Cranial ultrasound findings in well newborn Ugandan infants

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Abstract

Apparently well term-born Ugandan infants frequently have abnormalities on cUS. These are mainly increased WM echogenicity, SEP and CPC. These may relate to the reported high incidence of congenital infections in this population but this remains to be confirmed. The observations provide baseline data for comparison with scans from sick infants from similar communities and are also important for studies in which cUS will be used to assess progress.
Cranial ultrasound findings in well newborn Ugandan infants

CF Hagmann,1 NJ Robertson,1 D Acolet,2 D Chan,3 S Onda,3 N Nyombi,4 M Nakakeeto,4 FM Cowan3

ABSTRACT

Background There has been no study assessing cranial ultrasound (cUS) scans in newborn infants born in equatorial Africa.

Objective To assess the cUS scans of apparently well newborn term Ugandan infants and to correlate the findings with perinatal data.

Methods An observational study of apparently healthy postnatal ward term Ugandan infants at Mulago Hospital, Makerere University Hospital, Kampala, Uganda.

Results Data from 112 infants scanned at a median age of 1.4 postnatal days were analysed. Only 57 (51%) infants had scans considered normal, including 30 infants with isolated focal peritrigonal white matter (WM) echogenicity that was very common, occurring in 60 (53%) of infants. More extensive WM echogenicities were seen in nine (7.5%) and focal unilateral central grey matter echogenicity in eight (6.5%) infants. Haemorrhage was not common. Subependymal pseudocysts (SEP) and choroid plexus cysts (CPC) occurred in 19.6% of infants each. Four infants only had lenticulostriate vasculopathy. No correlation was found between mode of delivery, birth weight, head circumference or gestational age, maternal HIV status and any cUS abnormality.

Conclusions Apparently well term-born Ugandan infants frequently have abnormalities on cUS. These are mainly increased WM echogenicity, SEP and CPC. These may relate to the reported high incidence of congenital infections in this population but this remains to be confirmed. The observations provide baseline data for comparison with scans from sick infants from similar communities and are also important for studies in which cUS will be used to assess progress.

Abnormalities seen on cranial ultrasound (cUS) in apparently well term newborn infants are not uncommon. However, there is a large variation in the numbers of infants included in different studies, the incidence and type of abnormality reported and the clinical significance of the findings. An early study from 1986 found that 5.5% of 673 asymptomatic term infants had subependymal/intraventricular haemorrhages (IVH).1 In 1993 Heibel et al reported abnormalities in 90/1000 well term infants in the first three postnatal days including intracranial haemorrhage in 5.5%, subependymal pseudocysts (SEP) or choroid plexus cysts (CPC) in 3.4%, and in 2.1% anatomical variants such as cavum vergae, cavum septum pellucidum and enlarged cisterna magna. In a study of well term infants examined in detail neurologically soon after birth, cUS abnormalities were found in 20% (35/177); these included periventricular echo densities in 6%, unilateral thalamic echo densities in 2%, haemorrhage in 6%, focal ventricular dilatation in 4% and CPC in 2%.3 No structural abnormalities were reported. These abnormalities were not associated with neurodevelopmental problems at 12 and 18 months,4 although a non-significant lower gross motor score was found in infants with periventricular echo densities.

Major congenital or acquired structural brain abnormalities were found on cUS in six (0.26%) of 2309 apparently clinically normal term infants within 3 days of birth in Taiwan, four of whom had a poor outcome.5 In contrast, a study in a tertiary centre in Malaysia reported abnormalities in 39.5% of term control infants, but none had an abnormal outcome at 1 year. These abnormalities included slit-like ventricles in 9.2%, IVH in 6.6%, echodense thalami in 2.6% and nearly a third had increased echogenicity in the periventricular white matter (WM). These findings were highly significantly different from the asphyxiated infants they also reported on.6 None of those studies has reported lenticulostriate vasculopathy (LSV).
The studies were performed in developed countries such as the UK, Germany, USA, Taiwan and Malaysia. No study has described cUS findings in apparently well term infants in a low resource setting where a different range and incidence of comorbidities, particularly infection, exists and the quality and availability of antenatal and obstetric care is very variable.

