New insights in cerebral findings associated with fetal myelomeningocele: a retrospective cohort study in a single tertiary centre

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Shortened running Tittle: fetal cerebral anomalies associated with MMC

Abstract

Objective: to investigate cerebral anomalies other than Chiari type 2 malformation in fetuses with myelomeningocele.

Design: A retrospective cohort study in a single tertiary centre.

Setting: a review of associated cerebral anomalies in cases with prenatal diagnosis of myelomeningocele.

Population: 70 cases of foetal myelomeningocele.

Methods: Ultrasound and MRI images were blindly reviewed. Postnatal imaging and results of the **post-mortem results were also reviewed**. **The association between cerebral anomalies and the following US findings was measured: level of the defect, ventriculomegaly, microcephaly and foetal talipes**.

Main outcome measures: A microcephaly was observed in 32/70 cases (46%), a ventriculomegaly was observed in 39/70 cases (56%). Other cerebral anomalies were diagnosed in 47/70 (67%).

Results : Other cerebral anomalies were represented by 42/70 cases with abnormal CC (60%), 8/70 cases with PNH (11%), 2/70 cases with abnormal gyration (3%). MRI only performed in foetal surgery cases confirmed US findings in all cases, and provided additional findings in 2 cases (PNH). Risk ratios of foetal cerebral anomalies associated with MMC did not reach significance for microcephaly, ventriculomegaly, talipes and for the level of the defect There was an overall good correlation between pre and postnatal findings with a Kappa value of 0.79 $[0.57\text{-}1]_{CI95\%}$ and a proportion of agreement of 82%.

Conclusion: foetal brain anomalies other than Chiari type 2 malformation, are frequently observed in foetuses with myelomeningocele, predominantly

represented by CC anomalies. **Whether these associated cerebral anomalies should have an impact on selecting cases eligible for fetal surgery needs further evaluation.**

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Key-words: myelomeningocele, prenatal diagnosis, ultrasound, cerebral anomalies, corpus callosum

Tweetable abstract: foetal cerebral anomalies other than Chiari type 2 malformation, microcephaly and ventriculomegaly may be associated with MMC in up to 67% of the cases.

Introduction

Myelomeningocele (MMC) represents a specific form of neural tube defect with an incidence of approximatively 3-4 per **10.000** live births in Europe[1]. **The exposure of the non-neurulated spinal cord and nerve roots to external environment is responsible for motor dysfunction** (weakness or paralysis) and for both bowel and bladder dysfunction[2]. **In addition, there are specific brain anomalies associated with this defect, most commonly Chiari type 2 malformation and frequent associated ventriculomegaly and microcephaly[3].**

In neonates undergoing surgical repair of myelomeningocele, a wide spectrum in terms of size, shape, level of defect and appearance of cerebral structures is observed (the posterior fossa structures, the corpus callosum and the cerebral cortex)[3,4]. Chiari type 2 malformation is observed in almost all cases of MMC[4,5]. **Hydrocephalus is frequently seen, being present in about half of the patients with MMC**[3]. Corpus callosum (CC) anomalies are also frequent in cohorts of adult patients, with controversies on the underlying mechanism leading to these anomalies, as they are often associated with hydrocephalus in these patients[3,6,7].

There is no available data on the incidence of corpus callosum and cortex abnormalities in foetuses with MMC. **In the setting of foetal surgery, these data are of utmost importance since prenatal repair is theoretically reserved for foetuses presenting with MMC with no other anomaly than Chiari type 2 malformation, ventriculomegaly, microcephaly or talipes.**

We aimed to retrospectively review all cases of MMC referred to our centre and for **which** complete ultrasound examinations of the foetal brain performed by an

experienced sonographer were reviewed by two independent operators blinded to the perinatal outcome.

