Research in Developmental Disabilities 95 (2019) 103508

Contents lists available at ScienceDirect

Research in Developmental Disabilities

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

Inflammatory biomarkers in children with cerebral palsy: A systematic review

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ARTICLE INFO

Number of reviews completed is 2

Keywords:
Cerebral palsy
Inflammation
Oxidative stress
Cytokines
Neurodevelopment outcome

ABSTRACT

Background: An exacerbated systemic inflammatory response has been associated with the occurrence of central nervous system injuries that may determine, in long term, motor, sensorial and cognitive disabilities. Persistence of this exacerbated inflammatory response seems to be involved in the pathophysiology of cerebral palsy (CP).

Methods: A systematic search was conducted in Bireme, Embase, PubMed and Scopus including studies that were published until August 2019. The key words used were "cerebral palsy", "brain injury", "inflammation", "oxidative stress", "cytokines", "chemokines", "neuropsychomotor development", "neurodevelopment outcomes" and "child". The quality of the eligible studies was determined according to the criteria suggested by the Newcastle-Ottawa Scale (NOS).

Results: Fourteen eligible studies aimed to investigate the association between peripheral inflammatory molecules and neurodevelopment in infants. The studies differed regarding CP-related risk factors and its classification. Inflammatory proteins were measured in blood, plasma, serum, cerebrospinal fluid or urine. In ten studies, higher circulating levels of cytokines, including IL-1β, IL-6, TNF and CXCL8/IL-8, were associated with abnormal neurological findings.

Conclusion: The investigation of the potential association between inflammatory molecules and neurological development in children with CP requires further original studies in order to clarify the influence of prenatal and perinatal inflammation on neurological outcomes.

What this paper adds?

This systematic review about the relation between inflammatory molecules and neurodevelopment in children with cerebral palsy describes current evidence regarding the association of cytokines with brain injury. In this review, studies were selected through rigorous inclusion criteria and were carefully analyzed. The main finding was that higher circulating levels of IL-1β, IL-6, TNF and CXCL8/IL-8 were associated with abnormal neurological findings in patients with cerebral palsy.

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https://doi.org/10.1016/j.ridd.2019.103508
Received 4 September 2018; Received in revised form 4 September 2019; Accepted 1 October 2019
Available online 01 November 2019

1. Introduction

Cerebral palsy (CP) is a chronic non-progressive encephalopathy characterized by the occurrence of acquired brain injury associated with altered neuropsychomotor development (Chambers, Sokhey, Gaebler-Spira, & Kording, 2017; Colver, Fairhurst, & Pharoah, 2014; Dreher et al., 2017). It is the most common cause of motor disability in children worldwide with an estimated prevalence of 1.5–4 per 1000 children (Chambers et al., 2017; Franzén, Hägglund, & Alriksson-Schmidt, 2017; Monokwane et al., 2017), but with a higher prevalence in low-resource settings, of up to 10 per 1000 children (Monokwane et al., 2017).

The classification of CP varies according to the type and distribution of motor abnormalities and the location of the brain injury, including spastic (bilateral -quadriparetic, diparetic - or unilateral - hemiparetic), dyskinetic and ataxic subtypes (Longo & Hankins, 2009).

Central nervous system (CNS) injury is multifactorial and includes exposure of the fetus or the newborn to acute and chronic infection/inflammation and/or perinatal hypoxic-ischemia (HI) (Bennet et al., 2018). The exacerbated inflammatory response is related to neuronal death (Hagberg, Gressens, & Mallard, 2012; Falahati et al., 2013) and, as a consequence, long-term motor, sensorial, or cognitive disabilities (Falahati et al., 2013; Girard et al., 2009; Hagberg et al., 2012). There is also evidence that CP may be associated to the persistence of an exacerbated or chronic inflammatory process in CNS (Girard et al., 2009; Rosenbaum et al., 2007).

Neuronal lesions related to inflammation induce a cascade of immune responses, including elevation of circulating cytokines and chemokines that might participate in the establishment of brain injury (Kazak & Yarim, 2017; Malaeb & Dammann, 2009; Molnár & Rutherford, 2013). Some molecules, including interleukin (IL)-1β, IL-6, CXCL8/IL-8, and Tumor Necrosis Factor (TNF), have been more frequently associated with inflammatory response and adverse neurologic outcomes (Cordeiro et al., 2016; Magalhães, Pimenta et al., 2017).

The balance between pro-inflammatory and immunomodulatory processes modulates the repair/resolution continuum and the consequent occurrence of injury (Kinjo et al., 2011; Lou, Yu WB, Jiang, Xiao, & Liu, 2016; Magalhães, Pimenta et al., 2017; Stewart et al., 2013). It is important to emphasize that brain development after an inflammation related injury is not a static event, but a complex and dynamic process, in which several cellular and molecular cascades are involved, throughout lifetime (Hielkema & Hadders-Algra, 2016).

Thereby, we conducted a systematic review to evaluate the current findings regarding the association between inflammatory mediators, oxidative stress (OS) and neurodevelopmental outcome in children with CP. Our hypothesis is that exacerbated inflammatory response and increased OS may impair neurodevelopment in children with CP.

2. Objective

The aim of this study was to provide a systematic review on the evidence of the interaction between inflammatory biomarkers, oxidative stress and neuropsychomotor development in children with CP.

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, Liberati, Tetzlaff, Altman, & Group, 2009).

Criteria for Considering Studies for this Review

3.2. Types of studies

Observational studies, as well as transversal or cohort, were eligible for inclusion. The following studies were excluded from this review: (i) animal studies, (ii) review articles, (iii) intervention studies, or (iv) studies in which inflammatory or oxidative stress markers were not measured.

3.3. Studies populations

The target population of this review consisted of children with CP.

3.4. Search methods for identification of studies

An electronic search for relevant articles was performed independently by three authors (R.C.M., A.O.L. and A.A.S.S.) by using BIREME, EMBASE, PUBMED and SCOPUS. Articles published until August 2019 were included in this review. No language restrictions were applied. The search terms utilized were “cerebral palsy”, “brain injury”, “inflammation”, “oxidative stress”, “cytokines”, “chemokines”, “neuropsychomotor development”, “neurodevelopment outcomes” and “child”. The search combinations used were: ((cerebral palsy) OR (brain injury)) AND ((inflammation OR (oxidative stress) OR (cytokines) OR (chemokines))) AND ((neuro psychomotor development) OR (neurodevelopmental outcomes)) AND child.

