International Journal of Developmental Neuroscience 65 (2018) 29–37

Contents lists available at ScienceDirect

International Journal of Developmental Neuroscience

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

Review

Inflammatory molecules and neurotrophic factors as biomarkers of neuropsychomotor development in preterm neonates: A Systematic Review

Rafael C. Magalhães[a], Letícia P. Pimenta[a], Izabela G. Barbosa[a], Janaina M. Moreira[a,c], João L.V.M. de Barros[a], Antônio L. Teixeira[a,b], Ana C. Simões e Silva[a,c,*]

[a] Interdisciplinary Laboratory of Medical Investigation, School of Medicine, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil
[b] Translational Psychiatry Program, Department of Psychiatry and Behavioral Sciences, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, USA
[c] Department of Pediatrics, School of Medicine, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil

ARTICLE INFO

Keywords:
Inflammation
Cytokines
Neurotrophic factors
Motor development
Cognitive development
Preterm

ABSTRACT

Objective: To provide a systematic review investigating the role of inflammatory molecules and neurotrophic factors as biomarkers of neuropsychomotor development in preterm neonates. Data Source: Databases including PubMed, BIREME, and Scopus were systematically searched. Observational studies, as well as transversal, and cohort studies using human subjects published from 1990 to September 2017 were eligible for inclusion. Two authors independently identified eligible studies and analyzed their characteristics, quality, and accuracy in depth. Data synthesis: 11 eligible studies clearly investigated the association between peripheral inflammation and motor and/or cognitive development in preterm infants. However, the selected populations differed in relation to the events associated with prematurity and the risk factors to abnormal motor and/or cognitive development. These studies measured circulating levels of cytokines, chemokines, adhesion molecules, acute phase proteins, and growth factors. The most commonly analyzed proteins were IL-1β, IL-6, TNF, CCL5/RANTES, CXCL8/IL-8, IGFBP-1, and VEGF. In seven of the eligible studies, plasma levels of IL-6 correlated with development delay. Two studies reported correlation between CXCL8/IL-8 plasma levels with cognitive and motor delay. In one study, higher levels of MCP-1/CCL2 were associated with better cognitive and motor outcome. Conclusion: There is preliminary evidence indicating that circulating inflammatory molecules are associated with motor and cognitive development in preterm neonates, even considering different populations.

1. Introduction

Preterm birth (PTB) occurs in about 11% of all childbirths (Blencowe et al., 2012). Approximately 40% of preterm newborns present an elevated risk of perinatal mortality among other complications (Blencowe et al., 2013; Howson et al., 2013; Selip et al., 2012; Risso et al., 2012). Preterm neonates have high central nervous system (CNS) vulnerability, including abnormalities in white and gray matters, cerebellum volume, corpus callosum thickness and brain gyri which may alter the development and function of brain structures (Stewart et al., 2013; Molnár and Rutherford, 2013; Stephens and Vohr, 2009). These alterations can result in brain injury (Hielkema and Hadders-Algra, 2016), which is a severe perinatal complication that impacts the long-term neurodevelopment of the subject (Selip et al., 2012; Risso et al., 2012; Woodward et al., 2005; Holsti et al., 2002; Berger et al., 2012; Marc, 2013).

Technological and scientific advances in neonatology have led to increased survival rates of preterm newborns, even at younger gestational ages (Stewart et al., 2013; Molnár and Rutherford, 2013; Stephens and Vohr, 2009). Unfortunately, neither a reduction in the occurrence of delayed neuropsychomotor development nor an improvement in the related frequency and severity of behavioral disorders has followed these advances (Z et al., 2009; Lei et al., 2017). As a consequence of prematurity, motor, sensory, cognitive and/or behavioral impairments may persistent throughout lifespan (Stewart et al., 2013; Molnár and Rutherford, 2013; Stephens and Vohr, 2009).

Fetus growth and development require time and may be affected by multiple conditions that jeopardize healthy development, during the gestation period (Kelley et al., 2017; Talati et al., 2017). At this stage, the placenta provides the fetus with growth factors needed for normal body and brain development (Leviton et al., 2017a). Changes in placental function have been associated with many antenatal conditions,

* Corresponding author at: Interdisciplinary Laboratory of Medical Investigation Avenida Alfredo Balena, 190, 2nd floor, room #281, Belo Horizonte, MG, Zip Code: 30130-100, Brazil.
E-mail addresses: rafa_to@hotmail.com (R.C. Magalhães), leticiaprettip@gmail.com (L.P. Pimenta), izabelagb@gmail.com (I.G. Barbosa), jajammoreira@gmail.com (J.M. Moreira), jlvmb@yahoo.com (J.L.V.M. de Barros), altexr@gmail.com (A.L. Teixeira), acssilva@hotmail.com (A.C. Simões e Silva).

http://dx.doi.org/10.1016/j.ijdevneu.2017.10.006
Received 7 August 2017; Received in revised form 13 October 2017; Accepted 15 October 2017
Available online 16 October 2017
0736-5748/

which are risk factors for *in-utero* inflammation, PTB and/or atypical neurodevelopment (Hodyl et al., 2017). Inflammation is present in a significant proportion of PTB and can be associated or not with clinical infections (Nadeau-Vallée et al., 2017; Cordeiro et al., 2016). It is charac3)terized by activation and infiltration of macrophage and neutrophil into each of the uterine tissue compartments and amniotic cavity, in addition to increased levels of pro-inflammatory cytokines and chemokines (Hodyl et al., 2017; Nadeau-Vallée et al., 2017; Cordeiro et al., 2016; Gomez-Lopez et al., 2017a). It generally results in acute chorioamnionitis, which, in turn, contributes to PTB (Gomez-Lopez et al., 2017b) and the subsequent development of fetal inflammatory response syndrome (FIRS) (Nadeau-Vallée et al., 2017; Cordeiro et al., 2016; Lei et al., 2015).

