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G. Tortorolo
R. Luciano
P. Papacci
T. Tonelli

Intraventricular hemorrhage: past, present and future, focusing on classification, pathogenesis and prevention

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G. Tortorolo · R. Luciano (✉) · P. Papacci
T. Tonelli
Division of Neonatology,
Catholic University Medical School,
Largo Gemelli, 8,
I-00168 Rome Italy

Abstract The improvement in the survival rate of infants born at the limit of viability, i.e. <26 weeks of gestational age, raises concern about the risk of neurodevelopmental disabilities. The relevance of intraventricular hemorrhage (IVH), which is the most frequent cerebral lesion diagnosed in extremely low birth weight neonates, cannot then be underestimated. Pharmacological interventions designed to prevent the occurrence of IVH and its complications have not been entirely conclusive. The understanding of pathogenetic factors involved in the genesis of IVH is the key to planning of new strategies and meanwhile of implementing care guidelines aimed at its prevention.

Key words Intraventricular hemorrhage · Preterm babies · Post-hemorrhage hydrocephalus · Fibrinolytic endoventricular treatment

Introduction

The remarkable advances achieved in neonatal intensive care in the past three decades have greatly reduced mortality among very low birth weight (VLBW) neonates (<1500 g). The prevalence of survival in this population increased from around 65–70% in the early 1980s to around 80% in the early 1990s [6, 37]. A parallel reduction in the frequency of neurological sequelae following perinatal brain lesions was not observed, however, owing to the increased survival rate of infants born at the limit of viability i.e. <26 weeks of gestational age (GA) [13], who are at the greatest risk of severe neurodevelopmental disabilities [13, 57]. At this point, better understanding and prevention of brain damage should be the most important goal for neonatologists. In this paper we shall focus on intraventricular hemorrhage (IVH), which is by far the most frequent cerebral lesion diagnosed in premature neonates.

Pathogenesis

IVH is characterized by bleeding into the cerebral ventricles. The source of the bleeding is the germinal matrix, where cerebral neuroblasts originate at between 10 and 20 weeks of gestation and glioblasts originate in the third trimester. The germinal matrix, located in the subependymal region, is very richly supplied by a mesh of capillaries that are poorly supported by muscle or collagen [54] and are then particularly vulnerable to sudden hemodynamic changes, which may cause them to rupture. The germinal matrix is subjected to a remodeling process during pregnancy, modulated by a proteolytic system that includes plasminogen activator, plasminogen and plasmin, which is presumably responsible for the high fibrinolytic activity demonstrated in this region, which could in turn facilitate progression from a small capillary hemorrhage into a large lesion characteristic of IVH [66]. From the 2nd to the 5th month of gestation, neuroblasts, closely packed within the germinal matrix, migrate to the cortex, thus leaving those vessels further unsupported and vulnerable to insults. Astrocytic development, in fact, was shown to be still minimal at 27 weeks of gestation and not prominent until 31 weeks [16]; consequently, glial cells cannot play a major part in stabilization of the germinal matrix capillaries before that age. After neuronal migration, the germinal matrix starts to thin out in a caudal rostral direction, going from a width

of 2.5 mm at 23–24 weeks, to 1.4 mm at 32 weeks of gestation and undergoing near-complete involution by 36 weeks [58]. This is why IVH is closely related to gestational age and relatively uncommon after the 32nd week of gestation. Estimated frequencies of germinal matrix and IVH are, in fact, between 50% and 75% for infants born at less than 26 weeks GA, with a sharp decline after the 30th week of gestation and a decrease to less than 5% among unselected full-term infants [24]. In approximately 80% of cases with germinal matrix bleeding, hemorrhage in the ventricular system occurs [66]. In full-term neonates, although the choroid plexus is the usual site of origin of IVH, bleeding from residual germinal matrix may occur as well, and in a small minority of cases IVH is caused by extension of blood from a major hemorrhagic infarction, such as thalamic hemorrhage, or is the consequence of vascular lesions (arteriovenous malformations, aneurysms, coagulopathies or tumors) [66]. Since IVH is a lesion that is predominantly linked with prematurity, we shall focus on germinal matrix IVH of the premature infant and its complications.

