# ORIGINAL ARTICLES

# Neural migration disorders studied by cerebral ultrasound and colour Doppler flow imaging

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## Abstract

**Cerebral ultrasound and colour Doppler flow imaging (CDFI) were used to diagnose a wide spectrum of anomalies of cell migration (17 patients): presumed lissencephaly (n=12); schizencephaly of both fused (n=2) and open lips (n=2); hemimegalencephaly (n=1); and subependymal type grey matter heterotopia (n=12). The patients with grey matter heterotopia had irregular ventricular margins (n=10), periventricular hyperechogenic bands (n=12), and/or periventricular hyperechogenic nodules (n=7). Some patients had more than one type of migration disorder as well as other central nervous system malformations. Cerebral ultrasound diagnoses were confirmed by magnetic resonance imaging (MRI) or necropsy.**

**It is concluded that colour Doppler flow imaging is a worthwhile addition to the assessment of brain surface anomalies.**

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Keywords: cerebral ultrasound, neuroblast migration disorders, schizencephaly, colour Doppler flow imaging.

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Disturbances in the early migration of neuroblasts are rare but usually important causes of neurological impairment, such as motor, learning, and behavioural disorders, and epilepsy. The early recognition of neuroblast migration disorders (MD) is important. First, to establish the prognosis of future neurological abnormalities. Second, to make a correct syndromic diagnosis, because MD are an essential feature of chromosomal or genetic syndromes that have a particular rate of recurrence.[1–3]

Early disorders of neural cell migration produce several types of dysgenetic cerebral outcomes: agyria-pachygyria complex (lissencephaly), polymicrogyria, schizencephaly, unilateral megaloencephaly, and grey matter heterotopia.[4] Often, more than one is found in the same brain.

Our understanding of such disorders has been greatly enhanced by the use of high resolution magnetic resonance imaging (MRI).[4–9] There have been few reports on neural migration disorders diagnosed using cerebral ultrasound,[10–16] most reporting some aspect of the different dysgenetic changes that characterise such anomalies.

This paper aims to highlight the usefulness of cerebral ultrasound and colour Doppler flow imaging (CDFI) in the diagnosis of these disorders by describing a full spectrum of neural migration disorders that have been fully identified using this non-invasive method.

## Methods

From January 1991 to December 1993, 6337 cerebral ultrasound scans were performed on 2659 patients in our neonatal division, either during their hospital stay or after discharge. This study focuses on 17 patients who presented with different types of developmental brain anomalies which were studied by cerebral ultrasound and CDFI. The patients' mean birthweights and gestational ages were 2·5 kg (range 1·9–2·8) and 37·3 weeks (range 33–39), respectively (table). In seven patients (cases 1–3, 7, 11, 14, and 16) intrauterine ultrasonography suggested central nervous system (CNS) malformation. In the other 10 patients the cerebral ultrasound studies were made for abnormalities detected in the neonatal period: lumbar myelomeningocele (case 12), macroencephalia (cases 4, 5, and 17), dysmorphic syndrome (cases 6, 8, 9, and 13), forceps injury (case 10), and abnormal neurological assessment (case 15).

Real time sector scans were made using a Toshiba SSH-140 A CDFI system fitted with a 5 MHz probe. The brain was examined on several axes of the coronal, sagittal, and parasagittal planes, through the anterior fontanelle. To evaluate the brain surface, the transducer was angled (tangential plane): in the coronal plane it was angled towards the frontal and occipital brain surface, and in the sagittal planes, towards both hemispheric convexities.

CDFI studies were used to examine the abnormalities of brain surface vascular pattern, especially in those patients with ultrasonographic signs of cortical dysgenesis. All cerebral ultrasound scans were performed by the same researchers (AP and FC), and recorded on videotape.

