CRANIAL SONOGRAPHY AND NEUROLOGICAL EXAMINATION OF EXTREMELY PRETERM INFANTS

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The neurodevelopmental outcome of the extremely preterm infant cannot be predicted solely from birthweight, but also depends on the nature, severity and chronicity of perinatal insults to which the infant has been exposed (Shankaran et al. 1982, Papile et al. 1983, Meisels et al. 1986, Bozynski et al. 1987). Technological advances offer the opportunity to evaluate these insults. For example, longitudinal real-time sonographic scans of the neonatal brain provide information about the nature of the acute insult, e.g. intracranial hemorrhage (ICH), as well as the extent of the injury (McMenamin et al. 1984, DeVries et al. 1985, Graziani et al. 1986, Guzzetta et al. 1986). Recent studies have established the effectiveness of cranial sonography as a predictive tool for later neurodevelopmental outcome (Stewart et al. 1987, Bozynski et al. 1988, Nwasei et al. 1988).

The relationship between neonatal brain-injury and the neurological examination has also been explored by Dubowitz et al. (1984), Georgieff et al. (1986) and Stewart et al. (1988). Dubowitz et al. (1981) found an association between intracranial hemorrhage and abnormalities on neurological examination in the early days of life. In another report, Dubowitz et al. (1985) noted an increase in arm flexor tone, adducted thumbs, increased extensor tone in the legs, and poor visual attention in infants with periventricular leukomalacia (PVL) who were examined at term-corrected age.

Stewart et al. (1983) also studied the relationship between abnormal findings at neurological examination and sonographic findings in infants born before 33 weeks gestation, but found no reliable relationship between neurological signs and the timing of hemorrhage. However, serial neurological examinations performed after 34 weeks corrected age suggested that infants with hemorrhage complicated by ventricular enlargement or cysts continued to exhibit abnormal neurological findings, including hypotonia and clonus. To further investigate the usefulness of the neurological examination in predicting outcome, Stewart et al. (1988) compared the predictive properties of neonatal brain sonography and a structured neurological examination performed at term-corrected age. They found that, separately, sonography and neurological examination were not good predictors of later outcome, but were useful in combination in identifying normal preterm infants. A study carried out by Dubowitz et al. (1984) confirmed these findings. Most of the infants with abnormal scans who had poor outcomes in both studies were suspected of having PVL. Although infants with PVL might be expected to exhibit hypertonicity, a degree of hyper-

TABLE I
Characteristics of 51 study infants

Birthweight: g (SD)	956	(184)
Gestation: wks (SD)	27·9	(1·8)
Apgar score: median (range)		
1 min	4	(0–8)
5 mins	6	(1–9)
Age at neurological examination: wks (range)	40	(36–43)

TABLE II
Incidence and severity of chronic lung-disease

None (N = 24)	No evidence of respiratory distress, no diuretic or oxygen therapy
Mild (N = 16)	Tachypnea (respiratory rate >40), mild retractions and/or growth rate <25g/day, no diuretic or oxygen therapy
Moderate/ severe (N = 11)	Tachypnea, moderate/severe retractions, growth rate <25g/day, diuretic and/or oxygen therapy

tonicity is a normal physiological finding at term. Because of this, Stewart *et al.* (1988) postulated that the neurological examination was unable to separate infants with PVL and poor later prognosis from infants without PVL, who were more likely to have a satisfactory outcome.

Most studies to date have not controlled for other factors occurring in association with hemorrhage, *e.g.* bronchopulmonary dysplasia and lower birthweight. It is probable that perinatal conditions, other than hemorrhagic or ischemic brain lesions, also cause less optimal performance during the neurological examination at term and may mask the relationship between sonographic and neurological abnormalities. For example Georgieff *et al.* (1986) found muscle tone abnormalities to be common in compromised infants weighing <1750g at birth, especially in the first six months of life. Recently, Allen and Capute (1989) showed a marked correlation between the results of the neonatal neurodevelopmental examination and neuromotor outcome at one year in a group of high-risk preterm infants. Although Allen and Capute controlled for a number of variables in their study, they did not evaluate the term sonogram and PVL was

not diagnosed in any of their study infants.