Several pathologic conditions acting on the fragile germinal matrix are responsible for the genesis of IVH in preterm neonates, with a common factor recognizable in most cases, namely cerebral hemodynamic changes, which are especially dangerous when cerebral autoregulation is compromised. Conditions strongly related to IVH in prematures, such as perinatal asphyxia and RDS, cause important variations in cerebral blood flow (CBF):

- Perinatal asphyxia. A cascade of events leading to IVH is often triggered by noxae acting before labor, such as prolonged fetal distress, or intra partum. This is in accordance with the timing of the onset of IVH, which is usually soon after birth: nearly half of all cases are diagnosed on the 1st day of life, and about 90% within the first 3 days after birth [32]. Further support comes from the finding of a raised blood hypoxanthine concentration [52], a marker of preceding hypoxia, in infants developing severe IVH. Owing to the hypoxic damage caused by asphyxia, the endothelial wall of the germinal matrix capillaries is still more vulnerable to the cerebral hemodynamic changes that may passively follow variations in systemic blood pressure when autoregulation is impaired by asphyxia [29]. Even in the presence of preserved autoregulation, the occurrence of hypoxia, acidosis and hypercarbia, which are well-known cerebral vasodilatory factors [2], acts to increase CBF, inducing IVH after reperfusion.

- Respiratory distress syndrome. Hypoxia, acidosis and hypercarbia, commonly observed during RDS, may cause IVH by increasing CBF [2], and a positive correlation between hypercarbia and IVH has been demonstrated [68]. Such factors as tracheal suctioning, high peak inflation pressure during mechanical ventilation, and occurrence of pneumothorax were demonstrated to increase arterial pressure, cerebral venous pressure and/or CBF velocities in preterm babies, so theoretically predisposing to IVH [7, 21, 44]. Moreover, fluctuations in blood pressure and CBF velocities observed in babies not adapted to the ventilator were related to an increased risk of developing IVH [43, 45]. An increased risk of IVH was also reported following high-frequency ventilation (HFV) in the multicenter HIFI trial [20]. The authors suggest that the mechanism arises from the near-constant mean airway pressure used during HFV, which causes intracranial venous congestion, so restricting venous return. The particular importance of increased venous pressure is in part related to the venous anatomy in the region of the germinal matrix, where the direction of the deep venous flow takes a peculiar U-turn at the junction between the terminal vein, collecting medullary, choroidal and thalamostriate veins and the internal cerebral vein. Furthermore, HFV may induce hypocapnia, and experimental work has proved that hyperventilation-induced hypocapnia is followed by a sustained increase of CBF after normal CO_2 values have been restored [15]. A recent meta-analysis of prospective clinical trials comparing HFV and conventional ventilation showed no increased risk of IVH when only the subset of studies using HFV with a “high volume strategy” were included [3]. Ventilatory support modalities, then, should be taken into account when risk factors for IVH are considered.

Interaction of pathogenetic factors is obviously the rule, particularly in the smallest mechanically ventilated premature babies, and there are various factors that can be extremely critical in individual cases. Factors increasing blood pressure or CBF, such as caretaking procedures inducing noxious stimulations, rapid volume expansion (exchange transfusion, hyperosmolar solutions and blood or colloid infusion), ligation of a patent ductus arteriosus, and seizures must be considered potential risk factors for IVH [66]. Heterogeneity of cerebral vasoreactivity in preterm infants supported by mechanical ventilation was demonstrated by Pryds et al. [49]. They showed that cerebral vasoreactivity and pressure-flow autoregulation were absent in infants in whom severe intracranial hemorrhage subsequently developed. Compromised cerebral vasoreactivity, then, might be an important factor determining individual response to events potentially leading to IVH in preterm infants.

Disturbances of coagulation and platelet function may contribute to the pathogenesis of IVH, but a lack of uniformity in the results obtained on this topic suggests that its pathogenetic role is likely to be merely contributory, if it has any at all, in most patients, and important only in selected cases [66].

In recent years it has become evident that cerebral lesions can occur during fetal life with the same characteristics as in preterm neonates. Antenatal onset of IVH can be observed in association with maternal disease, such as idiopathic thrombocytopenic purpura or immunogenic

thrombocytopenia. In most cases, however, severe prenatal IVH occurs without any identifiable pathologic event, and as intraventricular clots are difficult to distinguish prenatally from the choroid plexus they are usually recognized at birth. Residual fragmented clots inside the ventricles or inside a partially cavitated porencephaly in communication with the ventricle are usually found, often in babies with a prenatal diagnosis of ventriculomegaly. In a recent report, de Vries et al. [11] pointed out the criteria that can be used to define an "antenatally acquired" cerebral lesion. As far as IVH is concerned, they consider there has been an antenatal onset when unilateral IVH is associated with parenchymal involvement present within 6 h of birth or with unilateral porencephalic cyst diagnosed within the first 3 days of life. In a population of 1,332 infants born at less than 34 weeks GA they found an antenatally acquired hypoxic-ischemic or severe hemorrhagic lesion on ultrasound in 26.9% of infants who died and in 7.3% of survivors who developed cerebral palsy. The mean GA at birth was significantly higher for the antenatal cases (30.9 weeks) than for the perinatal cases (28.9 weeks) [11].

