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Review

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

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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,

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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

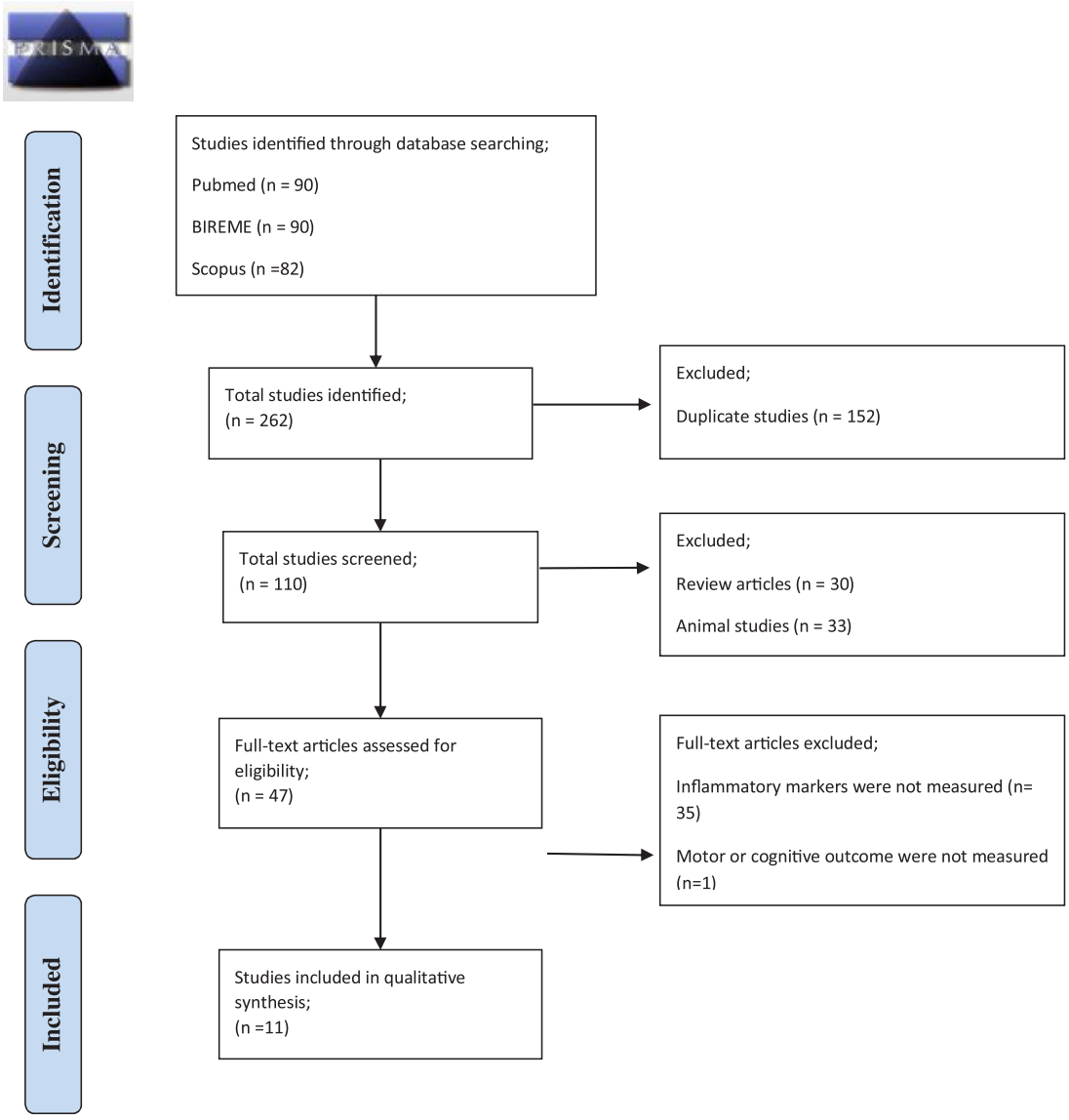

Fig. 1. PRISMA flow diagram for observational studies of correlation between inflammatory markers and neurodevelopment.

