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Value of Sonography in the Diagnosis of Intracranial Hemorrhage and Periventricular Leukomalacia: A Postmortem Study of 35 Cases

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Periventricular leukomalacia and germinal matrix hemorrhages are major causes of neurodevelopmental abnormalities in the premature neonate. Although sonography is widely used to detect these abnormalities and is thought to be sensitive for hemorrhages and the later cystic stages of periventricular leukomalacia, its sensitivity for the more acute phase of periventricular leukomalacia remains to be determined. It has been difficult to study this issue because periventricular leukomalacia often is not lethal, and in postmortem studies there is usually a considerable interval between the time of in vivo imaging, if any, and the death of the patient. A "prospective" autopsy study was performed on brain specimens from infants who died at less than 1 year of age during a 10-month period. Thirty-five formalin-fixed brains were studied and sonographic images of these specimens were compared with histologic findings in whole brain sections to determine the sensitivity and specificity of sonography for the detection of germinal matrix hemorrhage and periventricular leukomalacia. Sonography identified germinal matrix hemorrhages as small as 5 mm, although smaller lesions were not visualized. Postmortem sonography had a sensitivity of 27% and specificity of 88% for all germinal matrix hemorrhages, but a sensitivity of 100% and specificity of 91% for hemorrhages larger than 5 mm. Periventricular leukomalacia, seen as hyperechoic areas in the periventricular white matter, was not detected as readily. For periventricular leukomalacia, the overall sensitivity and specificity were 50% and 87%, respectively.

We conclude that sonography is useful for detecting the larger germinal matrix hemorrhages, but has more limited sensitivity in the early diagnosis of periventricular leukomalacia.

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Because of its portability, economy, and lack of ionizing radiation, cerebral sonography is widely used for the detection of perinatal hemorrhage and infarction [1]. Despite this broad application, however, the sensitivity and specificity of this technique remain to be defined, and in individual cases the significance of the subtle changes in echogenicity of the brain is often unclear. Inquiries into the accuracy of this sonographic method can be answered only by comparing sonographic images with histologic findings, but this has been difficult since the two principal lesions, germinal matrix hemorrhage (GMH) and periventricular leukomalacia (PVL), often are not lethal. In those few cases that have been studied postmortem, a considerable interval, anywhere from several days to several months, elapsed between the time of the imaging and the death of the patient [2-5]. Because GMH and PVL may evolve during this period of time, it is difficult to determine the sensitivity and specificity of sonography by comparing in vivo sonographic images with postmortem histologic findings.

With the above limitations, previous investigations have reported sensitivities ranging from 78% to 100% for the diagnosis of PVL [3-6]. However, one can question the applicability of these statistics derived from sporadically selected cases with highly abnormal in vivo images to clinical situations in which it is the

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significance of subtle changes in echogenicity that is often in doubt. In the present study the sensitivity and specificity of sonography are addressed systematically. Postmortem sonographic images were compared with the findings from whole-brain histologic sections from 35 infants.

Materials and Methods

Case Material

Over a 10-month period, the brains of 35 infants, of whom 22 were 34-weeks gestation or younger and 13 were less than 1 year old at the time of death, were studied postmortem. Criteria for inclusion in this study included availability of an adequately fixed brain from any infant who had a gestational age of at least 21 weeks but who survived less than 1 year. All brains satisfying these criteria were analyzed regardless of suspected pathology or clinical features suggesting an increased risk for intracranial hemorrhage and PVL. Cranial sonography had been performed during life in 13 cases but was not part of the selection criteria.

Of the 35 infant brain specimens, 20 were obtained through the autopsy service of Duke University Hospital and 15 were referred from outside institutions. The latter (and the number of cases) are as follows: Boston Children's Hospital, Boston, MA (three); University of Colorado Medical Center, Denver, CO (three); Roanoke Memorial Hospital, Roanoke, VA (two); Charlotte Memorial Hospital, Charlotte, NC (two); University of Texas Medical Branch, Galveston, TX (two); Texas Children's Hospital, Houston, TX (one); Cape Fear Valley Medical Center, Fayetteville, NC (one); and the University of Alabama Medical Center, Birmingham, AL (one).

The gestational ages of the infants at birth ranged from 21 weeks to full term, and the time of death occurred anywhere from in utero to 11 months of age. The majority of infants (22/35, 63%) were born prematurely and died of cardiorespiratory insufficiency within the first week of life.