History and classification

Although a rapidly evolving catastrophic deterioration and a slower saltatory course have been described by Volpe in preterm babies affected by IVH, IVH is clinically silent in about 50% of cases and lacks specific signs in many others [66], with the exception in some cases of an unexplained fall in the hematocrit. It is not surprising, then, that IVH was greatly underestimated in the past and often considered as a postmortem finding before advances in brain imaging technologies gave us the opportunity to routinely investigate the neonatal brain in living infants. Papile [42] was the first to describe the results of brain imaging, using computed tomography (CT) scans in an unselected sample of VLBW infants. It became clear that IVH was a frequent finding at low GA and that it is characterized by a spectrum of lesions amenable to classification by grade of severity. The first classification was then provided by Papile et al., and this is still in use in most neonatological units, even though neuroimaging of the premature brain is now substantially represented by ultrasound (US) and no longer by CT scans. Four kinds of IVH were recognized, numbered from mild to severe:

- Grade I: subependymal hemorrhage
- Grade II: IVH
- Grade III: IVH with ventricular dilatation
- Grade IV: IVH with ventricular dilatation and parenchymal extension

The merit of Papile's classification is that it laid the first stone in our understanding of the incidence and the evolution of the most frequent cerebral lesion encountered in preterm babies, giving the basis for formulation of a prognostic evaluation for long-term sequelae based on the IVH grades. In fact, it was soon evident that mild IVH (grades I and II) is benign if not progressive or complicated [10], while grade III and particularly grade IV may be related to early complications [exitus or post-hemorrhage hydrocephalus (PHH)] [35] and neurodevelopmental disabilities are to be expected in the presence of intraparenchymal extension [17]. A new era had begun, but a new turning point was to be encountered with the appearance on the scene of US scans, which offered a better correlation with necropsy findings than CT scans and permitted repeated re-examinations with no risk to the infant. Risk factors for IVH, which had historically relied on necropsy data with all the obvious limitations entailed, could then be analyzed sequentially in living babies [28]. The first US studies adopted the axial plane through the temporal bone [41], but it was soon evident that the anterior fontanel was the natural window for neonatal brain investigations [64]. An important consequence of sequential US examinations was the consideration that ventricular size evaluation was as much related to other factors as to the extent of the hemorrhage and varied with postnatal age. Further, unanimous consent was not achieved on the definition of ventricular enlargement, as several methods of measuring ventricular size were adopted [1, 27, 55]. It was estimated that the definition of ventriculomegaly should probably include minor loss of brain tissue caused by hypoxic-ischemic damage and also partial obstruction to cerebrospinal fluid (CSF) flow. Moreover, Papile's classification system considers IVH grades as cumulative, each one including the entities below it, and so leaving severe lesions, such as isolated parenchymal hemorrhage, unclassified. The concept that parenchymal hemorrhage is an extension of the original germinal matrix bleeding, which in consequence may rupture into the ventricles and if the hemorrhage continues may rupture into the parenchyma, has found little pathological support. One current concept, emphasized by postmortem microscopic studies [60], is that the parenchymal hemorrhage complicating approximately 15% of cases of IVH [66] should probably be regarded as a venous infarction secondary to the terminal vein obstruction by the intraventricular and germinal matrix blood clot. This area of hemorrhagic necrosis is characteristically found just dorsal and lateral to the external angle of the lateral ventricle. It closely follows the fan-shaped distribution of the medullary veins in periventricular cerebral white matter, where these veins become confluent before ultimately joining the terminal vein running through the germinal matrix towards the internal cerebral vein. Parenchymal hemorrhages are in fact observed in about 80% of cases in association with and on the same side as large germinal matrix IVHs that have previously been diagnosed, and the peak time of their occurrence is the 4th postnatal day, when 90% of cases of

Table 1 Grading of severity of germinal matrix-intraventricular hemorrhage by ultrasound scan according to Volpe's classification [67]

Grade I	Germinal matrix hemorrhage with no or minimal intraventricular hemorrhage (<10% of intraventricular area on parasagittal view)
Grade II	Intraventricular hemorrhage (10–50% of ventricular area on parasagittal view)
Grade III	Intraventricular hemorrhage (>50% of ventricular area on parasagittal view; usually distends lateral ventricle)
Separate notation	Periventricular echodensity (location and extent)

IVH have already occurred [32]. Grade IV hemorrhage is not, then, included in Volpe's [66] classification of IVH (Table 1) but is regarded as a neuropathological consequence of IVH.

