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ORIGINAL ARTICLE

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Prenatal diagnosis and postnatal outcome of closed spinal dysraphism

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Abstract

Objective: To evaluate the prenatal diagnosis of closed dysraphism (CD) and its correlation with postnatal findings and neonatal adverse outcomes.

Methods: A retrospective cohort study including pregnancies diagsnosed with fetal CD by prenatal ultrasound (US) and magnetic resonance imaging (MRI) at a single tertiary center between September 2011 and July 2021.

Results: CD was diagnosed prenatally and confirmed postnatally in 12 fetuses. The mean gestational age of prenatal imaging was 24.2 weeks, in 17% the head circumference was ≤fifth percentile and in 25% the cerebellar diameter was ≤fifth percentile. US findings included banana sign in 17%, and lemon sign in 33%. On MRI, posterior fossa anomalies were seen in 33% of cases, with hindbrain herniation below the foramen magnum in two cases. Mean clivus-supraocciput angle (CSA) was 74°. Additional anomalies outside the CNS were observed in 50%. Abnormal foot position was demonstrated prenatally in 17%. Neurogenic bladder was present in 90% of patients after birth.

Conclusion: Arnold Chiari II malformation and impaired motor function can be present on prenatal imaging of fetuses with CD and may be associated with a specific type of CD. Prenatal distinction of CD can be challenging. Associated extra CNS anomalies are frequent and the rate of neurogenic urinary tract dysfunction is high.

Key points

What is already known about this topic?

- Closed dysraphism poses a challenge in prenatal diagnosis.
- There is limited data on the prenatal findings and postnatal outcome.

What does this study add?

- Cranial findings associated with Arnold Chiari II (AC II) malformation and impairment of motor function can be present on prenatal imaging of fetuses with closed spinal

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dysraphism and may depend on the specific type of closed dysraphism. MRI adds important information.

- Ventriculoperitoneal Shunt rate is very low and abnormal corpus callosum seems not to be a typical finding. Anomalies of the urogenital and skeletal systems are frequently associated. Neurogenic bladder is a common finding.

1 | INTRODUCTION

Spinal dysraphism results from defective gastrulation affecting the primary or secondary neurulation. The defect can be open with the neural placode exposed to the intrauterine environment or closed (covered by soft tissue). The incidence of spinal dysraphism is about 1–2/1000 live births, most being ODs, mainly myelomeningocele.[1] In open dysraphism (OD), the nervous tissue is in direct contact with the amniotic fluid at the intrauterine environment.[2] This may lead to a progressive trauma, inflammation and degeneration of the exposed neural placode enhancing spinal cord injury with progressive functional loss known as the "second hit".[3–7] Arnold-Chiari II malformation is a congenital condition affecting the brain and spinal cord. It is characterized by a small posterior fossa and specifically involves the cerebellum and parts of the brainstem protruding downward through the foramen magnum, and into the spinal canal. AC II malformation may cause obstruction of cerebrospinal fluid (CSF) flow, leading to ventriculomegaly. Other brain abnormalities may include abnormalities of the corpus callosum, brainstem, and fourth ventricle.[8,9]

Early recognition of ODs and associated abnormalities make this malformation amenable to prenatal therapy.[10] Timely intrauterine repair reduces the degree of AC II malformation and ventriculoperitoneal shunt rate and has been found to be associated with better lower extremity motor function after birth.[11]

Closed dysraphysm (CD) is frequently associated with cutaneous stigmata such as hemangioma, hypertrichosis, skin dimple, or a deviation of the gluteal furrow.[2,12–15] There is a known association of CD with additional abnormalities outside the central nervous system (CNS), including omphaloceles, bladder exstrophy, imperforated anus (OEIS), and Vertebral anomalies, Anorectal malformations, Cardiovascular anomalies, Tracheo-Esophageal fistula/atresia, Renal anomalies, Limb defects (VACTERL).[2,16–18]

Impaired motor function, foot deformities, scoliosis and neurogenic urinary tract dysfunction are associated with CD. While in OD impaired motor function is at least partially secondary to the ongoing injury to the exposed placode, in CD this is associated with cord tethering and hence can be progressive with longitudinal growth.[19,20] CSF leakage into the amniotic cavity is not a feature of CD. As a consequence, AC II malformation is rarely present in CD.[12,17,21,22] Supratentorial brain lesions and ventriculomegaly are not typical findings in fetuses with CD.

Despite optimized imaging, differentiation between an open and closed dysraphism can be challenging and there may be common features shared by both entities, mostly in case of a limited dorsal myeloschisis (LDM)/Myelic Limited Dorsal Malformation.[23]

Limited data are currently available regarding the associated prenatal findings and neonatal outcomes of different CDs.

In this retrospective study, we aimed to describe prenatal diagnosis and associated findings of CD and correlated these findings with post-natal imaging and neonatal outcome.

2 | MATERIAL AND METHODS

This was a retrospective cohort study including pregnancies with suspected CD in the fetus, seen in the fetal center of our tertiary children's and women's hospital between September 2011 and July 2021. For the purpose of the study, our data repository of patients with prenatally diagnosed NTDs was searched for CDs. In the study period, 449 patients with spinal dysraphism (SD) were assessed at our institution. Of these, 36/449 were diagnosed with CD. Only fetuses with a prenatal diagnosis of CD were included in the analysis. Prenatal diagnosis was performed according to the protocol for the evaluation of fetuses with suspected NTDs and included a focused detailed US and fetal MRI at 21–34 weeks of gestation. Images were evaluated using specialized fetal radiologists as well as maternal fetal medicine specialists.

