Clinical Radiology 74 (2019) 408.e19–408.e25

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.clinicalradiologyonline.net

T2 prolongation in the cerebellar vermis on prenatal MRI of fetuses with Chiari 2 malformations

H.M. Warner [a,b], R. Batty [b], F.M. Warner [c,d], E.M. Fanou [e], P.D. Griffiths [a,*]

[a] Academic Unit of Radiology, University of Sheffield, Sheffield, UK
[b] Department of Radiology, Sheffield Teaching Hospitals Foundation Trust, Sheffield, UK
[c] School of Kinesiology, University of British Columbia, Vancouver, BC, Canada
[d] International Collaboration on Repair Discoveries (ICORD), University of British Columbia, Vancouver, BC, Canada
[e] Department of Neuroradiology, Atkinson Morley Ward, St George's Hospital, London, UK

ARTICLE INFORMATION

Article history:
Received 26 November 2017
Accepted 15 January 2019

AIM: To describe a new finding in fetuses with Chiari 2 malformations recognised at *in utero* (iu) magnetic resonance imaging (MRI), specifically T2 prolongation (high signal) in the cerebellar vermis.

MATERIALS AND METHODS: This was a prospective observational study of iuMRI studies performed at two time points on 20 fetuses with Chiari 2 malformations and 10 control fetuses at the same time points. High T2 signal in the cerebellar vermis was noted and correlated with posterior fossa dimensions was assessed.

RESULTS: High T2 signal in the cerebellar vermis was found in over half of the fetuses with a Chiari 2 malformation, but was not correlated with the degree of reduction in size of the bony posterior fossa.

CONCLUSION: The present findings suggest that abnormal high T2 signal in the cerebellum is common in fetuses with Chiari 2 malformations and although the cause of the signal change is not known at present it may represent vasogenic oedema as a result of restricted venous drainage.

Introduction

Open spinal dysraphism (OSD) is a term used to describe a class of developmental spine abnormalities resulting from abnormal closure of the neural tube. It is defined by the presence of a plaque of abnormal neural tissue without overlying skin coverage: a "placode". The commonest types of OSD, myelomeningoceles and myeloceles, are distinguished by the degree of protrusion of the placode from the skin surface.[1,2] The Chiari 2 (Ch2) malformation is a developmental anomaly of the cerebellum, brain stem, and cervical cord accompanied by a small bony posterior fossa and frequently, but not consistently, associated with OSD.

The post-natal imaging features of the Ch2 malformation are well described and include: inferior displacement of the medulla, downward herniation of the cerebellar vermis through the foramen magnum, vertically orientated fourth ventricle, superior herniation of the cerebellum through the

* Guarantor and correspondent: P. D. Griffiths
E-mail address: p.griffiths@sheffield.ac.uk (P.D. Griffiths).

https://doi.org/10.1016/j.crad.2019.01.001
0009-9260/

Table 1
A summary of skull circumference, area of the posterior fossa, area of the vermis, and transverse cerebellar diameter in the fetuses with Ch2 and age-matched controls at two time points (20–24 and 30–32 weeks gestation).

	Trigone diameter (mm)	Skull circumference (mm)	Mid sagittal vermis (mm^2)	Bony posterior fossa (mm^2)	Transcerebellar diameter (mm)	Tonsillar depth (mm)
Control group (SD) n=10	6.57 (1.65)	194.5 (21.97)	83 (19.26)	338.16 (61.38)	210 (22.2)	n/a
Chiari group (SD) n=20	11.65 (3.68)	185.3 (19.69)	81.76 (22.69)	207.47 (44.51)	185 (29.5)	9.9 (3.22)

See text for details.

tentorium, and abnormalities of the quadrigeminal plate.[3,4] Associated abnormalities such as ventriculomegaly (VM) and hypoplasia of the corpus callosum are common. The clinical sequelae of that malformation are variable but approximately one-third of children have some clinical problems relating to their Ch2 by the age of 5 years old. Children under 2 years old may present with respiratory distress, recurrent aspirations, or severe hydrocephalus, whereas older children tend to present with ataxia and/or symptoms and signs of syringomyelia.[5,6]

Most of the anatomical features of Ch2 malformations and the associated pathologies described above are readily recognisable on *in utero* (iu) magnetic resonance imaging (MRI).[7] In the early stages of the iuMRI programme, a feature that is not described on post-natal imaging was recognised, namely, T2 prolongation (high signal) in the cerebellar vermis that may extend into the medial portions of the cerebellar hemispheres. The aim of the present study was to assess how common that feature was, to try to ascertain if this was a transient feature, and to gain insight into its aetiology.