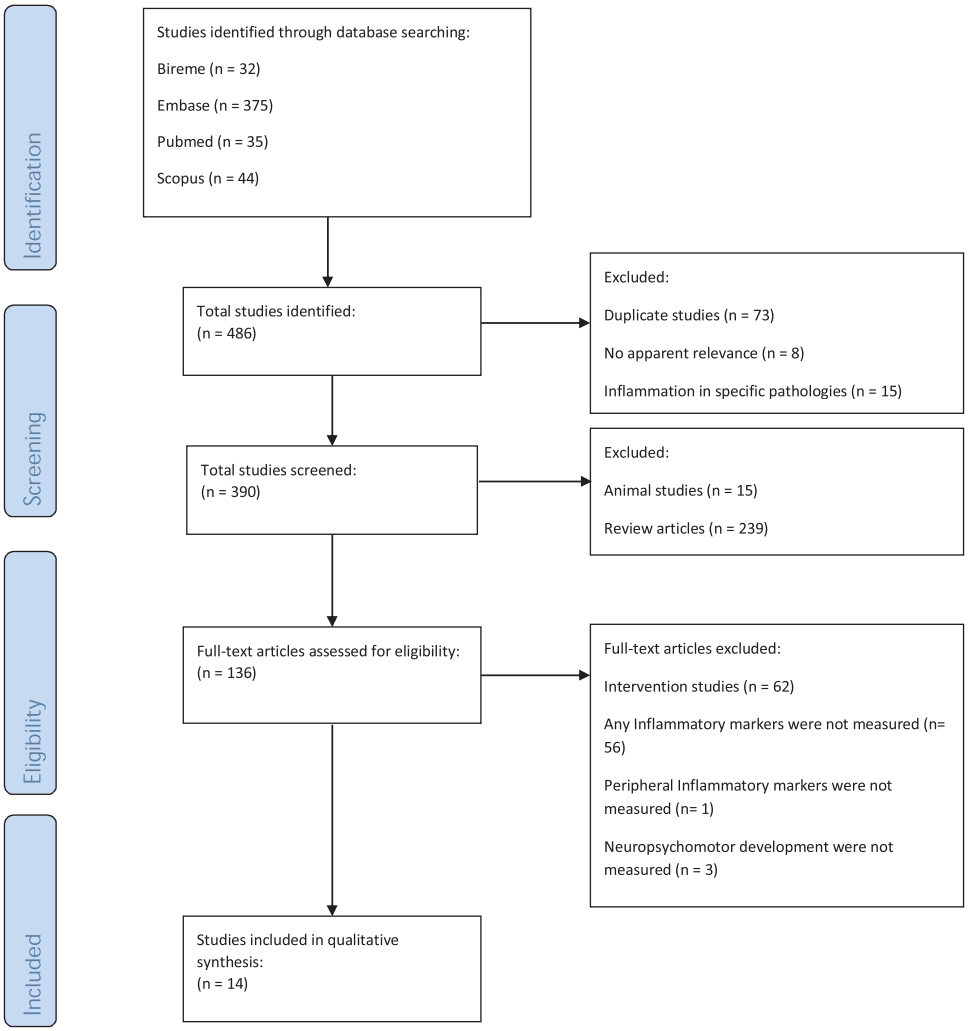

Fig. 1. PRISMA flow diagram for observational studies of correlation between inflammatory markers and neurodevelopment.

3.5. Selection of studies

Three researchers independently (R.C.M., A.O.L. and A.A.S.S.) 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 the authors. Once the studies to be included were established, the authors extracted relevant data. Whenever necessary, authors of the selected articles were contacted and asked to provide raw data. To describe potential for bias, the level of evidence of each retrieved study was evaluated according to the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses (Wells et al., 2017). The studies were evaluated by a 'star system" based on three aspects: the selection of subjects; the comparability; and the ascertainment of either the exposure or outcome of interest. In NOS, the studies can be awarded a maximum of four, two and three star for selection, comparability and exposure categories, respectively. The minimum for each item is zero. (Wells et al., 2017).

4. Results

The first search strategy identified 486 articles. Prisma Protocol was used to select the studies (Moher et al., 2009). Initial screening removed duplicates, studies with no apparent relevance and papers that included subjects with specific conditions, including autism, dysplasia bronchopulmonary, heart diseases and Zika virus, yielded 390 unique articles. After excluding non-experimental review articles, studies with animal models, and clinical trials in which inflammatory markers were not measured, 14 original studies were considered eligible for this systematic review (Fig. 1). All selected studies (Andrews et al., 2008; Bartha et al., 2004; Carlo et al., 2011; Chalak et al., 2014; Chu et al., 2006; Foster-Barber, Dickens, & Ferriero, 2001; Hoffmann et al., 2010; Kuban et al., 2015; Lodha, Asztalos, & Moore, 2010; Magalhães, Moreira et al., 2017; Shoji et al., 2014; Varner et al., 2015; Vasiljevic et al.,

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
Yanni et al. (2017))	★★★★	★★	★★★
Magalhães, Moreira et al. (2017)	★★★	★	★★
Varner et al. (2015))	★★★★	★★	★★★
Kuban et al. (2015))	★★★	★	★★
Chalak et al. (2014))	★★★	★★	★★★
Shoji et al. (2014))	★★★	★★	★★★
Carlo et al. (2011))	★★★★	★★	★★★
Vasiljevic et al. (2011))	★★★★	★★	★★★
Lodha et al. (2010))	★★★★	★★	★★★
Hoffmann et al. (2010))	★★★	★★	★★★
Andrews et al. (2008))	★★★★	★★	★★★
Chu et al. (2006))	★★★	★	★★
Bartha et al. (2004))	★★★★	★★	★★★
Foster-Barber et al. (2001))	★★★	★	★★

2011; Yanni et al., 2017) were assessed by the Newcastle-Ottawa Scale (Wells et al., 2017) (Table 1).

