Rate of head ultrasound abnormalities at one month in very premature and extremely premature infants with normal initial screening ultrasound

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Abstract
Background Premature infants are at risk for multiple types of intracranial injury with potentially significant long-term neurological impact. The number of screening head ultrasounds needed to detect such injuries remains controversial.
Objective To determine the rate of abnormal findings on routine follow-up head ultrasound (US) performed in infants born at ≤32 weeks’ gestational age (GA) after initial normal screening US.
Materials and methods A retrospective study was performed on infants born at ≤32 weeks’ GA with a head US at 3–5 weeks following a normal US at 3–10 days at a tertiary care pediatric hospital from 2014 to 2020. Exclusion criteria included significant congenital anomalies, such as congenital cardiac defects necessitating surgery, congenital diaphragmatic hernia or spinal dysraphism, and clinical indications for US other than routine screening, such as sepsis, other risk factors for intracranial injury besides prematurity, or clinical neurological abnormalities. Ultrasounds were classified as normal or abnormal based on original radiology reports. Images from initial examinations with abnormal follow-up were reviewed.
Results Thirty-three (14.2%) of 233 infants had 34 total abnormal findings on follow-up head US after normal initial US. Twenty-seven infants had grade 1 germinal matrix hemorrhage, and four had grade 2 intraventricular hemorrhage. Two had periventricular echogenicity and one had a focus of cerebellar echogenicity that resolved and was determined to be artifactual.
Conclusion When initial screening head ultrasounds in premature infants are normal, follow-up screening ultrasounds are typically also normal. Abnormal findings are usually limited to grade 1 germinal matrix hemorrhage.

Keywords Brain · Head · Infant · Intracranial hemorrhage · Premature · Ultrasound

Introduction
The developing brain of premature infants is at risk for several major types of pathology: germinal matrix hemorrhage with or without intraventricular hemorrhage (IVH), cerebellar hemorrhage, ventriculomegaly and white matter injury. Germinal matrix hemorrhage with or without IVH is the most common abnormality found on head ultrasound (US), reported in more than 30% of infants born at ≤28 weeks’ gestational age (GA), while ventriculomegaly without hemorrhage and white matter injury are identified in less than 5% [1]. Cerebellar hemorrhage has been detected on head US in up to 9% of infants born at <32 weeks’ GA when views are performed through the mastoid fontanelle in addition to the anterior fontanelle [2]. All of these brain injuries can initially be clinically silent but are often associated with long-term motor, cognitive and sensory impairment [3–10].

In 1978, Papile et al. [11] described a classification system for grading germinal matrix hemorrhage and IVH on computed tomography (CT), and they later demonstrated the prognostic utility of this classification system: Infants with grade 1 germinal matrix hemorrhage or grade 2 IVH had similar neurodevelopmental outcomes compared to infants with no hemorrhage, while infants with grade 3–4 IVH had a significantly increased incidence of neurodevelopmental impairment [12]. After its introduction in the late 1970s, US replaced CT as the predominant screening modality for...
detecting brain injuries of prematurity [13, 14]. An early
guide to neonatal head US in the radiology literature from
the 1980s recommended head US at 4–7 days of life for
premature infants born at ≤32 weeks’ GA and no further
ultrasounds if the initial was normal, in the absence of symp-
toms or clinical conditions increasing risk of late intrac-
ranial hemorrhage [15]. Over the years since, the optimal
number of screening head ultrasounds that should be per-
fomed in premature infants to detect asymptomatic intrac-
ranial injuries has remained a topic of extensive research
and controversy.