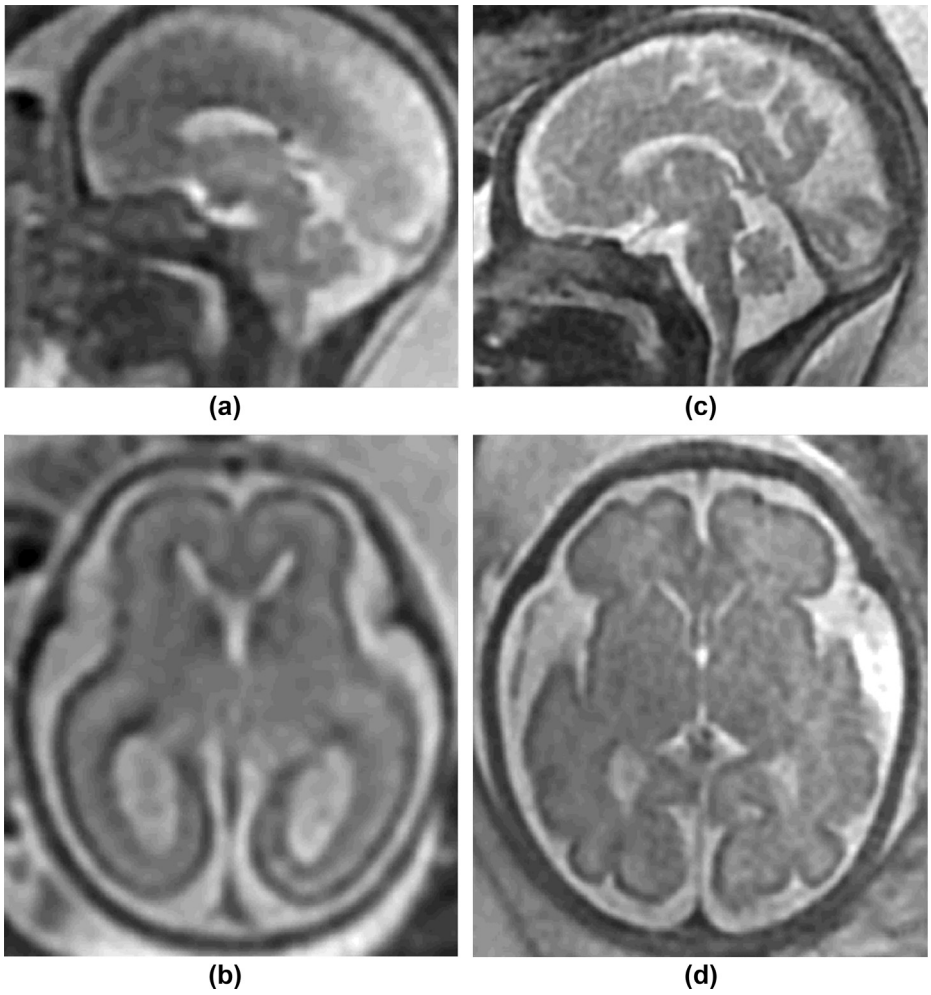

Figure 1 iuMRI images from a control fetus. (a) Sagittal and (b) axial images and at 22 weeks gestation and (c–d) equivalent images at 31 weeks gestation. Note that (a) the cerebellar vermis is well above the foramen magnum, (b) there is abundant CSF around the cerebellum, (c) there is abundant CSF over the cerebral hemispheres and (d) normal-sized lateral ventricles.