Sonographic Evaluation

Postmortem sonography was performed after fixation of the specimens in 20% formalin for at least 2 weeks. In preparation for imaging, the fixed brains were suspended in normal saline or sterile water overnight to permit the escape of gas bubbles. All studies were performed on a high-resolution electronically focused real-time system (Acuson, Mountain View, CA) using the 5-MHz linear transducer. Sagittal, coronal, and axial views were obtained routinely, with additional images tailored to the particular examination.

Each brain was scanned by one of two radiologists experienced in sonography but without prior knowledge of the clinical history or postmortem findings. In order to adjust for understanding of fixation artifacts and normal developmental changes acquired during the study period, the scans were reinterpreted blindly at the conclusion of the investigation by a single radiologist. The interpretations from the latter studies were used in the analyses below.

Images were studied for intracranial hemorrhage and PVL. Abnormal areas of echogenicity in the region of the caudothalamic groove were termed germinal matrix-related hemorrhages [7]. Choroid plexus hemorrhages were diagnosed if areas of increased echogenicity were seen adjacent to the choroid plexus, associated with an irregular "bumpy" contour of this structure. Intraparenchymal hemorrhages were defined as localized areas of increased parenchymal echogenicity. PVL was diagnosed when areas of diffusely increased

parenchymal echogenicity were at least equal in intensity to the choroid plexus and were confirmed in two scanning planes [8].

In order to evaluate possible effects of fixation on the sonographic appearance of the brain, one of the brains was studied by sonography both before and after fixation in formalin. In addition, *in vivo* images obtained in 13 infants from 1 day to 3 months prior to death were compared with the postmortem images of the same infants.

Pathologic Examination

Serial 0.5- to 1.0-cm coronal sections were made through all brains, with smaller sections made in areas of injury suspected by sonography. At least one, and often two or three, whole-mount histologic sections through the centrum semiovale were prepared in each case, regardless of the gross appearance. Small sections from the posterior periventricular areas, hippocampus, cerebellum, and brainstem were routinely prepared as well. Hematoxylin and eosin stains were used on all sections, with additional stains such as Luxol fast blue for myelin and Perls' for iron used as needed.

The size of any hemorrhages present was determined by gross and microscopic examination. The histologic diagnosis of "true" PVL was made if radiating periventricular foci of coagulation necrosis were observed, with or without a cellular reaction consisting of swollen axons, macrophages, and/or gliosis. Other histologic diagnoses included cerebral infarction, laminar necrosis, and white-matter gliosis. The last was considered present when the white matter was loose, pale-staining, and marked by fibrillary astrocytes with prominent perinuclear cytoplasm and clearly visible processes. For the calculation of sensitivity and specificity of PVL, the histologic diagnosis of true PVL and infarction were combined in the category PVL/Infarction. White-matter gliosis was not included.

Determination of Sensitivity and Specificity

The numbers of true-positive, true-negative, false-positive, and false-negative postmortem sonographic predictions for each pathologic diagnosis were determined. Sensitivity was calculated as true positive/(true positive + false negative) and specificity as true negative/(false positive + true negative). The accuracy of postmortem sonography was computed as (true positive + true negative)/total number of diagnoses.

Results

Pathologic examination revealed abnormalities in 21 (60%) of the 35 brains examined (Table 1).

Hemorrhages

Germinal matrix-related hemorrhages were present in 11 brains. In only three of six cases diagnosed by postmortem sonography as GMH (Fig. 1) were hemorrhages seen pathologically, resulting in a sensitivity of 27% and specificity of 88% (Table 2). Both hemorrhages larger than 5 mm were identified by sonography, whereas all but one of the 11 lesions 5 mm or smaller were overlooked (Fig. 2), as were resolving bilateral GMHs in two cases. If one considers only those hemorrhages larger than 5 mm, the sensitivity and specificity of sonography increase dramatically to 100% and 91%, respectively.