4.1. Study characteristics and methodological issues

The selected studies (n = 14) investigated diverse populations exposed to different risk factors for neurodevelopmental delay (Andrews et al., 2008; Bartha et al., 2004; Carlo et al., 2011; Chalak et al., 2014; Chu et al., 2006; Foster-Barber et al., 2001; Hoffmann et al., 2010; Kuban et al., 2015; Lodha et al., 2010; Magalhães, Moreira et al., 2017; Shoji et al., 2014; Varner et al., 2015; Vasiljevic et al., 2011; Yanni et al., 2017). The gestational age varied among the studies. Preterm (Andrews et al., 2008; Chu et al., 2006; Foster-Barber et al., 2001; Hoffmann et al., 2010; Kuban et al., 2015; Lodha et al., 2010; Magalhães, Moreira et al., 2017; Shoji et al., 2014; Varner et al., 2015; Vasiljevic et al., 2011; Yanni et al., 2017) and term neonates (Bartha et al., 2004; Chalak et al., 2014; Hoffmann et al., 2010; Vasiljevic et al., 2011) were included. Two studies had birth weight as an inclusion criterion either < 1500 g (Shoji et al., 2014) or between 401–1000 g (Carlo et al., 2011). Inflammatory molecules analyzed included IL-1β, IL-12p70, IL-2, IL-6, IL-6R, CXCL8/IL-8, IL-9, IL-10, IL-12, IL-13, IL-17, IFN-γ, TNF-α, TNF-β, TNF-R1, TNF-R2, CCL2/MCP-1, CCL4/MIP-β, CCL5/RANTES, CXCL9, CXCL10, CXCL11, CCL13, Neuregulin-1 (NRG1), Interferon-inducible T cell alpha-chemoattractant (I-TAC), Intercellular Adhesion Molecule (ICAM)-1, ICAM-3, Vascular Cell Adhesion Molecule (VCAM)-1, E-SEL, Matrix Metalloproteinase (MMP)-1, MMP-9, C-reactive protein (CRP), Serum Amyloid A (SAA), Myeloperoxidase (MPO) (Yanni et al., 2017; Chalak et al., 2014; Carlo et al., 2011; Lodha et al., 2010; Hoffmann et al., 2010; Andrews et al., 2008; Bartha et al., 2004; Foster-Barber et al., 2001) (Table 2). The samples for the analysis of these molecules were collected within the first three weeks after birth, and analyzed in whole blood, plasma, serum, cerebrospinal fluid or urine (Andrews et al., 2008; Bartha et al., 2004; Carlo et al., 2011; Chalak et al., 2014; Chu et al., 2006; Foster-Barber et al., 2001; Hoffmann et al., 2010; Kuban et al., 2015; Lodha et al., 2010; Magalhães, Moreira et al., 2017; Shoji et al., 2014; Varner et al., 2015; Vasiljevic et al., 2011; Yanni et al., 2017). Patients with diagnosis of sepsis or necrotizing enterocolitis (NEC) were included in three studies (Andrews et al., 2008; Carlo et al., 2011; Lodha et al., 2010). The results from these latter articles were shown separately, considering that infection may be an independent risk factor for increased inflammatory response (Andrews et al., 2008; Carlo et al., 2011; Lodha et al., 2010) (Table 3). Three studies analyzed OS markers, including 8-OHdG and of 8-isoprostane, Glutathione Peroxidase (GPX), Ethylmalonate, 3-hydroxy-3-methylglutarate, 2-hydroxyglutarate, 2-oxo-glutarate, Glutarate, Methylmalonate, 3-hydroxybutyrate and Orotate (Chu et al., 2006; Shoji et al., 2014; Vasiljevic et al., 2011) (Table 4).

In two studies, inflammatory molecules were analyzed in association with placental culture and histopathology (Andrews et al., 2008; Yanni et al., 2017). Comparison with a control group occurred in four studies (Chalak et al., 2014; Lodha et al., 2010; Varner et al., 2015; Vasiljevic et al., 2011). In ten studies there was no control group (Andrews et al., 2008; Bartha et al., 2004; Carlo et al., 2011; Chu et al., 2006; Foster-Barber et al., 2001; Hoffmann et al., 2010; Kuban et al., 2015; Magalhães, Moreira et al., 2017; Shoji et al., 2014; Yanni et al., 2017). These studies are longitudinal cohorts in which the biomarkers were measured at an initial time-point and neurodevelopment outcome was evaluated at a later time-point. Thus, these longitudinal studies can analyze the association between increased levels of a molecule at the baseline with worse neurodevelopment outcome later in life. (Andrews et al., 2008; Bartha et al., 2004; Carlo et al., 2011; Chu et al., 2006; Foster-Barber et al., 2001; Hoffmann et al., 2010; Kuban et al., 2015; Magalhães, Moreira et al., 2017; Shoji et al., 2014; Yanni et al., 2017). Blood samples were collected at different time points: at birth (umbilical cord serum) (Carlo et al., 2011, Andrews et al., 2008; Chalak et al., 2014; Hoffmann et al., 2010; Varner et al., 2015), at one (Bartha et al., 2004; Chalak et al., 2014; Foster-Barber et al., 2001; Kuban et al., 2015; Yanni et al., 2017), two (Chalak et al., 2014; Foster-Barber et al., 2001) three (Carlo et al., 2011; Chalak et al., 2014), seven (Carlo et al., 2011; Kuban et al., 2015; Yanni et al., 2017), fourteen or 21 days after birth (Carlo et al., 2011; Kuban et al., 2015; Yanni et al., 2017; Lodha et al., 2010). Urine samples were taken at different time-points too: at one (Chu et al., 2006), two (Magalhães, Moreira et al., 2017), three (Magalhães, Moreira et al., 2017) seven (Shoji et al., 2014), fourteen (Shoji et al., 2014), twenty one (Magalhães, Moreira et al., 2017) twenty eight (Shoji et al., 2014) and forty two days of life (Shoji et al., 2014). Only one study collected cerebrospinal fluid at two, three and

Table 2
Selected studies on the association between inflammatory markers and neurodevelopment.

