White matter damage in the preterm neonate

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Abstract

The most common form of brain injury in preterm infants is periventricular leukomalacia (PVL). PVL is also the most common cause of cerebral palsy in the smallest and most vulnerable preterm infant. The core theme in its pathogenesis is the effect of hypoxia, ischaemia, and inflammation on the vulnerable white matter of the developing brain. Over the last decade, with improved laboratory and imaging techniques, the complex relationships between the known associated factors involved in causation of PVL is becoming increasingly known. A better understanding of its pathogenesis provides the basis for future protective strategies against PVL.

Keywords cerebral blood flow; oligodendrocytes; periventricular leukomalacia (PVL); white matter

Introduction

Periventricular leukomalacia (PVL) was first described by Banker and Larroche in 1962, who described the white spots (*leukos*) and softening (*malacia*) seen at the periventricular white matter. The aetio-pathogenesis of white matter damage in the preterm neonate is less well understood compared to that of intraventricular haemorrhage and is increasingly thought to be multifactorial. A review of the cells in the central nervous system (CNS) allows for a better understanding of mechanisms involved.

Cells of the central nervous system

The basic functional unit of the nervous system is the neuron. These are electrically excitable cells that process and transmit electrical and chemical signals throughout the nervous system. Unsurprisingly, due to the complex nature of neurons, they are also extremely fragile and cannot survive or function optimally without the protection and support of their supporting cells, namely:

- *Ependymal cells* or *ependymocytes* which line the ventricles of the brain and the central canal of the spinal cord. They are responsible for the production of cerebrospinal fluid via the choroid plexus and in its propulsion throughout the nervous system.
- *Microglial* cells, which are specialised macrophages. These make up around 15–20% of the total cell population in the brain. As well as phagocytosis, they are also capable of cytotoxic destruction (with collateral damage to resident cells) via the release of nitric oxide (NO), hydrogen peroxide (H_2O_2), cytokines (e.g. IL-1) and through NMDA-mediated processes.
- *Astrocytes*, which are the most numerous cells in the central nervous system with multiple homeostatic and structural functions. Their functions include the provision of nutrients, repair and recycling of damaged cells and the maintenance of neurotransmitter and ionic balance. Astrocytes are particularly susceptible to damage themselves from any ischaemic process.
- *Oligodendrocytes*, which are responsible for the formation and maintenance of myelin in the central nervous system. Oligodendrocytes are also found in the grey matter of both developing and adult brains, though their function in these regions is unclear.

Mature oligodendrocytes are derived from oligodendrocyte-precursor cells or oligodendrocyte progenitors (OPC), which arise from distinct regions in the subventricular zones of the lateral and fourth ventricles. These then migrate into the developing white matter alongside emerging axonal fibres where they mature into functioning oligodendrocytes. Oligodendrocyte development is heavily dependent on complex neuro-electrical and biochemical interactions (including growth factors and cytokines from the interleukin class), with significant regulation from the other groups of cells in the central nervous system. Disturbance of these delicate developmental processes results in dysmyelination or hypomyelination.

Astrocytes and oligodendrocytes are also known as macroglial cells and via the production of neurotrophic growth factors, play a key role in the growth of neurons in the brain.

Pathophysiology

Damage to the white matter region of the developing brain of the preterm infant may be present in isolation, or found in conjunction with other pathologies such as intraventricular haemorrhage. It can also occur in pathologies in which cerebral white matter is specifically affected, for example in infectious processes, primary vascular insults or white matter metabolic derangements as seen in the leukoencephalopathies.

The pathophysiology of periventricular leukomalacia (PVL) is believed to be multifactorial, with three important triggers known so far:

Vascular factors, that increase the risk for cerebral hypoperfusion and ischaemia

Intracranial arterioles are different from elsewhere in the body, with a well-developed internal elastic membrane within a relatively thicker tunica intima and a correspondingly thinner tunica media and adventitia. The cerebral vessels' auto-regulatory process is regulated by an adventitial plexus of nerves which allow a more immediate homeostatic response. The cerebral arterioles in preterm neonates have a relatively underdeveloped internal elastic membrane and adventitial nervous plexus. They are also less sensitive in their chemoreception of the partial pressure of carbon dioxide in the blood stream ($PaCO_2$), which significantly diminishes their vasodilator responses.

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Another vascular factor which increases the risk of PVL is the relative paucity of vascular anastomoses in the premature infant's cerebral circulation. The vascular supply to the white matter of the brain is divided into:

- *Ventriculopetal branches*, which penetrate the cerebrum from the pial surface. These are mainly derived from the middle cerebral artery, with descending input from the posterior cerebral artery and followed by the anterior cerebral artery. These are also variously described as the cortical vascular circulation.
- *Ventriculofugal branches*, which extends from the ventricular surface and are derived from choroidal arteries and striate arteries. These consist of the medial striate, lateral striate, thalamoperforate and thalamogeniculate arteries, which are derived directly from the circle of Willis. These are also described as the striatal circulation.

