Neurodevelopmental Outcomes of Infants with Periventricular Leukomalacia at 2 and 7 years, Two Different Age Periods

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Abstract

Introduction: The main causes of chronic neurologic complications in preterm newborns are periventricular leukomalacia (PVL) and developmental delay in the form of cognitive impairment.

Materials and Methods: Observational, retrospective, analytic study of a cohort of children of 2 and 7 years who were previously diagnosed with PVL by an ultrasound during the neonatal period. Patients were divided into two groups according to time period: the first one from 1993 - 2004, the second one from 2005 - 2016. They were assessed by the different services involved in the Department of pediatric follow-up.

Results: During the 22 year study period the incidence was 3.5%. Average gestational age (GA) for both periods was 30.2 weeks; most patients needed ventilatory assistance for 11.5 days; there was a high percentage of neonatal sepsis in both periods, 82.3%; the percentage of intraventricular hemorrhage for both periods was 63.2%, with an increased risk during the first period. According to the Mayo Clinic neurological assessment at two years of age, of all alterations of CP that were greater during the first period, only quadriplegia with null functional ability was significant in this first group, p = 0.0009. In VIH grade I/II, CP was present in 50%, and in IVH grade III/IV in 32% for the whole sample. As to the 7-year old assessment of the intellectual quotient, using the Terman Merril (Stanford Binet) test, 33.5% of patients were below average.

***Keywords:** Prematurity; Periventricular Leukomalacia; Cerebral Palsy; Intellectual Quotient*

Introduction

Periventricular leukomalacia (PVL) is a white matter lesion affecting the premature brain. Surviving infants can have a severe impairment in their neurological development, such as cognitive deficits and motor impairment. In the United States, 63,000 infants are born with a weight under 1500g, of whom 25 to 50% present cognitive, behavioral, attention or socialization deficits and 5 to 10% have major motor deficits. Cognitive impairment without motor impairment is the predominant sequela in infants under 1500g, achieving a survival rate as high as 70% according to the latest reports [1,2]. Most studies report over 50% of impairment this subgroup [3]. The increase in premature births is considerable, but severe impairment has decreased from 25% to 5% from 1981 to 1994, just with a slight increase

of 8 to 9% in the following years. These modern data show the improvements in the intensive care units in Nottingham, compared to a minimum of 8-10% in other centers. For example, comparing cohorts of infants born in The Netherlands to those of the mid-80's, the former had 24.1 additional survivors and 7.2 cases of PC for every 100 live births; for those infants born in 1991-1994 the CP prevalence continued following a slight decreasing tendency [4]. In spite of the improvement achieved in the survival rate for this group of patients, since de 90's, the presence of impairment has remained relatively constant in up to 50%, Neurosensory damages are complex and often subtle and they can affect various aspects of the child's development [5,6].

In assessing changes in perinatal practices in four-year old children under 999g, survival rates improved from 31.6% in the first period to 49.2% in the second period, where mild impairment rates went from 10% to 7%. PC rates increased from 0 to 12% (p = 0.0); blindness from 0 vs 3%, deafness from 2 vs 2%, developmental delay of 12% vs 11% were not changed, in spite of an increase in the number of survivors of 41 vs 83, with severe impairments in 7 vs 17 [7].

PVL had an increase of 2 to 7%, CP increased from 16 to 25%, deafness from 3 to 7%, the Bayley mental development index of < 70 points increased from 26 to 36% from a first period to a second period in infants under 999g, so parents must be informed of these results for decision-making [8,9].

On the other hand, in comparing the same cohort of children less than 33 weeks at 8 and 15 years of age using the WISC-R test, which is a test for visual-motor integration, and a school questionnaire, there was a significant increase in the proportion of subjects classified as disabled with motor impairment from 11% to 8%, and 22% between 14 and 15 years; in subjects classified as disabled without motor impairment, the increase went from 16% to 8%, and 26% between 14 and 15 years. The intellectual quotient of 104 to 95 from infancy to adolescence warranted special educational services in 15% of 8-year olds and 24% of 15-year olds [10].

