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Mild peri-intraventricular hemorrhage (PIVH): factors associated with neurodevelopment and the parents' perception

Luara Fernandes Argenton Duarte[1], Gloria M. A. S. Tedrus[2,*]

[1]Master's in Health Sciences. Physiotherapist, Pontifical Catholic University of Campinas. Campinas, SP, Brazil.
[2]Professor - Health Sciences Program, Pontifical Catholic University of Campinas. Campinas, SP, Brazil.

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***Keywords*— neuropsychomotor development, peri-intraventricular hemorrhage, premature children.**

***Abstract*—** *Objective:To evaluate the relationship between clinical aspects and neurodevelopment in premature children with mild PIVH aged 6 to 24 months. The data were compared with that of children without PIVH. The parents' perception and adherence to the physiotherapy treatment was evaluated.*

Methods: Clinical aspects were related to data in the Denver II Test of premature children with mild PIVH and without PIVH, with statistical tests and p <0.05. The parents' perception of developmental delay and adherence to physiotherapy treatment were related to clinical aspects.

Results:We evaluated 34 children with mild PIVH and 36 children without PIVH, with a gestational age of 29 weeks. Risk of developmental delay was observed in 27 (79.4%) children with PIVH and in 10 (27.7%) children without PIVH. The risk factors associated with the occurrence of developmental delay, measured by the Denver II Test, were the presence of PIVH and the use of mechanical ventilation. In the regression test, it was observed that 12 (32.4%) parents noticed a developmental delay in the gross motor sector and was associated with the type of delivery, birth weight, gestational age, the presence of PIVH, the use of mechanical ventilation for> 7 days, and physiotherapy.

Conclusion: Premature children with mild PIVH had a worse neuropsychomotor outcome when compared to children without PIVH. Developmental delay was associated with the presence of PIVH and the use of mechanical ventilation. The parents' perception of neuropsychomotor delay was low and was associated to the low adherence to treatment.

I. INTRODUCTION

The prognosis of neuropsychomotor development in premature children with peri-intraventricular hemorrhage (PIVH) depends on a complex interaction between biological and environmental factors acting on the immature brain of these children. Some studies highlight several risk factors; however, the results are not yet unanimous and there is no single factor that can predict child development, despite the advances in perinatal and neonatal medicine.[1-8]

PIVH often occurs in the first 24 hours or the first days of life and is classified as mild or severe[9-12]. There are still controversies about the relationship between the degree of PIVH and vulnerability to deficiencies in neuropsychomotor development. There is a growing

number of studies that associate mild PIVH with neurodevelopmental impairment.[3-5]

On the other hand, it is known that rapid and effective early intervention in children with delayed neurodevelopment is of fundamental importance for the prognosis. The family's participation is decisive for the success of the therapeutic processes, however, there are still gaps in the knowledge of the parents' perception regarding the prognosis and adherence to the proposed treatment.

Thus, the objective of this study is to evaluate the relationship between clinical aspects with neurodevelopment data in premature children with mild PIVH, aged 6 to 24 months. Data from children with and without PIVH were compared. The perception of parents and/or guardians about developmental delay and adherence to physiotherapy treatment were related to obstetric, perinatal, and neonatal data.

II. METHODS

This is a cross-sectional, prospective, and observational study carried out at the outpatient clinic for the monitoring of high-risk newborns at the PUC-Campinas University Hospital, during the routine consultation at the pediatric services and the multidisciplinary team, in the period between August 2018 and July 2019.

Seventy children from 6 to 24 months of corrected age who were born prematurely at the PUC-Campinas University Hospital and who underwent the transfontanellar ultrasound examination before hospital discharge participated in this study.

Children with congenital malformations and genetic syndromes were excluded.

The Human Research Ethics Committee of the *Pontifícia Universidade Católica de Campinas*(PUC-Campinas,Pontifical Catholic University of Campinas) under protocol #73249517300005481, approved the study. Parents or guardians who agreed to participate in the research signed the informed consent form.

Procedures

Parents and/or legal guardians were evaluatedin the following aspects:

Clinical data: Maternal age and educational level, as well as obstetric, perinatal, and neonatal data were obtained from the hospital's medical records.