Material and Methods

This was a retrospective study of 70 cases of fetuses with MMC examined between November 2013 and February 2019 in the setting of the PRIUM study[8]: French study on prenatal repair of foetal myelomeningoceles using open surgery technique[9] (Clinical Trial registration NCT01983345; Institutional Review Board approval 13048). **There was no patient and public involvement**. Patients with suspicion of foetal MMC were referred to our centre. **As part of our usual plan of care, all cases are evaluated by a second line US examination performed by one experienced operator (CG). Additional MRI examination is offered either systematically in case of foetal surgery, or when additional anomalies are suspected at ultrasound examination. In our centre there is no policy of systematic fetal MRI in case of typical MMC at second line US examination.**

The second line ultrasound (US) was performed by an experienced operator using a Aplio 400 unit (Canon Medical Systems, Otawara, Japan) with vector and curved-array transducers and magnified images focused on the spine and spinal cord utilizing high frequency (8-15 MHz) linear array transducers. When abdominal route was not sufficient for detailed examination of the foetal brain, and depending on the foetal position, a vaginal examination was performed using high frequency vaginal probes. An entire examination of the foetal brain, including examination of the CC was performed. **The fetal MRI examinations were performed using a 1.5 Tesla Unit (Achieva;**

Philips Medical Systems, Best, The Netherlands from 2013 to 2015 and Optima MR450w; General Electric (GE), Waukesha, WI since 2016). SSFSE sequences were acquired for all foetuses in three orthogonal spaces. In order to reduce motion artefacts, maternal sedation was systematically offered. 2D images in the three planes of the space were repeated until the quality was deemed good.

The gestational age at diagnosis of MMC was recorded. When several US scans were performed, results of the first complete evaluation, the nearest to the diagnosis, were taken into account. **The level of the MMC defect was classified as low when the uppermost vertebral defect was below L3 or as high when it was L3 or higher. Regarding the fetal brain, the US parameters recorded were (1) microcephaly defined by head circumference < 3rd centile[10], (2) presence or absence of ventriculomegaly defined by a diameter of the ventricular atrium measured on the axial view ≥10 mm, (3) anomalies of the CC and (4) associated parenchymal anomalies represented by subependymal heterotopia or gyration disorders.** Anomalies of the CC included absent, short, thick or apparently normal but stretched CC. **The CC was defined as short when length measurement was < 3rd centile using reference curves by Cignini et al.[11]. A short CC was then classified as complete (figure 1) or incomplete (figure 2); when incomplete, the missing part was noted (rostrum, genu, body, splenium). A CC was defined as thick when ≥ 3 mm at the mid-coronal plane as described by Achiron et al. [12]. Extra-cranial anomalies and the presence of foetal talipes were also recorded.**

Parents were offered prenatal counselling involving a specialist in foetal medicine and a paediatric neurosurgeon, with information on the prognosis of the anomaly and

the benefice-risk balance of prenatal versus postnatal repair. **Foetal karyotype analysis was offered in all cases.** According to the French law, termination of pregnancy (TOP) was possible at parental request **irrespectively of gestational age**. All cases of confirmed diagnosis of MMC were included. Cases associated with chromosomal anomalies or polymalformative syndromes were excluded. We also excluded cases for which termination of pregnancy (TOP) was performed before 20 weeks of gestational age (GA) since corpus callosum anatomy could not be evaluated.

Results of the post-mortem (PM) examination were recorded when accepted by the parents in cases of TOP. **The PM examination protocol included a two-month period of formalin fixation of the foetal brain to allow anatomical examination of the foetal brain structures. As part of our usual plan of care in liveborn neonates, transfontanellar US examination is systematically performed during the first week of life and cerebral MRI examination is systematically performed during the first 3 months of life regardless of the timing of the surgery.**

Both prenatal and postnatal imaging (head US and/or brain MRI) were reviewed blind to the perinatal outcome by the same team (PM and JG). Cerebral anomalies were **analysed** as described above. **For the CC postnatal imaging, the following features were recorded: (1) length of the corpus callosum, considered as short when inferior to the 3rd centile according to C. Garel curve[13]** (2) objective thickness of the corpus callosum measured at the level of the genu, body, and splenium, and considered thickened when one of the measurement was superior to the 97th percentile[13].

Statistical analysis.

Statistical analysis was performed using R, version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria) and STATA, version 15 (StataCorp, College Station, Texas, USA). **The association between cerebral anomalies and the following US findings was measured by computing Risk Ratios (RR) and 95% confidence intervals: level of the defect, ventriculomegaly, microcephaly and foetal talipes.** The relationship between decision of TOP and cerebral anomalies was tested by Odds Ratio (OR), and a P value < 0.05 was considered statistically significant. Adjusted kappa coefficients (Cohen weighted kappa) for CC categories (normal, stretched, short and absent) were computed to test for the agreement between prenatal and postnatal findings. Adjusted kappa values <0.6, between 0.6 and 0.8, and >0.8 were considered to represent poor, moderate, and good agreement, respectively.

