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Review

Research Progress on the Role of the Interleukin Family in the Pathogenesis of Cerebral Palsy in Children

Mingbo Hu[1,†], Chao Bai[1,†], Hong Zhao[1,†], Junjie Wu[1,*], Xinping Luan[1,*]

[1]Cerebral Palsy Center in Neurosurgery, Second Affiliated Hospital of Xinjiang Medical University, 830063 Urumqi, Xinjiang, China
*Correspondence: wujunjie1583136159@outlook.com (Junjie Wu); luanxinping4324177@163.com (Xinping Luan)
[†]These authors contributed equally.

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Abstract

Cerebral palsy (CP), a common neurological disorder in children, remains a significant research focus. The interleukin (IL) family, pivotal mediators in inflammatory responses, shows increased expression in various neuroinflammatory diseases, markedly influencing their onset and progression. Elevated IL levels in the brains of children with CP, in contrast to healthy peers, reflect similar elevations in neurological conditions linked to CP, indicating a strong association between CP and the IL family. Anti-inflammatory therapies, particularly those targeting ILs, have shown effectiveness in animal models, diverging from traditional CP management methods. This shift suggests IL modulation as a promising therapeutic strategy in pediatric CP. This review consolidates recent findings on the IL family's role in CP, illuminating their evolving relationship.

Keywords: pathogenesis of cerebral palsy; interleukin; inflammatory factor; neuroinflammation

1. Introduction

Cerebral palsy (CP) is a predominant cause of childhood disability, with numerous risk factors originating in the perinatal period [1]. Diagnosing CP involves integrating clinical presentation, neuroimaging, and the evaluation of CP risk factors. Imaging in high-risk children often reveals white matter injury, periventricular hemorrhagic infarction, deep gray matter structure injury, cerebellar hemorrhage, and developmental brain malformations. Neurological assessments include the Prechtl Qualitative Assessment of General Movements (GMA), the Hammersmith Infant Neurologic Examination (HINE), and the Gross Motor Function Assessment (GMFM) [2]. Recent research has validated the continued necessity and reliability of early standardized assessments for CP diagnosis [3]. Additionally, evolving animal models, such as the 6-arm maze, provide reference standards for CP diagnosis [4]. Pathogenesis typically involves injury to the developing brain during fetal or perinatal stages, resulting in skeletal muscle dysfunction. This manifests as abnormal muscle contractions, postural difficulties, and restricted mobility, often accompanied by neurodevelopmental disorders including sensory and cognitive impairments, intellectual disabilities, epilepsy, and autism spectrum disorders. Clinically, CP is categorized into four primary types: spastic, dyskinetic, ataxic, and mixed [4,5]. Initial study identified hypoxia as a potential cause of CP, but subsequent research has revealed a multifactorial etiology involving various factors that impair brain function [6]. While the precise mechanisms triggering CP onset remain incompletely understood, emerging evidence highlights the significant role of inflammatory responses in its development. Comparative analyses show elevated levels of pro-inflammatory cytokines, such as interleukin (IL)-2, IL-6, and IL-10, in the blood and cerebrospinal fluid (CSF) of children with CP compared to healthy controls [7]. Biomarkers related to free radical production and antioxidant effects, indicative of cell damage, are also significantly increased among non-inflammatory markers [8]. A comprehensive review on inflammation and CP consistently demonstrates heightened inflammatory markers, particularly those of the IL family, in the CSF of affected children [9,10]. This review integrates advancements in understanding the IL family's impact on CP pathogenesis, analyzing their roles in disease development, and proposing novel avenues for inflammation-centric CP research.

2. The Pathogenesis of CP

The pathogenesis of CP is categorized into four primary stages: fetal, antenatal, perinatal, and post-delivery (Table 1). During the fetal stage, maternal age, lifestyle, intrauterine infections, and genetics are pivotal factors. Intrauterine hypoxia, primarily due to placental insufficiency and abruption in late pregnancy, is a significant prenatal contributor to CP. Prematurity is the predominant risk factor in the perinatal period, attributed to the heightened vulnerabilities of preterm infants due to their lower gestational age and developmental immaturity. Despite advancements in medical care improving survival rates of premature infants, the incidence of CP has remained stable at 0.2% to 0.3% in recent decades. Meconium aspiration and ischemic hypoxic encephalopathy are also critical factors in brain injury during this stage. Additionally, infants and toddlers up

Table 1. The pathogenesis of CP.

