PERIVENTRICULAR LEUKOMALACIA – DIAGNOSIS AND MORPHOPATHOLOGY

Marioara Boia[1,2], Aniko Manea[1,2], Iulia Andrei[2], Flavia Baderca[3], Roxana Folescu[4], Camelia Budisan[1]

Abstract

Periventricular leukomalacia (PVL) is a relatively frequent disease amongst premature newborns with severe hypoxic disorders at birth. It is the principal form of brain injury in the premature infant and the predominant pathologic finding underlying cerebral palsy. The studied contingent included a number of 12,548 preterm newborns admitted in our clinic over a period of 15 years. Our aim was to analyze the risk factors involved in the occurrence of the PVL, the neurological and clinical picture, imaging investigations and morphological findings. The risk factors found for periventricular leukomalacia were: Apgar score<7 (84.43%), the presence of meconium in the amniotic liquid, uterus-placentary lesions, long labor. In the majority of cases, 2 or more risk factors were present. The cystic formations appeared in the evolution of most cases (79.05%) in the hyperechogenic area. The persistence of the cystic formations (56.09%) and/or the presence of the echographical signs of the cerebral atrophy (32%) were correlated with the appearance of the neurological disorders.

Key words: neurological disorders, periventricular leukomalacia, premature, risk factors

Introduction

Periventricular leukomalacia (PVL) is a distinctive form of cerebral white matter injury, an ischemic necrosis of the white periventricular substance near the external angles of the lateral ventricles [1,2]. The ending branches of the main vessels are leading to this region and, therefore, make it more predisposed to ischemic necrosis.

By microangiographic techniques it was demonstrated that infarction is localized at the border between the afferent branches of middle cerebral artery and efferent branches of choroidal artery. The primary lesion is a coagulating necrosis; after 5-7 days the necrotized tissue phagocytosis begins and is finalized after approximately 2-3 weeks, leading to a cavity.

Material and method

The study took place in the Premature and Neonatology Clinic of the "Louis Turcanu" Children Hospital Timisoara over a period of 15 years (1999-2012). The degree of symptoms' intensity, the hospitalization period, the severity of distant sequels, all depend on the intensity of the initial lesion as well as on the dimension and persistency of the cyst. The studied contingent included a number of 12,548 preterm newborns admitted in our clinic in the aforementioned period, of which 312 with severe hypoxic disorders at birth, 72 of them satisfying the selection criteria: proper history, clinical characteristics and distinctive imaging exploration results.

Results and Discussions

PVL, profound infarction of the white substance near the external angles of the lateral ventricles, was found in 72 cases (23.07%). This high prevalence in premature newborns is in accordance with the specifications of medical literature; it is known that 80-90% of cases appear in premature infants [3, 4]. Also, the localization of the lesion was distinctive, at the border between afferent and efferent branches of the cerebral arteries, 3-10 mm from the ventricular wall. The aspect of the ailment included severe hypoxia, both in prenatal, perinatal and neonatal period, constantly:

- prenatal appearance of the affection in 45 cases: materno-fetal infections, utero-placentar disorders, hyperbilirubinemia, green amniotic fluid, membrane rupture over 72 hours, Apgar score <7;
- in 37 of the cases prenatal factors were associated with other impairments that influenced the neuropatological and clinical features: sepsis, repeated crisis of apnea, bradycardia, bronchopneumonia, Patent Ductus Arteriousus, pneumothorax, ADRS by surfactant deficiency.

The premature newborns included in this lot had clinically presented an intense neurological profile, including: severe hypotonia, repeated crisis of apnea, diminished archaic reflexes – especially in lower limbs, convulsions (see Table I).

The intensity and duration of the clinical signs were higher in cases of PVL associated with periventricular or intraventricular hemorrhage (especially in severe forms). An associated ultrasound hemorrhagic lession was found in 30 cases (42.00%), 13 of them with germinal matrix localization and 17 with intraventricular localization (Fig 1).

[1] Department of Neonatology; „Victor Babes" University of Medicine and Pharmacy Timisoara, Romania
[2] „Louis Turcanu" Children's Emergency Hospital Timisoara, Romania
[3] Department of Microscopic Morphology; „Victor Babes" University of Medicine and Pharmacy Timisoara, Romania
[4] Department of Anatomy and Embryology; „Victor Babes" University of Medicine and Pharmacy Timisoara, Romania
Email: marianaboia@yahoo.com, aniko180798@yahoo.com, dr_iulia@yahoo.com, falviabaderca@yahoo.com, roxanafolescu@yahoo.com, camelia_budisan@yahoo.com

Table I. Clinical signs identified in the premature newborns.