Unenhanced axial computed tomography (CT) scans were obtained in eight patients

*Patients and neuroimaging findings*

| Case No | Gestational age (week) Birth weight (kg) | Neuronal migration disorders | | | | | | Magnetic resonance imaging | Others (cerebral ultrasound and/or MRI) | Other main diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Cerebral ultrasound | | | | | | | | |
| | | Agyria/ pachygyria | Schizencephaly | Grey matter heterotopia | | | Unilateral megaloencephaly | | | |
| | | | | IVM | B | N | | | | |
| 1 | 34 2·2 | + | Fused lips | + | + | + | | Pachygyria, fused lips schizencephaly, PV grey matter heterotopia (thin layer and focal avoid nodules) | Dysgenesia CC, colpocephaly, Dandy-Walker malformation | Hydrocephalus, hyaline membrane disease |
| 2 | 36 2·8 | | | + | + | + | | PV grey matter heterotopia (thin layer) | Dysgenesia CC, encephalocele | Occipital encephalocele, hydrocephalus, coanae atresia |
| 3 | 39 2·7 | | | + | + | + | | PV grey matter heterotopia (thin layer) | Dysgenesia CC, Chiari malformation | Lumbar myelomeningocele |
| 4 | 33 2·2 | + | | | | | | Frontal agyria, parietal-occipital pachygyria | SE-IVH | Undefined dysmorphic syndrome |
| 5 | 37 3·2 | + | | + | + | | | Pachygyria, grey matter heterotopia (thin layer) | HTBG. Absent frontal interventricular septum. | Undefined dysmorphic syndrome |
| 6 | 36 2·7 | + | | + | + | | | Pachygyria, grey matter heterotopia (thin layer) | Dysgenesia CC, colpocephaly, cerebellar hypoplasia. HTBG | Smith-Lemli-Opitz syndrome |
| 7 | 38 1·9 | + | | | | | | Pachygyria | Ventriculomegaly, calcifications cerebral atrophy, HTBG | Congenital CMV infection |
| 8 | 37 2·2 | + | | + | + | + | | | Dysgenesia CC, cerebellar hypoplasia | Walker-Warburg syndrome |
| 9 | 40 1·9 | | | | | + | | Grey matter heterotopia (thin layer) | HTBG | Fetal alcohol syndrome |
| 10 | 35 2·8 | | | + | + | + | | Grey matter heterotopia (thin layer and ovoid focal nodules) | Megacisterna | Hyaline membrane disease |
| 11 | 39 2·2 | + | | + | + | + | + | Right sided megalencephaly, right temporal-occipital pachygyria, right PV grey matter heterotopia (thin layer and focal ovoid nodules) | | |
| 12 | 39 2·4 | | | + | + | | | PV grey matter heterotopia (thin layer) | Chiari malformation | Lumbar myelomeningocele |
| 13 | 40 2·4 | + | | | | | | Pachygyria (mainly frontal) | Cerebellar hypoplasia | Cornelia de Lange syndrome |
| 14 | 38 3·2 | + | | | | + | | Agyria, PV grey matter heterotopia (thin layer) | Dysgenesia CC and mesencephalon, ventriculomegaly, Dandy Walker malformation | Walker-Warburg syndrome |
| 15 | 39 2·9 | + | Open lips | | | | | Open lips schizencephaly, pachygyria | Dysgenesia CC, colpocephaly | |
| 16 | 38 3·3 | + | Open and fused lips | + | + | + | | Parieto-temoral-occipital pachygiria PV grey matter heterotopia (thin layer and focal ovoid nodules), open and fused lips schizencephaly | Dysgenesia CC, colpocephaly | |
| 17 | 36 2·5 | + | | | | | | Generalised pachygyria | Hydrocephalus, dysgenesia CC PV calcifications, multicystic encephalomalacia, HTBG | Congenital toxoplasma infection |

IVM=irregular ventricular margin; B=band; N=nodule; CC=corpus callosum; SE-IVH=subependymal intraventricular haemorrhage; HTBG=hyperechogenic areas in thalamus and basal ganglia; CMV=cytomegalovirus; PV=periventricular.

(cases 1, 4–7, 10, 14, and 15) using a high resolution technique on continuous 5 mm thick slices.

All patients in the study except case 8 had an MRI scan. The studies were obtained with MRI equipment operating at 0·5 T, with 5 mm thick slices spaced every 2 mm. Spin-echo pulse sequences were performed. T1 weighted 450/25, T2 weighted 2000/100, and proton density weighted 2000/35 MRI scans were obtained.

For computed tomography and MRI studies, patients were sedated with chloral hydrate and monitored by pulse oxymetry and/or cardiorespiratory monitoring during the procedure. All computed tomography and MRI scans were reviewed by one of the authors (AP-H), who was unaware of the cerebral ultrasound diagnosis and clinical condition of the patients. MD and other brain anomalies were diagnosed on the basis of MRI findings. In case 8, an infant who died in the neonatal period, the brain was also studied histologically.

