0021-7557/05/81-01-Supl/S23
Jornal de Pediatria

Ischemic brain damage in very low birth weight preterm newborn infants

Rita C. Silveira,[1] Renato S. Procianoy[2]

Abstract

Objective: To present a critical and up-to-date review of ischemic brain damage in premature, very low birth weight infants.

Sources of data: Articles were obtained by means of a search of the MEDLINE database, with those considered most representative by the authors being selected.

Summary of the findings: The most frequent ischemic injuries among preterm, very low birth weight neonates are hemorrhage progressing to with ischemic brain damage, cystic periventricular leukomalacia and diffuse lesions of the cerebral white matter. All of these conditions have multiple causative factors, which may include vascular, hemodynamic, inflammatory and infectious factors. These are disorders that can cause significant neuropsychomotor sequelae and lead to cerebral palsy and/or cognitive and behavioral deficits.

Conclusions: Early diagnosis and adequate management of the patient can minimize long-term problems caused by cerebral ischemic injuries. Prevention of premature labor and delivery is the most important prophylactic measure.

J Pediatr (Rio J). 2005;81(1 Suppl):S23-S32: Intracranial hemorrhage, periventricular leukomalacia, premature infant, cerebral palsy.

Introduction

The significant improvement in the intensive care of very low weight newborn babies has made increased survival rates possible for these premature infants and, as a result, certain pathologies that had previously received little attention have become the objects of increasing interest. The principle short-term morbidities related with premature birth are: hyaline membrane disease (HMD), bronchopulmonary dysplasia, sepsis, necrotizing enterocolitis, patent ductus arteriosus, retinopathy of prematurity, periventricular-intraventricular hemorrhage (PVIVH) and periventricular leukomalacia (PVL).[1]

There are many possible cerebral injuries in premature newborns and PVIVH continues to be the most described and best known, in particular that of the germinal matrix, which can progress, in the most serious cases, to bleeding into the adjacent ventricular system or the periventricular white matter.[2] Such hemorrhagic injuries, in common with parenchymal hemorrhagic infarction, are most common among preterm newborns whose gestational ages were less than 28 weeks at birth.[3]

Periventricular leukomalacia occurs in between 7 and 26% of premature infants with birth weights below 1,500 g with cerebral palsy (CP) being a very common result. Its incidence increases in line with reductions in mortality rates for very low weight neonates.[4]

The risk of these morbidities occurring is inversely related to birth weight and gestational age. The significance of PVIVH and PVL to the prospects for very low birth weight infant neuropsychomotor development has become more obvious as diagnostic methods have become more sophisticated and clinical and epidemiological findings have become better known.[2,5]

Those extremely premature infants that survive beyond the neonatal period present an elevated risk of neurodevelopment abnormalities over the long term. The incidence of CP is approximately, two newborn babies out of every 1,000 live births. While the majority of CP cases

1. Ph.D., Universidade Federal do Rio Grande do Sul (UFRGS). Neonatologist, Hospital de Clínicas de Porto Alegre, RS, Brazil.
2. Full professor, Universidade Federal do Rio Grande do Sul (UFRGS). Chief of the Neonatology Service, Hospital de Clínicas de Porto Alegre, RS, Brazil.

Suggested citation: Silveira RC, Procianoy RS. Ischemic brain damage in very low birth weight preterm newborn infants. J Pediatr (Rio J). 2005;81(1 Suppl):S23-S32.

are among full term infants after a hypoxic-ischemic cerebral insult or other unidentifiable etiology, extremely premature infants have a 40 times greater relative risk of developing CP.[6] It is worth bearing in mind that, for the present review, we defined extreme prematurity as a gestational age of less than 28 complete weeks and/or birth weight of less than 1,000 g.

Ischemic brain injuries that involve the immaturity of the infant brain are morbidities that are of great significance during this period and merit a detailed review. The current article covers certain conceptual definitions, the pathophysiology, diagnosis, prevention, treatment and prognosis of this group of conditions which are generically described as ischemic cerebral injuries of prematurity and which may be the result of injuries of a hemorrhagic nature or of damage to cerebral white matter with ischemic involvement from onset, known as leukoencephalopathy or PVL.[2,7]

Hemorrhagic injury progressing to ischemic brain damage

Conceptual definitions

The typical case PVIVH is an initially hemorrhagic injury and is a frequent complication of prematurity. Approximately 26% of very low birth weight infants between 501 g and 750 g and 12% of those between 751 g and 1,000 g will develop severe forms of hemorrhage.[2] Initial cerebral hemorrhage in the preterm occurs in the germinal matrix subependymal, which is a richly vascularized area located between the caudate nucleus and the thalamus, at the level of Monro's foramen. The vascular network that feeds the germinal matrix is very primitive during the early phases of pregnancy. Between 26 and 34 weeks' gestational age the vascular walls are made up only of endothelium, with no smooth musculature, elastin or collagen.[8]

A hemorrhage is defined as intraventricular when it affects the lateral ventricles and bleeding can occur in the posterior fossa with resultant arachnoiditis. Post-hemorrhagic ventricular dilatation is a common complication, probably due to compromised cerebrospinal fluid reabsorption as a result of obstructed Luschka & Magendie foramina.[8]

The most extensive type of PVIVH is parenchymal hemorrhage, involving the periventricular white matter. As the condition progresses, a porencephalic cyst may develop at the point where the original hemorrhage occurred. There is generally just one of these in contrast with cysts resulting from PVL.[9] This is an injury with hemorrhagic origins, but a number of different studies have found evidence of venous infarction among neuropathological findings, i.e. the subependymal hematoma causes an obstruction to venous blood flow and the elevated intraventricular pressure releases vasoconstrictive substances into the area, both of which conditions promote cerebral ischemia as a final result.[7]

Pathophysiology

The initial lesion is bleeding from the microcirculation into the germinal matrix with multifactor etiology. The reduced blood flow through the vessels within the germinal matrix is secondary to parenchymal hemorrhage, which may take place during intrauterine life or the postnatal period. The increase in venous pressure is also an important intravascular hemorrhage mechanism. In ailing newborns, cerebral circulation is pressure-passive, i.e. cerebral blood flow (CBF) is directly dependent upon systemic arterial pressure. The premature brain exhibits a vascular border zone in the germinal matrix, which is an area that is extremely vulnerable to damage when there is a drop in cerebral perfusion pressure.[2,7]

