REVIEW ARTICLE

Periventricular leukomalacia as causes of encephalopathy of prematurity

Leucomalácia periventricular como causa de encefalopatia da prematuridade

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ABSTRACT

Periventricular leukomalacia (PVL) is currently the most important cause of brain damage in premature infants determining sequels to neurodevelopment. This study aims to evaluate the current knowledge about the pathophysiology of PVL, its main types of lesions, diagnostic methods available, treatment, consequences to the neurodevelopment of preterms, and preventive methods. A search for articles in the Medline database through Pubmed was conducted using the terms: periventricular leukomalacia, cerebral palsy, and prematurity. The most relevant articles were selected in addition to historical studies. The diffuse PVL is characterized by microscopic lesions due to pre-oligodendrocyte destruction, and the neuropathological consequences are declining myelination and ventriculomegaly. There is a causal association between maternal infection, placental inflammation, and periventricular leukomalacia caused by inflammatory cytokines increase in fetal circulation. There is no current medical treatment for PVL. Free radical inhibitors are being investigated to determine whether they have a role in preventing injury to oligodendrocytes in the PVL. The prevention of a preterm birth is the most important means of preventing PVL; follow-up services to these newborns are necessary to diagnose early deficits and the start of stimuli that can minimize neurological damage.

Key words: Leukomalacia, Periventricular; Cerebral Palsy; Infant, Premature.

RESUMO

A leucomalácia periventricular (LPV) é, na atualidade, a causa mais importante de lesão cerebral no lactente prematuro, determinando sequelas ao neurodesenvolvimento. Este trabalho objetiva avaliar o conhecimento atual acerca da fisiopatologia da LPV, seus principais tipos de lesões, métodos diagnósticos disponíveis, tratamento e as consequências ao neurodesenvolvimento dos prematuros e métodos preventivos. Foi realizada a busca de artigos na base de dados do Medline, por meio do Pubmed, usando os termos: leucomalácia periventricular, paralisia cerebral e prematuridade. Foram selecionados os artigos mais relevantes, além de estudos históricos. A LPV difusa caracteriza-se por lesões microscópicas e deve-se à destruição de pré-oligodendrócitos e as sequelas neuropatológicas são a diminuição da mielinização e ventriculomegalia. Existe associação causal entre infecção materna, inflamação placentária e a leucomalácia periventricular, por ocasionarem aumento de citoquinas inflamatórias na circulação fetal. Não existe tratamento médico corrente para LPV. Inibidores de radicais livres estão sendo investigados para determinar se eles têm papel na prevenção da injúria aos oligodendrócitos na LPV. A prevenção do nascimento prematuro é o meio mais importante de prevenir LPV; e serviços de follow up para esses recém-nascidos são necessários para se diagnosticar déficits precocemente e iniciar estímulos que possam minimizar os danos neurológicos.

Palavras-chave: *Leucomalácia Periventricular; Paralisia Cerebral; Prematuro.*

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INTRODUCTION

Cerebral aggression in newborns may be caused by various factors such as germinative matrix bleeding, post-bleeding hydrocephaly, and periventricular leukomalacia (PVL). With the reduction in the incidence of the first two cited injuries, the third cause, which is periventricular leukomalacia, currently appears as the most significant cause of brain damage in premature infant determining the outcomes in neurodevelopment. Periventricular leukomalacia has been classically described as a disorder characterized by multifocal areas of necrosis, forming cysts in the deep brain white matter, which are often symmetric and occur adjacent to lateral ventricles. These necrotic lesions closely correlate with the development of spastic cerebral palsy in infants with extreme low birth weight.

The congenital encephalomyelitis was the term originally described by Virchow[1] in 1987 to describe a condition in newborns that showed areas of pallor and softening within the periventricular white matter in the autopsy. Banker and Larroche in 1962,[2] introduced the term periventricular leukomalacia to define the characteristic alteration found in 20% of lesions in infants who died before completing one month of age. PVL is the most common ischemic cerebral aggression in premature infants. Ischemia occurs in the vicinity of the terminal branches of the arterial vascularization, determining white matter lesions adjacent to lateral ventricles. The main findings for the diagnosis of PVL are periventricular echo densities or cysts detected by transfontanellar ultrasound. The diagnosis is important because of the significant percentage of surviving premature infants who develop cognitive delay, cerebral palsy, or sensorineural lesions.

