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Special Article

Diagnostic Imaging of the Neonatal Brain: Review and Protocol

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*A grievous burden was thy birth. . .
Tetchy and wayward was thy infancy.*

Shakespeare, *King Richard III*
(act 4, scene 4, line 168)

The neonatal brain, previously so inviolate to imaging techniques other than relatively crude radionuclide studies, direct contrast ventriculography, and rarely performed angiography or pneumoencephalography by only the most adventure-some or experienced neuroradiologists, now has been successfully and safely mastered by computed tomography (CT) and sonography. Widespread interest in and clinical importance of images so obtained has dramatically altered and improved diagnostic expertise and understanding in these most difficult of all patients.

The main features influencing the clinical and diagnostic efficacy of such imaging methods are: (1) their individual spatial resolution, (2) the reliability of each technique vis a vis each other, (3) their relative safety and ease of performance, and (4) a suitable imaging protocol.

An awareness is essential of the complex cerebral sequelae that can afflict neonates, their unique cerebral anatomy, the differences between preterm and term babies, the differing type and degree of cerebral damage in the preterm and term baby, and the long-term clinical sequelae from each type of disease at each level of maturity.

The neonate, particularly if premature, may have significant respiratory (e.g., respiratory distress syndrome) and intraabdominal (e.g., necrotizing enterocolitis) abnormalities in concert with cerebral damage. This latter damage may be varying ischemic changes, intracerebral hemorrhage, or both. Mortality may be influenced by one or more of the above disease processes, and it is often ultimately difficult to identify which is the prime agent. The treatment of one, such as respiratory distress syndrome, may create the circumstance for formation of another (e.g., cerebral hemorrhage).

An understanding of the basic features of fetal cerebral anatomy and the pathogenesis, morphology, and clinical significance of acquired postnatal cerebral abnormalities should precede the suggestion of a logical diagnostic imaging protocol. Abnormalities not associated with the birth process per se, such as congenital malformations and neoplasms, deem separate consideration and are not included here.

The Neonatal Brain

The complex anatomic cerebral development attendant to intrauterine growth was detailed by Larroche [1] and the developmental anatomy of the fetal cerebral vascular system by Padgett [2] and Van den Bergh and Van der Eecken [3]. Only those features that

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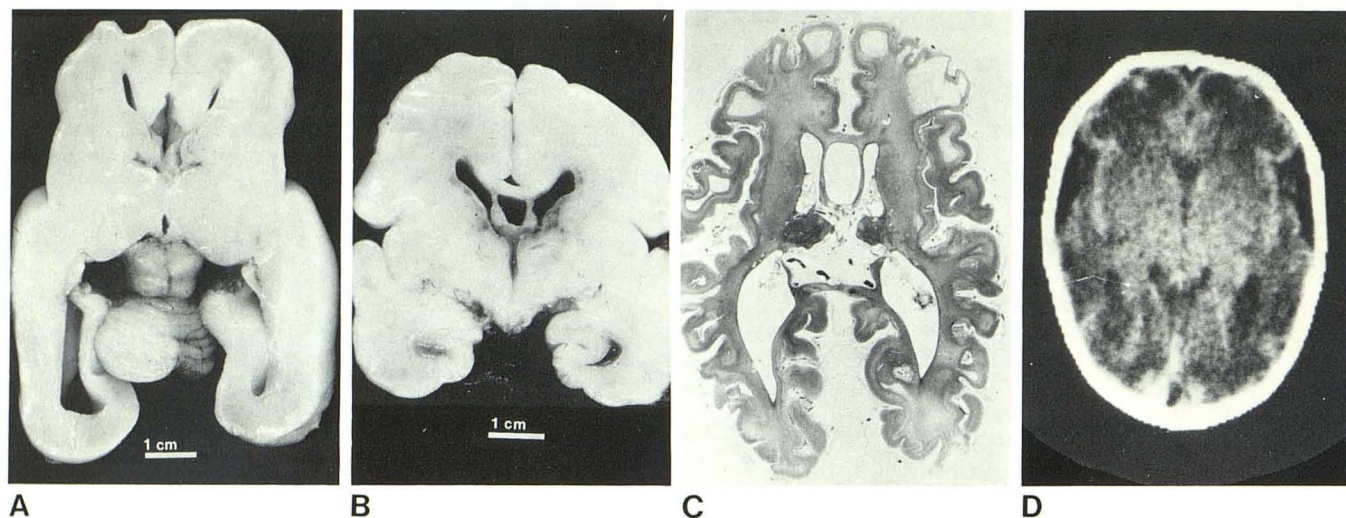


Fig. 1.—“Normal” premature brain. **A**, 24 weeks gestation, axial section. Poor development of gyri and sulci, rectangular shaped sylvian fissure. **B**, Another infant, same gestational age and findings plus common cavum septum pellucidum. **C**, Thin slice section of premature at 30 weeks gestation.

Poor sulcal development but white and gray matter differentiation with thin gray matter rim. **D**, CT scan in 26 weeks gestation. Poor gyral development, rectangular sylvian fissure, thin ribbon of gray matter, and large amount of white matter (cf. **C**).

now have a recognized anatomic relation to diagnostic imaging of cerebral disease processes will be considered.

The brain water content is about 88% at birth, diminishing to 82% at 6 months [4]. Cerebral white matter water content has variably been reported at 88%–97% in neonates of 27 weeks gestation to term [5]. The gray matter in premature infants weighing less than 1,500 g is a thin ribbon of cerebral tissue outlining relatively flat gyri and shallow sulci and a squared open sylvian fissure (fig. 1). A cavum septum pellucidum is usually present. The white matter is relatively extensive and the basal ganglia profusely vascular. However, at term, the sylvian fissure is closed, the gyri and sulci better formed, and the bulk of the white matter relative to gray matter reduced.

The computed tomographic (CT) numbers of relative attenuation of white matter in such small infants of 23–29 weeks gestation are 7–19 Hounsfield units (H) (average, 15 H; ventricular cerebrospinal fluid [CSF], 8–11 H) (C. R. Fitz, unpublished data). The gray matter readings in the same infants were 14–27 H (average, 22 H). The region of the head of the caudate nucleus was 21–39 H (average, 28 H, representing the highly vascular subependymal germinal layer complex [see below]). It must be recognized that it is difficult to define normality in such premature infants. Are the high water content and low Hounsfield units simply due to the early stage of maturation or are they due to anoxic damage with increased cellular and intercellular water? We think probably more of the former. Further myelinization proceeds irregularly and is not complete until early childhood.

Picard et al. [6] studied the relative Hounsfield units of different parts of developing brain at three different ages of maturity, 28, 34, and 39 weeks, and related these measurements to that of the insular cortex. The possible accuracy of these and the above figures was confirmed.

The concise summary of the blood supply of developing brain by Pape and Wigglesworth [7] is of a ventriculopetal arterial supply of peripheral cerebral origin and a ventriculofugal arterial complex of the basal origin, probably with no major interarterial communications occurring in the premature infant. This suggests a boundary zone between the two situated in the periventricular region and predominantly in the white matter.

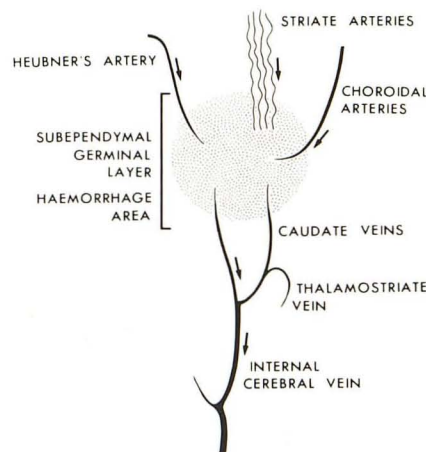
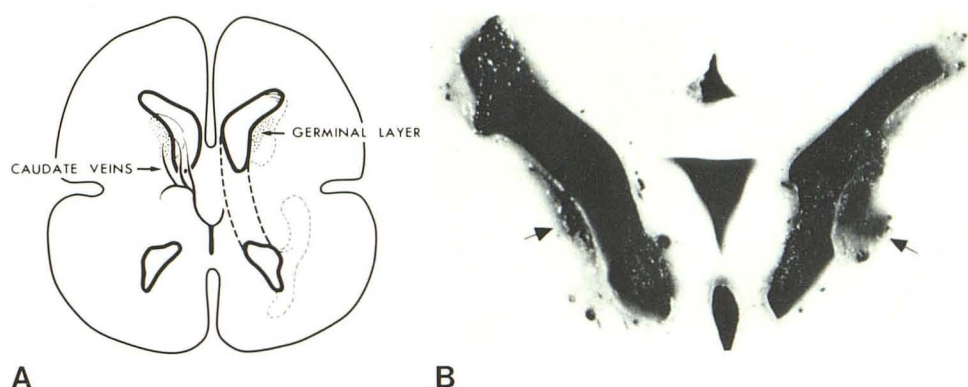


Fig. 2.—Subependymal germinal layer. Major arterial feeders and venous drainage system to subependymal germinal layer or primary hemorrhagic area.