There are clinical associations between fluctuations in systemic arterial pressure and CBF velocity in preterm newborns with HMD and mechanical ventilation with PVIVH. Rapid volume expansion or the existence of associated complications such as pneumothorax and interstitial emphysema promote increased CBF and consequently PVIVH.[10,11]

Diagnosis

Clinical diagnosis

Clinical findings are not specific to cerebral hemorrhage. Muscular spasms, characteristic leg movements ("pedaling"), convulsive crises, apnea, pallor and peripheral perfusion deficit are all common. A sudden drop in hematocrit and hemoglobin in association with an oversized, tense or bulging bregmatic fontanelle is highly predictive of PVIVH. Clinical PVIVH usually takes place during the first 72 hours of postnatal life or by the end of the first week. The characteristic clinical history is of a premature newborn, with respiratory insufficiency (HMD and/or congenital pneumonia), requiring mechanical ventilation, presenting systemic hypotension, pallor, no response to stimuli, in semi-coma or full coma or convulsive crisis with definite etiology related to metabolic problems and cerebral hypoxia. Peripheral perfusion deficits are common, reminiscent of septic shock. Metabolic acidosis and pulmonary hemorrhage are common findings.

Injuries that are initially hemorrhagic can be asymptomatic. Intracranial hemorrhage, diagnosed by transfontanellar ultrasound screening at 3 to 5 days of postnatal life, furnishes a diagnosis in 80% of newborn babies, many of whom are asymptomatic (more than 70% of cases are diagnosed by ultrasound alone). Nevertheless, newborn babies with severe PVIVH will often present symptoms and the hemorrhage has an earlier onset, often within the first 24 hours of life, with convulsive crises being the most frequently observed clinical presentation.[1,2]

Convulsions secondary to PVIVH are a sign of poor prognosis and are generally associated with severe cases of cerebral hemorrhage, with parenchymal complications or periventricular hemorrhagic infarction. They take place during the first 3 days of life, in very sick extreme preterms. Clinically they are tonic and generalized with a poor electroencephalogram (EEG) and dissociation between clinical and electroencephalographic findings. During the acute phase patients can progress to coma and death.

Cerebral ultrasound (US)

This is the test of choice for diagnosis. It should be performed for all newborn babies whose birth weights are below 1,500 g, in the first instance at 3 to 5 days of life and then weekly until hospital discharge, irrespective of the presence of symptoms. The US scan is performed via the anterior or bregmatic fontanelle, preferably with a 7.5 MHz transducer for routine scans and a 10-MHz transducer when a less common lesion is suspected. Images are recorded on video and can also be printed.[12] Serial US scans, after diagnosis, are important for monitoring the cerebral injuries and to define the extent of the hemorrhage and any post-hemorrhagic ventricular dilatation. This last is a serious condition requiring systematic monitoring in order to establish whether the dilatation is transitory, static or progressive.[12]

Cerebral ultrasound findings made possible an extremely simple method for classifying cerebral hemorrhage that is still used today:[13]

- Minor hemorrhage: degrees I and II
  Degree I = hemorrhage located in the germinal matrix only.
  Degree II = intraventricular hemorrhage, but with normal sized ventricles.
- Moderate hemorrhage: degree III
  Degree III = intraventricular hemorrhage with acute ventricular dilatation.
- Severe hemorrhage: degree IV
  Degree IV = intraventricular hemorrhage with cerebral parenchyma involvement.

Despite technological advances in imaging methods such as computerized tomography (CT) of the encephalon and cerebral nuclear magnetic resonance (NMR), the test most utilized for diagnosing cerebral lesions in preterm infants is transfontanellar ultrasound due to the ease with which it can be performed at the bedside with no need to transport the patient to radiology, because of the lower cost of the apparatus and because of the specificity of diagnosis when compared with NMR.[3,9,12,14]

Nowadays it is possible to relate certain definitions of lesions that can be detected via US, with great utility for differential diagnosis:[3,15,16]

- Hemorrhage of the germinal matrix and the intraventricular region without complications: this is a hemorrhage within the germinal layer or lateral ventricles, including subependymal pseudocyst, but without periventricular involvement, ventricular dilatation with cerebrospinal fluid in the spaces, parenchymal hemorrhagic infarction or loss of cerebral tissue.
- Subependymal pseudocyst: this is a cystic degeneration close to a hemorrhagic germinal layer, with no cystic abnormalities in the adjacent cerebral parenchyma.
- Parenchymal hemorrhagic infarction: this is seen as an image with greatly increased echodensity close to the cerebral parenchyma in the form of a "V", which extends to the ventricular margin, associated with hemorrhage in the germinal matrix and the intraventricular region.
- Periventricular involvement: identified by the abnormally elevated echodensity in the region of the periventricular white matter, with no hemorrhage in the germinal matrix and the ipsilateral intraventricular region.
- Cystic PVL: is a cystic lesion adjacent to the periventricular white matter, which is not preceded by parenchymal hemorrhagic infarction in the affected region. This type of injury will be dealt with in detail later in the review.
- Ventricular dilatation: this is dilatation of the lateral ventricle with such a large volume of cerebrospinal fluid that the depth of the frontal horn immediately anterior of the caudate nucleus is more than 3 mm (percentile 97).
- Post-hemorrhagic hydrocephalus: this is the result of an accentuated increase in pressure due to dilatation of the lateral ventricle, with excessive cerebrospinal fluid volume reaching a width of 5 mm or more (above the 97th percentile).
- Loss of cerebral tissue: easily observed on US. Reductions in cerebral tissue can be as a result of cystic PVL, parenchymal hemorrhagic infarction due to a porencephalic cyst or irregular widening of the lateral ventricles. Generalized cerebral atrophy can also be observed.

