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[Review]

**Prenatal ischemia deteriorates white matter, brain organization, and function: implications for prematurity and cerebral palsy**

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**ABBREVIATIONS**

PVL            Periventricular leukomalacia

WMI            White matter injury

**[Abstract]**

Cerebral palsy (CP) describes a group of neurodevelopmental disorders of posture and movement that are frequently associated with sensory, behavioral, and cognitive impairments. The clinical picture of CP has changed with improved neonatal care over the past few decades, resulting in higher survival rates of infants born very preterm. Children born preterm

seem particularly vulnerable to perinatal hypoxia-ischemia insults at birth. Animal models of CP are crucial for elucidating underlying mechanisms and for development of strategies of neuroprotection and remediation. Most animal models of CP are based on hypoxia-ischemia around the time of birth. In this review, we focus on alterations of brain organization and functions, especially sensorimotor changes, induced by prenatal ischemia in rodents and rabbits, and relate these alterations to neurodevelopmental disorders found in preterm children. We also discuss recent literature that addresses the relationship between neural and myelin plasticity, as well as possible contributions of white matter injury to the emergence of brain dysfunctions induced by prenatal ischemia.

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Review

**[TEXT]**

CP is a complex syndrome of various sensory, motor, and cognitive deficits, and is considered a main cause of physical disability in children. Although CP has a complex and multifactorial etiology, it appears to be primarily related to an injury to immature brain and/or abnormal development of brain organization and function.<sup>1</sup> In a recent meta-analysis of seven neuroimaging studies based on 1359 patients from five industrialized countries,<sup>2</sup> 86% of children with CP display magnetic resonance imaging (MRI)-detectable brain abnormalities, with white matter injury (WMI) being the most common imaging pattern (in 19%–45% of cases). WMI was diagnosed in 31% to 71% of children born at less than 37 weeks' gestation and in 67% to 79% of children born before 34 weeks. WMI seems to be related to preterm birth, minor motor deficiencies, and behavioral and cognitive impairments; whereas, severe motor disabilities appear to be related to neuronal damage (20%–70% of cases), focal vascular insult (4%–26%), malformations (9%–18%), and other miscellaneous abnormalities (8%–36%).<sup>2</sup> About 40% of extremely children born preterm (24–32wks' gestation) develop moderate to severe motor and/or cognitive impairments, while the rest often exhibit minor motor, behavioral, and cognitive disturbances. In addition, it should be noted that the proportion of preterm births in developed countries is steadily increasing since the early 1990s.<sup>3</sup>

To reproduce cerebral damage found in children born preterm, many animal models based on perinatal hypoxia-ischemia with or without infection/neuroinflammation have been used to elucidate cellular and molecular mechanisms and to develop therapeutic strategies. However, only a few studies were dedicated to neurodevelopmental disorders, and it is worth noting that hypoxia-ischemia represents one among the various mechanisms at the origin of CP. The Rice–Vannucci model, which combines carotid artery ligation with hypoxia exposure at postnatal day 7, has been widely used in rats and adapted to other species. This time point

was chosen based on histological similarities in human fetuses at 32 to 34 weeks' gestation and rat brains at postnatal day 7. This model primarily induces brain damage with sensorimotor and cognitive deficits that vary considerably according to the parameters of the hypoxia-ischemia, such as duration, time to reperfusion, and severity.<sup>4</sup> To reproduce the level and type of brain damage commonly observed in most immature preterm infants (which range from 23–32 gestational weeks in age), hypoxia-ischemia was performed even earlier at postnatal day 2 since this corresponds to the peak point of proliferation of vulnerable pre-myelinating oligodendrocytes.<sup>5</sup> Provision of hypoxia-ischemia even earlier at embryonic day 22, also produced dramatic WMI in rabbit survivors in a model in which hypoxia-ischemia was induced by transient uterine artery occlusion.<sup>6</sup> Since pre-oligodendrocyte proliferation begins at embryonic day 14 and proceeds until adulthood in rats,<sup>7</sup> prenatal ischemia at embryonic day 17 or 18 in rats has also been used and was observed to produce WMI that was present at birth and that lasted into adulthood.<sup>8–10</sup> Thus, prenatal ischemia represents a suitable model of WMI that appears to reproduce clinical situations of intrapartum vulnerability and risk factors encountered in prematurity, such as intrauterine growth restriction and very-low birthweight.

The first part of this review is focused on recent literature on white and gray matter injury in children born preterm, the impact of this injury on sensorimotor circuitry and outcomes, and the effects of WMI on the emergence of brain dysfunctions. The second part deals with prenatal ischemia in rodents and rabbits as a reliable model of white and gray matter damage that may recapitulate the main neurodevelopmental disorders observed in preterm children, and the putative mechanisms of WMI on sensorimotor brain functions and plasticity.