The subependymal germinal matrix layer, a discrete but extensive highly vascular subependymal collection of vessels and glioblastic cells (fig. 2), exists in the premature infant, diminishes at 30–35 weeks gestation, and then disappears. This is largest in the subependymal layer at the head of the caudate nucleus (fig. 3), fed mainly by a large recurrent artery of Heubner, and extending backward along the body and proximal tail of the caudate nucleus, fed largely by the anterior and posterior choroidal arteries. Injection studies by Pape and Wigglesworth [7] show the subependymal germinal matrix layer to be a collection of peripherally placed delicate capillaries with central immature vascular rete and glioblastic tissue.

The cortex in the preterm infant is supplied by branches of the superficial arteries and form centripetal arteries, fine spiral vessels coursing to the ventricular wall (particularly prominent at 24–26 weeks) and ultimately to a capillary bed (7). With fetal maturation,

Fig. 3.—Germinal layer and hemorrhage. **A**, Germinal layer maximal along-side lateral caudate nucleus extending backward into lateral aspect of lateral ventricle. **B**, Coronal pathologic specimen. Subependymal germinal matrix hemorrhage (arrows), ruptured through into ventricles, creates intraventricular hemorrhage. Clearly demarcated ependyma between subependymal hemorrhage and ventricular cavity.



short cortical arteries proliferate concurrent with gray matter and gyral development.

Pathogenesis of Cerebral Damage

Brain damage incurred during the natal or postnatal period may be of varying forms and degrees of hemorrhage, ischemia, or a combination of both. Traumatic intracranial sequelae [7] consist of epidural, subdural, and intracerebral hemorrhage usually in the supratentorial space, less commonly in the infratentorial space [8], and more often associated with a difficult or instrument-assisted birth in the near or full-term baby.

For several reasons discussed below, it is important to subdivide the neonates into different groups depending on maturity. For practical purposes, it is expedient to divide neonates into small preterm neonates weighing less than 1,500 g and a gestational age of less than 33 weeks and full-term neonates with a birth weight of 2,500 g and over and a gestational age of at least 36 weeks. In the intermediate group, it is not clear how to classify neonates reacting more like small preterm infants and those more similar to full-term. Without definite proof, we believe that gestational age is the most important indicator of maturity and the dividing line should be 34–35 weeks gestation. This is also a suggested clinical grouping on the basis of differing cerebral anatomy (see above) and differing frequency of specific intracranial sequelae [9]. This basic separation into preterm and term groups can be suitably used for diagnostic imaging purposes.

Ischemic Lesions

In general, asphyxia may occur in the partum and postpartum periods, the former period more common in the term [10] and the latter in the premature babies [11].

In the preterm baby, ischemic lesions often occur at the watershed boundary zones of the periventricular white matter and the centrum semiovale as periventricular leukomalacia (PVL) [7, 12, 13, 14]. PVL is simply a region of coagulation necrosis and rarified neuropil areas containing swollen axons or macrophages [13] followed by a reaction of microglial cells and then astrocytosis [7]. Hemorrhage may be an accompaniment if frank infarction is present and

this is often quite large. The areas of necrosis may then liquefy and cavitate [7]. In the very young, these areas may be punctate, progressing to massive areas in the older infant [12, 13]. PVL probably occurs due to hypertension associated with asphyxia affecting the boundary zones in particular [14–16]. In more mature infants, cortical gray matter and basal ganglia are more often involved by ischemic damage due to hypoxia. The preterm cortex is probably better protected by a profuse network of pial cerebral artery anastomoses than in the term infants. There is considerable associated edema, particularly in the full-term infant [9, 17]. Significant prolonged hypoxia in both preterm and term infants will produce widespread swelling, edema, and necrosis of both white and gray matter, with extreme cerebral destruction that often leaves only viable basal ganglia and cerebellum. The brain then goes on to extensive leukomalacia with gliosis and microcephaly.

Intracranial Hemorrhage

Other than obvious traumatic hemorrhagic sequelae, intracranial hemorrhage may occur in the *subarachnoid space* either secondary to intraventricular hemorrhage or primarily due to anoxia [16] or in the birth process itself [7], with a rupture of vessels about or bordering the subarachnoid space and the leptomeninges. In term neonates, intraparenchymal cerebral hemorrhage may be diffuse and petechial within the cortical areas associated with necrosis [7] due to cortical venous infarction or main artery or branch occlusions, all of which are uncommon. White matter hemorrhage occurs in both preterm and term neonates. In the former, it is associated with periventricular leukomalacia, a periventricular hemorrhagic infarction [13, 18], and is not uncommon. Rarely is it a mere extension of a subependymal hemorrhage into white matter. In term neonates, the etiology is less clear. There may be central venous thrombosis and ischemic necrosis of white matter. Rupture with extension of the hemorrhage in the ventricular system appears to occur quite frequently with this latter lesion.

Subependymal hemorrhage is the most common and typical appearance in the preterm neonate and occurs within the germinal matrix layer, particularly that located over the caudate head, extending over the body of the caudate nucleus in the lateral wall of the lateral ventricle in the more

immature neonate. The hemorrhage may be discrete or extensive, symmetrical or asymmetrical. The cause is most likely due to an increase in blood pressure [7] secondary to asphyxia, apneic attacks, or, indeed, the very resuscitation after such attacks. In the presence of inadequate autoregulation, the increased blood pressure results in increased flow through the fine capillary network in the germinal matrix layer, resulting in rupture of the vessels and hemorrhage [7]; alternating episodes of severe and persistent hypotension with episodes of increased blood flow may lead to a combination of ischemic infarctions with secondary hemorrhage into the infarcted areas and hemorrhage in the germinal matrix layer. This combination constitutes probably the most severe brain damage due to asphyxia. The role of venous thrombosis [19, 20] in this mechanism is probably less important and has not been confirmed.

Subependymal hemorrhage is the most common form in preterm neonates, but is less common in the more mature neonate [9]. Often, this hemorrhage ruptures through the ependymal ventricular wall, resulting in varying degrees and extent of *intraventricular hemorrhage*. This, together with a periventricular hemorrhagic infarct, probably represents the most severe form of brain damage and carries the highest mortality (100%) among neonates under 1,000 g [17]. In our experience, periventricular hemorrhagic infarction has not been detected as an isolated finding without a concomitant subependymal-intraventricular hemorrhage. Intraventricular hemorrhage can rarely be isolated due to a primary bleed in the choroid plexus, also probably due to rupture of primitive capillary vessels.

Cerebellar hemorrhage occurs rarely [7, 8]; it may be petechial in nature or it may be more extensive, located in the subcortical areas of the cerebellar hemisphere and due to traumatic breech extraction or a tight face mask [7]. On CT, these lesions can imitate an extracerebellar hemorrhage [8].

Thus, the significant cerebral damage in neonates, particularly the premature during the antenatal, intrapartum, and postnatal periods, is due to anoxia with its effect per se on the cerebral tissue. Subsequently, it and other factors may cause subependymal and cerebral hemorrhage, both of which may ultimately lead to intraventricular hemorrhage. Thus is there a triad of ischemic damage, cerebral hemorrhage, and intraventricular hemorrhage.

Incidence of Cerebral Damage and Sequelae

We believe that the two major forms of cerebral damage, ischemia and hemorrhage, are intimately related. Basic questions can be answered via objective imaging, clinical data, inference alone, or a combination of the three. Is the premature infant, because of its unique cerebral structure, particularly prone to anoxic damage, and is it also capable of satisfactorily compensating for such damage? Does evidence of similar damage to the term infant have a more serious connotation? Does the character of hemorrhage per se provide sufficient evidence to significantly alter the therapeutic philosophy and practice of the neonatologist? Could the more objective evidence of hemorrhage merely be a

marker of dire damage to cerebral function and architecture below the limits of present imaging resolution, such as caused by anoxia and ischemic cerebral damage?

In an attempt to answer these questions, the incidence and pattern of hemorrhage as imaged, and that of presumed anoxic damage itself, will be considered together with the respective clinical sequelae for constructing a practical protocol of diagnostic imaging. These lesions will also be considered as they involve the premature separate from the term infant, the former changing to the latter at about 34–35 weeks gestation.

Intracranial Hemorrhage

The classical signs of neonatal intracranial hemorrhage, especially intraventricular hemorrhage [21–24], are a sudden acute onset of seizures, coma, cardiac arrest, drop in hematocrit, etc. [7] together with a rapid clinical deterioration. These signs are now known to be less common than previously thought. Often, the onset is clinically latent or attended by very subtle alterations of clinical status, minor seizures, and increase in apneic episodes.