Prevention

Preventative strategies involve prenatal and perinatal care aimed at reducing premature birth rates and therefore afford survival with quality. Early postnatal screening of the most vulnerable population – preterm babies of very low weight – for cerebral injuries is of fundamental importance.[12]

During the prenatal period, it is important to assure the adequate management of high risk pregnancies, such as when the expectant mother presents with diabetes, previous arterial hypertension and hypertensive disease specific to pregnancy, nephropathies of diverse etiologies, rheumatic disease and uterine malformation, among other serious situations that require specialized prenatal care and clinical and laboratory-based monitoring .[17]

The hypertensive disorders of pregnancy (HDP) or maternal preeclampsia are related to a reduced incidence of PVIVH, compared with the incidence found among the children of mothers without HDP (8.2 *versus* 14%), probably due to antenatal magnesium sulphate use, which could accelerate cerebral maturation.[18,19] These results are controversial, to the extent that some authors associate the administration of tocolytic agents in general, including magnesium sulphate, with an increased risk of cerebral hemorrhage.[20,21]

The type of delivery is an important part of the pathogenesis of hemorrhage. Studies have found evidence of increased PVIVH risk when there is active labor, suggesting that vaginal delivery is of higher risk than caesarian. However, when confounding variables are controlled, the role of placental inflammation, in particular fetal vasculitis, assumes its true importance to the genesis of PVIVH.[22]

The pharmacological agents that have been most studied with respect of prenatal prevention are: intravenous vitamin K, phenobarbital and corticoids (betamethasone). Results are controversial even though many different publications have evaluated the risks and benefits of administering these drugs to mothers.[17] No advantages have been demonstrated in terms of reducing the incidence of neonatal hemorrhagic injuries from prenatal vitamin K and phenobarbital administration. In a multicenter study of 600 pregnancies resulting in premature births from 24 to 33 weeks, there were no differences in PVIVH incidence between placebo and phenobarbital groups. It is of interest that 58 and 59% of the mothers in the two groups were given prepartum betamethasone, demonstrating the beneficial effect of antenatal corticoid.[17,23]

The antenatal administration of intravenous corticoid appears to be effective. A single dose of betamethasone was effective for reducing the incidence of PVIVH.[23] Prenatal corticoid therapy is related with a reduction in severe PVIVH because it accelerates the maturation of the germinal matrix region, increases systemic arterial pressure with improved cerebral perfusion and appears to be related with less severe cases of HMD.[2] A single course of corticoid is recommended for all pregnancies that have run from 24 and 34 weeks and are at risk of birth within 24 hours, because it reduces the incidence of HMD, of cerebral hemorrhage and neonatal mortality.[17,24]

Post-natal preventative measures have been much studied, primarily the administration of phenobarbital, indomethacin and vitamin E, without compensating results, with the exception of intravenous indomethacin.[25,26] Postnatal phenobarbital use was not effective for reducing PVIVH.

Intravenous indomethacin has been used prophylactically during the first 24 hours of life of preterm very low weight infants, preferentially between 6 and 12 hours of life, reducing the incidence of severe PVIVH (degrees III and IV), in addition to its effect closing symptomatic ductus arteriosus. The neuroprotective effects are the result of an inhibition of the production of free radicals by the injured endothelium of the germinal matrix and an acceleration of the vascular maturation in the germinal matrix region. In animal models, indomethacin has been demonstrated to modulate changes in CBF in response to hypercarbic aggression, with reduced serum levels of prostaglandins and maturation of the germinal matrix microvasculature.[25,26]

When these babies are followed-up, the benefits of indomethacin are not well established, with no observed reduction in the incidence of CP or other neuromotor sequelae among patients treated prophylactically.[25] Its use is particularly indicated for preterms on mechanical ventilation whose birth weights are less than 1,250 g.[26]

Treatment

Clinical management of PVIVH includes the life support measures employed for all very low weight preterms with early respiratory difficulties and/or respiratory insufficiency, on mechanical ventilatory support, and at high risk of severe cerebral hemorrhage. Careful monitoring, together with supportive measures, will avoid the area of hemorrhage increasing in size. Maintaining cerebral perfusion stable, taking care to maintain normal circulatory volume and systemic arterial pressure is essential.[11]

The main life support measures are: maintenance of oxygenation and perfusion, homeostasis of body temperature, metabolic balance (glucose), hydroelectrolytic balance (primarily of ions of calcium, sodium and potassium) and acid-base equilibrium, in addition to early parenteral nutrition and treatment for convulsions, when present.[11,15,27]

Maintenance of adequate oxygenation and ventilation

This means maintaining PaO_2 levels in the range 50-70 mmHg and $PaCO_2$ between 35 and 50 mmHg. Hyperoxia can promote reductions in CBF or potentialize injuries caused by free radicals. The use of xanthines (aminophylline and derivatives) can reduce CBF and is not recommended for initial treatment of apnea in asphyxiated preterm neonates. Hyperventilation is also contraindicated since excessive hypocapnia (CO_2 < 25 mmHg) can reduce CBF.

Perfusion maintenance

It is important to maintain cerebral perfusion pressure (CPP), which is the difference between mean systemic arterial pressure (MAP) and intra-cerebral pressure (ICP). In other words CPP = MAP -ICP. Loss of cerebral-vascular auto-regulation means that CPP becomes a direct reflection of MAP and in order to maintain CPP a minimum MAP is required of 45-50 mmHg. The use of volume expanders and blood products should be criteria-based. It is important to avoid large variations in arterial and venous pressures. Judicious use of invasive procedures and the minimum possible handling of the infant help to avoid pneumothorax and pulmonary hypertension, which are situations in which there is a greater need for positive pressure ventilation and an imminent risk of severe cerebral hemorrhage for extreme preterms.

Body temperature

Maintaining body temperature within normal limits (36.5-37.2 °C) is a basic life support measure. At birth it is common for extreme preterms to maintain a temperature of less than 35 °C for hours, even with the incubator set to maximum temperature.

Glucose

Glycemia should be maintained at natural levels, i.e., 75-100 mg/dl. Hyperglycemia is as prejudicial to extreme preterms as hypoglycemia is. Test strips are a practical and effective method for monitoring capillary glycemia.

Hydroelectrolytic and acid-base balance

One should be alert to the maintenance of hydroelectrolytic and acid-base equilibrium. Nonoliguric hyperkalemia during the first 72 hours of life is common in very low birth weight infants due to inadequate sodium-potassium cellular pump function. Excessive urinary losses of sodium and of bicarbonate cause hyponatremia and metabolic acidosis in preterms with birth weights less than 1,250 g.

