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Original Scientific Paper

West Syndrome with Periventricular Leukomalacia: Ten-year Clinical Study

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ABSTRACT

The aim of the study was to evaluate magnetic resonance imaging (MRI) findings in infants with periventricular leukomalacia (PVL) and West syndrome (WS) and determine the neurodevelopmental outcome in children with West syndrome and PVL. Ultrasound and brain MRI were performed in 37 infants with recognized PVL. PVL was categorized according to De Vries, whereas West syndrome was categorized according to International League Against Epilepsy 1989. West syndrome in our patients developed during the first 2 years of life. The most common interictal abnormality was hypsarrhythmia. All, except two patients had delayed development and various degrees of mental retardation.The most characteristic neuroimaging findings were major reduction in cerebral cortical gray matter volume, reduction in the volume of brain myelin, and delayed myelination. These findings may explain the anatomical association between the West syndrome onset and PVL and intellectual and cognitive deficit in premature infants with PVL.

Key words: *newborns, West syndrome, periventricular leukomalacia, MRI*

Introduction

West syndrome (WS) is an age-dependent epileptic encephalopathy characterized by a clinical-electrical triad of epileptic spasms, arrest of psychomotor development, and hypsarrhythmia, although the second feature may be absent. It is a multi-etiological disorder considered to be a non-specific response of the immature brain to a variety of brain insults. Due to the development of investigative techniques, the number of causes or etiological factors associated with this syndrome is increasing[1].

West syndrome is caused by a large variety of conditions, which are usually categorized into prenatal, perinatal, and postnatal, depending on the time of the cerebral insult[2]. Today we are faced with an increasing proportion of prenatal causes of West syndrome due to an increased proportion of very low-birth weight infants and periventricular leukomalacia (PVL). Also, new neuroimaging techniques allow us to identify more possible causes today than before. Among various etiological factors, perinatal ones are the most important because they are relatively frequent and potentially preventable[1].

In the International Classification of Epilepsies and Epileptic Syndromes[3], West syndrome is classified according to its etiology into symptomatic and cryptogenic. Symptomatic form is caused by a known or suspected disorder of the central nervous system. Cryptogenic forms are presumed to be symptomatic, but their etiology is not known. The third form, idiopathic form, which has no underlying cause other than a possible hereditary predisposition, is not recognized in the current International Classification.

PVL is a most common substrate of perinatal brain injury in the premature infant, resulting in cerebral palsy and cognitive or attention deficit[4,5]. It consists of two components – focal necrosis with the loss of all cellular elements deep in the periventricular white matter and less severe, but more diffuse, white matter involvement characterized primarily by injury to glial cells presumed to be oligodendroglial precursors[6].

Our understanding of the effects of PVL on subsequent cerebral development has been limited, but quali-

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tative evidence of a subsequent impairment in myelination has been obtained by conventional imaging studies. Subtle cortical injury overlying periventricular leukomalacia is in the focus of current interest as a possible substrate for the cognitive difficulties observed in patients with cerebral palsy[7].

Although the relationship between West syndrome and term hypoxic-ischemic encephalopathy and intraventricular hemorrhage has been well described, only a few studies investigated the relationship between West syndrome and PVL[8–10].

The aim of this study was to determine the association between West syndrome and PVL according to magnetic resonance imaging (MRI) findings in patients with PVL and West syndrome.

Subjects and Methods

Subjects

The study included 37 premature infants born at 27–32 weeks of gestation and weighing 850–2500 g at Split University Hospital. Written informed consent was obtained from all parents.

Cranial ultrasonography

Cranial ultrasonography was performed with a 5- and 7.5-MHz transducers (Aloka SSD 1700) through the anterior fontanelle in infants with recognized PVL. PVL was classified according to De Vries into three types. PVL type I was defined as abnormally increased echodensities persisting for >14 days in the periventricular white matter without an ipsilateral germinal matrix/intraventricular hemorrhage (GMH/IVH); PVL type II was defined as persisting echo densities and ventricular dilation >5 mm; and PVL type III or cystic PVL was defined as cystic lesions within the periventricular white matter not preceded by hemorrhagic parenchymal infarction at the same site.