Table 1
Assessment of the studies by the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in *meta*-analyses.

Author	Selection	Comparability	Outcome
(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)	★★★★	★	★★★

week of gestation (Tilley et al., 2017; Korzeniewski et al., 2015; Kuban et al., 2015; Korzeniewski et al., 2014; Leviton et al., 2013; O'Shea et al., 2013; O'Shea et al., 2012) (Table 2). The inflammatory molecules and neurotrophic factors were measured during the first 2 weeks after birth and, in most studies, were considered elevated if concentrations were in the top quartile on two separate time-points during this period (Korzeniewski et al., 2015; Kuban et al., 2015; Korzeniewski et al., 2014; Leviton et al., 2013; O'Shea et al., 2013; O'Shea et al., 2012). Two studies recorded the level of these molecules until the 3rd or 4th weeks of postnatal age (Magalhaes et al., 2017; Kinjo et al., 2011). Patients with sepsis or at high-risk for early onset sepsis were included in three studies (Tilley et al., 2017; Rose et al., 2015; Silveira and Procianoy, 2011). The results from these latter subjects were shown separately (Tilley et al., 2017; Rose et al., 2015; Silveira and Procianoy, 2011) (Table 3). Only one study showed an association between intrauterine inflammation, altered gene expression and cognitive impairment (Tilley et al., 2017).

4.2. Blood analysis and neurodevelopment outcome

The inflammatory molecules and neurotrophic factors were assessed using different methods, including Meso Scale Discovery (MSD) electrochemiluminescence system (Tilley et al., 2017; Korzeniewski et al., 2015; Kuban et al., 2015; Korzeniewski et al., 2014; Leviton et al., 2013; O'Shea et al., 2013; O'Shea et al., 2012; Silveira and Procianoy, 2011), the Cytometric Bead Array (CBA), flow cytometry (Magalhaes et al., 2017; Kinjo et al., 2011), or Enzyme-linked Immunoassay (ELISA) (Magalhaes et al., 2017) techniques. One study did not specify the

Table 2
Studies that evaluated the association between inflammatory molecules and motor or/and cognitive development.