Post-hemorrhage hydrocephalus

The occurrence of progressive ventricular dilatation is directly related to the amount of intraventricular blood, being found in approximately 5–20% of cases after mild or -moderate GM-IVH but in 55% of cases after severe IVH, and in up to 80% when parenchymal hemorrhage is also present [67]. Because ventricular dilation may occur after IVH as a result of periventricular leukomalacia or periventricular hemorrhagic infarction or both, clinical distinction between ventriculomegaly secondary to periventricular cerebral atrophy and hypertensive ventriculomegaly caused by impairment of CSF dynamic is mandatory. Sequential ultrasonographic surveillance allows recognition of the initial cerebral lesions and afterwards the slow evolution over several weeks in the absence of signs of intracranial hypertension or the more rapid increase in ventricular size followed by changes in Doppler cerebral blood flow velocity and then by clinical signs of intracranial hypertension The usual time of onset of progressive hypertensive ventriculomegaly is 1–3 weeks after hemorrhage. Acute hydrocephalus, which is less frequently encountered, is caused by an impairment of CSF flow as a result of particulate blood clots, and late-onset hydrocephalus is thought to be caused by obliterative arachnoiditis [67]. Obstruction at the level of the aqueduct occurs less commonly, so that most cases of PHH are of the communicating type. Persistent progressive ventricular dilatation may undergo spontaneous resolution or may persist in the presence of overt hypertensive hydrocephalus, which necessitates neurosurgical intervention.

Prevention of IVH

Prenatal and postnatal interventions to prevent brain damage related o IVH and its complications rely on current concepts of pathogenesis:

- Germinal matrix vulnerability:
  Prevention of premature birth
- Fetal and perinatal asphyxia:
  Optimization of prenatal care
  Transportation in utero
  Prenatal pharmacological intervention
  Optimal management of labor and delivery
  Correct neonatal resusciation
- Hemadynamic changes:
  Respiratory stabilization
  Adaptation to the ventilator
  Blood pressure and blood volume stabilization
  Minimal handling
- Coagulation abnormalities:
  Correction with fresh frozen plasma infusion, vitamin K or coagulation factors

Several neonatal pharmacological intervention to prevent IVH have been proposed, but no one of these has reached a sufficient level of acceptance to be proposed for routine management.

- Phenobarbital. Phenobarbital is a potential neuroprotective agent that might act by protecting against free-radical-mediated ischemia-reperfusion injury or by reducing the fluctuations in blood pressure and cerebral perfusion. Postnatal treatment failed to show a positive effect in preventing IVH [26]. As many hemorrhages originate close to the time of birth, a prophylactic antenatal treatment was attempted. A significant reduction of all grades of IVH was reported in earlier trials, but over time and with improved trial quality this beneficial effect disappeared. A recent Cochrane library publication on this issue analyzed eight randomized or quasi-randomized trials. The conclusion was that at the present time, phenobarbital administration to the mother prior to preterm birth cannot be recommended as a routine clinical practice [9].
- Indomethacin. Indomethacin, a cyclo-oxygenase inhibitor of prostaglandin synthesis, may act as a means of preventing IVH on the basis of three known mechanisms : (1) decrease in cerebral blood flow as demonstrated in animal experiments and in newborn babies; (2) inhibition of the synthesis of free radicals that are generated by the cyclo-oxygenase-dependent prostaglandin biosynthesis and that could damage the endothelial cells in the germinal matrix; (3) acceleration of maturation of micro-

