John Caffey Award:

Intraventricular Hemorrhage and Hydrocephalus in Premature Newborns: A Prospective Study with CT

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In a prospective study, 100 premature infants were studied with computed tomography (CT) brain scans within the first week of life. In 44 of these, hemorrhages originated from the subependymal germinal matrix, and ranged in severity from isolated germinal matrix hemorrhages to blood-filled, dilated ventricles with extension of hemorrhage into the brain parenchyma. A system of grading the severity of hemorrhage was developed. Grades I and II hemorrhages resolved spontaneously and grades III and IV were associated with progressive hydrocephalus. Asymptomatic hemorrhages that would not have been diagnosed on clinical grounds were detected by CT. This study offers a clearer understanding of the true incidence and natural history of cerebroventricular hemorrhage and associated hydrocephalus in premature neonates and may clarify etiologic factors and identify children at risk for subsequent neurologic abnormalities.

Spontaneous hemorrhage into the cerebral ventricles is a phenomenon that occurs in premature neonates [1, 2]. It originates in the subependymal germinal matrix within the first 4 days of life [3, 4]. This study evolved from the observation that several premature neonates thought to have survived an intraventricular hemorrhage developed clinical hydrocephalus at 3–4 weeks of age. A second group of premature neonates who also developed hydrocephalus at 3–4 weeks old had no clinically apparent hemorrhage. This suggested that intraventricular hemorrhage might be clinically occult and still produce significant sequelae. In order to test this hypothesis, to determine the true incidence of intraventricular hemorrhage, and to study the relation between neonatal intraventricular hemorrhage and hydrocephalus, a prospective study using computed tomography (CT) brain scans of an at-risk population was performed. It is an extension of previous work in which we demonstrated that CT can be used to accurately diagnose germinal matrix hemorrhage and intraventricular hemorrhage in the living newborn [5].

Subjects and Methods

Computed tomography brain scans were performed before the seventh day of life on 100 consecutive premature neonates of birthweight less than 1,500 g admitted to the University of New Mexico Newborn Intensive Care Unit. Living infants were studied at 4–7 days of age. If the infant died before day 4, a postmortem CT scan was performed before brain fixation. None of the infants studied had congenital hydrocephalus at birth. The time of the initial scan was based on previous studies [3, 4] that indicated the majority of intraventricular hemorrhages in premature newborns occur before the fourth day of life. The infants were transported to the scanning suite in a transport isolette. Heart rate was monitored, heat lamps were used to prevent hypothermia, and a neonatologist was always in attendance. The scanner gantry was modified as previously described [5].

Serial CT scans were subsequently obtained on all surviving infants in whom the initial scan demonstrated a hemorrhage. Weekly scans were done until the hemorrhage was completely resolved and ventricular size was stable. There were no complications during transportation or scanning.

Results

Of the 100 neonates, 56 showed no evidence of hemorrhage on CT scan (table 1). Of these 56 infants, 13 died, most often of idiopathic respiratory distress syndrome or its complications. None of the 13 had evidence of hemorrhage or hydrocephalus at autopsy. The 43 remaining infants in this group survived and, although follow-up scans were not obtained, none of these infants had developed clinical hydrocephalus at 1-year follow-up.

Some degree of cerebroventricular hemorrhage was seen on CT scans in 44 of the 100 neonates. The mildest form (grade 1) was an isolated hemorrhage into one or both of the germinal matrices (fig. 1). Rupture of the germinal matrix hemorrhage into the ventricles was associated with either normal sized ventricles (grade II, fig. 2) or ventricular dilatation (grade III, fig. 3). The most extensive hemorrhages (grade IV, fig. 4) consisted of dilated blood-filled ventricles with extension of the germinal matrix hemorrhage into the adjacent brain parenchyma.

Weekly CT scans were performed on every infant with any grade of hemorrhage. Of the 44 neonates with hemorrhage, 22 survived at least 28 days, the length of time defined as the neonatal period. Serial scans were

TABLE 1

Cerebroventricular Hemorrhage, Neonatal Deaths, and Progressive Ventricular Dilatation in Premature Infants

Initial Findings	Survivors		Deaths	Total
	Hydroceph- alus	No Hydro- cephalus		
Cerebroventricular hem- orrhage:				
Grade I	0	7	3	10
Grade II	0	6	4	10
Grade III	5	1	8	14
Grade IV	3	0	7	10
Subtotal	8	14	22	44
No cerebroventricular hemorrhage	0	43	13	56
Total	8	57	35	100

Note—Grade of hemorrhage was assigned at initial CT scan. Grade I: isolated germinal matrix hemorrhage; grade II: intraventricular extension of hemorrhage with normal ventricular size; grade III: intraventricular hemorrhage with dilated ventricles; grade IV: grade III plus extension of germinal matrix hemorrhage into adjacent brain parenchyma. Survival period is first 28 days after birth.