Risk factors for periventricular leukomalacia

There are several risk factors for the presence of PVL, such as pathophysiological changes in the placenta, chorioamnionitis, twin placentation [11], hypocarbia when there are at least two of five values of $PaCo_2$ during the first 48 hours of life [12], as well as hypocarbia accumulation [13], low Apgar scores, neonatal seizures, early onset sepsis [14], prenatal steroids, acute respiratory distress syndrome, surfactant and hypocarbia were all significantly associated in PVL [15,16]. Some authors have blamed chorioamnionitis, especially the cystic type, as the culprit of PVL, but some studies deny it [17,18]. Newborns developing PVL have changes in brain blood flow and lower mean velocities just after birth [19,20]. Intraventricular hemorrhage (IVH) is usually associated to PVL in 15% [21] to 41.2% [22]; however, it can also be present independently. This is not the case though in grade 3 and grade 4 IVH, in which there is an increased risk for PVL [23].

Transfontanellar ultrasound

PVL is usually seen in premature babies, so a transfontanellar ultrasound is of the utmost importance for an early diagnosis, as well as determining the correlation between the degree of PVL and the neurological impairment in children with CP [22]. Brain ultrasound is the first technique that has enabled the diagnosis of PVL because it provides evolutionary data, it is easy to use and is available at the NICU, which renders it the technique of choice. It allows to identify: a) acute changes, b) late changes, c) long-term changes [24].

In 1992, De Vries classified PVL into four grades. The Quality Standards Committee of the American Institute of Ultrasound, Committee of Pediatric Neurology recommends: routine brain ultrasound to all newborns of less than 30 weeks, at 7 and 14 days, 36 to 40 weeks postmenstrual age [25].

Neurodevelopment at 2 years

Neurological lesions of the newborn are the main cause of intellectual impairment and motor impairment associated to CP. White matter lesions are a common characteristic in hypoxic ischemic encephalopathy, which affects term babies and PVL affects premature [26].

A study conducted on 50 newborns with PVL and weight under 1250g found that only 40% reached two years of age without sequelae [27]. Another study of 319 newborns with weight under 1500g reported 78% of sequelae due to PVL at 18 months of age, but the fact of

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having persistent to moderate hyperechogenicity increases the risk of sequelae 9 fold and having PVL up to 15 fold [28]. A study used the Griffiths development scale to assess 120 neonates less than 34 weeks at 18 months of age, giving similar results compared to controls. Only 13 infants (10.83%) with frontal PVL had a normal development [29].

A comparison was made between 24 premature newborns and 26 similar premature newborns, and they were assessed at 12 months of corrected gestational age, using the Bayley III scale, with scores of 86 to 88, language of 86 to 89, cognitive score of 90 to 92. This is consistent with the fact that persistent periventricular echogenicity without cystic changes can be a benign finding [30]. Using the Alberta infant motor scale (AIMS), 35 infants with PVL and 76 control term infants were assessed at 6, 8 and 18 months of corrected age. The group with PVL had lower subscales in prone, supine and sitting position at 6, 8 and 18 months with $p < 0.05$ [31].

Cognition

An intelligence test (IQ) was used in 148 infants up to the age of 10 to 13 where the maternal educational level was the most important factor, with an OR of 21.9, which is associated to a low IQ. IVH GIII or IV, as well as PVL were also associated to a low IQ, with an OR of 6.9 [32]. Likewise, 296 infants were assessed and data was compared from 36, 54, 72 and 96 months; 45% of children gained 10 points or more and 12.5% gained 5 to 9 points on intelligence test scores, Peabody Picture Vocabulary Test-Revised (PPVT-R). Studies showed that the fact of growing older, having both parents at the household, having high levels of maternal education as well as an early intervention have a $p < 0.001$. Another study also showed that the score at 3 years started at 84.1 and it increased 1.2 points per year [34].

Other studies show the opposite; in children with PVL, IQ at 8 years was 84, with a verbal IQ of 97 and normal visual acuity. The majority of children had unequal outcomes, with deficiencies in recognizing visual images, normal visuospatial ability, visual memory, non-verbal intelligence, face and letter recognition [35].

There is a lower performance in reading tests and spelling in infants less than 1000g, where 71% were located more than three standard deviations below average compared to term infants assessed with the Wechsler Intelligence scale [36]. When comparing scores from the Stanford Binet fourth edition with WISC-R for 19 exceptional children, there were no differences found in performance [37].

Objective of the Study

To compare neurodevelopmental outcomes of children with PVL at birth in two different periods, at 2 and 7 years of age.