Main stages of CP	Risk factors for cerebral palsy
Foetal	Maternal age older or younger, multiple pregnancies, miscarriages, short or long parity, history of intrauterine death
Antenatal	Intrauterine growth restriction, intrauterine infection, vitro fertilization, chorioamnionitis
Perinatal	Premature birth, meconium aspiration, hypoxic-ischemic encephalopathy
Post-delivery	Neonatal seizures, head trauma, drowning, meningitis

CP, cerebral palsy.

to the age of five face a reduced risk of CP following head trauma or infections like meningitis, due to their developing immune systems, classifying such instances as acquired CP [1,2].

Recent advancements in medical science and technology have highlighted the pathogenesis of CP as a significant research focus. Despite progress, substantial knowledge gaps remain, particularly regarding the molecular mechanisms underlying the disease [11]. Contemporary studies associate CP with neuroinflammation induced by conditions such as neonatal encephalopathy (hypoxic-ischemic encephalopathy), fetal inflammatory response syndrome, and white matter damage/periventricular leukomalacia. Additionally, maternal immune activation is increasingly recognized as a key factor in CP onset. An animal model of chorioamnionitis induced by Lipopolysaccharides (LPS) exposure in the cervix of pregnant rabbits demonstrated that perinatal intrauterine infections could lead to abnormal motor function in the fetus post-birth and a reduction in the synthesis of tetrahydrobiopterin in the brains of young rabbits with ischemic brain injury [12]. The role of tetrahydrobiopterin in preventing ischemia-induced CP has also been shown [13,14]. Another animal model of partial and total cerebral ischemia revealed minimal differences between acute and chronic ischemia in CP development [15]. However, these models, including most rodent models, share common limitations, such as the much smaller volume of cerebral white matter in rodents compared to humans, higher partial pressure of oxygen in human brain tissue, and differing degrees of cerebral white matter damage due to ischemia [16,17]. Following the onset of CP-associated diseases, a notable commonality is the elevated levels of inflammatory factors in the brain. This increase is partly due to microglial activation and the subsequent secretion of inflammatory mediators, with contributions from oligodendrocytes and oligodendrocyte precursor cells under conditions of oxidative stress and inflammation. These processes involve distinct mechanisms: (1) Microglia, which normally serve a neuroprotective function, differentiate into M1 and M2 subtypes upon activation. M1 microglia release pro-inflammatory mediators (IL-1α, IL-1β, IL-6, IL-12, and IL-23), while M2 microglia are associated with anti-inflammatory actions essential for maintaining inflammatory homeostasis [18–20]. Following cerebral ischemia or hypoxia, an imbalance occurs due to microglial activation and skewed polarization, reducing neuroprotective M2 microglia and increasing M1 microglia, thereby exacerbating inflammatory responses [21,22]. (2) Myelin sheath repair around damaged neurons is essential post-brain injury, requiring microglial engagement in phagocytosing fragmented myelin. Subsequently, oligodendrocyte precursor cells, driven by microglia-secreted inflammatory factors, migrate and differentiate to facilitate repair. Typically, this constitutes the repair mechanism; however, astrocyte activation disrupts this process. Astrocytes, crucial in metabolic maintenance, polarize into A1 (neurotoxic) and A2 (neuroprotective) subtypes upon activation. A1 astrocytes, stimulated by lipopolysaccharide-activated microglia, can precipitate oligodendrocyte precursor cell death through mediated inflammation. Hence, the excessive secretion of inflammatory factors by microglia results in significant oligodendrocyte precursor cell death, obstructing myelin repair and worsening brain damage [23,24]. (3) The inflammatory response, typified by cytokine release, is instrumental in the brain's reaction to pathogenic challenges such as ischemia, hypoxia, or infections. Elevated cytokine levels can provoke the excessive release of excitatory neurotransmitters, escalating neurotoxicity and further compromising brain tissue. Conversely, inadequate cytokine release may weaken neuroimmune function, heightening vulnerability to infections or impairing recovery, thereby potentially causing brain damage [25,26] (Fig. 1). This inflammatory response is not transient but a prolonged pathological process, characterized by the persistent accumulation of inflammatory cells in the brain's lesion area and sustained high levels of inflammatory factor expression. This condition may persist until adulthood, underscoring inflammation's significant impact on the development of cerebral palsy, suggesting that inflammation is a comorbid condition of cerebral palsy [27].