Cranial ultrasonography was performed within the first 48 hours of life, at 5–7 days of age, at 4–6 weeks of age, than at 3 and 6 months of age.

Magnetic resonance imaging protocol

MRI scanning was performed in infants early after the beginning of seizures with a Magneton Impact Expert 1.0 T (Siemens, Erlangen, Germany) in sagital, transversal, and coronal sections, SE (TR/TE 600/15), TSE (TR/TE 3500/90) and Flair (TR/TE 6500/105).

The diagnosis of PVL was based on the following MRI abnormalities:

1. Abnormally increased signal intensity of periventricular white matter on T2-weighted imaging and fluid-attenuated inversion recovery (FLAIR), most commonly observed bilaterally in the trigone regions of the lateral ventricles (Figure 1).
2. Loss of periventricular white matter in the regions of abnormal signal intensity and ventricular enlargement adjacent to the regions of the lateral ventricles (Figure 2).
3. Focal and extensive cystic changes in the white matter (Figure 3 and 4).

We have analyzed three features of gray matter, as adapted from the previously published system[10] in Table 1.

West syndrome was classified according to the International League Against Epilepsy 1989[3]. West syndrome was diagnosed when patients had a series of spasms and hypsarrhythmia indicated on interictal electroencephalography.

Neurodevelopment evaluation

Between 12 and 18 months of corrected age, infants underwent a pediatric physical examination by an experienced neurologist and/or a developmental examination based on the observational data from the parents and examination with the Denver Developmental Screening tool. Infants were classified as exhibiting severe disability if they had clinical evidence of severe abnormality on neurologic motor examination (e.g., pronounced spasticity, weakness, and developmental delay of >6 months), moderate disability if they had clinical evidence of moderate abnormality on neurologic motor examination and developmental delay between 4 and 6 months, or mild disability if they had only mild spasticity and/or motor deficit and developmental delay of 2–4 months.

A developmental psychologist measured cognitive outcome using the Mental Development Index (Bayley Scales Infant Development II)[11]. A score between 85 and 114 was considered to be within normal limits, a score between 75 and 84 signified mildly delayed performance, a score between 65 and 74 indicated moderately delayed performance, and a score 64 or lower showed a significantly delayed performance.

TABLE 1
THREE ITEMS OF GRAY MATTER ASSESSED DURING THE MRI EVALUATION

Subarachnoid space	Cortical gray matter signal abnormality	Gyral maturation
Normal	Nil	Normal for age
Mild enlargement 5–10 mm	Focal (one region only	Delay 2–4 weeks
Severe enlargment	Extensive > regions	Delay > 4 weeks

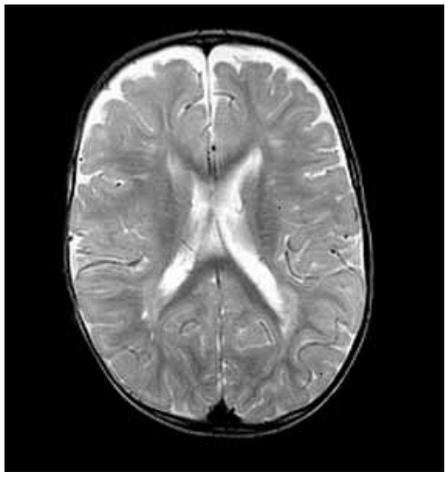

Fig. 1. Periventricular leukomalacia type I.

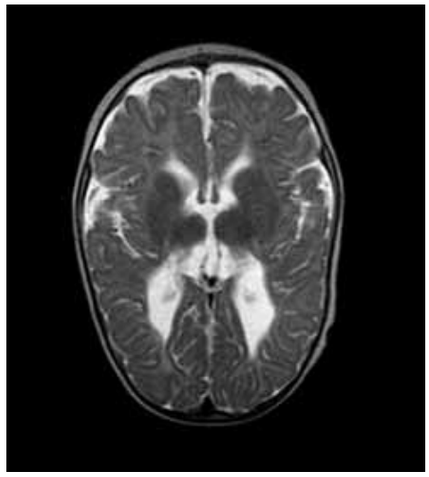

Fig. 2. Periventricular leukomalacia type II.