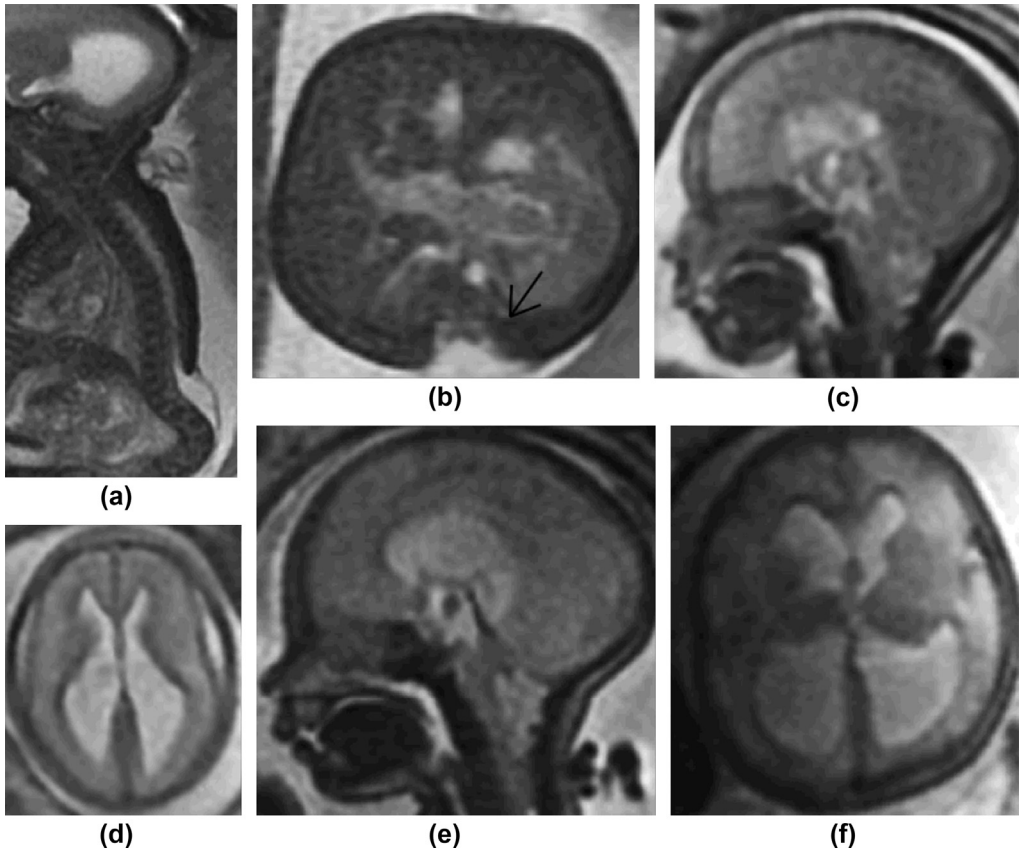

Figure 2 iuMRI images of a fetus with a myelomeningocele and Ch2 malformation at (a–c) 22 weeks and at (d–f) 31 weeks. (a,b) Sagittal and axial imaging of the spine show the open spinal dysraphism (marked with an arrow on axial imaging). (c) Sagittal imaging of the brain shows relatively minor descent of the cerebellar vermis below the foramen magnum and no T2-weighted signal abnormality in the vermis at 22 weeks, whereas at 31 weeks there is marked descent of the vermis and abnormal T2-weighted signal (e). (d,f) There was progressive VM and increasing effacement of the external CSF spaces.

Materials and methods

This was a prospective, observational study of fetuses with OSD and Ch2 malformations detected on ante-natal ultrasonography and confirmed on iuMRI. The "pathology" cohort consisted of 20 consecutive fetuses with Ch2 (identified primarily by descent of cerebellar tissue below the foramen magnum with an OSD and various associated features as previously described) who had two iuMRI studies, one in the second trimester (20–24 weeks gestation) and the other in the third trimester (30–32 weeks gestation). Ten pregnant women with normal fetuses acted as a "control" group and they also had two iuMRI studies at the same stages of pregnancy as the Ch2 group. Those women had iuMRI studies because their fetus was at an increased risk of a fetal brain malformation based on abnormalities in an earlier pregnancy, but had no abnormalities on ante-natal ultrasound and iuMRI examinations and had normal clinical outcomes. All of the pregnant women were referred by fetal medicine consultants working in seven centres in the UK over a 5-year period. The participants had no known or suspected contraindications to iuMRI and entered the study as research volunteers after providing informed written consent under the guidance and approval of the Institutional Research Ethics Committee. The participants were not paid for their involvement in the study, but travel expenses were offered to them and a companion. In addition, relevant review was sought, and approval obtained, from the Institutional Clinical Effectiveness Unit and Research Department to allow cases performed for clinical purposes to be reported in this paper.

All iuMRI examinations were performed at MRI research facilities on a whole-body 1.5 T system (either Infinion, Philips Medical Systems, Cleveland, OH, USA, or HDx, General Electric Healthcare, Waukesha, WI, USA) using flexible phased-array body coils. The standard iuMRI protocol has been described in detail elsewhere,[8,9] but in brief, consisted of single-shot fast spin-echo (ssFSE) T2-weighted sequences in the three orthogonal planes, axial ultrafast T1-weighted imaging, and diffusion-weighted imaging in the axial and/or sagittal planes. All iuMRI examinations were reported for clinical purposes at the time of the original studies, but were re-reviewed by a team of experienced paediatric neuroradiologists for the purposes of this study. Visual assessment of the fetal spine and brain confirmed the presence of an OSD (19 myelomeningoceles, one myelocele) and Ch2 malformations using standard clinical criteria. An assessment of the T2 signal of the cerebellar vermis was