To investigate further the relationship between the neurological examination at term and sonographic evidence of neonatal brain-injury in extremely preterm infants, a prospective study was performed. We hypothesized that sonographic evidence of neonatal brain-injury would be associated with an abnormal or suspect neurological examination at term-corrected age. We further hypothesized that infants who were extremely preterm or who had evidence of chronic lung-disease would have a higher incidence of suspect neurological examinations. The infant's Apgar scores, age at examination and gestational age were identified as additional possibly confounding variables.

Method
Subjects
From April 1986 to March 1988, 155 infants weighing <1250g and whose growth was appropriate for gestational age were admitted to the neonatal intensive care unit. 46 died in the unit and one infant died after discharge, but before his term examination. This study was part of a large longitudinal study examining cognitive and socio-emotional development and attachment, which required home visits and continuity of infant caregiving. Because of this, 42 infants were excluded for such reasons as residence >50 miles from the Medical Center, parental drug-addiction, foster care, congenital anomalies or visual impairment. Parental consent was not sought in one case and was refused in four others. Protocol errors occurred in three cases, two infants were too ill for examination, and five were discharged before the protocol was in place. Thus 51 infants were available for inclusion in the study.

The study infants' characteristics are given in Table I. 42 infants were inborn. Gestational age was determined from the mother's dates and by using the examination of Ballard *et al.* (1979). Each infant was evaluated by a single examiner at term-corrected age for continuing evidence of chronic lung-disease: all such infants had a history of mechanical ventilation in the first week of life, had received

oxygen therapy for more than 28 days, and had radiographic findings consistent with bronchopulmonary dysplasia. Chronic lung-disease was graded as none, mild or moderate to severe, depending on clinical signs and the infant's requirements for oxygen and diuretic therapy (Table II).

Cranial sonography
All the infants were examined with real-time ultrasonography through the anterior fontanelle at least once in the first five to seven days of life, twice within the first month, and once within one month of term-corrected age. The sonograms were reviewed by an experienced pediatric radiologist, who was unaware of the infant's clinical status and findings at the neurological examination. On the basis of sonographic findings, the infants were separated into three groups: group 1 (N = 27)—no abnormalities (*i.e.* no hemorrhage and normal sonographic examination at term); group 2 (N = 12)—initial intraventricular or germinal layer hemorrhage with a normal sonogram or only unilateral ventricular enlargement at term; and group 3 (N = 12)—intraparenchymal hemorrhage, cystic periventricular leukomalacia, porencephaly or bilateral ventriculomegaly at term. This categorization was supported by our previous work with another sample of preterm infants (Bozynski *et al.* 1987, 1988).

Neurological examination
Each infant was examined by one of three physical therapists, using *The Neurological Assessment of the Preterm and Full-term Newborn Infant* (Dubowitz and Dubowitz 1981, Dubowitz *et al.* 1981) at a median corrected age of 40 weeks (range 36 to 43 weeks). The therapists had been using this assessment tool for several years. For this study they used all items in the movement and tone section and the eye appearance and visual orientation items of the neurobehavioral section. The movement and tone section was divided into three subsections: extremities, trunk and over-all. The items used are listed in Table III. All infants were awake during the examination. After scoring each item, each subsection was scored and the infant was classified as normal, suspect or abnormal (Table IV).

