Original Research

Longitudinal evolution of central nervous system anomalies in fetuses with open spina bifida fetoscopic repair and correlation with neurologic outcome



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BACKGROUND: Open spina bifida is associated with central nervous system anomalies such as abnormal corpus callosum and heterotopias. However, the impact of prenatal surgery over these structures remains unclear.

OBJECTIVE: This study aimed to describe longitudinal changes of central nervous system anomalies before and after prenatal open spina bifida repair and to evaluate their relationship with postnatal neurologic outcomes.

STUDY DESIGN: Retrospective cohort study of fetuses with open spina bifida who underwent percutaneous fetoscopic repair from January 2009 to August 2020. All women had presurgical and postsurgical fetal magnetic resonance imaging, at an average of 1 week before and 4 weeks after surgery, respectively. We evaluated defect characteristics in the presurgical magnetic resonance images; and fetal head biometry, clivus supraocciput angle, and the presence of structural central nervous system anomalies, such as abnormalities in corpus callosum, heterotopias, ventriculomegaly, and hindbrain herniation, in both presurgical and postsurgical magnetic resonance images. Neurologic assessment was performed using the Pediatric Evaluation of Disability Inventory scale in children who were 12 months or older, covering 3 different sections, namely self-care, mobility, and social and cognitive function.

RESULTS: A total of 46 fetuses were evaluated. Presurgery and postsurgery magnetic resonance imaging were performed at a median gestational age of 25.3 and 30.6 weeks, with a median interval of 0.8 weeks before surgery, and 4.0 weeks after surgery. There was a 70% reduction in hindbrain herniation (100% vs 32.6%; P<.001), and a normalization of the clivus supraocciput angle after surgery (55.3 [48.8-61.0] vs 79.9 [75.2-85.4]; P<.001). No significant increase in abnormal corpus callosum (50.0% vs 58.7%; P=.157) or heterotopia (10.8% vs 13.0%; P=.706) was observed. Ventricular dilation was higher after surgery (15.6 [12.7-18.1] vs 18.8 [13.7-22.9] mm; P<.001), with a higher proportion of severe ventricular dilation after surgery (>15mm) (52.2% vs 67.4%; P=.020). Thirty-four children underwent neurologic assessment, with 50% presenting a global optimal Pediatric Evaluation of Disability Inventory result and 100% presenting a normal social and cognitive function. Children with optimal global Pediatric Evaluation of Disability Inventory presented a lower rate of presurgical anomalies in corpus callosum and severe ventriculomegaly. When analyzed as independent variables to global Pediatric Evaluation of Disability Inventory scale, the presence of abnormal corpus callosum and severe ventriculomegaly showed an odds ratio of 27.7 (P=.025; 95% confidence interval, 1.53) -500.71) for a suboptimal result.

CONCLUSION: Prenatal open spina bifida repair did not change the proportion of abnormal corpus callosum nor heterotopias after surgery. The combination of presurgical abnormal corpus callosum and severe ventricular dilation (\geq 15 mm) is associated with an increased risk of suboptimal neurodevelopment.

Key words: brain, central nervous system, fetal surgery, magnetic resonance imaging, neurologic assessment, spina bifida

Introduction

O pen spina bifida (OSB) is the most common neural tube defect, affecting up to 0.5% of pregnant women worldwide.^{1,2} In 2011, after the Management of Myelomeningocele Study (MOMS) results, prenatal surgery was defined as the reference standard for OSB repair.³ MOMS follow-up studies

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© 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/) http://dx.doi.org/10.1016/j.ajogmf.2023.100932 showed a significant reduction of postnatal cerebrospinal fluid (CSF) diversion, and better mental and motor function development up to 5 years of age,³⁻⁵ confirmed by other series.⁶⁻⁹ Since then, studies have mainly focused on the need for shunting and motor function evolution,^{10–13} while fetal CNS structures and its association with neurodevelopment remained poorly investigated.^{14–16}

