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ADVANCES IN PEDIATRIC RESEARCH

Early assessment of oculomotor behavior in infants with bronchopulmonarydysplasia: A transversal study

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Abstract

Background: In Brazil, where there are difficulties in accessing health services, the increasing number of comorbidities in preterm survivors diagnosed with bronchopulmonary dysplasia (BPD) necessitate the creation of a tool to effectively evaluate aspects of visual function in a short time. The objective of this study was to develop a simple protocol to evaluate the oculomotor system in newborns with BPD.

Methods: Our study compared two groups of preterm-born infants: those who were oxygen-dependent for longer than 28 days were included in the BPD group (BG), while babies given oxygen for a maximum of 10 days were included in the premature group (PG). Exclusion criteria were: babies under mechanical ventilation and/or vasoactive drugs, those with intracranial hemorrhage, retinopathy of prematurity, motor and/or neurological malformation. Assessments were performed while the baby was comfortably seated and evaluated four eye movement types: saccadic movements (SAC), smooth pursuit (SP), vestibulo-ocular reflex (VOR), and optokinetic nystagmus (OKN).

Results: Fifty-two infants were evaluated and of these, 22 were included in the BPD group and 30 in the premature group. Birth weight, gestational age and Apgar score at one and five minutes did not differ significantly between the two groups. Infants with BPD demonstrated the absence of three of the four eye movements types; according to a Chi-square test, this was statistically significant when compared with the premature group.

Conclusions: The protocol considered in this study was sufficient to evaluate the oculomotor system in newborns diagnosed with BPD. Ocular motility in these infants was found to be impaired when compared to babies without a BPD diagnosis.

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Introduction

The assessment of visual function has become a part of neonatal neurological examinations [1-3]. It is included in widely used methods such as the Hammersmith neonatal neurological examination [4], the Amiel-Tison examination [5] and the Brazelton examination [6]. Visual assessment has led to reports of the emergence and maturation of some aspects of newborn visual function including ocular motility,

acuity, color differentiation, attention and memory [2, 3, 7-9]. In this study, we highlight tests exploiting the oculomotor system [10, 11].

The oculomotor system is considered an indicator of neural functioning. It is represented by a complex interdependence between the sensorial system and ocular motility, and its command of muscular contraction is determined by the central nervous system [10-13]. However, the application of scales to assess the ocularmotor system is time consuming and requires appropriate training. Furthermore, they are largely directed at older, bigger babies; little is known about the development of the oculomotor system in premature babies [2].

Premature babies face the possibility of a life with significant disabilities, including cerebral palsy, cognitive impairments, and visual and hearing dysfunctions [14-16]. These diseases incur significant costs both for families and society, due to the loss of human potential to work, and in terms of long-term health care [14, 17]. Multiple factors may predispose the preterm newborn to these deficits; among these, the diagnosis of bronchopulmonary dysplasia (BPD) is one of the most important [18].

BPD is a major chronic lung disease of infants and it is indicative of comorbidities [16]. It generally occurs in preterm newborns undergoing oxygen therapy. Its evolution is associated with frequent and prolonged deaths and hospitalizations, especially those due to pulmonary complications, and comorbidities such as higher prevalence of cerebral palsy, neuropsychomotor development delay, cognitive impairment, and weight and height development disorders, thus giving rise to neurological and/or behavioral impairments [16,19]. As it is considered a sign of comorbidity, impairments resulting from neurological and/or behavioral disorders can interfere with the growth and physiological development of the newborn, and may cause changes in various sensory and motor systems [17, 20, 21].

In view of the difficulties in accessing health care services in Brazil, the increasing number of comorbidities in preterm survivors with a diagnosis of BPD [22] necessitates the creation of a tool that will effectively evaluate aspects of visual function in a short time, as part of a routine assessment of infants at risk of developing visual and neurological abnormalities [2,3]. The goal of this study is to develop a simple protocol to evaluate the oculomotor system in newborns with a diagnosis of BPD.

Methods

This is a transverse analysis of preterm newborns who were born and admitted to either: the Intensive and Intermediate Care Neonatal Unit at the Children's Hospital in Goiânia, Goiás, Brazil, or the Inpatient Unit of Kangaroo Care Rooming at Dr José Pedro Bezerra Hospital, in Natal, Rio Grande do Norte, Brazil.

Ethics statement

This study was approved by the Committee of Ethics in Research at the Institute of Psychology, University of São Paulo (2010.008), and by the Federal University of Rio Grande do Norte's Committee of Ethics in Research (065/11-P). Written parental consent was obtained for all neonatal subjects enrolled.