All fetuses with suspected NTD underwent a full prenatal diagnostic imaging investigation that included CNS focused on US (Voluson E8/E10, GE Healthcare Ultrasound, Milwaukee, WI, USA) according to current guidelines[24–27] and multiplanar, multisequence fetal MRI (1.5-T Phillips Ingenia scanner, software version 5.1.7, Phillips North America, Andover, MA, USA). Multiplanar T1- and T2-weighted ultrafast MRI was performed using a phased array surface coil centered over the pregnant uterus in the supine or left lateral maternal position. Slice thickness and field-of-view were optimized for the size of the patient and the age of the pregnancy. No maternal sedation was performed. Imaging planes were adapted to the position of the fetus in order to best display the fetal anatomy. In addition to anatomical imaging, whenever possible a dynamic sequence was added to evaluate fetal motion.

All prenatal US studies were performed/interpreted by a fetal sonographer/fetal center physician with more than 10 years of experience. Fetal MRI was read by expert fetal MRI radiologists with at least 10 years of fetal MRI experience. For the purpose of the study, the fetal MRI studies were again reviewed by a obstetrician/fetal medicine specialist with 24 years of experience and a fetal neuroradiologist with 29 years of experience. The final diagnosis was made in consensus.

Ventriculomegaly was defined as the atria of the lateral ventricles measuring 10 mm or more in cross-sectional diameter.[24] Mild ventriculomegaly was defined as lateral ventricles less than 15 mm, and severe ventriculomegaly was defined as ventricular size ≥15 mm.[28] Assessment of associated CNS anomalies included

anomalies of the corpus callosum, perinodular heterotopia and intraventricular hemorrhage. Continuous epidermis sign and sac wall thickness were measured on MRI as described by Nagaraj et al. and additionally on prenatal US.[17] The anatomic level of the lesion defined as the first affected vertebral arch was defined on prenatal US. Prenatal functional US was performed as previously published, including evaluation for abnormal foot position.[29] Ultrasound assessment of motor function was qualified according to the lower extremity movements: Level L1 corresponds to hip flexion, L2 corresponds to hip adduction, L3 corresponds to the knee extension, L4 to knee flexion, L5 to dorsal flexion of the ankle and S1 to plantar flexion of the ankle.[30]

Evaluation of the posterior fossa on fetal MRI included clivus-supraocciput angle (CSA) as published by Woitek et al., presence of hindbrain herniation below the foramen magnum (FM), presence of cerebellar towering, clival concavity, brainstem compression, and tectal beaking.[31] In addition, the presence of a banana sign in the suboccipital bregmatic view was analyzed on prenatal US.[31–35]

