Head Ultrasonograhy as a Screening Tool in Apparently Healthy Asymptomatic Term Neonates

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ABSTRACT: **Background:** The rate of brain abnormalities in asymptomatic term neonates varies substantially in previous studies. Some of these rates may justify general screening of healthy newborns by head ultrasound (HUS).

Objectives: To assess the incidence of intracranial abnormalities among asymptomatic term newborns with HUS and to detect high-risk populations that might need such screening.

Methods: This was a prospective study in 493 term newborns who underwent HUS and a neurological evaluation during the first 3 days of life. The neurological examination results were unknown to the sonographist and the examiner was blinded to the HUS findings. The abnormal HUS findings were classified as significant or non-significant according to the current literature.

Results: Abnormal HUS was found in 11.2% of the neonates. Significant findings were noted in 3.8% of the infants. There was no association between non-structural HUS findings (hemorrhage or echogenicity) and mode of delivery. There was no relationship between any HUS abnormality and birth weight, head circumference and maternal age, ethnicity, education or morbidity. The rate of abnormal neurological, hearing or vision evaluation in infants with a significant abnormal HUS (5.2%) was comparable to the rate in infants with normal or non-significant findings on HUS (3.1%).

Conclusions: There is no indication for routine HUS screening in apparently healthy term neonates due to the relatively low incidence of significant brain abnormalities in these infants in our population.

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KEY WORDS: head ultrasound, cranial ultrasound, neurological examination, screening; term infant

Head ultrasound is a useful tool to detect intracranial abnormalities in high-risk infants, especially those born prematurely. HUS is a highly available, easily performed procedure with no radiation or need for sedation.

HUS = head ultrasound

A few studies have reported brain abnormalities in apparently healthy asymptomatic neonates [1-5]. The incidence and significance of these findings were found to be highly variable. Furthermore, a large proportion of these children suffer from a mild to moderate degree of neurodevelopmental impairment. It is possible that some of those children might have experienced a subtle perinatal event that was clinically asymptomatic but could be detected by neonatal HUS. Thus, performing screening HUS at that period may be informative and may serve as an additional tool to explain some of the so-called idiopathic impairments among children, enabling early diagnosis and intervention.

The aim of our study was to assess the incidence and type of intracranial abnormalities among asymptomatic healthy term neonates by using HUS. We also attempted to detect high-risk populations that might need such screening.

SUBJECTS AND METHODS

This was a prospective study performed at Bnai Zion Medical Center, Haifa, Israel, from September 2006 until July 2007. The study was approved by the Institutional Review Board at our center.

The study population included all consecutive newborns who had parental consent for a HUS along with a neurological physical evaluation within 3 days of birth. Excluded were infants with congenital abnormalities, signs of illness or gross neurological deficit, born prematurely (< 37 weeks), or whose mothers were substance or alcohol abusers.

STUDY PROCEDURE

HUS was performed by one of two trained neonatologists. The study was performed on certain days, according to the attendance of these neonatologists. The ultrasound examination included coronal and sagittal images of the brain, through the anterior fontanel [6,7], using a 5 and 6.5 MHz transducer (Logiq 200, Pro Series, GE Medical Systems, Solingen, Germany). Evaluation of the imaging was performed in real time as well as by later review of the static images. The infants

were examined supine in their cot. Abnormal ultrasound findings were categorized as significant or non-significant.

All infants underwent a neurological evaluation by one of two physicians who were trained for this purpose by a certified neurodevelopmental pediatrician. The neurological evaluation consisted of: a) general neurological examination (postures, power and passive movement, reflexes and responses, muscle tone, cranial nerves assessment, primary and deep tendon reflexes, and fontanel size and tension); b) clinical evaluation of vision and eyes, habituation and orientation; and c) hearing evaluation based on responses to sounds and habituation [8-10].