3. IL Family

3.1 IL-1β

IL-1β, primarily secreted by monocytes, macrophages, and dendritic cells, functions as a central pro-inflammatory cytokine in modulating cell proliferation, differentiation, and apoptosis. It plays a critical role in initiating, regulating, and sustaining inflammatory responses. IL-1β contributes to neuronal damage via multiple mechanisms, including inducing nitric oxide synthesis, activating necrosis and apoptosis pathways, altering synaptic plasticity, and affecting the mitogen-

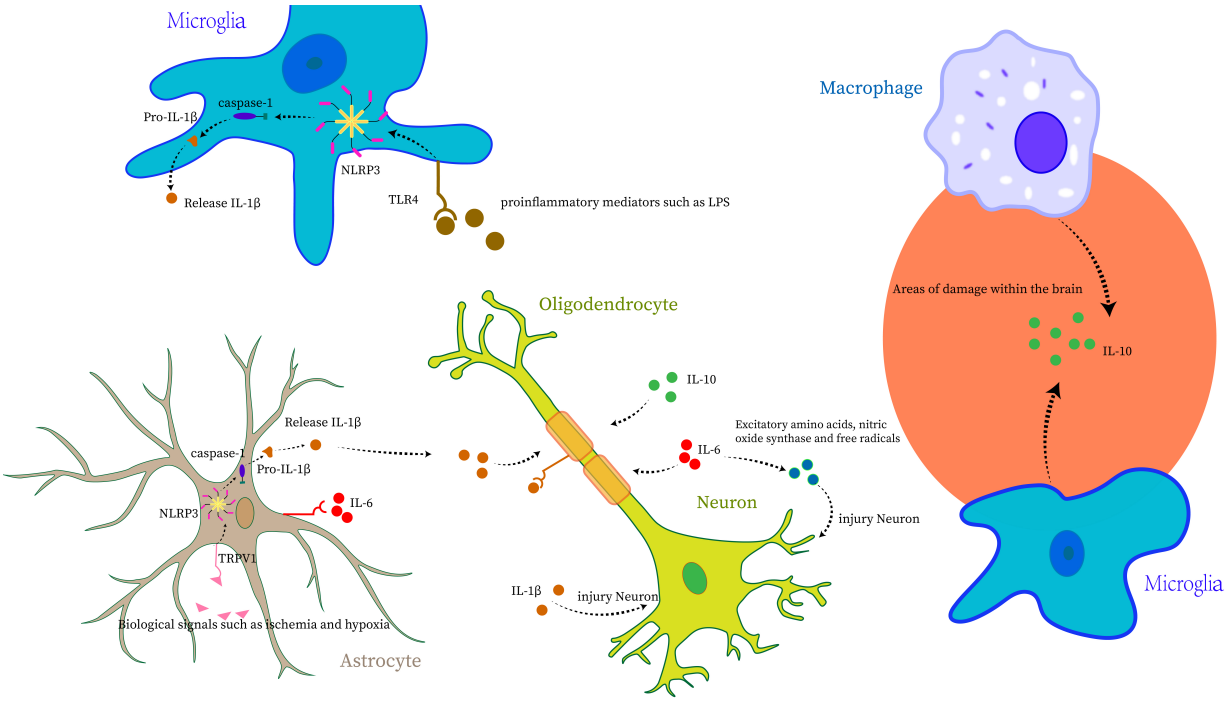

Fig. 1. Interleukin (IL)-1β disrupts the myelin sheath and hinders its regeneration, exerting direct neurotoxicity. IL-6, upon production, induces astrocyte proliferation, which parallels the myelin impact of IL-1β, and promotes the release of excitatory amino acids, nitric oxide synthase (NOS), and free radicals, leading to neuronal toxicity. Conversely, IL-10 supports neuronal homeostasis and cell viability, accelerating myelin repair. However, elevated IL-10 levels in the injured brain area attract peripheral macrophages and microglia, aggravating TBI, traumatic brain injury; NLRP3, nucleotide-binding oligomerization domain, leucine-rich repeat (NLR) family pyrin domain- containing 3; TLR4, toll-like receptor 4; LPS, Lipopolysaccharide; TRPV1, transient receptor potential vanilloid-1.