## Results
CEREBRAL ULTRASOUND FINDINGS
*Abnormal gyral development*
Lissencephaly was suggested by the presence of a smooth surfaced brain with poor sulci (fig 1B) and rudimentary sylvian fissures as an expression of absent or incomplete operculation, and absence of sulcation on the interhemispheric face in the coronal planes. Cases 1, 4–8, 11, 13–17 showed these characteristic findings to a variable degree (table). Using CDFI, we identified the middle cerebral artery in the sylvian fissure, in both the coronal and sagittal planes. In these patients the vessel showed a straight course without the normal branching pattern (figs 1A, B). The sulcal arteries on the brain surface were scanty and
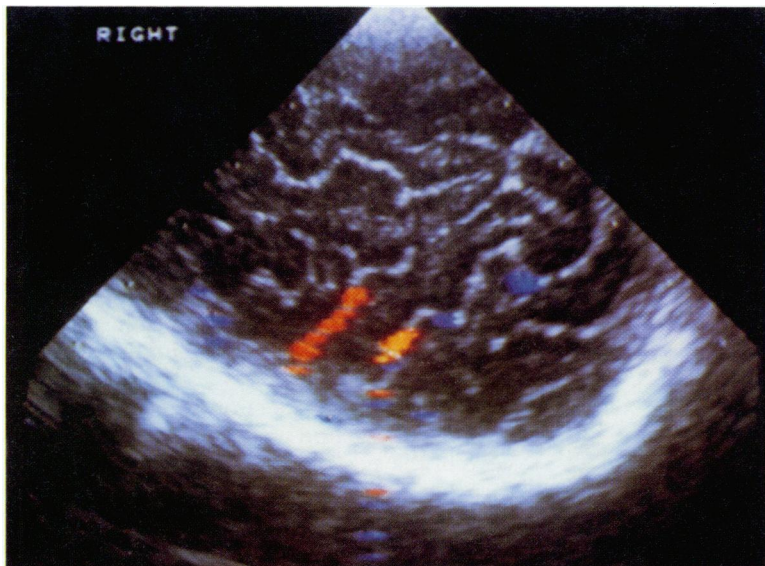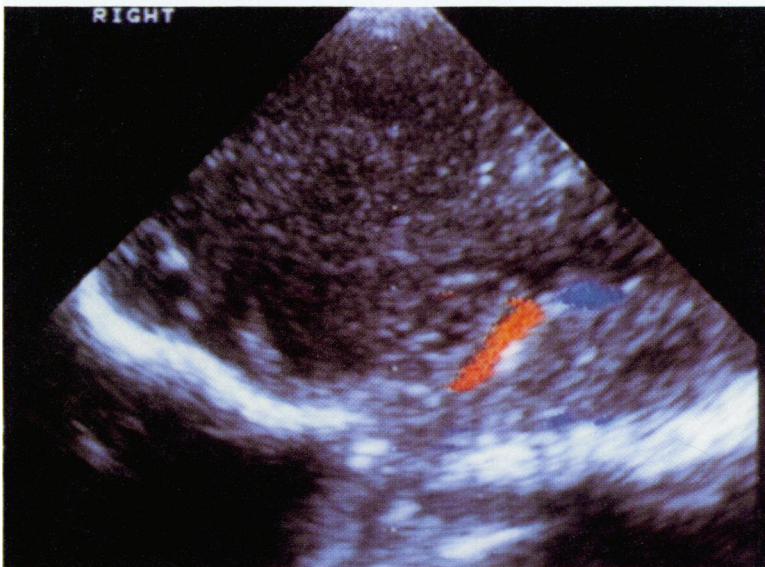
Fig 1A



Fig 1B

*Figure 1    (A) Sagittal sonogram showing a normal brain surface and its vascularisation. (B) Same view in a patient with lissencephalia (case 17). Note smooth surfaced brain with poor sulci. Cerebral vasculature is abnormally reduced.*

did not show the normal sinuosity in patients with poor sulcation (figs 1A, B).

*Grey matter heterotopia of subependymal type*
Three findings were considered to be primary cerebral ultrasound changes suggestive of grey matter heterotopia of the subependymal type. First, irregular ventricles – that is, an irregular outer contour of the lateral ventricles (figs 3A and 4A). Second, a periventricular band, defined as a hyperechogenic (different from the adjacent periventricular white matter but less echogenic than the choroid plexus) ribbon, either continuous or discontinuous, and present in the periventricular region (figs 3A and 4A). And third, a periventricular nodule, when the above mentioned hyperechogenicity had a rounded (or ovoid) appearance, occurred alone or as multiple nodules, and was located close to the ventricular wall, sometimes protruding into the ventricular lumen (fig 3A).

The table lists the patients in our series with such cerebral ultrasound findings (cases 1–3, 5, 6, 8–12, 14, and 16). Ten out of 12 patients had irregular ventricular margins and seven had bands and nodules as well.

*Schizencephaly*
Schizencephaly was suspected when there were breaks along the ventricular wall and in communication between the ventricular lumen and subarachnoid space. This cerebral ultrasound finding was identified as a cleft. Two patients (cases 1 and 16) did not have open communication between these two compartments, so a fused lips schizencephaly was suspected (fig 5A). We also had two cases of open lips schizencephaly (cases 15 and 16). Case 15 had a wide defect; case 16 had a narrow cleft in the occipital horn of the right ventricle (fig 6A).

*Unilateral megaloencephaly*
Unilateral megaloencephaly was considered when there was an interhemispheric asymmetry – that is, the presence of an unilaterally enlarged hemisphere with ipsilateral ventriculomegaly and shifting of the interhemispheric fissure, falx, and superior sagittal sinus to the opposite side (case 11).

OTHER TECHNIQUES
In all cases MRI confirmed the diagnoses of either MD or other associated dysgenetic findings suggested by cerebral ultrasound (figs 3B, 4B, 5C, and 6B) (table). With respect to cortical dysgenesis, the anomalies of the brain surface could be clearly visualised using this technique (table).