The aims of our study were: (1) to assess the cUS scans of well newborn term Ugandan infants; (2) to relate the scan findings to the available perinatal data; and (3) to provide normative scan data for later comparison with infants affected by hypoxic-ischaemic encephalopathy.7

METHODS
The Institutional Review Board of the Ethics Committee, Medical School, Makerere University, Kampala, Uganda, approved the study; permission from the Head of the Obstetric Department at Mulago University Hospital where the study was carried out was also obtained. Mulago is a large public hospital providing care for the population in and around Kampala. In a Ugandan population similar to this study deliveries are reported to be 11% home, 5% traditional birth attendant and the remainder (84%) in hospital.8 Therefore, our cohort seems representative of the majority of the population.

Patients
Between 24 July 2007 and 31 October 2007, 115 term infants were recruited from the postnatal wards at Mulago Hospital. Maternal informed consent was obtained by the ward nurses in the mother’s language and consent was confirmed by the study doctors before examining the infant. Inclusion criteria were: (1) direct admission to the postnatal ward from the labour ward; (2) gestational age 36 weeks or more; (3) Apgar scores of 8 or greater at 5 min; and (4) postnatal age 4 days or less. Antenatal and perinatal clinical details were obtained from obstetric notes and from the mother. Maternal HIV status was available from the notes in a coded form,including whether the mother had been treated or not. Nurses able to communicate in the local languages were available throughout availability of antenatal and obstetric care is very variable.

Teaching
Brain anatomy and cUS teaching was done by FMC and DA for the Ugandan neonatal consultants. Instructions for using the ultrasound machine and protocols for cUS scanning were written down and were available in ward files and as posters near the cots. Practical teaching sessions were held and scan training videos were also available.

Cranial ultrasounds
The cUS examinations were performed using a hand portable machine (z.one ultra Convertible Ultrasound System; Zonare Medical Systems Inc, Mountain View, California, USA) with an optimised probe frequency (P4-1c phased array transducer). The probe was cleaned with alcohol wipes between patients and disposable gloves were worn when scanning. The examinations were performed by FMC, DA, CFH, NN and MN. FMC, DA and CFH are experts in this methodology. NN and MN were trained by FMC and DA and later supervised by CFH.

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The scans were assessed for normal anatomy, ventricular size, haemorrhage, focal or diffuse increased WM and basal ganglia echogenicity, cortical injury, SEP, CPC, LSV and other calcification and developmental abnormalities. The scoring system for WM and basal ganglia abnormalities is given in table 1; grades of abnormality were from 0 (normal) to 3 (more severe). Focal homogenous trigonal WM echogenicity was very common and was included as a normal finding (figure 1).

Statistical analysis
All statistical analysis was performed with a software package SPSS 12 using parametric correlation as appropriate for the data.

RESULTS
Patients
Of the 115 Ugandan African infants who we scanned, three were excluded because of incomplete data. Demographic and clinical details are summarised in table 2.

Table 1 Scoring system for WM and BG/thalami

<table>
<thead>
<tr>
<th>Score</th>
<th>BG and thalami</th>
<th>WM</th>
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<tbody>
<tr>
<td>0</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>Focal unilateral abnormality</td>
<td>Mildly echogenic or patchy in parieto-occipital region</td>
</tr>
<tr>
<td>2</td>
<td>Clearly demarcated focal bilateral echogenicity</td>
<td>More diffuse and moderate/severe echogenicity</td>
</tr>
<tr>
<td>3</td>
<td>Severe and extensive abnormalities</td>
<td>Cystic changes</td>
</tr>
</tbody>
</table>

BG, basal ganglia; WM, white matter.

Figure 1 (A) Coronal and (B) parasagittal ultrasound images showing focal homogeneous increased echogenicity in the peritrigonal white matter (arrows, score 0). A small area of increased echogenicity is also seen adjacent to the anterior horn.
infants are included in those described below. There were no associations found between the observation of peritrigonal WM echogenicity and other abnormalities.

