shalev et al., 2014). Our main hypothesis was that exposure to environmental risk factors and parental mood disorder (PMD) would be associated with higher serum levels of IL6. Secondly, we predicted that there would be an interaction between the effects of PMD and environmental risk factors, wherein serum IL6 levels would be relatively higher among individuals with both exposure to environmental risk factors and familial mood disorder, when compared to those with only one or neither of these risk factors. Finally, we hypothesized that PMD and exposure to risk factors would moderate the association between mental health problems and serum IL6 levels, wherein symptoms and IL6 would be more strongly associated in children exposed to one or more risk factors.

2. Material and methods

2.1. Participants

The sample herein is part of the HRC Study, which has been described elsewhere (Salum et al., 2015). Our study population was composed of a subsample of 567 students with 6–12 years of age from 57 public schools in Porto Alegre and São Paulo, Brazil. To select this study population, we used a three-stage design: first we assessed child symptoms and family history of psychiatric disorders in a screening interview, wherein 9937 interviews (the biological mother in 88% of them) using the Family History Survey (FHS) were conducted. In the second stage, a random subsample (aimed to be representative from the community—n = 958) and a high-risk sub-sample (a sample with children with increased risk for mental disorders—n = 1554) were selected for further evaluation. For subjects in the random-selection stratum, a simple randomization procedure was used. The high-risk stratum was composed of children that screened positively for any of one of the five targeted domains (attention-deficit/hyperactivity disorder, anxiety, obsessive-compulsive disorder, psychosis, and learning disorders), which were selected to generate a sample with diverse psychopathology. Among those, children with higher number of family members affected were prioritized. The oversampling procedure was used to select a sample with higher family rates of mental disorders, and therefore, to enhance the power to identify developmental trajectories and underlying pathophysiological processes. Interviews were administered by trained lay interviewers.

A subsample composed of 750 children was randomly selected for blood collection. We were able to collect and process a valid blood sample from 567 children. Main reasons for lack of success in blood collection were: mother or children refusal, or technical problems with blood processing procedures. Children were also inquired about signs and symptoms of acute illnesses; if there were any blood was not collected. Written informed consent was provided by all parents of participants, and verbal assent was obtained from all children. The study was approved by the Ethics Committee of the University of São Paulo (IORG0004884, project IRB registration number: 1132/08). All families were invited for an appointment with a trained psychologist and social worker in case they were interested in receiving the results of the study evaluations. All children identified as being under the need of care were referred for clinical evaluation. Situations involving serious risk of physical or psychological harm received special attention in accordance to competent authorities' guidelines.

2.2. Measurements

2.2.1. Environmental risk factors

Questions about risk factors were determined after a critical review of the extant literature that has primarily reported on risk factors for mental disorders (Salum et al., 2015). We assessed demographic and social factors (e.g. socio-economic status, parental education), as well as perinatal factors (e.g. gestational age at birth, exposure to tobacco or alcohol intra-utero, gestational infections and clinical conditions). We created a cumulative risk index, conceptualized as each individual's cumulative exposure to a set of indicators of perinatal complications and social disadvantage, according to previous studies (Bannink et al., 2013; Flouri and Kallis, 2007; Flouri et al., 2010; Gustafsson et al., 2015; Shalev et al., 2014). Definitions and descriptive statistics of risk factors indicators are depicted in Table 1. Each indicator was weighted equally and summed. For analyses of interaction we created dichotomous variables for high exposure, defined as exposure to 2 or more risk factors. For perinatal complications 214 (36.7%) children met this