Sample characteristics

Preterm infants with a clinical diagnosis of BPD were included in the BPD group (BG) and preterm infants who were hospitalized and used oxygen for no more than 10 days [23, 24] were included in the premature group (PG). Infants were considered premature if they had a gestational age ≤36 weeks and a clinical diagnosis of BPD; infants with a gestational age ≤ 36 weeks who were dependent on oxygen concentrations above 21% for a period equal to or greater than 28 days were also included [23,24]. All newborns included in the study underwent ophthalmologic assessment of the fundus and returned normal results. The ophthalmologic assessment was performed by an ophthalmologist and followed the Unit's usual routine, namely clinical assessment of the eye, and ophthalmoscopy.

Exclusion criteria were: babies under invasive and/or non-invasive mechanical ventilation, the use of vasoactive drugs, diagnosis of intracranial hemorrhage or other neurological disorders acquired and identified during the neonatal examination, motor

and/or neurological malformation, retinopathy of prematurity and Apgar score at five minutes <5.

Assessment of eye movements

The proposed protocol was implemented in newborns 30 days old. Each assessment lasted 10 minutes on average, during which four eye movements were elicited: saccadic movements, smooth pursuit, optokinetic nystagmus and the vestibulo-ocular reflex. Eye movements were evaluated in a random order, and each one was tested three times to confirm its presence (1) or absence (0). A result of 0 was recorded when all three trials revealed no eye movements, and a result of 1 was given when eye movements were found in at least in one of the three tasks [2, 3].

With the exception of the vestibule-ocular reflex assessment, newborns were comfortably seated during the protocol, and/or placed lying in a stand with the head and trunk comfortably supported by the researcher's hand (Fig. 1a); during the vestibulo-ocular reflex assessment the baby was placed in the researcher's lap (Fig. 1b). Assessments were performed only once, responses were obtained binocularly, and newborns were in a state of spontaneous alert [10].

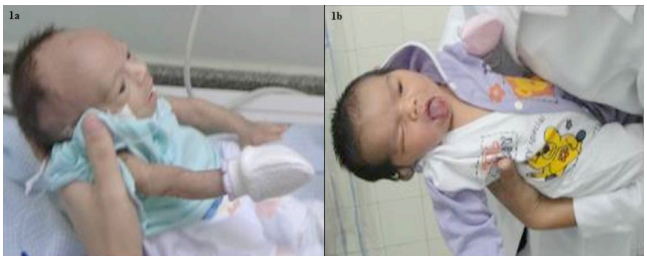

Figure 1. Positions used for the evaluation of eye movements.

(1a) Position for evaluation of optokinetic nystagmus, saccades and smooth pursuit movements. (1b) Position adopted to assess the vestibular-ocular reflex.

Assessment of optokinetic nystagmus (NOC)

A target-shaped drum (radius 6.5 cm, 12.4° of visual angle; height 17 cm, 31.6° of visual angle), with horizontal black and white stripes (4 cm each; 7.6 cycles per degree of visual angle), was presented 30 cm away from the baby. The drum was rotated in front of the baby in an attempt to attract attention and evaluate the optokinetic nystagmus. Vertical measurements were performed with the stripes rotating left and right (Fig. 2a), and horizontal measurements were taken by rotating the stripes up and down (Fig. 2b). During the assessment, it was expected that the baby would follow the movement of the drum by way of repeated and involuntary rhythmic, oscillating motions of the eyes (movements of smooth pursuit and saccadic movements of return).

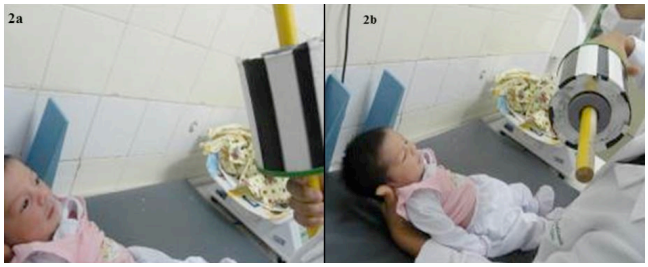

Figure 2. Assessment of optokinetic nystagmus (NOC)

A drum (radius 6.5 cm, 12.4° of visual angle; and height 17 cm, 31.6° of visual angle) with horizontal black and white stripes (4 cm each; 7.6 cycles per degree of visual angle was used to evaluate optokinetic nystagmus. Vertical measurements were performed with the stripes rotating left and right (Figure 2a), and horizontal measurements were made by rotating the stripes up and down (Figure 2b). During the assessment it was expected that the baby would follow the movements of the drum by presenting repeated and involuntary rhythmic, oscillating motions of the eyes (movements of smooth pursuit and saccadic movements of return).

Assessment of saccadic movements (SAC)

In order to evaluate saccadic eye movements, a stimulus of great importance for the baby was used: the human hand. With the baby's head fixed to prevent its movement, the researcher presented their hand 30 cm away from the baby (length 17 cm, 31.6° of visual angle; width 8 cm, 15.18° of visual angle). To stimulate the onset of saccades, the palm of the researcher's right hand was brought suddenly into the baby's visual field at an angle of approximately 30°, and moved left and right in an effort to measure the response to the baby's visual field. During the

assessment it was expected that the baby would look towards the target presented.