Autopsy studies have shown that 70%–75% of preterm babies (less than 33 weeks gestation) had germinal matrix layer and intraventricular hemorrhages [7]. In prospective CT studies of sequential premature babies using early CT machines, Lazzara et al. [22] and Burstein et al. [25] demonstrated unspecified combinations of subependymal hemorrhage and intraventricular hemorrhage occurring in 38% and 43%, respectively. In 1975, 41,000 infants born in the United States weighed less than 1,500 g [26]. Using the statistics of Burstein et al., 17,000 (43%) would have some form of intracerebral hemorrhage, one-half would have died, and the other half could be afflicted with possible sequelae of hemorrhage. Others have shown an incidence of hemorrhage of 70% [27]. In a prospective study at Toronto's Hospital for Sick Children of out-born infants weighing less than 1,250 g, an incidence of subependymal/intraventricular hemorrhage was seen by real-time sonography in 84% (K. Pape, personal communication), subependymal hemorrhage alone in 14%, and intraventricular hemorrhage in 70%.

There are no other accurate figures as yet to indicate the exact incidence of subependymal hemorrhage and intraventricular hemorrhage in neonates of all ages and weights, as most studies were either autopsy alone, CT alone, or sonography alone. Most were performed at differing times in the neonatal period on the basis of clinical signs, and very few had autopsy correlation. Similarly, in recent years, CT technology has significantly improved over that of the early studies.

In a large reported study of 476 neonates who suffered perinatal asphyxia, all had a CT examination on clinical grounds [17]. Statistics should be viewed in this light. CT was performed within the first week in 84%. *Some form of intracranial hemorrhage* within this selected group occurred in 341 (72%). Such hemorrhage occurred in 75% of infants weighing less than 1,500 g (85% of these weighed less than 1,000 g). Hemorrhage occurred in 68% of infants weighing over 1,500 g.

Of the 341 infants with hemorrhage in the same reported series, primary subarachnoid hemorrhage, as shown by CT, occurred in 27% (87% of these weighed over 1,500 g). However, it must be noted that in using the early model CT scanners, we believe many subarachnoid hemorrhages detected could actually have been normal thin gray matter, which is now seen so well on modern scanners (fig. 1). Extracerebral hemorrhage (one extradural, 20 subdural) occurred in 6%. Subependymal hemorrhage *without* intraventricular hemorrhage occurred in 14%; of these, 89% weighed less than 1,500 g. It must be noted that subependymal hemorrhage and periventricular hemorrhagic infarction are often exceedingly difficult to differentiate unless autopsies are available. *Intracerebral hemispheric hemorrhage* per se is different from the periventricular germinal matrix layer and periventricular hemorrhagic infarction and occurred in 7%; 90% of these were in infants weighing more than 1,500 g and most more than 2,500 g. *Intraventricular hemorrhage*, almost *always* associated with subependymal hemorrhage and less commonly with periventricular hemorrhagic infarction and choroid plexus hemorrhage, occurred in 50%. In intraventricular hemorrhage, the male to female ratio was 2 to 1. The proportion of infants with intraventricular hemorrhage who weighed less than 1,500 g was 72%. Only 4% weighed more than 2,500 g.

Grading hemorrhage, especially intraventricular hemorrhage, by CT or sonography, is not entirely dependable because blood clots change in character with time, ventricular size may be small or large or changing, late extension of hemorrhage may occur in the cerebral tissue, hemorrhage may occur at a later date than the immediate postnatal period, and the character of the hemorrhage has a different significance in premature and mature infants [17].

Burstein et al. [28] classified hemorrhage as grade 1, subependymal only; grade 2, intraventricular with normal-sized ventricles; grade 3, intraventricular with dilated ventricles; and grade 4, intraventricular with ventricular dilatation and cerebral extension of subependymal hemorrhage. Another study that compared the respective autopsy and a recent CT finding in individual neonates suggested a different classification [17]. This classification attempts to incorporate the clinical outcome and the CT appearance of hemorrhages in each neonate. It suggests that subependymal hemorrhage should be excluded as a separate entity for grading and deemphasizes the significance of initial ventriculomegaly. Grade 1 is described as a small amount of blood within the ventricle or ventricles; grade 2, large amounts of blood in the ventricle or ventricles but without periventricular hemorrhagic infarction; and grade 3, blood in the ventricular system plus periventricular hemorrhagic infarction. It was shown that subependymal hemorrhage by itself has a differing and less ominous clinical outlook than when associated with intraventricular hemorrhage. Conversely, the presence of a periventricular hemorrhagic infarct is an ominous sign.

The timing of bleeding into the germinal matrix layer as assessed by CT, sonography, and tagging of red blood cells [29] suggests an onset at 12–24 hr and up to 1–3 days, but possibly up to 2 weeks after birth. All investigators have stressed the poor correlation between the CT evidence of

hemorrhage and significant associated clinical evidence. The subependymal hemorrhage and *probably* the periventricular ischemic hemorrhagic infarct may rupture into the ventricles at any time. The natural history of an intraventricular hemorrhage as seen by CT [27, 30–32] has shown that with a fresh bleed the blood is freely mixed with CSF. Clotting soon occurs, usually surrounding the choroid plexus, and with retraction leaves a clear CSF space around it. Autolysis of the clot occurs 3–5 days later; the clot liquefies and fills the dependent part of the ventricles. A ventricular “cast” may also occur, clearly seen at CT, composed of blood adherent to the ventricular wall, or its breakdown products incorporated into the ependymal lining itself. The hemorrhage usually disappears by 2–3 weeks. Parenchymal hemorrhage passes through the same process but, after 2 weeks, it may become relatively isodense with brain [27]. However, with the next generation CT images, evidence of an abnormality is often still faintly seen. The areas of necrosis and lysed clot, about to become a cavity, are readily seen by sonography [33].

Cerebral Ischemia

Objective anatomic CT evidence of hypoxic or ischemic brain damage in neonates was first reported in 1978 by DiChiro et al. [34], who suggested that decreased attenuation on a CT scan in the periventricular area, particularly in the frontal region, may represent periventricular leukomalacia. However, great advances have been made since then in our understanding of this particular disease process, due to the improved spatial resolution of CT and partly to experience. The decreased attenuation seen on CT is now interpreted as increased water content of that part of the brain and, thus, may represent areas of reversible hypoxic brain damage, infarction, or, in the premature infant, simply poor myelination as part of the normal developmental process. As a result of the advances in CT technology, we now believe that the “normal” low attenuation areas in the *premature* brain with a high water content per se [1] may have been incorrectly interpreted as “ischemic areas” [9, 34, 35] from first or second generation CT scanners.

In a correlative study between CT and autopsy in premature and full-term infants who suffered perinatal asphyxia, Flodmark et al. [9] reported 90 cases, 60 weighing less than 1,500 g. Of the 60, all were thought to have abnormal periventricular and cortical decreased attenuation areas, as seen on early generation scanners. Only 28 had evidence of ischemic brain damage at autopsy; 32 did not. Since that study, performed with a Delta 50 scanner, CT images obtained with a new GE 8800 CT scanner have eliminated many of the false-positive interpretations, mainly by increase in spatial resolution. Another study, an evaluation of 460 CT examinations on neonates in whom the presence and extent of decreased brain attenuation was correlated with the maturity of neonates, showed that *minor* changes of decreased attenuation, considered abnormal, were seen virtually exclusively among the *mature* neonates [17]. Those that were considered to have normal brain attenuation and those that had the most severe generalized decreased attenuation (severe generalized cerebral edema) [36] were

also found among the more mature infants. However, moderate and severe focal areas of decreased brain attenuation were confined mainly to the immature neonate. This inverse relationship between the extent of decreased brain attenuation and maturity together with poor autopsy correlation suggest the "normality" of the *premature* white matter CT images. Furthermore, follow-up studies on the survivor support this proposition (see below).

Thus, the true incidence of ischemic brain damage in preterm neonates is not known. In the mature neonate, areas with decreased attenuation, other than the very minor, are thought to represent ischemic damage [9, 17] or, if found in the most severe form, generalized cerebral edema. Focal cortical and white matter areas of decreased attenuation asymmetrically distributed within the hemispheres are being detected with increasing frequency, but the significance of this finding has to be viewed in relation to the maturity of the neonate. In the premature, this must be examined with great care and prospectively related to the recent vintage CT scans and autopsy studies.

It is the *asymmetry and irregular* disruption of gray/white matter that is important in the diagnosis of ischemic damage. A suggested grading follows [17]: grade 1, mild scattered patchy areas of decreased attenuation on CT, which in old scanners may be a variant of normality; grade 2, extensive or confluent areas of involvement in one hemisphere or both, especially superior in the cortex; and grade 3, generalized hemispheric edema with diffuse decreased attenuation and small ventricles, fissures, and sulci, suggestive of significant cerebral edema and mass effect.