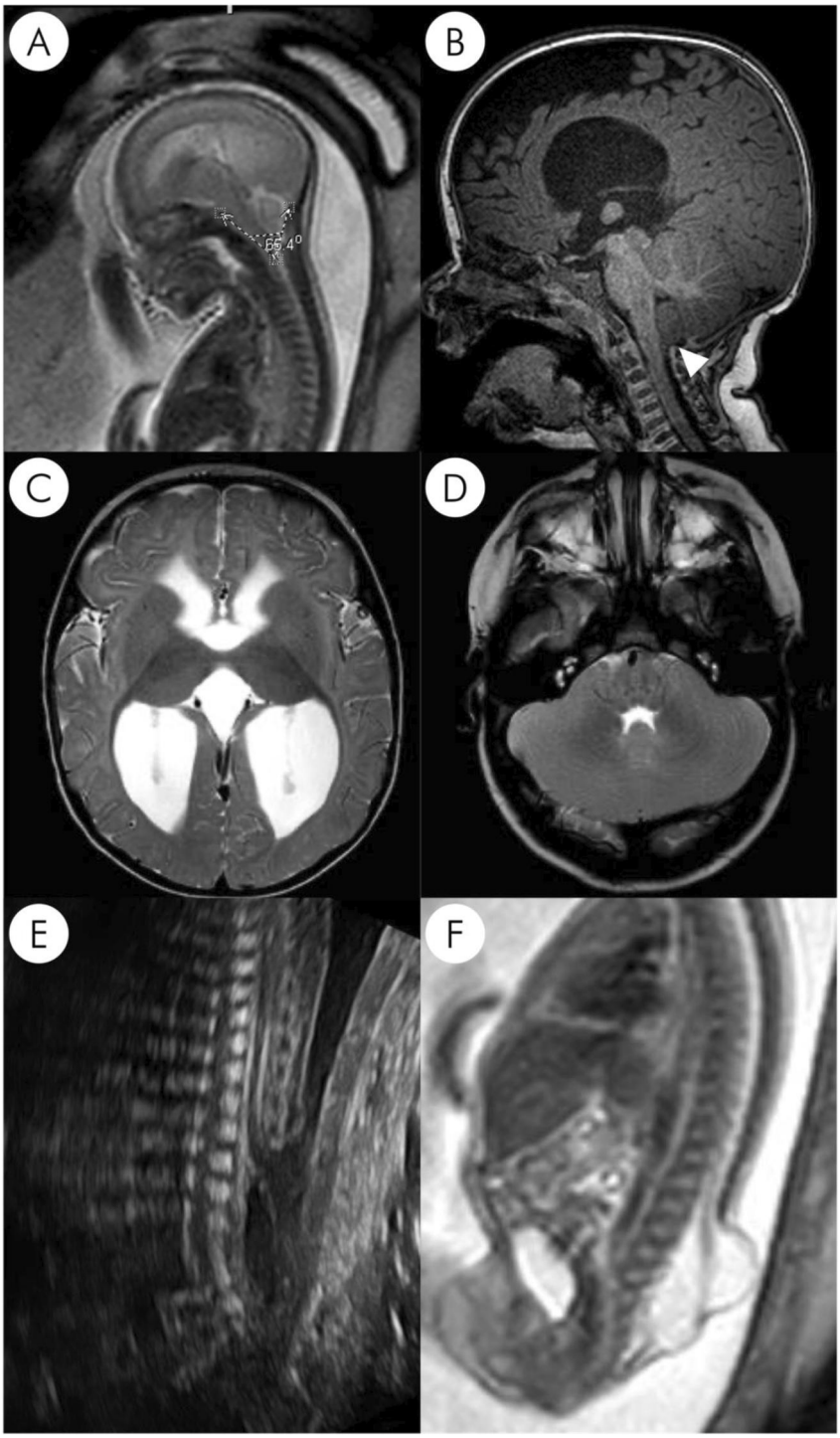

FIGURE 1 A-F: Pre- and postnatal images of posterior fossa and spine (case 11): (A) Sagittal T2-weighted MRI of the brain and upper spinal cord at 21.6 days GA shows a small posterior fossa with downward herniation of the inferior vermis and cerebellar tonsils below the foramen magnum (FM) with effacement of the fourth ventricle and cisterna magna. The Clivus-supraocciput angle measures 65°. (B–D) postnatal sagittal T1-weighted and axial T2-weighted MRI of the same child confirm the prenatal diagnosis of a Chiari II malformation with effaced basal cisterns, mild downward displacement of cerebellar tonsils and inferior vermis into the upper cervical spinal canal (arrowhead), embracement of the brainstem by the anteriorly extending cerebellar hemispheres, supratentorial hydrocephalus and prominent interthalamic adhesion. (E + F) prenatal sagittal US and sagittal T2-weighted fetal MRI performed at 21.6 days GA show the large spinal defect with dorsal protrusion of the low positioned spinal cord through the osseous defect. The dilated terminal ventricle and central canal partially herniated through the dorsal defect into a meningocele leading to "sac within a sac" image, typical for MCC.

Genetic work-up included karyotype and chromosomal microarray (CMA) pre- or postnatally. Anomalies not primarily affecting the CNS as noted on prenatal US and fetal MRI were confirmed on clinical evaluation and postnatal US and MRI were recorded.

Maternal serum alpha fetoprotein (MSAFP) was inconsistently measured and reported when available.

Post-natal evaluation included imaging with US and MRI as well as a clinical assessment of the motor function and bladder function by a dedicated team of neonatologists, pediatric neurologists, pediatric neurosurgeons, and pediatric urologists. Functional segmental motor function was determined by a detailed neurological evaluation in the first 48 h of life. Motor levels were defined by the lowest myotomes involved in active motor activity.[7,36,37] After discharge, the infants were followed up in our institution's multidisciplinary Spina Bifida Clinic. Neurogenic dysfunction of the bladder was defined as either overactive bladder, underactive bladder, or non-contractile detrusor as described by Weiss et al.[38] The diagnosis is made by urodynamic studies combined with video fluoroscopy. Our protocol includes controls after birth, at 3, 6, 9, 12–15 and 18 months of age and yearly controls thereafter. Ultrasound is performed after birth. First video-urodynamic studies (VUDS) are performed at 3 months of age together with US and dimercaptosuccinic acid scintigraphy (DMSA).

2.1 | Statistical analysis

Statistical analysis was performed using Excel spreadsheet mathematic functions (Version 16.69.1), using mean values, minimum and maximum.

2.2 | Ethics

The study was approved by the Baylor College of Medicine Institutional Review Board (H-34680, H-43359, H-33264, H-38479), and a Data Safety Monitoring Board sub-committee of the Texas Children's Hospital Fetal Therapy Board.

3 | RESULTS

After excluding the ones without confirmation of the diagnosis of CD, 12 fetuses with prenatally diagnosed CD were included in this study. Two were initially suspected of having an OD and consequently proceeded to prenatal surgery during which a CD was diagnosed, and surgery was abandoned (case 11 + 12). On MRI, both fetuses showed hindbrain herniation below the foramen magnum, mild ventriculomegaly, tectal beaking, cerebellar towering, brainstem compression and a cerebellar diameter ≤fifth percentile. CSA was 65° (case 11), and 56° (case 12). In case 11, extra axial fluid was decreased. On prenatal US, both lemon, and banana signs were demonstrated. In case number 11, a MCC was diagnosed, and the baby was operated on at the age of two months due to a progressive increase in the lesion (Figures 1 and 2). In case number 12, a dorsal MC was diagnosed without visible placode and no exposed spinal cord (Figure 3). A clubbed foot was demonstrated already in prenatal evaluation. The baby was delivered in another hospital, and we do not have follow-up information.

Baby number 6 was also delivered in another hospital, and we could get the confirmation of a CD, but not gather complete outcome and follow-up information.

Mean gestational age at referral and imaging in our institution was 24.2 weeks (21–33.9 weeks). The mean body mass index (BMI) was 31.2 (20.6–47.3 kg/m2). Mean maternal age was 29.8 years (19–46 years). Pregestational diabetes was diagnosed in 2/12 patients, chronic hypertension in 1/12, anemia in 1/12 patients.

MSAFP was available only in 42%. In 40% (2/5) it was >2.5 MoM (cases 8 and 11). In case no. 8, hindbrain herniation was not present but cerebellar towering was demonstrated on prenatal evaluation. Sac wall thickness was 2 mm on prenatal US and MRI. In case no. 11, hindbrain herniation was present before and after birth, sac wall thickness was 1.6 mm on prenatal US and 2.4 mm on MRI. Intrauterine rupture of the sac or fistula/cerebrospinal fluid leakage was not described after birth in both of these cases. Concordance between the pre- and postnatal type of spinal lesion was found in 58%. Table 1 shows the pre- and postnatal diagnosed type of lesion and AFP in maternal blood (Table 1).