Author	Age of subjects (weeks)	Subject/ Controls	Analyzed Material	Laboratory technique	Inflammatory markers	Development Assessment (months CA)	Neurological Assessment	Neurological outcome
Yanni et al. (2017)	< 28	763/–	Total blood	MSD Multiplex	IL-1β, IL-6, TNF, CXCL8, ICAM-1, CRP, SAA	24	BSID-II	High levels of TNF or ICAM-1 increase the risk of a low PDI score. SAA, CRP or IL-6 measurements were associated with very low MDI scores.
Magalhães, Moreira et al. (2017)	28-32	40/–	Urine	CBA	IL-1β, IL-6, IL-10, TNF e IL-12p70, CXCL8, CCL2/MCP-1, CCL5, CXCL10, CXCL9	34 weeks	TIMP	IL-1β and CXCL8/IL-8 values were higher in the group with typical motor development by TIMP.
Varner et al. (2015)	24-31	339/276	Umbilical cord serum	ELISA	CXCL8/IL-8, IL-1β and TNF	6,12,24	BSID-II	Cord serum IL-8, IL-1β, and TNF-α levels in preterm infants were not associated with subsequent cerebral palsy or neurodevelopmental delay
Kuban et al. (2015)	≤ 28	881/–	Total blood	MSD Multiplex	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	24	BSID-II	Elevation of cytokines, chemokines, adhesions and liver-produced molecules was associated with a higher risk of lower motor skills. Higher liver-produced molecules were associated with a higher risk of lower PDI.
Chalak et al. (2014)	≥ 36	20/7	Umbilical arterial serum or plasma	ELISA	IL-1 β, IL-6, CXCL8/IL-8, VEGF, TNF, IFN-γ, CCL5/RANTES, UCH-L1, GFAP	15-18	BSID-III	IL-6, IL-8 and VEGF were greater at 6-24 hours in moderate to severe versus mild hypoxic-ischemic encephalopathy. Elevated IL-1 β, IL-6, IL-8, VEGF, TNF-α, IFN-γ and GFAP were associated with abnormal neurological outcomes.
Hoffmann et al. (2010)	< 32	54/–	Umbilical cord serum	ELISA	NRG1	24	DDST	NRG1 might be a systemic endogenous neuroprotector in preterm newborns.
Bartha et al. (2004)	≥ 36	62/–	Whole blood (heel-stick)	RIC	IL-1 β, IL-6, CXCL8/IL-8, IL-12, IL-13, TNF	30	BSID-II	Children with abnormal neurodevelopmental outcome had higher neonatal levels of IL-1 β, IL-6, IL-8, and lower levels of IL-12. Elevated inflammatory cytokines were associated with impaired cerebral oxidative metabolism.
Foster-Barber et al. (2001)	≥ 36	64/–	Total blood	Multiplex Luminex Assay	IL-1 β, IL-6, IL-8, IL-9, TNF	12	BSID-II	Children with diagnose of cerebral palsy had elevated levels of the pro-inflammatory cytokines IL-1 β, IL-6, and TNF.

BSID II: Bayley Scales of Infant Development – Second Edition: indicative of delay if score < 70. BSID III: Bayley Scales of Infant Development – Third Edition: indicative of delay if score < 70; CA: Correct Age; CBA: Cytometric Bead Array; CCL/CXCL: Chemokines; CRP: C-reactive protein; DDST-II: Denver Developmental Screening Test II; ELISA: Enzyme-linked immunosorbent assay; EPO: Erythropoietin; E-SEL: Selectin; HIE: Hypoxic-Ischemic Encephalopathy; ICAM: Intercellular Adhesion Molecule; IGFBP: Insulin-like Growth Factor Binding Protein; IL: Interleukin; MDI: Mental Development Index; MMP: Matrix Metalloproteinase; MPO: Myeloperoxidase; MSD: Meso Scale Discovery electrochemiluminescence system; NGR1: Neuregulin-1 protein; PDI: Psychomotor Development Index; RIC: Recycling immunoaffinity chromatography; SAA: serum amyloid A; TIMP: Test of Infant Motor Performance - indicative of delay if percentile < 5th; TNF: Tumor Necrosis Factor; TNF-R: Tumor Necrosis Factor Receptors; VCAM: Vascular Cell Adhesion Molecule; VEGF: Vascular Endothelial Growth Factor; VEGF-R: Vascular Endothelial Growth Factor receptors.

Table 3
Selected studies on the association between inflammatory molecules, sepsis and motor or cognitive development.

Author	Gestational Age (weeks)	Patients/ Controls	Analyzed Material	Laboratory method	Development Assessment (months CA)	Inflammatory markers	Neurodevelopment Assessment	Neurodevelopmental Outcome
Carlo et al. (2011)	Newborn (401-1000 g)	755/-	Whole blood	Multiplex Luminex Assay	18-22	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	BSID-II	ILrα, TNF, IL-12, IL-17, MIP-1β and CXCL8 were altered on days 0-4 in infants who developed CP. CXCL8 remained higher subsequently.
Lodha et al. (2010)	≤ 37	27/13	Plasma	DPC Immulite System	24-28	TNF, IL-6, CXCL8	BSID-II	Elevated IL-6 was found in infants with proven necrotizing enterocolitis. Neonatal cytokines tended to be greater, with a wide variation, in infants later found to have abnormal cognitive and psychomotor outcomes.
Andrews et al. (2008)	23-32	424/-	Umbilical cord blood	ELISA	48	IL-6	PPVT-III, WISC-IV,DAS	Neonatal complications, gestational age at delivery, and caregiver IQ, but not *in utero* exposure to acute inflammation, were associated with increased risk of severe adverse neurodevelopmental outcomes at age 6 years.

BSID II: Bayley Scales of Infant Development – Second Edition: indicative of delay if score < 70; CA: Correct Age; CCL/CXCL: Chemokines; CRP: C-reactive protein; DAS: Differential Ability Scales, indicative of delay if score < 70; ELISA: Enzyme-linked immunosorbent assay; EPO: Erythropoietin; E-SEL: Selectin; ICAM: Intercellular Adhesion Molecule; IGFBP: Insulin-like Growth Factor Binding Protein; IL: Interleukin; MMP: Matrix Metalloproteinase; MPO: Myeloperoxidase; SAA: serum amyloid A; PPVT-III: Peabody Picture Vocabulary test 3rd edition – Third Edition, indicative of delay if score < 70;TNF: Tumor Necrosis Factor; TNF-R: Tumor Necrosis Factor Receptors; VCAM: Vascular Cell Adhesion Molecule; VEGF: Vascular Endothelial Growth Factor; VEGF-R: Vascular Endothelial Growth Factor receptors; WISC-IV: Wechsler Intelligence Scale for Children-IV, indicative of delay if score < 70.

Table 4
Selected studies on the subject of oxidative stress markers and neuropsychomotor development.

Author	Gestational Age (weeks)	Patients/ Controls	Analyzed Material	Laboratory method	Development Assessment (months CA)	Oxidative Stress/Inflammatory markers	Neurodevelopment Assessment	Neurodevelopmental Outcome
Shoji et al. (2014)	< 1500 g	35/-	Urine	ELISA	18	8-OHdG, 8-isoPGF	BSID-II	Urinary 8-OHdG levels associated with MDI rather than PDI at 18months'corrected age.
Vasiljevic et al. (2011)	< 32/ > 37	45/45	CSF	ELISA	12	GPX, IL-6, NSE, VEGF	DDST-II	Oxidative stress and upregulation of VEGF might be important contributing factors to the pathogenesis of hypoxic-ischemic brain injury, particularly in preterm neonates.
Chu et al. (2006)	≥ 37	256	Urine	spectrometry analysis	7 days	Ethylmalonate, 3-hydroxy-3-methylglutarate, 2-hydroxyglutarate, 2-oxo-glutarate, Glutarate, Methylmalonate, 3-hydroxybutyrate, Orotate	Neurological examination	Ethylmalonate, 3-hydroxy-3-methylglutarate, 2-hydroxy-glutarate and 2-oxo-glutarate were associated with good neonatal outcome, whereas glutarate, methylmalonate, 3-hydroxy-butyrate and orotate were associated with poor outcome.