Assessment of vestibulo-ocular reflex (VOR)

Newborns were laid comfortably on the researcher's forearms in a supine position. The assessment began by moving the baby vertically up and downwards in an effort to stimulate pendulum-like "doll's eye movements." The baby was also moved laterally from right to left and back again. During the assessment it was expected that the baby's eyes would shift in the opposite direction to the movement (movement presence). The eye movement was only counted as present or absent after the baby was returned to the starting position.

Smooth pursuit movements (SP)

As for the study of saccadic movements, the human hand was used as a stimulus to study smooth pursuit movements. With the baby's head fixed by the researcher to prevent its movement, the researcher's hand was presented in front of the baby (length 17 cm, 31.6° of visual angle; width 8 cm, 15.18° of visual angle); and it was moved slowly (approximately three degrees of visual angle per second), covering 30° of the visual field to the right and to the left. All movements were performed horizontally. During the assessment it was expected that the baby's eyes would shift in the same direction of the movement.

Statistical analyses

Two observers, trained by the researcher and naïve to the babies' clinical information and the results obtained, were responsible for evaluating a total of 17 newborns (32.6% of the sample). All three evaluators performed the data collection at the same time and the analysis was not discussed during the assessment of eye movements. No statistical difference was found between the frequencies expected by the three examiners in any of the analyzed movements ($p>0.05$, Kappa Test). Results observed in a higher frequency (by the principal investigator) were used as a reference in the analysis of eye movements.

To present the results, a complete descriptive analysis and verification of normal distribution using the Shapiro Wilk test was performed. The association between the two groups (BG and PG) for each of the qualitative variables was performed using a one-way ANOVA test. Results obtained from the assessment of eye movements between the two groups were validated using the Chi-square test. All data were tabulated using Statistica software version 10.0 (Statsoft Inc. Tulsa, OK, USA). A significance level of 5% was used for all statistical analysis. The fact that BG infants gave positive results for each of the four tested eye movements was considered the null hypothesis.

Results

Fifty-five preterm infants with gestational ages between 26 and 36 weeks were evaluated between January 2010 and July 2011. Fifty-two were selected to be part of the study: 22 babies were assigned to the BPD group (BG) and 30 babies to the premature group (PG); three newborns with a gestational age of < 37 weeks were excluded - two for having used oxygen for 15 days and one due to a diagnosis of intracranial hemorrhage. The mean gestational age of the 52 evaluated infants was 33 weeks (± 2.54 weeks) with a mean birth weight of 1874g (± 671.61). All infants were hospitalized (mean of 23 days ± 15.5 days) and 38 infants (73%) made use of oxygen (16 days ± 19.55 days).

BG babies presented with a significantly lower gestational age, birth weight and Apgar 1st minute, and made use of oxygen for a greater number of days compared to PG babies. Table 1 shows the sample characteristics between the two studied groups.

Of the four movements evaluated in BG, three were statistically different when compared to PG: OKN (χ^2=12.7, p<0, 05), VOR (χ^2=3.2, p=0.04) and SP (χ^2=3.9, p=0.02). Infants diagnosed with BPD were 14 times less likely to present OKN movements compared to PG babies. Table 2 presents the sample data.

We also studied the influence of length of hospital stay and the use of oxygen on the motor behavior of the evaluated infants. In this analysis we found that these variables negatively influence the oculomotor

response. Infants with a longer period of hospitalization and a longer period spent on oxygen were found not to have this movement.

Discussion

An important aspect of our study was to evaluate the oculomotor system of oxygen dependent preterm newborn babies, who were hospitalized within the Neonatal Intensive Care Unit. Length of stay and use of oxygen are known to be two of the main factors attributed to neonatal complications, and are related to postnatal developmental deficiencies, as well as gestational ages and birth weights [19, 25].

The transverse assessment of the oculomotor system performed in our study was sufficient to demonstrate that premature infants under prolonged use of oxygen (>28 days) present with functional impairments of the oculomotor system when compared to premature babies who have used oxygen for less than 10 days. BG babies demonstrated an absence of three of the four evaluated eye movements compared with PG babies, showing that difficulty in the acquisition of eye movements may be related to the prolonged use of oxygen; preterm babies that were not under prolonged use of oxygen were also included in this analysis. These babies were 14 times less likely to present with OKN movements compared to PG babies.

The consequences of variation in oxygenation and its effects on the visual system have already been identified in some studies. Children with BPD exhibit significantly lower performance in visual-motor integration tests when compared to children without BPD [26, 27] suggesting a delay in visual-spatial perception. Hospitalized premature infants may present with an early motor developmental delay, in a severe or limitrophe way. Birth weight, neonatal morbidities and the health care received in the neonatal unit were the factors most influencing the outcome [22].

