ARTIGO ORIGINAL

Hemorragia periventricular, intraventricular e mecanismos associados à lesão em recém-nascidos pré-termos

Intraventricular, periventricular hemorrhage and mechanisms associated to the lesion in preterm newborns

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RESUMO
Este trabalho aborda em seu contexto, a incidência da hemorragia periventricular e intraventricular (HPIV) e mecanismos associados como leucomalácia periventricular (LPV) e hidrocefalia pós-hemorrágica (HPH) em recém-nascidos pré-termos. Os dados da pesquisa foram obtidos no Centro de Reabilitação Umarizal, no período de janeiro de 2004 a julho de 2005 e comparados com a bibliografia de vários autores que descreveram esta incidência. Cada paciente foi analisado, sendo correlacionadas as seguintes variáveis: idade quando realizada a triagem, diagnóstico, idade gestacional, peso ao nascimento, etiologia e sexo. Após o estudo, os resultados foram significativos em algumas variáveis: por ocasião da triagem 46% (13) com idade entre 1 e 2 anos; diagnóstico- HPIV 14% (4); LPV-46% (13); idade gestacional de 24 a 26 semanas 32% (9); peso ao nascimento entre 2000 a 3000g 36% (10); etiologia 30% (8) com sépsis; 75% (21) dos prontuários analisados eram de crianças do sexo masculino. Considerando os dados coletados, é imprescindível que haja a atuação multidisciplinar através de ações preventivas proporcionando uma maior sobrevida ao recém-nascido considerado de risco ou portador de deficiência, com a estimulação adequada prevenindo ou impedindo danos mais graves, possibilitando a criança desenvolver o máximo do seu potencial.

PALAVRAS-CHAVE
hemorragia cerebral, leucomalácia periventricular, hidrocefalia, recém-nascido

ABSTRACT
The main purpose of this review was to analyze the incidence of periventricular, intraventricular hemorrhage (PIVH) and associated mechanisms such as periventricular leukomalacia (PVL) and post-hemorrhagic hydrocephalus in preterm newborns. The data were obtained at the Division of Rehabilitation Medicine (DMR- HC FMUSP), Umarizal Rehabilitation Center, from January 2004 to July 2005 and compared to the specialized literature. Each patient was thoroughly analyzed and the following variables were correlated: age at the triage, diagnosis, gestational age at birth, birth weight, etiology and gender. The results were significant for some variables: 46% (13) were aged 1 to 2 years at the triage; 14% (4) had a diagnosis of PIVH and 46% (13) of PVL; 32% (9) had gestational age of 24 to 26 weeks at birth; 36% (10) had birth weight of 2,000 to 3,000g; 30% (8) presented an etiology of sepsis and 75% (21) of the patients were males. Considering the data obtained, a multidisciplinary intervention is important to improve survival of these at-risk or impaired newborns through preventive actions, by providing adequate stimulation, averting further damage and allowing maximum development of the child’s potential.

KEYWORDS
cerebral hemorrhage, leukomalacia periventricular, hydrocephalus, infant, newborn
INTRODUCTION

The peri and intraventricular hemorrhage (PIVH) is the most important neurological affection of the neonatal period, affecting primarily the pre-term newborn (NB) with birth weight < 1,750 g, causing severe motor and cerebral sequelae. It is one of the most frequent causes of injury to the central nervous system in this period.1

The basic PIVH consists in bleeding of the germinative subependymal matrix between the thalamus and the caudatum, near Mono’s foramen. This region is vascularized by several arterioles and veins, presenting several drainage systems, which suggests that a large part of the blood flow to the brain is directed to these areas. Close to the term of pregnancy, there is a remodeling of the vascular bed to irrigate the cortex, which becomes the most differentiated area at this time. This phenomenon causes the rapid involution of the germinative matrix.2

