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Intraparenchymal Hemorrhage in Preterm Neonates: A Broadening Spectrum

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Among 800 neonates screened for cerebral bleeding, perinatal sonography identified 35 preterm neonates with intraparenchymal hemorrhage (IPH). The observed IPHs were categorized in five general groups: classical grade-IV hemorrhage (16 patients), grade-IV hemorrhage with coexisting but anatomically separate hemorrhages (four patients), grade-IV hemorrhage with later development of secondary parenchymal hemorrhages at distant sites (five patients), hemorrhagic periventricular leukomalacia (four patients), and parenchymal hemorrhage unrelated to grade-IV hemorrhages (six patients). Thirty IPHs had concurrent germinal matrix hemorrhages, but in only 16 patients did the IPH represent an extension of the subependymal hematoma and therefore qualify as pure grade-IV hemorrhage according to the most popular classification.

The high concurrence of periventricular leukomalacia (80–100% in most groups) and germinal-matrix-remote IPHs supports the concept that most IPHs in preterm neonates represent secondary hemorrhages into ischemic brain tissue.

Intraparenchymal hemorrhage (IPH) refers to bleeding into brain substance. Although the least common of all intracranial hemorrhages in preterm neonates [1–8], it has the poorest clinical outcome [9–11].

It is generally assumed that most IPHs originate in the germinal matrix. In the widely accepted classification of Burstein et al. [1] of germinal-matrix-related hemorrhages, IPH is considered a grade-IV hemorrhage. In the Burstein classification, a grade-IV hemorrhage is, by definition, a germinal matrix hemorrhage with extension into adjacent white matter and associated with intraventricular hemorrhage and ventriculomegaly. In the same grading system, a grade-I hemorrhage is confined to one or both germinal matrixes; grade-II hemorrhage denotes a germinal matrix hemorrhage that has ruptured into the ventricles; grade-III is similar to grade II but sufficiently severe to expand the ventricles. While IPH may represent merely an extension of the germinal matrix hemorrhage, there are IPHs that do not follow the above pattern [12].

This report is based on an analysis of 35 premature neonates with IPH who were diagnosed with sonography. To our knowledge, no previous report has studied as many living neonates with IPHs. This article concerns the variable presentations of IPHs and stresses the role of periventricular leukoencephalopathy in the production of IPH. Our in vivo observations support the notion that most IPHs are caused by prior cerebral infarction and not by mere physical extension of the germinal matrix hemorrhage. The debate on the precise causes of IPH is ongoing, but our observations are supported by earlier pathology reports from the presonography era [9, 13, 14].

Materials and Methods

At our institution, neonates of 32 weeks' gestational age or younger and neonates (term or preterm) who have an especially difficult clinical course are routinely selected for early

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TABLE 1: Findings in Preterm Neonates with Intraparenchymal Hemorrhage (IPH)

Finding	No. of Patients (n = 35)				
	Grade IV (n = 16)	Grade IV + IPH (n = 4)	Grade IV + IPH (sec) ^a (n = 5)	HPVL (n = 4)	Other IPH (n = 6)
Prematurity:					
<32 weeks	14	3	5	4	1
>32 weeks	0	0	0	0	5
? weeks	2	1	0	0	0
Respiratory distress	16	4	5	4	2
Rh incompatibility	0	0	1	0	3
Other bleeding diathesis	0	0	0	0	1
Pathologies predating IPH:					
PVL	2	2	0	1	0
Grades I-III GMH	3	0	0	0	0
Pathologies found with IPH:					
PVL ^b	13	4	5	4	2
Grades I-III GMH	0	0	0	3	1
Grade IV GMH	16	4	5	0	1
Late sequelae of IPH:					
PVCs	10	1	5	3	2
Porencephaly from hema- toma	7	1	1	2	0
Porencephaly from PVC	10	4	1	0	1
Death	4	2	0	1	1

Note.—Grade IV = classical grade-IV hemorrhage; grade IV + IPH = grade-IV hemorrhage with coexisting but anatomically separate IPHs; grade IV + 2° IPH = grade-IV hemorrhage with later development of secondary IPHs at distant sites; HPVL = hemorrhagic periventricular leukomalacia; other IPH = IPH unrelated to grade-IV hemorrhages or periventricular leukomalacia (PVL). GMH = germinal matrix hemorrhage; PVCs = periventricular cavities.