Clinical Sequelae

Again, it is important to separate the premature from the near- and full-term infant. These groups are relatively different in cerebral maturity. The incidence of respiratory distress syndrome and necrotizing enterocolitis as associated abnormalities is higher in the premature. In assessing clinical outcome, many features of cerebral damage must be considered, often two or more together, making it difficult to assess accurately the true impact of *one* objective abnormality: degree and extent of hemorrhage, ventricular size, weight and gestational age, ischemic lesions, or presence of extracranial disease as above. However, preliminary statistics and indications are useful, if for no other reason, to direct future prospective studies. Furthermore, the mortality in these various groups is often determined in part by the particular therapeutic philosophy and expertise of the neonatologists affiliated with individual perinatal units. The question as to how long one should persist in aggressive support therapy is not yet answered satisfactorily nor is a basic therapeutic approach agreed upon by neonatologists. The relation between *mortality* and the type and extent of hemorrhage can be derived from four studies: Flodmark et al. [17], considering all neonates; Burstein et al. [25], infants weighing less than 1,500 g; Ahmann et al. [37], those with gestational ages less than 35 weeks; and Ludwig et al. [36], full-term infants.

The mortality associated with *subependymal hemorrhage*

alone in the above group was 20%–30% (average, 24%) in premature infants; very few such hemorrhages occurred in the more mature infants. An *intraventricular* hemorrhage, usually associated with a subependymal hemorrhage, but sometimes with choroid plexus hemorrhage or periventricular hemorrhagic infarcts, had a variably reported mortality of 13%–48% in the mild hemorrhage to 49%–78% (average, 61%) in the severe grades of bleed. In those infants weighing less than 1,500 g, the mortality was 67%, but only 42% in the more mature child, and 17% in the full-term infant [17]. Thus, mortality was directly related to the severity of bleed, but inversely to the increasing maturity.

In considering objective evidence of *ischemic damage* by CT, it is extremely difficult to relate the decreased attenuation of the premature brain to mortality, even using the simple grading system suggested above. This excepts grade 3, the severe edema that occurs predominantly in the near or full-term infant, with a 53% mortality [17].

Hydrocephalus

The assessment of the occurrence of hydrocephalus in neonates who have suffered perinatal asphyxia must be qualified by certain definitions. Intraventricular hemorrhage may enlarge the ventricles *per se*; ventriculomegaly may be either due to brain tissue loss and atrophy or to hydrocephalus, by which is meant progressive increase in ventricular size attended by obstruction to the CSF flow with an abnormal increase in head size. A combination of both tissue loss and hydrocephalus may occur, one or the other being dominant or indeed mutually adjusted at the time of a particular examination. It is suggested that, before the state of hydrocephalus or nonhydrocephalic ventriculomegaly is established, infants who have had an intraventricular hemorrhage be followed closely by imaging techniques and by clinical examination until ventricular size is stabilized or returns to normal.

If clinical abnormal rate of head growth ensues with accompanying fontanelle pressure, suture changes, worsening clinical neurologic status, and abnormal CSF radionuclide flow studies, active intervention, either surgical or nonsurgical, should be contemplated.

Ventricular size does not always correspond to clinical status of hydrocephalus [38]. Moreover, Korobkin [39] and Volpe et al. [40] showed that ventriculomegaly in premature infants can be present in a normal-sized head up to 20 days after an intraventricular hemorrhage and only then be associated with an enlarging head (i.e., hydrocephalus). This lag time is probably due to an initial but limited displacement of the large neonatal fluid compartment of the brain and intracranial blood pool by the enlarged ventricles. Ventriculomegaly without subsequent head enlargement could, therefore, be due to loss of brain substance itself. Such cranial enlargement after this period is uncommon, however.

In early reports, the incidence of progressive increase in ventricular size after intraventricular hemorrhage was 18%–32% and was imprecisely categorized as "hydrocephalus" [24, 35, 37, 41]. LeBlanc and O'Gorman [42] reported that six of 11 infants with intraventricular hemorrhage developed

progressive hydrocephalus; Levene and Starte [43] reported four (8%) of 36.

In a larger prospective study, 130 infants who suffered perinatal asphyxia were subdivided into one group of 77 weighing less than 1,500 g and a gestational age of less than 33 weeks and another group 53 infants born with gestational age of 38 weeks or more [44]. Ventriculomegaly, hydrocephalus, and the presence or absence of hemorrhage was evaluated. All had CT at a mean of 11 and 5 days after birth, respectively, and all were followed clinically for at least 18 months and some for 32 months, with at least a CT scan at 6 months. Of the 77 premature infants, 49 had some form of intracranial hemorrhage and six (12%) of these developed hydrocephalus as defined above. All six had had an intraventricular hemorrhage. Of the 53 term infants, 32 had some form of intracranial hemorrhage, five (15%) of these developed hydrocephalus, and all had had an intraventricular hemorrhage. Of the 11 children with hydrocephalus after an intraventricular hemorrhage, 10 had initial enlargement of the ventricles with the intraventricular hemorrhage. Thus, 12% of all the 130 infants developed clinical evidence of hydrocephalus. Furthermore, another 67 who had a follow-up scan developed ventriculomegaly without clinical evidence of hydrocephalus. Non-hydrocephalic ventriculomegaly was as common in those with hemorrhages as in those without. An initial large intraventricular hemorrhage with large ventricles is more likely to develop subsequent hydrocephalus than other combinations of abnormalities, particularly in mature infants.

Neurologic Sequelae

It has been difficult to relate specific sequelae with specific forms of cerebral damage as detected by CT or sonography. However, a number of general conclusions can be made.

An 18–32 month follow-up study of infants who had perinatal asphyxia with CT was performed during the first admission, and a follow-up scan at 6 months showed that, of 62 full-term infants, major neurologic sequelae developed in 29 (47%) [45]. These included hydrocephalus in four, cerebral palsy in 22, and all had a mean Bayley score of less than 70. It was found that the only clinical factor that correlated with such a bad outcome was positive pressure resuscitation at birth followed by ventilatory support. Of the 15 infants with intraventricular or intracerebral hemorrhage, 11 were severely handicapped, and 18 of the 20 with grade 3 or extensive areas of decreased attenuation (i.e., ischemia) were also so handicapped. Preliminary results by the same authors in 94 premature infants weighing less than 1,500 g who survived the initial treatment period and were followed for at least 18 months were 55% normal, 6% with hydrocephalus, 8% with cerebral palsy, 9% retarded, 20% mildly abnormal, and 2% dead from other causes. Thus, 45% suffered some form of sequelae. In those with no hemorrhage or minor hemorrhage (subarachnoid only, subependymal only, and mild intraventricular), 40 (57%) of the 70 were normal, 30 (43%) abnormal, and, in those with major hemorrhages (moderate or severe intraventricular and

intracerebral), 12 (50%) of the 24 were normal and 12 (50%) were abnormal. However, initial mortality in these first and second groups of premature infants was 60% and 87%, respectively. No new specific predictive features as to poor outcome have yet been found other than the association of hydrocephalus and intraventricular hemorrhage and the increased mortality relative to severe bleeds.

Smaller studies relating specifically to the follow-up of survivors of intraventricular hemorrhage [41, 46, 47] report somewhat comparable data. Initial evidence is that long-term prognosis of survivors of intraventricular hemorrhage is not as dismal as previously thought. However, minor sequelae such as cognitive and perceptual disorders only detectable in older children, are common. Children with intraventricular hemorrhage with subsequent shunted hydrocephalus are found to have a poor prognosis [39, 48].

Other Abnormalities

The sequelae of cerebral ischemia (relative microencephaly, large ventricles, large sulci with small gyri, and often multiple lacunar areas of destruction) are thought to be an important causative factor in the severely handicapped child. Focal areas of porencephaly, often related to previous hemorrhage or infarction, occur in the periventricular area and will become cystic if they communicate with the ventricles. Gross forms of diffuse cerebral low attenuation on CT with no recognizable brain tissue above the basal ganglia may result in hydranencephaly or in gross cerebral distortion, gliosis, and shrinkage with multiple lacunar spaces. Focal or cortical calcification has been recognized in survivors as postinfarctive calcification, particularly in the peripheral cortex.

Congenital abnormalities unrelated to perinatal asphyxia, such as Dandy-Walker syndrome, and, in the supratentorial compartment, holoprosencephaly, Galenic varices with a central arteriovenous malformation, may coexist. These entities must not be confused with or misinterpreted as possible acquired cerebral damage.

Diagnostic Images

The study of the asphyxiated neonate demands an understanding of the nuances of neonatal anatomy, physiology, incidence, and significance of intracranial abnormalities and their clinical sequelae prior to establishing a pragmatic imaging protocol.