Materials and Methods

Study observational, retrospective and analytical cohort of newborns with PVL at birth at two and seven years of age, conducted at the Department of pediatric follow-up of the National Institute of Perinatology. The clinical records of newborns with PVL who were seen at the Department of pediatric follow-up were divided into two periods: first period from 1993-2004, second period from 2005 - 2016, using the following criteria:

- Infants with periventricular leukomalacia during the neonatal period.

- Complete clinical file.

- Neurodevelopmental assessment at 2 years.

- At least with one Terman Merril assessment at 7 years (IQ).

Exclusion criteria:

- Drop outs.

- Loss of the clinical record.

- Major congenital malformations.

- Not complying with pediatric follow-up appointments.

Assessment instruments at 2 years of age
Services involved in the pediatric follow-up

- Pediatrics: Amiel Tison neurological examination and neurological assessment at two years.
- Neuromotor stimulation: Neurobehavioral assessment.
- Psychology: Bayley II Psychomotor assessment.
- Human comunication: Hearing and language.
- Anthropometric measurements: Weight, height, head circumference.

Assessment instruments at 7 years of age

Evaluation of intellectual coefficient through the stanford binet terman merrill fourth edition.

Scales used for the assessment
Amiel tison neurological assessment

Neurological examination done during the first 12 months of corrected gestational age, including: skull clinical examination, answers from the mother's questionnaire, sensory development, posture and spontaneous motor activity, passive and active tone, primitive reflexes and postural reactions [38].

Classification of neurological abnormalities

1. Mild: Altered maneuver in active or passive tone, upper and/or lower extremity reflexes, no asymmetries, head control, sitting independently, balancing the extremities.
2. Moderate: Upper/lower extremity asymmetries, alterations in passive and/or active tone, head control, sit-up assistance, sitting up for 30 seconds, absence of balance reflexes.
3. Severe: Abnormal motor activity, poor for age, absence of head control, absence of independent sitting, legs get stiff or cross/scissor, opisthotonos [39].

Mayo clinic neurological examination

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

Cerebral palsy; motor examination

1. Monoparesis: Reduced strength of an upper or lower extremity.
2. Monoplegia: Loss of strength of an upper or lower extremity.
3. Paraparesis: Reduced strength in upper and lower extremities.
4. Paraplegia: Loss of strength in upper and lower extremities.
5. Hemiparesis: Reduced right or left strength.
6. Hemiplegia: Loss of right or left strength.
7. Quadriparesis: Reduced strength in the four extremities (with independent gait).
8. Quadriplegia: Loss of strength in the four extremities (absence of functional ability).
9. Tetraparesis: Reduced strength in upper extremities.
10. Tetraplegia: Loss of strength in upper extremities [40].

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 [41].

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 [42].

Human communication:

- Normal hearing international system 10-20db
- Superficial 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
- Language expressed in months at 24 months [43].

Anthropometric measurements

Weight in grams, height and head circumference in centimeters [44].

Terman merril (Stanford binet) fourth edition

Intelligence scale assessing normal IQ score ≥ 89, taking into account the following cognitive skills:

- Overall IQ
- Verbal reasoning
- Visual abstraction
- Mathematical reasoning
- Short-term memory [45].

The data analysis used measures of central tendency, Student's T-test, Pearson's Chi squared-test.

Results
Perinatal results

PVL diagnosis was made with cranial ultrasound. In the 22 years of the study, 8088 patients who were enrolled in the pediatric follow-up service were examined and they were divided into two periods. The first period from 1993 to 2004 enrolled 4256, only 48 (1.1%) had PVL, the second period from 2005 to 2016 enrolled 3832 patients and 93 (2.4%) had PVL; the incidence increased 32% from one period de the other. The average gestational age was 30.2 weeks, < 3 days, average weight 1196.8g, < 114.8g in females, with an increase of 9.9%, average maternal age 29.6 years, increase of 2.5 years, prenatal control increased 10.7%, prenatal steroids decreased 10.7%, c section de-

livery decreased to 6.8%, and there was an increase in eutocic delivery, being a healthy mother, use of surfactant, which were statistically significant favoring the second period. Apgar score and blood gases at birth were similar in both periods. Ventilation modes decreased, in spite of the increase in days; oxygen concentration decreased in the second period, which was statistically different, p = 0.050 (Table 1).