activated protein kinase (MAPK) pathway, ultimately leading to neurodegeneration. Additionally, IL-1β impacts neural network expansion by enhancing the release of neurotrophin-3 and neurogranin-1 while inhibiting cell differentiation through the blockade of specific proteins. Elevated IL-1β levels have been documented in various brain injuries and hemorrhagic conditions [19]. Evidence consistently shows that increased IL-1β levels exacerbate fetal white matter damage. Studies using IL-1 receptor antagonists have demonstrated reduced inflammation in the placenta and central nervous system, offering protection against inflammation-induced white matter damage [28,29]. Oligodendrocytes are implicated in myelin repair, yet experiments with rats have shown that IL-1β injection activates microglia, thereby inhibiting myelin regeneration and suppressing the maturation of myelin precursor oligodendrocytes [30]. Research on sex hormones' effects on perinatal inflammatory immunity revealed that androgens can enhance the inflammatory pathway following group B streptococcal (GBS) infection, resulting in the upregulation of IL-1β, tumor necrosis factor-alpha (TNF-α), and IL-6, all of which have pro-inflammatory effects [31]. The release of IL-1β triggers the activation of neutrophils, monocytes, and macrophages in the maternal system, leading to widespread intrauterine inflammation that impacts the maternal-placental-fetal axis, increasing inflammatory cells and molecules within the developing brain, thus accelerating neuroimmune damage [10].

3.2 IL-6

IL-6, secreted by T and B lymphocytes, monocytes, and various non-lymphoid cells, functions as a critical cytokine with both pro-inflammatory and anti-inflammatory effects [32]. It is integral to B cell antibody production, responding to viral and endotoxin infections, as well as cytokines like TNF-α. IL-6 also collaborates with colony-stimulating factors to support the growth and differentiation of bone marrow-derived cells and enhance natural killer cells' cytolytic activities [33]. It exerts its effects by binding to interleukin-6 receptor (IL-6R) on microglial membranes, activating the janus tyrosine kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) pathway, influencing acute-phase protein secretion, and initiating the MAPK pathway, thereby promoting the MAPK cascade. These pathways are essential for maintaining cytokine equilibrium and cellular regeneration. Importantly, IL-6 can interact with cells lacking Interleukin-6 receptor (IL-6R) through trans-signaling, which is pivotal for pathological responses [34,35]. IL-6 is key in the activation of pro-inflammatory cytokines and the initiation of acute phase responses. Elevated IL-6 levels at birth correlate

with higher risks of infectious diseases, disseminated intravascular coagulation, and periventricular leukomalacia (PVL) [36]. Research indicates that cytokine-driven inflammatory responses, particularly those involving TNF-α, IL-1β, and IL-6, can impede myelination and stimulate reactive astrocyte proliferation [37]. IL-6 directly augments neurospecific glutamatergic synapse functionality by enhancing the persistence and selectivity of glutamatergic receptors at elevated concentrations. Notably, it also influences synapse formation in the foetal brain during pregnancy, a capacity unique among inflammatory cytokines. This highlights IL-6's specific and pivotal role in synaptogenesis and the enhancement of synaptic functions [38]. IL-6 potentially contributes to CP development through multiple pathways. Post-brain injury, an abnormal surge in inflammatory factor release elevates excitatory amino acids, nitric oxide synthase, and free radical production, leading to neuronal toxicity. Increased inflammatory levels can also impair coagulation processes, inducing platelet activation, aggregation, and endothelial damage, potentially resulting in thrombosis and subsequent ischemic and hypoxic damage to white matter neurons. Furthermore, inflammation can compromise blood-brain barrier integrity, increasing the brain's vulnerability to peripheral infections or inflammatory factors, thereby exacerbating damage [39,40]. Additionally, IL-6 affects neurodevelopment through specific mechanisms, such as infection-induced hypoferritinemia that reduces non-heme iron in maternal circulation, potentially leading to brain development disorders and significantly impacting dopamine receptors [41].

During mid-pregnancy, maternal IL-6 can traverse the placenta to the fetus. Research indicates that maternal immune activation (MIA) during this period enables IL-6 to bind directly to placental receptors, initiating an inflammatory cascade within the fetal environment, contributing to neurodevelopmental disorders at birth [42,43]. Investigations involving full-term infants who later developed CP reveal significantly elevated perinatal levels of cytokines, including IL-1β, IL-6, and TNF-α. Analyses of blood and CSF from children with CP show a pronounced presence of these inflammatory cytokines, linked to extensive neuronal apoptosis and necrosis. This neurodegeneration diminishes neuroprotective responses, instigating further immune-inflammatory reactions and worsening brain damage, which contributes to the onset and progression of CP [40,44–46]. This evidence suggests that inflammatory brain damage may begin prenatally in individuals with CP and persist postnatally, emphasizing the potential of early interventions targeting inflammatory modulation to enhance recovery.