TABLE III
Items used for neurological examination

Extremities
Posture
Arm recoil, traction and release in prone
Leg recoil and traction
Popliteal angle

Trunk
Head control (anterior and posterior muscles)
Head lag
Ventral suspension
Head raising in prone

Over-all
Spontaneous body-movements
Tremors
Startles
Abnormal movment of posture

Visual
Eye appearances
Visual orientation

TABLE IV
Scoring system for neurological examination

Classification	Criteria
Normal	All normal
Suspect	All suspect;
	Any suspect—none abnormal; one abnormal, all others normal
Abnormal	More than two abnormal; one abnormal plus any suspect

Statistical Analysis
Analysis of variance was used for continuous variables. Variables that were not normally distributed were analyzed using the Kruskal-Wallis test. χ^2 analysis or the Fisher exact test were used for categorical variables. Logistic regression was used to develop the best model for predicting the infant's status on the neurological examination at term-corrected age. Variables considered for inclusion in the model were birthweight, gestational age, corrected age at the time of neurological examination, group assignment based on sonographic findings, Apgar scores at one and five minutes, and severity of chronic lung-disease at term-corrected age.

Results
The neurological examination was normal for 23 infants, suspect for 15 and abnormal

TABLE V
Variables on which neurological examination groups differed

Variable	Neurological group		
	Normal (N = 23)	Suspect (N = 15)	Abnormal (N = 13)
Birthweight: g (SD)	1055 (158)	955 (215)	906 (197)*
Gestation: wks (SD)	28·5 (1·8)	27·4 (2·1)	27·0 (1·5)**
Severity of chronic lung-disease: median (range)†	1 (1–3)	2 (1–3)	2 (1–3)**

*p < 0·06, **p < 0·04.
†1 = none, 2 = mild, 3 = moderate/severe.

TABLE VI
Association between abnormalities on sonography and on neurological examination

Sonographic group	N	Neurological examination		
		Normal	Suspect	Abnormal
1	27	13	12	2
2	12	5	1	6
3	12	5	2	5

$\chi^2(4) = 12·2$; $p < 0·02$.

for 13. Infants with abnormal examinations had a higher incidence of abnormal items on the extremities subsection of the neurological examination compared with those classified as suspect. These abnormalities included hypertonia (one), hypotonia (five), and asymmetry of extremity tone (five). The three groups formed on the basis of the neurological examination did not differ in Apgar scores or corrected age at the time of the neurological examination. There were significant differences between the groups in the severity of chronic lung-disease and gestational age, and a marginal difference in birthweight, as shown in Table V.

Based on sonographic findings, 27 infants were placed in group 1 (all examinations were normal), 12 in group 2 (normal or only unilateral ventricular enlargement), and 12 in group 3 (bilateral ventriculomegaly, cystic PVL or porencephaly). We found support for our first hypothesis of an association between sonographic findings and classification according to neurological examination (Table VI). 11 of 13 infants (84·6 per

cent) with abnormal neurological examinations had abnormal sonograms. On the other hand, 12 of 15 infants (80 per cent) classified as suspect had normal sonographic scans. Infants with PVL showed no clear pattern of abnormalities, but of the six infants with PVL who were neurologically examined, four were classified as abnormal and two as suspect.

To explore whether confounding factors might further explain the infant's neurological classification, logistic regression was used to define the best model for prediction of classification. Variables considered for inclusion were: group based on sonographic findings; birthweight; gestational age; Apgar scores at one and five minutes; and severity of chronic lung-disease. The best model included both the group based on sonographic findings (p = 0·008) and birthweight (p = 0·07); none of the other variables was significant.

There was no significant difference in performance on neurological examination between the two groups with any evidence of brain injury (sonographic groups 2 and 3). The three pairs of possible outcomes on neurological examination were compared (normal vs. abnormal, normal vs. suspect, suspect vs. abnormal), and the association of outcome and predictor variables (sonographic group and birthweight) was tested using multiple logistic regression. Sonographic group ($\chi^2 = 4·85$, p < 0·03) and birthweight ($\chi^2 = 4·57$, p = 0·03) were useful in differentiating infants classified as normal from those classified as abnormal, while suspect and abnormal infants were best differentiated by sonographic group alone ($\chi^2 = 9·54$, p = 0·002). Neither sonographic group

nor birthweight was helpful in differentiating normal from suspect infants.