METHODOLOGY

This study is a non-systematic review of the scientific literature. The search for articles in the Medline database through Pubmed was conducted using the terms: periventricular leukomalacia, cerebral palsy, and prematurity. The most relevant articles were selected, in addition to historical studies, totaling 28 publications. The selected studies were read in full, and information concerning the development of periventricular leukomalacia in premature neonates, its diagnosis, treatment, and prevention were identified.

MICROSCOPIC NEUROPATHOLOGY

The topography of lesions is uniform, affecting primarily the deep white matter of the sub corpus callosum, upper frontal-occipital fasciculus, and white matter adjacent to the horns of lateral ventricles and occipital regions. These areas appear pale in autopsy examinations, usually bilateral, but without defined symmetry.

MACROSCOPIC NEUROPATHOLOGY

Current studies have drawn attention to the damage in the diffuse white matter that is macroscopically characterized by atrophy of all white matter, thinning of the corpus callosum and ventriculomegaly with delayed myelination in late stages. The deep periventricular matter is prone to focal necrosis by being closely related to the terminal branches of the cerebral arterial vascularization, which is most evident in the central white matter while the diffuse lesion of the white matter could be characterized primarily by the death or injury of pre-oligodendrocytes.[3]

VULNERABILITY OF OLIGODENDROGLIA CELLS

Various sources of evidence indicate that the damage to immature oligodendrocytes, pre-oligodendrocytes, during a specific period of vulnerability, is the significant factor in the pathogenesis of PVL.[4]

Pre-oligodendrocytes proliferate and die through programmed cell death, which is regulated by trophic factors such as insulin-like growth factor and platelet-derived growth factors. However, the activation of cytokines receptors on the surface of these cells can lead to their early death. *In vitro* studies show that inflammatory cytokines such as tumor necrosis factor and interferon-gamma are extremely toxic to pre-oligodendrocytes. Immunocytochemical markers have identified increased cellular activity in microglia during aggression of the diffuse white matter. These cells are highly capable of producing potentially toxic inflammatory mediators, free radicals, and reactive oxygen intermediates. The phagocytic activity of microglia enhances the inflammatory effects of interleukin B, tumor necrosis factor, and bacterial liposaccharides. Micro gliocytes are already widely

present in the white matter of a fetus at 22 weeks of gestational age.

Although PVL lesions demonstrate widespread loss of oligodendrocytes[5], Damann et al.[6] added that the damage to white matter involves axons and not only oligodendrocytes.

PATHOPHYSIOLOGY

The two greatest proposed theories on the pathophysiology of PVL are:

- ischemia/reperfusion injury in arterial bordering areas in the periventricular area; and/or
- chorioamnionitis or maternal vasculitis with the production of cytokines leading to inflammatory damage in the periventricular area of the brain in development.

According to the ischemic theory, PVL is the bilateral white matter lesion in premature infants that can result from hypotension, ischemia, and coagulation necrosis in vascular areas that are adjacent to vessels of deep penetration in the middle cerebral artery. Premature infants have impaired vascular auto-regulation and are susceptible to intracranial hemorrhage, as well as PVL. When using mechanical ventilation, they can develop hypocarbia, which can also be one of the precursors in the onset of brain damage.[7]

The injury can cause functional deficits related to the descending corticospinal tract, and visual and acoustic radiations.

In a recent epidemiological study, Leviton et al.[8] evidenced an association between maternal infection, placental inflammation, and periventricular leukomalacia in a detailed analysis. They observed that the fetal inflammatory response is reflected by fetal vasculitis (infiltration of polymorphonuclear leukocytes in the chorionic band or umbilical cord), and not by the direct damage of intra-amniotic infection to the fetal brain. The maternal infection, reflected by the administration of antibiotics, is also linked to fetal brain damage, although it does not mean the existence of brain infection in the fetus. Several maternal cytokines are also associated with the pathogenesis of PVL.

There is no current medical treatment for PVL. Free radicals inactivating agents are being investigated to determine whether they play a role in preventing injury to oligodendrocytes in PVL.[9,10]

FREQUENCY

The incidence of PVL in the United States ranges from 4-26% among premature infants in neonatal intensive care units. The incidence is higher in autopsy studies, reaching more than 75% in the post-mortem examination. The incidence in autopsy varies considerably between neonatal centers. The classic form with porencephalic cysts corresponds to only a small portion of the total number of cases.