Table 2 shows the prenatal findings on US and MRI. Mean CSA was 74°. Signs of AC II malformation (lemon sign, banana sign, hindbrain herniation, cerebellar towering, clival concavity, brainstem compression, tectal beaking) could be demonstrated in 33%. The continuous epidermis sign was present in 92%. Mean sac wall thickness was 3.5 mm on prenatal US and MRI. Anomalies of the corpus callosum were not diagnosed before birth. One fetus (case 7) had a congenital absent cavum septum pellucidum (CSP) demonstrated on prenatal imaging. The leaflets were partially visible and there were no signs of rupture. This fetus also had mild ventriculomegaly (12 mm). He was diagnosed with a thinned corpus callosum after birth. In cases 1 and 12, diastematomyelie was present and in case number 1, there was an additional hydromyelia at T2-T6 demonstrated (Figure 4A–E).

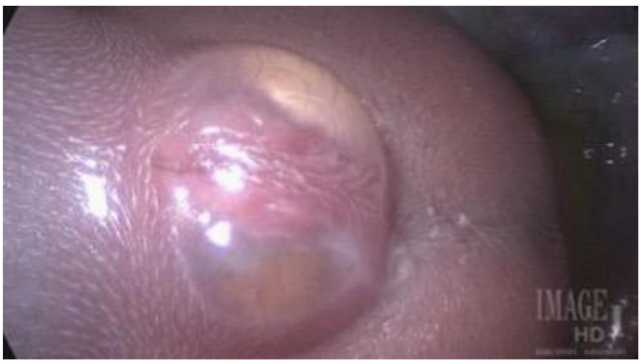

FIGURE 2 Findings at fetoscopy show the top of the cystic lesion covered by skin with thinning on the sides. The neural placode is not exposed (case 11). [Colour figure can be viewed at wileyonlinelibrary.com]

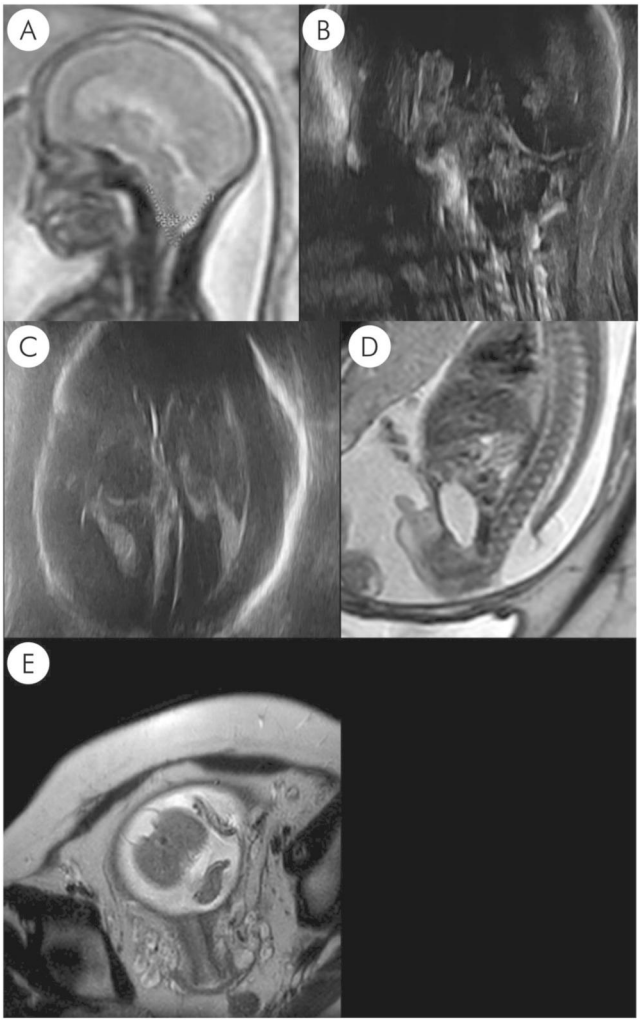

FIGURE 3 (A–E) Prenatal US and MRI images of case 12 at 22.9 weeks gestation: A + B Sagittal T2-weighted MRI and US of the brain and upper spinal cord show a small posterior fossa with downward herniation of the inferior vermis and cerebellar tonsils below the foramen magnum with effacement of the fourth ventricle and cisterna magna. CSA measures 56°. (C) Occipital colpocephaly and mild ventriculomegaly (12 mm). (D + E) T2-weighted sagittal (D) and axial (E) fetal MRI show the spinal defect with herniation of the neural structures.

Abnormalities outside the CNS were mostly linked to the urogenital and skeletal system, including left renal agenesis (case 1), scoliosis and hemivertebrae (case 2), multicystic dysplastic kidney disease (MDKD, case 3), hemivertebrae (case 7), congenital pulmonary airway malformation (CPAM) and left renal agenesis (case 8) and mild renal pyelectasis (case 12). In case 5 increased nuchal translucency (NT) in the first trimester and white spot were described but not classified as congenital anomalies. In babies born at our institution, anomalies have been confirmed after birth.