Author	Gestational Age (Weeks)	Subjects/ Controls	Analyzed Material	Laboratory technique	Development Assessment (months CA)	Inflammatory markers	Motor delay	Cognitive delay
(Magalhaes et al., 2017)	28–32	40/-	Serum	CBA	34 weeks	IL-1β, IL-6, IL-10, TNF e IL-12p70, CXCL8/IL-8, CCL2/MCP-1, CCL5/ RANTES, CXCL10/IP-10, CXCL9/ MIG	IL-1β and CXCL8/IL-8 values were higher in the group with typical motor development by TIMP.	–
(Korzeniewski et al., 2015)	≤ 28	786/-	Total blood	MSD Multiplex	24	IL-1β, IL-6, IL-6R, TNF, TNF-R1, TNF-R2, CXCL8, CCL2, CCL13, CCL4, CCL5, CXCL11, ICAM-1, ICAM-3, VCAM-1, E-SEL, MMP-1, MMP-9, CRP, SAA, MPO, EPO	CRP, SAA, MPO, IL-6, IL-6R, TNF, TNF-R2, CXCL8, CCL2, CCL13, CCL5, ICAM-1, ICAM-3, E-SEL levels in children with systemic inflammation and hypererythropoietin were at risk for very low psychomotor development (BSID II)	CRP, SAA, TNF, I-SEL levels were associated with very low mental development index (BSID II) in children with systemic inflammation; IL-1β, IL-6, IL-6R, TNF, TNF-R1, TNF-R2, CXCL8, CCL2, CCL4, CCL5, ICAM-1, ICAM-3, VCAM-1, E-SEL, CRP, SAA, EPO levels in children with systemic inflammation and hypererythropoietin were at risk for very low mental development (BSID II)
(Kuban et al., 2015)	≤ 28	881	Total blood	MSD Multiplex	24	IL-1β, IL-6, IL-6R, TNF, TNF-R1, TNF-R2, CXCL8, CCL2, CCL13, CCL4, CCL5, CXCL11, ICAM-1, ICAM-3, VCAM-1, E-SEL, MMP-1, MMP-9, CRP, SAA, MPO	Elevation of cytokines, chemokines, adhesions and liver-produced molecules associated with a higher risk of lower motor index	Higher liver-produced molecules associated with a higher risk of lower psychomotor index
(Korzeniewski et al., 2014)	≤ 28	786/-	Total blood	MSD Multiplex	24	IL-1β, IL-6, IL-6R, TNF, TNF-R1, TNF-R2, CXCL8, CCL2, CCL13, CCL4, CCL5, CXCL11, ICAM-1, ICAM-3, VCAM-1, E-SEL, MMP-1, MMP-9, CRP, SAA, MPO	ICAM-1 levels were associated with very low psychomotor development (BSID II) in children with systemic inflammation; CRP, SAA, IL-6, TNF-α levels in children with systemic inflammation and hyperthyrotropinemia were at risk for very low psychomotor development (BSID II)	CRP, SAA, IL-6, CXCL8, CCL2, ICAM-1 were associated with very low mental developmental index (BSID II) in children with systemic inflammation; CRP, SAA, IL-6, IL-1β, TNF, CXCL8, VCAM-1, E-SEL were associated with very low mental developmental index (BSID II) in children with systemic inflammation and hyperthyrotropinemia
(Leviton et al., 2013)	≤ 28	805/-	Total blood	–	24	IL-1β, IL-6, IL-6R, TNF, TNF-R1, TNF-R2, CXCL8, CCL2, CCL13, CCL4, CCL5, CXCL11, ICAM-1, ICAM-3, VCAM-1, E-SEL, MMP-1, MMP-9, CRP, SAA, MPO	–	IL-1β, IL-6, TNF, CXCL8 CCL4, ICAM-1, E-SEL, CRP and SAA were associated with low mental developmental index (BSID II)
(O'Shea et al., 2013)	≤ 28	800/-	Total blood	MSD Multiplex	24	IL-1β, IL-6, IL-6R, TNF, TNF-R1, TNF-R2, CXCL8, CCL2, CCL13, CCL4, CCL5, CXCL11, ICAM-1, ICAM-3, VCAM-1, E-SEL, MMP-1, MMP-9, CRP, SAA, MPO	–	Association of lower BSID II scores with elevated CRP, SAA, IL-6, TNF, CXCL8, CCL4, ICAM-1, E-SEL levels
(O'Shea et al., 2012)	≤ 28	939/-	Total blood	MSD Multiplex	24	IL-1β, IL-6, IL-6R, TNF, TNF-R1, TNF-R2, CXCL8, CCL2, CCL13, CCL4, CCL5, CXCL11, ICAM-1, ICAM-3, VCAM-1, E-SEL, MMP-1, MMP-9, CRP, SAA, MPO	Association of higher levels of CXCL8, CRP (elevated on 1 time point only) and IL-6, TNF, CXCL8, CCL2, ICAM-1, CRP, SAA, MPO (elevated on 2 time points) with Motor Scale Index below 55.	Association of higher levels of TNF, TNF-R1, MPO (elevated on 1 time point only) and IL-6, TNF, TNF-R2, CXCL8, CCL4, ICAM-1, VCAM-1, E-SEL, CRP, SAA (elevated on 2 time points) with Mental Scale Index below 55
(Kinjo et al., 2011)	24–32	29/-	Serum	CBA	36	CXCL8, CCL9, CCL10, CCL2, IL-1β, IL-6, IL-10, TNF, IL-12p70.	Negative correlation of CXCL-8, IL-1β (at birth), and positive correlation of CCL2 levels (4 wks) with KSPD score	Negative correlation of CXCL8, IL-1β, and IL-6 levels at birth with KSPD score.