Subependymal heterotopias appeared as isointense nodular masses of cortical grey matter of different size and distribution. Very small nodules formed a thin layer of heterotopic grey matter that completely or partially surrounded the lateral ventricles when distributed continuously (fig 4B). Larger, single, or multiple masses of grey matter heterotopia were typified as void focal nodules (table) (fig 3B).

In eight out of 17 patient computed tomography studies were also performed. There was a good correlation between computed tomography and MRI findings in all cases of cortical dysgenesis and/or schizencephaly (fig 5B), but computed tomography scans were not diagnostic of grey matter heterotopia in two patients (cases 5 and 10). MRI and computed tomography scans failed to indicate hyperechogenic areas detected by cerebral ultrasound in the thalamus and basal ganglia (table).

Histopathological evaluation of the brain of case 8 revealed dysgenesis of the corpus callosum and colpocephaly, generalised pachygyria without clear laminar stratification (type II lissencephaly), gross grey matter heterotopia in the subependymal and centrum semiovale regions, and a hypoplastic postero-inferior cerebellar vermix.
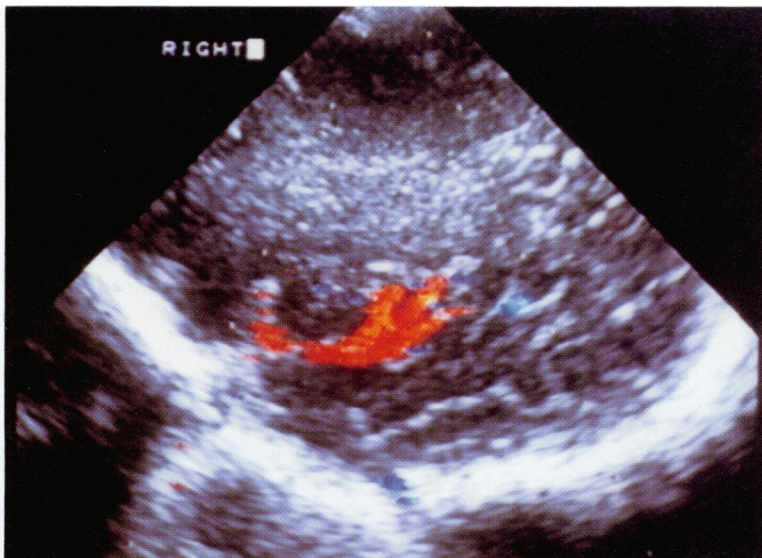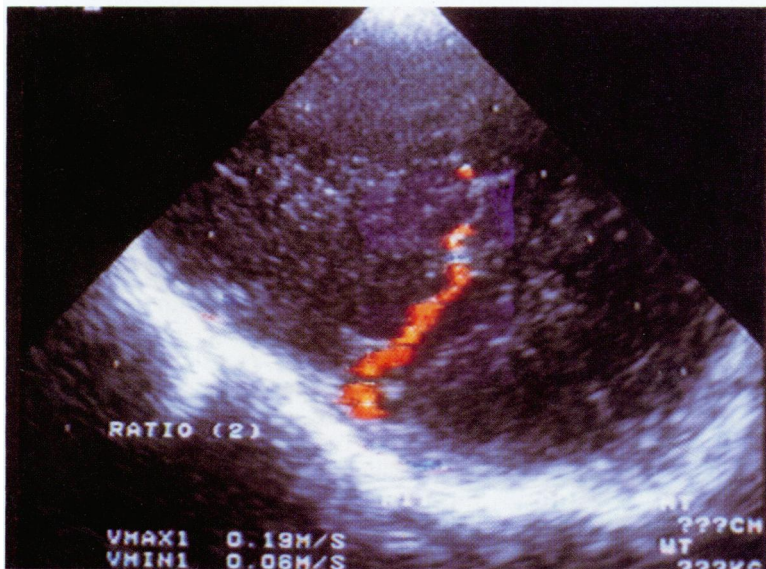
Fig 2A



Fig 2B

*Figure 2   (A) Parasagittal sonogram displaying brain cortex and the middle cerebral artery branching at the level of the sylvian fissure. (B) Sonogram illustrating a poor brain surface sulcation and middle cerebral artery in the sylvian fissure that is straight and without divisions (case 6).*

### Discussion

Almost all malformations of the brain are either primary disorders of neuroblast migration or affect migration secondarily. Disturbances of the process of early neuroblast migration, which occur between weeks eight and 20 of gestation, originate from major cerebral dysplasia. The causes are many and varied. Early neuroblast migration disorders are associated with chromosomal and genetic diseases. Environmental factors and trauma that occur at a critical developmental period can also generate MD.[17] Late migration of neurons from the germinal matrix occurs after week 20 of gestation and extends beyond term.[18] Disorders of this process may be due to acquired lesions occurring during the period of viability for preterm infants. The importance, in terms of subsequent neurological dysfunction, is unknown, and the ability of routine imaging

techniques to diagnose them is probably limited.