While hindbrain herniation was present in 17% of fetuses before birth (case 11 + 12), it was detected in another 4 fetuses after birth (for example case number 3, Figure 5). Mild ventriculomegaly was present in 3 fetuses before birth (case 7, 11, 12). Ventriculoperitoneal shunt placement was not required after birth. While impaired motor function/abnormal foot position was detected in 2 fetuses before birth, it developed in another 2 babies (case 1 + 2) with initially unimpaired motor function (motorlevel S1) in the first year of life (diagnosed at 6 and 9 months of age). Neurogenic bladder was detected in 9/10 babies, were this information was provided. Cases 6 and 12 were delivered in another hospital and we did not have the full follow-up (Table 3).

3.1 | Genetic work-up

Pre- and/or postnatal genetic diagnostic testing was performed in 7/12 pregnancies. Karyotype was normal in all fetuses. 4/12 fetuses had chromosomal microarray analysis (CMA) with normal results. Exome sequencing was not performed.

4 | DISCUSSION

In the current study, we aimed to describe prenatal findings of CD and evaluate its association with postnatal imaging and clinical presentations. The main findings included a) prenatal findings of AC II malformation, which were present in 33%. These were present specifically in cases of MCC and dorsal MC b) If not present at the first

TABLE 1 Pre- and postnatal diagnosed type of lesion and AFP in maternal blood.

Patient Nr	1	2	3	4[a]	5	6	7	8	9	10	11	12
Prenatal suspected type of lesion	LMMC/CSCL	LMMC/CSCL	t- MCC	LMMC/CSCL	t-MCC	LMMC/CSCL	t-MCC/LMMC	t-MCC/LMMC	LMMC	MC	MMC	MMC
Postnatal type of lesion	LMMC/CSCL	LMMC/CSCL	t-MCC	Non-t-MCC	t-MCC	MC	t-MCC	LMMC/CSCL	t-MCC	MC	t-MCC	MC
Serum AFP (MoM)	0.67	1.41		0.54				2.72			4.22	

Note: Alpha Fetoprotein (AFP), MoM (multiple of median), Lipomyelomeningocele (LMMC, new orphaned classification Conus spinal cord lipoma (CSCL), ORPHA #268835), posterior Meningocele (MC, ORPHA #268810), non-terminal Myelocystocele (non-t-MCC, ORPHA #645340), terminal Myelocystocele (t-MCC, ORPHA #645337).

[a]No prenatal MRI available due to patient rejection.

TABLE 2 Prenatal findings in fetuses with closed spinal dysraphism.

Patient Nr.	1	2	3	4[a]	5	6	7	8	9	10	11	12
Continuous epidermis sign	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Sac wall thickness (MRI)	6.3	12.7	3.9		2.3	1.6	1.5	2	2.4	2.3	2.4	1.4
Sac wall thickness (US)	5.9	13.1	1.6	5	2.1	1.7	1.5	2	2	2.5	1.6	
Hindbrain herniation below FM	No	No	No	No	No	No	No	No	No	No	Yes	Yes
CSA (MRI)	66°	92°	78°		73°	78°	61°	81°	87°	80°	65°	56°
Cerebellar towering (MRI)	No	No	No		No	No	No	Yes	No	No	Yes	Yes
Clival concavity (MRI)	No	Yes	No		Yes	No	No	Yes	No	No	Yes	No
Brainstem compression	No	No	No		No	No	No	No	No	No	Yes	Yes
Banana sign (US)	No	No	No	No	No	No	No	No	No	No	Yes	Yes
Lemon sign (US)	No	No	No	No	Yes	No	No	No	No	Yes	Yes	Yes
Head circumference (percentile)	<5th%	<5th%	58th%	77th%	6th%	8th%	37th%	36th%	12th%	34th%	15th%	14th%
Cerebellar diameter (percentile)	60th%	58th%	82n%	44th%	<5th%	49th%	45th%	54th%	56th%	36th%	5th%	<5th%
Ventriculomegaly	No	No	No	No	No	No	Yes	No	No	No	Yes	Yes
Tectal beaking	No	No	No		No	No	No	No	No	No	Yes	Yes
Extra axial fluid normal	Yes	Yes	Yes		Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Callosal anomaly	No	No	No	No	No	No	No con-genital absent CSP post-natal thinned CC	No	No	No	No	No
Heterotopia	No	No	No	No	No	No	No	No	No	Yes (sub ependymal)	No	No
Anatomic level	L4	L4	L3	L4	L2	S3	L4	L3	L5	T1	L2	L3
Motor level	S1	S1	S1	S1	L4	S1	S1	S1	S1	S1	S1	L4
Malposition of the foot	No	No	No	No	Yes Unil-ateral club foot	No	No	No	No	No	No	Yes Uni-lateral club foot

TABLE 2 (Continued)

Patient Nr.	1	2	3	4[a]	5	6	7	8	9	10	11	12
Syrinx	Yes	No	No	No	No	No	No	No	No	No	No	No
Split cord anomaly	Yes	No	No	No	No	No	No	No	No	No	No	Yes
Extra-cerebral anomaly	Yes	Yes	Yes	No	No	No	Yes	Yes	No	No	No	Yes
Type of extra-cerebral anomaly	Left renal agenesis	Scoliosis and hemi-vertebrae	Unilateral MDKD	None	None	None	Hemi-verte-brae	CPAM, left renal agenesis	None	None	None	Mild renal pyelectasis

Abbreviations: CSP, Cavum septum pellucidum; CPAM, Congenital pulmonary airway malformation; FM, Foramen magnum; MDKD, Multicystic dysplastic kidney disease; MRI, Magnetic resonance imaging; US, Ultrasound.