CA: Correct Age; MSD: Meso Scale Discovery electrochemiluminescence system; CBA: Cytometric Bead Array; PCR: Polymerase Chain Reaction; IL: Interleukin; IL-6R: Interleukin 6 Receptor.
.CRP: C − reactive protein; SAA: serum amyloid A; SEL: Selectin; ICAM: Intercellular Adhesion Molecule; CCL/CXCL: Chemokines; SAA: Serum Amyloid A; TNF: Tumor Necrosis Factor.
TNF-R1: Tumor Necrosis Factor Receptor 1; TNF-R2: Tumor Necrosis Factor Receptor2; EPO: Erythropoietin.
BSID II: Bayley Scales of Infant Development − Second Edition: indicative of delay if score < 55. KSPD: Kyoto Scale of Psychological Development: indicative of delay if score < 85.
BSID III: Bayley Scales of Infant Development − Third Edition: indicative of delay if score < 55 TIMP: Test of Infant Motor Performance − indicative of delay if percentile < 5^{th}.

Table 3
Studies that evaluated the association between inflammatory molecules and motor or/and cognitive development and sepsis.

Author	Gestational Age (weeks)	Patients/ Controls	Analyzed Material	Laboratory method	Development Assessment (months CA)	Inflammatory markers	Motor delay	Cognitive delay
(Tilley et al., 2017)	≤ 28	43/-	Placenta tissue	Quiagen RNeasy	120	IL-1β, IL-6, IL-6R, TNF, TNF-R1, TNF-R2, CXCL1, CXCL2, CXCL5, CXCL8, CCL2, CCL13, CCL4, CCL5, CXCL11, CCL20, ICAM-1, ICAM-3, VCAM-1, E-SEL, MMP-1, MMP-9, CRP, SAA, MPO, GUCY1A2, GUCY1A3, PPM1L, PLCE1, PRKAG2, PLCL1, CCR2, S100A8, CAV1, GUCY1A2, GUCY1A3, GAB1,PLCE1, PRKAG2, PLCL1	–	Genes expression levels are associated with both intrauterine inflammation and later-life neurocognitive impairment
(Rose et al., 2015)	≤ 32	102/-	Serum	–	18–22	CRP, albumin, bilirubin	Negative association of CRP levels with of BSID III score and gait	Negative correlation of BSID III score with CRP levels
(Silveira and Procianoy, 2011)	24–32	62/-	Serum	MSD Multiplex	22–24	IL-1β, IL-6, IL-10, TNF, CXCL8	IL-6, TNF and CXCL8 were associated with lower psychomotor development. However, this association was not significant by multivariate analyses.	IL-6 and CXCL8 were associated with lower mental development. However, these association was not significant by multivariate analyses.

CA: Correct Age; **MSD:** Meso Scale Discovery electrochemiluminescence system; **CBA:** Cytometric Bead Array; **PCR:** Polymerase Chain Reaction; **IL:** Interleukin; **CRP:** C − reactive protein; **CCL/CXCL:** Chemokines; **TNF:** Tumor Necrosis Factor; **TNF-R1:** Tumor Necrosis Factor Receptor 1. **BSID III:** Bayley Scales of Infant Development − Third Edition: indicative of delay if score < 55.

laboratory method of analysis (Rose et al., 2015). The only study which measured gene expression, RNA extraction was performed by the Qiagen RNeasy Mini Kit (Tilley et al., 2017).

