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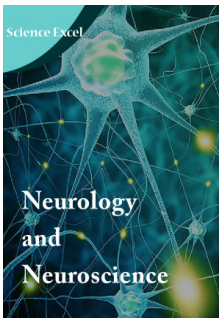

Neurodevelopmental outcomes of infants with periventricular leukomalacia at 2 years of age according to the De Vries classification

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Periventricular leukomalacia, neurodevelopment, prematurity, cerebral palsy

Abstract

Background: Periventricular leukomalacia is a white matter lesion, characterized by focal necrotic cysts, diffuse gliosis, ventriculomegaly, axonal damage. It is the most frequent cause of cerebral palsy and sensory deficits in premature infants.

Material and methods: Observational, retrospective, and analytical study of a cohort of newborns who presented periventricular leukomalacia at birth, according to the 4 stages of the De Vries classification. Patients were assessed at 2 years of age by Amiel Tison and Mayo Clinic neurological examinations, neurobehavioral assessment, Bayley Scale of Infant Development, Human Communication and Anthropometry services.

Results: 110 infants diagnosed by ultrasound were examined at two years of age. No correlation was found between the De Vries classification and the assessments. Average gestational age was 30.2 weeks, average weight 1197g. 35.5% were healthy mothers, followed by 28.2% with preeclampsia. The most frequent pathologies were neonatal sepsis and intraventricular hemorrhage, but they were not statistically significant. Amiel Tison neurological assessment was abnormal in 87.3% at one year of age, at two years of age cerebral palsy was present in 63.7%, the neurobehavioral assessment showed 15.5% of severe problems, there was severe hearing loss in 2.7%, and language at 2 years corresponded to the 15.8 month level. Bayley MDI was significantly delayed in 31.8% as well as PDI.

Conclusion: This work showed no correlation of the different variables with the De Vries Classification. In general terms, neurodevelopment assessments demonstrated an evident neurodevelopmental impairment with 63.7% of cerebral palsy and a significant delay of 31.8% for MDI and PDI.

Introduction

AAcknowledging the increase in survival of low birth weight infants during the past decades has been a detonator to generate interest and advances in knowledge of neonatal neurology. Currently, between 80-85% of newborns with weight less than 1500 g survive, of which 5-15% present cerebral palsy. Besides, 25-50% presents other minor neurodevelopmental impairments that affect not only the motor aspect but also cognitive and behavioral areas. Lesions with concomitant spastic motor deficits with or without intellectual deficits are periventricular leukomalacia and periventricular hemorrhagic infarction [1].

Periventricular leukomalacia (PVLM) represents the primary lesion of the preterm infant [2]. It was described over a century ago in 1962 by Banker and Larroche, who found a relationship between anoxia, the appearance of leukomalacia and the subsequent development of spasticity [3]. It occurs mainly in preterm infants, especially those born between 23 and 34 weeks of gestation, although it has also been reported in term newborns and those with cardiovascular and/or respiratory pathology. The fewer weeks of gestation, the greater the risk of PVLM [4].

There are multiple risk factors, which include mechanical ventilation, premature rupture of membranes, spontaneous labor, prematurity, hypocapnia, and perinatal hypoxia-asphyxia, intrauterine death of a twin, neonatal shock as well as variations in thalamic and lenticulostriated blood supply perfusion [2]. The blood flow of white matter is extremely low in preterm newborns (20-25% of gray cortical matter), which suggests that there is

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a minimal safety margin for the maintenance of blood supply to this area. The range of self-regulation is lower, making it more vulnerable to small changes in systemic pressure. Some risk factors include: systemic hypotension, acidosis, septic shock, hypocarbia, patent ductus arteriosus, retrograde diastolic flow, extracorporeal circulation, apneas and recurrent bradycardia [5]. Preterm infants with low birth weight have a greater risk of developing motor, cognitive and behavioral impairments compared with term newborns. In spite of a better rate of survival for this group of patients, since the 1990's, disability has remained relatively constant at up to 50%. These neurosensory damages are complex and often subtle, and can affect different aspects of the child's development [6,7].

Regarding current diagnosis, the preferred and most widely used method is the transfontanellar ultrasound, due to its accessibility and cost as compared to computerized tomography and nuclear magnetic resonance imaging [2].

Neurological prognosis is linked to signs of brain parenchyma involvement more than to the degree of hemorrhage, especially related to motor aspects. The development of cerebral palsy is considered typical of prematurity and is especially linked to PVLM.