^a Secondary IPH.

^b These cases include five patients in whom PVL predated IPH.

sonographic screening. Our study is based on a retrospective analysis of neurosonograms of 800 such neonates. Of the 40 patients in this group in whom IPH was identified, a total of 112 sonograms and 27 CT scans was obtained.

For this report, we subselected all patients of premature birth (35 patients); that is, neonates of 36 weeks' gestational age or younger. Among these, 27 infants were very preterm (32 weeks or younger). In three patients, the degree of prematurity could not be determined from the available charts. Fourteen patients were examined with sonography only, 16 patients had sonography and CT at comparable times, and five patients had early sonography and later follow-up CT examinations. Our findings are based mainly on sonographic findings; CT correlation is used where applicable.

The sonograms were obtained with a real-time sector scanner* equipped with 5- and 7.5-MHz transducers. The sonograms were sampled through the anterior fontanelle and included coronal, angled coronal, and axial images as well as sagittal and angled sagittal views. The sonograms usually were obtained by the sonographic technologists and reviewed and interpreted by the radiologist. The CT scans were obtained with a GE 9800 or Philips 310 scanner. The cuts were 5 mm thick and adjacent to each other. They were angled 20° to Reid baseline.

Results

Our IPH patients could be assigned to five major groups (Table 1): grade IV (16 patients)—classical grade-IV hemorrhage (Figs. 1 and 2); grade IV + IPH (four patients)—grade-IV hemorrhage with coexisting but anatomically separate IPHs (Figs. 3 and 4); grade IV + secondary IPH (five patients)—

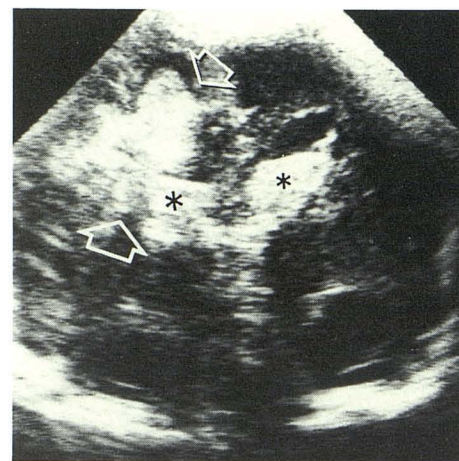


Fig. 1.—Coronal section shows classical grade-IV hemorrhage with bilateral subependymal hemorrhage that has ruptured into both ventricles (asterisk). Subependymal hemorrhage also extends into contiguous frontal lobe (arrows).

grade-IV hemorrhage with later (2–10 days) development of secondary parenchymal hemorrhages at distant sites (Fig. 5); hemorrhagic periventricular leukomalacia (PVL) (four patients) (Fig. 6); and other IPH (six patients)—parenchymal hemorrhage unrelated to grade-IV hemorrhages or PVL (for example, bleeding diathesis and Rh incompatibility) (Figs. 7 and 8). This grouping was established solely for this analysis and is not to be construed as a new classification of IPH.

