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Early cranial ultrasound lesions predict head circumference at age 2 in preterm infants

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Abstract

To assess how well early ultrasound lesions in preterm newborns predict reduced head circumference at two years, we followed 923 children born before the 28th week of gestation who were not microcephalic then until they were 2 years old. Two independent sonologists agreed on the presence/absence of four lesions, intraventricular hemorrhage (IVH), moderate/severe ventriculomegaly, an echodense lesion, and an echolucent lesion. Each also recorded the size, laterality and location. 6% of children who had a normal ultrasound scan were microcephalic compared to 15% who had IVH, 19% who had an echolucent lesion, and in 20% who had

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None of the authors listed have any financial conflict or disclosures.

I, K.S. Krishnamoorthy, M.D., the lead author contributed to the design of the data analytic strategy and data interpretation. I compiled the first full draft and contributed to rewriting subsequent revisions, and approved the submitted version.

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ventriculomegaly. The odds ratios (95% confidence intervals) for microcephaly associated with different ultrasound images were IVH: 1.5 (0.9, 2.4), ventriculomegaly: 2.7 (1.6, 4.8), an echodense lesion 1.4 (0.8, 2.3), and an echolucent lesion: 2.8 (1.4, 5.4). Ventriculomegaly and an echolucent lesion had very similar low positive predictive values (24% and 27%) and high negative predictive values (91% and 90%) for microcephaly. Ventriculomegaly had a higher sensitivity for microcephaly than did an echolucent lesion (24% vs 16%). Focal white-matter damage, as characterized by an echolucent lesion, and diffuse white-matter damage, as suggested by ventriculomegaly, predict an increased risk of microcephaly.

Introduction

A small head circumference usually indicates reduced brain volume^{1–4}. Infants born much before term tend to have less brain volume than their term-born peers at term equivalent and later^{4–10}. In addition, preterm newborns who become microcephalic are more likely than their normocephalic peers to have neurodevelopmental disabilities^{4, 9}.

Might brain ultrasound lesions identified when the preterm newborn is in the intensive care nursery predict microcephaly? We know of no study that has tried to answer this question.

The ELGAN (Extremely Low Gestational Age Newborn) Study of 1004 infants born before the 28th week of gestation and whose head circumference was measured at 24 months post-term equivalent provided us an excellent opportunity to evaluate how well early sonographic findings indicative of perinatal white-matter damage predict a very small head circumference at 24 months ‘corrected age.’

Methods

Patient Population

The ELGAN (acronym for Extremely Low Gestational Age Newborn) Study enrolled extremely low gestational age newborns (less than 28 weeks) from 2002 to 2004 at fourteen participating institutions in eleven cities in five states. Mothers were approached for consent either upon antenatal admission or shortly after delivery, depending upon clinical circumstance and institutional preference. 1249 mothers, who gave birth to 1506 infants, consented. Approximately 260 women were either missed or did not consent to participate. The enrollment and consent processes were approved by the individual institutional review boards.

Of the 1201 survivors who were eligible for a later assessment, 1004 (84%) infants had their head circumference measured at approximately 24 months post term equivalent. To avoid the error of attributing to the ultrasound lesion what might represent disordered brain growth prior to birth, we eliminated from this report the 81 children (8%) in our sample who were microcephalic at birth. The sample for this study thus consists of all 923 children whose head circumference Z-score was ≥ -2 at birth, who had a protocol ultrasound scan, and whose head circumference was measured at approximately 24 months post-term equivalent.

Head Circumference

All examiners were unaware of the neonatal medical history of the participating infants. Head circumference measurements were standardized across all examination sites with a multimedia-training video/CD-ROM developed for this study¹¹. Head circumference was measured as the largest possible occipital-frontal circumference. Because the head was measured at different approximations of 24 months corrected age (range: 16–44 months with 68% assessed between 23–25 weeks), we used Z-scores. These were based on gender- and gestational age-specific standards in the Centers for Disease Control data sets¹². The outcome of interest, microcephaly, is defined as a head circumference Z-score <-2 .

Protocol Cranial Sonograms

Routine cranial ultrasound scans were performed by the technicians at all the hospitals using digitized high frequency transducers (7.5 and 10 MHz). Ultrasound studies always included the six standard coronal views and five parasagittal views using the anterior fontanel as the sonographic window¹³.

The three sets of protocol scans were defined by the postnatal day on which they were obtained. Protocol scans were obtained between the first and fourth day (N=699); Protocol 2 scans were obtained between the fifth and fourteenth day (N=864) and Protocol 3 scans were obtained between the fifteenth day and 40th week (N=896).

Reading Protocol

After creation of a manual and data collection form, observer variability minimization efforts included conference calls to discuss aspects of images prone to different interpretations¹⁴. Templates, which illustrated levels of ventriculomegaly, were part of the data collection form¹⁵.