DATA INTERPRETATION AND ANALYSIS

HUS findings considered as significant were those previously reported to have a possible abnormal outcome: namely, intracranial (intraparenchymal or intraventricular) hemorrhage [2,3,5], brain infarction [5], focal periventricular white matter echogenicity (intensity that was equal to or higher than that of the choroid plexus seen simultaneously in both coronal and parasagittal scans) in cerebral hemisphere and basal ganglia [1,11,12], partial or total agenesis of corpus callosum [13,14], an enlarged cisterna magna [15], and a midline cyst [16]. Findings that were previously reported as variants of normal structure or very mild changes we considered as probably non-significant. These included: persistent cavum vergae [2], cavum septum pellucidum [2], choroid plexus cyst or germinolysis [17], mild ventriculomegaly (defined as < 10 mm diameter of one or both lateral ventricles. The ventricular atria were measured on an axial plane at the level of the thalami by positioning electronic calipers on the internal margins of the ventricular wall perpendicular to the long axis of the ventricles) [18], mild ventricular asymmetry [19] and caudothalamic cysts [20].

A neurological evaluation was considered abnormal if there were one or more abnormal neurological findings as well as an elicited deficit in vision or hearing functions, but not in cases of partial abnormality (for example, one-sided lack of habituation response to light or sound, or one reflex not elicited when the rest of the neurological examination is normal).

The results of the neurological examination were unknown to the sonographist, and the examiner was blinded to the ultrasound findings. The ultrasound examinations were recorded and later reviewed by a pediatric neuroradiologist who was unaware of the neonatologist's interpretation and was blinded to the neurological examination. In cases of disagreement between the neonatologist and the pediatric neuroradiologist regarding interpretation of the scan, it was reviewed a third time by the two neonatologists and a final decision was made by the neonatologist who performed the ultrasound and made the real-time assessment.

STATISTICAL ANALYSIS

Two-sample Student's *t*-test and ANOVA were used for comparison of continuous variables with normal distribution, and the Wilcoxon rank-sum non-parametric test was used where the distribution was skewed. For categorical variables we performed chi-square analysis. We also did linear regression analysis to check for correlations. The level of significance was set at $P < 0.05$. Data are presented as mean ± standard deviation or median with range. Analysis was performed using SigmaStat software (version 2.03, Chicago, IL).

RESULTS

During the study period 3171 infants were born at our center. We approached the parents of 896 unselected infants. The demographic characteristics of infants included or not included in the study were comparable [Table 1]. The recruitment process is summarized in Figure 1. A total of 493 neonates underwent HUS and neurological examination.

Fifty-five infants (11.2%) were found to have HUS abnormalities. The findings were significant in 19 infants (3.8%) and non-significant in 36 (7.2%). The incidence of the different sonographic findings is shown in Table 2.

Of the 19 infants with significant findings, 10 had an isolated abnormality and 9 had one or more associated abnormalities, although frequently non-significant. One infant (0.2%) had an intraventricular hemorrhage of III-IV degree. Her fetal and neonatal course was uneventful and her neurological examination was normal. Her blood count, prothrombin time and partial

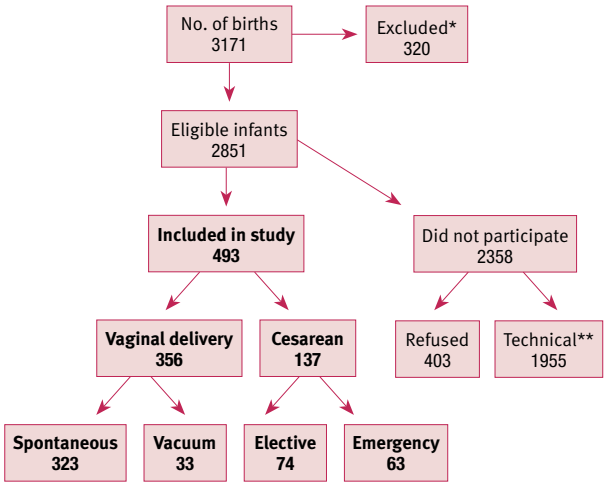
Table 1. Demographic data of the study population