The areas where cortical and striatal supply meet are called 'arterial border zones'; these correspond to the areas classically most commonly affected by PVL. As the unborn fetus or the growing preterm infant develops the capacity for these vascular structures to protect the brain from any ischaemic insult increases. As a result, the arterial border zones change with gestation. The fetus or infant who is less than 26 weeks gestation would reveal PVL changes classically in the immediate periventricular region. Thereafter, as the brain develops, these arterial border zones tend to move centrifugally or outwards into the more peripheral white matter and the cortical grey matter.

Overall the vascular perfusion of the premature brain is more passive and more directly determined by the systemic blood pressure. It is therefore susceptible to marked and acute changes in cerebral blood pressure and carbon dioxide levels, with a limited ability to compensate for periods of hypotension and hypocapnia. The efficiency of cerebral arterioles to auto-regulate increases with gestational age which explains the increasing resistance of the near-term or term brain to a similar insult.

The pro-inflammatory response in the premature brain mainly to infection and to hypoxia-ischaemia

Current evidence suggests an important role for pro-inflammatory cytokines including interferon-γ, TNF-alpha (TNF-α), interleukin-1b and interleukin-6. These are highly toxic in the fetal brain increasing apoptosis-mediated cell death. These cytokines are released by microglial cells after being damaged, leading to the secondary phase injury pattern. Increased levels of these cytokines are found in the preterm infants who subsequently develop cystic PVL when compared to those without PVL.

This microglial inflammatory response involves the release of a secondary cascade of pro-inflammatory cytokines, free radicals (NO and H_2O_2) and neuro-excitatory glutamate via NMDA-mediated channels. All these lead to the continuing pathological damage leading to the changes seen in PVL.

Conditions resulting in either a humoral-cytokine response (e.g. chorioamnionitis) or hypoxic-ischaemia, lead to the above process and thereafter the destruction of white matter, specifically

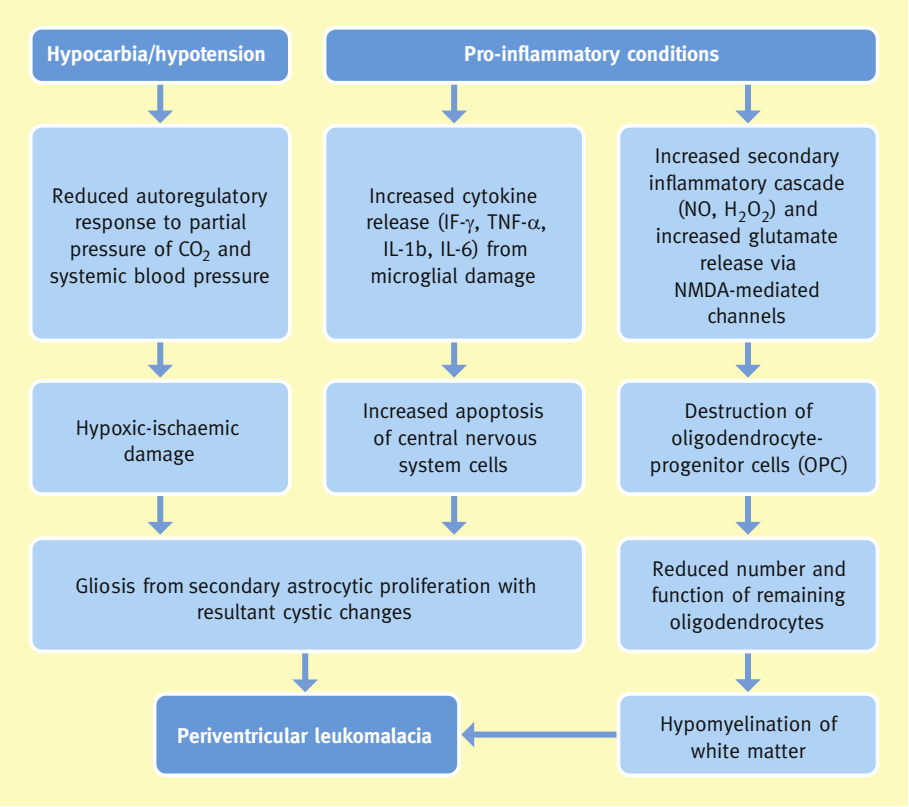

Figure 1 Pathogenesis of periventricular leukomalacia.