Germinal matrix hemorrhage was defined in the manual by an echogenicity in the thalamo-caudate region or in any other periventricular location where germinal matrix is usually found. A diagnosis of IVH was made only when echogenic material was seen in the ventricular cavity, or if a clot was adherent to the choroid plexus.

All cranial ultrasound scans were read by two independent readers who were not provided clinical information. Each set of scans was first read by the study sonologist at the institution where the infant was born. The ultrasound images, imbedded in viewing software (eFilm Workstation™, Merge Healthcare/Merge eMed, Milwaukee, WI), were sent to a sonologist at another ELGAN Study institution for a second reading.. When the two readers differed in their recognition of intraventricular hemorrhage (IVH), moderate/severe ventriculomegaly, an echodense (*i.e.*, hyperchoic) lesion, or an echolucent lesion (*i.e.*, hypoechoic lesion), the films were sent to a third reader (tie-breaking) reader who did not know what the first two readers reported.

The data collection form did not require a diagnosis to accompany echodense and echolucent lesions, nor were criteria provided for any diagnosis. Rather, the sonologist was

free to apply the labels of early periventricular leukomalacia (PVL), cystic PVL and periventricular hemorrhagic infarction (PVHI) as she/he felt appropriate¹⁶.

Data Analysis

We tested the generalized null hypothesis that no ultrasound lesion or characteristic predicts a small head. The primary ultrasound lesions evaluated were IVH, moderate/severe ventriculomegaly, an echodense lesion, and an echolucent lesion. The lesion characteristics included location, lesion size (as estimated by the number of anatomic locations involved), and laterality (unilateral or bilateral). We also assessed the contribution of what the sonologists called PVHI and PVL.

We present row percents in the first three tables to show the percent of children with a particular ultrasound lesion who also had a head circumference Z-score < -2 . The calculated risk ratios compare the children with a lesion to children who had no lesion and are adjusted for gestational age (23–24, 25–26 and 27 weeks) and a complete course of antenatal corticosteroid. We also evaluated the sensitivities, specificities, and predictive values of ventriculomegaly and an echolucent lesion seen on an ultrasound scan in the neonatal period as predictors of a head circumference Z-score < -2 .

Results

9% (82/923) of children were microcephalic at age two years (Table 1). Microcephaly at 24 months post term equivalent occurred in 6% of children whose cranial ultrasound scans in the neonatal intensive care unit were entirely normal (Table 1). In contrast, microcephaly occurred in 19% of children who an echolucent lesion in the cerebral white matter, and in 20% of children whose ultrasound scan had ventriculomegaly.

The locations of blood most closely associated with microcephaly were the third and fourth ventricles (20–25%) and the cerebellar parenchyma bilaterally (22%). Blood in one of the lateral ventricles was also associated with a modest risk for microcephaly (15%).

The occurrence of microcephaly did not vary appreciably with the location of ventriculomegaly on the earliest ultrasound scan (Table 2). On the other hand, children who had late enlargement of the lateral ventricles bilaterally were at prominently greater risk of microcephaly than children whose ventriculomegaly was unilateral. This was seen for enlargement of each of the horns and the body of the ventricles. None of the 22% (48/216) of children who had ventriculomegaly following IVH and had a shunt for progressive hydrocephalus had ventriculomegaly on the last protocol scan.

Bilateral echodense lesions were not associated with increased risk of microcephaly (Table 3). An echolucent lesion was much more strongly predictive of microcephaly than an echodense lesion in the same area (data not shown).

The risk of a small head circumference did not appear to vary with the number of zones that had an echodense lesion (data not shown). On the other hand, the risk of microcephaly increased as the number of zones with an echolucent lesion increased.

After adjustment for gestational age and a complete course of antenatal corticosteroid, ventriculomegaly, an echolucent lesion and a diagnosis of cystic PVL were associated with significantly increased risks of microcephaly (Table 4).

Ventriculomegaly and an echolucent lesion had very similar low positive predictive values (24% and 27%) and high negative predictive values (91% and 90%) for microcephaly (Table 5). Ventriculomegaly had a higher sensitivity for microcephaly than did an echolucent lesion (24% vs 16%).

Discussion

Overview

Among children who had moderate/severe ventriculomegaly on a late ultrasound scan, 20% had microcephaly at 24 months, whereas the incidence of microcephaly was 19% among those who had an echolucent lesion on any scan. In contrast, the incidence was 6% among children who had no ultrasound abnormality. These observations, in a sample of children who were not microcephalic at birth, support our hypothesis that white matter damage evident on cranial ultrasound scans obtained in the neonatal intensive care nursery predicts microcephaly.