vessels in the germinal matrix. The effect of indomethacin in preventing IVH was evaluated in six controlled studies, four of which showed a decreased incidence of overall IVH and only one a reduction in severe IVH [66]. More recently, a multicenter randomized trial reported by Ment et al. showed that indomethacin reduced the occurrence of both IVH and intraparenchymal hemorrhage [33]. Early-onset hemorrhages were, however, excluded in this study, and an unusual preponderance of grade 4 IVH relative to grade 3 IVH (10:1) was found in the control population. Thus, the results are not entirely conclusive [65]. Moreover, concern about the widespread use of indomethacin in preterm babies has also led to concern about the possible deleterious effect that a sustained decrease (24–40%) in CBF may have, taking into consideration that this effect begin within minutes, probably with a direct effect of the drug on cerebral vessels, and continues for at least 1 h [65]. This concern has probably limited the widespread use of indomethacin as a means of preventing IVH, even after a recent report by Ment et al. that showed no negative long-term sequelae in preterm babies treated with indomethacin [34]. Further, acute effects of indomethacin include renal insufficiency, impaired platelet aggregation, and decreased mesenteric and retinal blood flow. A meta-analysis demonstrated that treating 100 infants to have 4 fewer infants with grades 3 or 4 IVH with indomethacin will result in 5 extra infants with renal complications and perhaps an increased number with necrotizing enterocolitis [14]. Prenatal administration cannot be warranted because of the demonstrated potential deleterious effect of prenatal indomethacin on the fetus [36].

- Ethamsilate. Ethamsilate is an inhibitor of prostacyclin synthesis, a potent vasodilator and a promoter of platelet disaggregation, probably acting at a site that is distal to the cyclo-oxygenase pathway affected by indomethacin. Controlled studies demonstrated beneficial effects in reducing overall and severe IVH [66]. This effect is probably not related to a hemodynamic effect, as no change in Doppler CBF velocity has been demonstrated after ethamsilate administration. Effects relied presumably on promotion of platelet adhesiveness and on capillary membrane stabilization, as ethamsilate causes a polymerization of hyaluronic acid of capillary basement membrane. Prenatal administration could be considered, as ethamsilate crosses the placenta.

- Vitamin E. Vitamin E is a free-radical scavenger that might prevent IVH by protecting matrix capillary endothelial cells from hypoxic-ischemic injury. The sum of evidence accumulated in the past decade suggested that vitamin E supplementation might play a part in decreasing the incidence and severity of IVH, particularly in the smallest infants [47]. Caution in the widespread use of vitamin E was, however, suggested by the demonstration of increased susceptibility to bacterial sepsis and necrotizing enterocolitis. Moreover, a preparation of vitamin E for intravenous administration that is no longer available was found to be associated with fatalities.

Prevention of progression of the hemorrhage

Avoidance of abrupt increase in CBF and other hemodynamic disturbances already discussed in the pathogenesis of IVH is mandatory in the presence of minor IVH. Management of preterm babies with minor IVH should, then, be particularly focused on the following standpoints:

- Adaptation to the ventilator to avoid fluctuating CBF and management of ventilatory setting and thus high peak inflation pressure for babies in assisted ventilation
- Avoidance of fluctuating or increased systemic blood pressure
- Minimal handling
- Maintenance of PCO_2 and PO_2 in the physiological range as far as possible
- Control of acidosis
- Avoidance of hyperosmolar solutions and rapid volume expansion (reduction of amount of packed red blood cells when hemotransfusion is needed)
- Control of seizures
- Avoidance whenever possible of drugs known to increase CBF
- Avoidance whenever possible of interventions that abruptly increase CBF (ductus arteriosus ligation)

Prevention of PHH

- Lumbar punctures. Repeated removal of CSF by lumbar punctures has been widely used in preterm babies affected by post-hemorrhage ventricular dilatation (PHVD). A large multicenter randomized controlled study has shown that early removal of CSF by repeated lumbar punctures in PHVD did not reduce the need for shunting, and it was associated with a 9% incidence of central nervous system infections [62]. Furthermore, the percentage of neurodevelopmental abnormalities at follow-up examination did not differ between treated and control groups [62, 63]. Removal of CSF by lumbar punctures should therefore be restricted to cases presenting with signs and symptoms of raised intracranial pressure in whom surgery is contraindicated or not suitable.