In prenatal life, OSB is associated to hindbrain herniation (HBH), resulting in brain changes named Chiari II malformation. Ventriculomegaly¹⁷ is part of Chiari II and can require CSF diversion after birth.^{18,19} In addition, other CNS anomalies have been reported as part of the OSB spectrum, mainly in long-term studies with 75% of cases

with abnormal corpus callosum (CC) and abnormalities in cortical development,²⁰⁻²³ both related to poorer cognitive and motor outcomes.^{24,25} Periventricular heterotopias are also part of the OSB spectrum and postnatal studies have associated them to certain neurologic impairment and seizures.^{26,27} There is scarce data about the fetal period, but some reports demonstrated that these changes are already present before birth,^{15,26–31} although their development remains unclear. In addition, little is known about the influence of prenatal repair and whether these anomalies can be related to this postnatal outcome.

This study aimed to describe longitudinal changes of CNS anomalies before and after prenatal OSB repair, and to

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AJOG MFM at a Glance

Why was this study conducted?

Central nervous system anomalies such as abnormal corpus callosum have been reported in about half of the cases with open spina bifida before surgery. No data have been reported on the effect of open spina bifida prenatal repair on central nervous system anomalies.

An evaluation of the relationship between prenatal central nervous system anomalies and postnatal neurologic outcomes would be beneficial for prenatal counseling.

Key findings

Prenatal repair of open spina bifida does not have any effect on the proportion of anomalies in the corpus callosum.

Combination of abnormal corpus callosum and severe ventriculomegaly (\geq 15 mm) is associated with worst postnatal neurodevelopment outcomes.

What does this add to what is known?

The combination of abnormal corpus callosum and severe ventriculomegaly $(\geq 15 \text{ mm})$ is associated with a 2-fold increased risk of suboptimal neurodevelopment.

This information could be of interest in presurgical counseling.

evaluate their relationship with postnatal neurologic outcomes.

Materials and Methods

The study was approved by the ethics committee of the Hospital Israelita Albert Einstein in Sao Paulo, Brazil, under approval number SGPP-3715-19. The manuscript writing followed the STROBE guidelines for observational studies.

Study population

This was a retrospective cohort study of 49 fetuses with OSB who underwent fetoscopic repair from January 2009 to August 2020. All women had presurgical and postsurgical fetal magnet resonance assessment, with an average of 1 week before and 4 weeks after surgery, respectively. Inclusion criteria were similar to MOMS trial,³ except that there was no upper limit for gestational age (GA). Fetuses with low quality images that could jeopardize their brain structures evaluation were excluded (n=3).

Operating team

Since 2013, surgeries were always performed by the same experienced team of fetal medicine specialists³² and an experienced laparoscopic gynecologic surgeon.

Image acquisition

Fetal magnetic resonance imaging (MRI) was performed without fetal sedation and according to the American College of Radiology guidelines for MRI during pregnancy and lactation.³³ Images were obtained in the 3 orthogonal planes of the brain, whereas spinal images were acquired in axial and sagittal planes, using two 1.5 Tesla scanners (Optima, GE Healthcare, Waukesha, WI; and Espree, Siemens Healthineers AG, Erlangen, Germany), with 8-channel body coils. Acquisitions were as follows: GE scanner was a single-shot fast spin echo (SSSE) T2-weighted sequences (TR 2825 milliseconds [ms], TE 200 ms, FOV 350 millimeters [mm] and matrix 288×256), and Siemens scanner was a Half Fourier Acquisition Single Shot Turbo Spin Echo (HASTE) T2 weighted sequence (TR 1000 ms, TE 85 ms, FOV 370 mm and matrix 256×205). The slice thickness varied according to GA as follows: 3.0 mm (<28 weeks) and 4.0 mm (>28 weeks), with no gaps. Images were assessed by a trained obstetrician and reviewed by an expert neuroradiologist.