BSID II: Bayley Scales of Infant Development – Second Edition: indicative of delay if score < 70; CA: Correct Age; CSF: Cerebrospinal Fluid; DDST-II: Denver Developmental Screening Test II; ELISA: Enzyme-linked immunosorbent assay; GPX: Glutathione Peroxidase IL: Interleukin; NSE: Neuron-Specific Enolase; VEGF: Vascular Endothelial Growth Factor.

five days of life (Vasiljevic et al., 2011).

The methods used to assess inflammatory molecules differed among the studies. In regard to immunoassay techniques, six studies used Enzyme-linked Immunoassay (ELISA) (Andrews et al., 2008; Chalak et al., 2014; Hoffmann et al., 2010; Shoji et al., 2014; Varner et al., 2015; Vasiljevic et al., 2011) and eight used cytometry techniques, including Cytometric Bead Array (CBA) (Magalhães, Moreira et al., 2017), Multiplex Luminex Assay (Carlo et al., 2011; Foster-Barber et al., 2001), DPC Immulite System (Lodha et al., 2010), Meso Scale Discovery (MSD) electrochemiluminescence system (Kuban et al., 2015; Yanni et al., 2017), Recycling Immunoaffinity Chromatography (Bartha et al., 2004) and Spectrometry analysis (Chu et al., 2006).

All studies evaluated the association between inflammatory molecules and neuropsychomotor development (Andrews et al., 2008; Bartha et al., 2004; Carlo et al., 2011; Chalak et al., 2014; Chu et al., 2006; Foster-Barber et al., 2001; Hoffmann et al., 2010; Kuban et al., 2015; Lodha et al., 2010; Magalhães, Moreira et al., 2017; Shoji et al., 2014; Varner et al., 2015; Vasiljevic et al., 2011; Yanni et al., 2017). In these studies, the collection of biological material and the evaluation of neurodevelopmental outcome were not simultaneous (Andrews et al., 2008; Bartha et al., 2004; Carlo et al., 2011; Chalak et al., 2014; Foster-Barber et al., 2001; Hoffmann et al., 2010; Kuban et al., 2015; Lodha et al., 2010; Shoji et al., 2014; Varner et al., 2015; Vasiljevic et al., 2011; Yanni et al., 2017), except in two studies (Chu et al., 2006; Magalhães, Moreira et al., 2017). The protocol of each study had a different age parameter for the developmental evaluation, being performed only once within a corrected gestational age of six (Varner et al., 2015), 12 (Foster-Barber et al., 2001; Varner et al., 2015; Vasiljevic et al., 2011), 15–18 (Chalak et al., 2014), 18–22 (Carlo et al., 2011; Shoji et al., 2014), 24 (Hoffmann et al., 2010; Kuban et al., 2015; Varner et al., 2015; Yanni et al., 2017), 24–28 (Lodha et al., 2010) or 30 months (Bartha et al., 2004). Only one study investigated long-term outcome, at the age of five to eight years (Andrews et al., 2008). In the other hand, two studies made developmental evaluation at 34 weeks of gestational age (Magalhães, Moreira et al., 2017) and seven days of life (Chu et al., 2006).

The studies also differed in regard to the choice of developmental tests used to measure children's neuropsychomotor abilities. The most used test was Bayley Scales of Toddler Development II or III scale (BSID II/III) (Bartha et al., 2004; Carlo et al., 2011; Chalak et al., 2014; Foster-Barber et al., 2001; Kuban et al., 2015; Lodha et al., 2010; Shoji et al., 2014; Varner et al., 2015; Yanni et al., 2017), followed by Denver Developmental Screening Test II (DDST-II) (Hoffmann et al., 2010; Vasiljevic et al., 2011), Test of Infant Motor Performance (TIMP) (Magalhães, Moreira et al., 2017) and Peabody Picture Vocabulary test 3rd edition (PPVT-III), Wechsler Intelligence Scale for Children-IV (WISC-IV) or the Differential Ability Scales (DAS) (Andrews et al., 2008). The BSID II/III, PPVT-III and WISC-IV were indicative of delay or significant impairment if the scores were below 70 (Andrews et al., 2008; Bartha et al., 2004; Carlo et al., 2011; Chalak et al., 2014; Foster-Barber et al., 2001; Kuban et al., 2015; Lodha et al., 2010; Shoji et al., 2014; Varner et al., 2015; Yanni et al., 2017), while the TIMP was indicative of delay if percentile $< 5^{th}$ (Magalhães, Moreira et al., 2017). One study used only the neurological examination as the method of neurodevelopment assessment (Chu et al., 2006). In this paper, poor outcome was considered if the neonate died or developed seizures within 7 days of delivery (Chu et al., 2006).

The studies also diverged regarding the diagnosis and classification of CP. Different diagnostic criteria were used by the studies, including: (i) the proposed definition and classification of cerebral palsy (Carlo et al., 2011); (ii) abnormal tone, muscle tone and impaired range or control of movements assessed by a neurologist (Andrews et al., 2008; Carlo et al., 2011; Foster-Barber et al., 2001; Hoffmann et al., 2010; Lodha et al., 2010); (iii) asphyxia with metabolic acidosis (Bartha et al., 2004; Chalak et al., 2014; Chu et al., 2006; Vasiljevic et al., 2011); and (iv) magnetic resonance (MR) alterations (Bartha et al., 2004; Foster-Barber et al., 2001). Additionally, the age of diagnosis varied from 6 months to 8 years of age (Varner et al., 2015; Yanni et al., 2017; Bartha et al., 2004). Two studies stratified CP by standardized classification such as Gross Motor Function Classification System (GMFCS) (Varner et al., 2015), Eunice Kennedy Shriver National Institute of Child Health (NICHD) classification (Chalak et al., 2014). Other two studies presented CP classification according to severity type (Bartha et al., 2004; Lodha et al., 2010), while one study subdivided CP between bilateral -quadriparetic, diparetic - or hemiparetic/unilateral (Carlo et al., 2011). Two study did not rank the CP (Andrews et al., 2008; Foster-Barber et al., 2001).