Results

During the study period, 109 pregnant women with suspicion of foetal MMC were referred to our centre **(figure 3)**. The diagnosis was revised in 26 cases including limited dorsal myeloschisis (LDM)[14] (n=9) or borderline types of LDM-MMC (n=14), the latter being characterized by the association between a saccular dysraphism with a thick membrane coverage, a spinal cord stretched to the sac wall by a fibrous stalk, the absence of nerve roots within the sac and either a Chiari type 2 malformation or a reduced cisterna magna. Moreover, other types of dysraphisms were observed, including lipomyelomeningocele (n=1), complex dysraphism (n=1) and meningocele (n=1). The diagnosis of MMC was confirmed in 83 cases. Thirteen cases were excluded: polymalformative syndromes (n=6), MMC with associated diastematomyelia (n=3), TOP

before 20 weeks of gestation (n=2) and cases for which satisfying study of the corpus callosum was not available due to foetal position (n=2). **In these latter two cases, MRI was not performed since the parents opted for TOP and declined the PM examination**. The remaining 70 cases of MMC were included. **Fetal karyotype analysis was performed in 39/70 cases and revealed no chromosomal anomalies.**

Prenatal imaging findings

The median GA at second line US examination was 23 weeks^{+3d} (range: 20 weeks^{+3d} - 25 weeks^{+6d}). **The uppermost vertebral defect was below L3 in 45/70 cases (64%). Foetal talipes was associated with MMC in 20/70 cases (29%). A Chiari type 2 malformation was observed in all cases. A microcephaly was observed in 32/70 cases (46%), a ventriculomegaly was observed in 39/70 cases (56%). Overall, other cerebral anomalies were diagnosed in 47/70 (67%) of the cases in the prenatal period. We observed 42/70 cases with abnormal CC (60%), 8/70 cases with PNH (11%), 2/70 cases with abnormal gyration (3%). Additional fetal MRI was performed in 12/70 cases (17%) only in cases where foetal surgery was considered. MRI confirmed US findings in all cases, and provided additional findings in 2 cases (PNH).**

MMC associated with ventriculomegaly

In cases associated with ventriculomegaly, no additional cerebral

anomalies were observed in 10/39 cases (26%) (figure 3). In all these cases, patients opted for TOP and when performed, no additional findings were identified on PM examination. In the remaining 29 cases, the parents opted for prenatal repair in 6 cases, for conventional postnatal repair in 6, and for TOP in 17 cases.

The CC was considered as abnormal in 26/39 cases (67%). The CC was stretched in 5 cases, associated with ventriculomegaly ≥13 mm in all these cases. The CC was considered short and complete in 10 cases , and short but incomplete in 10 other cases. When the CC was short, it was thickened in 11/20 cases. There was a complete CC agenesis in one case.

PNH were diagnosed by prenatal imaging in 6/39 cases (15%). In four cases, they were detected at the second line of ultrasound examination. In addition, in two other cases, PNH were detected at systematic MRI examination performed as part of the management of prenatal surgery cases.

Abnormal gyration pattern was observed in 2/39 cases (5%) at the second line ultrasound examination only. In one case, the CC was normal and in the other case, the CC was short but complete. In these 2 cases, MRI was not performed and PM was declined.

MMC without ventriculomegaly

In cases not associated with ventriculomegaly, no additional cerebral anomalies were observed in 13/31 cases (42%) (figure 3). Among these cases, parents opted for prenatal repair in 3 cases, for conventional postnatal repair in 4

cases, and for TOP in 6 cases.

The CC was considered as abnormal in 16/31 cases (52%). The CC was considered short and complete in 14 cases, and short but incomplete in 2 other cases. When the CC was short, it was thickened in 2/16 cases.

PNH were diagnosed by prenatal imaging in 2/31 cases (6%). In one case, PNH was detected at the second line of ultrasound examination and confirmed by MRI. In the other case, PNH was detected at the systematic MRI examination. No case of abnormal gyration pattern was observed.

