Coll. Antropol. **32** (2008) Suppl. 1: 143–147
Original Scientific Paper

Neurodevelopmental Outcome in Children with Periventricular Leukomalacia

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A B S T R A C T

The purpose of this study was to question the correlation of different grades of periventricular leukomalacia (PVL) and subsequent neurodevelopmental outcome. In a prospective study we followed 52 preterm infants. Infants were divided into three groups according to their cranial ultrasound findings of PVL (De Vries classification). Seventeen children had PVL 1, 20 children had PVL 2, and 15 children had PVL 3. All 15 (100%) children with PVL 3 developed cerebral palsy with additional visual perceptual dysfunctions and epilepsy. Children with PVL 1 had high frequency of mild neuromotoric delay and visual impairment. PVL 2 and 3 have great predictive value for subsequent severe neurodevelopmental disorder which refers to cerebral palsy, different cognitive deficits, vision impairment and epilepsy. We have determined that due to high frequency of visual impairment and epilepsy we need to include neurophysiologic examinations very early in children with PVL lesions.

Key words: *periventricular leukomalacia, neurodevelopment, epilepsy, cerebral palsy, visual impairment*

Introduction

Brain injury in the premature infants consists of multiple lesions, principally germinal matrix-intraventricular haemorrhage and periventricular leukomalacia (PVL)[1,2]. The last one now appears to be the most important determinant of the neurological morbidity observed in survivors of birth weight <1500 g.[3] PVL refers to necrosis of white matter adjacent to the external angles of the lateral ventricles and is regarded as the principal ischemic lesion of the premature infant. Incidence of PVL ranged from 4–15%[3,4,5]. Part of this wide variation in incidence relates to the sonografic definition used by various authors to describe the condition. The most sensitive method of visualisation of PVL is magnetic resonance imaging (MRI)[6]. The pathologic features of PVL include focal periventricular as well as more diffuse cerebral white matter involvement[4]. The focal periventricular necrosis is distributed commonly at the level of the occipital radiation at the trigone of the lateral ventricles, and at the level of the cerebral white matter around the foramen Monroe[1,4]. The diffuse cerebral white matter necrosis less frequently undergoes cystic change and is more commonly noted in the smaller premature infant requiring prolonged ventilator support[1,4]. Although the pathogenesis of PVL is complex and likely multifactor, principle contributors include vascular factors which markedly increase the risk for ischemia during periods of systemic hypotension and the intrinsic vulnerability of the oligodendrocyte to neurotoxic factors such as free radicals or cytokines[1,3,4].

This study is based on pathogenetic and structural changes of the brain that are displayed with early ultrasound scans and control MRI scans, as well with the evaluation of the neurodevelopmental outcome in children with PVL.

Materials and methods

In a prospective study we have followed 52 preterm infants, gestational age <37 weeks who have been born in Gynaecology and Obstetrics Clinic, University Hospital of Split and in all we have diagnosed periventricular leukomalacia by ultrasound examination. We performed in all preterms in the first 3 days cranial ultrasound

Received for publication June 1, 2007.

scanning with ALOKA SSD 1700 mechanical sector scanner with a multifrequency transducer (from 5 to 7,5 MHz crystals). Control ultrasound was performed on the 7th, 15th, 21st day and in the 2nd, 4th month.

Classification of PVL based on cranial ultrasound findings[4]:

1. PVL 1 – periventricular echodense area, present 14 days or more
2. PVL 2 – periventricular echodense areas evolving into localized front parietal cysts
3. PVL 3 – periventricular echodense areas evolving into multiple cysts in the parietal-occipital white matter

MRI was performed (Magneton Impact Expert 1.0 T) in all of the examinees who had an indication according to their clinical findings. The final estimation of the neurodevelopmental outcome in these newborns was at their age of four.

In multidisciplinary neurodevelopmental observation included the following: estimation of motoric functions, intellectual functions, behavioural disorders, examination of vision functions and supervising of EEG recording changes.

The final estimation of neuromotoric outcome was marked as normal outcome, minimal neuromotoric dysfunction (MND) or cerebral palsy[7]. Psychology testing was performed in order to determine the level of intellectual functions. We used Wechsler's intelligence test and also we observed separately verbal and nonverbal abilities[8]. Assessment of the above mentioned intellectual abilities was performed by the following categories: above average intellectual abilities (IQ 110–119), average intellectual abilities (IQ 90–109), below average intellectual abilities (IQ 80–89), borders (70–79), mental retardation (69 and lower). For perceptive abilities, we used Bender-Santucci and Bender-Gestalt tests[9,10]. Assessment of language and speech functions was performed by speech pathologist according to Reynell's test[11,12]. Every infant was examined by an ophthalmologist. Eventual impairments were categorized as – there is or there isn't impairment. Epilepsy was categorized by International Classification of Epilepsy[13].

