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

3
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17 Shortened running Tittle: fetal cerebral anomalies associated with MMC

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22 **Abstract**

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

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

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

28 **Population:** 70 cases of foetal myelomeningocele.

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

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

36 **Results :** Other cerebral anomalies were represented by 42/70 cases with
37 abnormal CC (60%), 8/70 cases with PNH (11%), 2/70 cases with abnormal gyration
38 (3%). MRI only performed in foetal surgery cases confirmed US findings in all
39 cases, and provided additional findings in 2 cases (PNH). Risk ratios of foetal
40 cerebral anomalies associated with MMC did not reach significance for
41 microcephaly, ventriculomegaly, talipes and for the level of the defect There was
42 an overall good correlation between pre and postnatal findings with a Kappa value of
43 0.79 [0.57-1]_{CI95%} and a proportion of agreement of 82%.

44 **Conclusion:** foetal brain anomalies other than Chiari type 2 malformation, are
45 frequently observed in fetuses with myelomeningocele, predominantly

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

49 **Funding statement:** This study was funded by a grant from the Programme
50 **Hospitalier de Recherche Clinique – PHRC 2013 (French Ministry of Health) and**
51 **was promoted by La Délégation à la Recherche Clinique et l'Innovation de l'AP-**
52 **HP (Assistance Publique-Hôpitaux de Paris).**

53
54 **Key-words:** myelomeningocele, prenatal diagnosis, ultrasound, cerebral anomalies,
55 corpus callosum

56
57 **Tweetable abstract:** foetal cerebral anomalies other than Chiari type 2 malformation,
58 microcephaly and ventriculomegaly may be associated with MMC in up to 67% of the
59 cases.

60

61 **Introduction**

62 Myelomeningocele (MMC) represents a specific form of neural tube defect with
63 an incidence of approximatively 3-4 per **10.000** live births in Europe¹. **The exposure of**
64 **the non-neurulated spinal cord and nerve roots to external environment is**
65 **responsible for motor dysfunction** (weakness or paralysis) and for both bowel and
66 bladder dysfunction². **In addition, there are specific brain anomalies associated with**
67 **this defect, most commonly Chiari type 2 malformation and frequent associated**
68 **ventriculomegaly and microcephaly³.**

69 In neonates undergoing surgical repair of myelomeningocele, a wide spectrum in
70 terms of size, shape, level of defect and appearance of cerebral structures is observed
71 (the posterior fossa structures, the corpus callosum and the cerebral cortex)^{3,4}. Chiari
72 type 2 malformation is observed in almost all cases of MMC^{4,5}. **Hydrocephalus is**
73 **frequently seen, being present in about half of the patients with MMC³.** Corpus
74 callosum (CC) anomalies are also frequent in cohorts of adult patients, with
75 controversies on the underlying mechanism leading to these anomalies, as they are
76 often associated with hydrocephalus in these patients^{3,6,7}.

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

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

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

86

87 **Material and Methods**

88 **This was a retrospective study of 70 cases of fetuses with MMC** examined
89 between November 2013 and February 2019 in the setting of the PRIUM study⁸: French
90 study on prenatal repair of foetal myelomeningoceles using open surgery technique⁹
91 (Clinical Trial registration NCT01983345; Institutional Review Board approval 13048).

92 **There was no patient and public involvement.** Patients with suspicion of foetal MMC
93 were referred to our centre. **As part of our usual plan of care, all cases are evaluated**
94 **by a second line US examination performed by one experienced operator (CG).**
95 **Additional MRI examination is offered either systematically in case of foetal**
96 **surgery, or when additional anomalies are suspected at ultrasound examination.**
97 **In our centre there is no policy of systematic fetal MRI in case of typical MMC at**
98 **second line US examination.**

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

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

112 The gestational age at diagnosis of MMC was recorded. When several US scans
113 were performed, results of the first complete evaluation, the nearest to the diagnosis,
114 were taken into account. **The level of the MMC defect was classified as low when**
115 **the uppermost vertebral defect was below L3 or as high when it was L3 or higher.**
116 **Regarding the fetal brain, the US parameters recorded were (1) microcephaly**
117 **defined by head circumference < 3rd centile¹⁰, (2) presence or absence of**
118 **ventriculomegaly defined by a diameter of the ventricular atrium measured on the**
119 **axial view ≥ 10 mm, (3) anomalies of the CC and (4) associated parenchymal**
120 **anomalies represented by subependymal heterotopia or gyration disorders.**
121 Anomalies of the CC included absent, short, thick or apparently normal but stretched
122 CC. **The CC was defined as short when length measurement was < 3rd centile**
123 **using reference curves by Cignini et al.¹¹. A short CC was then classified as**
124 **complete (figure 1) or incomplete (figure 2); when incomplete, the missing part**
125 **was noted (rostrum, genu, body, splenium). A CC was defined as thick when ≥ 3**
126 **mm at the mid-coronal plane as described by Achiron et al. ¹². Extra-cranial**
127 **anomalies and the presence of foetal talipes were also recorded.**