A study was conducted in Mexico, at IMSS Monterrey, during 2 years, in which PVLM was diagnosed in preterm newborns using transfontanellar ultrasound at 4 weeks of life. In neonates with weight ≤ 2000g, there were changes suggestive of PVLM in 6.34%, 7.5% of newborns with weight ≤1500g and 4.6% of newborns with weight between 1501 and 2000g. The frequency of male:female was 2 to 1 and neurological evaluations were normal in everyone [2].

Yrigoyen et al. [8], conducted a cohort study en newborns with a weight less than 1500g at the Department of Neonatology of the Hospital 12 of October, ISSTE, and found an incidence of persistent hyper echogenicity, with an incidence of PVLM of 3%.

The main goal of this study was to analyze the outcomes of neurodevelopment of infants who presented periventricular leukomalacia during the neonatal period according the De Vries classification.

Materials and methods

Analytic, retrospective, observational study of a cohort of infants who were seen by the Department of Pediatric Follow-up of the National Institute of Perinatology at 2 years of age, from 1993-2011.

Inclusion criteria: all patients with a diagnosis of PVLM diagnosed by transfontanellar ultrasound during the period of study, who were seen by the Department of Pediatric Follow-up.

Exclusion criteria: patients with incomplete medical records and those who did not have at least one general evaluation at 2 years of age.

For the statistical analysis of data we used SPSS version 21 with the measures of central tendency Chi squared-test and Anova, with a p value < 0.05.

Periventricular leukomalacia was classified according to De Vries.

DE VRIES classification system of leukomalacia (1992)

Grade I: Transient periventricular densities (>7 days).

Grade II: Transient periventricular densities, evolving into small, localized cysts in the fronto-parietal region.

Grade III: Periventricular densities, evolving into extensive periventricular cysts.

Grade IV: Extended densities in subcortical white matter, evolving into extensive cysts [9].

1. In the initial phase during the first or second week of life: hyperechogenicity, usually triangular, in the external angle of the lateral ventricles (frontal, parietal, occipital) can be observed.
2. From the third week on, typical anechoic cavities appear.
3. From the fourth or fifth month on, a ventricular dilation develops, one that is generally moderate. The course of the disease is not always typical, since there are different presentations from the echographic perspective, with disappearance of initial echogenic images, the persistence of hyperechogenicity, total or parcial cavitation, disappearance of cavitation images and opening of periventricular cysts to the ventricular system giving the ventricles an irregular aspect characteristic of residual PVLM.

Assessment instruments at 2 years of age

- Amiel Tison neurological examination.
- Mayo Clinic neurological examination.
- Neuromotor stimulation: neurobehavioral assessment
- Psychology: Bayley II Psychomotor assessment
- Human communication: hearing and language

Description of assessment instruments

Amiel Tison neurologic examination:

Neurological examination done during the first 12 months of corrected gestational age. It includes: clinical examination of the head, answers from the mother's questionnaire, sensory development, posture and spontaneous motor activity, passive and active tone, primitive reflexes and postural reactions [10].

Classification of neurological abnormalities

1. ***Mild:*** altered maneuver for active and/or passive tone, reflexes in upper and/or lower extremities, no asymmetries, head control, independent sitting, balance reflexes.
2. ***Moderate:*** asymmetries in upper/lower extremities, altered active/passive tone, head control, sit-up assistance, sitting for 30 seconds, absence of balance reflexes.
3. ***Severe:*** abnormal motor activity, poor for age, absence of head control, absence of independent sitting, straightening of lower extremities in scissor position, opisthotonos [11].

Mayo clinic neurological examination

Neurological examination used from 2 years of age on, to interpret the muscular activity of the patient and to understand the motor examination by the assessment of movement, allowing for a quick identification of cerebral palsy.

Cerebral palsy; motor examination

- Monoparesis: reduced strength of an upper or lower extremity.
- Monoplegia: loss of strength of an upper or lower extremity.
- Paraparesis: reduced strength in upper and lower extremities.
- Paraplegia: loss of strength in upper and lower extremities.
- Hemiparesis: reduced right or left strength.
- Hemiplegia: loss of right or left strength.
- Quadriparesis: reduced strength in the four extremities (with independent gait).
- Quadriplegia: loss of strength in the four extremities (without independent gait, absence of functional ability).
- Tetraparesis: reduced strength in the four extremities, predominantly upper extremities.
- Tetraplegia: loss of strength in all four extremities, predominantly upper extremities [12].

Neurobehavioral assessment of the infant

Screening tool with the purpose of early detection of risks in developmental delay. It consists of observing how the child responds to relevant aspects of childhood development during the direct work with him, administered at 1, 4, 8, 12, 18 and 24 months. It includes 60 behaviors, 10 items per age.