PVL N = 141-100%	First Period N = 48 (34%)	Second Period N = 93 (66%)	P Value	In favor or against second period
Gestational age 30.2 wks Mn 24 Mx 41	30.4 25-36	30.1 24-41	*0,070	< 0.03wkd
Weight 1196.8g Mn 540 Mx 3319g	1272.5g 590-2050g	1157.7g 540-3319g	*0,117	< 114.8g
Female 65 (46.1) Male 76 (53.9)	19 (39.6) 29 (60.4)	46 (49.5) 47 (50.5)	**0,265	> 9.9% < 9.9%
Maternal age 29.6 years Mx 16 Mx 43 years	28.0 16-43	30.5 16-42	*0,166	> 2.5 years
Prenatal control 104 (73.8)	32 (66.7)	72 (77.4)	**0,169	> 10.7%
Prenatal steroids 48 (43.6)	23 (47.9)	31 (33.3)	**0,067	< 10.7%
Route of delivery				
C section 122 (87.2)	44 (91.7)	78 (84.9)	**0,126	< 6.8%
Eutoci 17 (12.1)	3 (6.2)	14 (15.1)		> 8.9%
Forceps 2 (1.42)	1 (0,74)	1 (0,74)		=
Healthy 46 (35.6)	21 (43.8)	25 (26.9)	**0,020	< 16.9%
Preeclampsia 43 (33.2)	17 (35.4)	26 (27.9)		< 7.5%
***UTI 17 (12.1)	6 (12.5)	11 (11.8)		< 0.7%
Chorioamnionitis 14 (10.0)	6 (4.3)	8 (5.7)		> 1.4%
Diabetes Mellitus 8 (5.7)	3 (6.2)	5 (5.3)		< 0.9%
Apgar 1: 5	5	5	*0,977	=
Apgar 5: 7	7	7	*0,697	=
Ph 7.2	7.2	7.2	*0,646	=
Co2 44.5	43.3	45.2	*0,796	> 1.9
Surfactant 88 (62.4)	20 (41.7)	68 (73.1)	**0,000	> 31.4%
Without Ventilation 9 (6.4)	2 (4.2)	7 (7.5)	**0,172	> 3.3%
****IMV 93 (66.0)	33 (68.8)	60 (64.5)		< 4.1%
*****HFOV 16 (11.)	2 (4.2)	14 (15.1)		> 10.9%
Cephalic helmet 13 (9.2)	7 (14.6)	6 (6.5)		< 8.1%
******CPAP 10 (7.1)	4 (8.3)	6 (6.5)		< 1.8%
Ventilation days 11.5 days	9.8 days	12.5 days	*0,159	> 2.5 days
Concentration of O_2 71.8%	79.5%	67.2%	*0,050	< 12.3%

Table 1: *Perinatal Results.*
**Student's T test, **Pearson's Chi squared test, ***Urinary tract infection, ****Mechanical ventilation,
High-frequency oscillatory ventilation, ******Continuous positive airway pressure.

Neonatal morbidity

Intrauterine growth restriction with a 38% increase for the second period (p = 0.000), intraventricular hemorrhage, ventriculomegaly, retinopathy of the premature with a decrease in the second period with a statistically significant p value. Neonatal sepsis, multifactorial

hyperbilirubinemia, neonatal apnea, bronchopulmonary dysplasia, visual disability, increase in hospital stay, no increase in neonatal seizures, in the second period, were not statistically different (Table 2).

PVL 141-100%	First Period N = 48 (34%)	Second Period N = 93 (66%)	P Value	In favor or against second period
***IUGR 50 (35.5)	5 (10.4)	45 (48.4)	**0,000	> 38%
Neonatal sepsis 116 (82.3)	36 (75.0)	80 (86.0)	**0,084	> 11%
****MFHB 92 (65.2)	35 (72.9)	57 (61.3)	**0,117	< 11.6%
*****IVH 70 (63.6)	39 (81.2)	47 (50.5)	**0,000	< 30.7%
Ventriculomegaly 22 (15.6)	15 (31.2)	7 (7.5)	**0,000	< 23.7%
Neonatal seizures 40 (28.4)	15 (31.2)	25 (26.9)	**0,586	< 4.3%
Neonatal apnea 81 (57.45)	25 (52.1)	56 (60.2)	**0,228	> 8.1%
Bronchopulmonary dysplasia 62 (44.0)	17 (35.4)	45 (48.4)	**0,098	> 13%
******ROP 51 (36.1)	24 (41.7)	31 (33.3)	**0,030	> 8.4%
Visual disability 3 (2.1)	1 (2.1)	2 (2.2)		> 1.1%
Hospital stay 65.1 days Mn 1-175	60.2d	67.6d	*0,582	> 7.4d