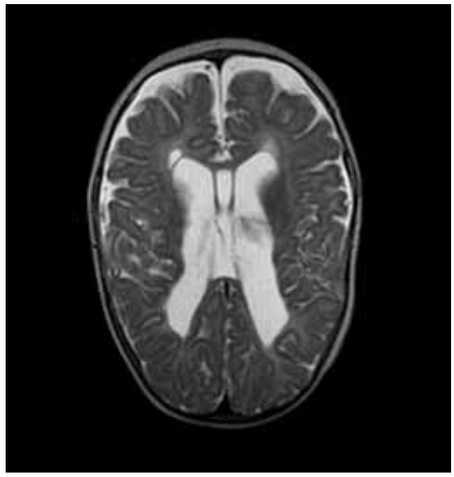

Fig. 3. Periventricular leukomalacia type III.

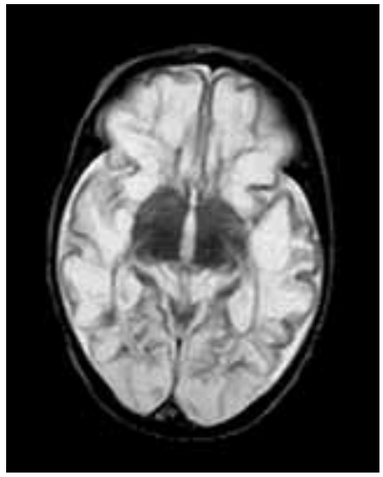

Fig. 4. Periventricular leukomalacia type III (extensive cystic change in the white matter).

Results

During the study period from 1995 to 2005, 37 infants were diagnosed with West syndrome caused by PVL.

Clinical features

The first series of spasms in all infants was noticed in the first year of life. Five of 37 infants had seizures before the fourth month of life. The youngest infant had its first seizures in the third week of life, but the final diagnosis was established only in the fourth month of life. Median age at onset was 7 months (range, 1–11 months) and male infants predominated (1.5:1). Flexor spasms were present in 24 infants, extensor spasms in 3 infants, and mixed spasms in 10 of 37 infants.

EEG was performed at median age of 7 months of life (range, 3–12 months). Hipsarrhythmia (Figure 5) was found in 23 and modified hipsarrhythmia (Figure 6) in 12 of 37 infants. In the remaining two infants, burst suppression pattern (Figure 7) was observed in one and generalized/focal spike and wave discharges (Figure 8) in the other.

Neuroimaging findings

Cranial ultrasonography showed PVL I in 2 infants, PVL II in 10, and PVL III in 21 of 37 infants. PVL with GMH/IVH was found in 4 infants.

MRI was peformed in most infants at the time when seizures were first noticed, but in 7 infants it was performed later.

In two infants with PVL I, MRI revealed periventricular gliosis in peritrigonal regions with a mild reduction in white matter volume and mild enlargement of subarachnoid space.

