Original Article

Magnetic Resonance Imaging of the Fetal Central Nervous System in Singapore

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Abstract

Introduction: Fetal imaging has improved with the development of faster magnetic resonance imaging (MRI) sequences, obviating the requirement for sedation. It is useful in characterising abnormality of the central nervous system in fetuses with abnormal or equivocal antenatal ultrasound findings. We reviewed all cases of fetal brain and spine MRI performed in our institution. Materials and Methods: All cases of fetal central nervous system MRI imaging from May 2006 to December 2008 were retrospectively reviewed, including fetal MRI, postnatal MRI and autopsy findings. Results: Thirty-one fetuses were imaged with MRI for evaluation of the central nervous system of which 3 were specifically for spinal evaluation. On fetal MRI, there were 11 normal fetuses (2 with minor ventricular asymmetry), 4 fetuses with minor ventriculomegaly and 16 fetuses with significant abnormalities. Twenty-three fetuses were delivered and 8 were terminated. Fifteen of 23 babies underwent postnatal imaging, 21 had clinical follow-up and 2 were lost to clinical follow-up. Of the 11 fetuses reported as normal on fetal MRI, 3 had additional postnatal findings. A fetus with a megacisterna magna on fetal MRI was diagnosed with a posterior fossa arachnoid cyst on postnatal MRI. One, who had fetal MRI to assess suspected absent inferior cerebellar vermis, had intracranial calcifications from rubella infection. One was diagnosed with cerebro-occular-facio-skeletal (COFS) syndrome postnatally, 1 was lost to follow-up and the rest were discharged well. Seven out of 16 fetuses with significantly abnormal fetal MRI findings had confirmation of the findings on postnatal imaging. Postnatal MRI detected 2 cases of polymicrogyria which were not seen on fetal MRI. Autopsy was available in 1 abortus confirming intrauterine diagnosis of Dandy Walker malformation. A myelomeningocele was clinically obvious in 1 abortus. Conclusion: Fetal MRI is a good method of assessing brain and spine abnormalities in utero. However, disorders of neuronal migration remain a challenging diagnostic problem in fetal imaging.

Ann Acad Med Singapore 2009;38:774-81

Key words: FIESTA, Polymicrogyria, Syndromes, Ventriculomegaly

Introduction

Fetal magnetic resonance imaging (MRI) has been performed for 2.5 decades,[1] with fetal motion being a limiting factor in early studies. With the introduction of the faster MRI sequences such as the half-Fourier acquisition single-shot turbo spin echo (HASTE) sequence which can obtain images in just 430 milliseconds,[2] sedation is no longer required for diagnostic images. Although other fast MRI sequences have been utilised in fetal MRI,[3] HASTE and single-shot fast spin echo (SSFESE) T2 remain the mainstay of fetal MRI.[4] Real time MRI[5] allows almost continuous imaging of the moving fetus, using the freshly acquired set of images for orientation, obviating the need for additional scouts and thus improving the efficiency of imaging a moving fetus. No adverse effects have been described on the fetus with a magnet strength of 1.5 Tesla or less.[6,7]

MRI is useful in characterising an abnormality of the central nervous system, showing its full extent as well as detecting associated abnormalities in fetuses with abnormal or equivocal antenatal ultrasound findings. It is particularly useful in complicated cases involving multiple pregnancies where ultrasound may be technically difficult. Currently fetal MRI is most frequently used to image the fetal

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central nervous system.[8] MRI gives important additional information in fetuses shown to have abnormalities on ultrasound.[9] Although cost and expertise are factors that need to be considered before setting up such a unit, fetal MRI is useful at specialised centres, particularly in centres where fetal surgery is performed.

Materials and Methods

This study was approved by KK Women's and Children's Hospital Institutional Review Board and carried out under the HSDP grant number EC200604053. Informed consent was obtained in all cases.

All cases of fetal central nervous system MRI from May 2006 to December 2008 were retrospectively reviewed, including fetal MRI, postnatal MRI and autopsy findings. Assessment of the outcome of live births was based on clinical notes, feedback from referring doctors, and occasionally, the paediatricians looking after the child.