Perinatal outcome

Overall, there were 25/70 liveborn neonates including 13 (52%) cases that underwent a prenatal repair performed at a median age of 24^{+5d} weeks (range: 21 $weeks^{+3d}$-25 $weeks^{+6d}$) (figure 4). One neonatal death occurred in one case at day 9 (postnatal repair group). Ventriculo-peritoneal shunt was indicated in 3 and 6 children in the prenatal repair and postnatal repair groups, respectively. The 24 live children are currently 6 to 40 months old with normal neurobehavioral development, including the 10 and the 5 cases with either PNH or CC anomalies in the prenatal surgery group and postnatal repair group, respectively.

A TOP was elected by the parents in 45 cases and a PM examination was performed in 39 cases. Detection of associated CNS anomalies (CC anomalies, PNH or abnormal gyration) was not significantly associated with a decision of

TOP (OR=1.2, p=0.06). Risk ratios of foetal cerebral anomalies associated with MMC did not reach significance for microcephaly, ventriculomegaly, talipes and for the level of the defect (Figure S1).

Correlation between prenatal imaging and postnatal or post-mortem findings

A complete review of the prenatal and postnatal imaging was possible in 18/25 live born neonates. Among the cases with a complete CC assessed prenatally, there were 2 cases with complete but stretched CC associated with a postnatal ventriculomegaly. There was an overall good correlation between pre and postnatal findings with a Kappa value of 0.79 $[0.57\text{-}1]_{CI95\%}$ and a proportion of agreement of 82%.

Discussion

Main findings

Foetal cerebral anomalies in case of MMC have been widely described and comprise Chiari II malformation, ventriculomegaly and microcephaly. Our study suggests that other cerebral anomalies may be present in up to 67% of the cases. CC anomalies were the most frequent (60%). Other anomalies included heterotopia or suspicion of gyration disorders.

Strengths and limitations

The strength of our study is represented by the fact that all cases were evaluated by an experienced sonographer in foetal brain imaging with an independent review performed by two observers blinded to the perinatal outcome using a standardized grid. In addition, we were able to demonstrate a good correlation between prenatal and postnatal imaging. However, considering the retrospective design of our study, correlation between prenatal imaging findings and PM examination was possible in only 40% of the cases in which the parents opted for TOP. Moreover, we observed some discrepancies between prenatal imaging and PM examination in up to 50% of the cases. This was in part the consequence of an absence of standardised grid and curves for examination of the CC at PM examination. In line with this, we observed that CC considered with abnormal length at prenatal imaging were classified as normal at PM examination.

Interpretations

Some structural anomalies are virtually unique to patients with MMC and are mainly represented **by a complex pattern of cerebral dysplasia known as Chiari II malformation, ventriculomegaly and microcephaly**[3,4,15]. Other cerebral anomalies, not **specific** to MMC, have been reported in cohorts of children and adults[4]. Among these lesions, CC anomalies are present in up to 70 to 90% of **postnatal cases**[16-19]. The most frequent CC anomalies comprise mainly CC hypoplasia, usually partial hypoplasia of the genu and body, but also CC partial agenesis (mostly rostrum agenesis)[6,16]. Complete CC agenesis remains extremely rare in this population[6,16]. The underlying pathological mechanism of these CC anomalies remains debatable. **In case of postnatal hydrocephalus, the CC often appears as stretched and thin and is**

considered as a usual finding[3]. Similarly, significant ventriculomegaly could be the underlying mechanism of the stretched CC feature we observed in 5 foetuses in our series. In the prenatal period, the high prevalence of early ventriculomegaly in case of MMC also raises the question of its impact on CC development, which is critical between 19 and 21 weeks, with significant growth of the splenium until 24 weeks [12,20]. Interestingly, our rate of CC anomalies of 60% appears to be lower than reported in children or adults patients[6,16-18]. **We also described a novel feature of short CC < 3rd centile, a majority of them < 1st centile (60% of cases), whether complete or incomplete and, in some cases, associated to a thickened feature. These CC anomalies were observed in cases, either with normal ventricular measurement or with moderate ventriculomegaly at midgestation. This casts doubt on a possible causal relationship between ventriculomegaly and CC anomalies and is a clue pointing to the existence of a spectrum of abnormalities of brain development in foetuses with MMC. Also, we would like to highlight the fact that in our experience (unpublished data), it is not possible to thoroughly discriminate a short but complete CC and a CC with very partial agenesis using current foetal imaging techniques. Thus, some CC considered short but complete in this study might be erroneously classified. Overall, the existence of these additional callosal anomalies raises the question of their impact on the postnatal development of these children and requires further evaluation. Indeed, even in normal foetuses, the prognosis of short or thick CC remains a matter of debate considering the very few data available[21-23].**

