PERIVENTRICULAR LEUKOMALACIA IN EXTREMELY LOW BIRTH WEIGHT NEWBORNS

Aniko Manea1*, Boia Marioara1, Daniela Iacob1, Mirabela Dima1*, Radu E. Iacob1

Abstract
The significant improvement in the intensive care of extremely low birth weight newborn has made increased survival rates possible for these premature and, as a result, certain pathologies that had previously received little attention have become the objects of increasing interest. One of the most common cerebral injuries at preterm newborns with gestational age less than 28 weeks at birth are intraventricular hemorrhage and periventricular leukomalacia (PVL).

Periventricular leukomalacia consists of an ischemic infarction in the region of the cerebral white matter adjacent to the lateral ventricles.

The pathogenesis of cerebral leukoencephalopathy have been influenced by different perinatal inflammatory and infectious conditions interrelated with the proinflammatory cytokines: TNF-α, IL-1β, IL-6 and IL-8.

Prognosis of LPV is greatly dependent on maternal infectious history, on the time of diagnosis, type of injury, whether diffuse or focal, and also on the preventative and therapeutic measured employed during the perinatal and postnatal periods.

Key words: Extremely low birth weight, periventricular leukomalacia

Background
The significant improvement in the intensive care of extremely low birth weight newborn has made increased survival rates possible for these premature and, as a result, certain pathologies that had previously received little attention have become the objects of increasing interest. (1)

Some particular diseases through frequency and severity are caused by the plurivisceral morpho-functional immaturity: respiratory distress syndrome, apnea crisis, patent ductus arteriosus, enterocolitic ulceronecrosis and infections, but the lesion background is mostly cerebral.

One of the most common cerebral injuries at preterm newborns with gestational age less than 28 weeks at birth are intraventricular hemorrhage and periventricular leukomalacia (PVL).(2)

Up to 26% of premature infants with birth weights below 1,500 g present periventricular leukomalacia with frequent lead to cerebral palsy (CP), intellectual impairment, or visual disturbances.

Due to lower mortality rates of very low birth weight neonates, thanks to developments in neonatal intensive care units, (90% survival of the approximately 000 infants in the United States yearly with birth weight less than 1500 g) cerebral palsy incidence increases.(3)

The prognosis and neurological outcomes are improved by prevention, diagnosis and early treatment of these neurological diseases. (4)

Periventricular leukomalacia consists of an ischemic infarction in the region of the cerebral white matter adjacent to the lateral ventricles.

The name is based on the characteristic distribution and consists of periventricular focal necrosis with subsequent cystic formation and more diffuse cerebral white matter injury (Volpe, 2008).

Less than 5% of premature newborn at whom serial ultrasonography shows only increased periventricular echogenicity without cysts will subsequently develop cerebral palsy but a significantly bigger number of them will present evidence of cognitive dysfunction.

Cerebral white matter injury is defined as at least one of the following echographic findings (3,5,6):
- The presence of cystic lesions of at least 0.5 cm in diameter. These are distributed bilaterally and located close to the external angles of the lateral ventricles.
- Image of diffuse echodensity persisting for a period of more than 14 days, without cystic formations.
- Unilateral parenchymal hyperdensity or unilateral porencephalic cyst, probably caused by ischemic and hemorrhagic infarction. There will be periventricular hemorrhagic parenchymal involvement, compromising the germinal matrix layer.

In specific literature there are several echographic classifications of periventricular leukomalacia:

- PVL I degree-over seven days persistent periventricular echodensities
- PVL II degree- transient periventricular echodensity evolving into small, localised fronto-parietal cysts
- PVL III degree- periventricular echodensities evolving into extensive periventricular cystic lesions
- PVL IV degree- densities extending into the deep white matter evolving intoextensive cystic lesions

II. Cranial ultrasound classification of PVL by Volpe (1990)(6):
- Mild- micro cysts smaller than 0.2 mm
- Moderate -cysts between 0.2 to 0.5 mm
- Severe- multiples cysts bilaterally bigger than 0.5 mm

1Victor Babeș University of Medicine and Pharmacy, Timișoara, *PhD Student
E-mail: aniko180798@yahoo.com, marianaboia@yahoo.com, danielariacob@yahoo.com, dima_mirabela@yahoo.com, radueiacob@yahoo.com,
The Quality Standard Subcommittee of the America Academy of Neurology and the Practice Committee of the Child Neurology Society recommends the following: routine ultrasound screening should be performed on all infants with gestational age less than 30 weeks. Screening should be performed at 7 to 14 days of age and repeated at 36 to 40 weeks postmenstrual age.