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

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

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

144 Both prenatal and postnatal imaging (head US and/or brain MRI) were reviewed
145 blind to the perinatal outcome by the same team (PM and JG). Cerebral anomalies were
146 **analysed** as described above. **For the CC postnatal imaging, the following features**
147 **were recorded: (1) length of the corpus callosum, considered as short when**
148 **inferior to the 3rd centile according to C. Garel curve¹³ (2) objective thickness of the**
149 corpus callosum measured at the level of the genu, body, and splenium, and considered
150 thickened when one of the measurement was superior to the 97th percentile¹³.

151

152 Statistical analysis.

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

164

165 **Results**

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

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

181

182 **Prenatal imaging findings**

183 The median GA at second line US examination was 23 weeks^{+3d} (range: 20
184 weeks^{+3d} - 25 weeks^{+6d}). **The uppermost vertebral defect was below L3 in 45/70**
185 **cases (64%). Foetal talipes was associated with MMC in 20/70 cases (29%). A**
186 **Chiari type 2 malformation was observed in all cases. A microcephaly was**
187 **observed in 32/70 cases (46%), a ventriculomegaly was observed in 39/70 cases**
188 **(56%). Overall, other cerebral anomalies were diagnosed in 47/70 (67%) of the**
189 **cases in the prenatal period. We observed 42/70 cases with abnormal CC (60%),**
190 **8/70 cases with PNH (11%), 2/70 cases with abnormal gyration (3%). Additional**
191 **fetal MRI was performed in 12/70 cases (17%) only in cases where foetal surgery**
192 **was considered. MRI confirmed US findings in all cases, and provided additional**
193 **findings in 2 cases (PNH).**

194

195 ***MMC associated with ventriculomegaly***

196 **In cases associated with ventriculomegaly, no additional cerebral**

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

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

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

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

214 *MMC without ventriculomegaly*

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

218 **cases, and for TOP in 6 cases.**

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

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

226

227 **Perinatal outcome**

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

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

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

242

243 **Correlation between prenatal imaging and postnatal or post-mortem findings**

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

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250

251 **Discussion**

252 Main findings

253 **Foetal cerebral anomalies in case of MMC have been widely described and**
254 **comprise Chiari II malformation, ventriculomegaly and microcephaly. Our study**
255 **suggests that other cerebral anomalies may be present in up to 67% of the cases.**

256 CC anomalies were the most frequent (60%). Other anomalies included heterotopia or
257 suspicion of gyration disorders.

258

259 Strengths and limitations

260 The strength of our study is represented by the fact that all cases were evaluated
261 by an experienced sonographer in foetal brain imaging with an independent review
262 performed by two observers blinded to the perinatal outcome using a standardized grid.
263 In addition, we were able to demonstrate a good correlation between prenatal and
264 postnatal imaging. However, considering the retrospective design of our study,
265 correlation between prenatal imaging findings and PM examination was possible in only
266 40% of the cases in which the parents opted for TOP. Moreover, we observed some
267 discrepancies between prenatal imaging and PM examination in up to 50% of the cases.
268 This was in part the consequence of an absence of standardised grid and curves for
269 examination of the CC at PM examination. In line with this, we observed that CC
270 considered with abnormal length at prenatal imaging were classified as normal at PM
271 examination.