The hemorrhage can be limited to the area of the germinative matrix (Grade I); however, more than half of the hemorrhages disrupt the ventricular cavities (Grade II), with the possibility of progressive augment of the ventricles (Grade III). Grade IV hemorrhages originate from the cerebral parenchyma and their location and size are the main factors that contribute to the perinatal mortality and neurological morbidity.2

The PIVH onset time, recently defined through the assessment by a series of ultrasonography scans, is the first day of life in 50% of the cases and up to third day of life in 90% of the cases.3

In conclusion, the perinatal injury that affects the developing NB brain is a progressive process, which affects the subsequent structural differentiation of the injured site and of the adjacent gray matter, and can have a role in the pathogenesis of the neurocortical dysfunction.

PIVH has been studied for over 25 years and its incidence is related to prematurity, increase in survival of NB with birth weight < 1,000 g and mainly, to the neonatal practices and the management of neonatal and obstetric services.4

Its incidence varies from 5% to 90%, depending on the Center, although it frequently ranges between 30% and 40%.5

In Brazil, the incidence of PIVH has shown a trend to decrease, described as being around 50% to 60% until the beginning of the 80’s and 23% at the end of the decade, which must be ascribed to early diagnosis and multidisciplinary care.6

An elevated number of risk factors have been associated with the development of PIVH and low birth weight and gestational age < 30 weeks are the two most important isolated factors. Other risk factors are: smoking mother, male sex, premature membrane rupture, intrauterine infection, prolonged labor, early sepsis, respiratory distress syndrome, pneumotorax, frequent tracheal tube aspirations, metabolic acidosis and rapid bicarbonate infusion and high-frequency ventilation.7

The prognosis of PIVH varies according to the degree of the lesion. Cases with grade I and II hemorrhages, with a survival frequency of 80% to 90%, usually evolve without evident neurological abnormalities. Grade III hemorrhages can evolve to static or reversible ventriculomegaly with normal pressure, or can be followed by hydrocephaly with an incidence of cerebral palsy (CP) and mental retardation of 40%. Grade IV hemorrhage has high mortality, especially when large lesions occur in infants with low gestational age. Those with smaller lesions can present periventricular cysts, with an incidence of 30%.2-8

Other mechanisms of cerebral lesion normally accompany PIVH, such as periventricular leukomalacia (PVL) and posthemorrhagic hydrocephalus (PHH).9

The PVL is the most common and severe cause of CP in pre-term children. It is a hypoxic-ischemic injury that leads to the necrosis of the periventricular white substance and the formation of multiple small cysts.10,11 By affecting mainly the descending fibers of the cortical-spinal tract to the lower limbs, it can lead to the topographic diagnosis of spastic diparesis,12 whereas the cysts in the subcortical white substance were associated to spastic tetraparesis and visual deficit.9 Studies carried out in children with PVL and PIVH showed that many children presented cognitive and visual deficits (nystagmus and strabismus).13,14

Dan and Kato et al affirm that the most common form is the spastic diparesis, which affect 9% of the world’s population.15,16

In Brazil there are no conclusive study regarding the incidence of CP, which depends on the diagnostic criteria of each study. Thus, an elevated incidence is presumed, due to the little prenatal care given to pregnant women.17 Non-official national data have reported an incidence of 5 to 10 children per thousand births.18

The increasing CP incidence in the beginning of the 80’s coincided with the increased survival of the premature infants. One of the most accepted possibilities for this fact is that CP represents the finishing point in a chain of aversive effects, occurring in a period when the brain is particularly vulnerable to ischemic injuries.19

The last important injury mechanism is the post-hemorrhagic hydrocephalus (PHH) defined as the progressive ventricular increase secondary to PIVH.

The PHH is caused by the obliteration of the circulation in the cerebrospinal fluid (CSF) system in the ventricular system or in the arachnoid region, with formation of blood clots, preventing the circulation.