4.2. Blood or urine analysis and neurodevelopment outcome

The neurodevelopment outcome was associated with peripheral inflammatory biomarkers (Andrews et al., 2008; Bartha et al., 2004; Carlo et al., 2011; Chalak et al., 2014; Foster-Barber et al., 2001; Kuban et al., 2015; Lodha et al., 2010; Varner et al., 2015; Yanni et al., 2017) (Table 5). Eight of the studies associated higher levels of cytokines and chemokines, including IL-1β, IL-6, CXCL8/IL-8 and TNF, adhesion molecule, as ICAM-1, the liver-produced SAA, CRP and trophic factors, such as VEGF and GFAP, with abnormal neuropsychomotor development (Bartha et al., 2004; Carlo et al., 2011; Chalak et al., 2014; Foster-Barber et al., 2001; Kuban et al., 2015; Lodha et al., 2010; Vasiljevic et al., 2011; Yanni et al., 2017). IL-6 and CXCL8/IL-8 have been described as responsible for a variety of inflammatory challenges and represent a final common pathway of brain injury (Chalak et al., 2014; Varner et al., 2015). CXCL8/IL-8 promotes the infiltration of activated neurotrophils in brain parenchyma and has been associated with neuropsychomotor delay or moderate-severe CP (Chalak et al., 2014; Varner et al., 2015; Carlo et al., 2011; Lodha et al., 2010). In addition, VEGF is a grow factor that may contribute to inflammatory responses by causing edema and vascular permeability (Chalak et al., 2014; Vasiljevic et al., 2011). The cytokine signaling is a potential mechanism through which IL-1β, IL-6, and TNF may lead to or exacerbate neonatal brain injury. Summarizing, in ten studies, peripheral inflammatory biomarkers can be predictive of abnormal neurological outcome (Andrews et al., 2008; Carlo et al., 2011; Chalak et al., 2014; Kuban et al., 2015; Lodha et al., 2010; Shoji et al., 2014; Yanni et al., 2017; Foster-Barber et al., 2001) and of increased risk for CP (Carlo et al., 2011). On the other hand, no significant relation between inflammatory molecules and neurodevelopment was found in two studies (Andrews et al., 2008; Varner et al., 2015). In addition, one study showed that increased levels of IL-1β and CXCL8/IL-8 were higher in the group of preterm

Table 5
Specific inflammatory markers more frequently evaluated in the selected studies on the association between inflammatory markers and neurodevelopment.

Inflammatory markers	Studies	Conclusion
IL-6	Yanni et al. (2017); Magalhães, Moreira et al. (2017); Kuban et al. (2015); Chalak et al. (2014); Carlo et al. (2011); Vasiljevic et al. (2011); Lodha et al. (2010); Andrews et al. (2008); Bartha et al. (2004); Foster-Barber et al. (2001)	Mixed results Seven studies showed that increased blood levels were associated with abnormal neurological outcome Three studies showed no association
IL-1β	Yanni et al. (2017); Magalhães, Moreira et al. (2017); Varner et al. (2015); Kuban et al. (2015); Chalak et al. (2014); Carlo et al. (2011); Bartha et al. (2004); Foster-Barber et al. (2001)	Mixed results Two studies showed no association Six studies showed that increased blood levels were associated with abnormal neurological outcome One study showed that increased urine levels were associated with typical motor development
CXCL8/IL-8	Yanni et al. (2017); Magalhães, Moreira et al. (2017); Varner et al. (2015); Kuban et al. (2015); Chalak et al. (2014); Bartha et al. (2004); Carlo et al. (2011); Lodha et al. (2010); Foster-Barber et al. (2001)	Mixed results Four studies showed no association Four studies showed that increased blood levels were associated with abnormal neurological outcome One study showed that increased urine levels were associated with typical motor development
TNF	Yanni et al. (2017); Magalhães, Moreira et al. (2017); Varner et al. (2015); Kuban et al. (2015); Chalak et al. (2014); Carlo et al. (2011); Lodha et al. (2010); Bartha et al. (2004); Foster-Barber et al. (2001)	Mixed results Three studies showed no association Five studies showed that increased blood levels were associated with poor neurological outcome One study showed that decreased blood levels were associated with poor neurological outcomes

CCL/CXCL: Chemokines; IL: Interleukin; TNF: Tumor Necrosis Factor.

newborns with typical motor development (Magalhães, Moreira et al., 2017). Other study concluded that NRG1 might be a systemic endogenous neuroprotector in preterm newborns (Hoffmann et al., 2010).

In four studies, neurological examination and MR or ultrasound (US) were used to correlate the inflammatory profile with neuropsychomotor development (Bartha et al., 2004; Chalak et al., 2014; Foster-Barber et al., 2001; Lodha et al., 2010). In these studies, neurological evaluation may help to understand the severity of brain injury. It was used to strength the correlation of inflammatory profile and neurological outcome (Bartha et al., 2004; Chalak et al., 2014; Foster-Barber et al., 2001; Lodha et al., 2010).

4.3. Oxidative stress analysis and neurodevelopment outcome

Three studies included in this review measured OS markers and the neurodevelopment outcome (Chu et al., 2006; Shoji et al., 2014; Vasiljevic et al., 2011). These studies had showed the activation inflammatory cascade in the immature brain and subsequent persistent neuroinflammation play principal roles in irreversible perinatal hypoxic-ischemic brain damage (Chu et al., 2006; Shoji et al., 2014; Vasiljevic et al., 2011).

The OS markers, 8-OHdG, 8-isoPGF, GPX, Ethylmalonate, 3-hydroxy-3-methylglutarate, 2-hydroxyglutarate, 2-oxo-glutarate, Glutarate, Methylmalonate, 3-hydroxybutyrate, Orotate, were associated with abnormal outcome and brain damage (Chu et al., 2006; Shoji et al., 2014; Vasiljevic et al., 2011). Oxidative stress and upregulation of VEGF seem to play a role in the pathogenesis of hypoxic-ischemic brain injury, particularly in preterm newborns (Vasiljevic et al., 2011).

5. Discussion

The current systematic review summarizes the available evidence on the association between inflammatory molecules and neurodevelopment outcome in children with CP. Fourteen studies were identified and the majority reported an association between peripheral inflammation and neurological impairment during the first years of life (Andrews et al., 2008; Bartha et al., 2004; Carlo et al., 2011; Chalak et al., 2014; Chu et al., 2006; Foster-Barber et al., 2001; Hoffmann et al., 2010; Kuban et al., 2015; Lodha et al., 2010; Magalhães, Moreira et al., 2017; Shoji et al., 2014; Varner et al., 2015; Vasiljevic et al., 2011; Yanni et al., 2017).