## **BRAIN DAMAGE IN PRETERM INFANTS**

Encephalopathy of prematurity is mainly characterized by white and gray matter injury in various brain areas resulting mainly from intrauterine hypoxia-ischemia and/or systemic infection/inflammation. The major component of encephalopathy of prematurity is defined as periventricular leukomalacia (PVL) or periventricular necrosis of pre-oligodendrocytes, and is associated with reactive gliosis, excitotoxicity microglial activation, the release of free radicals, and subsequent hypomyelination.<sup>11,12</sup> In the brains of preterm infants, pre-oligodendrocytes are the dominant cell type and are thus highly vulnerable to hypoxia-ischemia insults occurring around birth; the loss of this cell type leads to the observed WMI.<sup>13</sup>

#### White matter injury

In humans, PVL consists of two components: cystic and diffuse WMI. Cystic WMI is visible using ultrasonography (0.5–2mm) as a necrotic lesion with a loss of cellular elements partially filled by glial scars. Its prevalence is declining and it is now observed in only 5% of very-low birthweight survivors. The second component, diffuse and subtle WMI, is now the most common type of lesion (observed in 90% of infants with PVL and in 50% of very-low-birthweight survivors) and requires visualization using MRI in living newborn infants.<sup>13</sup> To explain such changes in PVL, recent studies emphasize a switch from a deficit in pre-oligodendrocytes to an excess of immature oligodendrocytes and low numbers of mature myelinating oligodendrocytes, suggesting a blockade of oligodendrocyte maturation as the underlying cause of the hypomyelination.<sup>13,14</sup>

#### Gray matter damage in the sensorimotor circuitry

Several studies have demonstrated neuronal and axonal degeneration, loss of excitatory and inhibitory neurons related to cortical subplate damage, and alterations of microstructure and functional connectivity in all brain areas – including the sensorimotor cortex, concomitant

with WMI.<sup>12,15,16</sup> For example, in a study examining children with spastic diplegia, spatiotemporal activity was reduced in the contralateral somatosensory cortex,<sup>17</sup> typical bilateral somatosensory cortical activation was disrupted,<sup>18</sup> as were typical oscillations and somatotopic organization.<sup>19,20</sup> In children with CP, transcranial magnetic stimulation induced abnormal bilateral activation of the motor cortex<sup>21</sup> and reduced excitability, findings that correlated with motor impairments.<sup>22</sup> In addition, sensorimotor thalamocortical, cortical, and pallidal circuitry appeared reduced and/or disrupted and were strongly predictive of motor outcomes.<sup>12,20,23,24</sup> Taken together, these studies suggest that abnormal somatosensory inputs may be a causal factor of motor impairments.

### Functional implications

Since survival rates of preterm infants have increased while cystic WMI has declined in recent years, there has been a decrease in major motor impairments, so that now behavioral, cognitive, and fine motor deficits are the dominant clinical picture in persons with encephalopathy of prematurity.<sup>14,25</sup> Unfortunately, CP is present in 75% to 86% of children with cystic WMI who display disabling motor impairments, such as spasticity and abnormal control of movement and posture.<sup>1</sup> In addition to impairments in motor skills, CP is also characterized by reduced abilities in touch and proprioception discrimination. These latter findings correlate with WMI and disruptions in afferent projections from the posterior thalamus, but not with WMI in the corticospinal tract, suggesting that abnormal somatosensory inputs are key contributions to the observed motor impairments.<sup>20,23,26–28</sup> In addition, children with spastic CP exhibit desynchronization in the somatosensory cortices during motor planning and execution.<sup>29</sup> The relationships between the neuropathology of encephalopathy of preterm birth or CP and subsequent sensorimotor outcomes are still unclear and are a matter of debate.

## Impact of WMI on human brain functions

Considerable interest has grown on the interplay among white matter, neural activity, motor learning, and cognition. Recently, several studies have focused on the role of WMI in several diseases in which WMI is a key predictor. The composition of myelinated versus unmyelinated axons is heterogeneous in the brain and myelination patterns even vary along a single axon. Such variations in myelination contribute to fine modulations of neuronal activity.<sup>30</sup> Myelin mainly controls the conduction velocity of action potentials through axons, and subsequently, the timing of the flow of information through the brain. Precision in this timing is crucial for synaptic plasticity, learning and memory, and for oscillation-mediated synchrony within and between distant cortical areas. Precise information timing and synchrony at millisecond levels is essential for the coordination of information processing, mediation of various neural functions (including attention, perception, memory, and cognition), and overall dynamical stability of the brain.<sup>31,32</sup> Even a 1 millisecond variation in conduction velocity may change the gamma oscillation phase by 30 degrees, a change that will impact signal amplitude and thus neural function.<sup>32</sup> One can expect that axonal degeneration and conduction velocity changes occurring with WMI could induce a wide range of brain dysfunctions. Finally, disruptions in brain synchronization or coupled oscillators alter coherence in brain rhythms and thalamocortical functional connections, slow cognitive processing speed, and reduce the ability to categorize information, changes thought to underlie diagnoses of autism and schizophrenia.<sup>32,33</sup> Thus, how WMI is involved in the emergence of neurodevelopmental disorders in children born preterm is of key interest.