Even in cases of severe augment of the ventricles, there can be no concomitant increase in the cephalic perimeter, as in the premature newborn, the arachnoid spaces above the convexity and the basal cisterns are large and easily accommodate the enlarged brain.2 Several authors have confirmed the direct association between the neurological sequelae with the extension of the PIVH associated to hydrocephalus, emphasizing that the PHH, in the absence of parenchymatous injury, is not associated to motor sequelae.9

The treatment of PHH is surgical, with the use of unidirectional valvular drains aiming at draining the excess liquid from the lateral ventricles to other body cavities, annulling the physiopathological basis of the intracranial hypertension. The most often used type of draining is the ventriculoperitoneal shunt (VPS).20,21

Linder et al, reporting on the surgical treatment of a group of 36 children with PIVH grades III and IV, showed that 31% of them evolved with PHH and 1 patient needed the VPS.
Considering the impairment severity and the sequelae presented by these patients, programs at the Rehabilitation Centers are developed by a multidisciplinary team, aiming the priorities and objectives of a program. Rehabilitation admits multiple possibilities, depending on the careful analysis of each individual patient. The physical therapy treatment must be initiated early, programmed according to each child, its characteristics, age and current life phase, aspects to developed, frequency and so on. The program must aim short- and long-term objectives, being directed to the quality of movement, the function and better postural control in the different postures and movements.

**OBJECTIVE**

The objective of the present study was to verify the incidence of PIVH and associated mechanisms such as PVL and PHH and characterize the presentation of the disease, supplying the basis for a better understanding of the disease, identify variables that affected the newborn, which resulted in the development of PIVH and how long, post-injury, the treatment was initiated at the rehabilitation center.

**METHODS**

A review of the literature was carried out using the websites of BIREME, SCIELO, LILACS and PUBMED and 27 journal articles were selected, from the period of 1990 to 2005, as well as 4 books and a retrospective analysis through the review of 100 medical files of patients, available at Unidade Umarizal da DMR, between January 2004 and July 2005. Of the latter, only 28 children presented the necessary criteria for the present study.

Each file was analyzed in categories with the following variables: age when the triage was carried out, diagnosis, gestational age, birth weight, etiology and sex.

The criteria for eligibility at Unidade Umarizal da DMR are: age range between 0 and 7 years; no history of mental retardation; family support and transport availability; no moderate to severe hearing or visual impairment and uncertain diagnosis (intelligible, at the moment, until diagnostic elucidation).

The cases were evaluated by the medical service responsible for the functional classification and that of the remaining impairments presented by the patients.

Subsequently, an evaluation is performed by the rehabilitation program professionals, who define the treatment objectives and the type of follow-up to be carried out, taking into account age range, level of development and neurological potential, according to the criteria of eligibility of Unidade Umarizal da DMR mentioned above.

**RESULTS**

By the time of the initial triage, 18% of the of patients (5) were between 3 and 12 months old, 46% (13) were between 1 and 2 years, 21% (6) were between 2 and 4 years, 11% (3) were between 4 and 6 years and 4% (1) were younger than 12 years.

According to the assessment, when the PIVH and associated mechanisms were identified: 14% (4) of the children presented PIVH; 7% (2) presented PIVH and PVL; 7% had (2) PIVH, PVL and PHH; 46% (13) had PVL; 10.5% (3) presented PHH and 14% (4) had neuropsychomotor development delay (NPMD). Regarding the analysis of hemorrhagic grade: 4% (1) had grade I; 21% (6) of the NB had IVH grades III and IV; in this group, 4 evolved to PHH and 3 mentioned cases, with surgical treatment to receive the ventriculoperitoneal shunt (VPS).

Regarding gestational age, 32.5% (9) had 24 to 26 weeks, 21% (6) 28 to 30 weeks, 32.5% (9) 32 to 34 weeks and 14% (4) had 36 to 37 weeks at birth.

As for birth weight, 36% (10) had between 2,000g to 3,000g, 25% (7) had between 1,510 to 2,000g, 21% (6), with very low birth weight, had less than 1,500g, 14% (4), with extremely low birth weight, less than 1,000g at birth and 4% (1) had no record of birth weight.