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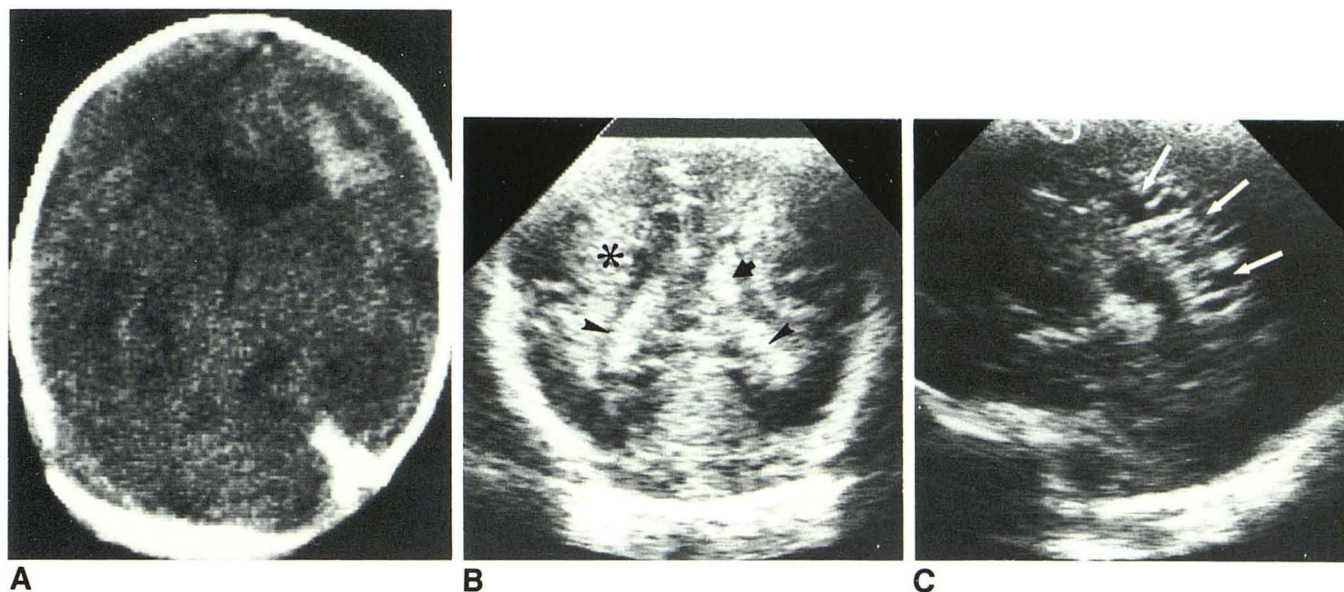


Fig. 2.—Classical grade-IV hemorrhage with periventricular leukomalacia in premature neonate (30 weeks' gestational age, 1600 g) with respiratory distress.

A, CT shows left frontal white-matter hemorrhage. Lower cut showed left subependymal hemorrhage.

B, Axial sonogram 4 days later shows bilateral periventricular leukomalacia, most pronounced on right (asterisk). Intraventricular blood is present also (arrow). Choroid plexus (arrowheads).

C, Right sagittal follow-up sonogram, 3 weeks later shows small, confluent cavities developing opposite cerebral hemorrhage in periventricular white matter of hemisphere (arrows).



Fig. 3.—Grade-IV hemorrhage with coexisting but anatomically separate intraparenchymal hemorrhage in premature neonate (24 weeks' gestational age, 740 g) with respiratory distress and necrotizing enterocolitis. Axial sonogram angled toward coronal plane shows subependymal hemorrhage with intraventricular extension (asterisk) as well as noncontiguous periventricular left-temporal-lobe hematoma (arrows). Hematoma wraps around trigone and merges laterally with calvarium.

In grade IV + IPH and grade IV + secondary IPH the coexisting or later-developing additional IPHs localized in areas not contiguous to the grade-IV hemorrhage. They were either in the same hemisphere or contralateral.

In hemorrhagic PVL, the IPH was characterized by diffuse, usually bilateral hemorrhage into periventricular white matter [15–18]. None of our four cases fulfilled the criteria of grade-IV cerebral hemorrhage. While germinal matrix hemorrhage (two patients) and associated intraventricular hemorrhage (one patient) were observed, none of the cases exhibited ventriculomegaly at the time of hemorrhage.