TABLE 1: Pathologic Diagnoses According to Gestational Age

Gestational Age of Infant at Death	No. (%)						
	Germinal Matrix Hemorrhage	Choroid Plexus Hemorrhage	Intraparenchymal Hemorrhage	"True" Periventricular Leukomalacia	White-Matter Gliosis	Cortical Infarction	No Pathologic Diagnosis
>34 weeks (n = 13)	1 (8)	2 (15)	1 (8)	0	3 (23)	2 (15)	4 (31)
≤34 weeks (n = 22)	10 (46)	1 (5)	4 (18)	4 (18)	3 (14)	1 (5)	10 (46)

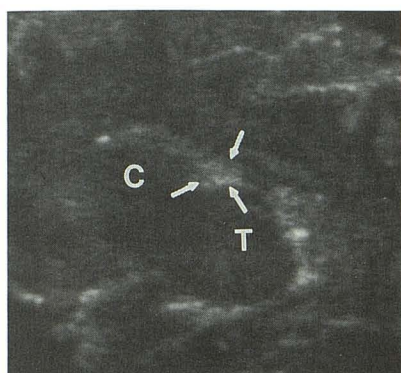
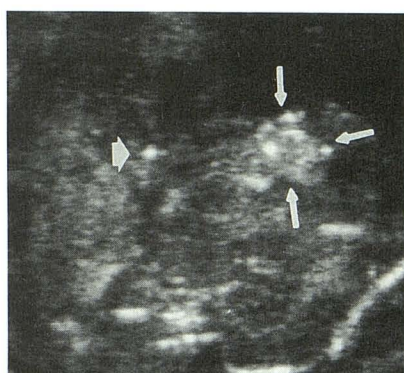
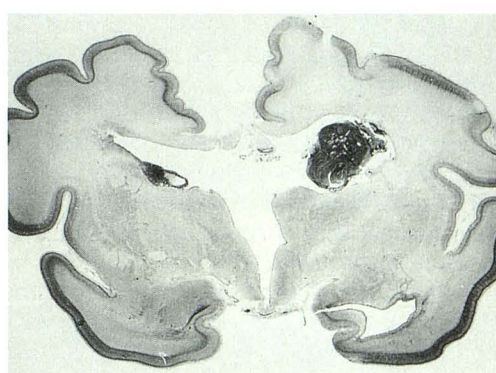


Fig. 1.—Postmortem scan in parasagittal plane records typical large germinal matrix hemorrhage (arrows) in caudothalamic groove. C = caudate nucleus; T = thalamus.



A



B

Fig. 2.—A, Coronal sonogram obtained postmortem illustrates sensitivity of sonography for large germinal matrix hemorrhages, but its insensitivity for smaller lesions. Area of increased echogenicity on right (long arrows) corresponds to germinal matrix hemorrhage, but there is no corresponding abnormality in echogenicity on left, where a 5-mm hemorrhage was found pathologically. Highly echogenic focus (short arrow) is an air bubble in lateral ventricle.

B, Histologic coronal section of specimen imaged in A reveals large germinal matrix on right that was visualized by sonography. Darkly staining smaller contralateral hemorrhage was not seen by sonography. (H and E)

TABLE 2: Sonographic Predictions for Hemorrhage

Statistical Measure	All Germinal Matrix Hemorrhages	Germinal Matrix Hemorrhage > 5 mm	Choroid Plexus Hemorrhage	Intraparenchymal Hemorrhage
True positive (TP)	3	2	0	2
True negative (TN)	21	30	28	30
False positive (FP)	3	3	5	0
False negative (FN)	8	0	2	3
% Sensitivity [TP/(TP + FN)]	27	100	0	40
% Specificity [TN/(TN + FP)]	88	91	85	100
% Accuracy [(TP + TN)/total]	69	91	80	91

Pathologic examination revealed choroid plexus hemorrhages in three brains; none of these hemorrhages had been predicted by postmortem sonography. In addition, five false-positive predictions of choroid plexus hemorrhage were made (Fig. 3) giving an overall 0% sensitivity and 85% specificity. Hemorrhages were found also in the cerebral parenchyma and cerebellum in five cases (Fig. 4). Although postmortem sonography readily identified an abnormality in three of the five cases, two of these three were identified as representing

PVL rather than hemorrhage. Therefore, a sensitivity of 40% and specificity of 100% were determined for intraparenchymal hemorrhages.

PVL/Infarction

There were seven examples of PVL/infarction, of which four were predicted by postmortem sonography. Altogether, sonography predicted eight cases of PVL/infarction by classic

criteria (Table 3); however, only four of these exhibited PVL/infarction histologically. An adult pattern of ischemia was seen in the brains of two of the term infants and classified by sonography as PVL since no other categories for ischemic injury were included in our sonographic evaluation. An overall sensitivity of 57% and specificity of 86% were calculated for the identification of the combined category of PVL and infarction.