As far as we know, the value of cerebral ultrasound for diagnosing MD has not been evaluated completely, although some dysgenetic changes characterising such anomalies have already been described as lissencephaly,[10 13 14] open lips schizencephaly (fig 7),[11 12 15] or hemimegalencephaly.[16] This is the first description of the cerebral ultrasound findings of a full spectrum of early MD in a series of patients. This is important because ultrasonography is the main neuroimaging tool in the neonatal period.

The grey matter heterotopias diagnosed by cerebral ultrasound in this group of patients were of the subependymal type.[6] Nevertheless, their distribution was not consistently symmetrical or bilateral, and band patterns outnumbered nodular patterns in our series. We do not think that this is a new pattern of grey matter heterotopia but, as previously reported,[19] that subependymal heterotopias form nodular masses ranging in diameter from 1 mm to 20 mm. A continuous distribution of smaller nodular masses along the subependymal zone could produce a band image on sonograms. This interpretation is supported by MRI findings[20] in which the heterotopia appears as small nodules suggesting a thin layer of grey matter lining the ventricles (fig 4). Likewise, the irregular ventricular margins are probably the consequence of such nodular displacement and were a consistent finding in these patients except in two cases. In case 9 the ventricular space was almost obliterated and its shape could not be discerned. In contrast, in case 14 the ventricular walls were distended by high intracranial pressure (obstructive hydrocephalus). Alleviation of intracranial pressure might have revealed an irregular ventricular contour. Couture *et al* suggest that the modification of the ventricular margin should evoke the presence of periventricular grey matter heterotopia.[13]

Although grey matter heterotopias are congenital anomalies to be expected in a child with severe dysmorphic features,[4 17 19] they may also be present in patients with otherwise 'minor' CNS malformations. It may be that when these grey matter heterotopias are not diffuse and the normal cortical gyral pattern is conserved, as was the case in some of our patients (table), the disruption of the migration process is less severe.[7] These patients may be almost normal in early childhood, and only later sustain onset of uncontrolled seizures.

Another interesting finding of our study is the diagnosis of fused lips squizencephaly in two patients using cerebral ultrasound. Although computed tomography showed the defect in one patient (case 1), axial computed tomography scans may not identify such anomalies.[4] Thus theoretically, cerebral ultrasound should be better for the diagnosis of small, narrow clefts because different planes can be obtained. Our two cases diagnosed by cerebral ultrasound provide further support for this.

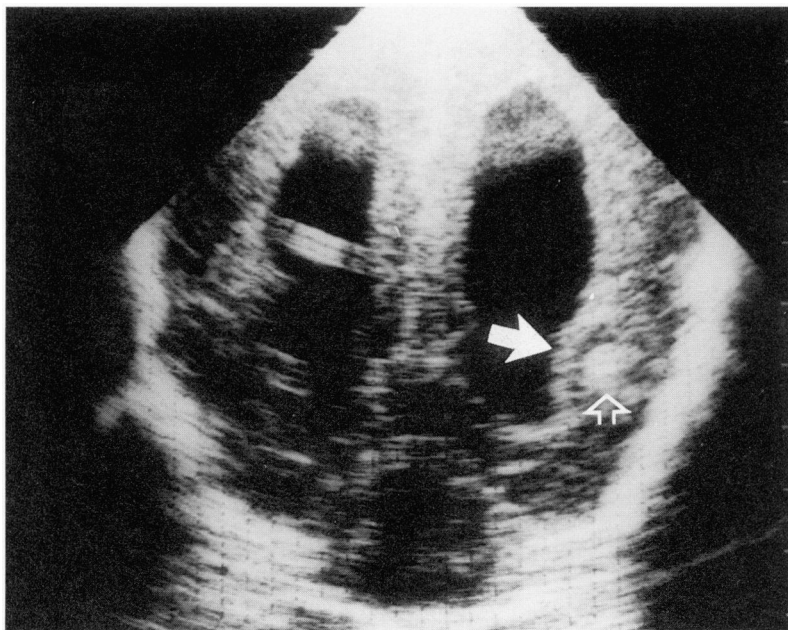Although the resolution of cerebral ultrasound is remarkable, MRI is still needed