Our study reveals that the longer the length of hospital stay, the worst the oculomotor evolution of vestibulo-ocular reflexes become. The VOR uses neural projections from the vestibular system as afferent stimuli to motor neurons of the eye muscles. This raises a first question as to whether changes should be made in the vestibular system of hospitalized babies who spend most of their time lying down, and who are under-stimulated [28].

The average length of hospital stay found in our study was 23 days; compared to the study of Serra et al., whose average length of stay was 15 days, this is rather high. In this study, 89.9% of the 117 evaluated babies presented with five-minute Apgar scores of six; 75.9% of the sample made use of oxygen for an average period of six days (± 11 days) [29].

We therefore believe that the long duration of hospital stay in our sample may be associated with the diagnosis of BPD. Such a result corroborates the findings of Furman et al. [30] and Smith et al [31], who showed that children with BDP spend more time in hospital than children without the diagnosis. The authors explain their findings by the fact that children with BPD require longer hospitalization during the neonatal period when compared to children without a diagnosis of BPD [30, 31].

Other relevant information in our study was the fact that the smooth pursuit movement was the second most affected among the four movements evaluated. This movement depends on a complex innervation network, which is perhaps later to develop [30]. Smooth pursuit in this phase is not continuous and thus reattachment adjustments are needed to track the object. During this period, visual warning is still very low, and fixation and visual tracking are just beginning to develop; there are few visual connections that can be found in the neonatal period, and since equally preterm babies that were not under use of oxygen were also part of this analysis, we believe that these few visual connections may be damaged by oxygen toxicity in this group.

Our data do not corroborate those presented by Ruas et al. [32], who evaluated 66 term infants in the first month of life, all asymptomatic with varying birth weight (range 3000-4140 g). For the assessment of visual behavior, these authors used a method of evaluating visual conduct composed of nine tests, and judgment was based on observation of the behavior of the child's response before stimuli were offered. One of the tests was a horizontal smooth pursuit task, which showed positive responses for 97.62% of the infants evaluated [32].

We have developed a protocol for early assessment of eye movements in infants diagnosed with BPD, as we believe that the motor components supplied by ocular muscles are complemented by similar data provided by means of pretension, manipulation and location [11]. Studies show that infants diagnosed with BPD are more likely to experience periods of falling blood oxygenation with subsequent episodes of cerebral hypoxia and damage in the neural pathways that control the eye muscles [33].

A hypothesis to explain the differences found between the two groups in our study suggests that BG babies may have suffered a negative adaptation to physiological responses caused by the prolonged use of oxygen; three of the four evaluated movements were different between the two groups.

Oxygen is essential for cellular life, but when used in excess (at concentrations greater than 60%) and over a prolonged period (longer than 15 days), it can lead to undesirable adaptations such as: frequent periods of falling oxygen desaturation at various times with impaired oxygenation in the central nervous system, and tissue injuries, such as respiratory depression, suppression of erythropoetin, pulmonary vasodilation, and systemic arterial vasoconstriction caused by oxygen toxicity [32, 34, 35].

Such adaptations can compromise the cellular defense system and contribute to the development of chronic lung disease since they may result in the release of free radicals and subsequent pulmonary fibrosis, and also impairment of the ventilation perfusion ratio. In addition, besides being a marker for the development of retinopathy of prematurity, characterized by retina vasoconstriction and neovascularization and its consequent traction, these alterations are also related to frequent fluctuations in the concentration of administered oxygen [34]. We can verify the existence of a direct relationship between BPD and the visual system, thus strengthening the need for early studies of visual functions in this population.

Longitudinal follow-up of these children would be required to further relate oculomotor assessment data with future motor and/or neurological problems. Despite this limitation, we have demonstrated that transverse assessment is sufficient to verify impairments of the oculomotor system in these infants.

Significant changes occur in a child's visual behavior within the first months of life, and these changes are influenced by factors of neurological maturation and environmental experience [31, 34]. Although visual disturbances are among the most commonly observed problems in preterm newborns [24, 25], we found no studies proposing a protocol for early assessment of eye movements for babies under these same conditions.

Due to the reciprocal relationship between visual function and motor function, we believe that the ability to detect early changes in the oculomotor system is attached to a timely diagnosis and prompt intervention, thus favoring the quality of life for children and their families.

Conclusions

The protocol considered in this study was sufficient to evaluate the oculomotor system in newborns diagnosed with BPD. Ocular motility in these infants was found to be impaired when compared to babies without a BPD diagnosis. We believe that prolonged dependence on oxygen in early life has a negative effect on preterm babies' pattern of eye movements.

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