Image analysis

In the presurgical MRI, we determined the upper level of the lesion (ULL) defined as the highest vertebral level affected in a midsagittal image of the spine, as previously described.³⁴ We divided the ULL into 3 groups as follows: thoracic-L2 (group 1), L3-L4 (group 2), and L5-sacral (group 3). We also characterized the defect into myelomeningocele or myeloschisis, according to the presence or absence of a cyst. Finally, the defect area was obtained by multiplying its largest sagittal and axial diameters by \prod and divided by 4.

At both presurgical and postsurgical MRI, we assessed the presence of structural CNS anomalies at different levels including cavum septum pellucidum (CSP) and CC anomalies, nodular heterotopias, ventriculomegaly, aqueduct stenosis, HBH, and interhemispheric cyst. In addition, we performed anatomic measurements of biparietal diameter, occipitofrontal diameter, transverse cerebellar diameter, HBH, clivus-supraocciput angle (CSA), and lateral ventricles, as previously described.³¹ Diameters were transformed into z-scores according to a standard reference for fetal magnetic resonance biometry³⁵ and HBH were presented as negative values when below the foramen magnum, and positive when above.

Neurologic assessment

We performed the Pediatric Evaluation of Disability Inventory (PEDI) scale, translated and validated in Portuguese.³⁶ The PEDI scale consists of a questionnaire of 197 questions that cover self-care (73 questions), mobility (59 questions) and social function and cognitive domains (65 questions) for children from 6 months to 7.5 years. It has been used worldwide as an important tool to identify functional independence delays or impairments.^{36–42} All questions were answered by the child's caregiver and describe the child as unable (score 0) or capable (score 1) of performing each task. For each section (self-care, mobility, and social function), the total score is normalized for the expected score according to their age, generating a final normative score. This score is considered optimal for the child's age when \geq 30, and suboptimal when <30. Finally, a PEDI scale is considered as optimal for the child's age when at least 2 out of 3 final scores have been classified as optimal.

The PEDI was applied by a certified occupational therapist at 2 moments of the study. Initially, the interviews were done during the Spina Bifida Marathon in September 2019, at the Hospital Israelita Albert Einstein, Sao Paulo, Brazil. Because of the COVID-19 pandemic, the second half of interviews were done online, by means of Zoom meeting platform (2020 Zoom Video Communications, Inc, San Jose, California, US), for children who were at least 12 months of age.

Statistical analysis

Data were stored and analyzed using STATA Statistical Software, release 13. (StataCorp LP, College Station, TX). Categorical variables were presented as number of cases and percentage and were compared using means of McNemar test when comparing presurgical and postsurgical findings for each individual. Pearson X^2 or Fisher exact test was used in subanalysis groups, when appropriate. Continuous variables were presented in median and interguartile range (IQR) and were compared by Wilcoxon signed-rank test to compare quantitative data. Multiple logistic regression was done to obtain independent variables associated with neurodevelopmental scale results. To rule out high correlations between groups, tetrachronic correlation for binary variables was adopted. A P value <.05 was set as statistically significant.

Results

The population characteristics are presented in Table 1. Sixty-three percent of our cases (29/46) were operated on at a GA >26 weeks. Presurgical and postsurgical MRI were performed at a median (IQR) GA of 25.3 weeks (23.9–26.9) and 30.6 weeks (29.7–31.6), respectively and with a median interval of 0.8 weeks (0.4–1.8) before surgery and 4.0 weeks (3.6–4.6) after surgery.

The CNS findings in both presurgical and postsurgical MRI are summarized in Table 2. All cases presented presurgical HBH, with a significant reduction of