	Study population (n=493)
Maternal age (yrs)*	30 (18–48)
Parity	
Primipara	37%
Multipara	60%
Grand multipara	3% (> 5 previous births)
Ethnicity	
Jewish	67%
Arab	26%
Druze	3%
Other	3%
Education (yrs at school)	
4–11 yrs	9%
12–23 yrs	91%
Mode of delivery	
Spontaneous vaginal	65%
Assisted (vacuum)	7%
Elective CS	15%
Emergency CS	13%
Birth weight*	3310 g (2120–4900 g)
Gestational age*	39.5 wks (37.0–42.1 wks)

* Median (range)

CS = cesarean section

Figure 1. Patient enrollment to the study



* Infants were excluded due to prematurity, illness or congenital anomalies

** Unable to conduct the ultrasound or physical examination due to attendance of the physicians performing the study

Table 2. Incidence of head ultrasound findings (study population = 493 infants)

Sonographic findings	incidence
Significant findings	
Hemorrhage	1 (0.2%)
Focal echogenicity	14 (2.8%)
Partial agenesis of corpus callosum	3 (0.6%)
Enlarged cysterna magna	2 (0.4%)
Midline cyst	1 (0.2%)
Non-significant findings	
Persistent cavum vergae	3 (0.6%)
Cavum septum pellucidum	15 (3%)
Choroid plexus cyst	10 (2%)
Ventricular asymmetry	9 (1.8%)
Germinolysis	4 (0.8%)
Mild ventriculomegaly	8 (1.6%)
Enlarged third ventricle	1 (0.2%)
Caudothalamic cyst	2 (0.4%)

thromboplastin time were normal. Repeat HUS during her first year showed resolution of the findings. At age 2 years she was reported to have a normal neurodevelopmental outcome.

Focal periventricular echogenicity was found in 14 infants (2.8%). In 8 infants (1.6%) the finding was isolated, and in 6 infants (1.2%) it was associated with other findings: cavum septum pellucidum in three, a choroid plexus cyst and ventricular asymmetry in one, a choroid plexus cyst and germinolysis in one, and partial agenesis of corpus callosum in one. Partial ACC was found in 3 infants (0.6%), always in association with other findings: one had an enlarged third ventricle, one had a midline cyst and mild ventriculomegaly, and one had focal echogenicity. An enlarged cisterna magna was found in 2 infants (0.4%), one isolated and one with a mild ventriculomegaly. A midline cyst was found in one infant (0.2%), who also had mild ventriculomegaly and partial ACC.

We found no significant association between the mode of delivery (spontaneous, vacuum, elective or emergency cesarean section) and non-structural abnormalities (focal echogenicity and/or hemorrhage) (data not presented).

The mean birth weight (± SD) and head circumference were comparable in infants with abnormal HUS findings (structural and non-structural findings) and in infants with normal scans (3306 ± 502 vs. 3328 ± 468 g, $P = 0.82$; and 34.9 ± 1.5 vs. 34.4 ± 1.3 cm, $P = 0.07$, respectively). We found no significant association between HUS findings (significant or non-significant) and maternal age, ethnicity, education or morbidity during pregnancy (gestational diabetes mellitus, eclampsia, etc.).

The rate of abnormal neurological evaluation (including neurological examination, hearing and vision assessment) (1/19, 5.2%) in infants with significant abnormal HUS did not differ significantly from the rate (15/474, 3.1%) in infants who had HUS with normal or non-significant findings ($P = 0.47$). Table 3 presents the data on HUS findings in relation to the different components of the neurological evaluation (no significant differences).

ACC = agenesis of corpus callosum

Table 3. Head ultrasound findings in relation to the different components of the neurological evaluation

	Neurological examination		Hearing assessment		Vision assessment	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Normal ultrasound	433	5	437	1	432	6
Insignificant finding	34	2	36	–	35	1
Hemorrhage	1	–	1	–	1	–
Focal echogenicity	14	–	14	–	13	1
Enlarged cysterna magna	2	–	2	–	2	–
Midline cyst	1	–	1	–	1	–
Partial agenesis of corpus callosum	3	–	3	–	3	–

NEUROLOGICAL EXAMINATION

The neurological examination was normal in all the children who had significant ultrasound findings. All seven infants with an abnormal examination had abnormal tone.