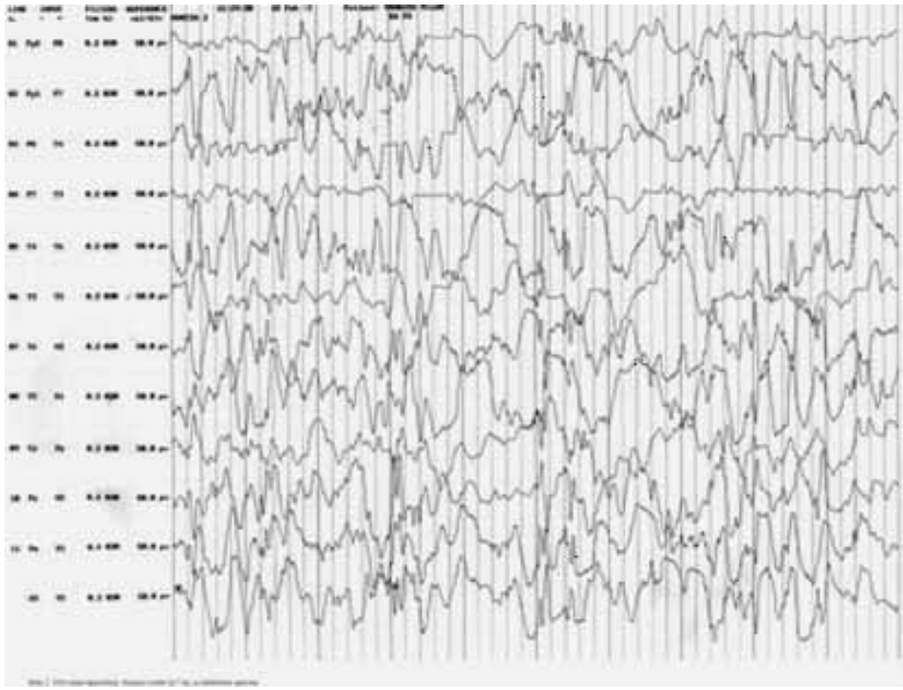

Fig. 5. Hipsarrhythmia.

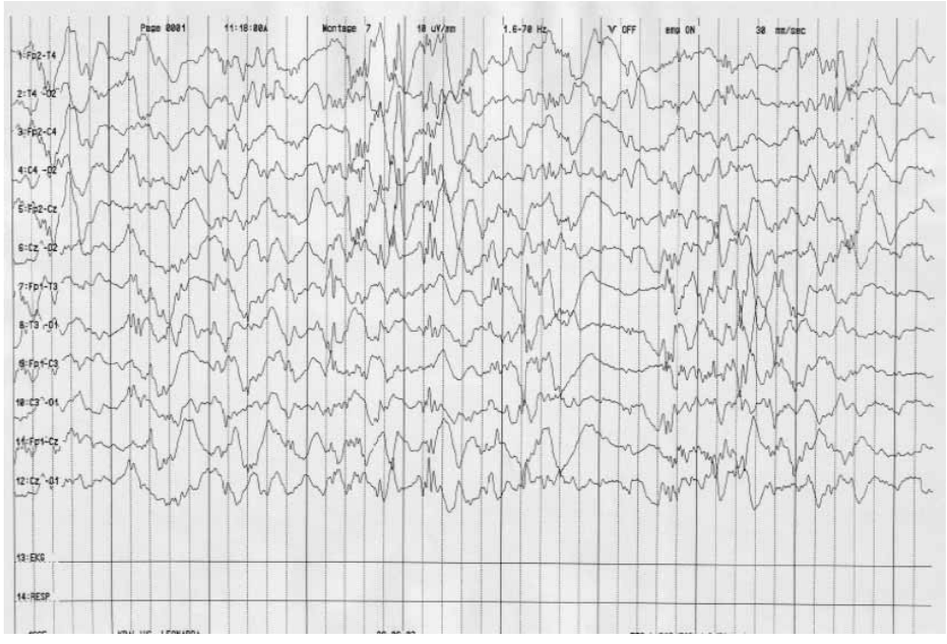

Fig. 6. Modified hipsarrhythmia.

In 10 infants with PVL II, MRI showed periventricular gliosis in peritrigonal regions, moderate loss in white matter volume, and moderate dilatation of lateral ventricles. Myelination was delayed and corpus callosum was partially thinning. Subarachnoidal space was mildly enlarged and cortical gray matter signal was abnormal in one region only.

In 21 infants with PVL III and 4 infants with PVL and GMH/IVH, the white matter signal was quite abnormal with diffuse volume reduction and extensive cystic changes in white matter. MRI showed a pronounced thinning of the corpus callosum and impaired myelination. Subarachnoid space was severely enlarged and cortical gray matter signal was abnormal in more than two re-