All mothers were screened with a questionnaire for any contraindication to MRI prior to the examination. The mothers were asked to abstain from food for 4 hours prior to the MRI.

MRI was performed on a General Electric 1.5 Tesla machine (General Electric Signa Excite Mallinkrodt), without maternal sedation using a body coil, under the supervision of the radiologists and tailored according to the clinical indication. Fetuses were imaged with FIESTA (Fig. 1) (TR 3.8ms TE 1.9ms, flip angle 60 degrees, bandwidth 125 kHz, slice thickness 2.2mm overlap1.1mm, matrix size 224 x 224, field of view 270 to 330, NEX 1), Single Shot Fast Spin Echo (SSFSE) T2-weighted sequences (TR 2150, TE 83, slice thickness 3 mm with a gap of 1 mm, 256 x 192 matrix, field of view ranging from 270 to 330), T1-weighted sequences (TI 2000, TR 2530, TE 36, slice thickness 3 mm with a gap of 1 mm, matrix size 256 x 192, field of view 270 to 330) and diffusion weighted imaging (TR 7550, TE 87, slice thickness 5 mm with a gap of 2 mm, matrix size 128 x 128, field of view 270 to 330, b=600). The fetal brains were imaged in orthogonal axial, coronal and sagittal planes. Imaging of the fetal spines was performed using sagittal FIESTA sequences (Fig. 2) with targeted axial sequences for any area of concern.

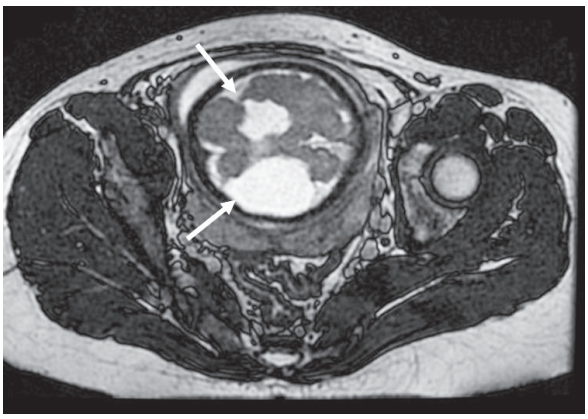


Fig. 1. Case 19: FIESTA fetal MRI sequence showing bilateral open lip schizencephaly (arrows) in a 31-week fetus. Postnatal MRI (not shown) confirmed bilateral schizencephaly with polymicrogyria. Baby had increased tone in all limbs, dystonia and roving nystagmus at 1 year of age.

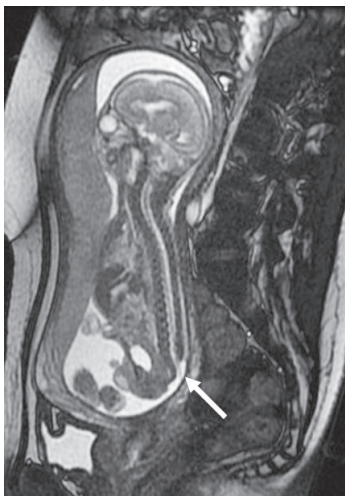


Fig. 2. Case 30: Sagittal fetal MRI image shows a myelomeningocoele (arrow) in a 30-week fetus. This pregnancy was terminated and abortus had an obvious myelomeningogoele.

Assessment of all MRI studies was performed by 2 unblinded radiologists. Ventriculomegaly on fetal MRI was defined as the size of the ventricle equal or exceeding 10 mm, measured at the atrium of the lateral ventricle on an axial section of the brain.[10] Outcome was classified as poor if the children had neurodevelopmental impairment.