Table 2: *Results neonatal morbidity.*

*Student's T test, **Pearson's Chi square test, ***IUGR intrauterine growth restriction,

****MFHB Multifactorial hyperbilirubinemia *****IVH intraventricular hemorrhage,******ROP retinopathy of prematurity.

Neurodevelopmental outcomes at 2 years

Amiel Tison neurological assessment at 12 months of corrected gestational age was normal in 8.3% vs 21.5% in the second period (p = 0.037); there were more abnormalities in the first period, with a decrease of 13.2% for the second period (p = 0.026). Mild and moderate abnormalities increased for the second period, with a decrease in severe abnormalities (Table 3).

PVL N = 141-100%	First Period N = 48 (34%)	Second Period N = 93 (66%)	P Value	In favor or against second period
Amiel Tison				
Normal 24 (17)	4 (8.3)	20 (21.5)		> 13.2%
Abnormal 117 (83.0)	44 (91.7)	73 (78.5)	*0,037	< 13.2%
Mild 37 (26.2)	10 (20.8)	27 (29.0)	*0,026	> 8.2%
Moderate 34 (24.1)	11 (22.9)	23 (24.7)		> 1.8%
Severe 46 (32.6)	23 (47.9)	23 (24.7)		< 23.2%
Mayo Neurological Examination				
Normal 58 (41.1)	9 (18.8)	49 (52.7)	*0,000	> 33.9%
Abnormal for ****CP 83 (58.9)	39 (81.2)	44 (47.3)	*0,000	< 33.9%
Monoparesis 2 (1.4)	2 (4.2)	0 (0)	-	< 4.2%
Paraparesis 7 (7.5)	0 (0)	7 (7.5)	-	> 7.5%
Hemiparesis (right) 15 (10.6)	7 (14.6)	8 (8.6)	*0,420	< 6.0%
Hemiparesis (left) 11 (7.8)	2 (4.2)	9 (9.7)	*0,130	> 5.5%
Quadriparesis **(IG) 21 (14.9)	11 (22.9)	10 (10.8)	*0,090	< 12.1%
Quadriplegia ***(NFA) 27 (19.1)	17 (35.4)	10 (10.8)	*0,000	< 24.6%

Table 3: *Amiel Tison/Mayo Neurological Assessments.*

*p = Pearson's Chi squared test, **IG Independent gait, ***NHF No functional ability, ****CP cerebral palsy.

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Neurological examination at two years of age was normal in 41.1%, with an increase in normality of 33.9% for the second period (p = 0.000). Cerebral palsy in the first period was 81.2% vs 47.3%, with a decrease of 33.9% (p = 0.000), mainly for the severe type (no functional ability), which was 35.4% for the first period vs 10.8%, the same for quadriparesis with a decrease in 12.1% for the second period, statistically significant (Table 3).

Neurobehavioral assessment of 141 children was 18.8% normal during the first period vs 40.9% for the second period with a p = 0.015, with an increase in normality of 22.1%. Mild delay increased for the second period from 14.6% to 19.4%, moderate delay decreased from 18.8% to 6.5%, severe delay decreased from 31.2% to 17.2%. Severe abnormalities were similar for both periods (Table 4).

PVL N = 141-100%	First Period N = 48 (34%)	Second Period N = 93 (66%)	P Value	In favor or against second period
Neurobehavioral assessment				
Normal 47 (33.3)	9 (18.8)	38 (40.9)	*0,015	> 22.1%
Mild delay 25 (17.7)	7 (14.6)	18 (19.4)		> 4.8%
Moderate delay 15 (10.6)	9 (18.8)	6 (6.5)		< 12.3%
Severe delay 31 (22.0)	15 (31.2)	16 (17.2)		< 14.0%
Severe abnormalities 23(26.3)	8 (16.7)	15 (16.1)		=
Audition				
Normal 134 (95.0)	44 (91.7)	90 (96.8)	*0,328	> 4.1%
Superficial hearing loss 3 (2.1)	2 (4.2)	1 (1.1)		< 2.1%
Moderate hearing loss 0 (0)	0 (0)	0 (0)		=
Severe hearing loss 3 (2.1)	2 (4.2)	1 (1.1)		<2 .1%
Unilateral hearing loss 1 (0.7)	0 (0)	1 (1.1)		> 1.1%
Language 16 months	11 months	18 months	**0,000	> 7 months
Min 2 Mx 24				
Anthropometry				
Weight 9.689g	9.698g	9.685g	**0,486	<13g
**SD 1611g				
Mn 4400 Mx 13 400	80.9 cm			
Height 81.2cm		81.3 cm	**0,455	> 0.4 cm
SD 5.2cm				
Mn 60.5 Mx 98.0cm	45.7 cm			> 0.3 cm
Head circumference 45.9 cm		46.0 cm	**0,913	
SD 32.4 cm				
Mn 37.5 cm Mx 51.0 cm				