Fig 3A

Figure 3 (A) Cerebral ultrasound scan showing bilateral ventriculomegaly of irregular margins in a coronal plane, a periventricular band (arrow), and a periventricular nodule (open arrow) (case 1). (B) T1 weighted MRI scan of an axial plane. Heterotopic grey matter surrounding the lateral ventricles (arrows) and a periventricular ovoid mass of grey matter (open arrow) protruding into the ventricular lumen.
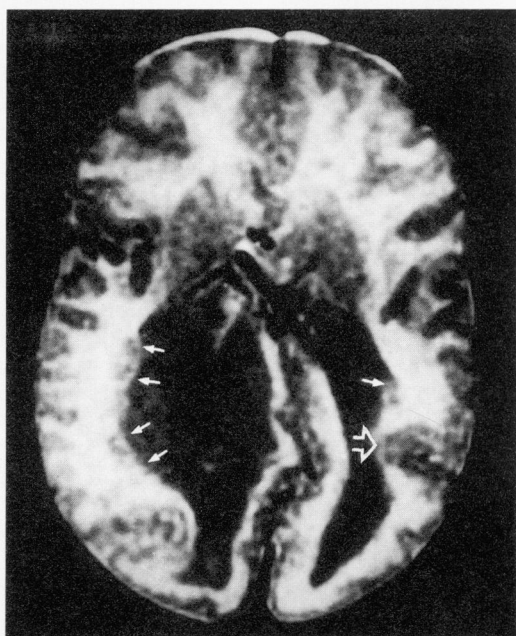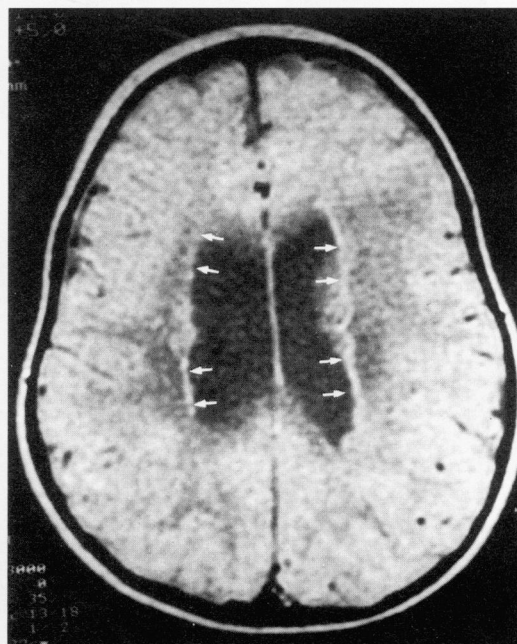


Fig 3B

Fig 4A (Below)