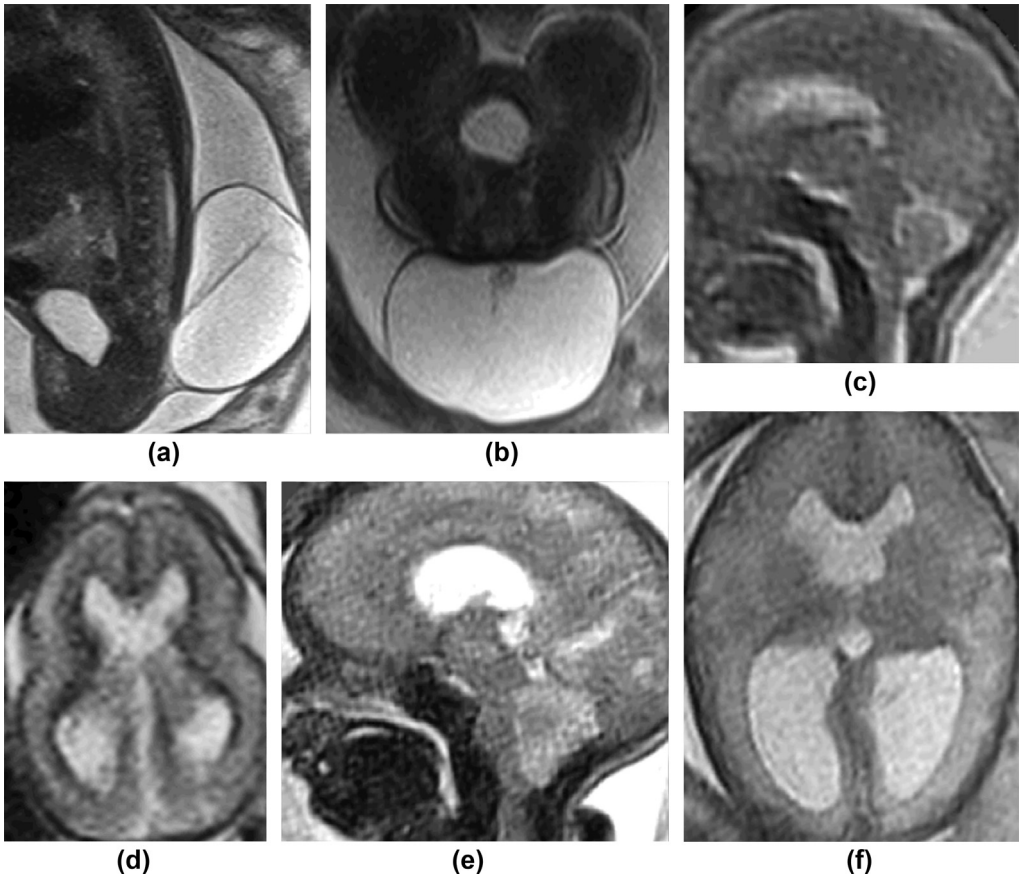

Figure 3 (a,b) iuMRI images of a fetus with a myelocele and a Ch2 malformation at (c,d) 23 weeks and (e,f) 30 weeks. (c) Sagittal imaging of the brain at 23 weeks shows marked tonsillar descent and modest abnormal high signal in the vermis that becomes more pronounced at 30 weeks (e). (e,f) There is progressive VM.

made by comparing it with the adjacent brainstem and occipital lobes.

A number of measurements were made by two of the paediatric neuroradiologists using previously published methods[7] specifically: transverse diameter of the trigones of the lateral ventricles, head circumference, area of the bony posterior fossa in the sagittal plane, area of the cerebellar vermis in the sagittal plane, and transverse cerebellar diameter. The degree of tonsillar descent was also recorded using a line from opisthion to basion as the best assessment of the level of the foramen magnum. Student's *t*-test was used to compare the linear and area dimensions whilst the Mann–Whitney *U*-test was used for comparisons between high signal in the cerebellum and the variables of interest (bony posterior fossa size and amount of tonsillar descent). *p*-Values of <0.05 were considered statistically significant.