Clinical signs	cases	%
hypotonia	48	70
repeated crisis of apnea	60	84
diminution/abolition of archaic reflexes	62	86
hyperexcitability	22	30
convulsions	20	28
opisthotonus	18	24

Ultrasound diagnosis of PVL was based on the characteristics and the localization of the lesion: echoic large band laterally positioned to the anterior horns of the lateral ventricles and to the trigons of the lateral ventricles. The hyper echogenicity in the anterior portion of the lateral ventricles has a typical localization on the anterior-external side.

The ultrasound examination was performed weekly and monitored the following aspects of the hyper echogenicity: intensity, dimension, localization, outline, homogeneity, the relation with the ventricular system. The echoic intensity of the lesion is important in order to appreciate the severity and the prognosis, especially in cases in which the evolution was towards cystic formations:

- 33 of cases (45.83%) were easy forms which presented periventricular echogenicity with an intensity
- lower than that of the choroid plexus and dimensions smaller than those of the lateral ventricular trigon (Fig. 2);
- 12 cases (16.7%) were moderate forms which presented periventricular echogenicity with an intensity
- similar to that of the choroid plexus and approximately equal dimensions to those of the lateral ventricular trigon (Fig. 3);
- 17 cases (23.61%) were severe forms which presented periventricular echogenicity higher than that of
- the choroid plexus and dimensions bigger than those of the lateral ventricular trigon (Fig. 4,5).

The visualized cystic formations were diagnosed on base of ultrasonography characteristics: transonic masses with homogeneous contents, homogeneous echogenicity of the contents, thick walls (intense echoic), single in 32 cases and multiple in 28 cases (Fig. 6). As time of appearance (excepting the cystic formations found on the first examination) the first cysts were observed three weeks after establishing the echogenicity.

The echogenicity evolution was: resorption – 12 cases, cystic formations – 49 cases (Fig. 7). Positioning of the cysts:

- in the anterior region (external angle of the lateral ventricles) – 40 cases
- posterior region (posterior side of the lateral ventricles) – 10 cases
- in only 9 cases cystic formations were found along the entire border of the lateral ventricles (Fig 8).

The anterior – external positioning of the lesions to the anterior horns of the lateral ventricles was confirmed by findings in the literature [5]; these areas are known to be susceptible to perfusion pressure and decreased cerebral blood pressure and, therefore, prone to the emergence of specific leukomalacia lesions.

The dimensions of the cystic masses are important in order to establish the prognosis and the neurological alterations over time. The cysts had diameters between 3-20mm. Increasing size of the cysts were associated with increasing risk of cerebral palsy, with a cut-off value of 10 mm and all infants with cysts larger than 20 mm in diameter had cerebral palsy. The high echogenicity (moderate and severe forms of the disease) was followed by big cysts, commonly supernumerary (29 cases – 40.27%). The severe clinical picture found in these cases included: recurrent convulsive syndrome (32 cases), severe hypotonia (12 cases), spasticity of the inferior limbs (16 cases) and opisthotonus (20 cases). Generally, the average periods of persistence were: echogenicity between 1-3 weeks and cystic formations 3 week to 3 months. In severe forms, transonic lesions and ventriculomegaly persisted until the age of 8-10 months.