From May 2006 to December 2008, 31 fetuses underwent MRI for an evaluation of the central nervous system. Twenty-five patients were selected from the 2,220 cases discussed at Birth Defect Rounds, and 6 patients were referred from other hospitals and private clinics. There were 27 singletons, 3 twin pregnancies with the demise of 1 twin, and 1 triplet. MRIs were performed between 13 and 35 weeks of gestation (average of 25 weeks gestation; median of 23 weeks gestation). One mother underwent MRI twice during the 2nd trimester. Maternal age ranged from 18 to 38 years with an average age of 29 years and a median age of 30 years.

All fetuses were imaged with FIESTA, 15 fetuses with SSFSE T2-weighted sequences, 24 with T1-weighted sequences and 11 fetuses with diffusion weighted imaging. Imaging of the 3 fetal spines was performed using FIESTA sequences.

The time taken for each MRI ranged from 13 minutes to 135 minutes with an average time of 48 minutes (median time of 45 minutes).

The fetal MRI findings, outcome following MRI, child's postnatal imaging and development are presented in Table 1.

Indication for Fetal MRI

Cases referred by obstetricians for fetal MRI was demise of one twin in 3 cases and maternal autoimmune thrombocytopenia in 1 case. The other cases were referred due to abnormal antenatal ultrasound findings of spinal abnormalities in 3 cases, cranial structural abnormalities in 16, ventriculomegaly in 7 cases (1 of which had marked ventriculomegaly) and prominent cisterna magna in 1 case.

Fetal MRI Findings

On fetal MRI, there were 11 normal fetuses (Cases 1 to 11 in Table 1) and 4 fetuses with minor minor ventriculomegaly ranging from 11mm to 13mm (Cases 12 to 15 in Table 1). Sixteen fetuses had significant abnormalities on fetal MRI (Cases 16 to 31), consisting of encephalo/myelocoeles, structural malformations, brain destruction (Fig. 3) and severe ventriculomegaly.

Results

Twenty-three fetuses were delivered and 8 were terminated. Twenty-one babies had clinical follow-up and 2 (Cases 11 and 23) were lost to follow-up as they were delivered outside the country. Of the 11 fetuses reported as normal on fetal MRI, 5 were discharged well without further postnatal imaging, 2 were well and had normal postnatal ultrasound study, 1 was lost to follow-up, but 3 babies had abnormal postnatal findings (Cases 6, 7, 8). Case 7 had a megacisterna magnum on fetal MRI which was diagnosed as a posterior cranial fossa arachnoid cyst on postnatal MR as there was more mass effect (Fig. 4). Case 8 had neonatal jaundice and rubella infection, and postnatal CT detected intracranial calcifications not seen on fetal MRI. Case 6 was born with dysmorphic facial features, limb abnormalities,

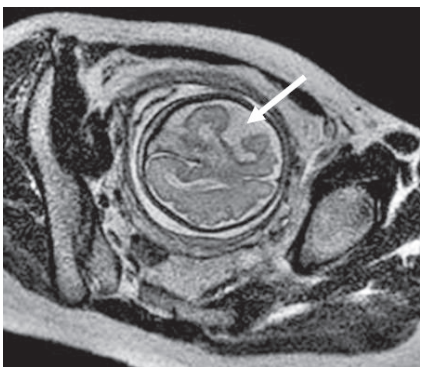
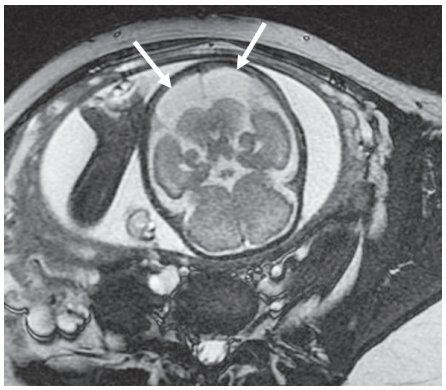


Fig. 3. Case 18: Fetal MRI shows in utero destruction of the left cerebral hemisphere (arrow) in a 29-week fetus. Baby developed increased tone in right arm and both lower limbs but was able to walk at 2 years 3 months after physiotherapy.