Fifty-five infants had findings considered abnormal. In eight (6.5%) there was focal central grey matter echogenicity, mostly unilateral and not graded greater than 1. In nine infants (7.5%) there was increased WM echogenicity beyond the periventricular trigonal region but not graded greater than 1. Typically, the central grey matter changes were unilateral increased thalamic echogenicity (figure 2A, B) and the WM changes were patchy echogenicity in the parieto-occipital region (figure 3, tables 1 and 3).

IVH (figure 4) was seen in one infant, echogenicity suggestive of a left middle cerebral artery infarction in another (figure 5), and a left temporal parenchymal haemorrhage was seen in one further infant. No evidence of subdural or subarachnoid haemorrhage was seen.

SEP (figure 6) and CPC were seen frequently, in 19.6% of infants each; 4.5% of infants had both. SEP occurred in 15% and CPC in 10% of infants with otherwise normal scans (tables 4 and 5). LSV was only seen in four infants (figure 7, tables 4 and 5) and not always with SEP.

No major structural abnormality was found. Seventy-two infants had a patent cavum septum pellucidum and in seven a cavum vergae was seen (table 4). The corpus callosum was complete in all infants. No cortical or cerebellar abnormalities were seen. No infant had an extracerebral space greater than 2.2 mm, and only three infants had an interhemispheric fissure greater than 3 mm. Only one infant with IVH had enlarged lateral, third and fourth ventricles.

**Relationship between perinatal data and cUS findings**

There was no correlation between mode of delivery, birth weight, head circumference or gestational age, maternal HIV status and any cUS abnormality.

**DISCUSSION**

We found cUS abnormalities in 51% of our cohort of clinically normal postnatal ward Ugandan infants; this incidence is considerably higher than in published equivalent studies. In the UK, Germany and Malaysia abnormalities were reported in 0.26–39.5% of asymptomatic term infants. The wide incidence range in these previous studies is most likely explained by differences in reporting criteria.

The most common abnormalities in our study were SEP and CPC and WM echogenicity; haemorrhage was uncommon, being limited to IVH in one infant and temporal lobe haemorrhage in another. In other studies intracranial...
haemorrhages were the commonest finding, with incidences ranging between 0.09% and 6%. Of all haemorrhages reported in these studies (n=89) IVH was the most common type (n=84). In five infants lobar haemorrhage was diagnosed.

The reason for this difference in the incidence of haemorrhage is not immediately clear. Ventricular and parenchymal haemorrhage is readily detectable using cUS soon after birth, and it is doubtful that this was missed in our study. The most common type of haemorrhage in asymptomatic term infants is posterior fossa subdural haemorrhage,14 which is difficult to detect on cUS15 16 and we did not see evidence of it. We mostly only performed cUS through the anterior fontanelle and had we used other acoustic windows for all infants we may have detected posterior fossa haemorrhage.15 17 However, it is also known that infants delivered by vacuum extraction or forceps have a significantly higher risk of haemorrhage than infants delivered by spontaneous vaginal delivery,18 19 and at Mulago Hospital no instrumental deliveries are performed. There may thus have been fewer haemorrhages in our population than in other studies.

The most common findings in this study were SEP and CPC, each occurring in nearly 20% of infants but only co-occurring in 4.5%, suggesting that their aetiology is different. 15% of infants with SEP and 10% with CPC had no other ultrasound abnormality. These rates are far higher than in other studies. SEP were reported in 0.5–5% of healthy term infants,2 20 21 in 3–5.23 % of preterm infants21–24 and in 4.1% of all admissions to a neonatal unit.25 SEP are associated with congenital infections, especially cytomegalovirus and rubella,21 22 24 25 26–28 with many metabolic disorders, for example Zellweger syndrome, mitochondrial disorders and sulphite oxidase deficiency,29 congenital abnormalities such as cardiac defects21 30 and a host of genetic abnormalities. A recent meta-analysis showed that there is a 20–25% chance of an underlying chromosomal anomaly or congenital infection if bilateral SEP are found on cUS,31 however, that review included asymptomatic and