Early parenteral nutrition

Adequate nutrition is critical for cerebral development. The dry weight of the human brain is predominantly composed of lipids and 25% of the white matter is made up of arachidonic acid and docohexaenoic acid, which are essential to the growth, functioning and integrity of the brain. A deficiency of essential fatty acids during the initial development of the brain is associated with hypomyelinization and cognitive and motor retardation. Neurodevelopmental abnormalities can be more accentuated in the presence of deficiencies of micronutrients such as zinc. Intolerance of enteral feeding makes preterms' development problematic when early parenteral nutrition is not introduced with an adequate supply of amino acids.[27,28]

Anticonvulsive treatment

The drug of choice is intravenous phenobarbital, administered at 20 mg/kg in bolus over a 15 to 20 minute infusion period. A further dose of 20 mg/kg in bolus may be necessary if crises persist, making a total dose of 40 mg/kg of phenobarbital, before other anticonvulsive drugs are associated to control the crisis. A maintenance dose of phenobarbital (3-5 mg/kg/day; every 12 hours) should be given 12 hours after the initial control dose.[27]

Prognosis

Long term follow-up studies of very low birth weight preterm infants continued until academic ages have found evidence of neurobehavioral problems when CP is not present in 30 to 50% of cases and, of these, 25 to 30% exhibit psychiatric disorders in adolescence, including schizophrenia, autism, hyperactivity and attention deficit.[28,29]

The prognosis of newborn babies with cerebral hemorrhage depends upon the severity and size of brain damage, in addition to the presence of complications. When the hemorrhage is degree I or II with no complications, prognosis is equivalent to that for any other preterm born at the same gestational age and weight. In other words, educational, cognitive and motor difficulties will be comparable.[2,27]

Gestational age is an independent risk factor for the development of ischemic and hemorrhagic injuries.[2,30] In a study of a cohort of 852 premature babies born at less than 33 weeks' gestational age, hemorrhagic injuries were directly related to lower birth weight and gestational age because of physiological and maturity-related changes to the vascular system, in particular the germinal matrix, which has already been covered earlier in the present review.[3]

Vollmer et al. assessed the efficacy of ultrasound for detecting brain damage in newborn babies with less than 33 weeks' gestation, aiming to define the role of these findings in neurodevelopment at 8 years of age. The authors found that, for premature babies born at 24 to 32 weeks' gestational age, unfavorable outcomes, with delayed neuropsychomotor development were dependent on the existence and type of injury seen by US.[3]

Preterm babies who had both hemorrhagic and periventricular white matter injuries, as the years pass, can present certain cognitive and learning difficulties in addition to varying levels of motor deficit. This combination is relatively common since the two share perinatal risk factors.[12]

Newborn babies who suffer localized, unilateral PVIVH can develop spastic hemiparesis , involving upper and lower limbs and mild cognitive retardation. Quadriparesis and significant cognitive deficit are observed after extensive and bilateral cerebral hemorrhage or when there is PVL in association.[31]

A number of studies have shown NMR to be superior to US for the detection, classification and prognosis of injuries that are initially hemorrhagic, progressing to ischemic injury, and also for periventricular white matter damage associated with cerebral hemorrhage.[7,14] The major limitation of NMR is the need to take the patient to the equipment and the elevated costs.

The complication that most determines the neurological morbidities observed in the prognosis of preterms of less than 1,500g who have suffered an initially hemorrhagic injury progressing to ischemic damage is post-hemorrhagic hydrocephalus.[2]

Ischemic brain damage

Conceptual definitions

Periventricular leukomalacia consists of an ischemic infarction in the region of the cerebral white matter adjacent to the lateral ventricles and is a common occurrence among premature infants born after less than 35 weeks' gestation. Diagnosis is made by US , which will initially show a periventricular area of increased echogenicity, with subsequent development of cystic lesions representing necrotic foci.[32] This is the classical concept that has been employed until recently to describe the neuropathological findings from a study by Banker & Larroche.[33] Nowadays, as image-based diagnosis methods have developed it is possible to observe a new conceptual pattern, cerebral leukoencephalopathy.[7] Findings from NMR scans of very low weight premature babies have found evidence of an elevated incidence of diffuse white matter damage, which is even more frequent than cystic PVL. Maalouf et al. followed 32 preterm newborn babies until 40 weeks' postconceptional age, when NMR was performed and diffuse brain damage

was found in 79% of the patients.[9] The term cerebral leukoencephalopathy includes cystic PVL together with the diffuse white matter injury component and should be used as a synonym of PVL.[7]

Focal periventricular necrosis is distributed at the level of the occipital radiation, at the trigon of the lateral ventricles, and at the level of the cerebral white matter, around the Monro foramen. Microscopic changes are the result of coagulation necrosis, with microglial infiltration, astrocytic proliferation and eventual cystic formation. Cysts are diagnosed by US when larger than 0.5 cm in diameter. Cystic cavities reduce in size over time as a result of progressive glucose metabolism. Long term sequelae include loss of myelin and focal ventricular dilatation in the trigon region of the lateral ventricles.[12,27]

Diffuse necrosis of the periventricular white matter is most frequent among very small preterm newborns who require prolonged ventilatory support, and ventricular dilatation, when present, is more preeminent than with focal necrosis.[7]

Premature newborns are more susceptible to predominantly ischemic injuries of the periventricular white matter for three basic reasons:[7,11]

- Cerebral blood flow is reduced more through the white matter than in other areas of the brain, such as the cerebral cortex.
- Immature oligodendrocytes are more susceptible to damage encouraged by free radicals and certain cytokines, such as interleukin-6 (IL-6), interleukin-1 (IL-1ß) and tumor necrosis factor alpha (TNF-α), in addition to the greater potential for toxicity induced by glutamate, when the brain is less mature.
- A previous history of intrauterine infection has a positive interaction with ischemic damage, potentializing the risk of white matter lesions.

These three motives will be dealt with in a more detailed manner later in the review in the section on the pathophysiology of white matter injuries.