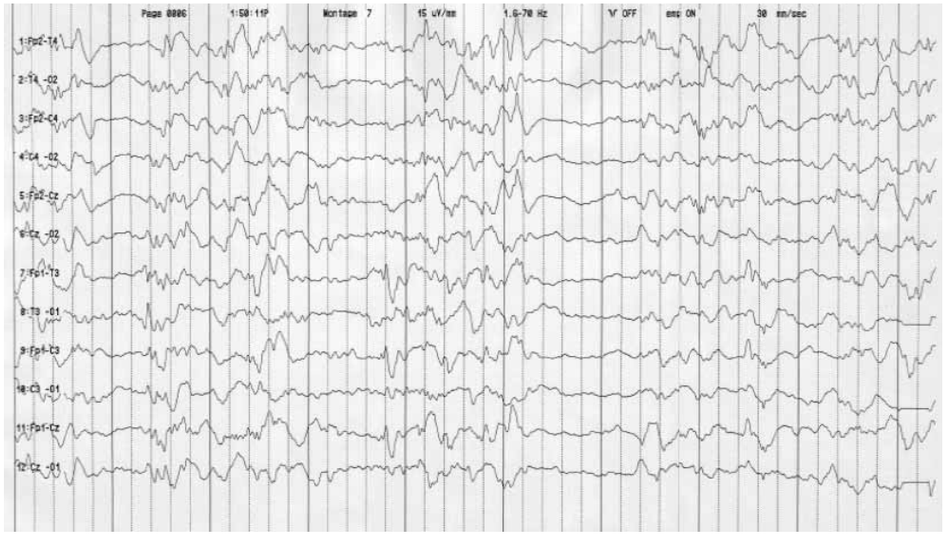

Fig. 7. Burst suppression pattern.

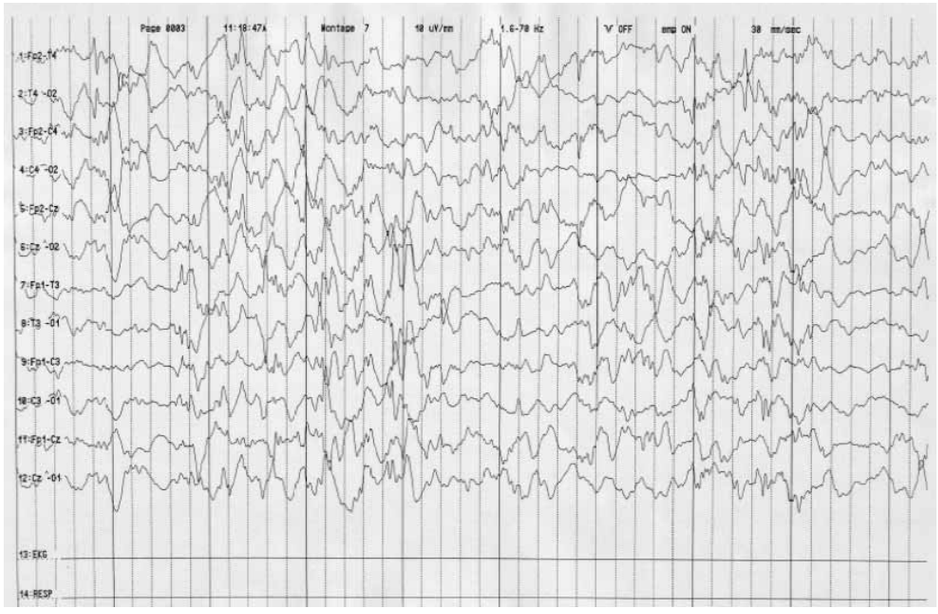

Fig. 8. Generalized/focal spike and wave discharges.

gions. Gyral maturation was delayed for more than four weeks in 2 of these 25 infants.

Neurodevelopmental outcome

Neurodevelopmental outcome of the participants correlated with the PVL grades and lesions of gray matter.

All 37 patients were examined at corrected age between 1 and 2 years. Twenty-five of them had severe abnormality on neurologic motor examination and significantly delayed cognitive development.

When analyzed according to their PVL grades, all 21 infants with PVL III had severe abnormalities on neurologic motor examination and 20 of them had significantly delayed cognitive development. One of these infants with PVL III had moderately delayed cognitive development.

All 4 infants with PVL with GMH/IVH had severe motor disability on neurologic motor examination and significantly delayed cognitive development.

Of 10 infants with PVL II, 4 had moderate motor disability and moderately delayed cognitive development. Mild motor disability and moderately delayed cognitive outcome was noticed in the remaining 6 infants.