Fig. 3.—Grade III hemorrhage, 2-day-old, 32-week-gestation, 1,191 g infant (postmortem). Hemorrhage in germinal matrix at junction of head of caudate nucleus and thalamus, in third ventricle, in somewhat dilated occipital horns of lateral ventricles (A), and in germinal matrix tissue adjacent to bodies of lateral ventricles (B).
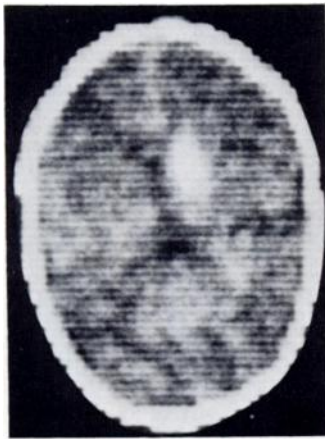

Fig. 1.—Grade 1 hemorrhage in 5-day-old, 28-week-gestation, 1021 g infant. Ovoid collection of blood on right side adjacent to third ventricle and frontal horn of lateral ventricle corresponds to location of largest concentration of germinal matrix tissue at junction of head of caudate nucleus and thalamus. Sections more cephalad and caudad did not show any hemorrhage.
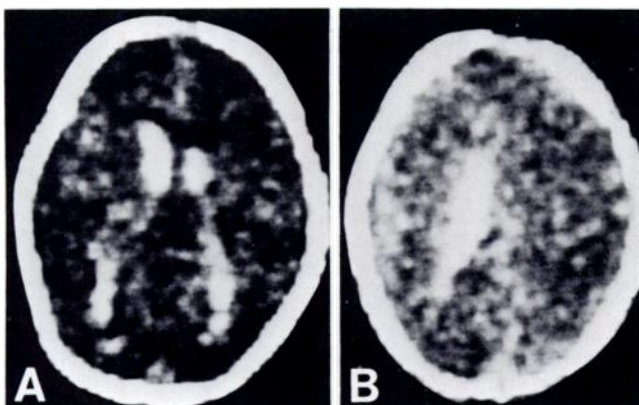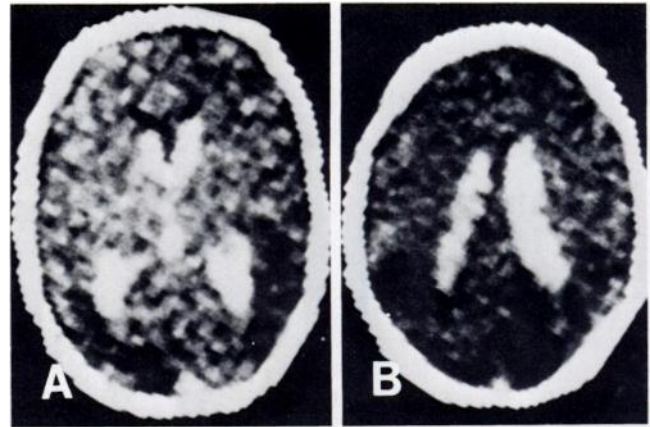

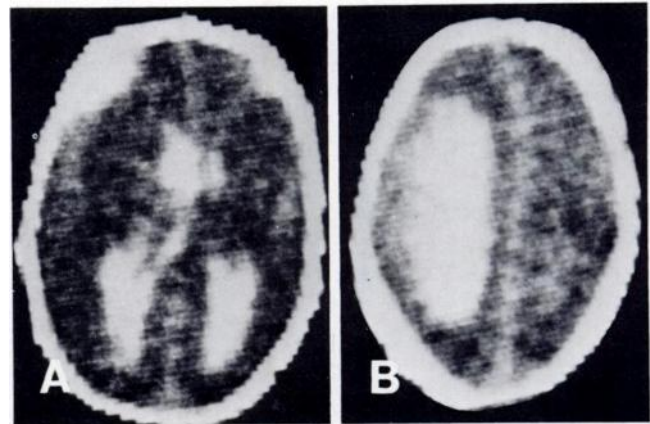Fig. 4.—Grade IV hemorrhage, 5-day-old, 30-week-gestation, 936 g infant. A, Bilateral germinal matrix hemorrhage, larger on left than right, has broken into dilated ventricles. B, Left-side germinal matrix hemorrhage extends into left cerebral hemisphere almost to the cortex, exerting mass effect with shift of interhemispheric fissure from left to right. Reason for increased absorption coefficients interhemispheric fissure unclear. Several infants with this finding studied at autopsy had no evidence of subarachnoid hemorrhage.