because it is the best technique for differentiating grey from white matter.[6] Sonography was not able to characterise the cortical surface precisely. Although we use the term 'lissencephalic brains', cortical anomalies could be clearly classified by MRI or histology only as agyria-pachygyria complex or polymicrogyria. Computed tomography scans are also limited in the diagnosis of polymicrogyria, possibly because of beam-hardening artefacts created by the bone.[4] Nevertheless, cerebral ultrasound is valuable for detecting brain surface anomalies when patients are mature enough, and so the diagnosis of lissencephaly has been made by cerebral ultrasound at 33 weeks of gestational age.[10] We performed serial cerebral ultrasound in all the patients. The earliest diagnosis of altered gyral development was made in a patient at 33 weeks' postconceptional age and confirmed in the cerebral ultrasound sequential evaluation. High frequency probes (10 MHz) were used to evaluate cortical-subcortical brain damage after hypoxia-ischaemia[21 22] and to identify changes in the brain surface suggestive of altered gyral development.[13] These transducers make it possible to show the brain surface in the projections usually included in routine cerebral ultrasound evaluation. Nevertheless, to visualise the brain surface we used tangential planes and added CDFI to identify both the gyri and the vessels. Murphy *et al*,[23] also using a 5 MHz probe, studied similar tangential planes to evaluate gyral development, and created a scoring system. The combination of cerebral ultrasound and CDFI clearly shows abnormal vascular patterns of the middle cerebral artery in the sylvian fissure and of the sulcal arteries on the brain surface (figs 1 and 2). Thus we found CDFI to be very useful
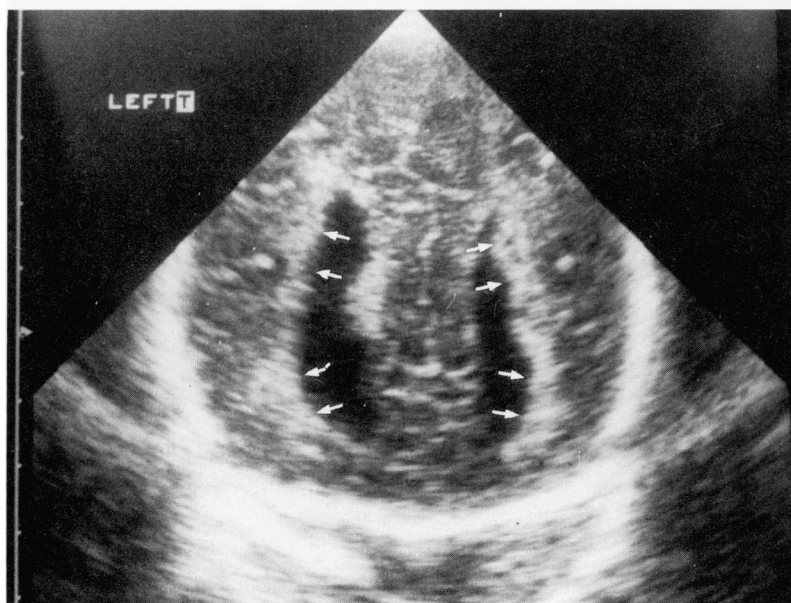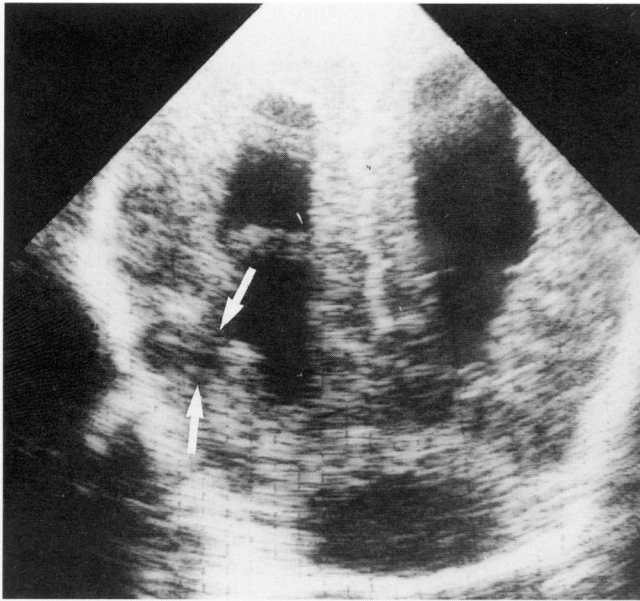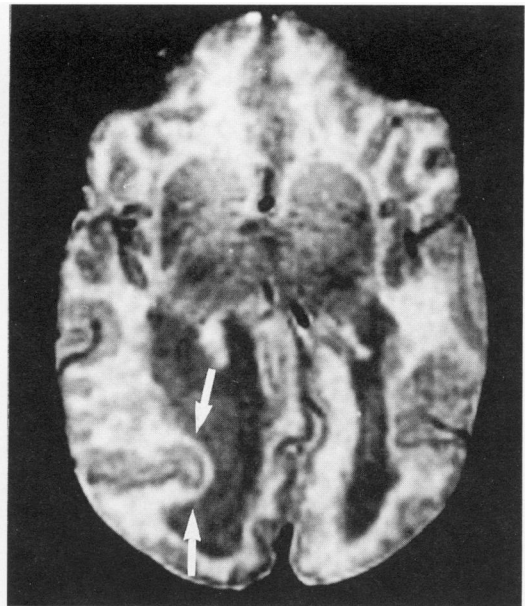


Fig 4B (Above)

Figure 4 (A) Coronal plane cerebral ultrasound scan showing both sides of a periventricular band (arrows) (case 10). (B) Proton density weighted MRI scan of the same patient showing a thin layer of heterotopic grey matter lining the ventricular walls (arrows).

Fig 5A



Fig 5C

*Figure 5 (A) Coronal plane ultrasound scan of case 1, who presented with a cystic malformation of the posterior fossa and a hypoechoic area extending from the bone and through the left hemisphere with no communication with the ventricle (arrows), as well as a hyperechogenic, almost horizontal band inside the hypoechoic zone. (B) Axial computed tomography scan representing the fused lips schyzencephalia (arrows) (C) The same view with T1 weighted MRI confirms the cerebral ultrasound and computed tomography findings (arrows).*



Fig 5B

addition to the assessment of cortical configuration.