3.3 IL-10

IL-10, primarily secreted by T helper 2 (Th2) cells, functions as a versatile cytokine. Its expression increases in response to ischemia, hypoxia, and various neurodegenerative conditions through receptor binding. This rise indicates IL-10's potential in mediating endogenous neuroprotective and neurotrophic activities. IL-10's critical roles in inflammation modulation include: (1) promoting cluster of differentiation 8-positive (CD8+) T cell proliferation and cytolytic activity, (2) inhibiting antigen presentation and pro-inflammatory cytokine production by antigen-presenting cells (APCs), and (3) reducing tumorigenic effects linked to chronic inflammation [47]. In conditions where IL-10 levels are inadequate and cytotoxic metabolites are elevated, the risk of brain damage increases [48].

Elevated levels of pro-inflammatory cytokines, including IL-6 and TNF-α, correlate with an increased risk of CP and brain lesions. In response to tissue damage, an inflammatory reaction ensues, followed by the release of anti-inflammatory cytokines to temper ongoing or excessive inflammation [49,50]. IL-10, a key anti-inflammatory cytokine, plays a pivotal role in immune regulation and neuronal homeostasis through mechanisms such as T-cell functional modulation. It reduces tissue damage by suppressing the secretion of pro-inflammatory cytokines like IL-6 and TNF-α by macrophages and dendritic cells. Additionally, IL-10 enhances immune defenses by promoting the proliferation and function of natural killer and CD8+ T cells and supporting B cells in survival, proliferation, differentiation, and antibody production, thus protecting microglial cells from inflammatory attacks [51–53]. In demyelination mouse models, increased IL-10 levels mitigate demyelination, highlighting its role in oligodendrocyte-mediated myelin repair [21]. Elevated plasma IL-10 levels may indicate prolonged microglial activation and an upsurge in cytokine production following CP-induced damage. This suggests that the immune system's suppression of pro-inflammatory cytokine expression results in increased IL-10 as a marker of heightened immune suppression. Although IL-10 has demonstrated efficacy in reducing inflammation and protecting neurons during immune responses, it has also been shown to enhance the early secretion of IL-1β and TNF-α in hypoxic-ischemic encephalopathy. Furthermore, IL-10 recruits peripheral macrophages and microglia to sites of brain injury, potentially exacerbating local damage [54]. Consequently, IL-10's role as an anti-inflammatory agent is dual-faceted: it mitigates tissue damage by attenuating inflammatory responses while concurrently suppressing the immune system. This suppression can lead phagocytic cells to cause secondary damage to already injured brain regions.

3.4 Other ILs

The IL family profoundly influences inflammatory responses, particularly in the context of CP and its etiological conditions. Besides the extensively studied ILs with elevated expressions in CP, other ILs—though less frequently encountered or expressed at lower levels—also contribute significantly to the disease's pathogenesis.

IL-2 emerges as a notable anti-inflammatory factor, primarily secreted by neuronal cells, with lower concentrations in CSF compared to serum. Animal studies highlight its neuroprotective capabilities, especially in promoting regulatory T (Treg) cell expansion and providing neuroprotection [55,56]. Moreover, IL-2 has been shown to transform activated microglia from the classical disease-associated microglia (DAM) phenotype to an atypical major histocompatibility complex class II (MHCIIhi) phenotype. MHCIIhi microglial cells under-express inflammatory mediators, and this phenotypic switch can decelerate the inflammatory response. This indicates IL-2's potential as a novel therapeutic approach for neuroinflammatory conditions in future research [57]. Most current studies focus on the beneficial aspects of IL-2 in anti-inflammatory therapy. However, previous research has shown elevated IL-2 levels in patients with white matter lesions, with the increase directly proportional to the severity of white matter damage [58–60]. Despite these data, the existing studies have limitations, and no consensus exists regarding IL-2's effects on nerve treatment and injury. Thus, future research should adopt more rigorous and representative designs to elucidate IL-2's role in nerve loss.