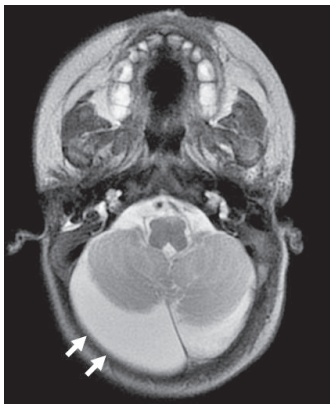


Fig. 4. Case 7: (a) Antental MRI shows megacisterna magna (arrows) in a 30-week fetus while (b) postnatal MRI done 3 weeks after birth shows a posterior fossa arachnoid cyst (arrowheads). Baby was developmentally normal at 2 months.

cataracts, but a normal postnatal brain MRI. The baby was finally diagnosed with cerebro-ocular-facio-skeletal (COFS) syndrome.

For the 4 fetuses with minor ventriculomegaly, all the babies were carried to term and well at last follow-up. Two babies were delivered by caesarean sections for unrelated reasons, and 2 were delivered vaginally. The ventriculomegaly resolved on follow-up postnatal cranial ultrasound in 1 baby (Case 12). One baby (Case 13) had bilateral subependymal cysts in the caudothalamic grooves on postnatal cranial ultrasound but was discharged well and 1 (Case 14) continued to have asymmetrical but undilated ventricles on postnatal cranial ultrasound. One baby, who did not have postnatal imaging, had normal developmental milestones.

There were 16 fetuses with significant abnormalities on MRI which resulted in 8 live births (1 delivered outside the country and was lost to follow-up), 7 terminated pregnancies, and selective fetocide on a fetus in a triplet pregnancy (Case 31). Seven babies had postnatal MRI confirming all the abnormal fetal MRI findings. In addition, 2 babies also had polymicrogyria on postnatal MRI that was not detected on fetal MRI. Autopsy was available in only 1 abortus (Case 24) confirming intrauterine diagnosis of Dandy Walker

Table 1. Fetal MRI Findings, Outcome Following MRI, Child's Postnatal Imaging and Development

Case	Indication for fetal MRI	Gestational age at MRI	Fetal MRI findings	Outcome	Postnatal imaging	Child's development
1	Alloimmune thrombocytopenia	31 weeks	Normal	Live birth	Nil	Normal
2	Demise of 1 twin	32 weeks	Normal	Live birth	Nil	Normal, returned to France.
3	Demise of 1 twin	32 weeks	Normal	Live birth	Nil	Normal
4	Demise of 1 twin	32 weeks	Normal	Live birth	Cranial ultrasound normal.	Normal
5	Left scalp cyst	13 weeks	Normal	Live birth	Nil	Normal, Left focal alopecia.
6	Hypoechoic mass in cerebral hemisphere, dilated ventricle	22 weeks	Normal	Live birth	Postnatal MRI normal.	Premature at 34 weeks. Microcephaly, dysmorphic with sloping forehead, broad nasal bridge, thin upper lip, smooth philtrum, cataracts, campylodactyly bilateral 3rd and right 4th fingers, adducted thumbs, rocker bottom feet, limited extension of elbows and knees, dislocated hips, overlapping left toes. Diagnosd as cerebro-oculo-facio-skeletal (COFS) syndrome. Able to sit with help at 1 year of age.
7	Megacisterna magna 16mm	30 weeks	Normal. Megacisterna magna	Live birth	Postnatal MRI showed posterior fossa arachnoid cyst.	Normal development at 2 months.
8	Absent inferior vermis	22 weeks	Normal	Live birth	Calcifications in deep white matter and basal ganglia on CT from congenital rubella infection. (Baby's Rubella Ig M positive.)	Cataract operation done.
9	Dilated left posterior horn	32 weeks	Normal. Asymmetrical posterior horns L 9mm (resolved on follow up antenatal ultrasound).	Live Birth	Cranial ultrasound normal.	Well at 1 month.
10	Borderline right VM. Absence of cavum months.	22 weeks	Normal. R 9mm, L 6mm, cavum present.	Live birth	Nil	Well according to mother at 10
11	Small inferior vermis	20 and 24 weeks	Normal for gestational age.	Live birth	Nil	Baby delivered in India.
12	Bilateral VM	23 weeks	Minor VM R 10mm L 11mm.	Live birth	Postnatal ultrasound normal.	Head circumference 3rd centile at birth and at 6 months, otherwise normal.