Cerebral leukoencephalopathy is the principal ischemic lesion in extreme preterms, occurring in 7 to 26% of these patients. Clinical and epidemiological findings indicate that cerebral white matter damage detected by ultrasound is the primary predictor of CP among very low birth weight newborns. Newborns with weights of less than 1,500 g and PVL present CP in 62 to 100% of cases.[4,12]

The type of ischemic damage to the white matter can define the problems that will be observed as extreme preterms progress. Diffuse periventricular white matter damage is related with cognitive and behavioral deficits, while focal necrotic damage in PVL, with profound white matter involvement is related to CP.[7,34,35]

Pathophysiology

Hypoflow and cerebral leukoencephalopathy

The factors that determine cerebral leukoencephalopathy or PVL have not yet been adequately established. Pathogenesis is complex and multifactor. The genesis of ischemic brain damage involves vascular factors that increase the risk of cerebral hypoperfusion and the intrinsic vulnerability that occurs due to the differentiation of oligodendroglial cells in the area of the cerebral white matter. As a result of this, prematurity and insufficient cerebral perfusion are very important causes of brain damage.[7,11,27]

Systemic hypotension causes an immediate reduction in CBF and, as a function of the immaturity of cerebral vasculature reactivity, premature infants' brains suffer from these alterations directly. A number of different conditions can cause systemic alterations in premature infants and are possibly involved in the pathogenesis of PVL.[11,30] Clinically, the reduction in CBF can take place in the preterm in response to a variety of different conditions: septic shock with systemic hypotension, persistent apnea, significant acidosis, hypocarbia, persistent ductus arteriosus and severe congenital heart disease with low systemic output are examples of conditions associated with PVL.[36]

Cerebral vascular bed development depends directly on gestational age. The shorter vascular branches which have less anastomosis, resulting in a border zone with insufficient vascularization and a predisposition to PVL, are more frequent in premature infants of 24 to 30 weeks' gestational age. From the 32nd week onwards there is significant development of the cerebral vascular bed, with longer vascular branchings appearing which have more anastomosis.[27] This being so, diffuse white matter injury is related with greater cerebral immaturity than focal necrotic damage.[7]

The periventricular white matter vascular bed exhibits a more limited vasodilatory response than other parts of the brain, with greater risk of ischemic injury from reduced CBF. During the post-ischemia reperfusion phase CBF drops and autoregulation is lost, increasing even further the risk of ischemia in the border zone regions of the white matter.[2,7,27]

Developing oligodendroglial cells (immature) are particularly susceptible to hypoxic-ischemic insult and reperfusion. The reduction in CBF causes anaerobic glycolysis and lactate production and, as a result, there is metabolic acidemia and increased calcium ions in the intracellular space. Calcium entering the cell activates the liberation of excitatory neurotransmitters such as glutamate and aspartate, with the liberation of free radicals. Ischemia-reperfusion encourages microglia activation, resulting in the formation of free radicals which lead to cell death, principally of the pre-oligodendrocyte cells. This pathophysiologic mechanism is characteristic of diffuse periventricular white matter damage. In other words, in diffuse injury there is predominantly a loss of cells from the oligodendroglial lineage.[37,38]

Cytokines, proteins with actions similar to hormones, are also mediators of oligodendroglial cell death. In animal models ischemia-reperfusion is responsible for rapid microglia activation, cytokine liberation and resultant

migration of a number of different inflammatory cells, such as monocytes and macrophages.[39]

Cytokines and cerebral leukoencephalopathy

A number of different perinatal inflammatory and infectious conditions have been implicated in the pathogenesis of cerebral leukoencephalopathy. The inflammatory pathway, mediated by cytokines is highly involved in nervous cell death by neuronal apoptosis.[40] In the central nervous system (CNS), microglia can liberate TNF-α, IL-1ß and IL-6, inducing reactive astrocytosis. The toxicity of TNF-α in inducing apoptosis has been demonstrated with cultures of oligodendroglial cells.[41] Tumor necrosis factor alpha appears to be a mediator of acute inflammatory response that regulates the secretion of IL-1ß, exhibiting effects in synergy with that cytokine. Tumor necrosis factor alpha stimulates the production of IL-1ß by monocytes, and is pyrogenic in the same way that IL-1ß is.[42] Elevated levels of IL-1ß can be related to disease severity if they are accompanied by elevated TNF-α levels.[43]

A diagnosis of fetal inflammatory response syndrome can be made by cytokine assay from umbilical cord blood, by means of cordocentesis. There is a causal interrelationship between ascendant intrauterine infection, with local cytokine production and premature labor. The proinflammatory cytokines most described in intrauterine infections are: TNF-α, IL-1ß, IL-6 and IL-8. Interleukin 6 is the best known mediator of acute inflammatory response, liberated quickly after a bacterial invasion. It is secreted by monocytes, macrophages, endothelial cells and fibroblasts in response to other inflammatory mediators such as TNF-α and IL-1ß.[39] Interleukin 6 is also synthesized within the neurons and neuroglia and its expression is elevated in a large variety of CNS disorders, presenting neuroprotective and neurotrophic effects.[44]

A number of different studies describe elevated IL-6 in cord blood in the presence of funiculitis and chorioamnionitis, showing that IL-6 assay in amniotic fluid is a sensitive and specific method for identifying microbial invasion of the amniotic cavity, although it is an invasive method and the ideal test would be safer, but deliver the same efficacy.[45-48]

Jong et al. assessed IL-6 levels at the uterine cervix of patients with premature membrane rupture, comparing them with IL-6 levels in amniotic fluid and concluded that IL-6 assays from cervical secretions have an excellent diagnostic value for bacterial invasion of the amniotic cavity and prognostic value for infectious complications during the neonatal period, although this last was only identifiable at extremely high IL-6 levels above 350 pg/ml.[49] Measurements of IL-6 at the uterine cervix can reduce the need for amniocentesis, which is routinely performed at the majority of services to identify maternal infections.

In a case-control study IL-1-ß, TNF-α and IL-6 were assayed by immunohistochemistry with significantly more elevated levels being observed among newborn babies who had had PVL listed in autopsy findings, when compared with those whose brains were normal on autopsy.[42] These cytokines induce the expression of adhesion molecules, such as the vascular cell adhesion molecule (VCAM-1), within the CNS, both in the parenchyma and the vascular endothelium, and can compromise microglia activation and lead to demyelination.[40]

Summing up, the pathophysiologic events of cerebral leukoencephalopathy are centered on two primary aspects: 1) The reduction of cerebral perfusion in very small preterms with deficient cerebral-vascular auto-regulation and a high risk for periventricular white matter injury 2) Preterm newborn babies exposed to intrauterine infection are vulnerable to pre-oligodendrocyte cell death in the face of ischemic insult, even if mild, which would not be sufficient to cause injury.