TABLE 1

Maternal and fetal characteristics		
Characteristics	N=46	
Maternal characteristics		
Age (y)	32.6 (27.4-34.8)	
Caucasian, n (%)	31 (67.4)	
Preconceptionally folic acid usage, n (%)	22 (47.8)	
Number of previous pregnancies	0 (0-1)	
Diabetes, n (%)	1 (2.2)	
Hypothyroidism, n (%)	5 (10.9)	
Fetal characteristics		
GA at presurgical MRI (wk)	25.3 (23.9–26.9)	
GA at surgery (wk)	26.5 (25.6–27.5)	
GA at postsurgical MRI (wk)	30.6 (29.7-31.6)	
GA at birth (wk)	33.9 (32.9–35.1)	
Male sex, n (%)	22 (47.8)	
Bilateral prenatal clubfoot, n (%)	5 (10.9)	
Type of defect, n (%)		
Myelomeningocele	36 (78.3)	
Myeloschisis	10 (21.7)	
Level of defect, n (%)		
T12-L2	8 (17.4)	
L3-L4	21 (45.6)	
L5-S1	17 (37.0)	
Kyphosis, n (%)	1 (2.2)	
Tethered cord, n (%)	44 (95.7)	
Data are presented in median (IQR) or number of cases (percentage).		

GA, gestational age; IQR, interquartile range; MRI, magnetic resonance imaging.

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herniation postsurgery (100% vs 32.6%; P<.001). No significant changes were observed among CNS anomalies, such as abnormal CC (50.0% vs 58.7%; P=.157), heterotopias (10.9% vs 13.0%; P=.706), abnormal ventricular wall contour (30.2% vs 32.6%; P=.796), or abnormal CSP (32.6% vs 41.3%; P=.157), neither when considering abnormal CC and/or heterotopias together, as the major CNS anomalies (26 [56.5%] vs 31 [67.4%]; P=.140). After surgery, fetuses presented a wider CSA (55.3 [48.8-61.0] vs 79.9 [75.2 -85.4]; P<.001), and larger lateral ventricles (15.6 [12.7-18.1] mm vs 18.8

[13.7–22.9] mm; P<.001), with a higher proportion of severe ventricular dilation (\geq 15 mm) (52.2% vs 67.4%; P=.020). Finally, when comparing CNS anomalies between those operated before and after 26 weeks, no significant difference was found in abnormal CC (P=.737) or heterotopias (P=.369).

Neurologic assessment was performed in all children who were at least 12 months old (n=34), as shown in Table 3. Fifty percent of the children presented a global optimal neurologic assessment, and 100% of the children had normal social and cognitive function. Children with an optimal global

TABLE 2

Central nervous system findings in presurgical and postsurgical fetal magnetic resonance imaging

	Presurgical MRI (N=46)	Postsurgical MRI (N=46)	<i>P</i> value
CNS findings			
Hindbrain herniation, n (%)	46 (100.0)	15 (32.6)	<.001 ^a
Hindbrain herniation (mm)	-10.4 (-13.1 to -8.2)	1.5 (-4.7 to 4.1)	<.001 ^a
Abnormal corpus callosum, n (%)	23 (50.0)	27 (58.7)	.157
Abnormal ventricular contour, n (%)	13 (30.2)	14 (32.6)	.796
Heterotopias, n (%)	5 (10.9)	6 (13.0)	.706
Major CNS (CC and/or HT), n (%)	26 (56.5)	31 (67.4)	.140
Abnormal cavum, n (%)	15 (32.6)	19 (41.3)	.157
Tectal beaking, n (%)	40 (86.9)	41 (89.1)	.739
Interhemispheric cyst	0 (0.0)	3 (6.5)	.083
CSA (degrees)	55.3 (48.8–61.0)	79.9 (75.2-85.4)	<.001 ^a
Larger lateral ventricle (mm)	15.6 (12.7–18.1)	18.8 (13.7–22.9)	<.001 ^a
Ventricular dilation \geq 10 mm, n (%)	42 (91.3)	45 (97.8)	.083
Ventricular dilation \geq 15 mm, n (%)	24 (52.2)	31 (67.4)	.020 ^a
TCD z-score	-3.0 (-4.0 to -1.3)	-2.8 (-4.6 to -2.1)	.177
BPD z-score	0.0 (-1.5 to 0.9)	0.6 (-1.0 to 1.5)	.020 ^a
OFD z-score	1.8 (0.2-2.6)	3.9 (1.3-5.2)	<.001 ^a

Data are presented in median (interquartile range) or number of cases (percentage).