Besides these already known CC anomalies associated with MMC, we also found PNH and cortical anomalies in 11% and 3% of the cases respectively. Interestingly, in

one of the two prenatal cases in **which** abnormal Sylvian appearance was suspected, gyration was considered as normal at postnatal imaging. Excessive thinness of the pericerebral space in foetuses with MMC makes it difficult to properly analyse the sylvian fissure and it probably accounts for one case being **inappropriately** classified as gyration abnormalities **at** the beginning of the study. The impact of these cortical associated malformations on the postnatal neurobehavioral development also requires further assessment.

The timing of the prenatal diagnosis of these associated cerebral anomalies requires specific attention, especially within the context of fetal surgery for MMC. The majority of the centres offering prenatal repair for MMC, whatever the technique used (open v. fetoscopic surgery), do comply with the MoM study criteria. Thus, only cases of isolated MMC are eligible to a prenatal repair[9]. The common associated findings, such as **talipes**, do not preclude prenatal surgery[9]**. In our centre, 10/13 cases with foetal surgery were found to be associated with cerebral anomalies suspected in the prenatal period and represented by short CC in 7 cases and/or PNH in 6 cases. In the first five cases, these anomalies were suspected between 28 to 32 weeks after foetal surgery had been performed. All these children, although still young, 24 months to four years old at the moment, display normal development. In the other five cases, either short appearance of the CC or suspicion of PNH were suspected before foetal surgery. The parents were informed of these findings and maintained their request for a prenatal repair.** Considering the high rate of CC anomalies in the postnatal series and the favourable outcome of isolated PNH in non-MMC foetuses[24,25], we did not consider these findings as a contraindication for a prenatal repair. However, these children will require specific neurobehavioral development follow-up in the future.

Conclusion

We conclude that foetal brain anomalies other than **Chiari II malformation, ventriculomegaly and microcephaly** are frequently observed during the prenatal period in foetuses with MMC and are predominantly represented by CC anomalies. **Whether these associated cerebral anomalies should have an impact on selecting cases eligible to a foetal surgery needs further evaluation.**

Disclosure of interest:

Non declared. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship:

JMJ, CG and PM contributed to the conception and design of the study and to drafting the work. PM and JG reviewed all prenatal and postnatal imaging. LG, EM, SF, FD, HDL and EB provided the statistical analysis and interpretation of data, and revised it critically for important intellectual content. All authors read and approved the final manuscript.

Details of ethical approval:

Clinical Trial registration NCT01983345; Institutional Review Board approval 13048 **Comité de Protection des Personnes Ile de France XI**, 04th July 2013.

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Legend to the figures:

Figure 1: Ultrasound midsagittal view of the brain in a foetus at 25 weeks with myelomeningocele (uppermost vertebral defect level L3). Short (length < 3rd centile) but complete corpus callosum (arrows).

Figure 2: Foetus at 24 weeks with myelomeningocele (uppermost vertebral defect level L3). Short (length < 1st centile) thickened and incomplete corpus callosum (arrows) with suspicion of rostrum and splenium agenesis. Midsagittal view of the brain: A ultrasound image, and B : T2 weighted MRI image.

Figure 3: Flow chart of the dysraphism cases. MMC: myelomeningocele; LDM: limited dorsal myeloschisis; TOP: termination of pregnancy; CC: corpus callosum; PNH: perinodular heterotopia.

Figure 4: Flow chart of the perinatal outcome of the 70 myelomeningocele cases. MMC: myelomeningocele; CC: corpus callosum; PNH: perinodular heterotopia.

Figure S1: Risk ratio of foetal cerebral anomalies other than Chari type 2 malformation in the 70 myelomeningocele cases. HC: head circumference.