There was also no significant association between performance on visual orientation items and sonographic findings. Only two infants scored as abnormal (both in group 2) and 16 infants scored as suspect (three in group 3, five in group 2 and eight in group 1).

Discussion

This study showed a strong association between neonatal brain injury, as detected by cranial sonography, and classification as abnormal by neurological examination in extremely preterm infants at term-corrected age. An abnormal performance on the neurological examination was also associated with a lower birthweight. Sonographic group and birthweight were not useful in predicting which infants would be scored as normal vs. suspect by examination. Although the severity of chronic lung-disease and gestational age differed for the various sonographic groups, these variables were not associated with a higher risk of poor performance. In addition, no association was found between sonographic abnormalities and performance on visual orientation items.

Infants who were abnormal by neurological examination demonstrated abnormalities of their extremities, including hypertonia, hypotonia and asymmetry. Unlike Dubowitz et al. (1984), we did not find more hypertonicity of the lower extremities or poorer visual orientation in infants with PVL. We did find, however, that infants with PVL had abnormal neurological examinations. This finding is supported by the study of Dubowitz et al. (1985), who found clusters of abnormal signs at term neurologic examination in infants suspected of having PVL.

Previous studies suggest that infants with group 3 sonographic abnormalities will continue to be at high risk for poor outcome, while the prognosis is better for group 2 infants whose sonograms have become normal by term (McMenamin et

al. 1984, DeVries et al. 1985, Graziani et al. 1986, Guzzetta et al. 1986, Stewart et al. 1987, Bozynski et al. 1988, Nwasei et al. 1988). Given this fact, we were surprised that infants with group 2 abnormalities were indistinguishable from those in group 3 on neurological examination. This may indicate that recovery from brain injury was incomplete for infants in group 2 and that abnormalities of tone, posture and movement may not resolve until several months post-term. It is not known whether infants with normal sonograms but suspect or abnormal neurological examinations will manifest later and more subtle problems. Hope et al. (1988) have documented the failure of sonography to detect pathologically verified ischemic lesions, and such lesions may be the cause of suspect or abnormal neurological examinations. They may also explain the high incidence of other problems with visual-motor integration and neurodevelopment seen in long-term follow-up studies of preterm infants. Further studies will help to clarify the best discharge assessment, or combination of assessments, that will predict outcome most accurately.

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SUMMARY
Fifty-one extremely preterm infants were studied to ascertain whether there is an association between sonographic abnormalities and neurological examination at term, controlling for factors such as low birthweight and chronic lung-disease. Their mean birthweight was 956g and mean gestational age was 27·9 weeks. Sonography was performed at least once during the first week, twice within the

first month, and once within a month of term-corrected age. Neurological assessment was used to classify the infants as normal, suspect or abnormal at term. Infants were divided into three groups, based on sonographic findings: group 1 (no hemorrhage), group 2 (grade 1 to 3 hemorrhage but normal sonogram or unilateral ventriculomegaly at term) and group 3 (periventricular leukomalacia, grade 4 hemorrhage or ventriculomegaly at term). On neurological examination, 23 infants were found to be normal, 15 suspect and 13 abnormal. On sonography, 27 infants were placed in group 1, 12 in group 2 and 12 in group 3. Sonographic findings and birthweight were the best predictors of the infant's performance on the neurological examination at term.