## **PRENATAL ISCHEMIA IN ANIMAL MODELS OF WMI**



The numerous rodent models based on postnatal hypoxia-ischemia and/or systemic inflammation often induce white and gray matter injury as well as sensorimotor deficits, but are often unilateral and vary with the parameters used during hypoxia-ischemia. More importantly, these postnatal models lack the maternal, placental, and fetal components that are crucial to replicate encephalopathy of prematurity features.<sup>4,10</sup> To reproduce pre-oligodendrocyte damage using prenatal ischemia, uterine blood supply is interrupted or reduced in anesthetized pregnant females by intrauterine artery ligation at embryonic day 17<sup>8</sup> or 18<sup>10</sup> in rats (which have a mean gestation duration of 22d) and at embryonic day 30 to 35 in guinea pigs<sup>34</sup> (65d gestation period), or transient uterine artery occlusion at embryonic day 22 to 25 in rabbits<sup>6</sup> (30d gestation period). Hypoxia-ischemia insults in rodents at embryonic day 17 to 18 appear to correspond to intrauterine events occurring in human infants at 23 to 25 weeks' gestation.<sup>10</sup> It is important to note that over 90% of the oligodendrocytes are at the pre-oligodendrocyte stage at 18 to 27 weeks' gestation in humans,<sup>35</sup> which corresponds to embryonic day 14 in rats. This time point in rodents also coincides with the onset of axonal tract development.<sup>7</sup>

#### White matter injury

After prenatal ischemia at the time points listed above, myelination deficits were found in the corpus callosum, cerebral cortex, cerebellum, and spinal cord of fetal guinea pigs,<sup>34</sup> and in the corpus callosum and cingulum of rat neonates when examined between birth and postnatal day 21.<sup>8,9</sup> In rats examined at adulthood after prenatal ischemia at embryonic day 17 to 18, hypomyelination and axonal degeneration persisted in the internal and external capsules, corpus callosum, fornix, pontocerebellar tract, and in white matter zones below the cingulum and primary somatosensory cortices, but was not detected in white matter zones below the primary motor cortex or in the corticospinal tract.<sup>36</sup> Interestingly, the severity of

hypomyelination in these adult rats correlated with the gradient of growth restriction at birth.<sup>8,9,36</sup> The prenatal ischemia also permanently altered the structure of myelin and axons in these rats, as existing myelin showed degeneration and axons displayed signs of swelling.<sup>12</sup> In guinea pigs subjected to prenatal ischemia at embryonic day 30 to 35, myelin sheaths were thinner relative to axon thickness.<sup>34</sup> Hypoxia-ischemia at embryonic day 22 in rabbits induced hypomyelination in similar brain areas. Hypomyelination peaked when hypoxia-ischemia was performed at embryonic day 25, a time point in rabbits that corresponds to the maximal differentiation window of oligodendrocyte progenitors into pre-oligodendrocytes.<sup>6,37</sup> All prenatal ischemia models reported diffuse WMI in various brain areas, a finding consistent with encephalopathy of prematurity and CP.<sup>38</sup>

#### Gray matter damage in the sensorimotor cortex

There are few preclinical studies investigating the sensorimotor cortex after prenatal ischemia. In rats examined at adulthood after prenatal ischemia at embryonic day 17, degraded topography of hindpaw maps and altered neuronal properties were observed in the somatosensory cortex.<sup>36</sup> Comparable changes in somatosensory maps and properties in rats correlated with deficits in tactile discrimination.<sup>39</sup> These map changes were concomitant to decreased neuronal densities in the somatosensory cortex (particularly inhibitory interneurons), decreased height of the cortical gray matter, and WMI and astrogliosis in white matter associated with the somatosensory cortex. In contrast, there were no structural and functional changes in the motor cortex or associated white matter in these ischemic rats.<sup>36</sup> Furthermore, abnormal lamination of the parietal cortex, presumably due to premature disruption of the cortical subplate, was associated with gait disturbances in adult rats exposed to prenatal ischemia at embryonic day 17 to 18.<sup>10,40</sup> Thus, animal studies highlight the higher vulnerability of somatosensory versus motor structures to prenatal ischemia.