BPD, biparietal diameter; CNS, central nervous system; MRI, manetic resonance imaging; OFD, occipitofrontal diameter; TCD, transverse cerebellar diameter.

^a statistically significant difference (p<0.05).

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TABLE 3

Neurologic assessment and characteristics in children \geq 12 months of age

Neurological outcome	n=34
Optimal PEDI scale	17 (50.0)
Optimal self-care domain	16 (47.1)
Optimal mobility domain	5 (14.7)
optimal social and cognitive function domain	34 (100.0)
Need of shunt	
<12 mo	16 (47.1)
12-30 mo	3 (8.8)
Replacement	6 (17.7)
Seizure >28 d	7 (20.6)

Data are presented in number of cases (percentage).

PEDI, Pediatric Evaluation of Disability Inventory.

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PEDI result presented lower rate of postnatal CSF diversion during the first year of their lives (23.5% vs 70.6%; P=.022). Prenatal CNS findings and postnatal characteristics according to PEDI results are shown in Supplementary Table 1. Children with an optimal global PEDI result had smaller presurgical lateral ventricles (13.4 [12.7–18.1] mm vs 16.2 [13.1–18.9] mm; P=.027), and lower proportion of severe ventriculomegaly (35.3% vs 58.8%; P=.025) and CC anomalies (35.3% vs 64.7%; P=.033).

We explored the relation between global PEDI result and the presence of severe VMG and/or abnormal CC. Multiple logistic regression showed that the presence of both presurgical abnormal CC and severe VMG increases the risk for a suboptimal global PEDI scale result (odds ratio [OR], 27.70; P=.025; 95% confidence interval [CI], 1.53 -500.71), whereas if only 1 of them is present, this association reduces and is not significant (OR, 9.36; P=.094; 95% CI, 0.69–127.72) (Supplementary Table 2). Finally, we explored whether abnormal CC and severe VMG were correlated, as occurs in cases with primary CC anomaly, but tetrachronic correlation showed a correlation index of 0.345, thereby not supporting this correlation.

Comment Principal findings

This study demonstrated that proportion of CNS anomalies associated with OSB, including abnormal CC and heterotopias did not change after prenatal repair. In addition, we found that the isolated diagnosis of abnormal CC was not associated with increased risk of suboptimal neurodevelopment, but the combination of presurgical abnormal CC and severe ventricular dilation increased its risk significantly.

Review in the context of what is known

Our results are in line with previous data showing that half of OSB fetuses had abnormal CC, which were already identified during presurgical MRI^{28,31,43,44} with no significant increase in postsurgical MRI. As for heterotopias, cases varied from 10.9% presurgical to 13.0% postsurgical, also in line with previous data.⁴⁴ This nonsignificant increase could be expected by the improvement of imaging quality owing to the more advanced GA and in regard to heterotopias, also owing to the natural history of this condition being more apparent in latter stages.

All our fetuses presented presurgical HBH, and almost 70% of them showed a complete reversion after surgery. This is in line with previous data regarding fetal surgery for spina bifida in animal models, single center experiences, and the MOMS trial.^{3,8,32,45-48} We also identified a more acute clivus supraocciput angle in the presurgical MRI (55.3 \pm 12.1°), as described by D'Addario et al⁴⁹ in fetuses with Chiari II malformation (CIIM) and Woitek et al⁵⁰ in fetus with OSB. Interestingly, in our cohort, the CSA normalized after surgery, reaching an angle of 79.9±10.2°, even performing repair in later GA. Both HBH reversal and CSA normalization reinforced the benefits of a later OSB fetoscopic repair even in this group of fetuses.