Table 4: Neurobehavioral assessment, hearing, language 2 years, anthropometry.
*P = Pearson's Chi squared test, **Student's T test, *** Standard Deviation.*

Hearing was normal in 95% for both periods, 91.75 vs 96.8% for the second period, there was no moderate hearing loss in any period. In the second period, mild hearing loss decreased, with a severe unilateral hearing loss, not statistically different. Language in months during the first period, 11 months, increasing to 18 months for the second period with a p = 0.000 (Table 4).

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Anthropometric measurements: Average weight 9.689g (p25), 13g less in the second period, height 80.9cm (p75) vs 81.3cm (p75) for the second period, with an increase of 0.4cm. Head circumference 45.7cm (p25) in the first period vs 45.0cm (p50) for the second period, and in spite of normalization, none of them were statistically significant (Table 4).

Bayley II in the mental scale (MDI): Normal 10.4% in the first period vs 31.2% in the second period, with p = 0.000. Mild developmental delay was in the first period of 14.6% vs 23.7%, significant delay 25.0% vs 38.8% for the second period. However, 21% of the population was within normal ranges (Table 5).

Motor scale (PDI): Normal 6.2% vs 17.2% for the second period, with p = 0.000. Mild developmental delay was found in 12.5% in the first period vs 26.9% in the second period, significant delay 27.1% in the first period vs 49.5% in the second period. Only 13.5% of the population was normal. The number of not assessed children for both scales was considerably less during the second period (Table 5).

PVL N = 141-100%	First Period N = 48 (34%)	Second Period N = 93 (66%)	P Value	In favor or against second period
Normal MDI 34 (24.1)	5 (10.4)	29 (31.2)		> 20.8%
Normal PDI 19 (13.5)	3 (6.2)	16 (17.2)		> 11.0%
Below average			*0,000	
MDI 77 (54.6)	19 (39.6)	58 (62.4)	*0,000	> 22.8%
PDI 90 (63.8)	18 (39.6)	91 (76.4)		> 36.8%
85-115 normal development				
MDI 34 (24.1)	5 (10.4)	29 (31.2)		> 20.8%
PDI 19 (13.5)	3 (6.2)	16 (17.2)		> 11.0%
70-84 mild developmental delay				
MDI 29 (20.6)	7 (14.6)	22 (23.7)		> 9.1%
PDI 31 (22.0)	6 (12.5)	25 (26.9)	*0,000	> 14.4%
< 69 Significant developmental delay			*0,000	
MDI 48 (34.0)	12 (25.0)	36 (38.7)		> 13.7%
PDI 59 (41.8)	13 (27.1)	46 (49.5)		> 22.4%
Not assessed MDI 30 (21.3)	24 (50.0)	6 (6.5)		< 43.5%
PDI 32 (22.7)	26 (54.2)	6 (6.5)		< 57.7%
MDI 73, ***SD 19.5 Mn 50 Mx 114	69.4	74.6	**0,766	> 5.1
PDI 68.2, SD 15.7 Mn 44 Mx 111	64.7	69.0	**0,081	> 4.3

Table 5: Bayley; MDI Mental Scale, PDI Motor Scale 2 years.
p= Pearson's Chi squared test, **Student's T test ***Standard Deviation.

As to the average score for MDI in the first period, it was 69.4 vs 74.6 points, with an increase of 5.1 points for the second period (p = 0.766). The motor scale (PDI) was 64.7 vs 69.0, with a 4.3 point increment (p = 0.081), which is important in spite of not being statistically significant (Table 5).