True PVL, defined by Banker and Larroche [9] as periventricular foci of coagulation necrosis, existed in only four cases, all in infants less than 34 weeks gestational age (Figs. 5 and 6). One of these infants, who was 32–33 weeks gestation and weighed 2240 g at birth, also had evidence of infarction in the distribution of the middle cerebral artery. Previous studies have combined true PVL with other forms of hypoxic-ischemic injury into the category of PVL [5, 10, 11]. If true PVL is considered as a separate diagnostic entity, the sensitivity and specificity of sonography for PVL decrease to 50% and 87%, respectively.

The histologic diagnosis of white-matter gliosis was made in six of the 35 cases. Although there were no specific sonographic criteria for white-matter gliosis, the one case identified as abnormal by sonography had a pattern of increased echogenicity similar to that seen with PVL (Figs. 7 and 8).

As described in prior reports [12], it was found that certain injuries were characteristic for different stages of develop-

ment (Table 1). True PVL, as well as GMHs, were seen almost exclusively in the brains of infants less than 34 weeks gestation, whereas cortical infarction, laminar necrosis, and hemorrhages in the choroid plexus and brain parenchyma were seen in the more mature infants (Fig. 9). It was of interest that the common consequence of hypoxia/hypertension in adults, hippocampal necrosis, was seen in only one of the 35 cases—a term infant with extensive laminar necrosis.

In addition, this study revealed striking changes in the normal echo pattern of the brain during development. Extremely premature neonates (less than 28 weeks) had areas of increased echogenicity in a well-defined, symmetric pattern surrounding the lateral ventricles (Fig. 10). Pathologic examination revealed this echogenic region to be concentric layers of migrating glial cells from the germinal matrix region in a band of developing white matter. Term infants had uniformly increased echogenicity in the periphery, which corresponds to increased cellularity in the cortex.

Discussion

Although there are optimistic figures as high as 91% for the sensitivity of sonography in the detection of GMHs [6], our study suggests that sonography is not as accurate for this diagnosis as previously documented. We were unable to detect the majority of GMHs 5 mm or smaller. The discrepancy between the high sensitivity previously reported and our

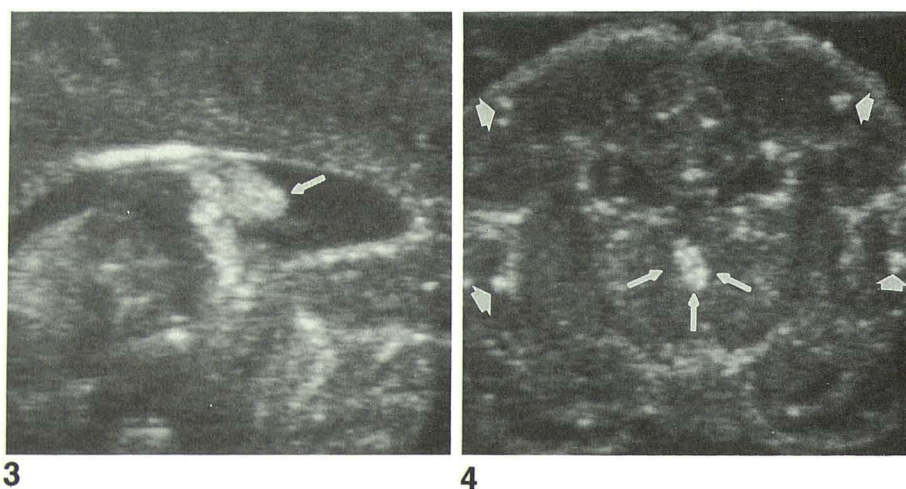


Fig. 3.—Irregular contours of normal choroid plexus were often misinterpreted as choroid plexus hemorrhages. On this sagittal image, protruding area of echogenicity (arrow) was normal choroid plexus on histologic study.

Fig. 4.—In contrast to the difficulty in identifying small germinal matrix hemorrhages, even small intraparenchymal hemorrhages were seen by sonography (short arrows). Also seen is echogenic intraventricular hemorrhage (long arrows).