Questionnaire to evaluate the perception of parents and/or guardians.The following question was applied: “Is your child's development normal or what problem did you observe?” - whichis part of the Parents’ evaluation of developmental status questionnaire.

The children were submitted to a clinical evaluation and the Denver II Test.

Denver Developmental Screening (Denver II Test) 13: a screening test, which evaluates areas of neurodevelopment, being a standardized test, of rapid application, and widely used in Brazil.

Statistical analysis

Data were analyzed using the IBM SPSS Statistics software, version 22. The significance level adopted for the statistical tests was $p < 0.05$.

We described categorical variables using absolute values and percentages, and continuous variables as means and standard deviations.

Univariate and multivariate logistic regression were performed to determine which factors are associated with PIVH, and demographic aspects (the child’s sex, and the mother’s educational level and age) and obstetric, perinatal, and neonatal data (type of delivery, an Apgar test in the first and fifth minutes of life, birth weight and gestational age).

Perinatal data (pulmonary bronchodysplasia, hyaline membrane disease, persistence of the ductus arteriosus, jaundice and anemia, the need for mechanical ventilation [> 7 days and non-invasive], and the occurrence of transient tachypnea) were evaluated, which are associated with PIVH in univariate and multivariate logistic regression.

Obstetric, perinatal, and neonatal data associated with the risk of developmental delay in the Denver II Test and parents' perception in univariate and multivariate logistic regression were evaluated.

III. RESULTS

A total of 34 children with mild PIVH (PIVH grade I, n = 20; PIVH grade II, n = 14), 17 (50%) of which were girls, and 36 children without PIVH, 17 (50%) of which were girls, all of them with a gestational age of 29 weeks, were evaluated. The birth weight of the 70 children was less than 1500 grams. At the time of the evaluation, the age group was 6 to 24 months old. There was no statistically significant difference in sex, age, and birth weight between children with mild PIVH and without PIVH.

It was observed that the prenatal and perinatal risk factors associated with PIVH were vaginal delivery (3.84; 95% CI; 1.19 - 12.38, $p = 0.024$), gestational age (0.637; 95% CI; 0.509 - 0.797, $p < 0.001$) and birth weight (0.755; 95% CI OR; 0.648 - 0.878, $p < 0.001$) in univariate and

multivariate logistic regression. The other aspects had no statistical significance and were excluded from the equation.

Postpartum factors associated with PIVH in univariate and multivariate logistic regression were pulmonary bronchodysplasia (OR 1.0 -0.11; 95% CI OR; 0.03 - 0.42; p = 0.011), hyaline membrane disease (OR 1.0 - 6.00; 95% CI OR; 1.52 - 23..74; p <0.001), mechanical ventilation> 7 days (OR 1.0 - 7.14; 95% CI; 2.35 - 21.70; p <0.001), non-invasive mechanical ventilation (OR 1.0 - 3.69; 95% CI OR; 1.16 - 11.80; p = 0.028), and transient tachypnea (OR 1.0 -0.11; 95% CI OR; 0.03 - 0.42; p = 0.001). The other variables were excluded from the equation.

Risk of neurodevelopmental delay

Risk of developmental delay, measured by the Denver II Test,was observed in 27 (79.4%) children with PIVH and in 10 (27.7%) children without PIVH. It was observed that the developmental delay in the gross motor, fine-adaptive motor, and language areas occurs significantly more in children with PIVH when compared to children without PIVH (Table 1).

When evaluating the risk factors associated with the occurrence of developmental delay using the Denver II Test, it was observed that only the presence of PIVH and the use of mechanical ventilation remained in the regression equation (Table 2).

Perception of parents and/or guardians and Adherence to physiotherapy treatment

Among children at risk of developmental delay in only 12 (32.4%) cases, there was a perception of delay by parents and/or guardians. This perception was associated with the delay in the gross motor sector, measured by the Denver II Test.