IL-4, primarily secreted by microglia and macrophages, with a minor contribution from astrocytes within the brain, functions as an anti-inflammatory factor that promotes neuroprotection. Its receptors are predominantly expressed on these producing cells and oligodendrocytes. Interestingly, IL-4 expression is generally higher in newborn brains compared to adults, yet its overexpression in newborns can inhibit oligodendrocyte differentiation. Moreover, macrophages bearing IL-4 receptors may become activated through overexpression, potentially intensifying inflammatory responses [61]. Similar to IL-10, the inflammatory cytokine IL-8 can recruit macrophages and microglia, exacerbating local damage [54]. Additionally, elevated IL-16 expression in patients with compromised blood-brain barriers indicates its role in mobilizing and activating cells at inflammation sites [62].

IL-17, primarily secreted by T helper 17 (Th17) cells, with additional contributions from non-lymphoid Paneth cells and neutrophils, comprises six variants, IL-17A to IL-17F. Among these, IL-17A is a prominent effector, crucial for neutrophil recruitment and mucosal barrier enhancement. Notably, IL-17 secretion from Th17 cells is tightly regulated by IL-6 levels, with elevated IL-6 correlating with increased IL-17 secretion. IL-17 acts as a potent stimulator for various inflammatory mediators, including granulocyte colony-stimulating factor, IL-6, IL-1β, TNF-α, and IL-1. These mediators collectively increase the permeability of the blood-brain barrier, heightening the brain's susceptibility to inflammation and immune cell infiltration. Furthermore, IL-6 and IL-17 engage in reciprocal stimulation, amplifying each other's secretion and exacerbating inflammatory responses. Maternal IL-6, which can traverse the placenta only during mid-pregnancy, can, during late pregnancy's MIA, initiate an immune cascade that stimulates IL-17 production. This cascade elevates IL-6 levels in the fetal brain, precipitating a series of brain injuries [19,42,43].

IL-35, a novel immunosuppressive cytokine, significantly dampens immune responses in various conditions, including inflammatory and infectious diseases, autoimmune disorders, and cancers. The study indicates that IL-35 also possesses anti-inflammatory and neurotrophic properties, especially in ischemic-hypoxic models [20] (Table 2).

4. The Relationship between ILs and the Onset of CP

Research consistently identifies neuroinflammation as a primary contributor to brain injury. The mechanisms by which inflammation leads to early brain injury include diminished cerebral blood flow, impairing oxygen and glucose uptake; compromised blood-brain barrier integrity, reducing protection for brain cells; the generation of free radicals; and the activation of microglia, astrocytes, and leukocytes, resulting in cerebral edema. These factors collectively lead to neuronal damage. Additionally, elevated levels of ILs and other inflammatory markers can adversely affect central nervous system development [48,63]. Studies have established a strong link between neuroinflammation in CP and infections. Infections trigger the release of inflammatory mediators, including microglial activation and increased levels of IL-1β, TNF-α, and IL-6 during pregnancy, as well as elevated IL-1β and TNF-α in the CSF associated with fetal inflammatory response syndrome. Notably, even in the absence of direct infection, the fetal brain remains highly vulnerable to postnatal diseases due to the presence of heightened inflammatory factors [64,65]. While maternal inflammatory factors were once believed to protect the fetus, emerging research now associates them with various neurological conditions. Pro-inflammatory ILs, produced in response to infectious or non-infectious stimuli during pregnancy, have been linked to systemic inflammation in newborns and fetal brain damage [66,67]. Chorioamnionitis has been identified as a mediator of cytokine-induced preterm birth and periventricular leukomalacia, both significant risk factors for CP [68]. Additionally, ILs impact other precursor diseases to CP. Hypoxic-ischemic encephalopathy (HIE) represents a critical neonatal condition at birth and a known precursor to CP, with astrocyte activation playing a pivotal role in its etiology. Research utilizing neonatal ischemia-hypoxia models has shown that activation of the transient receptor potential vanilloid 1 (TRPV1) prompts astrocytes to release IL-1β via the JAK2-STAT3 signaling pathway and the nucleotide-binding oligomerization domain, leucine-rich repeat (NLR) family pyrin domain-containing 3 (NLRP3) inflammasome. This triggers a maladaptive inflammatory response, exacerbating brain damage following

Table 2. Interleukin family classification.