Mild delay: 2 months' developmental delay.

Moderate delay: 4 months' developmental delay.

Severe delay: 6 months' developmental delay [13].

Bayley II scale of infant development

Scale for infant development, assessing functional development in children. It diagnoses developmental delay, allowing the planning of intervention strategies.

Mental and motor scales determine the levels of cognitive, language, personal, social, gross and fine motor skills.

Mental MDI scale, PDI motor scale scores

- 115 Accelerated development
- 85-114 Normal development
- 70-84 Mild developmental delay
- Less than 69 Significant developmental delay [14].

Human communication

- Normal hearing international system 10-20db
- Superficial or mild hearing loss 21-40 db
- Moderate hearing loss 41-70 db
- Severe hearing loss 71-90db
- Profound hearing loss, major deafness greater than 91 db [15]
- Language expressed in months at 24 months

Results

During the 18 years of the study, 6781 files of infants who were admitted to the Department of Pediatric Follow-up were reviewed. 110 (1.74%) neonates were diagnosed with periventricular leukomalacia by cranial ultrasonography, according to the De Vries classification.

Average maternal age for the whole sample was 29.5 years; most neonates were obtained by C-section (88%). Administration of prenatal steroids was achieved in 43% of patients, 35% of mothers were healthy. Regarding pathology, preeclampsia occupied the largest percentage with 28.2%, corioamnionitis with 7.3%, and diabetes mellitus with 5.4%. No statistically significant differences were found in any of the maternal variables in relation to the degree of leukomalacia. Average gestational age of the whole sample was 30.2 weeks, being 29.7 weeks, for both groups I and III, and an older age of 32.5 weeks for group II, p= 0.013, average weight was 1197g; the lowest found was in group III, with 1153g, although there were no statistical differences for the 4 groups (Table 1).

Table 1. *Maternal and neonatal variables. *One factor Anova , **Pearson's chi2 .*

PVLM N=110-100%	GI N=60 (54.5%)	GII N=12 (10.9%)	GIII N=25 (22.7%)	GIV N=13(11.8%)	P value=
Gestational Age 30.2 ±2.7 Mn 25 Mx 38	29.7±2.5 26-36	32.5±2.6 28-36	29.7±2.3 25-34	30.6±3.6 26-38	*0.013
Weight 1197g±403g Mn 540 Mx 2560	1158.7±354 570-1965	1468.3±545 650-2130	1153.4±310 620-1820	1214.6±555 540-2560	*0.096
Female N=47(42.7)	32(53.3)	5(41.7)	6(24.0)	4(30.8)	**0.068
Maternal Age 29.5±6.7 Mn 16 Mx 43	29.3±6.3 16-42	27.5±6.8 18-38	30.4±7.6 17-43	30.0±6.8 20-42	*0.665
Prenatal control 3.8 ±4.2 Mn 00 Mx 24	3.2±3.7 0-20	2.5±2.6 0-8	5.4±5.4 0-24	4.7±4.1 0-12	*0.328
Prenatal steroids N=48(43.6)	29(48.3)	4(33.3)	12(48.0)	3(23.1)	**0.300
C-section N=97(88.2)	55(91.7)	9(75.0)	21(84.0)	12(92.3)	0.538
Healthy N=39(35.5) Preeclampsia N=31(28.2) Corioamnionitis N=8(7.3) Diabetes Mellitus N=6(5.45)	22(36.7) 17(28.3) 7(6.36) 3(2.73)	2(16.7) 1(8.3) 0(0) 1(0.91)	11(44.0) 8(32.0) 1(0.91) 0-0	4(30.8) 5(38.5) 0(0) 2(1.82)	**0.183
Apgar 1 5.6 Apgar 5 7.8	5.8 7.8	5.9 7.9	5.2 7.8	5.1 7.7	*0.543 *0.990
pH 7.2 Co_2 45.5	7.3 45,0	7.2 53.6	7.3 41.4	7.2 48.2	*0.323 *0.032
Surfactant N=48(43.6)	29(48.3)	4(33.3)	12(48.0)	3(23.1)	**0.323
Without ventilation N= 8(7.3) With ventilation N=102(93) Days of ventilation N=11.7 Mx Concentration of O2 71.9%	3(5.0) 57(52) 10.6 72.10%	1(8.3) 11(10) 5.2 73.60%	2(8.0) 23(21) 15.8 69.40%	2(15.4) 11(10) 14.5 74.50%	**0.948 *0.278 *0.947