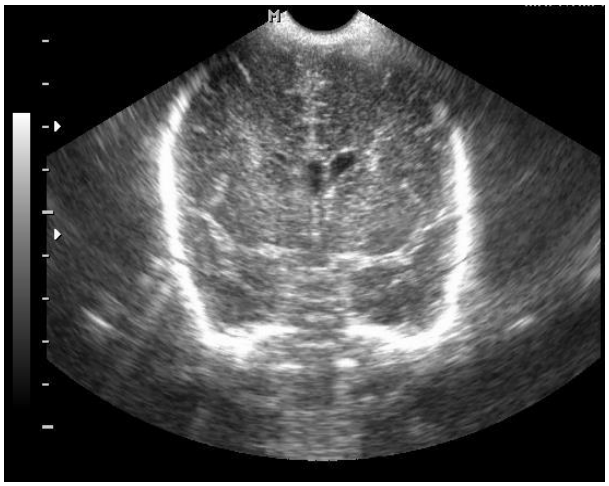

Fig. 2. LPV mild form

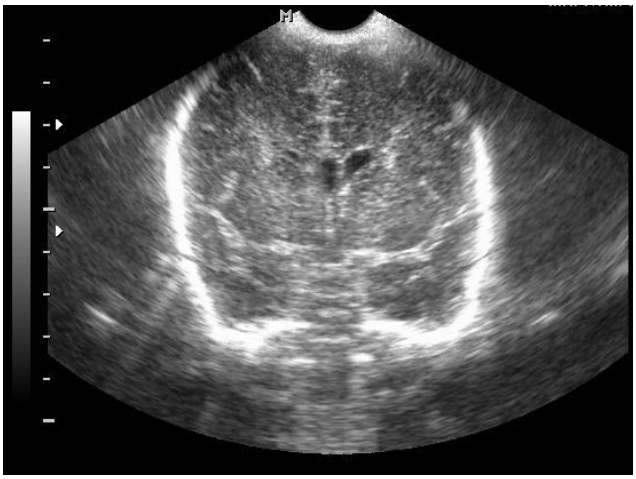

Fig. 2. LPV mild form

In the cases where the cystic masses persisted we had visualized the following aspects:
- cysts – 4 cases
- cysts accompanied by ventriculomegaly – 8 cases
- ventriculomegaly – cerebral atrophy – 23 cases

The diagnosis of cerebral atrophy was based on ventriculomegaly accompanied by the increase of the interhemispheric space and the increase of the distance between the gyrus in the anterior region.

The rupture of the septum between the cysts and the lateral ventricles produced the evolution towards ventriculomegaly. The cases in which the persistence of cystic formations was associated with cerebral atrophy, the following severe neurological modifications were found:
- recurrent convulsions – 23 cases;
- spastic dyplegia – 13 cases;
- sight disorders – 5 cases;
- speaking disorders – 4 cases;
- hearing disorders – 3 cases;
- mental retardation – 32 cases;
- minimum cerebral dysfunction – 14 cases.

The specific medical literature data referring to neurological disorders after PVL are varied. A study done by Pidcock and collabs on a lot of 127 premature newborns renders that there is a significant correlation between the appearance, dimension and localization of the cysts and the development of mental disorders. From the studied cases, 42 did not show evidence of cysts in evolution and had a good neurological outcome, unlike the 25 cases with moderate cystic lesions and the 20 cases with severe cystic lesions, which developed neurological disorders in 32% and 90% of the cases, respectively.

The association between PVL and periventricular and intraventricular hemorrhage is discussed extensively in the medical literature; most authors have observed associations in 28-59% of the cases [4,6]. In the lot that we studied there were hemorrhagic lesions (42%):
- in 13 cases subependymal hemorrhages;
- in 17 cases intraventricular hemorrhages.