In the regression test, there was an association between the perception of developmental delay by parents and/or guardians with the type of delivery, birth weight, gestational age, the presence of PIVH, the use of mechanical ventilation for a period longer than 7 days, and physiotherapy follow-up (Table 3).

Among the 12 children (with and without PIVH) at risk of developmental delay in the Denver II Test, four parents and/or guardians did not adhere to the physiotherapy treatment and justified it because they did not have the perception of the delay and/or for other reasons (Table 4).

Table 1. Presence of delayed neuropsychomotor development in the Denver II Test in children with and without PIVH.

	Mild PIVH (n=34)	Without PIVH (n=36)	*p*-value	OR	95% CI OR
Gross motor	24 (70.5%)	4 (11.1%)	<0.001*	64.39	3.60 – 1150.93
Fine-adaptive motor	12 (35.2%)	3 (8.3%)	0.002*	8.75	2.23 – 34.40
Personal-social	10 (29.4%)	0	0.051	4.33	0.99 – 18.81
Language	23 (67.6%)	9 (25%)	0.010*	8.18	1.64 – 40.86

PIVH: Peri-intraventricular hemorrhage;OR: Odds Ratio. *p<0.05.

Table 2. Factors associated with risk of developmental delay, according to the Denver II Test (n = 70).

Variables	Categories	*p*-value	OR	95% CIOR
HPIV	No (ref.)	---	1.00	---
	Yes	<0.001*	8.71	2.58 – 29.36
Mechanical ventilation	No (ref.)	---	1.00	---
	Yes	0.003*	8.35	2.08 – 33.48

PIVH: Peri-intraventricular hemorrhage; OR: Odds Ratio;ref: reference. *p<0.05.

Table 3. Factors associated with the perception of risk of developmental delay (n = 70).

Variable	Categories	*p*-value	OR	95% CIOR
Mother's educational level	Higher education (ref.)	---	1.00	---
	High school	0.452	1.59	0.07 – 37.44
	Complete elementary school	0.288	2.80	0.14 – 57.48
	Incomplete elementary school	0.071	9.53	0.44 – 207.37

Mother's age	Continuous variable (years)	0.851	0.991	0.903 – 1.088
First son	No (ref.)	---	1.00	---
	Yes	0.151	0.36	0.09 – 1.46
Type of delivery	Cesarean section (ref.)	---	1.00	---
	Vaginal	0.042*	3.83	1.05 – 14.03
Apgar - 1st minute	Continuous variable	0.647	0.943	0.735 – 1.210
Apgar - 5th minute	Continuous variable	0.668	0.843	0.387 – 1.837
Birth weight	Continuous variable (100g)	0.021*	0.786	0.642 – 0.964
Gestational age	Continuous variable (Weeks)	0.019*	0.736	0.569 – 0.952
HPIV	No (ref.)	---	1.00	---
	Yes	0.017*	7.08	1.42 – 35.28
Mechanical ventilation	No (ref.)	---	1.00	---
	Yes	0.006*	7.24	1.74 – 30.05
> 7 days	No (ref.)	---	1.00	---
	Yes	0.140	4.95	0.59 – 41.30
Non-Invasive Mechanical Ventilation	No (ref.)	---	1.00	---
	Yes	0.036*	4.11	1.10 – 15.36
Monitoring with Physiotherapy	No (ref.)	---	1.00	---
	Yes	<0.001*	32.84	1.86 – 581.14

PIVH: Peri-intraventricular hemorrhage; OR: Odds Ratio; ref: reference *p<0.05.

Table 4. Perception of delay in neurodevelopment and justifications for parents and/orlegal guardians.