- Diuretics. Drug therapy with diuretics (furosemide and acetazolamide) that reduce the formation of CSF has been widely used for many years, despite reports of side-effects with the treatment, such as acidosis, CO_2 retention, increased CBF velocity, poor feeding, electrolyte distur-

Table 2 Clinical trials of endoventricular fibrinolytic infusion in preterm neonates affected by progressive post-haemorrhagic ventricular dilatation

Reference	Treated babies with PHVD (*n*)	Fibrinolytic drug	Total dose	Days after IVH	Alive	Shunt	Rebleeding
[70]	9	Streptokinase	7,000–40,000 U	8–22	9	1	0
[22]	4	Urokinase	140,000 U	5–11	4	0	0
[71]	22	TPA	0.5–5 mg	8–26	21	9	1
[30]	6	Streptokinase	80,000 U	3–24	5	3	1
	6	None			5	3	0
[23]	18	Urokinase	110,000-280,000 U	2–35	18	12	0
	39	None			36	33	0
[19]	7	Urokinase	60,000 U	26–30	6	6	0

bance, nephrocalcinosis, osteopenia, diarrhea and vomiting. A recent multicenter randomized controlled trial testing furosemide and acetazolamide in preterm infants with PHVD showed a higher rate of shunt placement and increased neurological morbidity in the treated group [25].

• Fibrinolytic endoventricular treatment. Low-dose fibrinolytic endoventricular infusion was thought to be effective in decreasing the occurrence of PHH in preterm neonates affected by PHVD, the rationale for this being that a more rapid dissolution of blood clots might avoid the arachnoiditis and the chronic infiltration with collagen that cause a permanent obstruction in CSF pathways. Intraventricular fibrinolytic infusion after IVH caused a reduction in the occurrence of PHH in experimental and adult studies [40, 61]. Furthermore, absence of fibrinolytic activity earlier than 17 days after IVH was demonstrated in preterm neonates [69]. On this ground, Whitelaw et al. [70] attempted to prevent the occurrence of a permanent PHH by increasing intraventricular fibrinolysis in preterm infants affected by progressive but potentially reversible PHVD, which they defined in accordance with the criteria established by the Ventriculomegaly Study Group [62]. Preliminary experiences with streptokinase [70] or urokinase [22] administered intraventricularly through a percutaneous catheter, which showed an apparent beneficial effect in a restricted number of premature babies, were not supported by later studies [19, 30, 71]. In fact, recent series of patients [23, 30, 71] treated with fibrinolytic infusion demonstrated an incidence of shunt dependence similar to that expected without fibrinolytic treatment, i.e. about 60% [62], no matter whether the drug of choice was an endogenous (tPA, urokinase) or a nonendogenous (streptokinase) plasminogen activator (Table 2). Hudgins et al. reported a significantly reduced shunt requirement in grade 3 and grade 4 IVH patients after low-dose urokinase endoventricular treatment compared with historical controls [23], but the percentage shunt requirement in the control group was unusually high (92%) and not comparable with the commonly reported incidence [62, 66]. Furthermore, no such reduction was observed in the same study in babies treated with high-dose urokinase [23]. Endoventricular treatment was not effective in preventing hydrocephalus in spite of the significantly enhanced fibrinolysis in CSF and the rapid lysis of intraventricular clots which followed the infusion of fibrinolytic agents [30]. Failure of fibrinolytic endoventricular infusion in preventing PHH may be interpreted as follows:

1. Dosage, site and time of infusion were not optimal. Risk of intraventricular rebleeding must be taken into account when preterm babies with a fragile germinal matrix are treated with endoventricular infusion soon after IVH. Two cases of rebleeding were observed in reported series [30, 71]. Caution was also suggested in an adult study owing to the occurrence of secondary hemorrhage after intraventricular fibrinolysis [53]. Consequently, all the authors but one utilized only low doses of fibrinolytic agents (Table 2). No advantage in terms of percentage shunt requirement compared with the low-dose regimen was observed in the only trial with high-dose therapy [23]. As the risk of rebleeding cannot be excluded, in the light of overall experience [30, 53, 71], higher doses of fibrinolytic agents cannot, in our opinion, be proposed. Site of infusion could also influence the results: the increase in fibrinolytic activity registered in the ventricular fluid might not be obtained at the site of arachnoid villi where reabsorption of CSF occurs. Reducing the time interval between IVH and treatment could improve the results: fibrinolytic infusions had beneficial results in the experimental study where the treatment was started soon after intraventricular injection of blood [40] and in adult patients treated within 1 week following the episode of IVH [61]. However, in our experience, a baby treated as soon as 3 days after IVH went on to develop permanent PHH even if the clots were rapidly reabsorbed [31]. Furthermore, following Whitelaw's studies [69], it cannot be excluded that the delayed enhancement of endogenous fibrinolysis (not earlier than 17 days after IVH) might be regarded as a protective mechanism against rebleeding. There are also other considerations that make performance of a fibrinolytic treatment immediately after the occurrence of an IVH in preterm neonates seem ill advised: (a) ventriculostomy in itself is a risk factor in hemorrhage and entails a risk of local infections in such

small babies; (b) PHVD is observed only in one third of preterm neonates affected by IVH and tends to solve spontaneously in the majority of cases [66].