Neurodevelopment assessment was also evaluated with different instruments, such as the Differential Ability Scales II (DAS-II) and the Developmental Neuropsychological Assessment II (NEPSY II) (Tilley et al., 2017). The latent profile analysis (LPA) was used to classify the cognitive function in normal, low-normal, moderately impaired and severely impaired (Tilley et al., 2017). The Test of Infant Motor Performance (TIMP) was indicative of delay if scored below the 5th percentile (Magalhaes et al., 2017). The Bayley Scales of Infant Development (BSD) was suggestive of delay if scores were below 55 (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; Silveira and Procianoy, 2011) and the Kyoto Scale of Psychological Development (KSPD) if scores were below 85 (Kinjo et al., 2011).

Three studies included patients with sepsis or at high-risk for early onset sepsis (Table 3) (Tilley et al., 2017; Rose et al., 2015; Silveira and Procianoy, 2011). In two of them, no relevant association was found between neonatal inflammatory markers elevation and neurodevelopment outcome at the age of 2 years old (Rose et al., 2015; Silveira and Procianoy, 2011). However, the other one showed the association of altered gene expression in umbilical cord tissue and prenatal intrauterine inflammation, whereas six of the genes significantly predict the risk of future neurocognitive impairment (Tilley et al., 2017).

Eight studies showed association between the elevation of inflammatory molecules (Table 2) and/or neurotrophic factors (Table 4) and neurodevelopment (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; Silveira and Procianoy, 2011). Most of these studies reported that high levels of inflammatory molecules were associated with neurodevelopment impairment. Only one study observed that this association was not significant in multivariate analyses (Silveira and Procianoy, 2011).

Two studies reported correlation between higher levels inflammatory markers and normal neurodevelopment (Magalhaes et al., 2017; Kinjo et al., 2011). One study showed that higher levels of IL-1β and IL-8/CXCL8 were associated with typical motor development, while increased levels of GDNF were associated with delayed motor development (Magalhaes et al., 2017). The other study reported that serum levels of the chemokine MCP-1/CCL2 measured at 4 weeks of gestacional age were higher in infants who attained normal developmental quotients at 3 years of age in comparison with infants with delayed development (Kinjo et al., 2011).

Only one study has adopted birth weight as one of the inclusion criteria (Leviton et al., 2013). This study enrolled 805 patients small for gestational age (SGA) (Leviton et al., 2013). Lower birth weight appears to be an aggravating factor for worse mental developmental index (MDI) in preterm neonates with systemic inflammation (Leviton et al., 2013). The authors considered SGA all newborns in the lowest decile of the birth weight distribution in an external standard or birth weight lower than 1.28 standard deviations below the mean of a reference population. Data concerning cranial circumference was not informed.

5. Discussion

The current systematic review summarizes all available evidence on the association of inflammatory molecules and neurotrophic factors measured in the perinatal period in preterm neonates and subsequent neurodevelopment impairment. 11 observational studies were selected and most of them reported an association between peripheral inflammation and cognitive or motor delay in preterm infants.

Overall, high levels of inflammatory biomarkers, including cytokines, chemokines adhesion molecules, growth factors, neurotrophic factors, liver-produced molecules and activated neutrophils, during the

Table 4
Studies that evaluated the association between neurotrophic factors and motor and/or cognitive development.