In other IPH there was either total absence of subependymal hemorrhage (four patients) or the existing subependymal hematoma did not extend into neighboring cerebral parenchyma (two patients). The parenchymal hematomas were randomly scattered and had no connection with the germinal matrix. This group comprised three patients with Rh incompatibility and one with a bleeding diathesis.

PVL, a form of cerebral ischemia [1, 2, 13, 14, 19–24], the most prevalent disease found with fresh parenchymal bleeding, was found in 28 (80%) of 35 patients. Among the 28 patients in whom IPH and PVL were seen together, PVL was seen to have started before the inception of the parenchymal hemorrhage in five (Figs. 4 and 8). Since sonograms before the hemorrhagic event often were unavailable, its temporal relationship to PVL could not be documented consistently.

In its early stages, PVL typically presented as edema and produced high-level echoes (Figs. 2B, 4A, 5B, 7B, and 8A). It occurred both uni- and bilaterally, commonly spread throughout hemispheric white matter, and was either focal or multifocal. When direct CT/sonographic correlation was not available, the sonographic parameters used for the diagnosis of parenchymal hemorrhage were echogenic texture and/or associated mass effect [20, 24]. Also, the change from medium-

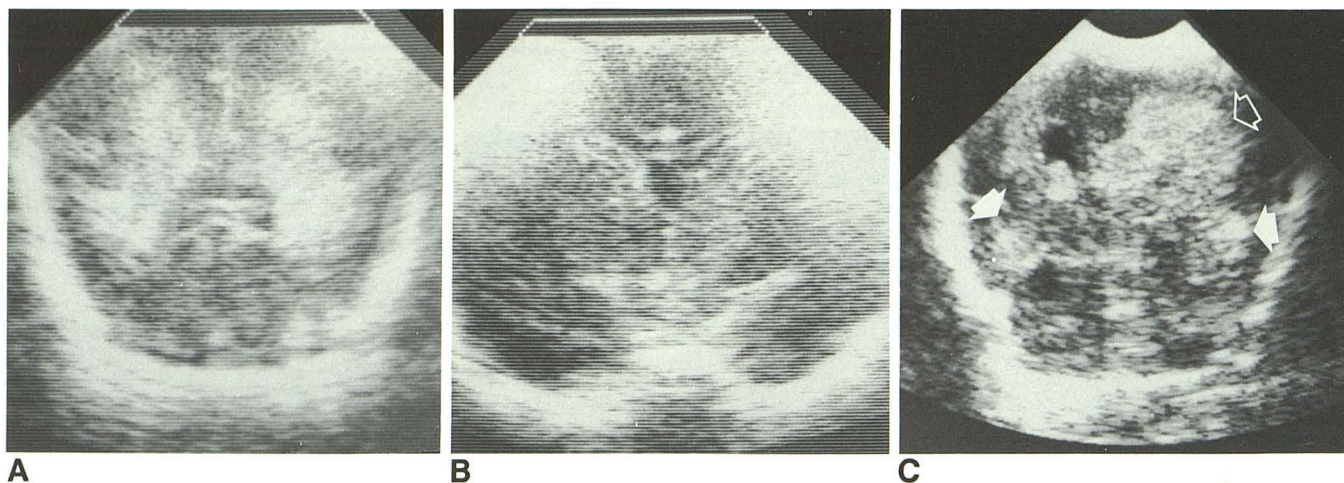


Fig. 4.—Grade-IV hemorrhage with coexisting but anatomically separate intraparenchymal hemorrhage and preceding periventricular leukomalacia in premature neonate (30 weeks' gestational age, 1200 g) with respiratory distress, delivered by cesarean section.

A and B, Initial sonograms. High axial cut (A) shows dense, high-level echoes in periventricular distribution, consistent with leukomalacia. Coronal cut through frontal horn region (B) shows absence of subependymal hemorrhage.