For data processing we used Hi-quadrant with significance level $p=0.05$.

Results

We followed 52 preterm infats, gestational age <37 weeks with diagnosed PVL. According to classification 17 children had PVL 1 (Figure 1), twenty had PLV 2 (Figure 2), and 15 children had PVL 3 (Figure 3 and 4).

Frequency of different grades of PVL according to gestational age

There is statistically significant frequency of PVL 1 and PVL 2 between 30 and 35 weeks of gestation (Figure 5).

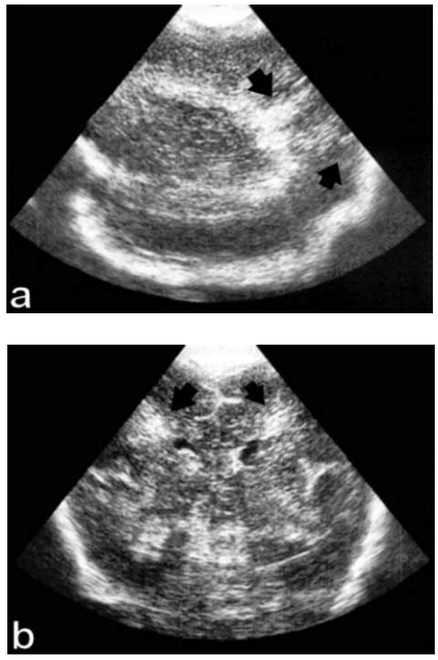

Fig. 1. a) Parasagittal ultrasound scan from a preterm infant showing increased echogenicity within periventricular white matter (black arrows) without evolution of cyst formations (PVL 1). b) Frontal ultrasound scan showing hiperechogenicity also (black arrows).

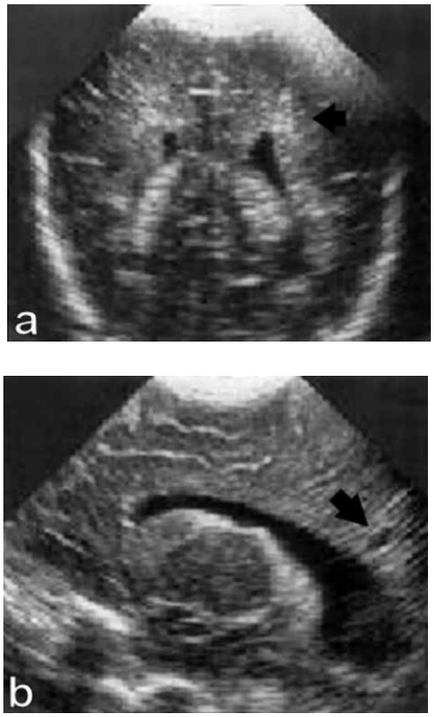

Fig. 2. a) Frontal ultrasound scan showing evolution of cystic formations in the brain of preterm infant with PVL 2 (black arrow). b) Parasagittal ultrasound scan showing hiperechogenicity and evolution in cyst (black arrow).

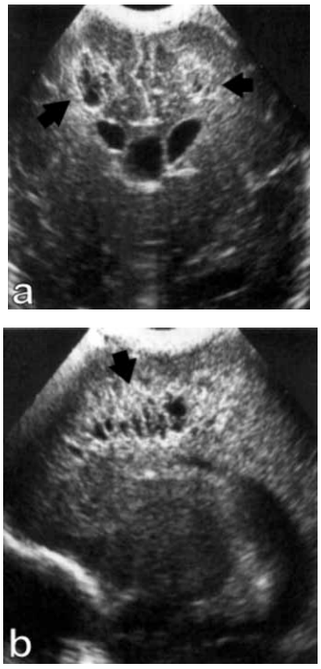

Fig. 3. a) Frontal ultrasound scan of preterm infant at 6 weeks of age with PVL 3. Note the appearance of cystic formations (black arrows). b) Parasagittal ultrasound scan showing small cysts frontoparietal (black arrow).

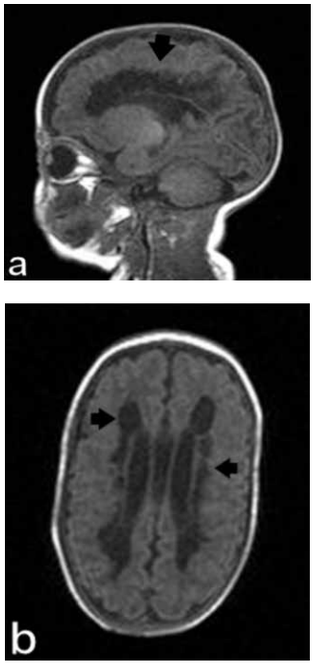

Fig. 4. a) Magnetic resonance imaging scan of preterm infant at 4 months of age with cystic PVL and subsequent evolution of epileptic encelopathy. Note the appearance of cystic formations (black arrow). b) Magnetic resonance imaging scan of the same preterm infant showing cystic formations and ventriculomegaly (black arrows).