Author	Gestational Age (weeks)	Patients/ Controls	Analyzed Material	Laboratory method	Development Assessment (months CA)	Analyzed neurotrophins	Motor delay	Cognitive delay
(Magalhaes et al., 2017)	28–32	40/-	Serum	ELISA	34 weeks	BDNF, GDNF	Higher levels of GDNF were found in the group with lower than expected motor development by TIMP.	–
(Korzeniewski et al., 2015)	≤ 28	786/-	Total blood	MSD Multiplex	24	VEGF, VEGF-R1, VEGF-R2, IGFBP-1.	Negative correlation of BSID II score and IGFBP-1 levels	Negative correlation of IGFBP-1 levels in children with systemic inflammation; And negative correlation of BSID II score with VEGF-R2 and IGFBP-1 levels in children with systemic inflammation and hypererythropoietin
(Korzeniewski et al., 2014)	≤ 28	939/-	Total blood	MSD Multiplex	24	VEGF, VEGF-R1, VEGF-R2, IGFBP-1.	Negative correlation of BSID II score and IGFBP-1 levels	Negative correlation of IGFBP-1 levels in children with systemic inflammation; Negative correlation of BSID II score with VEGF-R2, and IGFBP-1 levels in children with systemic inflammation and hyperthyrotropinemia
(Leviton et al., 2013)	≤ 28	805/-	Total blood	–	24	VEGF, VEGF-R1, VEGF-R2, IGFBP-1.	–	Negative correlation of BSID II score with IGFBP-1 and VEGF-R2 levels
(O'Shea et al., 2013)	≤ 28	800/-	Total blood	MSD Multiplex	24	VEGF, VEGF-R1, VEGF-R2, IGFBP-1.	Negative correlation of BSID II score and IGFBP-1 levels	Negative correlation with IGFBP-1 levels
(O'Shea et al., 2012)	≤ 28	939/-	Total blood	MSD Multiplex	24	VEGF, VEGF-R1, VEGF-R2, IGFBP-1.	No significant association with these molecules with BSID II scores if elevated on 1 or 2 time points	Negative correlation with BSID II score and VEGF-R2 levels (elevated on 1 time point only) and IGFBP-1, VEGF-R2 (elevated on 2 time points)

CA: Correct Age; **GA:** Gestational Age; **ELISA:** Enzyme-linked immunoassay; **BNDF:** Brain-Derived Neurotrophic Factor; **GDNF:** Glial cell-Derived Neurotrophic Factor; **IGFBP-1:** Insulin-like growth factor binding protein-1; **VEGF:** Vascular Endothelial Growth Factor; **VEGF-R1/Flt-1:** Vascular Endothelial Growth Factor Receptor 1; **VEGF-R2/KDR:** Vascular Endothelial Growth Factor Receptor 2. **BSID II:** Bayley Scales of Infant Development − Second Edition: indicative of delay if score < 55. **TIMP:** Test of Infant Motor Performance − indicative of delay if percentile < $5^{th.}$.

first few weeks after birth, have been associated with poor motor and cognitive performances at later time (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). Metalloproteinases were the only class of molecules analyzed that did not have any association with neurodevelopment impairment. In contrast, two studies detected elevated levels of inflammatory molecules associated with typical neurodevelopment (Magalhaes et al., 2017; Kinjo et al., 2011). Increased levels of IL-1β were associated with typical development at 34 weeks postnatal age (Magalhaes et al., 2017), while elevated concentrations of MCP-1/CCL2, measured at 4 weeks after birth, were associated with normal developmental quotients at 3 years of age (Kinjo et al., 2011).

The literature on SGA preterm babies is sparse. In one study, association between the presence of inflammatory markers and neurodevelopment impairment in SGA preterm babies (Leviton et al., 2013) was reported, in which preterm with systemic inflammation and lower weight were at high risk for worse MDI (Leviton et al., 2013). The authors raised two possible explanations for this observation. One is that blunted growth mechanisms associated with SGA and processes associated with systemic inflammation contributed independently to the risk of a very low Bayley Mental Development Indices. The other explanation is that processes associated with SGA may sensitize the brain to adverse effects of postnatal inflammation (Leviton et al., 2013).