In 2002, the American Academy of Neurology published
practice guidelines for screening neuroimaging in premature
infants. They recommended an initial head US in all infants
born at <30 weeks’ GA within the first 7–14 days of life and
repeat US at 36–40 weeks age corrected [5]. The rationale
behind this staged approach to screening is that early head
US should detect germinal matrix hemorrhage or IVH, and
delayed US should detect white matter injury and ventric-
ulomegaly, which may be due to posthemorrhagic hydro-
cephalus or parenchymal volume loss [4, 5, 16–18]. Most
germin al matrix hemorrhage or IVH, as well as cerebellar
hemorrhage, can be diagnosed within the first week of life
[5, 8, 19–22]. In contrast, white matter injury can be unde-
tectable or subtle on initial head US, when it may manifest
as increased or asymmetrical periventricular white matter
echogenicity [4, 16, 23, 24]. Echogenicity may be replaced
as increased or asymmetrical periventricular white matter
echogenicity [4, 16, 23, 24], and ventriculomegaly may be the only residual visible
abnormality on US after the cysts are resorbed over several
months [4, 16, 24–26]. The age at which white matter injury
is diagnosed on US varies widely in the literature, from 10
to 104 days [18, 27–29], and may depend on underlying
risk factors such as perinatal depression or late-onset sepsis.

Since the publication of the American Academy of
Neurology guidelines, multiple other head US screening
protocols have been described in the literature [6, 24, 25,
29], as actual screening practices remain highly depend-
ent on the institution. The American Academy of Neu-
rology guidelines were never updated and were retired in
2018, but the American Academy of Pediatrics recently
published new guidelines for screening neuroimaging in
premature infants in 2020. These guidelines recommend
screening all infants born at ≤30 weeks’ GA with head
US by 7–10 days of life, with earlier screening for infants
with concerning clinical abnormalities, follow-up US
at 4–6 weeks, and finally US at term equivalent age or
before hospital discharge. They also recommend screening
infants born at >30 weeks’ GA with clinical risk factors
for intracranial injury. Routine screening magnetic reso-
nance imaging (MRI) is not recommended, but the guide-
lines state that MRI may be obtained in “high-risk infants”
at term equivalent age if the prognostic limitations of MRI
are discussed with the patient’s family [30], although high-
risk is not explicitly defined. In the absence of clinical
concerns, our institution’s screening protocol calls for an
initial head US in all premature infants born at ≤32 weeks’
GA at 7 days and 28–30 days. Head US at term equivalent
age is optional, and MRIs are obtained at the discretion of
the attending neonatologist.

While most head US screening protocols include at least
one delayed US to detect abnormalities that may not have
been present on the initial exam, a few studies in the neo-
atology literature have challenged the need for delayed US
if the initial exam is normal [31–33]. These studies have
demonstrated very low rates of abnormal delayed head US
following normal early US; the majority of new abnormali-
ties are low-grade germinal matrix hemorrhage, and the rare
abnormalities that are more significant tend to develop in
infants who are critically ill. The goal of our study was to
determine the predictive value of normal initial screening
head US in asymptomatic premature infants by examining
the incidence of abnormalities on routine follow-up head US
after normal early screening US.

Materials and methods

The institutional review board approved this retrospective
cohort study, which was compliant with HIPAA guidelines. For this type of study, written informed consent is
not required.

Patient population

Patients who underwent head US at a tertiary care academic
pediatric hospital over a 7-year period from January 2014 to
December 2020 were reviewed. Inclusion criteria included
premature infants born at ≤32 weeks’ GA with initial
screening head US at 3–10 days of life interpreted as normal
for a premature brain and follow-up screening head US at
21–35 days of life (3–5 weeks). Infants with severe congeni-
tal defects, such as congenital cardiac defects necessitating
surgery in the neonatal period, congenital diaphragmatic
hernia or spinal dysraphism were excluded. Infants with
indications for head US other than routine screening docu-
mented in the radiology reports, such as sepsis, other risk
factors for intracranial injury besides prematurity, or clin-
ical neurological abnormalities, were excluded. Infants with
head US in between the initial screening US and follow-up
at 3–5 weeks were excluded to ensure that the final study
population comprised only those infants in whom head US
was obtained for screening, as opposed to clinical concerns
prompting earlier repeat imaging.