The incidence of PVL varies according to the imaging modality used; the cystic form of the disease can only be diagnosed by magnetic resonance imaging. Magnetic resonance imaging can identify either the cystic and non-cystic forms of PVL, which is difficult to establish due to microscopic areas and subsequent glial scarring in non-cystic PVL. Several facts are very clear regarding PVL and lesions are observed particularly in the following situations: in premature infants, with a few days of survival, who had intracranial hemorrhage, in infants with evidence of cardio respiratory disorder, heart failure, severe hypotension, cardiac surgery, use of extracorporeal membrane oxygenation, and with evidence of fetal infection.

MORBIDITY AND MORTALITY

Cerebral palsy can occur in approximately between 60 and 100% of cases of infants with late signs of PVL. The spastic diplegia is the most common form of cerebral palsy and is associated with mild forms of PVL; quadriplegia is often associated with the severe forms of the disease. The cognitive system can present varying degrees of delay, possibly associated with neuro psychomotor developmental alterations in severe PVL. Visual dysfunction can occur with nystagmus, difficulty for fixation, strabismus, and blindness. Some cases of visual dysfunction in association with PVL occur in the absence of retinopathy of prematurity, suggesting damage to optical radiation. The age at which PVL most often occurs is in premature infants under 32 weeks of gestational age and in those weighing less than 1,500 g. Many of the cases presented respiratory disease such as hyaline membrane disease, pneumonia, hypotension, as well as necrotizing enterocolitis or patent ductus arteriosus. On physical examination, many premature infants are asymptomatic, although subtle symptoms may occur in 10-30% of infants such as the following: decreased tone in

lower extremities, increased tone in neck extensors, apneic events, bradycardia, irritability, scarce feeding with pseudo bulbar palsy, and seizures.[11]

Causes associated with PVL:

- mechanically ventilated preterm infants born less than 32 weeks of gestational age and/or weighing less than 1,500 g;
- hypotension, hypoxemia, and acidosis can result in cerebral ischemic aggression and PVL;
- pronounced hypocarbia in ventilated infants;
- placental vascular anastomosis, twin pregnancy, pre-labor bleeding, chorioamnionitis, and funisitis.

ENCEPHALOPATHY OF PREMATURITY MODELS: IMPLICATIONS FOR PATHOGENESIS

Hypoperfusion and ischemia-hypoxia as a cause of periventricular leukomalacia

Insults of hypoperfusion and ischemic-hypoxic have been reproduced on a large variety of animal species including rats, rabbits, pigs, and dogs. They produce damage in the gray matter (mimicking lesions observed in newborn infants) in most of the studies.[12] Fetal asphyxia in sheep showed that it can induce disease in the periventricular white matter, focal or diffuse, accompanied by acute loss of astrocytes and oligodendrocytes. These studies confirm the concept of periventricular focal lesions (cystic lesions) and diffuse lesions (diffuse microglial activation and destruction of pre-oligodendrocytes) occurring in the white matter.[13] Excitatory amino acids also actively participate in the pathogenesis of lesions in the white matter.

The many pre-conception, perinatal, and postnatal factors implicated in the pathophysiology of these lesions include hypoxic-ischemia, endocrine imbalance, genetic factors, growth factor deficiency, overproduction of free radicals, maternal infection with overproduction of cytokines and other inflammatory agents, exposure to toxins, maternal stress, and malnutrition. Therefore, this is a multifactorial disease in which hypoperfusion, ischemia–hypoxic, and inflammation play special roles. Several experimental studies in animals have been conducted with the ischemic-hypoxic model and in many cases resulted in insult to the gray matter and extension to the white matter in severe cases.[14]

The exposure of pregnant rats or their newborns to hypoxia induces pathological alterations in the periventricular white matter that reproduces the periventricular leukomalacia in human newborns with inflammation, astrogliosis, intense retardation of myelination in the prenatal model, white matter atrophy, ventriculomegaly, and alteration in synapse maturation. Although the initial insult is exclusively hypoxic, the observed effects are common in a combination of different mechanisms such as hypoperfusion, ischemia, inflammation and/or oxidative stress induced by protracted hypoxia, and subsequent reperfusion phase.