HEARING ASSESSMENT

There was only one infant in this study who did not respond to the sound of the standard examination bell. He had an otherwise normal examination and a normal HUS. All the infants with significant or non-significant ultrasound findings responded to sound. There was no correlation between abnormal habituation and abnormal HUS ($P = 0.844$).

VISION ASSESSMENT

Vision assessment was abnormal in eight infants. Object tracking was abnormal in all of them; seven had a normal visual response to light, and one did not. Only one of the infants had a significant HUS finding (focal echogenicity). She could not track an object during the neurological examination despite having a normal visual response to light. The single infant who did not respond to light stimulation and also could not track an object had an otherwise normal examination and a normal brain ultrasound. No association was found between abnormal habituation to light and abnormal ultrasound.

DISCUSSION

Our prospective study found that the rate of significant abnormal HUS findings in apparently healthy term infants is low. Mode of delivery and use of instrumentation were not associated with increased rate of abnormal non-structural findings in HUS.

The rate of brain abnormalities in asymptomatic term neonates varied substantially in previous studies [1,2,4,5,18,21]. Heibel et al. [2] reported a 9% rate of abnormal head ultrasounds in 1000 healthy neonates, employing the same technique as in the present study (anterior fontanel views). Mercuri and co-authors [3] reported a 19.7% rate of abnormal HUS in 177 unselected neonates ("standard views" – not specified). Wang et al. [5], who conducted the largest study so far, on 2309 term healthy newborns, reported a strikingly lower incidence (0.25%) of abnormal HUS (anterior fontanel views). Some studies emphasize the much higher yield in detecting abnormal findings provided by magnetic resonance imaging [4,21]. In our study the rate of abnormal scans was more consistent with that of Heibel et al. [2] and not at the extreme ends reported by the other studies [3-5]. The different results of the studies may be due to different techniques (HUS, MRI), methodology of HUS performance (frontal vs. posterior or mastoid fontanel), operator dependency and different populations. While the rates reported by some of the studies may justify general screening of healthy newborns our results do not lend support to such an approach.

The significance of the HUS findings is derived from its future outcome. Heibel and team [2] reported that 3 of 20 children with intraventricular hemorrhage developed contralateral hemiparesis. One child with subependymal hemorrhage developed infantile spasm. In the study of Wang et al. [5], of the two children with IVH, one had a minor developmental delay that had resolved by the age of 3 years and the other still had a significant developmental delay at 2 years. Haataja and collaborators [1] reported that the six infants who had IVH were neurologically and developmentally normal. The rate of hemorrhage in our study was low (0.2%), similar to the 0.1% found by Wang et al. [5] and much lower than the 3.5% and 5.6% found by others [2,3]; all used HUS for imaging.

We found a 2.8% rate of focal echogenicity, lower than the 8.4% observed by Mercuri et al. [3]. None of the other recent studies reported this sonographic finding, which is relatively frequent in premature infants and can precede periventricular leukomalacia [11] or represents edema or hypoxic-ischemic encephalopathy in symptomatic patients [10]. The significance of such a finding in term asymptomatic neonates is yet unclear [4].

ACC can be partial or complete, isolated or associated with other malformations. In our study the rate of ACC was 0.6%, all were partial and none was isolated. Wang et al. [5] reported a 0.08% rate of isolated complete ACC. The significance of such findings is controversial [5,13,14].

An enlarged cisterna magna was found in 0.4% in our study, similar to the 0.3% reported by Heibel and colleagues [2]. This finding, when isolated, had been generally found to have either no influence or a mild influence on cognitive function [15,22].

We found no cases of brain infarct, which occurred in 0.04% of infants in the study of Wang et al. [5], but not in others [2,3]. This may be attributed to the smaller study population, as well as to the timing of performing the HUS [23]. Furthermore, we did not perform MRI, which is more sensitive than HUS [23].