13	Bilateral VM	20 weeks	Bilateral mild VM R 12 L 11mm normalizing on follow up antenatal ultrasound scan.	Live birth	Postnatal ultrasound showed bilateral subependymal cysts in right and left caudothalamic grooves measuring 1.7 x 0.4 cm and 1.8 x 0.6 cm respectively.	Was discharged well.
14	Left VM	32 weeks	L mild VM 13mm.	Live birth	Asymmetrical undilated ventricles with left ventricle slightly more prominent on ultrasound.	Admitted at 11months for gastroenteritis. No other problems.
15	Borderline VM	21 weeks	Isolated bilateral mild ventriculomegaly (11mm).	Live birth	Nil	Normal developmental milestones.
16	Frontal encephalocele	35 weeks	Fronto-ethmoidal encephalocoele.	Live birth	Frontal encephalocoele on CT and MRI.	Encephalocoele excised at 3.5 months of age. Well with normal milestones at 6months.
17	Septo-optic dysplasia	26 weeks	Poor visualisation of cavum septum pellucidum. Optic nerves seen.	Live birth .	Absent cavum septum pellucidum, R polymicrogyria, heterotopia on MRI	Clinical follow-up normal development at 18 months.
18	Porencephaly, schizencephaly	29 weeks	Defect in left fronto-parietal part of brain suggesting	Live birth	Porencephaly antenatal insult, past haemorrhage on MRI.	Moved all 4 limbs at birth. Developed increased tone R arm and both lower limbs, able to walk at 2 years 3 months after porencephaly.
19	Missing left brain cortex at 31 weeks	31 weeks	Bilateral schizencephaly.	Live birth	Bilateral open lip schizencephaly and bilateral polymicrogyria on MRI.	Increased tone all 4 limbs with marked dystonia and roving nystagmus at 1 year of age.
20	Family history of sex-linked hydrocephalus	27 weeks	VM R 31mm L 33mm.	Live birth	Marked hydrocephalus, Aqueductal stenosis on ultrasound, CT and MRI.	Shunted, developed subdurals which were in turn drained. Diagnosed to have L1 gene spectrum. Has increased tone in the lower limbs since birth. At 8 months, unable to roll or sit.
21	arachnoid cyst	22 weeks	Possible interhemispheric cyst, may have a dysgenetic corpus callosum.	Live birth	Partial agenesis of the corpus callosum, interhemispheric cyst on MRI.	Normal development at 1 year. Able to stand, walks with support, transfers with with hands, stacks cups, draws with pen. Seckel syndrome with high nasal bridge, beaked nose, sloping forehead, microcephaly.
22	Low sacral meningocoele	21 weeks	Sacral meningocoele.	Live birth	Open spina bifid a and meningomyelocoele on MRI.	Operated, developed a syrinx on follow-up spine MRI performed at 9 months of age

23	Bilateral VM	27 weeks	Thining of occipital cortex and subendymal cysts in the frontal regions, bilateral VM, atrial ventricular diameter 15mm each.	Live birth	Nil	Baby delivered in India.
24	Posterior fossa cyst	19 weeks	Dandy Walker malformation.	Aborted	Nil	Post mortem diagnosed Dandy Walker malformation, cystic renal dysplasia, post axial polydactyly.
25	Occipital encephalocele	15 weeks	Occipital encephalocoele including ventricle.	Aborted	Nil	Nil
26	Dysplastic inferior vermis	23 weeks	Dandy-Walker variant, asymmetrical ventricles.	Aborted	Nil	Nil
27	Hypoplastic corpus callosum, VM	21 weeks	Agenesis of corpus callosum, colpocephaly.	Aborted	Nil	Nil
28	Agenesis of the corpus callosum and VM	23 weeks	Agenesis of the corpus callosum and VM R 11 L 15.	Aborted	Nil	Nil
29	Complete agenesis of the corpus callosum.	23 weeks	Complete agenesis of the corpus callosum, megacisterna magna.	Aborted	Nil	Nil
30	Spinal lipoma?	30 weeks	Spinal myelomeningocoele.	Aborted	Nil	Clinically apparent myelomeningocoele
31	Spinal bifida triplet A	20 weeks	Spinal bifida and lumbosacral myelomeningocoele.	Therapeutic Fetocide triplet A. Triplet B and C delivered healthy.	Nil	Nil