Diagnosis

The diagnosis of ischemic brain injuries involves the determination of factors associated with cystic PVL.[30] In cystic PVL, the presence of cysts can be observed from birth onwards due to the occurrence of an intrauterine injury, or appear after birth, generally at 2 to 3 weeks of life. The perinatal events which can cause intrauterine injuries are: clinical or subclinical maternal chorioamnionitis (microscopic diagnosis), premature rupture of amniotic membranes, funiculitis, and other maternal infectious conditions during the peripartum period.[30]

Neonatal factors frequently associated with a diagnosis of leukoencephalopathy are: perinatal asphyxia, hypovolemia, sepsis, hypocarbia, symptomatic patent ductus arteriosus and recurrent apnea with bradycardia. Many of these factors cause a reduction in systemic blood pressure. Immaturity is most important factor for diagnostic suspicion and, the greater the complications during the preterm's hospital stay, the greater the chances of leukoencephalopathy. It is often not possible to establish whether leukoencephalopathy is the cause of unfavorable neonatal outcomes or a consequence of the innumerable intercurrent clinical conditions that are common during this period.[27,39]

Early diagnosis of white matter injuries, in common with injuries that begin as hemorrhagic and progress to ischemia, is obtained by US because, in the majority of cases, presentation is subclinical.[2,27]

Ultrasound is a rapid test, easy to perform, that can be realized without taking the patient to the Radiology Service, using a 7.5 MHz high-frequency transducer. Serial US scans should be taken until term (40 weeks' postconceptional age) in order to identify cases that could develop cystic PVL during the first month of life.[3] The protocol employed is 1 or 2 scans during the first week of life, indicated from the 3rd day of life onwards. Further ultrasound control scans should be performed at around days 10, 14, 21 and 28. For babies born at gestational ages of less than 30 weeks an additional scan is required at approximately 45 days of life.[12] If any abnormality is observed on US , scans should be repeated weekly, or even more frequently, if clinically indicated.[30] Cerebral

white matter injury is defined as at least one of the following echographic findings:[3,12,27]

- The presence of cystic lesions of at least 0.5 cm in diameter. These are distributed bilaterally and located close to the external angles of the lateral ventricles.
- Image of diffuse echodensity persisting for a period of more than 14 days, without cystic formations.
- Unilateral parenchymal hyperdensity or unilateral porencephalic cyst, probably caused by ischemic and hemorrhagic infarction. There will be periventricular hemorrhagic parenchymal involvement, compromising the germinal matrix layer.

Ventricular dilatation without cerebral hemorrhage

Nuclear magnetic resonance is an expensive test and should be reserved for special cases. It is indicated for premature infants whose gestational ages were less than 30 weeks at birth at the point of their hospital discharge. The finding that is characteristic of PVL is a diffused, excessively high intensity signal located in the region of the white matter.[50]

Magnetic resonance imaging by diffusion is an NMR technique that measures the movement of the liquid part of cerebral tissue, making it possible to detect white matter abnormalities in the brains of preterms before conventional NMR. A normal result on this test reveals a reduction in the measurement of the liquid in the cerebral white matter of preterms when corrected age approaches term (40 weeks' postconceptional age).[51,52]

Prevention

Currently, the preventative measure which has the greatest impact is the adoption of strategies aimed at adequate prenatal care aimed at reducing the rates of premature births. Infectious intrauterine conditions are present in more than 25% of premature births and prematurity is highly associated with the occurrence of CP.[53] The administration of antibiotic therapy to mothers in premature labor can bring indirect benefits, reducing the fetal inflammatory response and thereby diminishing the chance of PVL.

Preventative measures adopted during the neonatal period are not easily implanted because they involve all of the neonatal care offered to premature newborns, since the pathophysiology is complex, multifactor and remains ill-defined and also because newborn babies are frequently asymptomatic, with diagnosis established by neuroimaging methods.[2,7] It is of fundamental importance to perform ultrasound and magnetic resonance imaging as screening tests at suitable points, in order to prevent or minimize sequelae with the employment of a multidisciplinary approach as early as possible.

The prevention of small ischemic insults, especially in newborn babies exposed to maternal intrauterine infection, such as chorioamnionitis, includes agents that reduce the production of free radicals, antioxidants, other components that clear free radicals, glutamate antagonists and agents that prevent microglial activation of infection products.[7,39]

Treatment

The principal life support measures are the same as those employed for PVIVH, i.e. the maintenance of tissue oxygenation and perfusion, homeostasis of body temperature, metabolic balance (glucose), hydroelectrolytic balance and acid-base equilibrium, early parenteral nutrition and treatment for convulsions, when present.[27]

Strategies that are more specific to cerebral leukoencephalopathy are:

- Suitable treatment for children with blood pressure low for their age, with rapid volume expansion and/or inotropic support, depending on clinical condition and arterial pressure.[11,27]
- Judicious use of mechanical ventilation for lung diseases, avoiding hypocarbia caused by inappropriate ventilation techniques. Hypocarbia induced by mechanical ventilation is associated with increased average airway pressure, which provokes a fall in venous return and cardiac output, increasing pressure at the sagittal sinus. The increase in venous pressure and reduction in CBF provoked by hypocarbia result in a reduction in cerebral perfusion pressure, including of the periventricular white matter.[11]
- Treatment of apnea with bradycardia. Xanthines are indicated to treat apnea of prematurity and, in some cases ventilatory support may be necessary.[1,2]

Prognosis

Wu & Colford, in a meta-analysis (19 studies), found a significant association between clinical maternal chorioamnionitis and CP and cystic PVL in preterms. Microscopic chorioamnionitis (seven studies) was significantly associated with the development of cystic PVL.[54,55] Microscopic chorioamnionitis has been identified as a risk factor for CP among very low birth weight infants.[54,56] Observed levels of IL-6, IL-8, TNF-α and IL-1ß are elevated in the cord blood of newborn babies who later develop PVL and CP.[48] These cytokines may possibly be useful in the future as early markers of neurological prognosis.