A prolonged or exacerbated inflammatory response may be characterized by the elevation of inflammatory molecules, including cytokines, chemokines, adhesion molecules, liver-produced proteins, neutrophil activation molecules and also growth factors (Kuban et al., 2015). Three studies have analyzed all these molecules together (Carlo et al., 2011; Kuban et al., 2015; Yanni et al., 2017). The majority of selected studies analyzed cytokines, chemokines and neurotrophic factors. Three studies evaluated markers of oxidative stress (Chu et al., 2006; Shoji et al., 2014; Vasiljevic et al., 2011). One of these studies analyzed the association of OS with cytokine and growth factors (Vasiljevic et al., 2011).

Inflammation is considered a physiological and necessary process for the protection and development of the CNS (Magalhães, Pimenta et al., 2017, 2017b; Mallard, Davidson, & Tan, 2014; Nadeau-Vallée et al., 2017; Ranchhod, Gunn, & Fowke, 2015). It can become pathological depending on its location, timing, intensity, and chronicity (Magalhães, Pimenta et al., 2017; Nadeau-Vallée

et al., 2017). Systemic inflammatory response characterized by higher levels of cytokines, including IL-1β, IL-6, TNF and the chemokine CXCL8/IL-8 may result in activation of the cerebrovascular endothelium and surrounding cells, contributing to the rupture of the blood-brain-barrier (BBB) (Diaz-Cañestro et al., 2018; Piro et al., 2018). As a consequence, there is infiltration of circulating immune cells and overflow of plasma components into the brain tissue, resulting in brain damage (Diaz-Cañestro et al., 2018; Piro et al., 2018). In addition, neuroinflammation plays a central role in the pathogenesis of brain injury (Colella et al., 2018; Hagberg et al., 2012). It is characterized by infiltration of leukocytes in the brain parenchyma, with activation of microglia and astrocytes, which can cause neuronal death and impairment of white matter development (Paton et al., 2018). Several mechanisms related to the immune system, including cytokine release and T-cell activation, may contribute to neuroinflammation, which, in turn, potentially interferes with the development of the central nervous system (CNS) (Lei et al., 2017).

According to this theory, systemic and CNS inflammation can alter the proliferation, differentiation of microglia and neuronal cells and can also increase the rate of cell death with neuronal injury, astrogliosis and oligodendrocyte loss (Hielkema & Hadders-Algra, 2016; Paton et al., 2018; Stewart et al., 2013). The possible mechanisms by which inflammation promotes early brain injury are: (i) reduced blood flow to the CNS, which reduces the availability of oxygen and glucose; (ii) blood-brain barrier (BBB) rupture; (iii) leukocyte infiltration into the CNS; (iv) increased release of cytokines and chemokines in the brain parenchyma; (v) mitochondrial dysfunction and power failure; (vi) increased calcium influx, neurotoxin release, production of reactive oxygen species (free radicals) and nitric oxide; (viii) cerebral edema. These mechanisms have been associated with neuronal and glial cell apoptosis (Magalhães, Pimenta et al., 2017; Paton et al., 2018).

The exacerbated release of proinflammatory cytokines in plasma and brain tissue is responsible for cellular interactions related to brain injury (Cordeiro et al., 2016; Galinsky, Davidson, Dean, Green, & Bennet, 2018; Magalhães, Pimenta et al., 2017; Paton et al., 2018). Leukocytes and endothelial cells are sensitive to neuronal lesions and may release and/or respond to cytokines and chemokines (De Luca, Colangelo, & Alberghina, 2018). These molecules in the blood are also associated with the onset and maintenance of the inflammatory response, as well as adverse neurological outcomes (Galinsky et al., 2018). Because these molecules can cross the BBB (Koh, Hwang, Lim, Kim, & Lee, 2015, 2018; Magalhães, Moreira et al., 2017), the peripheral levels of these molecules may also reflect their levels in the brain (Koh et al., 2015).

Inflammatory response triggered by cytokines may induce neuronal and glial cell apoptosis in CNS, therefore interfering in axonal growth and myelin sheath formation (Coronel-Restrepo, Posso-Osorio, Naranjo-Escobar, & Tobón, 2017; Jaeger et al., 2015; Tomasoni et al., 2017; Vinall & Grunau, 2014). Problems with neuronal migration, division and synaptic development may also occur, resulting in neurodevelopmental alterations (Vasconcelos et al., 2014). When this response occurs and is fully resolved without brain cells death, typical abilities are maintained (Hassell, Ezzati, Alonso-Alconada, Hausenloy, & Robertson, 2015). On the contrary, if this response is prolonged or exacerbated, cell death in CNS and consequent loss of function may occur (Magalhães, Pimenta et al., 2017, 2017b). In summary, brain damage and lasting functional impairment most likely result from the abnormal balance between injury mechanisms and endogenous protection (O'Shea et al., 2012). Circulating cytokines (TNF, IL-1β and IL-6) and chemokines (CXCL8/IL-8 and CXCL9/MIG) have been related to the development of brain injury (De Luca et al., 2018; Xia et al., 2018) and CP (Xia et al., 2018). In addition, anti-inflammatory and inadequate regulatory responses, detected by low levels of IL-10 and high levels of cytotoxic metabolites, may increase the risk for brain injury (Wixey, Chand, Colditz, & Bjorkman, 2017). In this sense, oxidative metabolism continuously produces free oxygen radicals at high rates within the brain (Shoji et al., 2014). OS due to overproduction of reactive oxygen species and impairment of antioxidant defense mechanisms have been suggested as factors also responsible for brain injury by means of lipid peroxidation, impaired myelination of white matter tracts, axonal injury and excessive neural apoptosis (Chu et al., 2006; Palmer et al., 2019; Shoji et al., 2014).

MR findings are important resources to evaluate the extension and severity of brain injury (Bartha et al., 2004; Chalak et al., 2014; Willianson, Morgan, & Klein, 2017), aiding in the detection of ischemia and/or diffuse axonal injury, and complementing the neurological evaluation to establish the prognosis (Willianson et al., 2017). Nevertheless, in the studies that analyzed inflammatory molecules and MR, peripheral cytokine levels were not associated with structural MR findings (Bartha et al., 2004; Chalak et al., 2014). The majority of neuropsychomotor deficits did not relate to specific patterns of injury, including severe grade intraventricular hemorrhage with post hemorrhagic ventricular dilatation, hemorrhagic parenchymal infarction or cystic periventricular leukomalacia (PVL) (Patra, Huang, Bauer, & Giannone, 2017). This suggests that there might be damage and remodeling in the developing brain that result in a more diffuse process, not detected as brain lesions on MR imaging (Patra et al., 2017).