HUS as a screening tool requires further assessment, which is done by comparing its yield with that of neurological evaluation. The rates of abnormal neurological examination reported by Mercuri et al. [3] were 68% and 10% of infants with and without abnormal ultrasounds, respectively ($P < 0.0001$). Unlike previous studies [3,5] we found no correlation between an abnormal HUS and neurological examination, or with abnormal assessment of vision and hearing. This may be due to the nature of the findings compared to those of Wang et al. [5] and to a lower incidence of findings compared to the study of Mercuri et al. [3].

IVH = intraventricular hemorrhage

Further investigation could determine whether there are high-risk subgroups that would especially benefit from HUS screening. A large retrospective study performed in symptomatic infants by Towner and co-researchers [24] showed a higher rate of intracranial bleeding in infants delivered by vacuum extraction, forceps or cesarean section than among infants delivered spontaneously. Contrary results were found by Rooks et al. [4] who examined asymptomatic neonates. The rate of subdural hemorrhage was significantly higher in vaginal deliveries as compared to cesarean section (elective or emergency), and there was no difference between the vaginal delivery groups (spontaneous, vacuum, forceps) [4]. Our study, as well as that of Mercuri et al. [3], did not show a significant association between abnormal HUS and any of the modes of delivery. Furthermore, in our study there was no correlation between abnormal sonographic findings and birth weight or head circumference, in contrast to Mercuri et al. [3] who demonstrated a higher incidence of abnormal HUS in infants with intrauterine growth retardation. The difference may be due to the fact that infants < 37 weeks of gestation were not excluded from their study. Mercuri and group [3] did not find a correlation between a sonographic abnormality and maternal age, parity, presence of meconium, or signs of fetal distress. Thus, based on the available data we cannot define a high-risk group for abnormal HUS.

The limitation of our study lies in the number of participants and the low incidence of significant findings. Furthermore, no posterior fontanel or posterior fossa views were obtained through the mastoid approach (a limitation found in most previous published studies). It is possible that complete evaluation by a specialized pediatric radiologist [25] would have yielded more findings. However, such an evaluation performed as a routine screening in all newborns is probably not feasible. Determining the prognostic importance of the findings requires long-term follow-up. An inherent limitation of all studies using ultrasonography is operator-dependency. We tried to minimize this by the use of separate analysis on the part of trained neonatologists and an independent neuroradiologist who was blinded to their findings.

We conclude that due to the relatively low incidence of significant abnormalities in our study, there is no indication for routine general screening in apparently healthy term infants in our population. Larger studies or a meta-analysis with long-term neurodevelopmental follow-up are warranted to confirm our findings.