C, Follow-up sonogram 4 days later, level and plane similar to B. Large, left frontal intraparenchymal hemorrhage (open arrow) is contiguous to subependymal hemorrhage. Ipsilateral intraventricular and contralateral subependymal hematomas are seen also. Note noncontiguous, intraparenchymal hematomas in posterior temporal lobes (solid arrows).

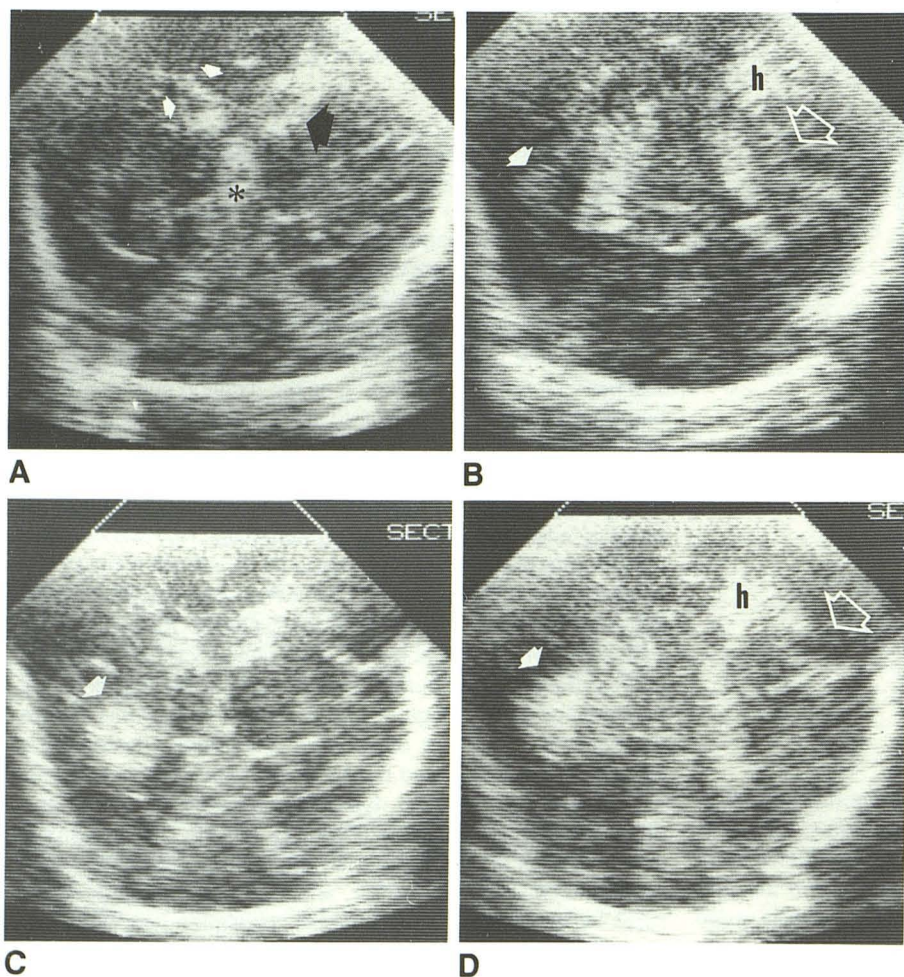


Fig. 5.—Grade-IV hemorrhage with later development of secondary parenchymal hemorrhages at distant sites in premature neonate (32 weeks' gestational age, 1940 g) with respiratory distress.

A, Initial sonogram (axial plane, angled toward coronal plane) shows bilateral subependymal hemorrhage with intraventricular extension. Moderate expansion of lateral ventricles (white arrows) and third ventricle (asterisk) by intraventricular clot. On left, germinal matrix hemorrhage (black arrow) extends also into contiguous frontal lobe (arrow).

B, Higher axial cut shows further parenchymal extension of hematoma (h). Speckled, intermediate-level echoes in both parietal lobes (arrows) are consistent with leukomalacia.

C, Follow-up sonogram 5 days later, plane similar to A. Note development of right posterior temporal hematoma (arrow).