The most common sequela of cystic PVL is spastic diplegia. Diffuse white matter injuries exhibit wider involvement, with spastic quadriplegia, in addition to cognitive and behavioral deficits.[7,34,35] The cause of the cognitive deficits has not yet been identified. It is possible that the white matter damage alters the organization of cortical neurons, causing damage to the subplate neurons.[2,27]

Prognosis is greatly dependent on maternal infectious history, on the time of diagnosis, type of injury, whether diffuse or focal, and also on the preventative and therapeutic measured employed during the perinatal and postnatal periods.

The disease is new, since it is the consequence of the survival of ever more immature babies and of improved neuroimaging methods, making diagnoses more precise. There is a need for more in-depth clinical studies which provide a basis for preventative and therapeutic strategies, in order to improve the prognosis of these extremely preterm newborn babies, which is the population most vulnerable to these insults.

References

1. Lee SK, McMillan DD, Ohlsson A, Pendray M, Synnes A, Whyte R, et al. Variations in practice and outcomes in the Canadian NICU Network: 1996-1997. Pediatrics. 2000;106:1070-9.
2. Shalak L, Perlman JM. Hemorrhagic-ischemic cerebral injury in the preterm infant: current concepts. Clin Perinatol. 2002;29: 745-63.
3. Vollmer B, Roth S, Baudin J, Stewart AL, Neville BGR, Wyatt JS. Predictors of long-term outcome in very preterm infants: gestational age *versus* neonatal cranial ultrasound. Pediatrics. 2003;112:1108-14.
4. Leviton A, Paneth N. White matter damage in preterm newborns – epidemiologic perspective. Early Hum Dev. 1990;24:1-22.
5. Robertson PA, Sniderman SH, Laros Jr RK. Neonatal morbidity according to gestational age and birth weight from five tertiary care centers in the United States, 1983 through 1986. Am J Obstet Gynecol. 1992;166:1629-41.
6. Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. Multivariate analysis of risk. N Engl J Med. 1986;315:81-6.
7. Volpe JJ. Cerebral White matter injury of the preterm infant - more common than you think (commentaries).Pediatrics. 2003;112:176-80.
8. Ghazi-Birry MS. Human germinal matrix: venous origin of hemorrhage and vascular characteristics. Am J Neuroradiol. 1997;18:219-24.
9. Maalouf EF, Duggan PJ, Cousell SJ, Rutherford MA, Cowan F, Azzopardi D, et al. Comparison of findings on cranial ultrasound and magnetic resonance imaging in preterm infants. Pediatrics. 2001;107:719-27.
10. Perlman JM, McMenamin JB, Volpe JJ. Fluctuating cerebral blood flow velocity in respiratory distress syndrome. Relation to development of intraventricular hemorrhage. N Engl J Med. 1983;309:204-9.
11. Tsuji M, Saul JP, Du Plessis A, Eichenwlad E, Sobh J, Crocker R, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. Pediatrics. 2000;106:625-32.
12. De Vries LS, van Haastert IC, Rademaker KJ, Koopman C, Groenendaal F. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. J Pediatr. 2004;144:815-20.
13. Papile L, Burstein J, Burstein R, Koffler H. Incidence and evaluation of subependymal haemorrhage: a study of children with a birthweight less than 1500g. J Pediatr. 1978;92:529-34.
14. Maalouf EF, Duggan PJ, Rutherford MA, Cousell SJ, Fletcher AM, Battin M, et al. Magnetic resonance imaging of the brain in a cohort of extremely preterm infants. J Pediatr. 1999;135:351-7.
15. Amess PN, Baudin J, Townsend J, Meek J, Neville B, Wyatt J. Epilepsy in very preterm infants: neonatal cranial ultrasound reveals a high-risk subcategory. Dev Med Child Neurol. 1998;40:724-30.
16. Levene MI, Starte DR. A longitudinal study of post-haemorrhagic ventricular dilatation in the newborn. Arch Dis Child. 1981;56:905-10.
17. Ramsey PS, Rouse DJ. Therapies administered to mothers at risk for preterm birth and neurodevelopmental outcome in their infants. Clin Perinatol. 2002;29:725-43.
18. Perlman JM, Risser RC, Gee GB. Pregnancy induced hypertension and reduced intraventricular hemorrhage in preterm infants. Pediatr Neurol. 1997;17:229-33.
19. Kuban KC, Leviton A, Pagano M. Maternal toxemia is associated with a reduced incidence of germinal matrix hemorrhage in premature babies. J Child Neurol. 1992;7:70-6.
20. Atkinson MW, Goldberg RL, Gaudier FL. Maternal corticosteroid and tocolytic treatment and morbidity and mortality in very low birthweight infants. Am J Obstet Gynecol. 1995;173:299-304.
21. Groome LJ, Goldberg RL, Cliver Sp. March of Dimes Multicenter Study Group. Neonatal periventricular-intraventricular hemorrhage after maternal b-sympathomimetic tocolysis. Am J Obstet Gynecol. 1992;167:873-9.
22. Hansen A, Leviton A. Labor and delivery characteristics and risks of cranial ultrasonographic abnormalities among very-low-birth-weight infants. The Developmental Epidemiology Network Investigators. Am J Obstet Gynecol. 1999;181:997-1006.
23. Shankaran S, Papile LA, Wright LL. The effect of antenatal phenobarbital therapy on neonatal intracranial hemorrhage in preterm infants. N Engl J Med. 1997;337:466-71.
24. Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes. Effect of corticosteroids for fetal maturation on perinatal outcomes. JAMA. 1995;73:413-8.
25. Ment LR, Vohr B, Allan W, Westerveld M, Sparrow SS, Schneider KC, et al. Outcome of children in the indomethacin intraventricular hemorrhage prevention trial. Pediatrics. 2000;105:485-91.
26. Ment LR, Oh W, Ehrenkranz RA, Philip AG, Vohr B, Allan W, et al. Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. Pediatrics. 1994;93:543-50.
27. Volpe JJ. Neurology of the Newborn. 4th ed. Philadelphia: WB Saunders; 2001.
28. Perlman JM. Neurobehavioral deficits in premature graduates of intensive care-potential medical and neonatal environmental risk factors. Pediatrics. 2001;108:1339-48.
29. Botting N, Powls A, Cooke RW, Marlow N. Attention deficit hyperactivity disorders and other psychiatric outcomes in very low birth-weight children at 12 years. J Child Psychol Psychiatry. 1997;38:931-41.
30. Perlman JM, Risser R, Broyles S. Bilateral cystic periventricular leukomalacia in the premature infant: associated risk factors. Pediatrics. 1996;97:822-7.
31. Peterson BS, Anderson AW, Ehrenkranz R, Staib LH, Tageldin M, Colson E, et al. Regional brain volumes and their later developmental correlates in term and preterm infants. Pediatrics. 2003;111:939-48.
32. Leviton A, Paneth N, Reuss L. Maternal infection, fetal inflammatory response, and brain damage in very low birth weight infants. Pediatr Res. 1999;46:566-75.
33. Banker BK, Larroche JC. Periventricular leukomalacia of infancy. Arch Neurol. 1962;7:386-410.
34. Wood NS, Markow N, Costeloe K, Gibson AT, Wikinson AR. Neurologic and developmental disability after extremely preterm birth. N Engl J Med. 2000;343:378-84.
35. Hack M, Wilson-Costello D, Friedman H, Taylor GH, Schuluchter M, Fanaroff AA. Neurodevelopment and predictors of outcomes of children with birth weights of less than 1000g. Arch Pediatr Adolesc Med. 2000;154:725-31.
36. Volpe JJ. Neurobiology of periventricular leukomalacia in the premature infant. Pediatr Res. 2001;50:553-62.
37. Back SA, Luo NL, Borenstein NS, Volpe JJ, Kinney HC. Arrested oligodendrocyte lineage progression during human cerebral white matter development: dissociation between the timing of progenitor differentiation and myelinogenesis. J Neuropathol Exper Neurol. 2002;61:197-211.
38. Back SA, Luo NL, Borenstein NS, Levine JM, Volpe JJ, Kinney HC. Late oligodendrocyte progenitors coincide with the developmental window of vulnerability for human perinatal white matter injury. J Neurosci. 2001;21:1302-12.
39. Dammann O, Phillips TM, Allred EN, O'Shea M, Paneth N, van Marter LJ, et al. Mediators of fetal inflammation in extremely low gestational age newborns. Cytokine. 2001;13:234-9.
40. Kadhim H, Tabarki B, Verellen G, De Prez C, Rona A-M, Sébire G. Inflammatory cytokines in the pathogenesis of periventricular leukomalacia. Neurology. 2001;56:1278-84.
41. Andrews T, Zhang P, Bhat NR. TNF-a potentiates IFNg-induced cell death in oligodendrocyte precursor. Neurosci Res. 1998;54:574-83.
42. Yoon BH, Romero R, Kim CJ, Koo JN, Choe G, Syn HC, et al. High expression of tumor necrosis factor-a and interleukin-6 in periventricular leukomalacia. Am J Obstet Gynecol. 1997;177:406-11.
43. Dinarello CA, Sharber M, Kent EF, Wolff SM. Production of leukocyte pyrogen from phagocytes of neonates. J Infect Dis. 1981;144:337-42.
44. Stroemer P, Rothwell NJ. Exacerbation of the ischaemic brain damage by localized striatal injection of interleukin-1ß in the rat. J Cereb Blood Flow Metab. 1998;18:833-9.