We found that cerebral ultrasound and MRI[4][6][7][9][11] were better diagnostic tools for grey matter heterotopias than computed tomography especially for small, focal lesions. On the other hand, neither MRI nor computed tomography recognised hyperechogenic areas
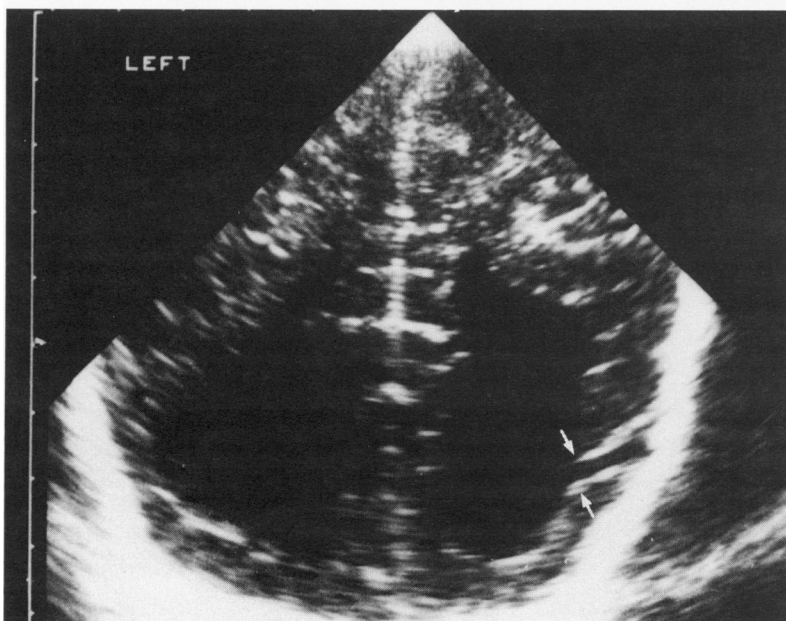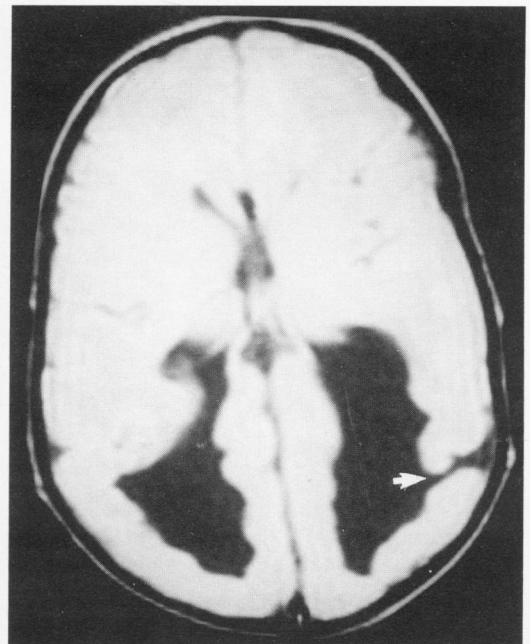


LEFT

Fig 6A



Fig 6B

*Figure 6 (A) Coronal plane sonogram at parietal-occipital level, depicting open lips schyzencephalia (arrows) (case 16). (B) Proton density MRI scan of axial plane confirming the cleft (arrow).*
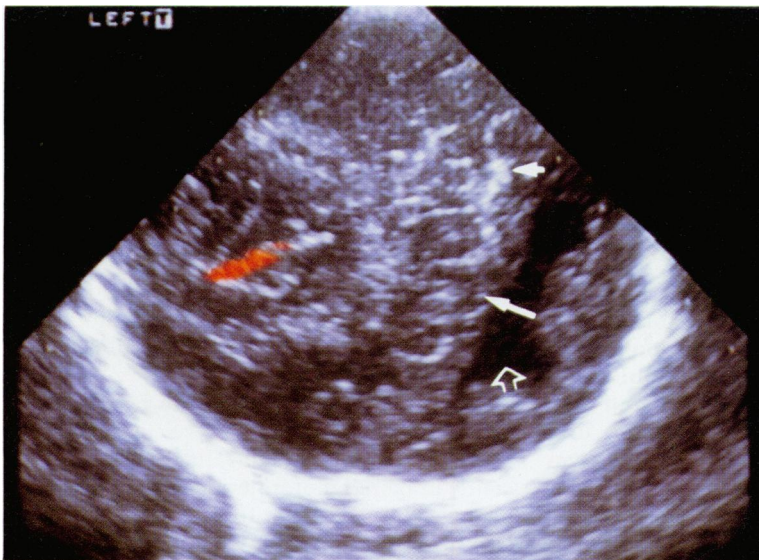
*Figure 7   Open lips schizencephalia surrounded by abnormal cortex and CDFI.*

cerebral ultrasound findings are suggestive of MD, a full MRI study should be done.

detected by cerebral ultrasound in the thalamus and basal ganglia (table), as has been reported before.[24]

The association of MD with other dysgenetic brain anomalies in this series was noteworthy. Barkovich *et al* also noted that the observation of isolated dysgenesis of the corpus callosum is rare and that patients with this anomaly usually are symptomatic, suggesting the presence of other associated congenital brain anomalies.[25] Thus as the index of suspicion rises and more imaging studies are done, a larger number of grey matter heterotopias and/or other types of MD patterns will appear. It is to be expected that the spectrum of neuroimaging abnormalities will correlate with the clinical evolution of these patients.[20]

Finally, we can conclude that, although this study was not designed to assess the value of cerebral ultrasound for diagnosing MD, our results show that certain sonographic findings are suggestive of MD and may be diagnostic of some types.

In summary, cerebral ultrasound is a good method for screening for MD. Tangential planes allow cortical gyral development to be assessed. CDFI improves the sensitivity of cerebral ultrasound by showing abnormalities in the brain surface vascular pattern in cases of abnormal sulcation. Although subependymal grey matter heterotopia usually accompany more complex dysgenetic cerebral disorders, and thus are an indicator of their presence, they may also occur as isolated malformations with an unpredictable prognosis, so these patients must be followed up. In any case when

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