The two imaging techniques are CT and sonography. Both have and are rapidly improving their imaging sensitivity, spatial resolution, and ease of performance. Many previous reports and findings were based on images from less sophisticated equipment; many institutions do not have both sonography and CT and have relied on and often promoted one or the other. Comparison studies between the two with autopsy correlation are now available.

The earlier reports of detection of intracranial hemorrhage in neonates [27, 30, 36, 38, 49, 50] indicated considerable imaging sensitivity. Less certainty was found in the correlation of possible neonatal brain hypoxia and ischemia [34,

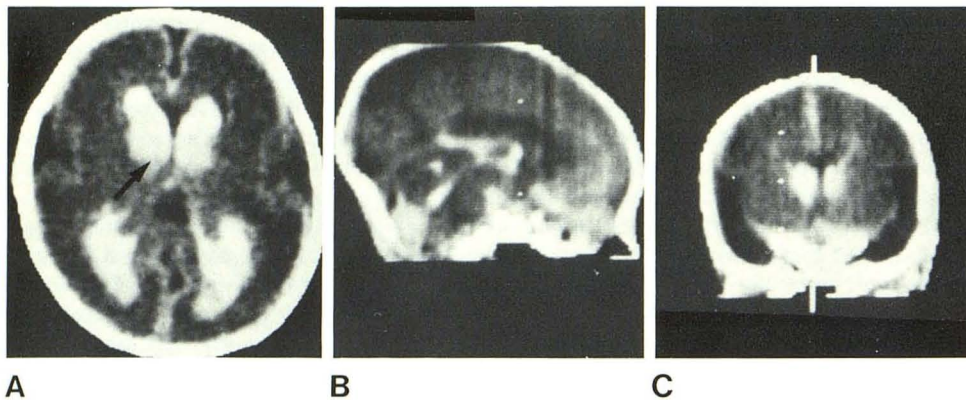


Fig. 4.—Intracranial hemorrhage. A, Axial scan. Bilateral subependymal hemorrhages, faint outline of ependyma (arrow), and bilateral intraventricular hemorrhage. Normal ribbon of cortical gray matter and relatively large amount of white matter (29 weeks gestational age). Sagittal (B) and coronal (C) reformatted images. Bilateral subependymal hemorrhage greater on right than on left, rectangular Sylvian fissure with ribbon gray matter well seen in C, and intraventricular hemorrhage into third ventricle, aqueduct, fourth ventricle, and basal cisterns well seen in B.

35, 51] vis a vis cerebral areas of low attenuation as seen on CT.

The accuracy of early generation CT scanning in the detection of cerebral hemorrhage in the asphyxiated neonate has been reported by Flodmark et al. [9] relative to autopsy findings. Ninety infants who died and had a CT scan within 10 days after death were studied. All had had neonatal asphyxia. The overall accuracy, in detecting even small hemorrhages in the germinal matrix, was high, and false-positives were rare. In subarachnoid hemorrhage, with autopsy correlation, only 64% were correctly identified by CT (61% correct in prematures, 88% correct in full-term), most being secondary to intraventricular hemorrhage.

Subependymal hemorrhage was correctly identified in 91%. However, the false-negatives may have been due to a possible premortem bleed occurring after CT.

Intraventricular hemorrhage was seen with CT in 91% and confirmed by autopsy; the false-negative explanation above may apply here also. In all, a subependymal hemorrhage was present also and directly implicated. In only one case was a hemorrhage in the choroid plexus suspected as a source of intraventricular hemorrhage.

Intracerebral hemorrhage other than subarachnoid hemorrhage was detected accurately in 71% in the supratentorial compartment but detected poorly in the posterior fossa, mainly because most were incorrectly diagnosed as subdural collections or else the cerebellar hemorrhages were very small. Virtually all of the supratentorial parenchymal hemorrhages found at autopsy [9] were the periventricular hemorrhagic infarct type [5]. These may erupt into the ventricles, but extension of the subependymal hemorrhage out into the cerebrum occurred very rarely. Both subependymal hemorrhage and periventricular hemorrhagic infarcts adjacent to one another may occur concurrently in premature infants.

The inaccuracy of early CT equipment in detecting ischemic changes in premature infants has already been detailed. Flodmark et al. [9] reported good correlation at autopsy in 28 premature infants with evidence of ischemia, but 32 similar premature infants with identical CT findings had no ischemic damage at postmortem. Furthermore, of the 28, the sites of ischemia coincided on CT and autopsy

in only 15. Follow-up of 57 survivors with similar CT findings and similar weights at birth showed no correlation between CT findings and neurodevelopmental outcome, thus emphasizing the poor sensitivity and specificity of CT in this respect. However, in full-term babies, nine of nine showed good correlation between the presence and extent of ischemia at autopsy and diffuse decreased attenuation and small ventricles on CT. Furthermore, in the follow-up of 62 full-term survivors, such CT evidence of decreased attenuation in 20 was related to severe neurologic deficits in 18, a significant prognostic relationship. Images obtained with newer equipment that show the normal white and gray matter and cerebral hemorrhage so much better (figs. 4 and 5), particularly in the premature infant, will provide the needed material for future autopsy correlation of anoxic damage (fig. 6). We believe that what we now know as "normal" white matter in the premature brain was called periventricular leukomalacia in many instances, and that well seen but normal germinal matrix layer in the premature infant was called a subependymal hemorrhage (C. R. Fitz and D. Martin, unpublished data) (fig. 7).

Sonography

With the recent advent of higher resolution real-time sector sonographic scanners with 5 MHz and higher transducers, in addition to static B-scanners and the Octason, imaging practice and philosophy have changed dramatically [52-60]. Sonography is also being used to examine the ventricular and vascular anatomy of the fetal brain in utero [61] and to assess complex cerebral congenital anomalies [62].

It is now customary to use the anterior fontanelle as an acoustic window, and the coronal and sagittal planes are the most rewarding for detecting cerebral hemorrhage and delineating the ventricular system (fig. 8). However, axial scans may better reveal CSF to blood fluid levels in the lateral ventricles with the infant supine. The usual measurements of the frontal horn dimensions from 13 weeks after gestation to term have been established by Denkhuis and Winsberg [63] and the lateral ventricular/hemispheric ratio

Fig. 5.—Intracranial hemorrhage, 28-week-gestation infant. Subarachnoid hemorrhage in basal cisterns (top left) with bilateral subependymal hemorrhage, greater on left than on right, and bilateral intraventricular hemorrhage.

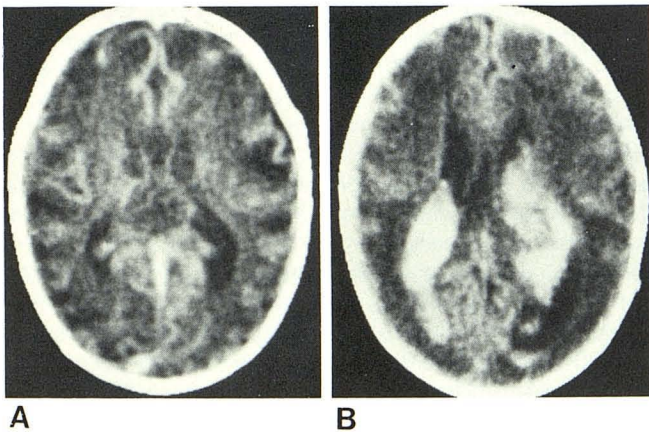
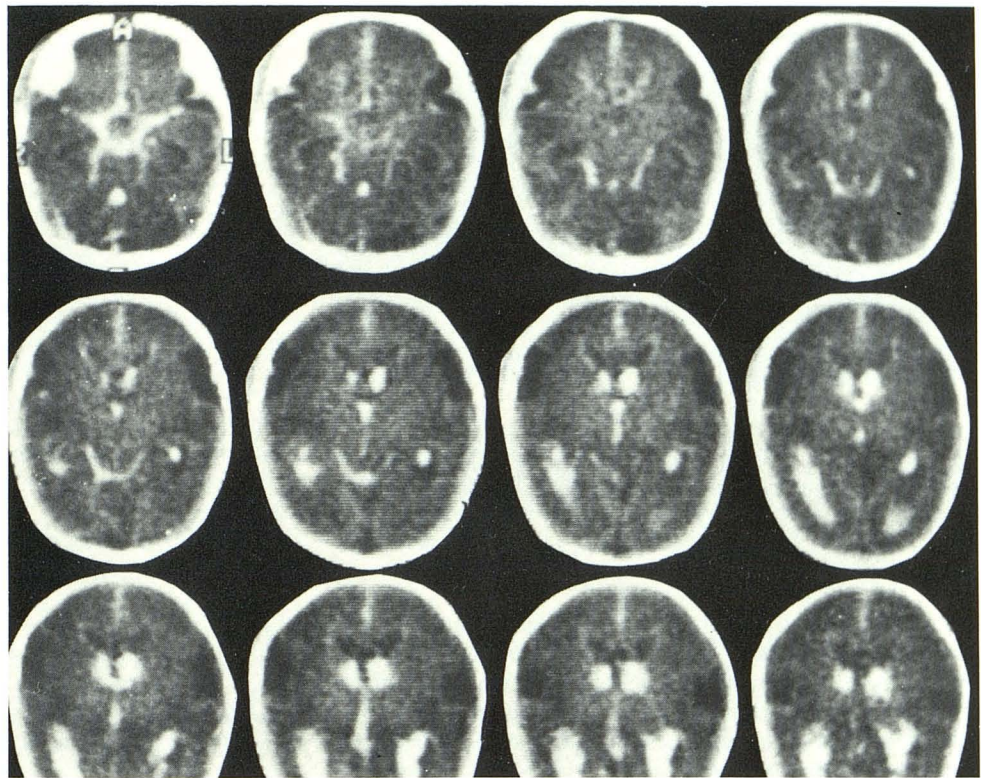