From the studies reporting inflammatory molecules in preterm babies, only one described, quantitatively, the correlation between the systemic inflammation and neurodevelopment impairment (Leviton et al., 2013). Also, this study identified which increased biomarkers on multiple days were more often associated with lower development than elevations present only for a day (Leviton et al., 2013). Preterm infants who had persistently increased blood levels of inflammatory proteins in the first two postnatal weeks were at increased risk for severely limited development two years later (O'Shea et al., 2012). This study raised three possible reasons for this finding. Firstly, the increasing vulnerability of preterm neonates due to the lower protection provided by the placenta and by the mother in course of time. Secondly, the systemic inflammatory response caused by prenatal brain damage or due to brain injury during the first postnatal days, including strokes. Lastly, the damage to other organs, including lungs and gut, that may cause developmental delay (O'Shea et al., 2012). More recently, the same research group measured concentrations of 25 inflammatory proteins, representing six functional categories (cytokines, chemokines, growth factors, adhesion molecules, metalloproteinases, and liver-produced acute phase reactant proteins) on postnatal days 1, 7, and 14. The authors showed that the risk of abnormal brain structure and function was increased among children who had recurrent and/or persistent elevations of these proteins. Furthermore, a score of risk was built based on the number of protein elevations or the number of protein functional classes increased, being 0–1 points indicative of low risk of motor and cognitive delay, 2–4 points of intermediate risk and five or more of high risk (O'Shea et al., 2012).

Although sepsis has been described as an independent risk factor for neuromotor development impairment in preterm infants (Ferreira et al., 2014), only one study found positive correlation with inflammatory process and poor cognitive outcome (Tilley et al., 2017). The other two studies that analyzed patients with sepsis did not show a relevant association between inflammatory markers and neurodevelopment outcome in prematures with sepsis or at high-risk for early onset sepsis (Rose et al., 2015; Silveira and Procianoy, 2011).

One study focused on association of prenatal intrauterine inflammation with altered gene expression in umbilical cord tissue (Tilley et al., 2017). In this sample, the inflammatory profile changed not only cytokines, chemokines and neurotrophic factors, but also, mRNA for these molecules, which was associated with worst cognitive development later in life[34].

The action of these molecules seems to affect neuropsychomotor performance (Wells et al., 2017; 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). Most studies measured biological markers at first weeks after birth, while the neuropsychomotor development was assessed at 24 (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; Silveira and Procianoy, 2011), 36 months of corrected age (Kinjo et al., 2011) and at ten years of age (Tilley et al., 2017). However, the relationship of these molecules with motor development at the first month after birth was analyzed by only one study (Magalhaes et al., 2017), in which the time points of biological markers measurements occurred closely to assessment of motor development.

The originality and strength of the current manuscript is its proposal to review the association between inflammatory molecules and neurotrophic factors with motor and cognitive development in preterm babies. We are aware of the limitations of this systematic review. First, six among ten selected studies were conducted by the same research team (Korzeniewski et al., 2015; Kuban et al., 2015; Korzeniewski et al., 2014; Leviton et al., 2013; O'Shea et al., 2013; O'Shea et al., 2012). This fact may increase the risk of bias (Korzeniewski et al., 2015; Kuban et al., 2015; Korzeniewski et al., 2014; Leviton et al., 2013; O'Shea et al., 2013; O'Shea et al., 2012). Finally, as the etiology of the inflammatory process is not always clear, many studies fail to detect the trigger of the inflammatory stimuli.

The 11 selected studies included preterm neonates from different locations (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), which may justify some of the differences encountered. Demographic factors including extremes of maternal age, maternal malnutrition, different races and ethnic groups, short inter-pregnancy interval, lack of prenatal care, previous PTB, low socioeconomic status and cigarette smoking are likely to alter the risk for PTB (Talati et al., 2017). In addition, the most common risk factors for inflammation in preterm neonates and assisted ventilation and congenital or iatrogenic infection (Allred et al., 2017; Patra et al., 2017). The various possibilities of combinations of these risk factors may interfere in the inflammatory and anti-inflammatory responses and, consequently, in the neuropsychomotor outcome.