D, Corresponding higher cut, similar to B. Frontal hematoma (h) remains unchanged. New parenchymal hematoma in right parietal lobe (solid arrow). Increased echogenicity in left anterior parietal lobe (open arrow) was interpreted as zones of new hemorrhage.

Fig. 6.—Hemorrhagic periventricular leukomalacia in premature neonate (28 weeks' gestational age) with respiratory distress.

A, CT shows hemorrhagic periventricular leukomalacia. White-matter hemorrhage was associated with intraventricular and subependymal hemorrhage.

B, Sonogram, same plane as A. Very dense periventricular echoes suggest hemorrhage.

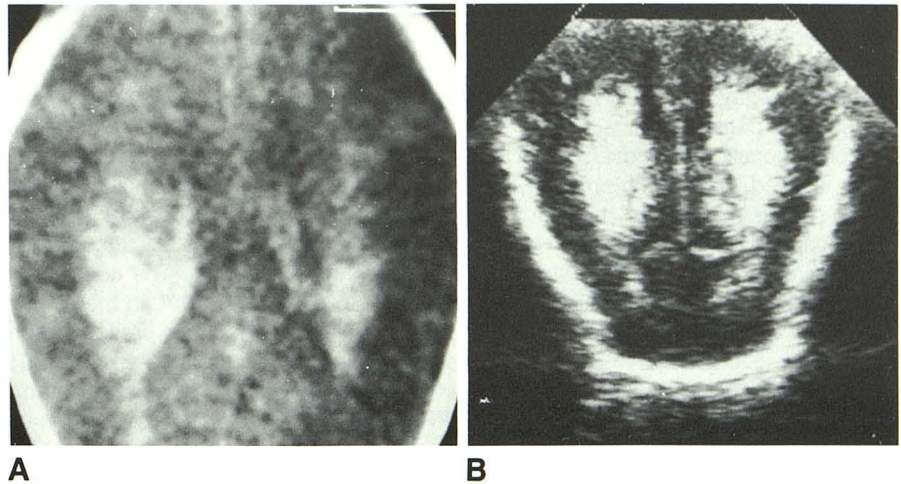


Fig. 7.—Other intraparenchymal hemorrhages in near-term neonate (36 weeks' gestational age, 2600 g) with bleeding diathesis.

A, Large hematoma in midbrain (asterisk), posterior to third ventricle (straight arrows). Hematoma extends into vermis and pons. Cavum septi pellucidi (curved arrow).

B, Follow-up sonogram shows periventricular leukomalacia giving rise to small, partly confluent cavities (arrow).