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References

1. Haataja L, Mercuri E, Cowan F, Dubowitz L. Cranial ultrasound abnormalities in full term infants in a postnatal ward: outcome at 12 and 18 months. *Arch Dis Child Fetal Neonatal Ed* 2000; 82: F128-33.
2. Heibel M, Heber R, Bechinger D, Kornhuber HH. Early diagnosis of perinatal cerebral lesions in apparently normal full-term newborns by ultrasound of the brain. *Neuroradiology* 1993; 35: 85-91.
3. Mercuri E, Dubowitz L, Brown SP, Cowan F. Incidence of cranial ultrasound abnormalities in apparently well neonates on a postnatal ward: correlation with antenatal and perinatal factors and neurological status. *Arch Dis Child Fetal Neonatal Ed* 1998; 79: F185-9.
4. Rooks VJ, Eaton JP, Ruess L, Peterman GW, Keck-Wherley J, Pedersen RC. Prevalence and evolution of intracranial hemorrhage in asymptomatic term infants. *AJNR Am J Neuroradiol* 2008; 29: 1082-9.
5. Wang LW, Huang CC, Yeh TF. Major brain lesions detected on sonographic screening of apparently normal term neonates. *Neuroradiology* 2004; 46: 368-73.
6. American Institute of Ultrasound in Medicine (AIUM) practice Guidelines – Neurosonography in Neonates and Infants. http://www.aium.org/publications/guidelines.aspx. 2006.
7. Rennie JM. Neonatal Cerebral Ultrasound. Cambridge, UK: Cambridge University Press, 1997.
8. Boukydis CF, Bigsby R, Lester BM. Clinical use of the Neonatal Intensive Care Unit Network Neurobehavioral Scale. *Pediatrics* 2004; 113: 679-89.
9. Lester BM, Tronick EZ, Brazelton TB. The Neonatal Intensive Care Unit Network Neurobehavioral Scale procedures. *Pediatrics* 2004; 113: 641-67.
10. Prechtl H. The neurological examination of the full-term newborn infant. In: Clinics in Developmental Medicine. No. 63. Philadelphia: JB Lippincott, 1977.
11. Yamamoto N, Utsu M, Serizawa M, et al. Neonatal periventricular leukomalacia preceded by fetal periventricular echodensity. *Fetal Diagn Ther* 2000; 15: 198-208.
12. Ivanov I, Neshterova M. The diagnostic and prognostic implications of brain hyperechogenicity in hypoxic-ischaemic encephalopathy grade II. *Eur J Ultrasound* 1998; 8: 7-15.
13. Francesco P, Maria-Edgarda B, Giovanni P, Dandolo G, Giulio B. Prenatal diagnosis of agenesis of corpus callosum: what is the neurodevelopmental outcome? *Pediatr Int* 2006; 48: 298-304.
14. Volpe P, Paladini D, Resta M, et al. Characteristics, associations and outcome of partial agenesis of the corpus callosum in the fetus. *Ultrasound Obstet Gynecol* 2006; 27: 509-16.
15. Zimmer EZ, Lowenstein L, Bronshtein M, Goldsher D, Aharon-Peretz J. Clinical significance of isolated mega cisterna magna. *Arch Gynecol Obstet* 2007; 276: 487-90.
16. Epelman M, Daneman A, Blaser SI, et al. Differential diagnosis of intracranial cystic lesions at head US: correlation with CT and MR imaging. *Radiographics* 2006; 26: 173-96.
17. DiPietro JA, Costigan KA, Cristofalo EA, et al. Choroid plexus cysts do not affect fetal neurodevelopment. *J Perinatol* 2006; 26: 622-7.
18. Gaglioti P, Danelon D, Bontempo S, Mombro M, Cardaropoli S, Todros T. Fetal cerebral ventriculomegaly: outcome in 176 cases. *Ultrasound Obstet Gynecol* 2005; 25: 372-7.
19. Kinzler WL, Smulian JC, McLean DA, Guzman ER, Vintzileos AM. Outcome of prenatally diagnosed mild unilateral cerebral ventriculomegaly. *J Ultrasound Med* 2001; 20: 257-62.
20. Makhoul IR, Zmora O, Tamir A, Shahar E, Sujov P. Congenital subependymal pseudocysts: own data and meta-analysis of the literature. *IMAJ Isr Med Assoc J* 2001; 3: 178-83.
21. Holden KR, Titus MO, Van Tassel P. Cranial magnetic resonance imaging examination of normal term neonates: a pilot study. *J Child Neurol* 1999; 14: 708-10.
22. Haimovici JA, Doubilet PM, Benson CB, Frates MC. Clinical significance of isolated enlargement of the cisterna magna (> 10 mm) on prenatal sonography. *J Ultrasound Med* 1997; 16: 731-4, quiz 735-6.
23. Cowan F, Mercuri E, Groenendaal F, et al. Does cranial ultrasound imaging identify arterial cerebral infarction in term neonates? *Arch Dis Child Fetal Neonatal Ed* 2005; 90: F252-6.
24. Towner D, Castro MA, Eby-Wilkens E, Gilbert WM. Effect of mode of delivery in nulliparous women on neonatal intracranial injury. *N Engl J Med* 1999; 341: 1709-14.
25. Daneman A, Epelman M, Blaser S, Jarrin JR. Imaging of the brain in full-term neonates: does sonography still play a role? *Pediatr Radiol* 2006; 36: 636-46.