VM: ventriculomegaly

R: right lateral ventricular atrial diameter

L: left lateral ventricular atrial diameter

malformation. A myelomeningocele was clinically obvious in 1 abortus (Case 30) and was confirmed on post-mortem ultrasonography. No post mortem was available in the other 6 abortuses.

Clinical outcome data is limited as the oldest child from our cohort is only 2 years 3 months old. Based on this short-term follow-up data, all the babies with normal or isolated minor abnormalities of the ventricles on fetal MRI had good outcomes apart from the child who had congenital rubella infection (Case 8) and the baby with COFS (Case 6). For the babies with significant abnormalities seen on fetal MRI, the impairment is related to the location of the abnormality. Three babies were diagnosed with syndromes. The diagnosis of COFS syndrome was made based on a cluster of physical signs such as facial dysmorphism, limited joint mobility and cataracts. The baby with severe ventriculomegaly (Case 20) was diagnosed to have L1 syndrome/CRASH spectrum (Corpus callosal abnormality, mental Retardation, Adducted thumbs, Spasticity both lower limbs, Hydrocephalus). A baby with partial agenesis of the corpus callosum and interhemispheric cyst (Case 21) was diagnosed with Seckel syndrome based on typical facial features.

Discussion

Of the 11 fetuses with normal fetal MRI, 6 were presumably normal, 1 was lost to follow-up and 4 had differing postnatal findings. Of these 4, 2 (cases 5 and 7) were minor differences whilst 2 (Cases 6 & 8) had significant additional findings: 1 with COFS and the other with congenital rubella. COFS is a rare autosomal recessive syndrome of facial dysmorphism and limb abnormalities.[11] Even though some of the brain abnormalities associated with it (corpus callosal defect, abnormal deep grey nuclei configuration and neuronal heterotopia),[12] may be detected on fetal MRI, demonstration of the anomalies in other extracranial structures can require a significant amount of MRI time and is probably not feasible on fetal MRI which was performed specifically for the brain. COFS-associated microcephaly could have been sought if cranial biometry was used, but this was deemed unnecessary given that biometry had been performed as part of the prior ultrasound examination. In the child with calcifications associated with congenital rubella, small CT-visible calcific lesions may be missed on MRI, or they may have developed after the fetal MRI, which was performed during the 2nd trimester. Those cases with minor differences between fetal MRI and postnatal findings included Case 5 and 7. Case 5 had a scalp cyst that was clearly demonstrated on ultrasound, but could not be detected by MRI. Postnatally, the baby was well apart from a patch of alopecia that corresponded to the location of the scalp cyst. The cyst was no longer clinically evident. Fetal MRI is known to have lower spatial resolution compared to ultrasound, and the lack of visualisation of the thin cyst wall probably accounts for the non-visualisation of the scalp cyst in this case. Megacisterna magna on fetal MRI in 1 baby was reported as a posterior fossa arachnoid cyst on postnatal MRI due to the slightly greater mass effect of this cyst, although this did not result in change in management.

For the 4 fetuses with minor ventriculomegaly on fetal MRI, all were well at last follow-up. Most babies with normal or minor isolated ventricular abnormalities on fetal MRI have good outcomes consistent with the literature.[13] Ventriculomegaly in some fetuses is known to resolve in utero[14] and the prognosis of minor ventriculomegaly is related to the presence of additional abnormalities. Fetal MRI can detect up to 50% of sonographically occult abnormalities of the central nervous system in fetuses with ventriculomegaly[5] and is a useful tool for diagnosing additional abnormalities which may result in a less favourable outcome. It is thought that the baby with bilateral subependymal cysts who was discharged well developed these long after the fetal MRI as they were not present on the subsequent antenatal ultrasound which showed resolution of the ventriculomegaly seen on fetal MRI.