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Imaging technique

Head ultrasounds were all performed by US technologists using a GE Logiq E9 or S8 ultrasound machine (GE Healthcare, Chicago, IL). Our institution’s head US protocol includes still and cine images through the coronal, bilateral coronal obliques, parasagittal and mastoid planes with a 10- to 7-MHz (10- to 4-MHz with harmonics off) neonatal head probe. Additional coronal and parasagittal views with a high-frequency 4- to 15-MHz linear probe are obtained. Color Doppler interrogation of the anterior cerebral artery and the superior sagittal sinus is performed.

Image evaluation

As this was a retrospective study, ultrasounds were classified as normal or abnormal based on the original radiology reports. Head ultrasounds at our institution are all interpreted by pediatric radiologists with American Board of Radiology certificate of added qualification in pediatric radiology. While the radiologists at our institution often describe germinal matrix hemorrhage and IVH qualitatively rather than using the Papile grading system, for data analysis we classified all germinal matrix hemorrhage and IVH based on the original report descriptions using the Papile grading system published in 1978 [11].

For cases with abnormal follow-up US, initial screening images were reviewed by two investigators (J.L.C. and M.A.Z., with 10 years and 6 years of experience as attendings with certificate of added qualification in pediatric radiology, respectively) to assess reader agreement. The reviewers were instructed to classify the initial head US as normal, abnormal or possibly abnormal if they were unsure of their assessment and to describe the abnormalities identified.

Statistical analysis

Statistical analysis was performed in Microsoft Excel (Version 16.40). Statistics are reported as mean ± standard deviation unless otherwise specified.

Results

Study cohort

Six hundred and seven infants were identified who were born at ≤32 weeks’ GA and had a head US at 3–10 days of life during the study period. Two hundred thirty-three met inclusion criteria and had a normal initial head US and a follow-up head US at 3–5 weeks (Fig. 1). The average GA of the study cohort was 29.0 ± 1.9 weeks (range: 25–32 weeks), and the average birth weight was 1,259.9 ± 360.6 g. Additional demographic information stratified by GA (extremely premature or very premature) is displayed in Table 1. The average age at initial head US was 7.0 ± 0.7 days (range: 3–10 days), and the average age at follow-up US was 29.3 ± 2.0 days (range: 21–35 days).

Ultrasound results

Of the 233 premature infants with initial normal head US, 200 (85.8%, overall negative predictive value for normal follow-up head US) had a normal US at 3–5 weeks based on the original radiology reports. Thirty-three infants

Fig. 1 A flow chart depicts the study cohort selection resulting in a final cohort of 233 premature infants meeting inclusion criteria with normal head ultrasound (US) at 3–10 days and follow-up at 3–5 weeks
(14.2%) had an abnormal follow-up US with a total of 34 abnormal findings. Of the 33 infants, 27 (81.8%) had grade 1 germinal matrix hemorrhage (Figs. 2 and 3), and 4 (12.1%) had grade 2 IVH (Fig. 4). One infant with grade 2 IVH also had periventricular echogenicity that eventually decreased on follow-up exam at 2 months. Another infant developed periventricular echogenicity that was no longer visualized on US at 2 months, although a new possible grade 1 germinal matrix hemorrhage was identified on this subsequent US. One infant developed an echogenic focus in the cerebellum that was determined to represent specular artifact when it was not seen on subsequent head ultrasound.

### Table 1  
Cohort demographic data stratified by gestational age (GA)

|                        | Extremely premature (<28 weeks’ GA) | Very premature (28–32 weeks’ GA) |
|------------------------|-------------------------------------|----------------------------------|
| Number of infants      | 54                                  | 179                              |
| Average GA (weeks)     | 26.2 ± 0.8                          | 29.8 ± 1.2                       |
| Average birth weight (grams) | 868.8 ± 157.0                       | 1,377.9 ± 319.0                   |
| Male gender, n (%)     | 25 (46.3)                           | 87 (48.6)                        |
| Vaginal delivery, n (%)| 17 (31.5)                           | 42 (23.5)                        |
| C-section delivery, n (%) | 37 (68.5)                          | 137 (76.5)                       |
| Multiple gestation, n (%) | 13 (24.1)                         | 90 (50.3)                        |

**Fig. 2** A sagittal image from a normal head ultrasound (US) at 7 days of life in a girl born at 31 weeks’ gestational age (a). A sagittal image from a follow-up US at 30 days shows new grade 1 germinal matrix hemorrhage (arrow) (b). A sagittal image from a subsequent US at 50 days shows expected cystic evolution of the germinal matrix hemorrhage (arrow) (c).