TABLE 3: Sonographic Predictions for Parenchymal Lesions

Statistical Measure	"True" Periventricular Leukomalacia	Periventricular Leukomalacia/Infarction	White-Matter Gliosis	All Parenchymal Lesions
True positive (TP)	2	4	1	3
True negative (TN)	27	24	25	19
False positive (FP)	4	4	4	4
False negative (FN)	2	3	5	9
% Sensitivity [TP/(TP + FN)]	50	57	17	25
% Specificity [TN/(TN + FP)]	87	86	86	83
% Accuracy [(TP + TN)/total]	83	80	74	63

Fig. 5.—Acute phase of true periventricular leukomalacia was seen in this specimen from a premature infant, although it frequently could not be detected by sonography. Increased echogenicity in deep periventricular white matter (arrows). V = ventricle.

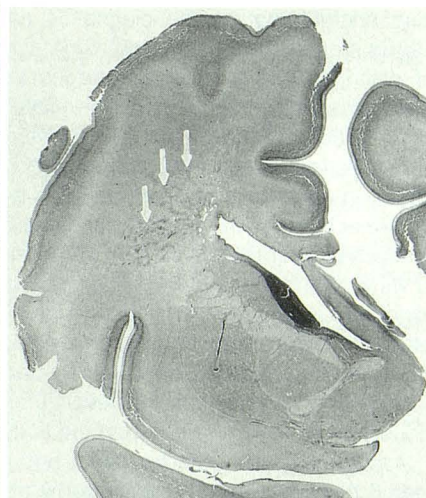
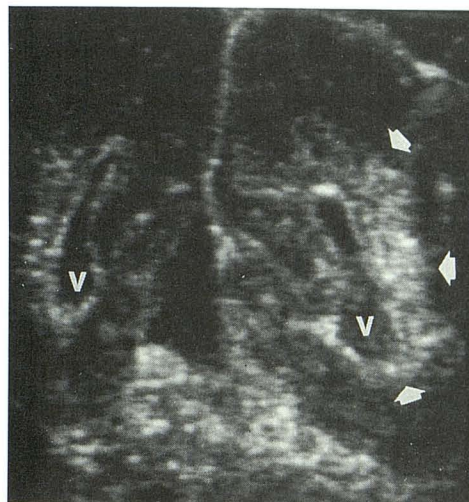


Fig. 6.—As in this premature infant, true periventricular leukomalacia appears as radiating lines of parenchymal necrosis (arrows) with epicenter at angle of lateral ventricle. Note normal darkly staining germinal matrix. (H and E)

5

6

Fig. 7.—Diagnosis of this large diffuse area of increased echogenicity (arrows) on coronal scan was illustrative of semantic issues involved in periventricular leukomalacia. Although interpreted sonographically as periventricular leukomalacia, histologic examination disclosed white-matter gliosis.

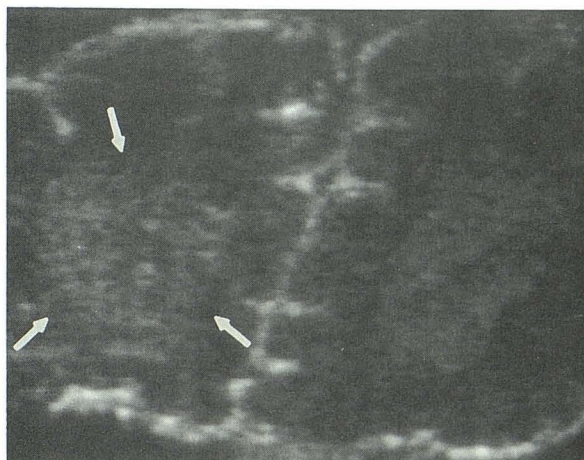


Fig. 8.—As seen on this oblique section, white-matter gliosis produces pallor and edema of periventricular white matter. It is more extensive than periventricular leukomalacia and lacks radiating foci of coagulative necrosis.

7

8

Fig. 9.—Large cerebral infarcts that extended into deep white matter (arrows) could appear similar to periventricular leukomalacia. In contrast to periventricular leukomalacia, however, lesion extends to cortical surface and is not centered in angle of lateral ventricle. The patient was a term infant.