Neuroinflammation is thought to be one of the main factors involved in neurodevelopmental impairment in preterm infants (Z et al., 2009; Lei et al., 2017). This hypothesis proposes that enhanced CNS and related systemic inflammation contribute to neuronal damage, astrogliosis, and oligodendrocytes loss (Stewart et al., 2013; Molnár and Rutherford, 2013; Guimarães Filho et al., 1992; Vinall and Grunau, 2014; Jaeger et al., 2015). The inflammatory process alters neuronal and glial cells proliferation, differentiation, and may also increase cell death rate (Vasconcelos et al., 2014; Wikström et al., 2008; Ohls et al., 2014). The possible mechanisms by which inflammation intensifies early brain lesion are: (i) reduced blood-flow to the CNS, which reduces oxygen and glucose availability; (ii) blood-brain barrier rupture; (iii) leukocyte infiltration into the CNS; (iv) increased cytokines and chemokines release in the cerebral parenchyma; (v) mitochondrial dysfunction and energy failure; (vi) increased calcium influx, neurotoxins release, oxygen and nitric oxygen free radicals formation; (viii) brain edema. All these mechanisms have been associated with neuronal and glial cells apoptosis (Vasconcelos et al., 2014; Wikström et al., 2008; Ohls et al., 2014).

The increase in proinflammatory cytokines represents an independent risk factor for neonatal morbidities (Cordeiro et al., 2016). Some molecules, such as interleukin (IL)-1, IL-6, IL-8, and Tumor Necrosis Factor-α (TNF-α), are described as biomarkers and are associated with fetal inflammatory response and adverse neurologic outcomes (Cordeiro et al., 2016). On the other hand, growth factors with neurotrophic and/or angiogenic properties, such as neurotrophin-4 (NT-4), brain-derived neurotrophic factor (BDNF) and basic fibroblastic growth factor (bFGF), have the potential to promote the survival and differentiation of brain cells and minimize the brain damage (Howson et al., 2013; Allred et al., 2017).

For these reasons, we conducted a systematic review to investigate the role of inflammatory molecules and neurotrophic factors in neuropsychomotor development in preterm neonates. This study aimed to better understand the relationship of these molecules with neuropsychomotor development. Our hypothesis is that preterm neonates due to exposure to intrauterine inflammation are at greater risk for brain injury and for adverse neurological outcomes, including cognitive and motor disabilities.

2. Objective

The aim of this study was to provide a systematic review investigating the role of inflammatory biomarkers and neurotrophic factors in neuropsychomotor development in preterm neonates.

3. Methods

3.1. Design

This systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009).

3.2. Inclusion criteria

3.2.1. Types of studies

Observational studies as well as transversal and cohort studies were eligible for inclusion. Studies excluded from this review included: (i) studies with animal models, (ii) review articles, (iii) intervention studies or (iv) studies in which inflammatory molecules were not measured.

3.2.2. Studies populations

The target population of this review was preterm neonates at all gestational ages.

3.3. Search methods for identification of studies

An electronic search for relevant articles was performed independently by two authors (R.C.M. and L.P.P.) using PUBMED, BIREME and SCOPUS. Only articles published from 1990 to September 2017 were included in this review. The search terms were “inflammation”, “cytokine”, “neurotrophic factors”, “motor development”, “cognitive development”, “preterm”, without language restriction. The search combination used was: (inflammation OR cytokine OR (neurotrophic factors)) AND ((motor development) OR (cognitive development)) AND preterm.

3.4. Selection of studies

Two researchers independently (R.C.M. and L.P.P.) reviewed the eligibility of the studies and analyzed their characteristics, quality, and accuracy. Studies were initially extracted for abstract screening and those found to be relevant were fully retrieved for a detailed review. Disagreements on eligibility were resolved by discussion between authors. Once the eligible studies were established, data were extracted by authors. Whenever clarifications were necessary, manuscripts’ authors were contacted and asked to provide raw data if available. To describe potential for bias, the level of evidence of each retrieved study was evaluated according to the criteria suggested by the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in *meta*-analyses (Wells et al., 2017).

4. Results

A total of 262 articles were retrieved from our search. Initial screening to remove duplicates and studies with no apparent relevance yielded 110 unique articles (Fig. 1). After excluding non-experimental review articles, studies with animal models, and clinical trials in which inflammatory markers or motor/cognitive development were not measured, 11 studies were found to be relevant to assess the association of inflammatory markers in the first postnatal weeks and subsequent neurodevelopment. All selected studies (Tilley et al., 2017; Magalhaes et al., 2017; Korzeniewski et al., 2015; Kuban et al., 2015; Rose et al., 2015; Korzeniewski et al., 2014; Leviton et al., 2013; O'Shea et al., 2013; O'Shea et al., 2012; Kinjo et al., 2011; Silveira and Procianoy, 2011) were assessed by the Newcastle-Ottawa Scale (Wells et al., 2017) (Table 1).

4.1. Study characteristics

The selected studies (n = 11) investigated in this systematic review had very diverse populations with different risk factors (Tilley et al., 2017; Magalhaes et al., 2017; Korzeniewski et al., 2015; Kuban et al., 2015; Rose et al., 2015; Korzeniewski et al., 2014; Leviton et al., 2013; O'Shea et al., 2013; O'Shea et al., 2012; Kinjo et al., 2011; Silveira and Procianoy, 2011). In regard to gestational age, only preterm delivered before 32 weeks were described in all selected studies and, in seven studies, the sample was composed only by patients born before the 28th