PERIVENTRICULAR LEUKOMALACIA IN EXTREMELY LOW BIRTH WEIGHT NEWBORNS

Aniko Manea[1*], Boia Marioara[1], Daniela Iacob[1], Mirabela Dima[1*], Radu E. Iacob[1]

Abstract

The significant improvement in the intensive care of extremely low 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-1ß, 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 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 ulceronecrotis 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 50 000 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 clasifications of periventricular leukomalacia:

I. *Cranial ultrasound classification of PVL by Linda de Vries* (1992)(7):

- PVL I degree-over seven days persistant periventricular ecodensities
- 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 I Vdegree- 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

[1]Victor Babeş University of Medicine and Pharmacy, Timişoara, *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 nervous 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-1ß.(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-1-ß, 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).

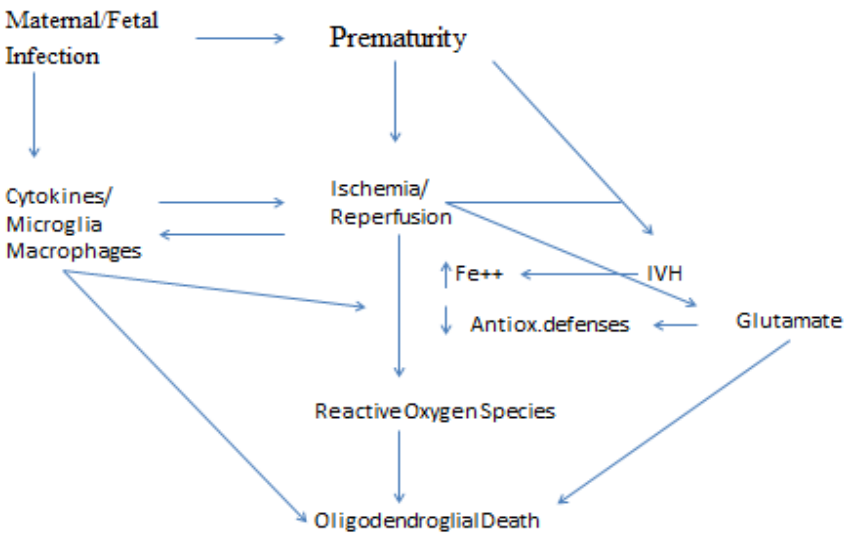

Figure 1. Pathogenesis of oligodendroglia (OL) death in PVL. (35)

Consideration of the pathogenetic scheme depicted in figure 1 raises the possibility of several promising interventions to prevent PVL. Perhaps of greatest value is prevention of the cascade to OL death related to free radical attack (Fig. 1). Thus, the use of clinically safe free radical 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 the 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.

References

1. Lee SK, McMillan DD, Ohlsson A, Pendray M, Synnes A, Whyte R, et al. Variations in practice and outcomes in the Canadian NICU Network: 1996-1997. Pediatrics. 2000;106:1070-9.
2. Vollmer B, Roth S, Baudin J, Stewart AL, Neville BGR, Wyatt JS. Predictors of long-term outcome in very preterm infants: gestational age versus neonatal cranial ultrasound. Pediatrics. 2003;112:1108-14.
3. Leviton A, Paneth N. White matter damage in preterm newborns – epidemiologic perspective. Early Hum Dev. 1990;24:1-22.
4. Parenchymatous Brain Injury in Premature Infants: Intraventricular Hemorrhage and Periventricular Leukomalacia Mauricio Barría and Ana Flández Universidad Austral de Chile, Hospital Clínico Regional Valdivia, Chile
5. De Vries LS, van Haastert IC, Rademaker KJ, Koopman C, Groenendaal F. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. J Pediatr. 2004;144:815-20.
6. Volpe JJ. Neurology of the Newborn. 4th ed. Philadelphia: WB Saunders; 2001.
7. Kaske T.I., Rumak C.M., Harlow C.L. – Neonatal and infant brain imaging, in RUMAK C.M.: Pediatric Sonography, W.B. Saunders, 1996, 3rd ed, 1443-1447;
8. Volpe JJ. Cerebral White matter injury of the preterm infant - more common than you think (commentaries).Pediatrics. 2003;112:176-80.
9. 9.Tsuji M, Saul JP, Du Plessis A, Eichenwlad E, Sobh J, Crocker R, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. Pediatrics. 2000;106:625-32.
10. 10.Kadhim H, Tabarki B, Verellen G, De Prez C, Rona A-M, Sébire G. Inflammatory cytokines in the pathogenesis of periventricular leukomalacia. Neurology. 2001;56:1278-84.
11. 11.Dammann O, Phillips TM, Allred EN, O'Shea M, Paneth N, van Marter LJ, et al. Mediators of fetal inflammation in extremely low gestational age newborns. Cytokine. 2001;13:234-9.
12. 12.Stroemer P, Rothwell NJ. Exacerbation of the ischaemic brain damage by localized striatal injection of interleukin-1ß in the rat. J Cereb Blood Flow Metab. 1998;18:833-9.
13. 13.Yoon BH, Romero R, Kim CJ, Koo JN, Choe G, Syn HC, et al. High expression of tumor necrosis factor-a and interleukin-6 in periventricular leukomalacia. Am J Obstet Gynecol. 1997;177:406-11.
14. Perlman JM, Risser R, Broyles RS 1996 Bilateral cystic periventricular leukomalacia in the premature infant: associated risk factors. Pediatrics 97:822–827 | PubMed | ISI | ChemPort |
15. Zupan V, Gonzalez P, Lacaze-Masmonteil T, Boithias C, d'Allest AM, Dehan M, Gabilan JC 1996 Periventricular leukomalacia: risk factors revisited. Dev Med Child Neurol 38:1061–1067 | PubMed |
16. Grether JK, Nelson KB, Emery ES, Cummins SK 1996 Prenatal and perinatal factors and cerebral palsy in very low birth weight infants. J Pediatr 128:407–414 | Article | PubMed | ISI | ChemPort |
17. O'Shea TM, Klinepeter KL, Meis PJ, Dillard RG 1998 Intrauterine infection and the risk of cerebral palsy in very low-birthweight infants. Pediatr Perinatal Epidemiol 12:72–83
18. Baud O, Ville Y, Zupan V, Boithias C, Lacaze-Masmonteil T, Gabilan JC, Frydman R, Dehan M 1998 Are neonatal brain lesions due to intrauterine infection related to mode of delivery?. Br J Obstet Gynaecol 105:121–124 | Article | PubMed | ISI |
19. Dammann O, Allred EN, Veelken N 1998 Increased risk of spastic diplegia among very low birth weight children after preterm labor or prelabor rupture of membranes. J Pediatr 132:531–535
20. Leviton A, Paneth N, Reuss ML, Susser M, Allred EN, Dammann O, Kuban K, Van Marter LJ, Pagano M, Hegyi T, Hiatt M, Sanocka U, Shahrivar F, Abiri M, Disalvo D, Doubilet P, Kairam R, Kazam E, Kirpekar M, Rosenfeld D, Schonfeld S, Share J, Collins M, Genest D, Shen-Schwarz S 1999 Maternal infection, fetal inflammatory response, and brain damage in very low birth weight infants. Pediatr Res 46:566–575 | Article | PubMed | ISI | ChemPort |
21. Hansen A, Leviton A 1999 Labor and delivery characteristics and risks of cranial ultrasonographic