Intellectual quotient results at seven years of age

At the time of the study, only 83 children who were 7 years old were assessed by the Terman Merril (Stanford Binet) Intelligence Scale. For both periods, 56.5% were normal, with an increase in normality during the second period of 40.9% vs 62.3%, statistically significant (Table 6). The average and above average intellectual quotient was 66.5%, 54.5% in the first period vs 70.5%, favoring the second period,

with a p = 0.000, below average 45.4% during the first period vs 29.5%, with a p = 0.011 (Table 6). Cognitive abilities from both periods were 90.2, 87.8 for the first period vs 91.0 points (p = 0.406). Verbal reasoning 93.2, first period 91.9 vs 93.6, (p = 0.773). Visual abstraction was 86.8, first period 85 vs 87.5 (p = 0.773). Numerical reasoning 94.0, first period 83.7 vs 90.0 second period (p = 0.458), not statistically different. Short-term memory 91.6, first period 87.2 vs 91.5 second period (p = 0.047), being statistically different. Cognitive abilities were recovered by the second period except for visual abstraction, in spite of its increase by the second period (Table 6).

PVL N = 83-100%	First Period N = 22 (45.8%)	Second Period N = 61 (65.6%)	P Value	In favor or against second period
132 very superior	0 (0.0)	0 (0.0)	-	-
121 - 131 superior	0 (0)	0 (0)	-	-
111 - 120 high average 8 (9.6)	3 (13.6)	5 (8.2)	**0,744	< 5.4%
89 - 110 average 47 (56.6)	9 (40.9)	38 (62.3)	**0,047	> 21.4%
79 - 88 low average 11 (13.3)	5 (22.7)	6 (9.8)	0,240	< 12.9%
68 - 78 very low 7 (8.3)	2 (9.1)	5 (8.2)	0,750	< 0.9%
< 67 extremely low 10 (12.0)	3 (13.6)	7 (11.5)	0,900	< 2.1%
IQ average and above 55 (66.5)	12 (54.5)	43 (70.5)	0,000	> 16%
IQ below average 28 (33.5)	10 (45.4)	18 (29.5)	0,011	< 15.9%
Cognitive Ability	87.8	91.0	**0,406	> 3.2
Overall 90.2				
**SD 16.6 Mn 44 Mx 118				
Verbal Reasoning 93.2	91.9	93.6	**0,773	> 1.7
SD 19.4 Mn 36 Mx 136				
Visual abstraction 86.8	85.0	87.5	**0,773	> 2.5
SD 169.48 Mn 00 Mx 120				
Numerical reasoning 94.0	83.7	90.0	**0,458	> 6.3
SD 15.8 Mn 52 Mx 120				
Short-term memory 91.6	87.2	91.5	**0,047	> 4.3
SD 15.2 Mn 43 Mx 123				

Table 6: Intellectual quotient using Terman Merril (Stanford Binet) at 7 years.
**Student's T test, ** Standard deviation.

Discussion

Periventricular leukomalacia is a severe complication of premature delivery that leads to cerebral palsy in the majority of affected children [14], sensory deficiencies [21]. In the last three decades, there have been remarkable survival rates in very low weight babies, however, long term severe neurological complications such as motor deficiency in the form of cerebral palsy, is the main cause of chronic neurologic complication in newborns with PVL and severe intraventricular hemorrhage. Our sample confirmed that this pathology has the highest rates in prematurity, with a mean of 30.2 weeks along with low birth weight [54,55].

On the other hand, it is well established that when subjected to different prenatal risk factors, newborns can develop PVL. Clinical and epidemiological studies suggest a relationship between maternal-fetal infection, inflammation and the onset of PVL [46,47]. It has been demonstrated that intrauterine or neonatal infection and inflammation related to septic episodes in premature infants have a high impact on periventricular leukomalacia due to the activation of excitotoxicity mechanisms and attack of free radicals. In our work, a high percent-

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age of sepsis was found, more than 80%, which might have possibly contributed to the generation of PVL [14-16]. In this regard, various publications report that the timely diagnosis and treatment of chorioamnionitis can prevent PVL. In our study, chorioamnionitis did not represent a risk factor because of its low incidence in the whole sample. Large, multicenter studies use rigorous definitions of chorioamnionitis in placental pathologies that clarify its impact on cerebral health. Reports have described that prenatal betamethasone given to mothers at 24-32 weeks, reduces the risk of PVL, which suggests a possible effect of steroids on the fetal inflammatory response. In our study, less than 50% received prenatal steroids, so we could not document any effect on PVL [17,18]. Mechanical ventilation has been reported as an important risk factor for PVL. Newborns requiring prolonged ventilation often suffer from recurrent episodes of hypoxia, which causes a disturbance on brain blood flow, with an increased risk in IVH [56]. Furthermore, proinflammatory cytokines produced in injured lungs can damage the immature brain through the systemic circulation, thus IVH and a prolonged dependence on a ventilator can act in synergy for the development of PVL. In our sample, 94% required ventilatory assistance, with an average of 11 days of ventilation. Even though there was no difference between the two periods, the percentage of ventilation was high for both periods, which probably influenced the development of PVL.