Results

By definition, there were no structural brain abnormalities on either iuMRI studies performed on the 10 fetuses in the control group, including no displacement of cerebellar tissue below the foramen magnum. VM was defined as trigone measurements of $\geq$10 mm (the definition used clinically by all of the referring fetal medicine centres) and was present in 14/20 (70%) of the fetuses with Ch2 at the time of the iuMRI examination at 20–24 weeks. When the iuMRI studies were repeated at 30–32 weeks VM was present in 17/20 (85%) of the fetuses with Ch2. Fourteen fetuses had VM on both examinations and all fetuses showed increasingly severe VM on the third trimester iuMRI study. There were no statistically significant differences in the skull circumferences of fetuses from the control and Ch2 groups at either time point (Table 1).

The bony posterior fossa area was smaller in the Ch2 group compared with the control group at both time points studied: 20–24 weeks: mean 207.5 versus 338.1 mm^2, $p<0.001$) and 30–32 weeks: mean 468 versus 800.9 mm^2, $p<0.001$. There was no statistically significant difference in the area of the vermis between the two groups at either time point ($p=0.88$ at 20–24 weeks, $p=0.10$ at 30–32 weeks) but the transverse cerebellar diameter in the fetuses with Ch2 group was reduced when compared with the control group at 30–32 weeks ($p<0.001$). All fetuses with Ch2 had vermes below the foramen magnum (an entrance criterion for enrolment) and the herniation was progressive with a mean descent of approximately 10 mm at 20–24 weeks and approximately 15 mm at 30–32 weeks.

There was no subjective difference in T2 signal in the cerebellar vermis when compared with the brainstem/occipital lobes in the control group on either the second or the

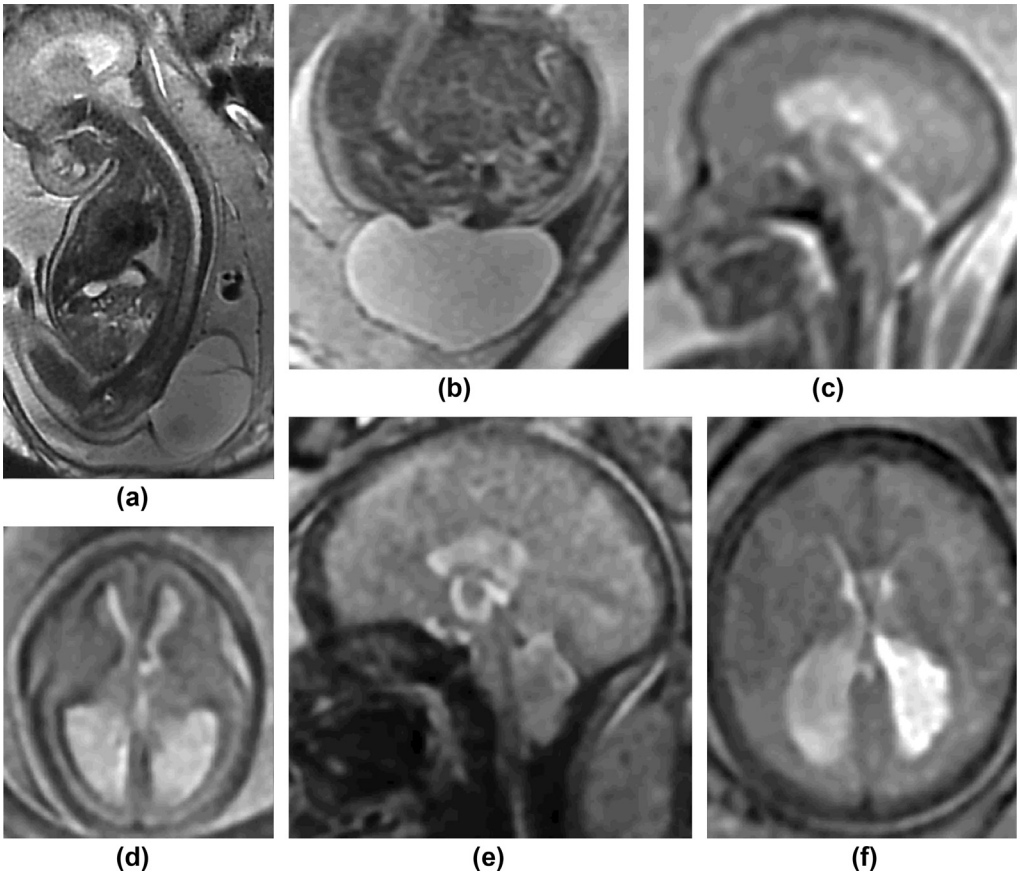

Figure 4 iuMRI of a fetus with a myelomeningocele and Ch2 malformation at 24 weeks. (a,b) Sagittal and axial imaging of the spine shows the open spinal dysraphism. (c,d) Single-shot fast spin-echo imaging of the brain in sagittal and axial planes shows marked cerebellar descent and abnormal high T2 signal in the cerebellar vermis, which progresses with gestation (e,f).