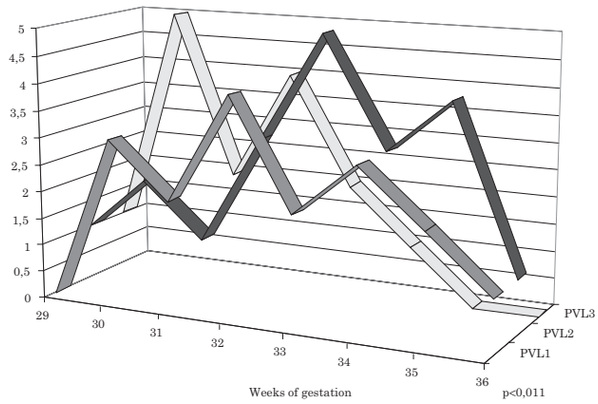

Fig. 5. Frequency of different grades of periventricular leukomalacia according to the weeks of gestation

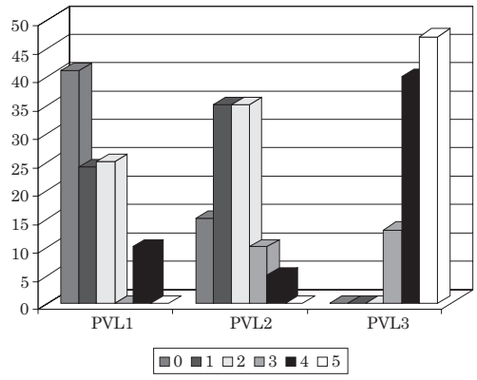

Fig. 6. Number of impairments according to different grades of periventricular leukomalacia (0-psychomotoric development, 1-minimal neuromotoric dysfunction, 2-cognitive impairments, 3-vision dysfunctions, 4-cerebral palsy, 5-epilepsy)

Neurodevelopmental outcome according to different grades of PVL

All 15 children with PVL 3 had disrupted neurodevelopmental outcome. In children with diagnosed PVL 2, 80% had different neurodevelopmental disorder, whereas in children with PVL 1, normal psychomotor development had 7 children (41.2%). There is statistically significant frequency of neurodevelopmental impairments in children with different grades of PVL, especially regarding PVL 3 ($p<0.011$).

Cognitive deficits according to different grades of PVL

In the group of children with PVL 1 only 3 of them were demonstrating deficit in cognitive development whereas 14 of them had normal cognitive development. Out of 20 children with PVL 2, 10 demonstrated different grade of cognitive deficit whereas all 15 children with PVL 3 had mental retardation. There is statistically significant frequency of cognitive deficits in children with PVL 3 ($p<0.001$).

Language dysfunctions

All children with PVL 3 had language dysfunctions, whereas in children with PVL 2 16 (80%) of them had normal language development. In the group of children with PVL 1 only 3 (15%) of them had disrupted language development.

Vision impairment

Vision imparment was present in all the children with statistically significant frequency in children with PVL 3.

Epilepsy

Only one child in the group of children with PVL 1 and PVL 2 developed epilepsy whereas 80% of children with PVL 3 developed epilepsy. Therefore, there is statistically significant frequency of epilepsy in children with PVL 3 ($p<0.007$).

Minimal neuromotoric dysfunction

This neuromotoric disorder developed 35% of children with PVL1 and 20% of children with PVL 2 whereas children with PVL 3 did not develop this kind of disorder. Therefore, minimal neuromotoric dysfunction was more present in the group of children with PVL 1 and PVL 2 than in group of children with PVL 3 ($p<0.007$).

Cerebral palsy

All 15 children with PVL 3 (100%) developed cerebral palsy while in the group of children with PVL 2 only 10 (50%) of them developed cerebral palsy. In the group of children with PVL 1 only 2 developed cerebral palsy. Frequency of cerebral palsy is statistically significant in children with PVL 3 ($p<0.001$).

Number of impairments according to different grades of PVL

Analysing groups of children with different grades of PVL we can notice that 40% of children with PVL 1 had normal psychomotor development. Additional impairment such as cerebral palsy, visual perceptive problems and minimal neuromotoric dysfunction were also present, however in statistically insignificant number. In children with PVL 2, 18% of them had normal psychomotor development while 35% had symptoms of minimal neuromotoric dysfunction with mild deviation of cognitive development. Children with PVL 3 had cerebral palsy, cognitive and visual impairments (Figure 6).