[a]No prenatal MRI available due to patient rejection.

evaluation, hindbrain herniation could develop in the course of pregnancy c) In CD signs of impaired motor function may be present already on prenatal evaluation d) precise prenatal diagnosis of CD type is limited e) abnormalities outside the CNS were seen in 50% of fetuses f) Independent of the type of lesion, CD was associated with a significant rate of neurogenic bladder.

In contrast to previous studies that showed a normal cranial and CNS anatomy, we could show that signs of AC II malformation may be present in fetuses with CD.[39–41] In our study, small HC, cerebellar diameter <fifth percentile and lemon sign were present on prenatal US. Although more subtle findings of AC II malformation can be seen on prenatal MRI, the presence of intracranial findings in CD may also be associated with the specific type of closed lesion, the anatomic level, and the size of the lesion. Hindbrain herniation may be particularly seen in fetuses with large meningocystocele (MCC) or posterior meningocele.[12,17,42,43] In these cases, large, albeit skin-covered, CSF-filled pouches or celes likely allow for a sufficient degree of CSF hypotension within the developing neural tube to initiate/facilitate the developmental cascade that ultimately leads to the AC II malformation.[12,44] In various degrees of for example, MCCs, the outpouching membrane may have varying pressure dynamics on the development and expansion of the rhombo-encephalic vesicle. A small myelocystocele may allow for a more effective expansion of the rhomboencephalic vesicle compared with a large myelocystocele. Moreover, during surgery, frequently a thin membrane is noted covering the neural placode; the associated pressure dynamics and the possible impact on the leakage of the CSF at the level of the spinal dysraphia are not yet fully understood and require further research. Another reason for progressive hindbrain herniation can be a fistula on a thin top of a saccular form of limited dorsal myeloschisis (LDM) or a posterior meningocele that has ruptured during prenatal surveillance.[45,46] Wong and Pang have described AC II malformation also with LDM after birth.[47,48]

Unfortunately, a detailed description of the individual lesion is not always provided in previous publications/studies. Often, lesions are listed under the "umbrella term" of closed lesions, occult spinal lesions or skin covered lesions without further ascertainment. This complicates comparability. In the study by Ghi et al., 4 patients were diagnosed prenatally with a closed lesion by US. One lesion was an MC, and 3 lesions were lipomeningoceles, all lesions were in the sacral area. Cranial findings were absent in all patients in this US-based study.[39] Advances in prenatal US may also lead to the detection of more subtle findings of AC II malformation.

Hindbrain herniation below the foramen magnum can be present in the second trimester or may develop later in pregnancy or after birth.[9,17,21,49] In our study, hindbrain herniation was present in 2/12 cases at the first evaluation in our institution and in an additional 4 cases after birth, including one child with a classical Chiari I malformation postnatally (case 9). In the study of Hüsler et al., the authors found that in a group of fetuses with spinal dysraphism without hindbrain herniation, 81% had a closed lesion and 19% had open spinal defects. Prenatal distinction between open and closed defects was correct in 83%. 2 cases of OD were incorrectly diagnosed as CD

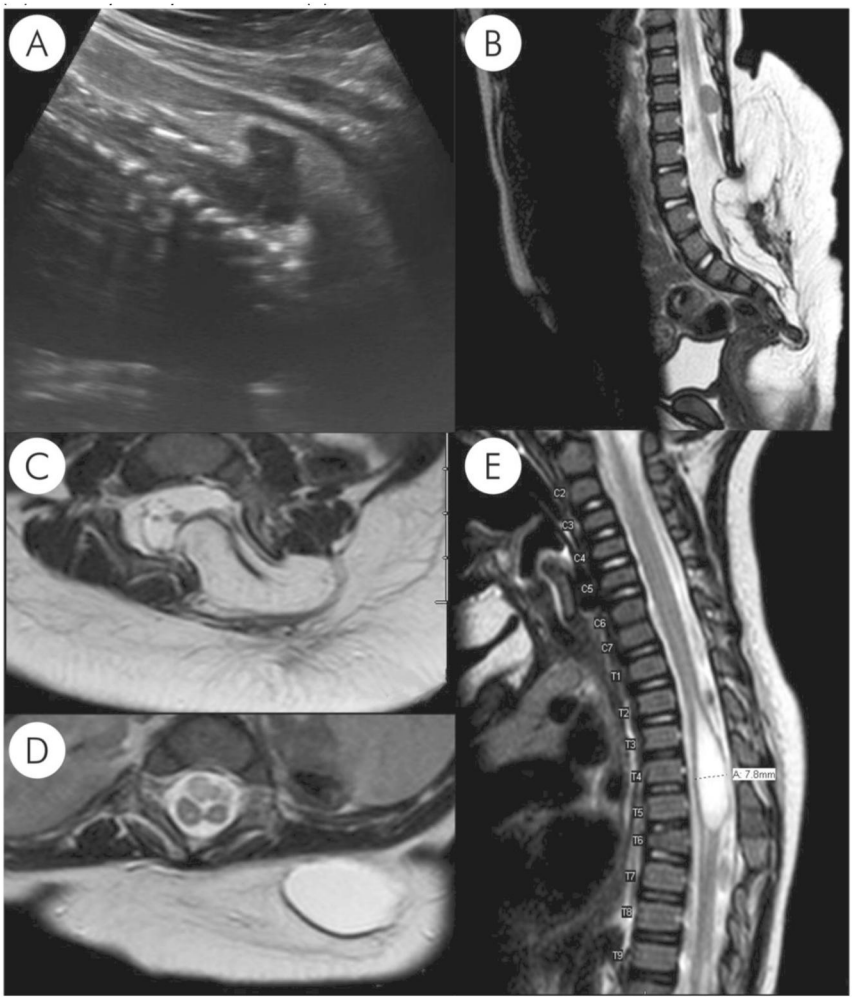

FIGURE 4 (A–E) Pre- and postnatal US and MRI of case 1: A: Prenatal US of the fetal spine at 22.4 weeks GA shows the spinal defect, positive continuous epidermis sign (B + C) postnatal T2-weighted sagittal and axial MRI image of the spine show a large and complex lumbo-sacral malformation with imaging features compatible with a lipomyelomeningocele. (D + E) postnatal T2-weighted sagittal MRI image of the spine show a diastematomyelie at Th12/L1 (D) and a hydromyelia at T2-T6 (E).