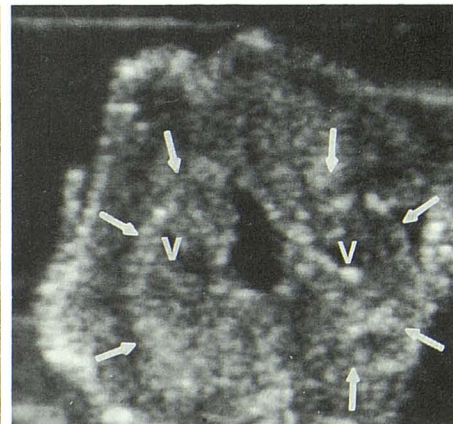


Fig. 10.—Migrating germinal matrix cells in a band of developing white matter on coronal sonogram of normal premature brain create periventricular zone of echogenicity (arrows) that should not be misinterpreted as periventricular leukomalacia. V = lateral ventricles.

9

10

lower figure (27%) likely reflects the design and patient populations of the respective investigations. Trounce et al. [6] studied only infants with a birth weight of 1500 g or less in whom at least one sonogram had been obtained while alive,

whereas our investigation focused on patients selected largely for gestational age rather than a history of hemorrhage. Thus, it is not surprising that our study included more of the smaller, difficult-to-image hemorrhages. Previous reports [8, 13] have

also commented on the diagnostic difficulty in identifying GMHs smaller than 5 mm, and attributed this to the difficulty of distinguishing small hemorrhages from normal vascular structures in the region of the germinal matrix. Normal vascular structures imaged in oblique planes also may be responsible for the two false-positive diagnoses of GMH in this study. In addition, small hemorrhages were missed because of artifacts from intraventricular air introduced during the process of postmortem fixation and suspension of the brains in water baths. Intraventricular air partially obscured the germinal matrix region in five cases, but this would not pose a problem during *in vivo* studies. Two cases of resolving GMHs were missed because they were isoechoic relative to the surrounding parenchyma; however, these lesions were previously diagnosed *in vivo* during the acute stages.

Sonography was able to detect both of the GMHs larger than 5 mm. Although these hemorrhages accounted for only two of the 11 GMHs seen, they probably represent the more prognostically significant lesions if extrapolated to the surviving population. Prospective developmental studies have indicated that the size of the hemorrhage and the extent to which it disrupts the ventricle, adjacent parenchyma, or both determines the degree of neurologic sequelae [11, 14–18]. The smaller hemorrhages may be asymptomatic or may produce subtle neurologic deficits that do not contribute to increased mortality. Disregarding the smaller GMHs and choroid plexus hemorrhages, sonography remains a sensitive tool for the detection of intracranial hemorrhages, although three false positives were noted. The clinical significance, if any, of the smaller (<5 mm) lesions is unclear.

In contrast, the diagnosis of choroid plexus hemorrhage was especially difficult because of the considerable variations in the size, configuration, and echogenicity of the normal choroid plexus. This suggests that the choroid plexus is not a fixed anatomic structure with uniform sonographic characteristics. The assumption that irregularity in the shape of the choroid plexus as seen by sonography always signifies choroid plexus hemorrhages [7] is incorrect and, therefore, choroid plexus hemorrhages should be diagnosed with caution [1]. Choroid plexus hemorrhage was found primarily in term infants; it was found in only one preterm infant and was associated with GMH extending into the ventricle. Although a high specificity was calculated for choroid plexus hemorrhages, this result is misleading. The fact that no true-positive diagnoses were made shows the limitation of sonography in this setting. From these findings, we propose that the prevalence of choroid plexus hemorrhage is lower than would be expected from sonographic imaging, and that sonographers should accept a wide range of variation in the appearance of the normal choroid plexus.

Hemorrhages in the brain parenchyma outside the germinal matrix were identified as foci of altered echogenicity in four of five cases, the one exception being a case with only microscopic foci measuring less than 1 mm. The brains of three older infants weighing more than 2000 g contained isolated parenchymal hemorrhages in association with diffuse cortical ischemia; therefore, these hemorrhages presumably differ in etiology from those originating in the region of the

germinal matrix. Sonography therefore seems a sensitive tool in detecting intraparenchymal hemorrhages outside the germinal matrix, even those less than 0.5 cm in largest dimension.

In regard to the issue of parenchymal ischemic change, this study demonstrated the limitations of sonography, particularly in the prediction of true PVL. The sensitivity and specificity issue of PVL is clouded by the fact that at least three histologic lesions are included in the diagnosis reached by classic sonographic criteria. These lesions are true PVL, cerebral infarction whose wedge-shaped extensions reach the deep white matter, and an entity referred to as white-matter gliosis.