Discussion

Periventricular white matter injury, specifically cystic periventricular leukomalacia, contributes significantly to neonatal mortality and long-term neurodevelopmental deficits in the premature infant[14]. The most commonly described long-term motor sequelae of PVL is spastic diplegia. This is consistent with the anatomical course of the corticospinal tracts that traverse from the motor cortex in close proximity to the periventricular region into internal capsule[1,3].

The genesis of the cognitive deficits with PVL remains unclear. It has been speculated that the injury may secondarily affect neuronal cortical organization due to injury to subplate neurons or late migrating astrocytes. Kostovic and al. described in their study transient foetal zones important for the development of neuronal connections and interpretation of neurological sequelae after PVL[15,16.] The periods when transient foetal zones are present and periventricular crossroads contain abundant extracellular matrix represent a prospective developmental window for the vulnerability of foetal cortical circuitry, and developmental fate of these zones can be successfully traced in vivo by modern neuroimaging methods [15,16.] The disorganization of extracellular matrix and the death of cells that produce axonal guidance molecules is likely a consequence of both focal and diffuse PVL lesions. Such lesions lead to variable combinations of motor, sensory, and cognitive deficits because they simultaneously damage projection, associative and commissural axons that intersect in multiple and topographically defined periventricular crossroads[15–17].

In a prospective study we have determined that the frequency of PVL, according to gestational age, is around 30 to 35 weeks of gestation. Neurodevelopmental outcome in children with different grades of PVL is different. The worst outcomes have children with PVL 3. The deep focal necrotic lesions of PVL 3 occur in areas that are considered arterial end zones. These arterial end zones are essentially »distal fields«, and, as such, these periventricular zones would be accepted to be most susceptible to a fall in perfusion pressure and cerebral blood flow[1]. All children with PVL 3 have developed cerebral palsy because the most common site in brain that is afflicted is corticospinal tract. Although, neurodevelopmental outcome in children with PVL 2 is much better than in children with PVL 3, they also show some deviations in cognitive functions as well as in neuromotoric development. High prevalence of epilepsy in children with different grades of PVL, especially those with PVL 3, was noticed in our study. That is because subsequently after periventricular white matter injury comes secondarily to disturbance in development of cortex. This discovery suggests that we should include neurophysiologic examination[18], especially EEG[19], in future prospective follow up. Therefore, we could act protective and we could also diagnose early epileptic seizures characteristic for this age. Vision impairment was present in all three groups of children with PVL, mainly in children with diagnosed PVL 3. This is due to the contiguity between the site of PVL and the optic radiations[20]. Cerebral damage in premature infants can also involve other visual pathways structures (e.g. lateral geniculate body, calcarine cortex and visual associative areas) and gives rise to various disorders, ranging from reduced visual acuity/visual field and oculomotor incoordination to complex visual-cognitive disorders (visual perceptual impairment (VPI)). The term CVI covers all these disorders. Of the various manifestations of CVI, VPI emerges as one of the most frequent in PVL subjects[21,22].

Conclusions

Children with PVL 3 have the worst outcome with statistically significant frequency of cerebral palsy, cognitive deficits, vision dysfunctions and epilepsy. Children with PVL 1 had statistically significant frequency of minimal neuromotoric dysfunction and vision impairments. In all 3 groups of children there is statistically significant presentation of vision impairments which demands an earlier control of vision. Statistically significant frequency of epilepsy indicates that EEG recording should be done very early in follow-up of children with PVL.

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NEURORAZVOJNI ISHOD U DJECE S PERIVENTRIKULARNOM LEUKOMALACIJOM

SAŽETAK

Cilj rada je ispitati korelaciju različitih stupnjeva PVL i kasnijeg neurorazvojnog ishoda. Prospektivno je praćeno 52 prijevremeno rođene djece. Ispitanici su podijeljeni u tri skupine prema UZV nalazu periventrikularne leukomalacije (stupnjevanje prema deVries-u). PVL 1 stupnja imalo je 17 djece, 20 djece PVL 2 stupnja te PVL 3 stupnja 15 djece. Svih 15 (100%) ispitanika sa PVL 3 razvili su cerebralnu paralizu sa dodatnim oštećenjem vida, sluha i pojavom epilepsije. Djeca sa PVL 1 imali su učestalost blažih neuromotornih odstupanja i oštećenja vida. Djeca sa PVL 2 i PVL 3 imaju veliku vjerovatnost za kasnija neurorazvojna odstupanja poput cerebralne paralize, različitih kognitivnih poremećaja, oštećenja vida i epilepsije. Učestalost oštećenja vida i razvoja epilepsije zahtijeva rano uvođenje neurofizioloških pretraga u djece s PVL oštećenjima.