Table 2. *Neonatal morbidity. *One factor Anova, **Pearson's chi2, ***IUGR intrauterine growth restriction, ****IVH intraventricular hemorrhage *****ROP retinopathy of prematurity*

PVLM N=110(100%)	**GI N=60(54.5%)**	**GII N=12(10.9)**	**GIII N=25(22.7)**	**GIV N=13(11.8)**	**P value=**
***IUGR N=41(37.3)	24(40.0)	6(50.0)	5(20.0)	6(46.2)	**0.199
Neonatal sepsis N=87(79.19)	47(78.3)	9(75.0)	22(88.0)	9(69.2)	**0.550
****IVH N=70(63.6)	38(67.3)	9(75.0)	17(68.0)	6(46.2)	**0.101
Ventriculomegaly N=22(20.0)	14(23.3)	0-0	6(24.0)	2(15.4)	**0.573
Seizures N=32(29.1)	17(28.3)	3(25.0)	6(24.0)	6(46.1)	**0.519
Neonatal Apnea N=63(57.3)	36(60.0)	4(33.3)	18(72.0)	5(38.4)	**0.069
Broncopulmonary dysplasia N=46(41.8)	24(40.0)	4(33.3)	10(40.0)	8(61.5)	**0.466
*****ROP N=40(37.3) Visual impairment 1(0.9)	24(40.0) 0-0%	3(25.0) 0-0%	9(39.1) 1-0.9%	4(30.8) 0-0%	**0.433
Days of hospital stay 64.5± 34.2	64.2d	62.3d	67.2d	62.3d	*0.969

Table 3. *Amiel Tison neurological assessment at 12 months of corrected gestational age. p= Pearson's*

PVLM N=110(100)	**GI N=60(54.5%)**	**GII N=12(10.9%)**	**GIII N=25(22.7%)**	**GIV N=13(11.8%)**	**P value=**
Normal N=14(12.7)	9(15.0)	1(8.3)	1(4.0)	3(23.1)	0.327
Abnormal N=96(87.3)	51(85.0)	11(91.7)	24(96.0)	10(76.9)	0.267
Mild N=29(26.4)	21(41.1)	1(9.0)	5(20.8)	2(20.0)	0.134
Moderate N=31(28.2)	14(27.4)	4(36.3)	10(41.6)	3(30.0)	0.524
Severe N=36(32.7)	16(31.3)	6(54.5)	9(37.5)	5(50.0)	0.394

Table 4. *Neurological assessment at 2 years of age. p=Pearson's Ch2, *Cerebral palsy **IG independent gait ***NHF null functional ability.*

PVLM N=110(100)	GI N=60(54.5%)	GII N=12(10.9%)	GIII N=25(22.7%)	GIV N=13(11.8%)	P Value=
Normal N=40(36.3)	21(35.0)	5(41.7)	7(28.0)	7(53.8)	0.446
Abnormal by *CP N=70(63.7)	39(65.0)	7(58.3)	18(72)	6(46.2)	0.749
Monoparesis N=2(1.8)	2(5.1)	0-0	0-0	0	0.633
Paraparesis N=7(6.4)	5(12.8)	0-0%	2(11.1)	0-0	0.627
Right hemiparesis N=16(14.5)	10(25.6)	0-0	4(22.2)	2(33.3)	0.499
Left hemiparesis N=7(6.4)	5(12.8)	0-0	1(5.5)	1(16.6)	0.606
Quadriparesis **(IG) N=20(18.2)	11(28.2)	4(57.1)	5(27.7)	0-0	0.306
Quadriplegia ***(NFA) N=18(16.4)	6(15.3)	3(42.8)	6(33.3)	3(50)	0.219

Table 5. *Neurobehavioral assessment. hearing. language at 2 years of age. p= **Pearson's Ch2.*

PVLM N=110(100)	**GI** N=60(54.5%)	**GII** N=12(10.9%)	**GIII** N=25(22.7%)	**GIV** N=13(11.8%)	**P value=**
Normal N=31(28.2)	19(31.7)	2(16.7)	7(28.0)	3(23.1)	
Mild delay N=20(18.2)	12(20.0)	2(16.7)	3(12.0)	3(23.1)	
Moderate delay N=15(13.6)	9(15.0)	0-0	4(16.0)	2(15.4)	0.665
Severe delay N=27(24.5)	14(23.3)	3(25.0)	6(24.0)	4(30.8)	
Severe abnormalities N=17(15.5)	6(10.1)	5(41.6)	5(20.0)	1(7.7)	
***Human Communication Normal N=104(94.5)	57(95.0)	12(100)	23(92.0)	12(92.3)	
Superficial hearing loss N=3(2.7)	1(1.7)	0-0	1(4.0)	1(7.7)	
Moderate hearing loss 0-0	0-0	0-0	0-0	0-0	**0.825
Severe hearing loss 3(2.7)	2(3.3)	0	(4.0)	0-0	
Language 15.8 months ±7.2 Min 3 Mx 24	17.0 months	14.4 months	12.4 months	18.4 months	*0.023