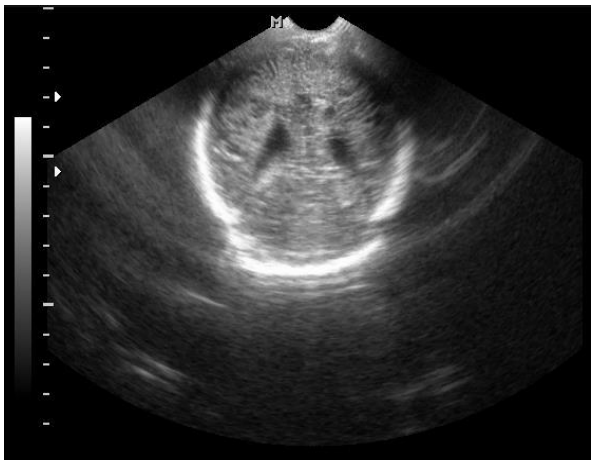

Fig. 3. LPV moderate form

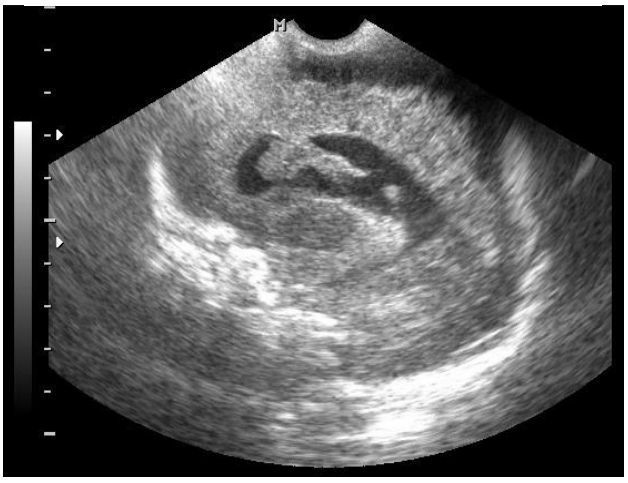

Fig. 4. LPV severe form

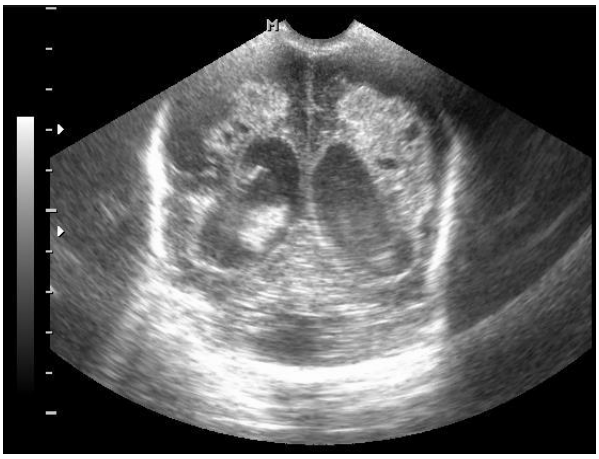

Fig. 5. LPV severe form

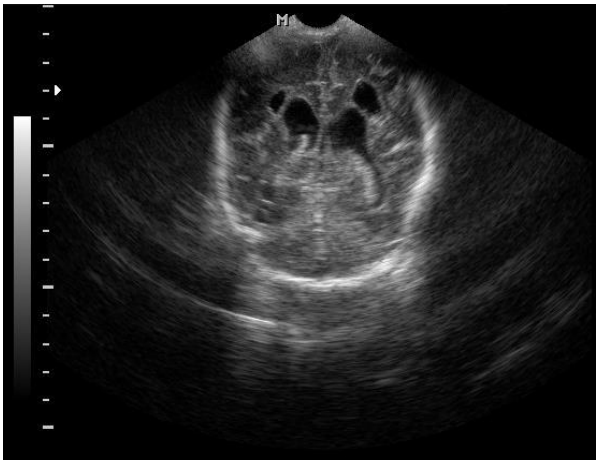

Fig 6. LPV cystic form

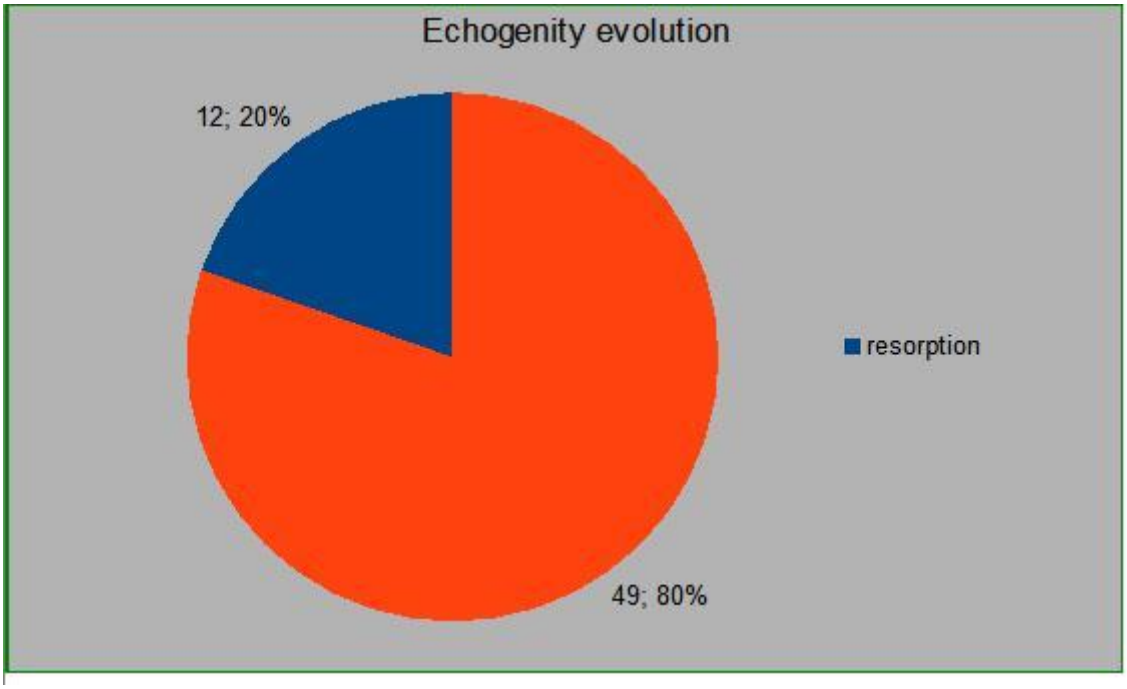

Fig. 7. Echogenicity evolution

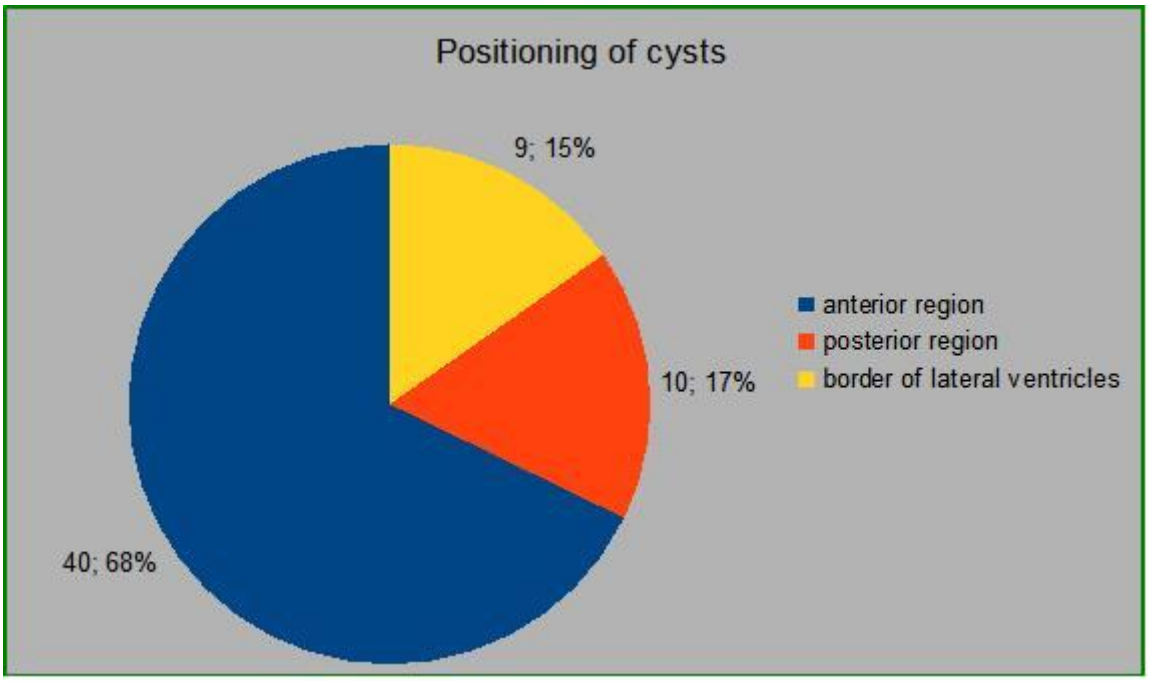

Fig. 8. Positioning of cysts

The distinction between the hemorrhagic and non-hemorrhagic PVL was difficult to prove based on ultrasonography, because the echogenicity has the same characteristics. The presence of hyperechoic lesions inside the non-dilated ventricles and in the cerebral intraventricular parenchyma (laterally from the anterior region, the posterior region and along the ventricular wall) oriented the diagnosis towards PVL associated with an intraventricular hemorrhage. In the presence of big lesions in the cerebral parenchyma, accompanied by hyperechogenicity inside the lateral, dilated ventricles, the distinction between the hemorrhagic and non-hemorrhagic forms was very difficult, as these forms represent the severe forms of intraventricular hemorrhage (IV degree).