Focal necrotic lesions occur deep in the cerebral white matter, primarily in the distribution of the final zone of long penetration arteries. The two most common sites for focal necrosis in PVL are at the white matter level close to the trigone of lateral ventricles and around the foramen of Monro.[15] The fondness for these locations can be related to anatomical factors and a high concentration of vulnerable pre-oligodendrocytes. The diffuse injury to the cerebral white matter has been emphasized in many small infants with long postnatal survival periods.[16]

In non-cystic periventricular leukomalacia, focal lesions are microscopic and not commonly detectable in cerebral ultrasound.[17]

The evolution of cellular aspects provides an important clue to its pathogenicity. The cellular neuropathology of the classic focal component in periventricular leukomalacia is characterized in the first six to twelve hours from a hypoxic-ischemic insult by coagulation necrosis in sections of the periventricular focal lesion. This lesion appears as a loss of normal tissue architecture and subsequent tissue dissolution with the formation of cavities (cysts) between one and three weeks. These multiple small cysts are generally large enough (> 3 mm) to be detected by transfontanellar ultrasound.

The neuropathology of the diffuse component in cystic necrotic classical PVL was initially emphasized by Gilles *et al*.[18]

The main cellular characteristic of the diffuse lesion is the presence of glial pycnotic nuclei (glial cells that suffered acute damage) and hypertrophy of

astrocytes. Unlike in focal necrosis, the diffuse lesion is less severe. Although more widespread, lesions do not affect all cellular components. The neuropathological sequelae of diffuse lesions are decreased myelination and ventriculomegaly. Afterward, a reduction in brain volume and ventriculomegaly are observed. Immunocytochemical studies show an important decrease in pre-oligodendrocytes in the white matter of infants with PVL. The cellular targets in diffuse lesions are pre-oligodendrocytes.

Brain studies in infants who died from PVL showed that the injury to the white matter was regionalized, with focal necrosis when present, located deeply and less severe in the periventricular white matter; and the specific cellular injury more diffusely in the central white matter. The necrotic areas were followed by small glial scars, but not cysts. These regional characteristics are consistent with neighboring and terminal vascular zones that are more pronounced in the periventricular white matter and less marked more diffusely in the central white matter.

In the diffuse injury, the preferred death is on pre-oligodendrocytes, which are the dominant cells in the lineage of oligodendrocytes. Therefore, they are the key target cells in diffuse white matter aggression. The injury to diffuse white matter contains marked prominence of astrocytes and activated microglia. Specific markers also show that lipid peroxidation can play an important role in periventricular white matter lesions. These findings suggest that the death of these cells is through the attack of reactive oxygen species and nitrogen.[18]

Infection and inflammation have an important role in the genesis of PVL and are considered the second most important causes in its pathogenesis. Epidemiological and clinical studies suggest a link between maternal infection and fetal impairment causing PVL. The fetal inflammatory response is defined by the presence of cytokines in the fetal blood.[18]

The relationship between PVL and intrauterine infection has been suggested by several factors such as chorioamnionitis, funisitis, premature rupture of membranes, high levels of cytokines, especially interleukin 6 and interleukin 1 in the amniotic fluid and umbilical cord, in addition to the evidence of intrauterine T cell activation. Periventricular leukomalacia is now recognized as able to cause only 5% of injury in the white matter; the common presence of non-cystic PVL in controls of epidemiological studies makes it difficult to interpret the data. The postnatal infection has also been associated with PVL, although in weak epidemiological studies. However, in the diffuse form of PVL, an abundant expression of interferon-gamma has been shown to be present in pre-oligodendrocytes. These findings are of great interest because interferon-gamma is particularly toxic to pre-oligodendrocytes, and this toxicity might be mediated by the tumor necrosis factor. Neuropathological findings indicate that cytokines are present in human PVL and that the most common targets of injury are microglial cells and astrocytes.[19,20]

Neuroimaging of the injury in the cerebral white matter

Neonatal ultrasound is one of the most important imaging techniques for the neonatal brain.[8] In 1990, the ultrasound of eco-densities and ecoluscences in the white matter predicted alterations in psychomotor development better than any other previous exam. Usually, the echogenicity found in precocious periventricular leukomalacia is similar in intensity to that of the choroid plexus. The ultrasound can be seen as an optimal mode of imaging for cystic PVL; however, it has a very limited value to detect injury in the diffuse white matter and the process that leads to encephalopathy of prematurity as shown in studies comparing ultrasound with neonatal magnetic resonance imaging.[21-23]

Conventional magnetic resonance imaging

Magnetic resonance imaging has no decisive role in the early assessment of PVL and is more useful in monitoring infants with suspected PVL, and infants who developed suggestive clinical signs, because it is capable to demonstrate the loss of white matter, increased signal intensity of the deep white matter, and ventriculomegaly. Magnetic resonance imaging has demonstrated thinning of the posterior body and splenius of the corpus callosum in severe cases of PVL.[24] It may show signs of abnormality in the periventricular white matter, which are different from cystic lesions detected by ultrasound.