Table 6. *Bayley II Scale: Mental (MDI) and Motor (PDI).*

PVLM N=110(100%)	**GI N=60(54.5%)**	**GII N=12(10.9%)**	**GIII N=25(22.7%)**	**GIV N=13(11.8%)**	**P value=**
85-115 normal development					
MDI 20(18.2)	12(20.0)	0-0	4(16.0)	4(30.8)	
PDI 10(9.1)	8(13.3)	1(8.3)	0-0	1(7.7)	
70-84 mild developmental delay					
MDI 27(24.5)	18(30.0)	4(33.3)	1(4.0)	4(30.8)	
PDI 25(22.7)	14(23.3)	0-0	6(24.0)	5(38.5)	**0.124
< 69 significant developmental delay					
MDI 35(31.8)	18(30.0)	5(41.7)	10(40.0)	2(15.4)	
PDI 47(42.7)	26(43.3)	8(66.7)	9(36.0)	4(30.8)	
Not assessed			10(40.0)		
MDI 28(25.5)	12(20.0)	3(25.0)	10(40.0)	3(23.1)	
PDI 28(25.5)	12(20.0)	3(25.0)		3(23.1)	
MDI average score 73.5±19.6	75.1	64.1	70.1	79.7	*0.287
PDI average score 67.5±16.1	70.4	59.2	65	64.9	*0.209

It is worthwhile to note that for the 4 groups we found an Apgar score lower than 6 at 1 minute, increasing at 5 minutes, although there were no differences found between them. When analyzing the pH at birth, the average was normal at 7.20. CO2 for the whole sample was 45.5, although it was found to be significantly lower for group III with 41.4, p=0.032. A total of 43.6% of the whole sample received surfactant. 93% required some form of ventilation with an average of 11.7 days of ventilation and O2 concentration of over 70% (Table 1).

Table 2 shows the pathology presented in newborns during their hospital stay, the main ones are sepsis, with 79%, intraventricular/ subependymal hemorrhage with 63.3% and apnea with 57.3%. There was no significance found between groups. There was an average prolonged hospital stay of 64.5 days (Table 2).

Neurological abnormalities at 12 months of life were found in 87.3%, the largest percentages found in group I and III with 92% and 96%, respectively, and 32.7% were diagnosed with a severe alteration. No differences were observed between groups (Table 3).

The Mayo Clinic neurological assessment was used at 2 years of life, diagnosing 63.7% of patients with cerebral palsy without statistical difference between the groups although it was observed to be 65% for group I (Table 4).

The neurobehavioral assessment, which measures the risk of delay in development, was applied from the first month of life until 2 years of age. It reported some sort of delay in 72%, and severe delay in 15.5% of the whole sample, being 41.6% for group II, although there was no statistical significance between groups (Table 5).

Regarding language and hearing, 94% of the whole sample was normal, only 2.7% presented severe hearing loss, 3.3% for group I and 4% for group III. The average language at 24 months was reported at 15.8 months, with approximately a 7-month delay, being statistically significant for group III with 12.4 months of delay, p= 0.023 (Table 5).

For the Bayley II Mental Scale (MDI) just 18.2% of the whole sample was reported normal. In general, the average score for the whole sample was 73, below the score considered normal (85 to 114), and there was significant developmental delay (a score of less than 69) in 32% with high percentages of 30% or more for groups I, II and III. Regarding the Motor Scale (PDI), just 9.1% of the sample was normal with scores lower than those reported for MDI, average scores of 67, with significant delay in 31.8% of the whole sample; this significant delay was over 30% in all groups, and it is noticeable that in group II it was 66.7% (Table 6).

Discussion

The incidence over the period of study was 1.7%, which concurs with incidence reported in the literature [16-19]. Newborns with some degree of PVLM have a greater risk of presenting cerebral palsy and sensory deficit. Nevertheless, it is important to mention that in general terms for this sample according to the classification by De Vries, there was no significant difference in the parameters evaluated when comparing the groups studied.