Fig. 6.—Cerebral ischemia. **A**, 30-week-old premature infant. Irregularity of normal regular gray ribbon in right frontal region, particularly in right parietooccipital region, indicates peripheral ischemic damage. **B**, 35-week-old mature infant with bilateral intraventricular hemorrhage. Area of ischemic damage in left occiput with diffuse area of low attenuation and no gray matter and sulci.

is said to vary from 0.25 to a maximum of 0.35 [53, 55, 64].

The accuracy of detecting intracerebral and intraventricular hemorrhage with sonography versus CT and/or autopsy is 88%–100%, depending on the site of the abnormalities [33, 65–68].

Better results are obtained in the caudate region than further back toward the trigone [34]. Small germinal matrix layer hemorrhages about the caudate were most frequently the cause of the rare false-negative findings. Small intraventricular hemorrhages with small ventricles and coating of the choroid plexus with blood were also difficult to detect at times, either alone or relative to adjacent subependymal hemorrhage. Hemorrhages near the periphery of the brain, in the posterior fossa, and in the subarachnoid space were often difficult or impossible to detect. The normal but large subependymal germinal matrix layer may be confused with a false-positive hemorrhage (that is, a small "subependymal hemorrhage") both on CT and sonography.

Sonography is excellent for detecting ventricular shape and size and the natural history of intracerebral hemorrhage through liquefaction and ultimate porencephaly, with or without ventricular connection [68, 69]. Sonography yields poor visualization of the cerebral substance and is defective in the detection of focal central and peripheral ischemic damage in the early stages before necrotic liquefaction or the demonstration of diffuse ischemic damage and edema, particularly in the mature infant.

The ease of performing sonography, the portability of the equipment, the nonionizing nature of the imaging, and the preservation of the neonatal environment are significant advantages over CT. The role of sonography in the examination of the neonatal head was recently reviewed and summarized by Fleischer et al. [70].

Therefore, it seems that preliminary detection of intracere-

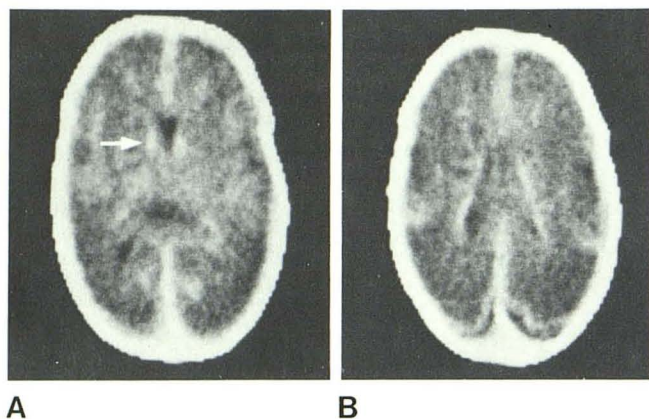


Fig. 7.—Phantom hemorrhage in 26-week-gestation premature infant. A, Clearly seen but normal subependymal germinal matrix layer at heads of caudate nucleus and no hemorrhage (arrow). B, 5 mm higher. Continuation of subependymal matrix layer alongside lateral ventricle wall. Again, thin ribbon of gray matter is clearly seen.

rebral hemorrhage and most intraventricular hemorrhages in the neonate should be by real-time sonography performed on the neonatal ward through the anterior fontanelle in the coronal and sagittal planes. This is strongly recommended for the initial study and for sequential studies, both in the hospital and after discharge.

Proposed Protocol

Before implementing any protocol, the three basic clinical tenets—identify the abnormality, understand its pathology, and recognize its sequelae—must be fulfilled.

A *preterm infant* less than 32 weeks gestational age weighing less than 1,500 g should have a real-time sonogram of the brain obtained on the ward within 48 hr of birth and at least before 7–10 days after birth, as most bleeds occur within this period and may or may not progress [65, 70]. All infants should be presumed to have suffered episodes of asphyxia with hypoxia and may or may not have respiratory distress syndrome followed by assisted ventilation. If the latter exists, the incidence of intracerebral hemorrhage is extremely high. CT may be performed after sonography if the hemorrhage is very large and/or if the *clinical status is worse* than the initial findings would indicate or if more information is needed to assist in the management decision. Conversely, massive intracerebral hemorrhage may occur with relatively little clinical indication, and these patients should also have CT to assess the remaining brain tissue. If a posterior fossa hemorrhage is suspected, CT should be performed. Even though it is difficult to detect small areas of ischemic damage with CT at this age, it is clinically valid to ascertain whether widespread or asymmetric ischemic damage is present, particularly in the thin gray matter at the periphery. This should soon be possible with increasing CT sensitivity and further correlative clinical/CT/autopsy studies. However, at present, we believe that irregular edematous change involving this thin gray

matter ribbon and erasing the clear image most probably represents ischemic damage at this age.

Follow-up studies on an inpatient or outpatient basis should be by sonography to determine ventricular size relative to head size and growth, and possible porencephalic cyst development. The natural history of intracerebral hemorrhage is of only academic interest and does not add to the clinical management of the child.

Needless to say, except for the radiation, transport difficulties, and long examination time, CT is now the best single study to demonstrate most accurately the entire neonatal cranial contents. Depending on the availability of CT time, it may be of value to use CT on premature infants who survive to their 40 week “gestational” age to determine white and gray matter geography and character. An associated sonographic examination to detect possible small infarct lacunes in the white matter, so difficult to see on CT, is also necessary.

If the infant is *at or near term* and has suffered a difficult delivery with or without instrumentation, *CT should be performed as soon as possible*. Sonography may follow if necessary. Similarly, if hypoxic episodes or seizures are present, if ventilation assistance is needed, or if there is clinical evidence of intracerebral hemorrhage, CT should be performed, particularly at days 4–7. Significant cerebral ischemic damage and post fossa hemorrhage is relatively common in either or all of these circumstances and is, therefore, best detected by CT. Massive intraventricular hemorrhage and large ventricles at this age more commonly lead to hydrocephalus in the mature neonate, and a close clinical and sonographic follow-up is necessary. However, the main rationale for CT is the detection of possible anoxic or ischemic brain damage as well as possible hemorrhage, particularly that of hemorrhagic ischemic infarct and hemorrhage away from the ventricles seen at the periphery or in the posterior fossa. The correlation between CT findings and the prognosis in the above lesions is particularly good at this age (see above).

Infants 1,500–2,500 g or 32–36 weeks gestation should probably have a screening sonogram if clinically warranted to rule out hemorrhage, but it would be worthwhile to follow with a CT scan as soon as the infant can be safely moved in order to detect possible associated ischemic damage. We believe this is valid because the effects of anoxia are progressively better detected as a child matures, and because the clinical significance of such anoxia correlates with the CT findings. A sudden change in clinical status at *any age or weight* is ominous and may be associated with massive brain damage of both hemorrhagic and ischemic type. CT should be performed then regardless of the preliminary CT and/or real-time sonographic results.