Age (months)	*PIVH*	*Physiotherapy*	*Denver II Test - Sector with Change*				*Reason*
			Personal-social	Fine-adaptive motor	Language	Gross motor	
11	Yes	Yes	No	No	Yes	Yes	Delay in sitting
11	Yes	Yes	No	No	Yes	Yes	Delay in sitting
20	Yes	Yes	No	No	Yes	Yes	Still does not speak
10	Yes	No	Yes	Yes	Yes	Yes	Born premature
13	Yes	No	No	No	Yes	Yes	Still does not speak
13	Yes	No	Yes	Yes	Yes	Yes	Born premature
8	Yes	Yes	No	Yes	Yes	Yes	Does not sit yet
8	Yes	Yes	Yes	Yes	No	Yes	Does not sit
9	Yes	Yes	No	No	Yes	Yes	Does not sit yet
6	Yes	Yes	No	Yes	Yes	Yes	Does not sit
8	Yes	No	No	No	Yes	Yes	Born premature
6	No	Yes	No	No	No	Yes	Born premature
21	No	Yes	No	No	Yes	Yes	Cannot speak

PIVH: Peri-intraventricular hemorrhage.

IV. DISCUSSION

The results of our study show a high risk of neurodevelopmental delay in children aged 6 to 24 months, who were premature, with PIVH grades I and II, and significantly higher than that observed in children without PIVH. These data suggest that lesions in the germinal matrix caused by PIVH affect the neuronal and glial precursor cells involved in the process of neural migration, causing impairment of myelination and cortical and subcortical development, with worse outcomes and short and long-term neurological sequelae.[11,12]

Our data showed that the gross motor, fine-adaptive motor, and language areas were the ones of greatest risk of developmental delay,according to the Denver II Test, and similar to those found by other authors.[7,8]

The high risk of neurodevelopmental delay observed in children with mild PIVH compared to children without PIVH, aged 6 to 24 months, has been observed in other studies that evaluated children aged 2 to 3 years and at 5 years of age.[4,7,8] In a different way, other studies did not evidence any risks to the neuropsychomotor outcome caused by mild PIVH, when comparing the risks of children without PIVH.[5,12]

Risk factors associated with PIVH and developmental delay

The obstetric, perinatal, and neonatal risk factors for PIVH observed in our study are similar to those described in the literature.[1,9,11,15] However, in a different way, demographic and clinical aspects such as sex, maternal educational level and age, and low Apgar scores were risk factors described by other authors.[10]

The risk factors associated with unsatisfactory neurological development in the Denver II Test were the presence of PIVH and the use of mechanical ventilation. It is known that prolonged assisted ventilation can lead to significant changes in cerebral hemodynamics and to increased intracranial pressure, which are deleterious mechanisms to the developing brain and can lead to motor, cognitive or global damage. These risk factors are similar to those described in other studies. [11,12,16]

Parents' perception: child development

Despite the risk of developmental delay observed in our study, only a third of parents noticed a developmental delay, and the rest stated that their child's development was normal. This finding may be related to the high expectation that parents have about their children or the difficulty and/or reluctance to recognize that children have any changes and/or delays.

The family of children with neurological problems in childhood often faces the crisis of losing a perfect child, often having doubts about the clinical and prognostic profile, and this finding is often associated with cultural factors, social risks, and family prejudices.[17,18]

Adherence to physiotherapy treatment

Of the sample of children with and without PIVH, at risk of developmental delay, approximately half of the cases did not adhere to the indicated physiotherapy treatment. In most cases, parents and/or guardians did not notice adevelopmental delay due to difficulty or underestimating and/or not following the guidelines, which suggests that the parents' perception is fundamental and influences treatment adherence. Similarly, other studies have found that the Denver II test was more capable of detecting the risk of developmental changes than the parents' perception.[19] This data is essential to be considered in public health, as it will interfere in child development in the short and long term, and thus promote health, improve skills, minimize delays, and prevent the functional, cognitive, motor, and behavioral deterioration of children.

V. CONCLUSION

Premature children with mild PIVH had a worse neuropsychomotor outcome when compared to children without PIVH. Mild PIVH and the use of prolonged mechanical ventilation had a significant impact on the outcome of neurodevelopment in premature children. The parents' perception of neuropsychomotor delay was low and was associated with the low adherence to treatment.

Highlights

- Premature children with mild PIVH had a worse neuropsychomotor outcome when compared to children without PIVH.
- Mild PIVH and the use of prolonged mechanical ventilation had a significant negative impact on the neurodevelopment of premature children.
- The parents' perception of neuropsychomotor delay was low and was associated with the low adherence to treatment.

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