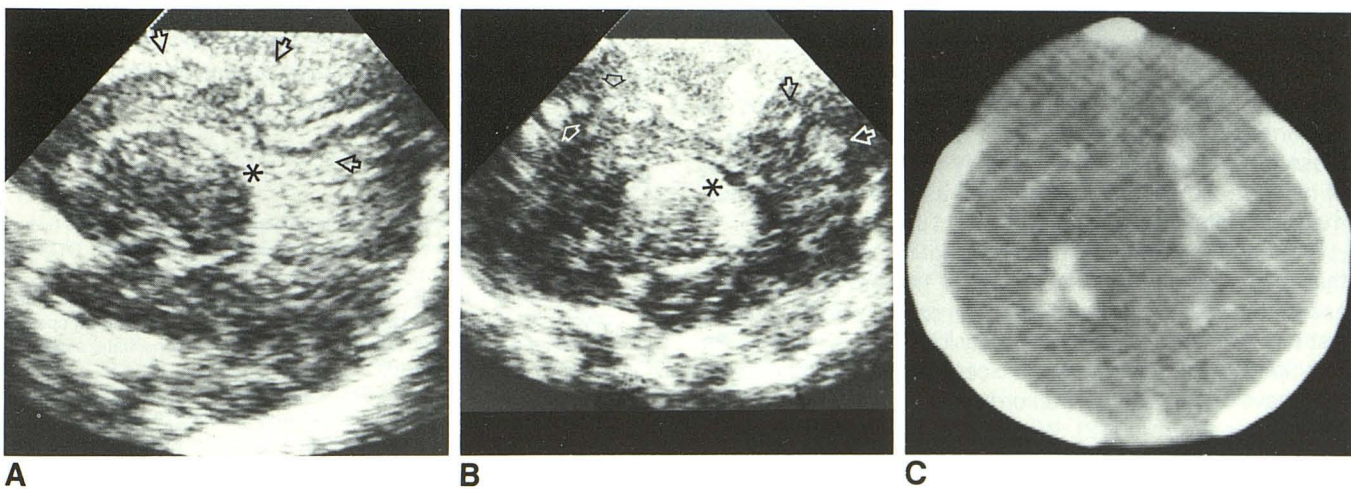
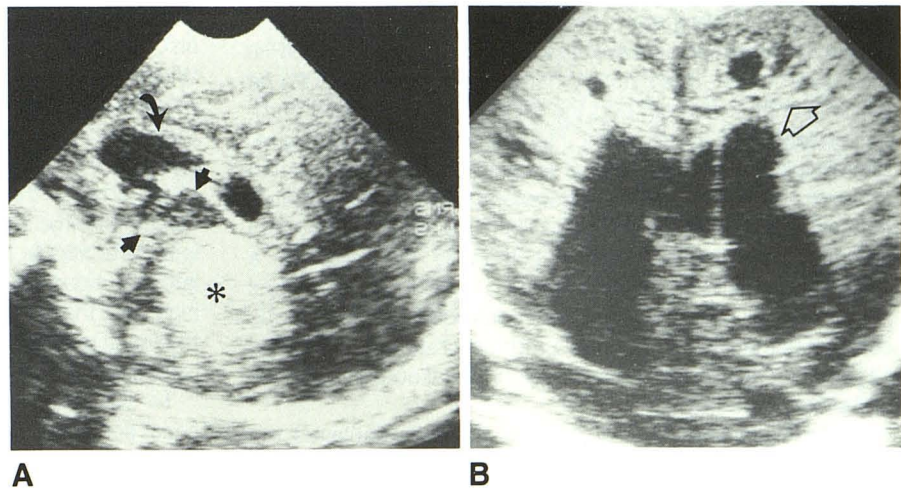


Fig. 8.—Other intraparenchymal hemorrhages in full-term neonate with meconium aspiration who was intubated and on a ventilator.

A, Initial sonogram, angled sagittal plane. Increased periventricular echogenicity (arrows) is consistent with periventricular leukomalacia. Choroid plexus (asterisk). Development of thrombocytopenia necessitated platelet transfusion.

B, Follow-up sonogram 11 days later, same plane as A. Generalized periventricular leukomalacia is less pronounced. Within same territory and peripheral to choroid plexus (asterisk) are punctate hemorrhages (arrows).

C, CT shows same punctate hemorrhages.

to high-level echogenicity on sequential sonograms was interpreted as developing hemorrhage. The evolution of small cavities in the follow-up period (Figs. 2 and 7) usually corroborated the diagnosis of PVL [15, 16]. This confirmation was made in 21 patients.

Porencephalic cysts developed in 27 patients. In 11 patients they evolved from hematoma [8], and in 16 patients, PVL gave rise to microcysts that later converged to a solitary porencephalic cavity [15, 16].

Respiratory distress and prematurity of 32 weeks or less were common features in all groups, except for other IPH (Table 1). The death rate for the entire series was 26%. It was highest in grade IV + IPH, in which it reached 50%, followed by grade IV + secondary IPH (40%), grade IV and hemorrhagic PVL (25% each), and other IPH (17%).