Two infants with PVL I had normal motor outcome and mildly delayed cognitive development.

Discussion

The purpose of this study was to analyze brain tissue abnormalities on MRI in infants with periventricular leukomalacia and West syndrome and to evaluate PVL as a possible cause of West syndrome.

PVL is the most common ischemic brain injury in premature infants. The ischemia occurs in the border zone at the end of arterial vascular distribution. In particular, PVL refers to necrosis in the white matter dorsal and lateral to the external angles of the lateral ventricles, involving particularly the centrum semiovale (frontal horn and body) and optic (trigone and occipital horn) and acoustic (temporal horn) radiations[12]. The pathological features of PVL are distinctive and consist primarily of both »focal« periventricular necrosis and more »diffuse« cerebral white matter injury. These more diffuse lesions sometimes undergo major cystic changes and are more likely to be undetected by cranial ultrasonography[13]. The major long-term sequelae of PVL are cerebral palsy, delayed cognitive development, visual impairment, and seizures[12]. PVL was an uncommon underlying cause in patients presenting with epilepsy; however, patients presenting with motor disability and PVL had a high incidence of seizures[14]. PVL in epileptic patients is associated with multiple seizure types and medically refractory disease[14].

In our study, infants with PVL and West syndrome had changes in white matter, but they also had abnormalities in gray matter (enlargement of subarachnoid space, abnormality of cortical gray matter signal, and delayed gyral maturation). The full extent of the role of periventricular white matter injury in the genesis of gray matter lesion remains to be clarified. Using an advanced quantitative volumetric 3D-MRI technique, Inder et al[15] measured brain tissue volumes at term in preterm infants with early ultrasonographic and MRI evidence of periventricular white matter injury. They found that preterm infants with early periventricular white matter lesions had a pronounced reduction at term in the volume of cerebral cortical gray matter, similar to the reduction in myelinated white matter. A compensatory increase in cerebrospinal fluid volume, both ventricular and extracerebral, was also found. In that study was shown for the first time that periventricular white matter injury in the premature infant leads to the impairement of both subsequent cerebral cortical development and myelination. These findings may provide insight into the anatomical correlate of the intellectual deficits associated with periventricular white matter injury in the premature infant. The reduction in cortical gray matter volume opens the possibility that PVL is causally related to the subsequently impaired cortical neuronal development. Parameters such as enlargement of subarachnoid space, abnormality of cortical gray matter signal, and delayed gyral maturation may prove to be valuable predictors of impaired cerebral cortical development.

These advanced technique doesn't available on daily work, it is possible that parameters like enlargement of subarachnoid space, abnormality of cortical gray matter signal, delayed gyral maturation will be good predictors for cerebral cortical development disturbance.

A few studies indicated that cerebral white matter injury plays a role in the reduction in cerebral cortical gray matter at term, because a significant reduction in cerebral gray matter volumes by term was found in a small case series of premature infants with periventricular leukomalacia[15,16].

In our study, the severity of gray matter abnormalities depended on the severity of white matter abnormalities. In infants with PVL I, mild enlargement of subarachnoid space was found, but in infants with PVL II or PVL III in whom white matter abnormalities were severe and more diffuse, abnormality of gray matter was also more severe and diffuse. In case that white matter signals were extensive in 2 or more regions with diffuse reduction in white matter volumes and extensive cystic changes, in 100% of the cases the MRI showed pronounced thinning of corpus callosum, impaired myelination, and severe enlargement of subarachnoidal space. Also, cortical gray matter signal was abnormal in more than two regions, mostly parieto-occipital regions. A role for cerebral white matter injury in the genesis of the changes in cerebral cortical gray matter is clear from the current data. The reduction in cortical gray matter volume in premature infants with cerebral white matter injury could reflect blunted neuronal differentiation caused by destruction of ascending and descending axons (corticopetal, corticofugal, and corticocortical association fibers) in white matter, with resulting input deprivation and output isolation of the overlying cortical gray matter. As a consequence of this cortical isolation of gray matter, its differentiation may be impaired. These conclusions are based on the findings of Marin-Padilla, who analyzed Golgi stained specimens of cortical gray matter overlying destructive white matter lesions in the newborn brain after autopsy or neurosurgical procedure[17]. Marin-Padilla found that the neuronal changes included impaired development of neuropil, which may explain the changes in both white and gray matter found on MRI in infants with PVL[17].