third trimester iuMRI studies. Abnormal high T2 signal was found in the cerebellar vermis in 10/20 (50%) of fetuses with Ch2 at 20–24 weeks and in 11/20 (55%) at 30–32 weeks' gestation. In six fetuses with Ch2 the T2 signal change was not present on either iuMRI study and in seven fetuses the abnormal signal was present on both iuMRI studies. Four fetuses developed abnormal high T2 signal change between the two iuMRI examinations, and in three the abnormal high signal seen in the second trimester was no longer present at 30–32 weeks. The Mann–Whitney *U*-test determined that high T2 signal in the cerebellar vermis was not related to bony posterior fossa size in the Ch2 group (p=0.57). Diffusion-weighted imaging of diagnostic quality was obtained in approximately 80% of all cases and there was no evidence of restricted diffusion on any of those studies. Representative cases are shown in Figs 1–5.

Discussion

There is no single, unifying theory to explain the aetiology of Ch2 and most authorities acknowledge a range of potential contributions from different and probably overlapping factors. Cleland postulated that Ch2 was primarily a dysgenetic abnormality of the hindbrain[10] whereas McLone & Knepper[11] have discussed the importance of compression of the cerebellum secondary to restricted development of the bony confines of the posterior fossa. Several authorities have attempted to explain the reduced volume of the posterior fossa as a sequelae of reduced cerebral spinal fluid (CSF) flow/pressure disturbance because of the open spinal dysraphism.[11–13] The present study describes a new observation in fetuses with Ch2, specifically abnormal high T2 signal in the cerebellar vermis in a high proportion of involved fetuses. This finding appears to have been overlooked in several series that reviewed iuMRI in these fetuses.[16]

There are two major advantages in the design of the present study: first, the presence of an age-matched control group (although with fewer fetuses than the pathology group), and secondly, all fetuses had iuMRI both in the late second trimester and third trimester allowing a dynamic assessment. There were no unexpected findings in the control group, in particular the trigone sizes were always <10 mm and there was no descent of cerebellar tissue below the foramen magnum. In spite of relatively small numbers, the control group provided apparently robust "normal" data concerning skull circumference, area of the bony posterior fossa, area of the vermis, and transverse cerebellar diameter at two time points in pregnancy. Cerebellar descent was a defining feature of Ch2 in this study, although it is appreciated that there are some cases of OSD with posterior fossa abnormalities that do not result in protrusion of cerebellar