Discussion

Cerebral hemorrhage is the most common structural lesion of the CNS in premature neonates and includes germinal matrix hemorrhage, intraventricular hemorrhage, and IPH. The majority of these hemorrhages are considered to be germinal-matrix-related, and the most commonly used grading system, by Burstein et al. [1], is based on that premise. Bleeding into ventricles and brain parenchyma is presumed to develop by direct physical extensions of the germinal matrix hemorrhage. IPH in association with germinal matrix and intraventricular hemorrhage is commonly classified as a grade-IV hemorrhage. It constitutes 11–26% of all cerebral hemorrhages [1–8] and is the least common but most serious cerebral hemorrhage. It carries a mortality rate of 25–69% [9, 11] and has an adverse neurodevelopmental outcome in 54% of the survivors [25].

Surprisingly, only 46% of our IPH patients displayed the classical pattern of a grade-IV hemorrhage (Table 1). The remaining IPHs did not fit the Burstein et al. classification. Twenty-six percent had grade-IV hematomas with additional hematomas that were geographically distant (grade IV + IPH and grade IV + secondary IPH). These hematoma types have not attracted much attention in the literature.

Diffuse, bilateral white-matter hemorrhage, classified as hemorrhagic PVL, was found in 11% of our sample. None of these IPHs fit the criteria of grade-IV hemorrhage. This type of hemorrhage has been recognized as a secondary hemorrhage into infarcted white matter [17, 18].

Finally, 17% (other IPH) had IPHs that did not follow any of the above patterns. Germinal matrix hemorrhage is rarely associated with prematurity, and prematurity with respiratory distress is less common. Other plausible causes, such as Rh incompatibility (three cases) and bleeding diathesis (one case), may have triggered the hemorrhage in this group. These hematomas are rare [12]. We previously reported this form of IPH in erythroblastosis fetalis [26]. It is also seen in disseminated intravascular coagulopathy [27] and in thrombocytopenia.

In this discussion, we wish to focus on the first four groups (29 patients). Respiratory distress, with presumed cerebral hypoxia, occurred in all patients. These groups shared a

higher degree of prematurity. Also, the mortality rate was consistently higher than that found in other IPH.

Of the 29 patients in this conglomerate, 26 (90%) had associated PVL, a recognized marker of cerebral ischemia [1, 2, 13, 14, 19–21, 24] in the boundary zone between central and cortical arterial supplies [6, 28–30]. In some, PVL could be shown to have preceded the grade-IV hemorrhage, and secondary hemorrhage always erupted in territories previously affected by PVL.

The concurrence of PVL and IPH implies a major role of PVL in the epidemiology of IPH. While this was discussed in the presonography pathology literature [9, 13, 14], only isolated reports [20] have alluded to it since the introduction of neurosonography. Flodmark et al. [2] have shown with CT/autopsy correlation that parenchymal hemorrhages in the premature neonate represent secondary hemorrhage within periventricular infarcts or PVL. However, this observation has not been commonly accepted. Donat et al. [31], in their autopsy-based report, showed that approximately 25% of distressed premature infants with intraventricular hemorrhage also had PVL with secondary hemorrhage into it. Pape and Wigglesworth [12] identified primary white-matter hemorrhages that were thought to represent secondary hemorrhages into infarcted brain. Volpe et al. [32] documented with positron emission tomography an absence of demonstrable blood flow at the site of IPH in two premature neonates. Concomitantly, there was also reduced blood flow in the ipsilateral middle cerebral artery distribution and the contralateral subcortical white matter. Their data support our findings and the notion that intracerebral hemorrhage is either the result of widespread cerebral ischemia or induces cerebral ischemia that may involve both hemispheres.

To our knowledge, ours is the first large series in which serial sonographic observations in living neonates have provided evidence that germinal-matrix-remote IPHs represent hemorrhages into areas that are predamaged by PVL. Spread of hematomas away from the germinal matrix into adjacent brain parenchyma, therefore, is facilitated by or may require prior ischemic damage of white matter. This mechanism of parenchymal hemorrhage probably applies to most IPHs observed in the distressed premature neonate.

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