Although corioamnionitis was found in only 7.3% of the sample, there are studies [20-22] that report a strong association with periventricular leukomalacia and cerebral palsy. It is important to mention that 45% of the mothers of these patients presented some pathology such as preeclampsia, corioamnionitis and diabetes mellitus. Gestational age and weight continue to be a known risk factor for PVLM as demonstrated in this work. 90% of PVLM is observed in premature infants, being more severe the lesser the gestational age; term newborns present with milder forms of PVLM. Prenatal exposition to betamethasone can be associated with a decrease in the risk of cystic PVLM more than those newborns whose mothers did not receive glucocorticoids. In our sample, for these pathologies only 43.6% received steroids. Although many of our patients have a poor prenatal control, when compared with the classification by De Vries no significant differences were found [23-25].

PVLM has been related fundamentally to hypoxic-ischemic events; although the ultimate factors that condition it are unknown, it has also been related to hypocapnia, hypotension and acidosis. Low Apgar scores have been documented with PVLM as a hypoxic factor, especially in scores at 5 and 10 minutes, as demonstrated by Wang with Apgar scores less than 5, RR (2.50; 1.48-4.21) at 5 minutes. In our study, although Apgar was low at one minute, it had an acceptable recovery at 5 minutes.

On the other hand, it is also mentioned that pH and CO2 have a role in PVLM; early hypocarbia in preterm neonates was significantly associated with cerebral palsy as well as late-onset PVLM, but not with early-onset PVLM. Nevertheless, in our sample patients had a normal average of pH and CO2, although we found an isolated significance with a lower CO2 for group III of De Vries [126-28.

There is a strong association between PVLM and mechanical ventilation. 93% of our infants required some sort of respiratory support with an average of 11.7 days of ventilation and an oxygen concentration of 71.9%. Wang points out that prolonged mechanical ventilation with an increased risk (RR 3.36; 1.88-6.01) contributes to PVLM and is associated with intraventricular hemorrhage grade III/VI. It should be noted that 63.6% of our infants presented intraventricular hemorrhage [27].

Some neonatal pathology has found to be involved as a positive predictive factor for PVLM, being sepsis of the most significant (likelihood ratio 2.39; confidence interval of 95% 1.52-3.77) [27]. Chasco points it out as well [28], with a significantly greater incidence of late neonatal sepsis in the PVLM group (p=0.001). Our infants had sepsis almost in 90%, so this pathology likely increased the risk for PVLM. On the other hand, the participation of intraventricular hemorrhage (IVH) in the presentation of PVLM is indisputable; our patients had a high percentage of hemorrhage although there was no difference between them when compared according to the classification by De Vries. Some articles point out that babies with PVLM and IVH of all degrees had a greater risk of abnormal outcomes in neurological development at 24 months of age [27,29]. Apneic events have also been related to PVLM. Damage to white matter probably explains the significantly greater prevalence of apneas (p<0.001); more than half of our patients presented apneas, which could have been a risk factor. 30% of our infants presented seizures, which have been associated with PVLM as documented by Mulas (p<0.001) [30,31]. Almost a third of patients with periventricular leukomalacia develop epilepsy that is untreatable to a great extent. Neonatal seizures and severe findings in MRI are important clues that can indicate the development of epilepsy in these patients [32].

Bronchopulmonary dysplasia (BPD), severe retinopathy of prematurity (ROP) and cystic periventricular leukomalacia are 3 of the main morbidities with long-term neurological development deficiencies in premature infants. Although our patients presented high percentages of BPD and ROP, 41.8% and 37.3%, respectively, there were no significant differences found in the groups [33].

Cerebral palsy is one of the most common disorders in pediatric neurology, with an incidence of two to three cases per 1000 term births. Likewise, periventricular leukomalacia is the most frequent cause of cerebral palsy in premature infants and it usually presents in the diplegic form, whilst in term newborns it may be due to other causes such as asphyxia without ischemia. The incidence varies according to different authors, and is estimated at 3 to 9% in premature infants [28,34]. In general terms, our patients had significant neurodevelopmental disabilities. Evaluations at 2 years of age reported 63.7% of cerebral palsy, 18.2% of quadriparesis with independent gait and 16.4% of quadriplegia with no functional ability [30]. In respect thereof, Imamura reported mental retardation in 50% and cerebral palsy in 83.6% [35]; 40% of quadriplegics achieved independent gait at 36 months with orthopedic braces, while 52% did not achieve independent gait. As observed, their results were not better than ours; 69% of their sample with PVLM grade 2 or 3 had IVH grade III o IV according to Papile [19].

With regards to hearing, in our sample we found only 3 patients with severe hearing loss (2.7%), although in language we observed a significant delay of approximately 7 months. Hearing loss is also more frequent in those with cerebral palsy compared with the general population. Speech disorders, such as the difficulty forming words and speaking clearly, are present in more than one third of those with cerebral palsy [36].