abnormalities among very-low-birth-weight infants. Am J Obstet Gynecol 181:997–1006
22. Redline RW, Wilson-Costelo D, Borawski E, Fanaroff AA, Hack M 2000 The relationship between placental and other perinatal risk factors for neurologic impairment in very low birth weight children. Pediatr Res 47:721–726 | Article | PubMed |
23. Resch B, Vollaard E, Maurer U, Haas J, Rosegger H, Muller W 2000 Risk factors and determinants of neurodevelopmental outcome in cystic periventricular leucomalacia. Eur J Pediatr 159:663–670 | Article | PubMed | ChemPort |
24. Wu YW, Colford JM 2000 Chorioamnionitis as a risk factor for cerebral palsy: a meta-analysis. JAMA 284:1417–1424 | Article | PubMed | ChemPort |
25. Yoon BH, Romero R, Park JS, Kim CJ, Kim SH, Choi JH, Han TR 2000 Fetal exposure to an intra-amniotic inflammation and the development of cerebral palsy at the age of three years. Am J Obstet Gynecol 182:675–681 | Article | PubMed | ISI |
26. De Felice C, Toti P, Laurini RN, Stumpo M, Picciolini E, Todros T, Tanganelli P, Buonocore G, Bracci R 2001 Early neonatal brain injury in histologic chorioamnionitis. J Pediatr 138:101–104 | Article | PubMed | ChemPort |
27. Yoon BH, Romero R, Yang SH, Jun JK, Kim IO, Choi JH, Syn HC 1996 Interleukin-6 concentrations in umbilical cord plasma are elevated in neonates with white matter lesions associated with periventricular leukomalacia. Am J Obstet Gynecol 174:1433–1440 | Article | PubMed | ChemPort |
28. Yoon BH, Jun JK, Romero R, Park KH, Gomez R, Choi JH, Kim IO 1997 Amniotic fluid inflammatory cytokines (interleukin-6, interleukin-1β, and tumor necrosis factor-α), neontal brian white matter lesions, and cerebral palsy. Am J Obstet Gynecol 177:19–26 | Article | PubMed | ISI | ChemPort |
29. Grether JK, Nelson KB 1997 Maternal infection and cerebral palsy in infants of normal birth weight. JAMA 287:207–211
30. Nelson KB, Dambrosia JM, Grether JK, Phillips TM 1998 Neonatal cytokines and coagulation factors in children with cerebral palsy. Ann Neurol 44:665–675 | Article | PubMed | ISI | ChemPort |
31. Grether JK, Nelson KB, Dambrosia JM, Phillips TM 1999 Interferons and cerebral palsy. J Pediatr 134:324–332
32. Deguchi K, Mizuguchi M, Takashima S 1996 Immunohistochemical expression of tumor necrosis factor α in neonatal leukomalacia. Pediatr Neurol 14:13–16 | Article | PubMed | ISI | ChemPort |
33. Deguchi K, Oguchi K, Takashima S 1997 Characteristic neuropathology of leukomalacia in extremely low birth weight infants. Pediatr Neurol 16:296–300
34. Yoon BH, Romero R, Kim CJ, Koo JN, Choe G, Syn HC, Chi JG 1997 High expression of tumor necrosis factor-alpha and interleukin-6 in periventricular leukomalacia. Am J Obstet Gynecol 177:406–411 | PubMed |
35. Neurobiology of Periventricular Leukomalacia in the Premature Infant, Joseph J. Volpe, Pediatric Research Vol. 50, No. 5, 2001 , 0031-3998/01/5005-055
36. Rita C. Silveira,1 Renato S. Procianoy2,Ischemic brain damage in very low birth weight preterm newborn infants, 0021-7557/05/81-01-Supl/S23 Jornal de Pediatria Copyright 2005 by Sociedade Brasileira de Pediatria, REVIEW ARTICLE

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