2. Inhibition of fibrinolysis by plasminogen activator inhibitor-1 (PAI-1). PAI-1 is the principal inhibitor of fibrinolysis in blood. Its concentration in CSF is higher in babies requiring surgery after endoventricular infusion [18]. However, babies treated with streptokinase, a non-endogenous plasminogen activator not inhibited by PAI-1, did not show better results than babies treated with tPA that is inhibited by PAI-1.

3. Fibrinolysis is not the main mechanism involved in clearing blood clots after IVH. In Whitelaw's study on neonatal CSF fibrinolysis, preterm babies who developed PHVD reached even greater fibrinolytic activity than babies affected by IVH without PHVD [69]. Mechanisms other than fibrinolysis, such as phagocytosis by macrophages, could be then more important in clearing small blood clots from CSF pathways.

In conclusion, at the present time, endoventricular fibrinolytic treatment with the aim of preventing PHH cannot be recommended for routine clinical practice. However, low-dose endoventricular infusion of streptokinase may still be suggested in some cases of PHVD, for different purposes. In fact, its effect of enhanced fibrinolysis and rapid lysis of intraventricular clots has been demonstrated to be life saving in term neonates affected by acute PHH, as it ensures maintenance of the patency of the external drainage, making it possible to remove intraventricular blood and to counteract severely increased intraventricular pressure [31].

Perspectives

An overall reduction of IVH in VLBW infants from about 40–50% to about 20–30% has been widely observed in the past decade. The underlying reasons are still not entirely clear, as such a decrease has been reported either in centers where specific prevention protocols were adopted or in centers where no preventing interventions were planned [39, 46, 66]. Two major widespread changes have occurred after 1990 in perinatal clinical practice, i.e. the introduction of surfactant into the management of hyaline membrane disease and the use of antenatal steroids to accelerate fetal lung maturity before preterm birth. Surfactant was not demonstrated to influence the incidence of IVH [4], whilst antenatal corticosteroid therapy has been proved to reduce the risk for IVH [8]. Szymonowicz et al. [59] reported a fall in the incidence of IVH during two consecutive time intervals, implementing specific care guidelines to minimize cardiorespiratory instability during the second time interval (1983–1984). A decreased rate of IVH among VLBW babies is to be expected with a general improvement in perinatal care, better control of respiratory distress, hemodynamic stabilization and minimal handling policies. Since these strategies are also of decisive importance in the achievement of a better survival rate in the same population of neonates born at very low GA and therefore at the highest risk of IVH, one can speculate that in terms of absolute numbers the importance of IVH in preterm babies surviving the neonatal period cannot be underestimated. Special attention has to be paid to the management of preterm babies affected by minor IVH. In these babies every possible effort to avoid risk factors involved in the progression of IVH is mandatory. Nowadays, we are conscious that the lesion previously called grade IV hemorrhage, i.e. a large echodense area in white matter adjacent to the lateral ventricle, may be a hemorrhage venous infarction, may not be hemorrhage at all, or may be a component of complex white matter damage, such as hemorrhage into a pre-existing ischemic lesion or hemorrhage accompanied or followed by periventricular leukomalacia. Distinction among these histopathologically different lesions is sometimes difficult in vivo, notwithstanding the typical features described for use in differential diagnosis [51]. Volpe et al. used positron emission tomography to evaluate CBF, showing that the impairment of CBF in the hemisphere containing the periventricular hemorrhagic lesion is much more extensive than could be accounted for by the locus of the echodensity diagnosed by US [67]. It is now not uncommon with US equipment and protocols of sequential US investigations, to observe a crown of small cysts surrounding the locus of a previous diagnosed periventricular hemorrhagic infarction or extending posteriorly towards the parieto-occipital region in the same hemisphere. Local impairment of cerebral perfusion in the site of a previous hemorrhagic infarction might account for this peculiar kind of asymmetric periventricular leukomalacia that secondarily complicates the hemorrhagic lesion. The possibility that hemorrhage could contribute to periventricular ischemia is in accordance with experimental studies suggesting that impairment of periventricular blood flow may be secondary to increased intraventricular pressure and/or local release from hemolyzed red blood cells of vasoconstricting compounds such as K+ or injurious factors such as lactic acid or even iron, possibly inducing the occurrence of iron-catalyzed free radical formation [12, 48]. It is probably necessary to reconsider our current terminology when we describe brain lesions in premature neonates. Paneth [38] has recently proposed a classification of the brain lesions of premature infants that considers three general categories:

- White matter damage
- Hemorrhages in nonparenchymal areas of the brain
- Lesions in other brain locations (cerebellum, basal ganglia, brain stem)

There are two good reasons for taking account of this classification. First of all, it would be more consonant with neuropathologic findings. In fact, it is based on location of the lesions and does not depend on the hypoxic-ischemic or hemorrhagic nature of the damage. The term 'white matter damage' embraces a variety of pathologic entities with the common feature of affecting the developing white matter. We are aware that hemorrhage and hypoxic-ischemic lesions are often encountered together in the presence of white matter involvement, and it is often difficult to distinguish clearly on the basis of ultrasound images the precise neuropathologic entity that underlines the finding of echodensity or echolucency. Secondarily, regarding prognosis little risk of neurodevelopmental abnormalities is related to hemorrhages confined to germinal matrix, choroid plexus, intraventricular or subarachnoid spaces, unless they are combined with hypoxic-ischemic damage or are subsequently followed by complications, such as periventricular infarction or PHH. Third, damage in other sites of the brain also finds a place in the classification of brain damage, although brain stem lesions are a pathologic finding and only a percentage of basal ganglia and cerebellum lesions are diagnosed in vivo by ultrasound, so that we are not presently able to understand their clinical importance.

Three considerations must be stressed on the other side. First, infectious diseases are not included either in the form of prenatal diseases, such as TORCH group infections, or postnatal lesions, such as bacterial abscess or meningitis. Secondarily, massive IVH, even when it is not associated with parenchymal lesion, has a worse short-term outcome than mild IVH, as far as mortality and progressive post-hemorrhage ventriculomegaly are concerned [35]. Third, ventriculomegaly is not considered either in the form of hypertensive hydrocephalus or as evidence of white matter damage without cystic changes, in spite of modern evidence showing up ventriculomegaly an important prognostic factor. In 1987, Stewart et al. [56] reported the calculation of probabilities for neurodevelopmental disorders in preterm infants born at a GA <32 weeks, relating the outcome both to the early neonatal US diagnosis (first week of life) and to the cerebral US appearance at discharge, which made it possible to assign the infants to a low-, intermediate- or high-risk group. Discharge diagnosis as ventricular dilatation, hydrocephalus or cerebral atrophy carried a significantly increased probability of neurodevelopmental disorders (moderate- to high-risk group) compared with a low-risk group of patients with uncomplicated IVH, i.e. small or large IVH not associated with parenchymal echodensities and not followed by ventricular dilatation or hydrocephalus. PHH is the most serious complication of IVH, since it is associated with a high risk of death and neurodevelopmental disorders [25, 63]. Although the presence of a parenchymal brain lesion determines the outcome [5] even in patients with PHH, some of the dysfunction may also be the result of a prolonged period of raised intracranial pressure before the insertion of a shunt becomes appropriate or of the high rate of complications related to the treatment, such as blockage and infections [50].

We would like to stress that we can no longer regard IVH as the only main cause of brain damage in preterm neonates as it was in the past and is sometimes still seen to be in reports dealing with the outcome in low-birthweight babies. IVH is sometimes part of a complex histopathologic lesion, preceding or following or originating at the same time as hypoxic-ischemic damage, and then, when the prognosis is considered, we should not merely look at the grades whatever classification is adopted, but should consider the complications (post-hemorrhagic hydrocephalus or late persistent ex vacuo ventriculomegaly) and the location and extent of accompanying parenchymal lesions.

The development of new strategies for prevention of PHH is urgently needed in the light of the reported high rate of death or disability in affected children [25, 63]. Anecdotal evidence of a beneficial effect of prevention protocols has to be confirmed by controlled trials before becoming a form of routine management, in view of the potential adverse effects of treatment in this high-morbidity group of patients. Given the lack of clear evidence of any benefit from medical intervention, conservative management, under close ultrasound and Doppler surveillance, is appropriate until criteria for surgical intervention are fulfilled. The effects on the outcome of different surgical strategies are to be addressed in future multicenter randomized controlled trials:

- Different methods of increased intracranial pressure management before shunt placement (subcutaneous reservoir, external ventricular drainage)
- Role of III ventriculostomy
- Shunt placement criteria

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