<table>
<thead>
<tr>
<th>Cysts and calcifications</th>
<th>Study infants, no (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEP</td>
<td>22 (19.6)</td>
</tr>
<tr>
<td>CPC</td>
<td>22 (19.6)</td>
</tr>
<tr>
<td>SEP and CPC</td>
<td>5 (4.5)</td>
</tr>
<tr>
<td>LSV</td>
<td>4 (3.6)</td>
</tr>
</tbody>
</table>

**Figure 4** Left parasagittal ultrasound image showing intraventricular haemorrhage (arrows).

**Figure 5** Posterior coronal ultrasound images showing a large area of increased echogenicity with a sharp medial border (long arrows) typical of infarction within the territory of the left middle cerebral artery. There is also some increased echogenicity in the peritrigonal region on the right (short arrow).

**Figure 6** (A) Coronal and (B) parasagittal ultrasound images showing bilateral multiple subependymal cysts in the caudothalamic notches (arrows). No evidence of lenticulostriate vasculopathy or other calcification is seen.
symptomatic term and preterm infants and not just term infants considered clinically normal as in our study.

At autopsy Shuangshoti et al found CPC histologically in 66% of fetuses and neonates. CPC occur in approximately 1% of pregnancies and they usually resolve by 26–28 weeks. There is an association with chromosomal abnormalities such as trisomy 18 if the cysts are greater than 1 cm, bilateral and if other structural abnormalities are present, and some reports associate CPC with cytomegalovirus. The largest study of CPC seen on postnatal cUS in 70 preterm and term infants (age range 1 day to 1 year) reported an incidence of 3%, in our cohort 19.6% had CPC of which 10% were isolated, the remaining cases had abnormal tissue echogenicities but not structural abnormalities.

One explanation for the high rate of SEP and CPC in our study might also be that we performed high-resolution cUS; van Baalen and Versmold found, using high-resolution cUS, that 5% of German infants had CPC, higher than found in other studies.

No study so far has investigated the incidence of SEP and CPC in an African population; we found that both were common in our Ugandan infants. While this might be due to congenital infections such as cytomegalovirus and HIV, the mothers whose infants we scanned had been tested for HIV and only 5% were found positive. In addition, we did not find more SEP or CPC in the infants of HIV-positive mothers than others. TORCH screening was not routine and cytomegalovirus is a possible cause, but it is likely that most mothers have been exposed in childhood and would not have a primary infection in pregnancy. In addition, the SEP were seldom associated with any signs of calcification and the infants were not growth restricted, making significant cytomegalovirus infection unlikely. The reason for the high number of CPC is also unclear. We did not detect dysmorphisms and clinically we did not suspect any metabolic or chromosomal disorders. Only five infants were less than the third centile for weight by WHO criteria (http://www.who.int/childgrowth/standards/en/). Malaria was not common but there may have been illnesses, medications or unusual diets of which we are unaware that might be relevant. Despite a lack of positive evidence, it remains most likely that some infective exposure accounts for these findings. Supportive evidence for this might come from placental examination but this was not available to us.

Many of the infants showed homogeneous increased echogenicity in the peritrigonal WM, either in isolation or in combination with other abnormalities. This phenomenon, described as peritrigonal blush, is considered a normal finding mainly in preterm infants, but it is also seen in normal term infants. It is thought to be due to the orientation of normal WM fibre tracts and their accompanying vasculature, the fibres being perpendicular to the sonographic beam. Whereas this may be normal it was very marked in many infants, more so than we personally have observed in the UK. It might relate to the mean gestational age being only 38.2 weeks, with less mature WM than in full-term infants.