There is a close relationship between IVH and PVL with hypoxia/ischemia and infection/inflammation, which are the two main mechanisms in the pathogenesis of the white matter lesions and many risk factors in premature newborns can be understood by these two mechanisms [14]. Approximately 40 - 70% of PVL is associated to different IVH grades in premature newborns, specially the one that takes place within 48 - 72 hours after birth. Studies have demonstrated that IVH, in particular high grade IVH, can predispose to PVL, and is also a significant predictor of CP. Our study could indeed corroborate the information coming from different articles; hemorrhage was present in 63.6%, significantly higher in the first period, and it was also associated to ventriculomegaly.

The behavior of the Amiel Tison neurological examination for the detection of neurological abnormalities showed an increase in normality and a decrease in abnormality, with mild abnormalities showing an increase in 8.2%, moderate 1.8%, and severe 23.1%, favoring the second period. At two years it is amazing that normality was increased, with a reduction in CP which tends to slightly reduce the mild forms of CP, reducing the most severe forms such as quadriparesis from 22.9% to 10.8% with a decrease of 12.1% and for the most severe forms of CP with no functional ability from 35.4% to 10.8%, favoring the second period by a 24.6% reduction. This behavior of an increase of mild-moderate lesions has already been reported by other authors, who refer that children from the ninety's are not the same as children of the present time, and even though the prevalence of cerebral palsy remains the same, there has been a change in severe forms, with an increase in mild-moderate forms [1,2,7-10]. In developmental delays, there is a 22.1% increase in normality, with a 4.8% increase in mild delay, a 12.3% decrease in moderate delay, and 14% decrease in severe delay, favoring the second period. Severe alterations were similar in both periods. It is the same evolution that severe forms are preserved or reduced at the expense of mild-moderate delays.

There are no other authors reporting hearing in infants with PVL, but we did observe a reduction by the second period. Language couldn't improve in the second period, in spite of an increase in language. Language as a way of expression is an important achievement in development, and we can expect to see some delay in premature babies, but when there is an established brain lesion it's almost certain that this delay will be present, but the child's brain is highly plastic, which allows the appearance of alternative "cerebral plans" for language [49].

Nutrition-anthropometry of these children at two years shows low average weight, normal range height and normal head circumference in the second period.

The results of the Bayley scale are somewhat discouraging and controversial, both the mental and motor scales are different, showing very low scores, unlike the ones in the present study [8,9], with motor results being lower as expected. However, there are other studies showing successful results [30].

Few studies have investigated the impact of PVL on cognitive abilities in children with white matter abnormalities. Fortunately, the intellectual quotient increases with age; in the second period of the study, the intellectual quotient reached normality at seven years, better than what it reported by Italian studies [50]. Some only report normality of cognitive ability in verbal reasoning [51], other studies report

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an overall quotient below normal just as the overall quotient of both periods in this study [52]. Choi followed premature newborns at 3 and 9 years of age, using the WPPSI and WISC tests. Fifteen children with severe PVL had 50% intellectual disability, while 82.3% of children with mild periventricular leukomalacia had a normal intelligence. We confirmed the information of other authors in regards to the results, since only 66.5% (p = 0,000) were normal and one third, 33.5% (p = 0.011) were below average. Visual abstraction is maintained below normal overall, something to be expected because it has been described that visual perception is deteriorated in infants with PLV. 14 children with PVL were assessed at 5 years of age, with poorer perceptive visual abilities compared to infants with intraventricular hemorrhage. Children with PVL are at a high risk of visual perception deterioration, something that did not happen in this study.

Conclusion

The Department of pediatric follow-up of the National Institute of Perinatology found a low incidence of 3.1% in both periods. Sepsis, ventilatory assistance and intraventricular hemorrhage were present in PVL, as well as CP at two years of age, which was reduced 33.9% overall, 24.6% for quadriplegia with no functional ability. At seven years of age, one third of the patients had scores below average in their intellectual quotient, the majority of them with intraventricular hemorrhage.

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