Cranial sonograms with no lesions

Fully 70% (644/923) of the children in our sample had no ultrasound scan abnormality. Among these lower risk children, we would have expected a microcephaly incidence of about 3%. The higher than expected incidence of 6% is in keeping with reports from the MRI literature that much of white matter damage is not evident sonographically^{17–20}. Further support for this explanation is provided by reports that between one third and one half of children diagnosed with cerebral palsy at approximately 24 months of age did not have any lesion on any neonatal cranial sonogram^{21, 22}.

It is also possible that some of our subjects with entirely normal scans and reduced head circumference did not have white matter damage. In preterm infants, impaired postnatal head growth has been associated with nutritional factors³, lung disease²³, intrauterine growth retardation²⁴, and post natal steroids²⁵.

Ventriculomegaly

One third of all children who had bilateral ventriculomegaly on the last protocol scan were microcephalic at 24 months post-term equivalent. After adjustment for potential confounders, children who had moderate/severe ventriculomegaly on any scan were almost three times more likely to have a head circumference Z score <-2 than children who had no abnormality on any scan. These findings suggest that processes that result in ventriculomegaly appreciably impair brain growth.

Some very low birth weight infants develop ventriculomegaly even with no ultrasonographic evidence of preceding intracranial hemorrhage²⁶. This ventriculomegaly is attributed to white matter injury or loss. This seems reasonable in light of evidence that a proportion of children who have no ultrasound abnormality have white matter damage on early MRI^{17–20}.

and that later MRIs of preterm infants with white matter injury show reduced white matter volume²⁷. Our findings underscore the significance of ventriculomegaly as an important antecedent of later microcephaly in preterm infants.

Hemorrhage

Blood in the 3rd or 4th ventricles was a better predictor of microcephaly than blood in the lateral ventricles. Perhaps blood in these locations reflects the severity of intraventricular hemorrhage, which might be a correlate of ependymal tears²⁸ and greater access of intraventricular contents to periventricular white matter^{29–31}, thereby resulting in white matter damage. Blood in these ventricles might also be associated with periventricular white matter lesions not detected by ultrasound.

Almost 80% of our ELGAN Study subjects with bilateral cerebellar hemorrhage had abnormal head growth at 24 months. Others have found a high prevalence of neurological disability and microcephaly following bilateral cerebellar hemorrhage in extremely premature infants^{32, 33}.

Even IVH that does not lead to ventriculomegaly can result in injury to the developing brain. For example, reduced cortical volume especially of the cortical gray matter, subcortical gray matter, and white matter can follow uncomplicated IVH³⁴.

Echolucent Lesions

Echolucent lesions are the sonographic hallmarks of focal white matter injury. We found that both the number and distribution of the echolucent lesions predicted microcephaly at 24 months corrected age. Children whose scan had an echolucent lesion either anterior or posterior to the lateral ventricles were more likely to be microcephalic than children who had an echolucent lesion lateral to one of the ventricles. These zones might correspond to the common sites of periventricular white matter injury²⁶.

Echodense Lesions

We did not find a significant correlation between echodense lesions and microcephaly. Echodense lesions can be the first indicator of the white matter damage that results in an echolucent lesion. They can also be transient and not followed by other indicators of white matter damage³⁵. Thus, it is possible that only some echodense lesions are the first indicator of the processes that lead to microcephaly. Another explanation for the poor predictability of echodense lesions is that this lesion was the one with the highest observer variability in our study¹⁴.

Diagnoses

The diagnosis of cystic PVL is the only one that predicted microcephaly significantly. This was expected in light of observations that children with this diagnosis are at heightened risk for cerebral palsy and developmental disabilities [O'Shea, 2008 #858;Kuban, 2009 #915]]. We did not, however, establish criteria for any of the diagnoses as we had for each of the individual lesions, nor did we require agreement by two readers, as we had for each of the individual lesions¹⁶.

Explanation

We hypothesize that a common final pathway to microcephaly in our ELGAN Study subjects is reduced brain volume due to widespread white matter injury. We come to this hypothesis from several observations. First, ventriculomegaly is often synonymous with hydrocephalus *ex vacuo*, and a consequence of diffuse white matter damage²⁶. Second, focal white matter damage is often accompanied by diffuse white matter damage^{19, 20, 36}. Third, gray matter damage can accompany, or be part of, the processes leading to white matter damage³⁷. Fourth, MRI studies in preterm infants have demonstrated co-occurrence of gray matter and white matter abnormalities and reduced brain volume⁴. Thus, the same processes that lead from ventriculomegaly to microcephaly might also account for the microcephaly that follows focal white matter damage.