For the 16 fetuses with significant fetal MRI abnormalities, the abnormal fetal MRI findings were confirmed with postnatal MRI in 7 and by inspection of the abortuses in 2. Six fetuses were aborted without autopsy, and one was lost to follow-up. Among 7 abnormal fetal MRI studies, postnatal imaging revealed additional abnormalities of the central nervous system in 2 (Cases 17 and 19) and 2 other patients (Cases 20 and 21) had additional syndromic abnormalities not phenotypically apparent on imaging. In Cases 17 and 19, postnatal MRI detected 2 cases of polymicrogyria which were not seen on fetal MRI. Polymicrogyria can occur secondary to ischaemic insults or infections during pregnancy and some have been linked to syndromes, and it is therefore not surprising that these 2 patients also had schizencephaly and absent septum pellucidum.[15] Its manifestation will probably be related to the underlying etiology and its visibility is also dependant on the timing of the MRI. Although polymicrogyria and other forms of neuronal migration have been reported on fetal MRI, the accuracy of such diagnoses on antenatal imaging has not been firmly established.[16]

In 2 patients, abnormal fetal MRI findings were part of underlying syndromes: L1 gene spectrum and Seckel syndrome. The entity, formerly called CRASH syndrome, is now known as the L1 gene spectrum and its manifestations is related to the degree of severity of the L1 gene mutation.[17] It should be a diagnosis to be considered in male fetuses with hydrocephalus and relevant family history, as in case 20, since the mode of inheritance is X-linked. The ventriculomegaly may not be apparent on first trimester imaging but the diagnosis of such a syndrome can be made

from genomic data obtained from chorionic villi sampling at 10 to 15 weeks of gestation.[18] Seckel syndrome was diagnosed based on a bird-like head postnatally and recent reports have suggested the possibility of antenatal imaging diagnosis.[19,20] Prenatal diagnosis of such syndromes is of relevance if the parents of such babies plan for future pregnancies. However, antenatal diagnosis may be difficult due to their subtle features requiring a high level of suspicion. This usually requires good communication and co-operation between the parents, paediatrician, obstetrician, geneticist and radiologist.

For the fetuses that were terminated, fetal MRI concurred with the antenatal ultrasound findings. Post-mortem may not be readily available as it is dependent on parental consent, hence some workers have used MRI to image the abortus as an adjunct to autopsy.[21]

Timing of the fetal MRI is important if termination of pregnancy is an option. In Singapore, the legal limit for termination of pregnancy is 24 weeks. Beyond 24 weeks, termination of pregnancy in Singapore is only to be carried out if it is immediately necessary to save the life or to prevent grave permanent injury to the physical or mental health of the pregnant woman, and for certain forms of severe or lethal fetal malformations.[22] Hence, if the 20-week antenatal ultrasound is suspicious, there exists a 1-month window of opportunity to perform confirmatory MRI to better characterise the anomaly, especially central nervous system abnormalities which can be lethal or disabling. In our study, not all of the mothers were considering termination of pregnancy, hence the larger number of patients scanned beyond 24 weeks.

Conclusion

Fetal MRI is a good method of assessing brain and spine abnormalities in utero. It can be used to detect additional abnormalities in fetuses shown to have ventriculomegaly on antenatal ultrasound. Disorders of neuronal migration remain a challenging diagnostic problem in fetal imaging. Imaging findings in syndromes may be subtle and require high clinical suspicion and a multi-disciplinary approach.

Acknowledgements

The authors wish to thank the MRI radiographers (Salem Koh, Tan Ker Sin, James Gu) for their technical support and Ms Coleen Beck (Assistant Manager, Department of Diagnostic Imaging) for her help in co-ordinating the MRI scans.

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