Brain injury around birth is associated with nearly half of all cases of cerebral palsy. Although brain injury is multifactorial, particularly after preterm birth, acute hypoxic-ischemia is a major contributor to injury (Dhillon et al., 2018).

Brain injury at birth is multifactorial, frequently correlated to preterm birth and hypoxia-ischemia. External factors can modulate how injury evolves, and affect the measurements used for diagnosis and prognosis. (Dhillon et al., 2018). Hypoxic-ischemia at birth and prematurity were associated with nearly half of all cases of CP (Dhillon et al., 2018). Subjects included in these fourteen selected studies diverge in clinical characteristics and in the exposure to risk factors related to brain injury and CP. Demographic factors, gestational age and neonatal care may be key factors, capable to influence the pro or anti-inflammatory response and neurodevelopmental outcomes (Allred et al., 2017; Patra et al., 2017; Talati, Hackney, & Mesiano, 2017). Also, birth weight is a known independent risk factor for worst neurodevelopment, and is associated with systemic inflammation (Leviton et al., 2013). However, only two study had low birth weight as the single inclusion criterion. Perinatal infection and inflammation are also independent risk factors related to brain injury (Tann et al., 2017) and neuropsychomotor delay (Ferreira, Mello, & Silva, 2014). Recent reports have shown that systemic inflammation triggered by infection, such as sepsis, meningitis with or without bacteremia, TORCH, bronchopulmonary dysplasia (BPD) and NEC were all associated with impaired growth and increased risk of adverse neurologic sequelae in premature neonates (Ostrander & Bale, 2019; Palmer et al., 2019). Three among the fourteen selected studies included subjects with

sepsis, although with contradictory results (Andrews et al., 2008; Carlo et al., 2011; Lodha et al., 2010). In two of them, elevated cytokine levels were associated with worst development (Carlo et al., 2011; Lodha et al., 2010). In contrast, one, study did not find an association between acute inflammation caused by infection with worst neuropsychomotor development (Andrews et al., 2008). However, studies have generally considered *in utero* exposure to bacterial infection and/or inflammation as a risk factor for brain injury or CP [31,33,57,69,70]. The presence of neonatal bacteremia may imply in the activation of the fetal inflammatory response [66,71]. It is a key event, in which the duration of exposure to inflammation can aggravate brain injury and adverse development (Tann et al., 2017). Both a sensitizing and preconditioning role of bacterial endotoxin upon the effect of hypoxia-ischemia on the immature brain have been seen in animal models, but supporting clinical data are limited (Tann et al., 2017). In this regard, Cordeiro and co-workers developed a mathematical modeling of the biomarker *milieu* to identify preterm neonates at risk for adverse neonatal outcomes (Cordeiro et al., 2016). The authors found that lower levels of BDNF and NT-3 in the cord blood were associated with NEC and sepsis, respectively, but not with neurological outcomes (Cordeiro et al., 2016). These findings suggest that neurotrophins may have additional roles in the inflammatory response and may interact with cytokines (Cordeiro et al., 2016). Accordingly, neurotrophic factors, as BDNF and GDNF, concentrations can also be reduced in response to increased levels of cytokines or chemokines in the brain parenchyma (Magalhães, Moreira et al., 2017). In one study, neonatal complications, gestational age at delivery and caregiver intelligence quotient were related to neuromotor impairment, but not to in utero exposure to acute inflammation (Andrews et al., 2008). These findings emphasize the crucial impact of demographic characteristics on neurodevelopment.

This systematic review has limitations. The studies used different time-points in their research, impairing the comparison of their findings. Different results, diverse etiology and poor understanding of the exactly trigger or moment of the inflammatory stimuli hinder the definition of cause or consequence of the elevated levels of inflammatory markers in relation to brain injury and neurological outcome. The knowledge gap regarding the mechanisms by which the neurodevelopmental delay occurs is also considered another problem. As a matter of fact, it is hard to define whether the elevation of inflammatory related-proteins is responsible for the neurodevelopmental impairment or if both processes occur in parallel. It is also difficult to obtain homogenous groups in observational studies. In addition, only few studies have a control group. The use of a control group may help to detected differences between concentrations of the molecules in children with typical neurodevelopment in comparison to patient with CP. On the other hand, longitudinal studies including only children with CP can analyze the association between increased levels of a molecule at an initial time-point (baseline) with worse neurodevelopment outcome later in life.

This review summarizes the current results regarding the association of inflammatory molecules and neurodevelopment outcome in children with CP. Still, more knowledge is necessary in order to discriminate reliable biomarkers that might assist in the prediction of outcomes and be used in clinical practice.

6. Conclusion

There is growing evidence of alterations in inflammatory markers and circulating neurotrophic factors due to neuroinflammation in neonates and their potential role in early detection of brain injury (Allred et al., 2017; Koh et al., 2015, 2018; Magalhães, Pimenta et al., 2017). However, there is little information on the longitudinal behavior of these biomarkers after the acute phase of brain injury and their association with neurodevelopment during the first years of life. Studies including children with CP are also very scarce and its pathogenesis remains unknown.

Our systematic review showed that the fourteen selected studies are quite variable in terms of methodology, molecules measured, time-points of sample collections and types of fluid collected. However, most studies (ten of fourteen) indicated an association between increased levels of inflammatory and OS biomarkers with worse neurodevelopment outcome. On the other hand, controversial results were also obtained. In conclusion, the association of inflammatory molecules with CP and neurodevelopment outcome requires further investigation in order to clarify the real impact of early life brain inflammation on neurological outcomes.

Financial disclosure

The authors do not have any financial relationships relevant to this article to disclose.

Funding source

None.

Contributors' statement

Dr. Magalhães conceptualized and designed the study, reviewed identified articles to determine if they met defined study inclusion and exclusion criteria, drafted the initial manuscript, and approved the final manuscript as submitted.

Dr. Simões e Silva conceptualized and designed the study, reviewed identified articles to determine if they met defined study inclusion and exclusion criteria, critically reviewed the manuscript, and approved the final manuscript as submitted.

Drs. Lauar and Saldanha da Silva reviewed identified articles to determine if they met defined study inclusion and exclusion criteria, critically reviewed the manuscript, and approved the final manuscript as submitted.

Drs. Moreira and Teixeira conceptualized the study, critically reviewed the manuscript, and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

None.

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