Care Implications of our findings

Very preterm children who have microcephaly at age 2 years are much more likely than their normocephalic peers to be given a cerebral palsy diagnosis, have low scores on the Bayley mental and psychomotor developmental indices, and screen positive for an autism spectrum disorder¹⁰. These correlates emphasize the need for early recognition of microcephaly in ELGAN children so that early intervention services can be implemented, close surveillance of their development encouraged, and prognostic guidance to caretakers and families provided.

The Practice Parameter for Neuroimaging of the Neonate has recommended that cranial sonograms be part of the surveillance of preterm infants³⁸. Although reliance on MRI technology to evaluate the extent of brain injury in the neonate and especially in the preterm infant appears to be increasing^{5, 39}, the limited availability of this technology in many medical centers, and the financial demands made on hospitals and medical centers means that ultrasound scans will remain the standard for some time. Our findings support claims that these ultrasound scans provide useful prognostic information.

Strengths and Limitations

Our study has several strengths including agreement on lesions by two unbiased sonologists unaware of clinical information, the large number of study subjects, and a prospective design with a standardized follow-up evaluation. Perhaps the most important limitation is the relatively small numbers of infants in some groups. For example, only 24 children had an echolucent lesion in each cerebral hemisphere, and only 46 children were given a diagnosis of cystic PVL.

Conclusion

We conclude that two neonatal sonographic lesions, namely ventriculomegaly and an echolucent lesion, and one diagnosis, cystic PVL, have acceptable predictive values for microcephaly at approximately 24 months corrected age. This information might be helpful to clinicians in discussing prognosis and arranging appropriate follow up interventions for these infants. These findings also add to the weight of evidence that early cerebral white matter damage reduces brain volume.

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Table 1

The percent of children who had the ultrasound lesion listed on the left whose head circumference Z-score at 24 months was < -2 (microcephaly). These are row percents.

Ultrasound lesions		Head circumference Z-score		Total number
		< -2	-2	
GMH	Yes	10	260	270
	No	9	644	653
IVH*		15	182	197
Ventriculomegaly		20	78	98
Echodense lesion		15	103	118
Echolucent lesion		19	49	68
No lesion**		6	638	644
Column N		82	841	923

* Intraventricular hemorrhage

** The referent group consists of children who did not have ventriculomegaly, an echodense lesion, or an echolucent lesion. GMH was not an exclusion criterion.

The percent of infants whose first or last protocol scan had ventriculomegaly in the location listed on the left, who had a head circumference Z-score of < -2 at 24 months. These are row percents.

Table 2

Lateral ventricle component enlarged	1 st protocol scan		Last protocol scan	
	< -2	Total N*	< -2	Total N*
Frontal	Unilateral	20	14	7
	Bilateral	24	31	42
Body	Unilateral	20	9	11
	Bilateral	23	33	43
Occipital	Unilateral	18	8	12
	Bilateral	22	31	45
Temporal	Unilateral	25	14	7
	Bilateral	24	33	41

* Total number

Table 3

The percent of infants whose scan had an echodense or echolucent lesion unilaterally or bilaterally who had a head circumference Z-score of < -2 at 24 months. These are row percents.

Echo characteristic		Head circumference Z-score < -2	Total number
Echodense lesion	Unilateral	12	68
	Bilateral	9	113
Echolucent lesion	Unilateral	11	44
	Bilateral	32	22

Table 4

Odds ratios (and 95% confidence intervals) for a head circumference Z-score of < -2 or in the -2 and < -1 range at 24 months after adjustment for gestational age (23–24, 25–26, 27 weeks) and a complete course of antenatal corticosteroids.

		Odds ratio
Ultrasound finding	IVH [*]	1.5 (0.9, 2.4)
	Ventriculomegaly [*]	2.7 (1.6, 4.8)
	Echodense lesion [*]	1.4 (0.8, 2.3)
	Echolucent lesion [*]	2.8 (1.4, 5.4)
	No US lesion [§]	1.0
Ultrasound diagnosis	Early PVL [*]	0.6 (0.3, 1.3)
	Cystic PVL [*]	3.2 (1.4, 7.4)
	PVHI [*]	1.8 (0.8, 3.4)
	No US diagnosis [‡]	1.0

^{*} Alone or with other lesions

[§] The referent group consists of children who did not have IVH, ventriculomegaly, an echodense lesion, or an echolucent lesion.

[‡] The referent group consists of children who were not give an unsolicited diagnosis.

Table 5

Measures of the ability of head ultrasound abnormalities evident before discharge from the neonatal intensive care unit to predict a small head circumference Z-score at 24 months corrected age.

	Ventriculomegaly	Echolucent lesion	Cystic PVL
Positive predictive value	24	27	9
Negative predictive value	91	90	96
Sensitivity	24	16	20
Specificity	91	95	90