The association between a pro-inflammatory profile and poor cognitive and motor development is not completely elucidated. One of the possible explanations is that inflammatory molecules, including cytokines, are able to cross the compromised blood–brain barrier and to activate the microglia (Kelley et al., 2017; Patra et al., 2017). This might induce neuronal and glial cell apoptosis, therefore interfering in axonal growth and myelin sheath formation (Burd et al., 2012; Guo et al., 2010; Jenster et al., 2014). Problems with neuronal migration, division, and synaptic development might also occur and result in neurodevelopment changes (Ferreira et al., 2014; Malaeb and Dammann, 2009). On the other hand, neurotrophins in CNS may also provide trophic support to neurons and play a crucial role in development, maintenance and survival of the nervous system and synaptic plasticity, thus improving neurodevelopmental process (Kazak and Yarim, 2017).

Indeed, the physiological role of the inflammatory response in brain development and in the mechanisms of CNS protection appears to be crucial (Nadeau-Vallée et al., 2017; Magalhaes et al., 2017; Chhor et al., 2013), though it may become pathological depending on its location, timing, intensity, and chronicity (Nadeau-Vallée et al., 2017). Inflammation is a complex and dynamic process, involving different proteins, signals and pathways (Leviton et al., 2017b). Our review specifically focused on the relationship of cytokines, chemokines and neurotrophic factors with motor and cognitive development. Levels of

these molecules were analyzed in cord blood, amniotic fluid, cerebrospinal fluid and urine in preterm neonates. The most commonly analyzed proteins were IL-1β, IL-6, TNF, CCL5/RANTES, CXCL8/IL-8, IGFBP-1, and VEGF (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). Some molecules have been associated more frequently with neuropsychomotor development in several studies. For instance, plasma levels of IL-6 were linked to development delay (Wells et al., 2017; Tilley et al., 2017; Korzeniewski et al., 2015; Kuban et al., 2015; Rose et al., 2015; Korzeniewski et al., 2014; Leviton et al., 2013), while higher levels of MCP-1/CCL2 were associated with better cognitive and motor outcome (Leviton et al., 2013). However, conflicting results were also reported. Increased levels of CXCL8/IL-8 were associated with typical motor development (Magalhaes et al., 2017) and also with cognitive and motor delay (Korzeniewski et al., 2015; Leviton et al., 2013). This finding reinforces the hypothesis that inflammation may be both beneficial and harmful to the CNS, depending on its regulation and intensity.

Some degree of neuroinflammation is necessary for remyelination, neuroprotection and brain development. There are several inflammatory cytokines that regulate the production of neurotrophic factors by neurons and glia cells (Magalhaes et al., 2017; Rosa et al., 2016; Wee Yong, 2010). Furthermore, mutual interactions among cytokines and neurotrophic factors (Magalhaes et al., 2017; Kuban et al., 2015; Ranchhod et al., 2015) may result in dynamic variations in the concentration of these molecules, in which the increase or reduction of one molecule in response to others is common (Magalhaes et al., 2017; Ranchhod et al., 2015). When there is an insult of the CNS, an up regulation of neurotrophic factors may occur, as a compensatory response, in order to protect the neurons and induce the formation of new synapses (Magalhaes et al., 2017; Kinjo et al., 2011). A dynamic relationship between cytokines, chemokines and neurotrophic factors may contribute to brain development and neuropsychomotor skills acquisition.

There is still no defined reference range of physiological levels for these biomarkers, nor which values would provoke benefits or induce harm in this population. The eligible studies showed an association of these molecules and neuropsychomotor development and highlighted interesting targets for further investigations. However, more studies are needed in order to clarify this relationship and to select molecules that may be useful in the screening of infants at risk of adverse outcomes and to monitor the progression of brain injury. Additionally, studies should also define standard tests with good reproducibility and reference ranges specific for this population, according to international requirements established by regulatory agencies as Food and Drug Administration (FDA) and the European Medicine Agency (EMA) (Serpero et al., 2013).

6. Conclusion

The association of inflammatory molecules and neurotrophic factors with motor and cognitive development requires further research in order to better understand the influence of these molecules on neurodevelopment.

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