on prenatal imaging.[21] Whereas ventriculomegaly is present in about 85% of cases with OD in the third trimester, it can occasionally also be present in CDs.[17,21,50,51] In our cohort, mild ventriculomegaly was present in 25% of fetuses in the second trimester evaluation. Severe ventriculomegaly was not seen before or after birth and none of the newborn babies in our cohort required a shunt after birth. The mean CSA was 74° (54–92°), which corresponds to the finding of Woitek et al. that showed a mean CSA angle of 75° ± 11.1 for closed lesions and 53.4° ± 10.4 for open lesions.[31] Exception was case 12, were CSA was 54°. In this case, the fetus was first thought to have an open lesion (MMC) but during prenatal surgery a skin covered dorsal meningocele was diagnosed and surgery was abandoned. This fetus showed several signs of AC II malformation. Prenatal motorlevel was L4 and the fetus had a unilateral clubbed foot.

Concordance between the pre- and postnatal type of spinal lesion was found in 58% of our cohort. Prenatal distinction between different types of closed lesions may be difficult as different lesions may have a very similar appearance.[52] One reason may be that fetuses develop the subcutaneous fat mainly in the third trimester and that different types of closed defects may contain fat to varying degrees. Even on prenatal MRI, T1-hyperintense subcutaneous or intraspinal fat may not always be visualized and the distinction between lipomatous and non-lipomatous lesions can be challenging.[17] Some extension of fat into the spinal canal in MCC or some dilatation of the central canal at the distal spinal cord in lipomatous malformations with extraspinal extension may be present and complicate the differential diagnosis.[53] In addition, fetal motion, unfavorable positioning of the fetal back relative to the uterine wall and the small size of the studied anatomy early during pregnancy may impact the correct differentiation. In particular, the differentiation between a neural placode and intact skin may be challenging. In questionable cases, the identification of AC II malformation points toward an OD while a normal sized posterior fossa would suggest a CD. The continuous epidermis sign was analyzed on prenatal US and MRI and was present in most of the cases (11/12); mean sac wall thickness was 3.5 mm on prenatal US as well as on prenatal MRI. This is in line with the findings of Nagaraj et al., reporting on a mean sac wall thickness of 2.9 ± 1.3 mm[17].

Anomalies of the corpus callosum are frequent in OD.[54–58] There is very little information on callosal anomalies in the case of a CD. The limited literature existing on this topic does not show an increased rate of abnormalities of the corpus callosum in fetuses with CD.[57,59] A severe ventriculomegaly can occasionally cause rupture of the septal leaflets and a thinned and stretched corpus callosum that is mistaken

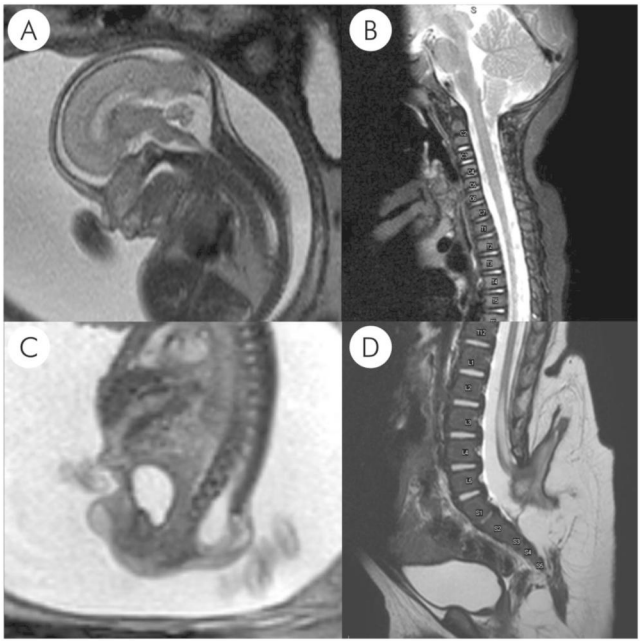

FIGURE 5 (A–D) Pre- and postnatal MRI images of case 3 at 24 weeks GA and after birth (case 3): (A) Sagittal T2-weighted fetal MRI reveals a normal sized posterior fossa, with a well-defined, non-compressed fourth ventricle and a mega cisterna magna; (B) Postnatal sagittal T2-weighted MRI shows a downward displacement of cerebellar tonsils into the upper cervical spinal canal, the fourth ventricle is patent. (C + D) Fetal (24 weeks GA) and postnatal T2-weighted sagittal MRI image of the spine show a large and complex lumbo-sacral malformation with imaging features compatible with a myelocystocele (case 3).

by the absence of the structure. Nevertheless, in our cohort, one fetus had a thinned corpus callosum, diagnosed on postnatal imaging and an absent cavum septum pellucidum with only mild ventriculomegaly, hence assumed to be unrelated to the absent CSP.