Finally, ventricular size increased after surgery in our population, similar to previous data.^{19,48,51} Recently, data has shown that prenatal OSB repair does not slow the progression of ventriculomegaly.⁵² Fetuses who undergo prenatal repair may have a sudden increase in ventricular size immediately after surgery, whereas those postnatally repaired have an increase of their ventricular size at about 30 weeks of gestation.⁵² Presurgical severe VMG showed to be an important marker for the need of postnatal CSF diversion, as shown by Tulipan et al.⁵³ This severe VMG was more prevalent in myelomeningocele fetuses (91.3% vs 63.6%; P=.035) who presented increased HBH (-12.0 [-13.7 to -9.9] vs -8.6 [-11 to -5.9];P=.004). Our presurgical findings agreed with Zarutskie et al,¹⁹ that highlighted these parameters as important presurgical markers for postnatal hydrocephalus treatment.¹⁹ In our population, 68.8% (11/16) of the severe VMG (\geq 15 mm) and only 27.8% (5/18) of the nonsevere VMG fetuses underwent a CSF diversion within the first year of their lives

(*P*=.017). Interestingly, the presurgical and postsurgical lateral ventricle range was wider in fetuses that already had severe VMG before surgery (4.0 [2.6 -5.3] vs 2.1 [0.3-3.4]; *P*=.030), in agreement with Zarutskie et al.¹⁹

Regarding neurodevelopment, although we have a slightly higher rate of suboptimal results compared with other series,^{9,54} this does not represent the entire cohort of patients, but only those with presurgical and postsurgical MRI. In addition, all children included in the study had an optimal cognitive function according to the neurodevelopment scale. Children with a suboptimal neurodevelopment presented higher proportion of abnormal CC, reinforcing the already described relation between an abnormal CC and some neurologic impairment.^{25,55} In addition, the combination of both presurgical severe VMG and abnormal CC resulted in a higher risk of abnormal neurodevelopment, which was also reported by Li et al,⁵⁶ that showed a significant increase of moderate to severe suboptimal neurodevelopment in children with CC abnormalities and VMG in comparison with those with isolated CC abnormalities (67% vs 7%; P=.003).

Clinical applications

Our findings stress the importance of a detailed presurgical scan, which will allow us to diagnose CNS anomalies and give a more personalized prenatal counseling in each case.

The diagnosis of severe VMG or abnormal CC at presurgical MRI does not contraindicate fetal surgery, but its combination is more associated with suboptimal neurodevelopmental outcome and should be considered in the decision-making process with the parents. In addition, we have shown that a prenatal repair of OSB beyond 26 weeks is not related to a significant increase in CNS anomalies as compared with other series,^{29,31,43} including abnormal CC and heterotopias. Because improvements in ambulation and reduction of CSF diversion and bladder catheterization have already been shown in this profile of patients,⁵⁷ our findings reinforce the point that the neuroprotection of the procedure is not affected in fetuses operated on beyond the standard age of the MOMS trial (19 -25.9 weeks). The concept of "the earlier the better" may not apply for risk of CSF deviation, and operating after 26 weeks avoids the risk of extreme premature birth.

Strengths and limitations

Our study has some limitations that must be taken into consideration. First, the time range between our first and last OSB was of 10 years. This is because of the difficulty of managing patients and the impossibility of performing MRI scan as protocol in some cases, owing to financial and/or geographic factors in Brazil, preventing the inclusion of all cases managed in the center. As a retrospective analysis, in which all cases were operated on using the same technique (SAFER technique), our results may not be extrapolated to other techniques. Moreover, when analyzing our postnatal outcomes in children at least 12 months of age, only 34 out of 46 children in our study cohort had reached that age, reducing the final population for statistical analysis, with a follow-up rate of 73.9%. The main strength of our study was that it analyzed the longitudinal evolution of presurgical and postsurgical CNS anomalies, and its correlation with postnatal neurologic outcomes.

Conclusions

We have shown that prenatal OSB repair did not change the proportion of abnormal CC or heterotopias associated with this condition. We have also demonstrated that the combination of presurgical abnormal CC and severe ventricular dilation is associated with higher risk of suboptimal neurodevelopment. Further studies that evaluate long-term results of the SAFER technique, and explore the specific effect of early vs late repair, aiming to reduce the risk of extreme prematurity, are warranted.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ajogmf.2023. 100932.

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