Anti-inflammatory interleukins	IL-2: ① neuroprotective capabilities. ② converting activated microglia from the DAM phenotype to an atypical MHCIIhi phenotype. IL-4: ① enhancing neuroprotection. ② overexpression in newborns can obstruct oligodendrocyte differentiation. IL-10: ① supporting neuronal homeostasis and cell activity and accelerating myelin sheath repair. ② elevated levels cause the aggregation of peripheral macrophages and microglia. IL-35: demonstrating anti-inflammatory and neurotrophic properties.
Pro-inflammatory interleukin	IL-1β: ① induces neuronal damage and degeneration and prevents the expansion of neural networks and affects cell differentiation. ② exacerbates white matter damage and hinders myelin regeneration. IL-6: ① enhancing neuroselective glutamatergic synapses. ② directly affects synapse formation in the fetal brain during pregnancy. ③ infection triggers a reduction of non-heme iron in maternal circulation. ④ direct binding to receptors on the placenta leads to neurodevelopmental disorders in the fetus at birth. IL-8: high expression results in peripheral macrophage and microglia aggregation. IL-17A: its secretion is regulated by IL-6, and it promotes the release of pro-inflammatory factors.

MHCIIhi, major histocompatibility complex class II; DAM, disease-associated microglia; IL, interleukin.

ischemia and hypoxia [69]. Fetal inflammatory response syndrome (FIRS), triggered by infections and inflammatory mediators in the amniotic fluid, frequently occurs in preterm infants and following premature membrane rupture. This systemic response, characterized by elevated IL-6 levels, can lead to significant neonatal complications, including intraventricular hemorrhage, periventricular leukomalacia, and CP [70]. Post-MIA, inflammatory cytokines including IL-1β, IL-6, IL-13, IL-17, and TNF disrupt the inflammatory equilibrium of the foetal brain. This imbalance impedes neural connectivity and synaptic function, potentially compromising foetal neurodevelopment [19,71]. Inflammatory responses are intricately linked to white matter injury, particularly in preterm infants. Pathogens and related factors trigger microglia and astrocytes, leading to cellular and molecular mechanisms that increase excitotoxic glutamate, damaging pre-oligodendrocytes and hindering myelination. Concurrently, activated microglia exacerbate white matter damage by releasing various ILs and other inflammatory mediators [22,72]. Periventricular leukomalacia (PVL) significantly contributes to behavioral abnormalities and neurodevelopmental delays in children, representing a key pathological shift towards brain injury and a precursor to CP. The underlying mechanism involves cytokine release during brain inflammation, with pro-inflammatory ILs damaging periventricular white matter and promoting the progression to CP [73]. This highlights the central role of ILs as mediators in CP-associated brain damage.

From a cellular and molecular perspective, the inflammation process, from its onset to pathogenesis, can be detailed: upon encountering innate immunity challenges such as bacterial and viral invasions, endotoxin release, or sterile stimuli, the immune system triggers cellular apoptosis mechanisms. Central to this process is the NLRP3 inflammasome, a recently identified protein expressed by myeloid immune cells that functions as a cellular stress sensor. Its activation, regulated by the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway (triggered by TLR4) and the MAPK pathway, enhances the release of pro-inflammatory cytokine IL-1α and promotes the secretion of IL-1β and IL-18. This activation cascade culminates in cell pyroptosis, thereby exacerbating brain damage [17,74–76]. Within the inflammatory response, IL-1β acts as an initiator, stimulating the release of other inflammatory cytokines, including IL-6 and TNF-α. Concurrently, the anti-inflammatory cytokine IL-10, through activation of the immune-neuro-endocrine network, modulates the inflammatory reaction post-brain injury [28,39]. Thus, the IL family is integral to CP's pathogenesis, playing a key role in disease onset and indirectly influencing disease progression through various inflammatory pathways.

5. Treatment Aspects

Current therapeutic strategies for CP primarily focus on post-onset interventions, including rehabilitation training, intrathecal baclofen injections, and selective posterior rhizotomy (SPR) to reduce limb spasticity. Cervical perivascular sympathectomy (CPVS) is also employed to address cerebral ischemia symptoms [77]. While these treatments offer symptomatic relief, they neither address the underlying causes of CP nor fully reverse neurological damage. Recent studies exploring the link between CP and inflammation have demonstrated promising outcomes in treating mild to moderate CP in rabbit models with anti-inflammatory agents. These treatments not only improved survival rates but also enhanced motor function recovery, nearly matching that of unaffected controls [78,79]. This breakthrough highlights the potential of targeting brain inflammation in CP treatment, utilizing anti-inflammatory cytokines like IL-4 and IL-10 to counteract pro-inflammatory cytokine effects and employing IL antagonists such as the IL-1 receptor antagonist. Anakinra,