Fig. 2.—Grade II hemorrhage in 4-day-old, 30-week-gestation, 1,200 g infant. A, At level of germinal matrices and occipital horns of lateral ventricle. B, 8 mm higher. Bilateral germinal matrix hemorrhages larger at left than right. Hemorrhage extended into part of germinal matrix tissue adjacent to body of left lateral ventricle (B) and ventricles, settling into the occipital horns of the lateral ventricles. Normal ventricular size.

continued in the subgroup of surviving infants with hemorrhage until the hemorrhages were resorbed and ventricular size stabilized.

None of the 13 infants with grade I or II hemorrhages who survived the neonatal period developed either CT or clinical hydrocephalus. One infant had an isolated germinal matrix hemorrhage without rupture into the ventricles or extension into the brain parenchyma (grade I). Serial scans showed resorption of the fresh blood with the final scan appearing normal. The child died at 28 days of age of a perforated duodenum. At autopsy, there was a thick-walled cystic lesion at the site of the germinal matrix hemorrhage (fig. 5). Therefore, even though a grade I or grade II hemorrhage was not associated with the development of hydrocephalus, structural damage to

the brain did occur in at least one case as a direct result of an isolated germinal matrix hemorrhage.

Weekly serial CT brain scans of the nine surviving infants with a grade III or grade IV hemorrhage demonstrated progressive ventricular dilatation (fig. 6) in eight (89%). Developing hydrocephalus was evident on CT scans before the development of an abnormal increase in head circumference. Early detection of ventricular dilatation by CT allowed early institution of appropriate therapy. In the three surviving infants in whom the initial germinal matrix hemorrhage extended into the brain parenchyma (grade IV), serial scans showed residual areas of paraventricular porencephaly, often of considerable size (fig. 7).
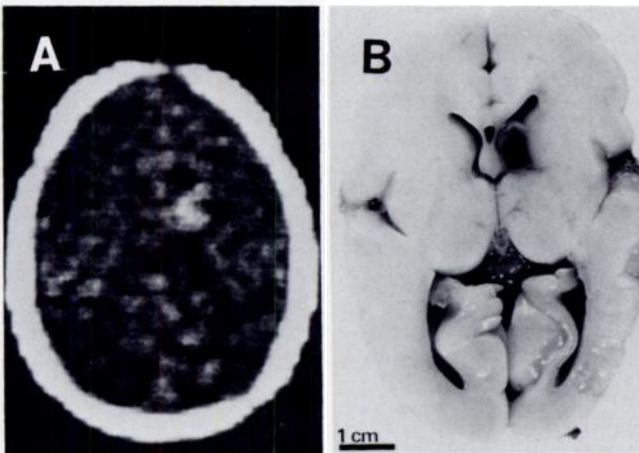

Fig. 5.—Grade I hemorrhage with residual paraventricular cyst in 5-day-old, 28-week-gestation, 721 g infant. **A,** Initial study at 5 days of age. Isolated right-side germinal matrix hemorrhage with no rupture into ventricles or extension into brain parenchyma. Follow-up sections were normal with no evidence of hydrocephalus or paraventricular cystic lesions. The child died of age 28 days of perforated duodenum. **B,** Autopsy section of the brain. Thick-walled cystic lesion at site of previous germinal matrix hemorrhage.

Discussion

Cerebroventricular hemorrhage originates in the germinal matrix [2], a structure located beneath the ependymal lining of the ventricles and largest in the groove between the head of the caudate nucleus and the thalamus. It is a highly vascular structure with little supporting tissue. It is a source of neuroblasts which migrate peripherally during development of the fetal brain. The germinal matrix is largest at 24–32 weeks gestation and then involutes so that it is much smaller in full term infants than prematures [6].