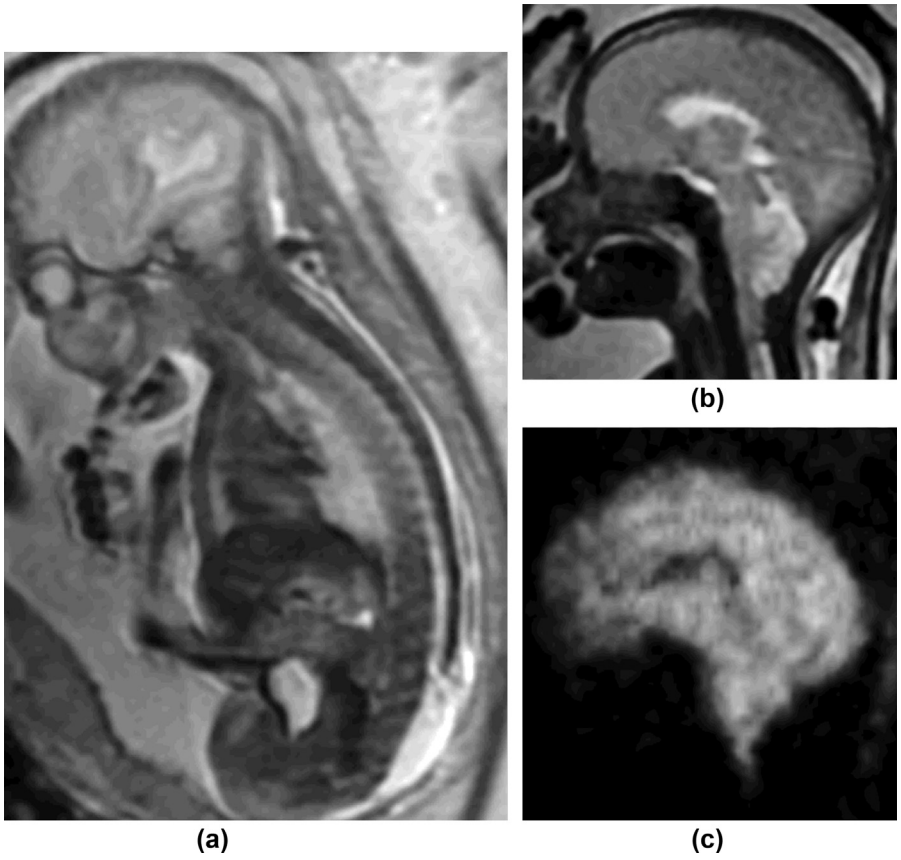

Figure 5 iuMRI images of a fetus with a myelomeningocele and Ch2 malformation at 24 and 33 weeks. (a) Sagittal imaging at 24 weeks demonstrates the spinal dysraphism. (b) Imaging at 33 weeks demonstrates marked T2 high signal within the cerebellar tonsils. (c) The sagittal diffusion-weighting imaging did not show increased cerebellar high signal, and there were no areas of low signal on the ADC map indicating probable vasogenic rather than cytotoxic oedema.

tissue below the foramen magnum.[7] Because cerebellar descent was used as a defining feature of Ch2, this was not used as an independent factor when the association with abnormal T2 signal was analysed.

As expected, VM was common in the fetuses with Ch2 occurring in 70% of the 20–24 group and rising to 85% in the 30–32 week group and the trigone size always increased in individual fetuses with Ch2 between the two time points. There were no statistically significant differences in skull circumference between the control and Ch2 groups at either 20–24 or 30–32 weeks. In contrast, the size of the bony posterior fossa was significantly smaller in fetuses with Ch2 fetuses at both time points between the case and control cohorts confirming the reports of earlier studies, e.g., Naidich *et al.*[14] Although the transverse cerebellar diameter in Ch2 tended to lower values at 20–24 weeks statistical significance was not reached but at 30–32 weeks the results showed statistically significant reduction in the Ch2 fetuses. This measurement is primarily influenced by the lateral bony walls of the posterior fossa and further underlines the restricted size of the bony compartment, which was in contrast to the similar areas of the cerebellar vermis in the two groups.

Abnormal high T2 signal was seen in 50% of the 20–24 week fetuses with Ch2 and in 55% of those at 30–32 weeks. It was not seen in any of the iuMRI examinations performed on control fetuses. Abnormal high T2 signal was seen on both studies in the same fetus in seven cases only, whereas the abnormal signal was present only on the 30–32 week study in four fetuses. An important observation was the three fetuses with Ch2 in whom abnormal high T2 signal present at 20–24 weeks was no longer visible at 30–32 weeks. In spite of the surrogate indicators of markedly reduced volume of the bony posterior fossa, there was no clear relationship between the measures of bony posterior fossa size and the presence of abnormal high T2 signal in the cerebellar vermis. These two features suggest that reduced volume of the bony posterior fossa and resultant compression of cerebellar tissue may not be the direct cause of the T2 prolongation.

In many clinical situations diffusion-weighted imaging can give further insight into the cause of abnormal high T2 signal in the brain, specifically it is possible to distinguish between cytotoxic and vasogenic oedema. There was no evidence of restricted diffusion (high signal on diffusion-weighted imaging matched with reduced signal on apparent diffusion coefficient parametric maps) in any of the cases with abnormal T2 signal in the cerebellar vermis. This is corroborated by prior published series, where no reduced ADC values were appreciated in the cerebellums of Ch2

fetuses.[17] The appearance suggests that vasogenic oedema is the likely cause of T2 prolongation, but this observation needs to be interpreted with caution. Diffusion-weighted imaging is exceptionally sensitive to movement artefact and is difficult to perform in the fetus for that reason. No usable diffusion data were present in 20% of the cases overall. There is also the possibility that diffusion restriction was present, but the examinations were degraded to a degree that cytotoxic oedema could not be detected despite the images appearing of adequate quality. It is also well recognised that the high signal on diffusion-weighted imaging caused by cytotoxic oedema is transient if due to hypoxia or infarction, with pseudo-normalisation occurring in approximately 7 days in children and adults and possibly earlier in neonates. The timescale of this process is not known in the fetal brain, but may lead to cytotoxic oedema being overlooked.