Nine infants had increased and patchy echogenicity in the parieto-occipital WM but none had cystic WM changes or signs of atrophy. Increased echogenicity in WM is seen in bacterial and viral infections. It is the most common cUS finding in newborns with bacterial meningitis, being present and becoming extensive within the first 12–24 h after infection. However, all our infants were clinically well and it is unlikely that this was the cause for the WM appearance. In viral infections, mild but diffuse involvement of the periventricular and deep WM is seen. A few mothers were known to be HIV positive, and maternal antiviral treatment has been associated with abnormalities in the neonatal WM, but this patchy WM change was not more common in infants of HIV-positive mothers. There was no corroborating evidence for cytomegalovirus or other congenital viral infections. We had no evidence for entero, echo, paraecho or parvovirus but these remain a possibility. As with the cysts, it would be useful to know more about the pregnancy history and have placental data.

**Table 5** WM, central grey matter (BG) and haemorrhagic abnormalities: numbers with cysts (SEP/CPC) or calcification (LSV)

<table>
<thead>
<tr>
<th></th>
<th>SEP and CPC (n=5)</th>
<th>SEP only (n=17)</th>
<th>CPC only (n=17)</th>
<th>LSV (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WM and BG score = 0</td>
<td>3 (2.7%)</td>
<td>17 (15%)</td>
<td>11 (10%)</td>
<td>4 (3.6%)</td>
</tr>
<tr>
<td>WM score =1</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>BG score =1</td>
<td>1</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>IVH</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>MCA infarction</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

BG, basal ganglia; CPC, choroid plexus cyst; IVH, intraventricular haemorrhage; LSV, lenticulostriate vasculopathy; MCA, middle cerebral artery; SEP, subependymal pseudocyst; WM, white matter.
Hypoglycaemia can lead to WM injury, particularly occipital, at least in symptomatic term infants. As our infants were well it is unlikely that hypoglycaemia was the cause for the WM changes although blood glucose levels were not checked. In addition, all infants were scanned soon after birth and typically too early to see any effects of hypoglycaemia on WM.

Eight infants had unilateral increased echogenicity in the central grey matter. Unilateral thalamic densities have been described in apparently well term infants and in preterm infants. However, infarction in the territory of the perforator arteries could explain the observation, such perforator strokes not being always associated with acute symptoms. Although the mean age of scanning in our cohort was only 1.4 days, stroke and/or basal ganglia abnormalities would be expected. Hypoxia-ischaemia in which bilateral more diffuse thalamic abnormalities may also result from thalamic haemorrhage related to venous thrombosis usually associated with IVH. However, no IVH was seen in these infants.

We wondered whether the changes we found in the WM and central grey matter might relate to stresses in labour. The mean gestational age of the infants was only 38.2 weeks, in keeping with the data from Balchin and Steer, who found that black UK born infants have a shorter gestation than white European infants. Despite this they found that there was a higher rate of meconium passage and respiratory morbidity, and suggested that these infants may mature earlier and be more susceptible to the normal stresses of labour and delivery. Although delays in delivery were common all the infants we scanned were well grown and had good Apgar scores, and the infants with increased WM and focal grey matter echogenicity had similar delivery profiles to those without those findings.

The long-term significance of the CUS findings in our study is difficult to know. Neurodevelopmental follow-up in our population would be desirable, but logistically difficult. In addition, these children are exposed to many postnatal events that may make the interpretation of subtle neonatal CUS findings difficult. However, if the findings do represent exposure to antenatal infection or delays in delivery it is important to understand whether this has an effect on motor or cognitive outcomes.

This is the first study describing CUS findings in a normal African neonatal population. Our findings suggest that in apparently well Ugandan infants abnormalities detected with CUS are more common than reported in other populations. WM abnormalities, SEP and CPC may be frequent due to a higher incidence of congenital infections, but the cause is uncertain. The findings provide baseline data for comparison with CUS scans from sick infants from similar communities at risk of impaired neurodevelopmental outcomes such as preterm infants and/or infants with neonatal encephalopathy or seizures. The data are also important for studies or trials of neonatal treatments in which CUS will be used to assess progress and predict outcome.

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Competing interests None.

Patient consent Obtained from the mothers.

Ethics approval This study was conducted with the approval of the Institutional Review Board of the Ethics Committee, Medical School, Makerere University, Kampala, Uganda.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

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