45. Yoon BH, Romero R, Park JS, Kim M, Oh SH, Kim JC, et al. The relationship among inflammatory lesions of the umbilical cord (funisitis), umbilical cord plasma interleukin-6 concentration, amniotic fluid infection, and neonatal sepsis. Am J Obstet Gynecol. 2000;183:1124-9.
46. Naccasha N, Hinson R, Montag A, Ismail M, Bentz L, Mittendorf R. Association between funisitis and elevated interleukin-6 in cord blood. Obstet Gynecol. 2001;97:220-4.
47. Baund O, Emilie D, Pelletier E, Masmonteil-Lacaze T, Zupan V, Fernandez H, et al.. Amniotic fluid concentrations of interleukin-1ß, interleukin-6 and TNF-a in chorioamnionitis before 32 weeks of gestation: histological associations and neonatal outcome. Br J Obstet Gynaecol. 1999;106:72-7.
48. Yoon BH, Romero R, Park JS, Kim JC, Kim HS, Choi JH, et al. Fetal exposure to intra-amniotic inflammation and the development of cerebral palsy at the age of three years. Am J Obstet Gynecol. 2000;182:675-81.
49. Jun KJ, Yoon BH, Romero R, Kim M, Moon JB, Ki SH, et al. Interleukin-6 determinations in cervical fluid have diagnostic and prognostic value in preterm premature rupture of membranes. Am J Obstet Gynecol. 2000;183:868-73.
50. Cousell SJ, Allsop JM, Harrison MC, Larkman DJ, Kennea NL, Kapellou O, et al. Diffusion-weighted imaging of brain in preterm infants with focal and diffuse white matter abnormality. Pediatrics. 2003;112:1-7.
51. Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR Imaging of intravoxel incoherent motions: Application to diffusion and perfusion in neruologic disorders. Radiology. 1986;161:401-7.
52. Inder T, Huppi PS, Zientara GP, Maier SE, Jolesz FA, Salvo DD, et al. Early detection of periventricular leukomalacia by diffusion-weighted magnetic resonance imaging techniques. J Pediatr. 1999;134:631-4.
53. Kuban CK, Leviton A. Cerebral palsy. N Engl J Med. 1994;330: 188-95.
54. Wu WY, Colford JM. Chorioamnionitis as a risk factor for cerebral palsy (a meta-analysis). JAMA. 2000;284:1417-24.
55. Hillier SL, Martius J, Krohn M, Kiviat N, Holmes KK, Eschenbach DA. A case-control study of chorioamnionic infection and histologic chorioamnionitis in prematurity. N Engl J Med. 1988;319:972-8.
56. Yoon BH, Jun KJ, Romero R, Park KH, Gomez R, Choi J-H, et al. Amniotic fluid inflammatory cytokines (interleukin-6, interleukin-1ß, and tumor necrosis factor-a), neonatal brain white matter lesions, and cerebral palsy. Am J Obstet Gynecol. 1997;177: 19-26.

Correspondence:
Renato S. Procianoy
Rua Tobias da Silva, 99/302
CEP 90570-020 – Porto Alegre, RS
Brazil
E-mail: renatosp@terra.com.br