Our study demonstrated a broad spectrum of germinal matrix–related hemorrhage in the premature neonate, ranging from isolated germinal matrix hemorrhage to massive intraventricular hemorrhage with extension into the brain parenchyma. Cerebroventricular hemorrhage has been found at autopsy in 55%– 75% of premature newborns who died from any cause [2, 4, 7]. The CT diagnosis of cerebroventricular hemorrhage in 22 of the 35 (63%) deaths in our series agrees with these figures. However, there has been no way to determine whether or not the rate found at autopsy could be extrapolated to the entire at-risk population. We found an incidence of 44% in all premature infants (survivors and nonsurvivors) weighing less than 1500 g studied by CT on one occasion between the fourth and seventh day of life.

Of the 44 infants with cerebroventricular hemorrhage, 22 survived the neonatal period. Before the advent of CT, such hemorrhage was diagnosed at autopsy or by the sudden development of hypotonia, hypotension, falling hematocrit, bulging fontaneles, acidosis, and seizures. We compared the accuracy of the clinical diagnosis of cerebroventricular hemorrhage in survivors to the CT diagnosis. Of the 22 infants who had CT-proven hemorrhages and survived the neonatal period, the diagnosis was not suspected clinically in 15 (68%). Therefore, since 15 of the 65 survivors of the neonatal period had sustained a clinically silent hemorrhage, there was a one
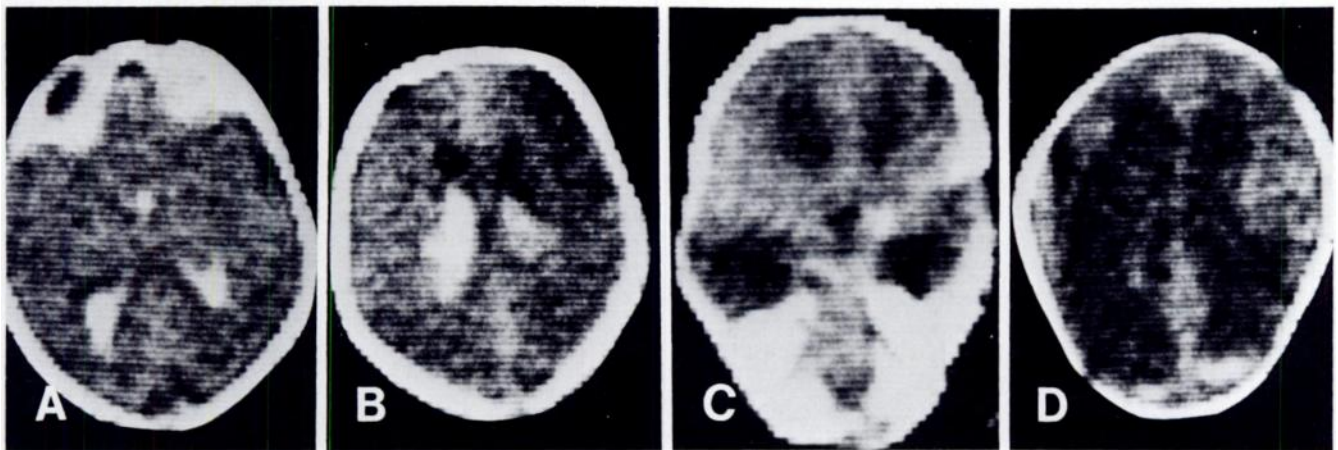