In spite of these caveats, one possible explanation for the abnormal high T2 signal in the cerebellar vermis that would be that the brain changes are due to vasogenic oedema resulting from venous restriction. This would be consistent with the present findings and could arise from transient/intermittent obstruction to venous drainage of the structures in the posterior fossa. The typical features of venous outflow obstruction on MRI in other age groups is high signal on T2-weighted images usually without obvious restricted diffusion probably indicating vasogenic oedema, but this is variable depending of the stage and severity of venous restriction.[15]

In conclusion, the majority of the recognised findings of the Ch2 malformation in children are demonstrable on iuMRI of the fetus. Over half of the fetuses had an additional imaging finding not previously described, namely high T2 signal in the cerebellar vermis. The aetiology of this finding remains unclear, but vasogenic oedema resulting from restriction of venous drainage may be a potential cause.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This study was funded in part by SHINE (spina bifida, hydrocephalus, information, networking, equality).

References

1. Naidich T, Zimmerman RA, McLone DG, *et al*. Congenital anomalies of the spine and spinal cord—embryology and malformations. In: Atlas S, editor. *Magnetic resonance imaging of the brain and spine*. Philadelphia: Lippincott: Williams and Wilkins; 2002. p. 1527–631.
2. Barkovich AJ, Raybaud CA. Congenital anomalies of the spine. In: Barkovich AJ, Raybaud CA, editors. *Pediatric neuroimaging*. 5th ed. Philadelphia Lippincott: Williams and Wilkins; 2012. p. 857–922.
3. Barkovich AJ, Raybaud CA. Congenital malformations of the brain and skull. In: Barkovich AJ, Raybaud CA, editors. *Pediatric neuroimaging*. 5th ed. Philadelphia Lippincott: Williams and Wilkins; 2012. p. 367–568.
4. Chiari H. Ueber veränderungen des kleinhirns infolge von hydrocephalie des grosshirns. *Deut Med Wochenschr* 1891;**17**:1172–5.
5. Pollack IF, Pang D, Albright AL, *et al*. Outcome following hindbrain decompression of symptomatic chiari malformations in children previously treated with myelomeningocele closure and shunts. *J Neurosurg* 1992;**77**(6):881–8.
6. Iskandar BJ, Oakes WJ. Chiari malformations. In: Albright L, editor. *Principles and practice of pediatric neurosurgery*. New York: Thieme; 1999. p. 165–87.
7. Batty R, Telegunti L, Whitby EH, *et al*. Is there a causal relationship between open spinal dysraphism and Chiari II deformity? A study using in-utero magnetic resonance imaging of the fetus. *Neurosurgery* 2012;**70**(4):890–8.
8. Whitby E, Paley MN, Davies N, *et al*. Ultrafast magnetic resonance imaging of central nervous system abnormalities *in utero* in the second and third trimester of pregnancy: comparison with ultrasound. *BJOG* 2001;**108**(5):519–26.
9. Griffiths PD, Widjaja E, Paley MNJ, *et al*. Imaging the fetal spine using *in utero* MR: diagnostic accuracy and impact on management. *Pediatr Radiol* 2006;**36**(9):927–33.
10. Cleland J. Contribution to the study of spina bifida, encephalocele, and anencephalus. *J Anat Physiol* 1883;**17**:257–91.
11. McLone DG, Knepper PA. The cause of Chiari II malformation: a unified theory. *Pediatr Neurosci* 1989;**15**:1–12.
12. Marin-Padilla M, Marin-Padilla TM. Morphogenesis of experimentally induced Arnold–Chiari malformation. *J Neurol Sci* 1981;**50**:29–55.
13. Griffiths PD, Wilkinson ID, Variend S, *et al*. Differential growth rates of the cerebellum and posterior fossa assessed by postmortem MR imaging of the fetus: implications for the pathogenesis of the Chiari 2 deformity. *Acta Radiol* 2004;**45**(2):236–42.
14. Naidich TP. Cranial CT signs of the Chiari II malformation. *J Neuroradiol* 1981;**8**:207–27.
15. Yuh WTC, Simonson TM, Wang AM, *et al*. Venous sinus occlusive disease: MR findings. *AJNR Am J Neuroradiol* 1994;**15**:309–16.
16. Nagaraj UD, Bierbrauer KS, Zhang B, *et al*. Hindbrain herniation in Chiari II malformation on fetal and postnatal MRI. *AJNR Am J Neuroradiol* 2017;**38**:1031–6.
17. Mignone Philpott C, Shannon P, Chitayat D, *et al*. Diffusion-weighted imaging of the cerebellum in the fetus with Chiari II malformation. *AJNR Am J Neuroradiol* 2013;**34**:1656–60.