Finally, our results in MDI are similar to other publications, where significant developmental delay on average occupies 31.8%, as well as for PDI, demonstrating an impairment caused by PVLM. This means almost 4 out of 10 of our patients had an intellectual quotient with scores under 69, when normal development for both scales ranges from 85-115. In general, the majority of the articles report Bayley

scores under 70 points for intellectual quotient as well as motor development [37-40].

In conclusion in this work there was no correlation of the different variables with the classification by De Vries. In general terms, we observed an evident impairment in neurodevelopment of 63.7% for PCI and MDI and PDI of 31% with significant delay in those patients, derived from the neurological assessments applied.

References

1. Cabañas F, Pellicer A. Lesión cerebral en el Niño Prematuro. Protocolos Diagnòstico Terapeùticos de la AEP. Neonatologìa. 2008; 27: 253-269
2. Hernàndez-Cabrera MA, Flores-Santos JF, Garcìa-Quintanilla RJ, et al. Prevalencia de leucomalacia periventricular en neonatos prematuros. Rev Med Inst Mex Seguro Soc. 2009; 47: 147-150.
3. Chasco A, Pallàs CR, Miralles M, et al. Leucomalacia periventricular e hiperecogenicidad persistente: Relación entre hallazgos ecográficos y secuelas. Medicina Fetal y Neonatología. 1997; 46: 471-476.
4. Himmelmann K. Uvebrant P. Function and neuroimaging in cerebral palsy: A population-based study. Dev Med Child Neurol. 2011; 53: 516-21.
5. Romano C, Macaya A. Evolución neurológica, radiológica y cognitiva en niños nacidos con leucomalacia periventricular. Tesis de Doctorado. Universidad Autónoma de Barcelona. 2013.
6. Spittle A, Orton J, Anderson P, et al. Early developmental intervention programmes post-hospital discharge to prevent motor and cognitive impairments in preterm infants. Cochrane Database Syst Rev. 2012; 12: CD005495.
7. Sans A, Boix C, Lòpez-Sala A, et al. Trastornos visuoconstructivos en la leucomalacia periventricular. Rev Neurol. 2002; 34: 34-40.
8. Eken P, de Vries LS, van der Graaf, et al. Haemorragic-Isquemic lesions of the neonatal brain: correlation between cerebral visual impairment, neurodevelopmental outcome and MRI in infancy. Dev Med Child Neurol. 1995; 37: 41-55.
9. de Vries LS, Eken P, Groenendaal F, van Haastert IC, et al. Correlation between the degree of periventricular leukomalacia diagnosed using cranial ultrasound and MRI later in infancy in children with cerebral palsy. Neuropediatrics. 1993; 24: 263-268.
10. Amiel-Tison C. Vigilancia neurològica durante el primer año de vida. 1ª ediciòn española. Masson S.A. Barcelona; 1988.
11. Arreola-Ramírez G, Fernàndez-Carrocera LA, Ramirez Lòpez CZ, et al. Desarrollo neurológico en el primer año de vida de infantes prematuros con peso menor a 1,500g en una institución de tercer nivel. Perinatol Reprod Hum. 2011; 25: 146-154.
12. Examen clínico neurológico por miembros de la Clínica Mayo. 1ª edición. México: Ed. La Prensa Mexicana; 2008.
13. Benavides González HM, Fernández Carrocera LA, Venta Sobero JA, et al. Utilidad de una valoración neuroconductual de tamiz en el primer año de vida. Perinatol Reprod Hum. 1989; 3:193-8.
14. Bayley N. Bayley Scales of Infant Development. Second Edition (BSID-II). San Antonio: Hartcourt Brace & Company 1993.
15. Lowe A. Audiometría en el niño, implicaciones pedagógicas. Buenos Aires Argentina: Editorial Médica Panamericana 1988.
16. Hamrick SE, Miller SP, Leonard C, et al. Trends in severe brain injury and neurodevelopmental outcome in premature newborn infants: the role of cystic periventricular leukomalacia. J Pediatr. 2004; 145: 593-599.
17. Resch B, Resch E, Maurer U, et al. Periventricular leukomalacia and neurodevelopmental outcome. J Pediatr. 2011; 159: 1049-1050.
18. Barrìa RM, Flàndez-J A. Leucomalacia y ecogenicidad periventricular en prematuros de muy bajo peso al nacer. Rev Neurol. 2008; 47: 16-20.