RÉSUMÉ

Echographie cranienne et examen neurologique chez les grands prématurés

Cinquante et un grands prématurés ont été examinés pour apprécier s'il y avait une association entre les anomalies échographiques et l'examen neurologique à terme contrôlant des facteurs tels qu'un faible poids de naissance ou une affection pulmonaire chronique. La moyenne des poids de naissance était de 956g et la moyenne d'âge gestational de 27,9 semaines. L'échographie fut réalisée au moins une fois durant la première semaine, deux fois durant le premier mois ey une fois à un mois d'âge corrigé. L'appréciation neurologique fut utilisée pour classer les nourrissons comme normaux, suspects ou anormaux au terme. Les nourrissons furent divisés en trois groupes à partir des données échographiques: groupe 1 (sans hémorragie), groupe 2 (hémorragies de niveau 1 à 3 mais échographie normale ou ventriculomégalie unilatérale à terme) et groupe 3 (leucomalacie péri-ventriculaire, hémorragie de niveau 4 ou ventriculomégalie au terme). A l'examen neurologique, 23 nourrissons furent trouvés normaux, 15 suspects et 13 anormaux. En échographie, 27 nourrissons furent placés dans le groupe 1, 12 dans le groupe 2 et 12 dans le groupe 3. Les données échographiques et le poids de naissance étaient les meilleurs pronostics des capacités du nourrissons à l'examen neurologique à terme.

ZUSAMMENFASSUNG

Schädelsonographie und neurologische Untersuchungen bei Fruhgeborenen

Einundfünfzig extrem vorzeitig geborene Kinder wurden untersucht, um festzustellen, ob es eine Beziehung zwischen abnormen Ultraschallbefunden und neurologischen Untersuchungsergebnissen am Termin gibt, wobei Faktoren, wie niedriges Geburtsgewicht und chronische Lungenerkránkung, berücksichtigt wurden. Das mittlere Geburtsgewicht betrug 956g und das mittlere Gestationsalter 27·9 Wochen. Die Ultraschalluntersuchungen wurden mindestens einmal in der erster Woche, zweimal im ersten Monat und einmal im korrigierten Alter von einem Monat durchgeführt. Die neurologischen Beurteilungen dienten zur Einteilung der Kinder am Termin in normal, auffällig und abnorm. Die Kinder wurden, basierend auf den Ultraschallbefunden, in drei Gruppen eingeteilt: Gruppe 1 (kleine Blutung), Gruppe 2 (Blutung Grad 1 bis 3, aber normales Sonogramm oder unilaterale Ventrikulomegalie am Termin) und Gruppe 3 (periventrikuläre Leukomalazie, Blutung Grad 4 oder Ventrikulomegalie am Termin). Bei der neurologischen Untersuchung waren 23 Kinder normal, 15 auffällig und 13 abnorm. Nach den Ultraschallbefunden wurden 27 Kinder in Gruppe 1, 12 in Gruppe 2 und 12 in Gruppe 3 eingeteilt. Die sonographischen Befunde und das Geburtsgewicht warn die besten Parameter für die neurologischen befunde am Termin.

RESUMEN

Sonografia craneal y examen neurológico en lactantes extremadamente pretérmino

Cincuenta y cinco lactantes extremadamente pretérmino fueron estudiados para ver si existía una asociación entre las anomalias sonográficas y el examen neurológico a término, controlando factores tales como el bajo peso al nacer y enfermedad pulmonar crónica. Su peso promedio al nacer fue de 956g y la edad gestacional media fue de 27·9 semanas. La sonografia se practicó por lo menos una vez durante le primere semana, dos veces durante el primer mes, y una vez dentro del mes después de la termino corregida. La evaluación neurológica se usó para clasificar los lactantes en normales, sospechosos o anormales al término. Los niños se dividieron en tres grupos según los hallazgos sonográficos:grupo 1 (no hemorragia), grupo 2 (hemorragia de grado 1 a 3 pero con un sonograma normal o una ventriculomegalia unilateral al término) y grupo 3 (leucomalacia periventricular, nunca hemorragia de cuarto grado o una ventriculomegalia al término). En el examen neurológico se halló que 23 niños eran normales y 13 anormales. En la sonografía 27 niños fueron colocados en el grupo 1,12 en el grupo 2 y 12 en el grupo 3. Los hallazgos sonográficos y el peso al nacer fueron los mejores predictores de lo hallado en el examen neurológico al término.

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