Macroscopy:

- necrotic foci usually within 15 mm of ventricular wall, 2-6 mm in diameter, with the following common locations:
  - anterior to the frontal horn,
- lateral corners of the lateral ventricles at level of foramen of Monroe
- lateral regions of the trigon and occipital horn (including optic radiations)
- acute foci of coagulation necrosis not visible in gross;
- organized foci seen as "White spots" due to lipid-laden macrophages;
- cavitation follows, then collapse into a glial scar (or remains cystic if severe);
- long-standing damage shows thinned white matter and corpus callosum, and ventriculomegaly [7].

Histopathology:

- coagulation necrosis within 24 hours of insult (dissolution of all cell types, hypereosinophilia, nuclear pyknosis, acutely necrotic, swollen axons - spheroids - confirmed with human beta-amyloid precursor protein immunostaining;
- within a week, organization of necrosis with infiltrating macrophages and reactive astrocytes in the margin;
- in a few weeks, cavitation into periventricular cysts, collapse of cysts into glial scars with lipid-laden macrophages and mineralized axons, gliosis preferentially in deep white matter compared to intragyral white matter;
- PVL usually coexists with other perinatal pathologies including grey matter lesions;
- long-term consequence of delayed myelination (from loss of developing oligodendrocytes or from deprivation of afferent terminals from underlying white matter lesion) [7].

Joseph J Volpe [8] argued in 2009 that brain abnormality in the premature infant is unlikely to consist of a straightforward addition of destructive non-hemorrhagic and hemorrhagic lesions, such as PVL and, less commonly, GMH-IVH (germinal matrix hemorrhage/intraventricular hemorrhage) with perfusion harmonic imaging. Recent insights into the full spectrum of the encephalopathy of prematurity and into the remarkable series of developmental events that occur in the brain during this period indicate a complex amalgam of destructive and developmental mechanisms. Although further clarification of this amalgam is needed, the general principle that in the premature period brain abnormality involves destructive and developmental mechanisms seems established.

Saraid S. Billiards [9] conducted a study in 2008 on myelin abnormalities without oligodendrocyte loss in PVL, indicating that myelin abnormalities and, in some instances, loss of preoligodendrocyte lineage cell processes occur in PVL without a loss of oligodendrocyte lineage cell density. Their findings raise the intriguing possibility that a hyper acute loss of preoligodendrocyte lineages is replenished by proliferation and migration of oligodendrocyte lineage progenitors from subventricular zones, a process that may not always be adequate and thereby result in neurological disability. They also suggest that the deficits in myelination are caused by loss of oligodendrocyte lineage - cytoplasmic processes and defective myelin basic protein trafficking, perhaps secondary to process loss. The study highlights the need to analyze in greater depth the potential factors critical for oligodendrocyte lineage proliferation, migration and repair for optimal myelination in long-term survivors of PVL as crucial leads for the development of successful therapeutic strategies in PVL.

Conclusions

1. The moment of action upon the CNS was both in the ante- and intranatal period, and in the neonatal period. The risk factors were: Apgar score<7 (84.43%), the presence of meconium in the amniotic liquid, uterus-placentary lesions, long labor. In the majority of cases, 2 or more risk factors were present.

2. The cystic formations appeared in the evolution of most cases (79.05%) in the hyperechogenic area. Big cysts, usually multiple, followed the big echogenyties. In this situation, in 48.78% of the cystic formations, the clinical picture was severe.

3. The evolution towards cerebral atrophy (32%) presented the following aspects: growth of the interhemispheric space, the growth of the distance between the gyruses, the accentuated hyperechogenity of these spaces, especially in the anterior region and the slow ventriculomegaly.

4. The persistence of the cystic formations (56.09%) and/or the presence of the echographical signs of the cerebral atrophy (32%) was correlated with the appearance of the neurological disorders: convulsive recurrent syndrome (32%), infantile spastic diplegia (18%), sight disorders (8%), hearing disorders (6%) and neuro-psychomotor retardation (44%).

5. In this study we tried to present current concepts on PVL pathogenesis and underline evidence of an inflammatory pathogenic component to this illness, resulting from either hypoxic-ischemic injury or infection. These findings render the basis for clinical approaches targeted at protecting the premature brain from inflammatory alteration, which may prove beneficial for treating PVL, if identified early in pathogenesis.

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Correspondence to:

Camelia Budisan
Department of Neonatology
„Victor Babes" University of Medicine and Pharmacy"
2A E. Murgu Sq. 300041 Timisoara, Romania
Tel. +40724822665
E-mail: camelia_budisan@yahoo.com