Fig. 6.—Hydrocephalus after grade III hemorrhage in 6-day-old, 30-week-gestation, 1,191 g infant. **A** and **B,** At 6 days of age. Grade III hemorrhage, greater on left than on right, and extravasation of blood into ventricles, which are only mildly dilated. **C** and **D,** At 13 days of age. Dilatation of lateral ventricles and third ventricle, with small amount of blood settled in most dependent portions of occipital horns of lateral ventricles.
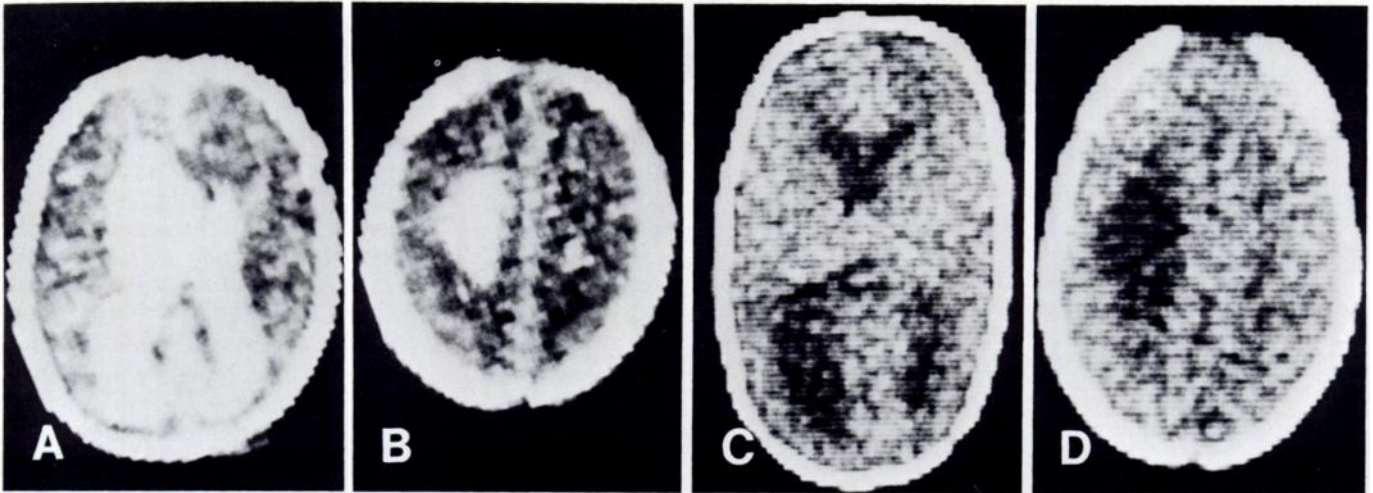
Fig. 7.—Grade IV hemorrhage with residual paraventricular porencephaly in 6-day-old, 28-week-gestation, 1,021 g infant. A and B, At 6 days of age. Grade IV hemorrhage with rupture into ventricles, dilated blood-filled ventricles, and extension of hemorrhage into left cerebral hemisphere. C and D, At 3 months of age. Slight dilatation of ventricular structures, but area of paraventricular porencephaly in left cerebral hemisphere at site of initial cerebral extension of left-side germinal matrix hemorrhage.

in four chance that a premature infant discharged from the Newborn Intensive Care Unit had experienced a clinically silent cerebroventricular hemorrhage.

The etiology of this hemorrhage is unknown. If it is due only to the fragility of the angioarchitecture of the germinal matrix [8], increasing the case findings with prospective CT studies will add little to the understanding of the disease process. However, since not all premature neonates have cerebroventricular hemorrhage, there must be other causative factors. These may include perinatal events such as asphyxia, method of delivery, development of idiopathic respiratory distress syndrome, and use of intravenous bicarbonate therapy [9]. Unfortunately, there are limitations to the use of the previously available autopsy data in evaluating these relationships [10], since cerebroventricular hemorrhage is survivable and often clinically occult. By identifying the hemorrhage in the entire population at risk, it should be possible to make a more accurate analysis of risk factors.

Hydrocephalus may develop after intraventricular hemorrhage as a result of inflammatory ependymitis, obstruction of the aqueduct or fourth ventricles by clot, or basilar arachnoiditis. Previous studies [11–14] reported the development of hydrocephalus in premature infants surviving intraventricular hemorrhage. However, diagnosis of such hemorrhage was made on clinical grounds without the use of CT. In this study, there were 15 surviving infants who had CT-documented intraventricular hemorrhage (grades II–IV). Eight (53%) of this group developed hydrocephalus, but seven did not. It seems that intraventricular hemorrhage is etiologic for hydrocephalus since there were no cases of hydrocephalus that were not associated with it. However, it is unclear why some premature newborns with intraventricular hemorrhage develop hydrocephalus and others do not. But since over one-half of the surviving infants with

intraventricular hemorrhage develop hydrocephalus, we feel that once intraventricular hemorrhage has been documented with CT, serial scans should be performed until ventricular size has stabilized or until treatment is considered necessary. Serial scans were often useful in detecting the development of hydrocephalus before the onset of rapid head growth. This confirms previous reports [12, 15] that there is a lag between increasing ventricular size and increasing head circumference.

Accurate case findings with prospective CT scans have implications beyond the better understanding of incidence and etiology. Children born prematurely have a higher incidence of neurologic abnormalities than those born at term [16–18]. We have now identified a population of infants with clinically silent cerebral hemorrhages in the neonatal period. A long-term neurologic and psychometric follow-up of this group, using infants without hemorrhage as controls, has been instituted, which may help explain the higher rate of neurologic disability.

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