Premature infants with West syndrome and PVL in our study mostly had severe grade of PVL. The presence of cystic PVL (PVL III) was strongly associated with changes in cerebral cortical gray matter. Although the precise nature of the neuropathological abnormalities associated with cortical atrophy is unknown, it is likely that either neuronal loss or impaired neuronal differentiation is the reason for the impaired dendritic and axonal development[15]. Marin-Padilla's study again could provide some explanations[18]. The gray matter often survived an infarction of the subjacent white matter, since its circulation remained intact. However, post-natal development of the gray matter next to these lesions was altered

in a specific manner. It is suggested that these changes in the gray matter secondary to subpial hemorrhage and hypoxic-ischemic perinatal infarctions are accompanied by functional changes, which may play an important role in the pathogenesis of epilepsy (infantile spasm) and infantile cerebral palsy. In acquired encephalopathies, the progressive postinjury reorganization of the undamaged cortex and its consequences (acquired cortical dysplasia), rather than the original lesion, represent the main underlying mechanism in the pathogenesis of neurological sequelae, such as epilepsy, cerebral palsy, dyslexia, cognitive impairment, and/or poor school performance[17].

The relationship between the adverse neurodevelopmental outcome and the level of immaturity at birth in the preterm infant is well documented[19]. Neurodevelopmental outcome of children with PVL correlates with the severity of MRI findings. Children with low PVL grades will have minor motor problems or normal to mildly impaired functional outcome. MRI classification of PVL has a significant prognostic value not only for neurodevelopmental outcome, specifically motor and visual, but also for epilepsy[20 21].

Neuromotor outcome of infants in our study was worse in those with moderate to severe MRI abnormalities, which is in line with previous research[20]. 67.5% (25/37) of the participants had severe motor and cognitive delay. In this group, 84.0% (21/25) had PVL III, and 16.0% had PVL +HIC. Infants with PVL I and West syndrome had normal motor outcome and mildly delayed cognitive development.

In conclusion, the reduction in white matter volume, ventricular dilatation, and impaired myelination commonly accompany the changes in cortical gray matter, such as enlargement of subarachnoid space, delay in gyral maturation, and abnormality in cortical gray matter signals. Presence of such cortical atrophy may play an important role in the pathogenesis of epilepsy (infantile spasms) and cognitive impairment.

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WEST SINDROM S PERIVENTRIKULARNOM LEUKOMALACIJOM: DESETOGODIŠNJA KLINIČKA STUDIJA

SAŽETAK

Westov sindrom (WS) je maligni epileptički sindrom koji se javlja u dojenačkoj dobi. Periventrikularna leukomalacija (PVL) je tipično hipoksičko-ishemičko oštećenje mozga nedonoščadi. Korelacija između opsežnosti i težine PVL i epilepsije do kraja nije razjašnjena. Ovom studijom smo pokušali povezati neurorazvojni ishod djece sa WS s obzirom na stupanj PVL . U studiju je bilo uključeno 37 pacijenata gestacijske dobi od 28 do 32 tjedna, koji su razvili WS. Po porodu učinjen je ultrazvuk mozga, u doba prvih napada magnetna rezonancija središnjeg živčanog sustava te je na taj način dokazana PVL. WS se razvio tijekom prve dvije godine života. Svi pacijenti, izuzev dvoje, imali su usporen motorni razvoj, s različitim stupnjem mentalne retardacije. Najčešća obilježja slikovnih pretraga mozga su bila: redukcija volumena kortikalne sive tvari mozga, redukcija volumena bijele tvari mozga i usporena mijelinizacija. Takve promjene mogu biti anatomska podloga koja dovodi do WS kod djece s PVL te mogu objasniti intelektualni i kognitivni deficit u prijevremeno rođene djece s PVL.