Conventional magnetic resonance findings that are compatible with chronic white matter injuries in immature brains are characterized also by cysts that are comparable by ultrasound, but also and more importantly, by the persistent high signal intensity

in white matter representing the diffuse image of the injury. This characterized imaging has lately been associated with thinning of the corpus callosum and loss of white matter volume resulting in a deep and imminent groove. The lack of myelination in the posterior branch of the internal capsule at term age is a great indicator of late neuromotor injury. However, about half of pre-term infants who showed medium abnormalities in the white matter had only marginal mental development indexes at the age of two years.

Magnetic resonance diffusion imaging

The early evaluation of the periventricular white matter in preterm infants with magnetic resonance with diffusion can reveal restriction in periventricular diffusion, similar to the typical distribution of PVL when the ultrasound and conventional magnetic resonance did not identify any specific change. It is important to mention that the chronic phase of PVL is characterized by the formation of cysts and hyper-intensities located in the white matter. The magnetic resonance imaging analysis by diffusion tensor has provided new discoveries within the microstructure of the development of periventricular white matter and seems to be ideal for evaluating neurological diseases in the white matter.[4]

Magnetic resonance imaging by spectroscopy

One of the essential contributors to the progress in the non-invasive detection of tissue and biochemical metabolism at present is magnetic resonance by spectroscopy, which provides specific chemical information on the biochemistry of many intracellular metabolites. Similar to the high diagnostic value of magnetic resonance in suffocation, it can also detect damage to the white matter based on anaerobic glycolysis indicators with increased intracerebral lactate.

Long-term alterations in brain growth and development

The periventricular white matter injury has been strongly associated with deficits in neuro psychomotor development in premature infants.[24,25] A correlation between delayed neuro psychomotor development and delayed myelination has been reported.[26] The most complex morbidity of the PVL focal component is spastic diplegia. This motor disorder has the spastic paresis of extremities as its central point, with a much greater effect on lower than upper limbs. The most serious injuries with posterolateral extension within the semi-oval center and corona radiata are associated with effects on upper extremities and cognitive and neural sensory areas.

New techniques of magnetic resonance imaging in three dimensions have allowed quantifying brain volume and absolute quantification of myelination. These findings with deficient myelination in infants with early lesions may explain the high incidence of cognitive deficits. Alterations in the cortical volume in three dimension magnetic resonance imaging are representative of cortical lesions and may explain the increased risk of cognitive impairment and epilepsy in infants with classic motor deficits (spastic diplegia) after injury to the immature white matter.

The ultrasound is the initial mode of choice for damage caused by ischemic-hypoxic to the central nervous system in premature infants. The ultrasound can be performed within the neonatal unit without the need to transport fragile children. The earliest ultrasound signal in periventricular leukomalacia is an augmented echotexture on the periventricular white matter. This is a non-specific finding that must be differentiated from the normal periventricular halo and mild periventricular edema, which may not result in permanent injury. The abnormal periventricular echotexture in PVL usually disappears between two and three weeks. Approximately 15% of infants who suffer of PVL demonstrate periventricular cysts that appear initially two to three weeks after the initial increase in eco-densities. The severity of PVL is related to the size and distribution of cysts. Ultrasound findings may be normal in patients who will later develop images of periventricular leukomalacia.[27,28]

FINAL CONSIDERATIONS

The prevention of preterm birth is the most important way to prevent PVL. The follow-up is required because of its association with cerebral palsy. Before birth, the early diagnosis and management of chorioamnionitis may prevent PVL. The administration of betamethasone to pregnant women between 24 and 31 weeks of pregnancy can significantly reduce the occurrence of periventricular leukomalacia suggesting the possible anti-inflammatory effect of corticosteroids on the fetal

response. Avoiding the maternal use of cocaine and alterations in fetal and neonatal blood flow may decrease the occurrence of periventricular leukomalacia. Infants with periventricular leukomalacia are at high risk of deficits in neuro psychomotor development. Mild PVL is associated with spastic diplegia and serious quadriplegia, with a high incidence of cognitive and sensorineural problems. The timing of the initial ultrasonography can be useful in determining the received insult. Cystic LPV can be identified by ultrasound in the first day of life indicating that hypoxic or infectious events may have been prenatal instead of perinatal or postnatal.

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