**Fig. 3** A coronal image from a normal head ultrasound (US) at 7 days of life in a boy born at 29 weeks’ gestational age (a). A coronal image from a follow-up US at 29 days shows new bilateral posthemorrhagic cysts (arrows) compatible with prior grade 1 germinal matrix hemorrhage (b).
US. Results stratified by GA are presented in Table 2. No infants developed grade 3 or 4 IVH, ventriculomegaly, definite cerebellar hemorrhage or cystic white matter injury at 3–5 weeks.

Of the 200 infants with normal head US at 3–5 weeks of age, 18 (9.0%) had at least 1 additional head US. Six of these infants had indications for US other than routine screening. Of the 12 infants with a routine screening head US at term equivalent age, 3 (25%) had an abnormal head US, all of which demonstrated grade 1 germinal matrix hemorrhage only.

On image review of the initial screening examinations in all 33 cases with abnormal follow-up US at 3–5 weeks based on the original radiology reports, the 2 reviewers had 84.8% agreement on whether examinations were normal or abnormal. Cohen’s kappa coefficient was 0.46, corresponding to moderate inter-reader agreement. There were three cases with initial US interpreted as abnormal or possibly abnormal by both reviewers, two with grade 1 germinal matrix hemorrhage and one with grade 2 IVH. Of note, in the case of grade 2 IVH, the abnormality was characterized as asymmetrical choroid plexus on the original report, which was classified as normal. Reviewers disagreed on five (15.2%) of the initial examinations, four with grade 1 germinal matrix hemorrhage described by one reviewer and one with grade 2 IVH described by one reviewer. Four of the five cases in which reviewers disagreed involved “possibly abnormal” assessments, which were classified as abnormal in line with the classification of the original radiology reports.

Table 2 Distribution of head ultrasound (US) results at 3–5 weeks stratified by gestational age based on the original radiology reports

| Follow-up head US results                      | Extremely premature infants, n (%) | Very premature infants, n (%) |
|-----------------------------------------------|-----------------------------------|------------------------------|
| Normal                                        | 50 (92.6)                         | 150 (83.8)                   |
| Grade 1 germinal matrix hemorrhage            | 1 (1.9)                           | 26 (14.5)                    |
| Grade 2 intraventricular hemorrhage           | 2 (3.7)                           | 2 (1.1)                      |
| Periventricular echogenicity                   | 1 (1.9)                           | 1 (0.6)                      |
| Cerebellar echogenic focus                    | 1 (1.9)                           | 0 (0)                        |

Of note, one of the extremely premature infants who developed grade 2 intraventricular hemorrhage also developed periventricular echogenicity

Fig. 4 A sagittal image from a normal head ultrasound (US) at 7 days of life in a boy born at 26 weeks’ gestational age (a). A sagittal image from a follow-up US at 29 days shows new grade 2 intraventricular hemorrhage on the patient’s left (arrow) (b). A comparison sagittal image of the patient’s normal right side on a follow-up US at 29 days (c). A sagittal image from a subsequent US at 36 days shows decreased echogenicity of the grade 2 intraventricular hemorrhage on the patient’s left compatible with expected evolution of hemorrhage (d)
Discussion