Of the acquired etiologies, it is important to mention 30% (8) with sepsis 14% (4) with anoxia, 21% (6) with hyaline membrane disease (HMD), 14% (4) with eclampsia, 7% (2) with congenital infection and 14% (4) with fetal distress. Regarding the gender, 75% (21) of the evaluated patients were males and 25% (7) were females.

**DISCUSSION**

The aim of this study was to verify the occurrence of PIVH, PVL and PHH in premature children receiving rehabilitation due to cerebral palsy through the analysis of medical files of the Centro de Reabilitação Umarizal – DMR-HC/FMUSP and compare the data with those found in the literature.

The age distribution observed at the time of the triage in most of the children was between 1 and 2 years (46%). Therefore, these children were probably diagnosed before one year of age.

Studies have demonstrated the efficacy of the early intervention in minimizing the motor and cognitive sequelae, based on the fact that, the later the children is referred to a rehabilitation center, the harder it becomes to inhibit the already established patterns, which makes it difficult to establish normal patterns. The first two years of life constitute a critical period for the stimulation, due to the brain plasticity and the rapid period of development and growth. The investment in early intervention programs allows the creation of a potential for normal development, providing a better quality of life, as well as the possibility of integration into society for high-risk newborns.

The frequency of PIVH was observed in premature newborns, with an incidence of 28% (14% IVH; 7% IVH and PVL; 7% PVL and PHH). The data found are in agreement with those shown...
in the literature, especially those reported by Volpe, who reports an incidence of 34 to 39% of PIVH. Although the incidence varies from 30% to 40%, they also showed the importance of detecting this pathology due to its aftermath, mainly in premature newborns with severe PIVH and that despite the severe risk factors, these NB have shown increasingly higher survival rates and considering that not only mortality, but also the neurobehavioral deficits occur more frequently in these NB.

Regarding the analysis of the degree of PIVH, 21% (6) of the NB presented PIVH grades III and IV; of this group, 5 evolved to PHH and 3 mentioned cases received the ventriculoperitoneal shunt (VPS).

Authors reporting on the surgical procedure showed that in a group of 36 children with PIVH grades III and IV, 31% evolved with PHH and 1 patient needed the VPS.

PVL had an incidence of 46% and PVL associated to PIVH had an incidence of 7%. The hemodynamic alterations are etiological factors that are possible for both PVL and PIVH. The variability in the brain blood flow or in the arterial blood pressure was associated with the development of PIVH. In contrast, the PVL was attributed to the brain hypoperfusion.

Regarding the acquired etiologies, it was observed that an important risk factor was sepsis. Linder et al demonstrated that early sepsis and the assisted reproduction treatment were risk factors for the development of IVH grades III or IV in very-low birth weight NB. The risk of IVH and early sepsis is reduced when antenatal antibiotics are used.

A recent study has demonstrated neurological deficit, especially CP, in children born to mothers who underwent in vitro fertilization (IVF), probably due to the prematurity and multiple pregnancy. It is possible that the maternal problems that prevent pregnancy from occurring spontaneously influence the uterus-embryonic environmental conditions, leading to a higher risk of IVH and also that the medications used in the IVF can increase the risk of IVH, by altering the vasoreactivity or platelet aggregation.

It is important to identify the risk factors associated to PIVH in order to intervene, in an attempt to decrease its incidence and mortality and consequently, the neurological sequelae.

The characterization of the patients disclosed a predominance of the male sex, as reported by other literature sources. Stopiglia correlated this observation to a possible retardation in the vascular maturation of the male in relation to the female sex. Thus, it becomes necessary to perform further studies regarding the higher incidence in the male compared to the female sex, in order to define the actual importance of gender as a risk factor for PIVH.