Strictly speaking, true PVL, as defined by Banker and Larroche [8], consists of focal nodular or linear areas of coagulation necrosis within the periventricular white matter. These undergo cystic degeneration over a period of 1–4 weeks. The evolution of these lesions involves the proliferation of microglia and astrocytes at the periphery within 24 hr, followed by an increase in macrophage activity with resultant liquefaction necrosis. Such lesions were observed in four of the 35 cases in our study; two of these were missed by sonography even though they were as large as 1.1×1.3 cm. One would assume that these lesions would have become apparent if they had had time to evolve into cysts [2, 5, 19, 20].

Cerebral infarction is a category of ischemic injury that mimics PVL on sonography when it extends into the deep white matter. In our three cases, all were identified as deep-seated foci of increased echogenicity and assumed to be PVL. Examination of the brain postmortem confirmed the abnormality but showed that it was part of a wedge-shaped infarct whose cortical base was not well visualized sonographically, thus underestimating the extent of injury [10]. This type of injury was found in three neonates older than 34 weeks and contrasts with true PVL, which is restricted to the premature.

White-matter gliosis may simulate PVL on sonography as well. In the present study, large diffuse areas of increased echogenicity correlated with large histologic areas of white-matter gliosis as described in detail by Rorke [21]. It was in this manner that one false-positive sonographic diagnosis of PVL was made. If white-matter gliosis and PVL infarction are considered as a single entity, as they have in other reports, then the specificity of sonography is 83%, approaching the values seen in the other studies [3, 5, 6]. This entity of gliosis is distinct from PVL and is relatively common, found in anywhere from 15 to 40% of a high-risk infant population seen at autopsy [21] and in six (17%) of 35 members of our autopsy population. In five cases small areas of white-matter gliosis were overlooked as normal by sonography. Epidemiologic factors most closely associated with white-matter gliosis include cardiorespiratory problems such as respiratory distress syndrome, congenital heart disease, and perinatal asphyxia, similar to those in PVL.

Our findings suggest that PVL overlaps sonographically with other types of parenchymal injuries such as white-matter gliosis, hemorrhage, and cortical infarction in the acute stages. Periventricular echogenicity by itself is not a specific indicator of necrosis within the white matter [2]. Therefore,

the sonographer must consider the gestational age of the infant in order to accurately assess the location and type of injury present, if any. Serial examinations also may be necessary to follow the progression of brain injury [5, 22].

The use of postmortem imaging after tissue fixation in the present studies raises several issues that relate to the sensitivities and specificities of sonography in vivo. The most important is the extent to which formalin fixation alters the echogenic properties of the brain. Previous studies [23] have shown that there is little change in attenuation of ultrasound waves caused by formalin fixation. We found only minimal differences in the images produced before fixation compared with those after fixation. The postmortem images also correlated well with the in vivo scans, and actually reveal improved resolution of intracranial structures because of the absence of any barrier to visualization produced by the skull. In addition, it was our belief that the anatomic details were seen better in postmortem imaging than in in vivo imaging. Furthermore, without the restriction as to scanning plane dictated by the fontanelle, the brains could be studied freely from any angle. In short, we do not believe that the formalin fixation contributed to the lower sensitivity of sonography to lesions, as has been reported previously. The primary limitation of postmortem imaging was in visualizing the germinal matrix region owing to occasional trapping of gas within the ventricles. This artifact was minimized by suspending the formalin-fixed brain in water for 1–2 days before scanning, but still precluded visualization of the germinal matrix region in some cases.

We conclude that sonography is sensitive for the detection of GMHs larger than 5 mm, but insensitive for the smaller and perhaps biologically less significant lesions. For choroid plexus hemorrhages, the technique appears insensitive given the overlap in sonographic appearance between choroid plexus hemorrhages and normal plexus in its normal wide range of sonographic profiles. In regard to parenchymal forms of perinatal hypoxic/ischemic injury, increased parenchymal echogenicity is not specific for PVL or infarction, but rather is a predictor of a wide variety of abnormalities including white-matter gliosis, PVL, hemorrhage, and cortical infarction. In this setting the gestational age of the neonate, the location and pattern of echogenicity, as well as the progression of echogenicity over time must all be considered in the evaluation of abnormal sonographic images.

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