272

273 Interpretations

274 Some structural anomalies are virtually unique to patients with MMC and are
275 mainly represented **by a complex pattern of cerebral dysplasia known as Chiari II**
276 **malformation, ventriculomegaly and microcephaly**^{3,4,15}. Other cerebral anomalies,
277 not **specific** to MMC, have been reported in cohorts of children and adults⁴. Among
278 these lesions, CC anomalies are present in up to 70 to 90% of **postnatal cases**¹⁶⁻¹⁹.
279 The most frequent CC anomalies comprise mainly CC hypoplasia, usually partial
280 hypoplasia of the genu and body, but also CC partial agenesis (mostly rostrum
281 agenesis)^{6,16}. Complete CC agenesis remains extremely rare in this population^{6,16}. The
282 underlying pathological mechanism of these CC anomalies remains debatable. **In case**
283 **of postnatal hydrocephalus, the CC often appears as stretched and thin and is**

284 **considered as a usual finding³. Similarly, significant ventriculomegaly could be**
285 **the underlying mechanism of the stretched CC feature we observed in 5 fetuses**
286 **in our series. In the prenatal period, the high prevalence of early ventriculomegaly**
287 **in case of MMC also raises the question of its impact on CC development, which**
288 **is critical between 19 and 21 weeks, with significant growth of the splenium until**
289 **24 weeks^{12,20}. Interestingly, our rate of CC anomalies of 60% appears to be lower than**
290 **reported in children or adults patients^{6,16-18}. We also described a novel feature of**
291 **short CC < 3rd centile, a majority of them < 1st centile (60% of cases), whether**
292 **complete or incomplete and, in some cases, associated to a thickened feature.**
293 **These CC anomalies were observed in cases, either with normal ventricular**
294 **measurement or with moderate ventriculomegaly at midgestation. This casts**
295 **doubt on a possible causal relationship between ventriculomegaly and CC**
296 **anomalies and is a clue pointing to the existence of a spectrum of abnormalities**
297 **of brain development in fetuses with MMC. Also, we would like to highlight the**
298 **fact that in our experience (unpublished data), it is not possible to thoroughly**
299 **discriminate a short but complete CC and a CC with very partial agenesis using**
300 **current foetal imaging techniques. Thus, some CC considered short but complete**
301 **in this study might be erroneously classified. Overall, the existence of these**
302 **additional callosal anomalies raises the question of their impact on the postnatal**
303 **development of these children and requires further evaluation. Indeed, even in**
304 **normal fetuses, the prognosis of short or thick CC remains a matter of debate**
305 **considering the very few data available²¹⁻²³.**

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

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

315 The timing of the prenatal diagnosis of these associated cerebral anomalies
316 requires specific attention, especially within the context of fetal surgery for MMC. The
317 majority of the centres offering prenatal repair for MMC, whatever the technique used
318 (open v. fetoscopic surgery), do comply with the MoM study criteria. Thus, only cases of
319 isolated MMC are eligible to a prenatal repair⁹. The common associated findings, such
320 as **talipes**, do not preclude prenatal surgery⁹. **In our centre, 10/13 cases with foetal**
321 **surgery were found to be associated with cerebral anomalies suspected in the**
322 **prenatal period and represented by short CC in 7 cases and/or PNH in 6 cases. In**
323 **the first five cases, these anomalies were suspected between 28 to 32 weeks after**
324 **foetal surgery had been performed. All these children, although still young, 24**
325 **months to four years old at the moment, display normal development. In the other**
326 **five cases, either short appearance of the CC or suspicion of PNH were suspected**
327 **before foetal surgery. The parents were informed of these findings and maintained**
328 **their request for a prenatal repair.** Considering the high rate of CC anomalies in the
329 postnatal series and the favourable outcome of isolated PNH in non-MMC foetuses^{24,25},
330 we did not consider these findings as a contraindication for a prenatal repair. However,
331 these children will require specific neurobehavioral development follow-up in the future.

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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:

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436 **Legend to the figures:**

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

440
441 **Figure 2: Foetus at 24 weeks with myelomeningocele (uppermost vertebral defect**
442 **level L3). Short (length < 1st centile) thickened and incomplete corpus callosum**
443 **(arrows) with suspicion of rostrum and splenium agenesis. Midsagittal view of**
444 **the brain: A ultrasound image, and B : T2 weighted MRI image.**

445
446 **Figure 3:** Flow chart of the dysraphism cases. MMC: myelomeningocele; LDM: limited
447 dorsal myeloschisis; TOP: termination of pregnancy; CC: corpus callosum; PNH:
448 perinodular heterotopia.

449
450 **Figure 4: Flow chart of the perinatal outcome of the 70 myelomeningocele cases.**
451 MMC: myelomeningocele; CC: corpus callosum; PNH: perinodular heterotopia.

452
453 **Figure S1: Risk ratio of foetal cerebral anomalies other than Chari type 2**
454 **malformation in the 70 myelomeningocele cases. HC: head circumference.**