Yet, several studies have shown that MRI (magnetic resonance imaging) is more sensitive than cranial ultrasound for detection of PVL especially for non cystic form of PVL (Maalouf et al., 2001; Roelants-van Rijn et al., 2001).

Three main reasons are the base of to predominantly ischemic injuries of the periventricular white matter at premature newborn: (8,9)

- Reduced cerebral flow in the white matter
- Immature oligodendrocytes are more susceptible to damage encouraged by free radicals and certain cytokines, such as interleukin-6 (IL-6), interleukin-1 (IL-1ß) and tumor necrosis factor alpha (TNF-α), in addition to the greater potential for toxicity induced by glutamate, when the brain is less mature.
- Intrauterine infection (Preterm newborn babies exposed to intrauterine infection are vulnerable to pre-oligodendrocyte cell death in the face of ischemic insult)

The pathogenesis of cerebral leukoencephalopathy have been influenced by different perinatal inflammatory and infectious conditions. The inflammatory pathway, mediated by cytokines is highly involved in neuronal cell death by neuronal apoptosis.(10)

The proinflammatory cytokines most described in intrauterine infections are: TNF-α, IL-1ß, IL-6 and IL-8. Interleukin 6 is the best known mediator of acute inflammatory response, liberated quickly after a bacterial invasion. It is secreted by monocytes, macrophages, endothelial cells and fibroblasts in response to other inflammatory mediators such as TNF-α and IL-1β.(11 ) Interleukin 6 is also synthesized within the neurons and neuroglia and its expression is elevated in a large variety of CNS disorders, presenting neuroprotective and neurotrophic effects.(12)

Testing of IL-1ß, TNF-α and IL-6 at a newborn babies who had had PVL listed in autopsy findings has shown significantly more elevated levels compared with those whose brains were normal on autopsy.(13)

Thus, the incidence of PVL and cerebral palsy in premature infants is increased in the presence of 1) evidence for maternal, placental, or fetal infection (14–26), 2) elevated levels of IL-6 in cord blood (27), 3) elevated levels of IL-6 and IL-1 in amniotic fluid (28), and 4) elevated levels of all interferons and IL-1 and IL-6, among other cytokines, in neonatal blood (29-31). Moreover, although potentially a secondary effect of ischemia, the demonstration of IL-6 and TNF-α within PVL lesions is also possibly supportive of a relation of PVL to intrauterine infection and cytokines (32-34).

In the figure below is shown how the action of maternal/fetal infection, inflammation, and cytokines are involved in the death of oligodendroglia (OL) precursors in LPV (Fig. 1).

![Figure 1. Pathogenesis of oligodendroglia (OL) death in PVL. (35)](image-url)
Cytokines (Fig. 1) caused by maternal/fetal infection or inflammation and may ultimately prove valuable in preventing the injury in figure 1 raises the possibility of several promising research. Maternal antimicrobials and anticytokine agents scavengers, e.g. vitamin E, could be beneficial, after further research. Maternal antimicrobials and anticytokine agents may ultimately prove valuable in preventing the injury caused by maternal/fetal infection or inflammation and cytokines (Fig. 1)

Conclusions

As a role for subclinical intrauterine infection in the genesis of neonatal brain white matter damage and permanent handicap is supported by clear evidence and there are data that strongly suggest that inflammatory cytokines participate in this damaging process.

Prognosis of LPV is greatly dependent on maternal infectious history, on the time of diagnosis, type of injury, whether diffuse or focal, and also on the preventative and therapeutic measured employed during the perinatal and postnatal periods (36)

Periodic neurological evaluation for finding behavioural and cognitive impairments is needed for giving them the best expectations in their quality of live.

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Correspondence to:
Aniko Manea,
University of Medicine and Pharmacy "V. Babes" Timisoara
P-ta E. Murgu, No. 2,
Timisoara,
Romania,
E-mail: aniko180798@yahoo.com