19. Choi JY, Rha DW, Park ES. The Effects of the Severity of Periventricular Leukomalacia on the Neuropsychological Outcomes of Preterm Children. J Child Neurol. 2016; 31: 603-612.
20. Kumazaki K, Nakayama M, Sumida Y, et al. Placental features in preterm infants with periventricular leukomalacia. Pediatrics. 2002; 109: 650-655.
21. Wu YW, Colford JM Jr. Chorioamnionitis as a risk factor for cerebral palsy: A meta-analysis. JAMA. 2000; 284: 1417-1424.
22. Wu YW. Systematic review of chorioamnionitis and cerebral palsy. Ment Retard Dev Disabil Res Rev. 2002; 8: 25-29.
23. Resch B, Vollaard E, Maurer U, et al. Risk factors and determinants of neurodevelopmental outcome in cystic periventricular leucomalacia. Eur J Pediatr. 2000; 159: 663-670.
24. Barrìa M, Flandez A. Parenchymatous Brain Injury in Premature Infants: Intraventricular Hemorrhage and Periventricular Leukomalacia. Neonatal Care. 5: 87-102.
25. Romero-Guzmán GJ, López Muñoz F. Prevalence and risk factors for periventricular leukomalacia in preterm infants. A systematic review. Rev Neurol. 2017; 65: 57-62.
26. Murase M, Ishida A. Early hypocarbia of preterm infants: its relationship to periventricular leukomalacia and cerebral palsy, and its perinatal risk factors. Acta Paediatr. 2005; 94: 85-91.
27. Wang LW, Lin YC, Tu YF, et al. Isolated Cystic Periventricular Leukomalacia Differs from Cystic Periventricular Leukomalacia with Intraventricular Hemorrhage in Prevalence, Risk Factors and Outcomes in Preterm Infants. Neonatology. 2017; 111: 86-92.
28. Lida K, Takashima S, Takeuchi Y. Etiologies and distribution of neonatal leukomalacia. Pediatr Neurol. 1992; 8: 205-209.
29. Bae MH, Jang HJ, Lee NR, et al. The clinical characteristics and neurodevelopmental outcome of preterm infants with persistent periventricular echogenicity. Pediatr Neonatol. 2018; 59: 606-610.
30. Resch B, Resch E, Maurer-Fellbaum U, et al. The whole spectrum of cystic periventricular leukomalacia of the preterm infant: results from a large consecutive case series. Childs Nerv Syst. 2015; 31: 1527-1532.
31. Mulas F, Smeyers P, Téllez de Meneses M, et al. Leucomalacia periventricular: secuelas neurológicas, radiológicas y repercusiones neuropsicológicas a largo plazo. Rev Neurol. 2000; 31: 243-252.
32. Ekici B, Aydinli N, Aydin K, et al. Epilepsy in children with periventricular leukomalacia. Clin Neurol Neurosurg. 2013;11: 2046-2048.
33. Wang LW, Lin YC, Wang ST, et al. Identifying Risk Factors Shared by Bronchopulmonary Dysplasia, Severe Retinopathy, and Cystic Periventricular Leukomalacia in Very Preterm Infants for Targeted Intervention. Neonatology. 2018; 114: 17-24.
34. Barboza-Ubarnes M, Segovia-Fuentes J, Guerrero-Tinoco G, et al. Secuelas neurocognitivas de leucomalacia periventricular. Rev. Cienc. Biomed. 2014; 5: 345-350.
35. Imamura T, Ariga H, Kaneko M, et al. Neurodevelopmental outcomes of children with periventricular leukomalacia. Pediatr Neonatol. 2013; 54: 367-372.
36. National Institute of Neurological Disorders and Stroke. Cerebral Palsy. NINDS. National Institutes of Health. NIH Publication No. 13-159. 2013.
37. Woo MK, Kim DW, Huh K, et al. Study on the neurodevelopmental predictors for the results of the Bayley Scales of Infant Development II in high-risk neonates. Kr J Pediatr. 2009; 52: 1221-1227.
38. Fernandez LV, Goulart AL, Santos AM, et al. Neurodevelopmental assessment of very low birth weight preterm infants at corrected age of 18-24 months by Bayley III scales. J Pediatr. 2012; 88: 471-478.
39. Ahn JH, Seo YJ, Yoon JR, et al. Risk Factors and Prognosis for Periventricular Leukomlacia According to Neuroimage in Preterm Infants. Neonatal Med. 2010; 17: 64-74.
40. Ohgi S, Akiyama T, Fukuda M. Neurobehavioural profile of low-birthweight infants with cystic periventricular leukomalacia. Dev Med Child Neurol. 2005; 47: 221-228.