The impairment of motor function and/or abnormal foot position is a major concern in fetuses with ODs and can be detected already during pregnancy.[29] In our series of fetuses with CDs, we could show abnormal foot position already at the first evaluation in our institution (case 5 + 12). In case 1, weakness of the left foot was diagnosed at the age of 5 months and impairment of knee extension (L3) was diagnosed at the age of 6 months. In case 2, unilateral club foot was diagnosed at the age of 9 months. In closed lesions, impairment of motor function is mainly due to cord tethering and impaired perfusion of the spinal cord.[60] Spinal dysraphism is a common reason for neurogenic lower urinary tract dysfunction.[21,61–64] The evaluation of bladder function is currently not properly assessed prenatally. While cycles of bladder emptying and refilling are observed in routine anatomical scans, no metric parameters have been suggested to assess the function.[65,66] Special consideration should be taken in cases with suspected CD, as we have demonstrated significant rates of neurogenic bladder.

Associated anomalies of the urogenital tract und skeletal system are frequent and affect 50% of fetuses in this cohort. Whereas an "omphalocele-extrophy-imperforate anus-spinal defect" (OEIS) was frequently found in other studies, mostly in association with MCC, we did not find this association in our cohort.[17,21,67] This may be due to the small number of cases and the rarity of OEIS.

With high detection rates of SD on prenatal high-resolution US and routine use of cell-free DNA (cfDNA) screening for chromosomal

TABLE 3 Postnatal outcome.

Patient Nr	1	2	3	4	5	6[a]	7	8	9	10	11	12[b]
Hindbrain herniation below foramen magnum	No	No	Yes	No	No	n/a	Yes	Yes	Yes, Chiari I	No	Yes	n/a
Shunt	No	No	No	No	No	n/a	No	No	No	No	No	n/a
Motorlevel after birth	S1 At 6 months: S1 (right) L3 (left)	S1 At 9 months: L4 (left) S1 (right)	S1	S1	L4	n/a	S1	S1	S1	S1	S1	n/a
Abnormal foot position	No	Yes Unilateral club foot diagnosed at 9 months of age	No	No	Yes Bilateral clubfeet, bilateral hip and knee dis-location	N/a	No	No	No	No	No	N/a Club foot was diagnosed on prenatal evaluation
Impairment of bladder function	Yes	Yes	Yes	Yes	No	N/a	Yes	Yes	Yes	Yes	Yes	N/a

[a]Baby was delivered in another hospital. Closed lesion was confirmed, data on neonatal outcome were not available.

[b]Delivery in another hospital. Hindbrain herniation (HBH) and clubbed foot were present already on prenatal evaluation. n/a (not applicable), LTF (lost to follow-up).

anomalies, maternal serum AFP (MSAFP) screening is increasingly being abandoned.[68,69] It was reported in 42% in our cohort. Cut-off levels for ODs range between 2.0–2.5 multiple of the median (MoM).[70] MSAFP has a sensitivity of 75% and a specificity of 97.7%.[71] Measurement of MSAFP has a high false positive and false negative rate and may be normal (<2,5 MoM) in cases of ODs.[72] In our cohort, the cut-off of 2.5 MoM was exceeded in two cases of CDs (8 and 11). In case 8, AFP in the amniotic fluid was available and below the critical cut off (1,2 MoM); in case 11, this additional information was not available. MSAFP can be influenced by the time of testing and different maternal, fetal, and placental factors. Maternal factors are weight, ethical background, and insulin-dependent diabetes mellitus. In case 8, maternal BMI was not reported, in case 11, it was 20.3. None of the two patients suffered from diabetes mellitus. Fetal factors like intrauterine growth restriction (IUGR) or abdominal wall defect or chromosomal anomalies were not present in these fetuses, and placental anomalies were not reported. Milunsky et al. reported a case of a closed lesion with elevated AFP.[73] It can be hypothesized that a thin covering membrane of a closed lesion, like in huge meningoceles or meningocystoceles may allow for diffusion into the amniotic fluid and be elevated in maternal serum.

Our study has several strengths. To the best of our knowledge, this is the first time that prenatal findings on US and MRI as well as prenatal evaluation of motor function, genetic findings and postnatal adverse outcome have been comprehensively investigated in a cohort of fetuses with CDs. The results of our work may alert the reader to the complexity of spinal dysraphism and may be helpful in prenatal counseling.

Limitations of our study is mainly due to retrospective study design, postnatal follow - up, and lack of long-term outcomes in some of the patients have been managed in medical centers non-affiliated with our hospital. A second limitation is our relatively small cohort, and a possible selection bias due to the evaluation in a single high complexity tertiary referral center. All our cases have been CDs with subcutaneous mass and we cannot extend our findings to occult NTDs. Our results need to be validated on a larger cohort.

5 | CONCLUSION

Intracranial findings associated with AC II malformation and impairment of motor function can be present on prenatal imaging of fetuses with CDs and may depend on the specific type of closed dysraphism. Prenatal ascertainment is not always possible. Screening second trimester US of the posterior fossa can also be abnormal in case of a CD and may lead to further detailed multi-modal examination. MRI adds important information and should be performed in all cases of spinal dysraphism. Hindbrain herniation can be present in CDs and may be progressive during pregnancy or after birth. Mild ventriculomegaly may be present, but shunt placement is seldom required after birth. Anomalies of the corpus callosum are an infrequent finding in CDs. Anomalies of the urogenital and skeletal systems are frequently associated. The impairment of motor function, mainly abnormal foot position, can be present already before birth. Neurogenic bladder is a frequent finding in closed lesions.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon reasonable request. The data from this manuscript has been uploaded as an abstract for ISPD 2023. The data of the manuscript have also been presented at the Dreiländertreffen in Mainz/Germany, October 11-14, 2023.

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