The rationale of this protocol is that of knowing as much as possible as early as possible about the neonatal intracranial contents by present imaging techniques and within patient safety. Knowledge so acquired may significantly alter the form, complexity, and intensity of the treatment of such neonates. Furthermore, close clinical follow-up with and without sonography or CT according to the clinical

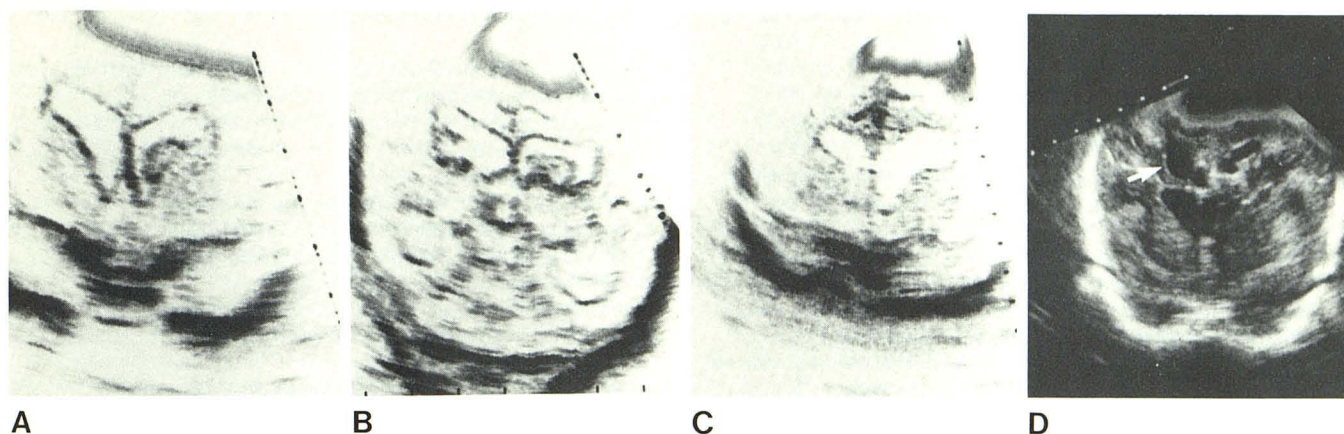


Fig. 8.—Sonography: ventricular size and hemorrhage. **A**, Coronal views in 29-week-gestation infant. Left-sided subependymal germinal matrix layer hemorrhage extends into left lateral ventricle. **B**, Section through body of lateral ventricles in same patient. Left intraventricular hemorrhage. Dilated ventricles in both **A** and **B**. **C**, Clear outline of both ventricles in 32-week-

gestation infant 3 weeks after anoxic postnatal period. Asymmetrical dilatation of both lateral ventricles larger on left than on right. **D**, 24 days after birth. Bilateral cystic cavities (arrow) above lateral ventricles but within distribution of anterior cerebral arteries represent postinfarcted cerebral cystic areas. Ventricles are mildly dilated.

findings is essential for at least 12 months to detect possible hydrocephalus or cerebral atrophy and their effects. Routine repeated CT scanning is not recommended, but CT should be performed if the clinical status is such that the integrity of the brain substance is questioned, or if the fontanelle is closed and knowledge of the ventricular size in an enlarging head is required to rule out the hydrocephalus.

Conclusions

Most hemorrhages within the neonatal brain are both sensitively and specifically detected by CT or sonography together or separately. It is probably the ischemic cerebral damage after hypoxia that provides the more significant permanent damage, hemorrhage only being an associated change, possibly a less significant but more obvious finding from an imaging point of view.

However, it seems reasonable to ask if the readily detectable sonographic evidence and degree of hemorrhage in the immediate postnatal stage in the premature infant parallels the concomitant ischemic damage and, therefore, enables prediction of clinical outcome. This we do not yet know correctly and, therefore, we now believe it is wise to image the cerebral tissue per se by CT whenever possible and whenever clinically indicated.

It seems reasonable to perform CT early on all neonates with clinical suspicion or sonographic evidence of severe intracerebral damage or hemorrhage, relying on sonography for the preliminary image of the premature infant and for follow-up studies on all neonates.

The unique cerebral structure of the premature may be more prone to damage as a result of hypoxia, but it is also more capable of compensating for such damage. As much as sonography cannot examine *all* the intracranial cavity, must CT, once performed, image the *entire* intracranial

cavity from base to vertex, and not merely a "slice or two through the ventricles."

In an attempt to answer the questions posed earlier, we suggest that hemorrhage per se is not sufficient to alter the therapeutic philosophy and that subependymal hemorrhage is probably of limited significance. However, hemorrhage is probably a marker to underlying yet more significant ischemic damage, and the use of CT in the detection of ischemic damage is paramount. We know that the premature brain can probably compensate for many of the insults, that the mortality in neonates with intracranial hemorrhage is inversely proportional to maturity, and finally that the mature infant is far more prone to damage, best detected by CT, and thus permanent sequelae.

Continuing careful clinical examination, CT, and sonographic imaging, follow-up protocols, and autopsy correlation, when possible, are essential. The imaging of *brain tissue* itself and its alterations and not hemorrhage or ventricular size will, we believe, ultimately be the key factor in the detection and prediction of significant brain damage. Much improvement of both CT and sonographic imaging is needed. New imaging methods of positron emission tomography and nuclear magnetic resonance and the increasing sophistication of CT and sonography may yet provide us with more objective signs of brain dysfunction in the neonate during the acute postnatal and neonatal phases of its compromised brain.

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REFERENCES

- Larroche JC. Development of the central nervous system. In: *Developmental pathology of the neonate*. Amsterdam: Excerpta Medica, **1977**;319-353
- Padget DH. The development of the cranial arteries in the human embryo. *Contrib Embryol* **1948**;32:205-261
- Van den Bergh R, Van der Eecken H. Anatomy and embryology of cerebral circulation. *Prog Brain Res* **1968**;30:1-25
- Dobbing J, Sands J. Quantitative growth and development of human brain. *Arch Dis Child* **1973**;48:757-767
- Armstrong DL, Goddard J, Schwartz M, Stenback W. Another look at the pathology of intraventricular hemorrhage. In: *Perinatal Intracranial Hemorrhage Conference Syllabus*. Columbia, OH: Ross Labs, **1980**:1-21
- Picard L, Claudon M, Roland J, et al. Cerebral computed tomography in premature infants, with an attempt at staging developmental features. *J Comput Assist Tomogr* **1980**;4:435-444
- Pape KE, Wigglesworth JS. Hemorrhage, ischemia and the perinatal brain. Philadelphia: Lippincott, **1979**
- Scotti G, Flodmark O, Harwood-Nash DC, Humphreys R. Posterior fossa hemorrhages in the newborn. *J Comput Assist Tomogr* **1981**;5:68-72
- Flodmark O, Becker LE, Harwood-Nash DC, Fitzhardinge PM, Fitz CR, Chuang SH. Correlation between computed tomography and autopsy in premature and full-term neonates that have suffered perinatal asphyxia. *Radiology* **1980**;137:93-103
- Brown JK, Purvis RJ, Forfar JO, Cockburn F. Neurological aspects of perinatal asphyxia. *Dev Med Child Neurol* **1974**;16:567-580
- Smith JF, Reynolds EOR, Taghizadeh A. Brain maturation and damage in infants dying from chronic pulmonary insufficiency in the postnatal period. *Arch Dis Child* **1974**;49:359-366
- Banker B, Larroche JC. Periventricular leukomalacia of infancy: a form of neonatal anoxic encephalopathy. *Arch Neurol* **1962**;7:386-410
- Armstrong D, Norman MG. Periventricular leukomalacia in neonates: complications and sequelae. *Arch Dis Child* **1974**;49:367-375
- Leech RW, Alvord EC. Morphological variations in periventricular leukomalacia. *Am J Pathol* **1974**;74:591-602
- Volpe JJ. Neurologic disorders. In Avery GB, ed. *Neonatology: pathophysiology and management of the newborn*. Philadelphia: Lippincott, **1975**;729-752
- Volpe JJ. Perinatal hypoxic-ischemic brain injury. *Pediatr Clin North Am* **1976**;23:383-397
- Flodmark O, Fitz CR, Harwood-Nash DC. CT diagnosis and short term prognosis of intracranial hemorrhage and hypoxic/ischemic brain damage in neonates. *J Comput Assist Tomogr* **1980**;4:775-787
- DeReuck J, Chattha AS, Richardson EP. Pathogenesis and evolution of periventricular leukomalacia in infancy. *Arch Neurol* **1972**;27:229-236
- Towbin A. Cerebral intraventricular hemorrhage and subependymal matrix infarction in the fetus and premature newborn. *Am J Pathol* **1968**;52:121-134
- Towbin A. Central nervous system damage in the human fetus and newborn infant. Mechanical and hypoxic injury incurred in the fetal neonatal period. *Am J Dis Child* **1970**;119:529-542
- Volpe JJ. Neonatal intracranial hemorrhage: pathophysiology, neuropathology and clinical features. *Clin Perinatol* **1977**;4:77-102
- Volpe JJ. Neonatal periventricular hemorrhage: past, present and future. *J Pediatr* **1978**;92:693-696
- Lazzara A, Ahmann P, Dykes F, et al. Clinical predictability of intraventricular hemorrhage in preterm infants. *Pediatrics* **1980**;65:30-34
- Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 grams. *J Pediatr* **1978**;92:529-534
- Burstein J, Papile LA, Burstein R. Intraventricular hemorrhage and hydrocephalus in premature newborns: a prospective study with CT. *AJR* **1979**;132:631-635
- National Center for Health Statistics. *Prenatal care in the United States, 1969-1975*, DHEW publication no. 78-1911. Hyattsville, MD: National Center for Health Statistics, **1978**:19-25
- Rumack C, McDonald M, O'Meara O, Sanders B, Rudikoff J. CT detection and course of intracranial hemorrhage in premature infants. *AJR* **1978**;131:493-497
- Burstein J, Papile L, Burstein R. Subependymal germinal matrix and intraventricular hemorrhage in premature infants; diagnosis by CT. *AJR* **1977**;128:971-976
- Triantos A, Victorin L, Relier JP, et al. Intracranial hemorrhage in the prematurely born infant. Timing of clots and evaluations of signs and symptoms. *J Pediatr* **1974**;85:854-859
- Lee BCP, Grassi AE, Schechner S, Auld PAM. Neonatal intraventricular hemorrhage: a serial computed tomography study. *J Comput Assist Tomogr* **1979**;4:483-490
- Norman D. Computed tomography in intracranial hemorrhage. In: Norman D, ed. *Computed tomography*. St. Louis: Mosby, **1977**:279-299
- Albright L, Fellows R. Sequential CT scanning after neonatal intracerebral hemorrhage. *AJNR* **1981**;2:133-137
- Johnson ML, Rumack CM, Mannes EJ, Appareti KE. Detection of neonatal intracranial hemorrhage utilizing realtime and static ultrasound. In: *Perinatal intracranial hemorrhage conference syllabus*. Columbus, OH: Ross Labs, **1980**:344-369
- DiChiro G, Arimitsu T, Pellock JM, et al. Periventricular leukomalacia related to neonatal anoxia: recognition by computed tomography. *J Comput Assist Tomogr* **1978**;2:352-355
- Schrumpf JD, Sehring S, Killpack S, Brady JP, Hirata T, Mednick JP. Correlation of early neurologic outcome and CT findings in neonatal brain hypoxia and injury. *J Comput Assist Tomogr* **1980**;4:445-450
- Ludwig B, Brand M, Brockerhoff P. Postpartum CT examination of the heads of fullterm infants. *Neuroradiology* **1980**;20:145-154
- Ahmann PA, Lazzara A, Dykes F, et al. Intraventricular hemorrhage in the high-risk preterm infant; incidence and outcome. *Ann Neurol* **1980**;7:118-124
- Epstein F, Naidich T, Kricheff I, Chase N, Lin J, Ransohoff J. Role of computerized axial tomography in diagnosis, treatment and follow-up of hydrocephalus. *Childs Brain* **1977**;3:91-100
- Korobkin R. The relationship between head circumference and the development of communicating hydrocephalus in infants following intraventricular hemorrhage. *Pediatrics* **1975**;56:74-77
- Volpe JJ, Pasternak JF, Allan WC. Ventricular dilatation preceding rapid head growth following neonatal intracranial hemorrhage. *Am J Dis Child* **1977**;131:1212-1215
- Krishnamoorthy KS, Fernandez RA, Momose KJ, et al. Evaluation of neonatal intracranial hemorrhage by computerized tomography. *Pediatrics* **1977**;59:165-172
- LeBlanc R, O'Gorman AM. Neonatal intracranial hemor-