When analyzing the gestational age, 33% of the newborns presented gestational age between 24 and 26 weeks. Several authors have reported that, the younger the gestational age, the lower the birth weight (<1,750 g), vaginal delivery and male sex are factors that are strongly associated with the presence of PIVH. The most frequently associated factor is the younger gestational age due to the immaturity of the vascular system of the germinative matrix found in preterm infants; that is the site of the hemorrhage and it tends to disappear after the maturation of the vascular system. According to Tavares et al, gestational age or the frequency of PIVH is inversely related to birth weight, with rates of 50% to 60% having been described in newborns with birth weight < 1,000 g and rates of 10% to 20% in those with birth weight between 1,000 g and 1,500 g.

Every NB whose gestational age is below 32 weeks and whose birth weight is < 1,500 g must be submitted to a cerebral ultrasound within the first 3 days of life, which should be repeated at 7 days of life and at 30 days/at hospital discharge in the normal cases and weekly in those cases with PIVH for the diagnosis of PHH.

The sensitivity of the cerebral ultrasound in the detection of small areas of necrosis or diffuse cell injury is relatively low.

The magnetic resonance imaging (MRI) previews high-resolution cerebral images with no ionizing radiation and can be of value in the detection of white matter abnormalities.

Regarding the weight, Margotto reports an incidence of 35 to 45% of NB with birth weight < 1,500 g. The present study shows that 35% (10) of the neonates had birth weight < 1,500 g. Therefore, it can be concluded that the survival of the newborns at these weight ranges has been increasingly rising and that not only mortality, but also the neurobehavioral deficits more likely occur in newborns with severe PIVH (grade IV).

The early diagnosis of perinatal brain lesions allow the intervention to be carried out during the prolonged hospital stay, having an impact on the severity of the ensuing neuromotor alterations.

Among the aspects that are noteworthy are the possible sequelae presented by the patients (diparesis, hemiparesis, double hemiparesis, quadriparesis, neuropsychomotor development regression, etc.), which are limiting factors to the children’s potential and the cause of family and social impairment.

Therefore, the prevention of the brain lesion manifestations in the preterm newborn requires the knowledge of the pathogenesis of each injury. Prevention is the main objective of the multidisciplinary team.

The physical therapy aims at inhibiting the abnormal reflex activity in order to normalize muscle tonus and aid the normal movement, with a consequent improvement in strength, flexibility, range of movement (ROM), patterns of movement and, in general, of the basic motor skills, necessary for functional mobility.

The aims of the rehabilitation program are to reduce the impairment and optimize the function. Currently, there is not enough evidence to indicate that the facilitation and inhibition techniques or the proprioceptive neuromuscular facilitation techniques are better when compared to each other and that the traditional exercises are less costly.

Therefore, the musculotendinous stretching must be slow and carried out daily in order to maintain the ROM and reduce muscular tonus.

The intervention inside the family environment of these children has shown to be effective by teaching the mothers to observe and interpret their babies’ behavior, enabling them to modify their actions, adapting them to the needs of these children’s development and hence, allowing more synchronic and reciprocal interactions to take place.
CONCLUSION

The PIVH is an affection that mainly affects preterm newborns as well as and its associated mechanisms, such as PVL, hypoxic-ischemic lesion, which results in CP and PHH defined as progressive ventricular increase that is secondary to PIVH.

There are many risk factors for the development of PIVH, but two important isolated ones are: low birth weight and gestational age < 30 weeks.

The literature has shown that early sepsis and in vitro fertilization are also significant risk factors for the development of PIVH, but this risk is reduced when antenatal antibiotics are used.

The presence of a multidisciplinary team since the neonatal period is necessary and such measure can prevent the sequence of an abnormal motor development through the establishment of a rehabilitation program, aiming at obtaining the maximum benefit of the multidisciplinary team follow-up, so these children will receive the early care they need in order that the sequelae are minimized or even prevented.

Thus, these children can be given not only a higher survival likelihood, but also a dignified existence, with the possibility of integration into society.

REFERENCES