commercially available as IL-1Ra, has been used in clinical settings for over two decades to treat various inflammatory syndromes, including sepsis. Its ability to rapidly cross the blood-brain barrier [9] has led to its recent use in investigating the control of neuroinflammation. Study has indicated that Anakinra can effectively regulate GBS-induced MIA [80]. Addressing IL-6-induced hypoferritinemia through maternal iron supplementation presents a novel strategy to prevent fetal developmental issues [34]. Recent study has emphasized the use of IL-2/IL-2R in the prognostic treatment of brain hypoxia, primarily by increasing regulatory T cell populations that provide neuroprotection. These cells can reduce IL-6 levels and promote macrophage polarization to an M2 phenotype, thereby diminishing ischemia-induced inflammation [81]. Additionally, melatonin, an endogenously produced hormone, has been shown to counteract inflammation by enhancing mitochondrial autophagy and inhibiting the TLR4/NF-κB signaling pathway. This mechanism offers potential for mitigating brain damage caused by endotoxins and ischemic hypoxia [82]. Research on the IL family highlights that early intervention in the inflammatory response is essential for managing the progression of CP and its precursor conditions. Notably, evidence indicates potential prenatal brain damage, advocating for treatments to begin during the fetal period. However, current medical limitations make fetal interventions challenging, necessitating further animal studies to develop treatments safe for both fetus and mother. Future CP treatment strategies should aim to elucidate its detailed pathogenesis, identify ILs and other inflammatory factors crucial to its development, and employ targeted therapies for early intervention and prevention.

6. Summary and Outlook

This review offers the first systematic analysis and synthesis of ILs' impacts on CP onset. By integrating insights on neuroinflammation, CP development, and the specific ILs driving neuroinflammation, this study elucidates the significant influence of ILs on CP's underlying mechanisms. Extensive research consistently indicates that IL levels in children with CP are markedly elevated compared to healthy counterparts and remain elevated over time. This persistent inflammation highlights its continuous role in the development and progression of CP. Although the inflammatory response serves as a protective mechanism against external pathogens, it simultaneously acts as a double-edged sword. By producing cytotoxic effects on normal cells, inflammation can paradoxically exacerbate the condition it initially aims to ameliorate. Experimental studies using animal models of CP have shown that precursor diseases leading to CP trigger inflammatory responses and dysregulate inflammatory factors within the brain. This evidence further solidifies the connection between inflammation and CP onset. At the core of these inflammatory responses is a complex network of signaling among various factors and cells, with the IL family emerging as a significant mediator closely associated with CP.

Current investigations into CP mechanisms face ethical constraints, necessitating reliance on animal models for experimental studies. Consequently, this review predominantly incorporates data from animal research, with human studies remaining largely observational. The absence of experimental human models impedes a detailed understanding of the IL-CP relationship. Addressing this requires further research using primates and other models closely mimicking human physiology, contingent upon increased funding. This review's limitations include the lack of gender-segregated experimental data, precluding conclusions on potential gender-dependent differences in the findings. In summary, this review addresses methodological considerations and suggests potential therapeutic avenues for future CP research. Future efforts should aim to elucidate the molecular mechanisms of ILs in CP and develop innovative screening methods, essential for translating animal model findings into human health applications.

7. Conclusion

Although research on inflammatory factors has advanced recently, the exploration of their specific mechanisms and direct links to CP remains limited. Therefore, investigating the role of ILs in CP's development is a crucial and long-term research priority. The primary aim of ongoing CP research is to deepen understanding of its specific mechanisms, elucidate the role of ILs in its pathology, thoroughly examine the IL family's impact on the nervous system, and identify the triggers for inflammatory responses through various pathways. Furthermore, monitoring the dynamics of inflammatory responses and IL levels during anti-infection and anti-inflammatory treatments is essential. This comprehensive approach aims to enhance therapeutic strategies for CP, providing more effective interventions.

Author Contributions

MBH, JJW and CB were responsible for setting the direction of the study, analyzing the data, and writing the manuscript. HZ was responsible for reviewing the literature and organizing the references. XPL was responsible for developing writing ideas, guiding the writing process, interpretation of data, designing the figures and finalizing the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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