## Functional implications

Adult rats that were submitted to prenatal ischemia exhibited minor locomotor deficits on treadmill, mild signs of spasticity, and increased variations in locomotor kinematics that were mainly related to disorganization in the somatosensory cortex but not the motor cortex,<sup>36,41</sup> as in humans.<sup>29</sup> Grip strength and motor coordination was slightly impaired in prenatal ischemic rats<sup>42</sup> while mild locomotor disturbances were significant only in male rats.<sup>40</sup> Prenatal hypoxia delayed the development of motor skills and impaired motor learning in rats<sup>43</sup> while prepulse inhibition was impaired in adult prenatal ischemic guinea pigs, suggestive of abnormal somatosensory gating.<sup>38</sup> In prenatal ischemic rabbits, muscle hypertonia and various motor deficits correlated with WMI,<sup>6</sup> although the contribution of unmyelinated fiber reduction seemed greater than that of myelinated fiber loss.<sup>44</sup> These studies address the question of how WMI is involved in the development of sensorimotor impairments.

## Putative impact of WMI on brain functioning and plasticity

In adult mice, changes in activity in neurons stimulates myelination, production of new pre-oligodendrocytes,<sup>45</sup> and drives synaptic plasticity that mediates memory formation.<sup>46</sup> Learning a new task, such as skilled reaching of pellets, increases myelination in the white matter below the motor cortex of adult rats. Rats displaying higher myelination learn this new motor task faster.<sup>47</sup> Adult mice that learn a 'complex running wheel' task display oligodendrocyte proliferation while mice lacking the capacity to produce new oligodendrocytes failed to learn the motor task,<sup>48</sup> suggesting that myelin plasticity is a substrate for optimal information flow during neural learning and plasticity.

It is now widely accepted that WMI-induced changes in conduction velocity mediate abnormal transmission and integration of afferent and efferent information, leading to brain

dysfunctions as observed in several pathologies, such as autism and schizophrenia.<sup>32,33</sup>

Animal models based on prenatal ischemia reproduce WMI and appear to recapitulate the diversity of sensorimotor deficits found in encephalopathy of prematurity and several symptoms of CP. One can speculate that WMI below the somatosensory cortex may alter timing precision in somatosensory afferent inputs from the periphery to the somatosensory cortex arising from spontaneous movements and locomotion during development. Because precision in timing of action potentials is fundamental in brain plasticity, such abnormal feedback inputs may have induced the observed degraded hindpaw map organization and altered neuronal properties in the somatosensory cortex of adult rats exposed to prenatal ischemia at embryonic day 17.<sup>36,40,43</sup> Several studies have shown that abnormal processing and integration of afferent information in the somatosensory cortex is sufficient to drive disturbances in motor planning and execution.<sup>20,23,29</sup> Somatosensory map disorganization in prenatal ischemic rats may lead to abnormal development of locomotion patterns, which in turn feed the somatosensory cortex with aberrant somatosensory inputs, thus increasing the degradation of map topography and neuronal properties in the somatosensory cortex through a vicious cycle.

In previous studies, we tested the impact of abnormal patterns of somatosensory inputs on both the topographical organization of the somatosensory cortex and motor outcomes. Hindlimb movement restriction during postnatal development was provided by daily casting of the pups, and induced significant hindlimb musculoskeletal pathologies and drastically impaired locomotion that likely drove aberrant inputs to the somatosensory cortex. These aberrant inputs resulting from the movement restriction induced severe topographical disorganization in the sensorimotor cortex and altered neuronal properties,<sup>49,50</sup> although no WMI was observed in the brains of the movement-restricted rats.<sup>51</sup> Interestingly, in rats in which developmental movement restriction was combined with prenatal ischemia, several

pathologies were observed, including knee and ankle musculoskeletal pathologies, locomotor impairments, brain WMI, and structural and functional disorganization in the sensorimotor cortex.<sup>51</sup>

## CONCLUSIONS

Several studies highlight the clinical changes occurring over the last decades in individuals with CP or PVL. First, prevalence of prematurity continues to rise. Second, for WMI cystic PVL has changed towards diffuse, microcystic PVL. Third, as a consequence, the severe motor outcomes usually related to cystic PVL encountered in CP have evolved towards mild motor impairments that are frequently associated with behavioral, cognitive, and learning impairments and related to diffuse PVL, the so-called encephalopathy of prematurity. Finally, animal models based on prenatal ischemia exhibit WMI in various brain areas and appear to recapitulate the main clinical symptoms of encephalopathy of prematurity, including impaired behavior and cognition.<sup>38,52</sup> These preclinical models may also contribute to elucidating the possible involvement of WMI on neural activity, brain plasticity, and function. Further studies are required to enlighten the role of WMI in the emergence of encephalopathy of prematurity and CP symptoms.

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