In our study population of very premature and extremely premature infants with normal initial screening head US, the vast majority also had a normal follow-up US at 3–5 weeks of age, and the few abnormalities identified on follow-up were almost all low-grade germinal matrix hemorrhages. Our findings are in line with those of previous studies in the neonatology literature suggesting that premature infants with early normal head US usually have normal delayed head US, and the abnormalities that do develop are mild [31–33]. Nwafor-Anene et al. [31] found that of 98 premature infants with 2 initial normal or “slightly abnormal” head ultrasounds (i.e. with grade 1 germinal matrix hemorrhage) at least a week apart, 94% continued to have normal ultrasounds at 1 month and beyond; the 6 infants who had abnormal follow-up ultrasounds were clinically unstable with significant comorbidities such as necrotizing enterocolitis or sepsis. Kaeppler et al. [32] further argued that just one normal screening head US may be sufficient. In their study, among 228 premature infants with normal head US before 4 and 10 days of life, on US at 1 month, 6 had grade 1 germinal matrix hemorrhage and 3 had grade 2 IVH; 1 infant had ventriculomegaly presumably due to known prior meningitis, and 1 infant had transient periventricular echogenicity that resolved on follow-up. In a more recent study by Khazanchi et al. [33], among 205 premature infants with normal head US before 14 days of life, on US at 25–35 days, 2 had grade 1 germinal matrix hemorrhage; 2 had periventricular echogenicity, which resolved on follow-up in 1, and only 1 had cystic white matter injury.

As one of the main purposes for delayed screening head US is to detect late manifestations of white matter injury, it is important to acknowledge both the low pretest probability of cystic white matter injury and the significant limitations of US in diagnosing non-cystic white matter injury. Since the introduction of head US, with improvements in neonatal critical care, the incidence of cystic white matter injury has markedly decreased. A study of more than 3,500 neonatal critical care, the incidence of cystic white matter injury has markedly decreased. A study of more than 3,500

Another limitation of our study is the small number of infants who underwent term equivalent head US, which is optional in our screening protocol. De Vries et al. [6] found...
that 17 (29%) of 58 very premature infants with major head US abnormalities who developed cerebral palsy did not develop cystic white matter injury until after 4 weeks of age. However, some of these infants developed other serious conditions before their diagnosis of cystic white matter injury, such as sepsis or severe recurrent apnea; such infants would have been excluded from our study population. Of the few infants in our study with normal head US at 3–5 weeks who had an additional US at term equivalent age for routine screening, the only new abnormalities were grade 1 germinal matrix hemorrhage.

As all but one of the abnormalities on routine follow-up head US in our study were low-grade germinal matrix or intraventricular hemorrhage or periventricular echogenicity, it is important to note that the diagnosis of low-grade hemorrhage or white matter injury on US has been shown to have poor inter-reader reliability and accuracy [42]. The subjectivity in diagnosis of mild abnormalities is a problem inherent to US. Multiple different radiologists interpreted the ultrasounds included in this study, and we used their original reports for our analysis. While the resulting variability in interpretation is a limitation of the study, it also mirrors the current reality of clinical practice. On two investigators’ image review of the initial examinations from cases with abnormal follow-up, the reviewers disagreed on whether ultrasounds were normal or abnormal in 15% of examinations. In addition, both on image review and in the original radiology reports, radiologists frequently described “possible” abnormalities, which were classified as abnormal for the purposes of data analysis but further highlight the difficulty in identifying subtle abnormalities on head US.

Finally, we did not review the neurodevelopmental outcomes of the infants in our cohort, as an examination of the relationship between imaging findings and outcomes was outside the scope of this study. Even if some infants had adverse neurodevelopmental outcomes, the small number of infants with abnormal follow-up head US in our study would preclude drawing any significant conclusions.

Conclusion

In asymptomatic very premature or extremely premature infants, routine screening head ultrasounds at 4 weeks of life following a normal US at 1 week of life are usually also normal, and the abnormalities that are newly identified are typically mild. In our study, no cases of cystic white matter injury or ventriculomegaly were detected on follow-up head US, which are the pathologies that the follow-up US was originally intended to capture. These findings add to the body of similar evidence in the neonatology literature. Given our study limitations, we are not recommending specific new guidelines for screening neuroimaging in premature infants. We suggest a larger multicenter study with multidisciplinary input to further investigate the utility of serial screening head ultrasounds in premature infants with an initial normal head US.

Declarations

Conflicts of interest None

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