- rhage—a clinical and serial computerized tomographic study. *J Neurosurg* 1980; 53:642–651
43. Levene MI, Starte D. A longitudinal study of post hemorrhagic ventricular dilatation in the newborn. In: *Perinatal intracranial hemorrhage conference syllabus*. Columbus, OH: Ross Labs, 1980:391–409
 44. Flodmark O, Scotti G, Harwood-Nash DC. The clinical significance of ventriculomegaly in children who suffered perinatal asphyxia with or without intracranial hemorrhage: an 18 month follow-up study. *J Comput Assist Tomogr* 1981;5:663–673
 45. Fitzhardinge PM, Flodmark O, Fitz CR, Ashby S. The prognostic value of computed tomography as an adjunct to assessment of the fullterm infant with post-asphyxial encephalopathy. *J Pediatr* (In press.)
 46. Schechner S. Developmental follow-up at one year post-term of infants with intracranial hemorrhage. In: *Perinatal intracranial hemorrhage conference syllabus*. Columbus, OH: Ross Labs, 1980:724–735
 47. Williamson WD, Desmond MM, Wilson GS, Andrew L, Garcia-Prat JA. Early neurodevelopmental outcome of low birth weight infants surviving neonatal intraventricular hemorrhage. In: *Perinatal intracranial hemorrhage conference syllabus*. Columbus, OH: Ross Labs, 1980:736–751
 48. Wise BL, Ballard R. Hydrocephalus secondary to intracranial hemorrhage in premature infants. *Childs Brain* 1976; 2:234–241
 49. Pevsner PH, Garcia-Bunuel R, Leeds N, et al. Subependymal and intraventricular hemorrhage in neonates. Early diagnosis by computed tomography. *Radiology* 1976;119:111–114
 50. Kirks DR, Maravilla KR, Maravilla AM. Craniocerebral computed tomography in the neonate. *Comput Tomogr* 1978; 2:207–220
 51. Hirabayashi S, Kitahara T, Hishida T. Computed tomography in perinatal hypoxic and hypoglycemic encephalopathy with emphasis on follow-up studies. *J Comput Assist Tomogr* 1980;4:451–456
 52. Garrett WJ, Kossoff G, Jones RFC. Ultrasonic cross-sectional visualization of hydrocephalus in infants. *Neuroradiology* 1975;8:279–288
 53. Johnson ML, Mack LA, Rumack CM, et al. B-mode echoencephalography in the normal and high risk infant. *AJR* 1979;133:375–381
 54. Johnson ML, Rumack CM. Ultrasonic evaluation of the neonatal brain. *Radiol Clin North Am* 1980;18:117–131
 55. Babcock DS, Han BK, LeQuesne GW. B-mode gray scale ultrasound of the head in the newborn and young infant. *AJR* 1980;134:457–468
 56. Babcock DS, Han BK. The accuracy of high resolution, real-time ultrasonography of the head in infancy. *Radiology* 1981;139:665–676
 57. Haber K, Wachter RD, Christenson PC, Vaucher Y, Sahn DJ, Smith JR. Ultrasonic evaluation of intracranial pathology in infants: a new technique. *Radiology* 1980;134:173–178
 58. London DA, Carroll BA, Enzmann DR. Sonography of ventricular size and germinal matrix hemorrhage in premature infants. *AJNR* 1980;1:295–300
 59. Grant EG, Schellinger D, Borts FT, et al. Real-time sonography of the neonatal and infant head. *AJNR* 1980;1:487–492
 60. Edwards M, Brown DL, Muller J, Grossman CB, Chua GT. Cribside neurosonography: real-time sonography for intracranial investigation of the neonate. *AJNR* 1980;1:501–505
 61. Hadlock FP, Deter RL, Park SK. Real-time sonography: ventricular and vascular anatomy of the fetal brain in utero. *AJNR* 1980;1:507–511
 62. Sauerbrei EE, Cooperberg PL. Neonatal brain: sonography of congenital abnormalities. *AJNR* 1981;2:125–128
 63. Denkhau H, Winsberg F. Ultrasonic measurement of the fetal ventricular system. *Radiology* 1979;131:781–787
 64. Morgan CL, Trought WS, Rothman SJ, et al. Comparison of gray-scale ultrasonography and computed tomography in the evaluation of macrocrania in infants. *Radiology* 1979;132:119–123
 65. Pape KE, Szymonowicz W, Britton BS, Murphy W, Martin DJ. Ultrasound diagnosis of neonatal intracranial bleeding. In: *Perinatal intracranial hemorrhage conference syllabus*. Columbus, OH: Ross Labs, 1980:447–454
 66. Silverboard G. Sector ultrasound imaging of posthemorrhagic hydrocephalus. In: *Perinatal intracranial hemorrhage conference syllabus*. Columbus, OH: Ross Labs, 1980:469–500
 67. Slovis TL, Shankaran S, Bedard MP, Poland RL. Assessment of intracranial hemorrhage utilizing realtime ultrasonic sector scanning as the primary modality: a one year experience. In: *Perinatal intracranial hemorrhage conference syllabus*. Columbus, OH: Ross Labs, 1980:536–562
 68. Sauerbrei EE, Digney M, Harrison PB, Cooperberg PL. Ultrasonic evaluation of neonatal intracranial hemorrhage and its complications. *Radiology* 1981;139:677–685
 69. De Crespigny LBCH, Robinson HP, Murton LJ, O'Herlihy C. Realtime scanning of the neonatal brain. In: *Perinatal intracranial hemorrhage conference syllabus*. Columbus, OH: Ross Labs, 1980:314–332
 70. Fleischer AC, Hutchinson AA, Allen JH, Stahlman MT, Meacham WF, James AE. The role of sonography and the radiologist-ultrasonologist in the detection and follow-up of intracranial hemorrhage in the preterm neonate. *Radiology* 1980;139:733–736