Longitudinal evaluation of brain development in fetuses with congenital diaphragmatic hernia on MRI: an original research study

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Abstract

Objective To document longitudinal changes in brain development in fetuses with congenital diaphragmatic hernia (CDH). Design Retrospective cohort study Setting Single tertiary fetal surgery center Population Fetuses with isolated CDH and at least two MRI-examinations (n=42 fetuses). Fifty-six fetuses who underwent MRI for a condition not interfering with fetal brain development or fetuses from healthy volunteers served as controls. Methods Biometry included biparietal and fronto-occipital diameter, ventricular atrial width, transcerebellar diameter, head circumference and width of the extra-axial space. Cortical maturation was assessed using a qualitative and quantitative grading system. 3D volumes were segmented for white matter, intra-axial and extra-axial cerebrospinal fluid and cerebellum. Main outcome measures Brain development on MRI with subjective and objective assessment. Results The mean GA at first MRI was 28.0 ± 2.1 wks and at the second 33.2 ± 1.3 wks. The mean GA in controls was 30.7 ± 4.2 wks. At 28 weeks CDH fetuses displayed abnormal maturation grading ($p<0.003$) and fissure depth ($p<0.05$). By 33 wks, the brain grading indices were still abnormal ($p<0.01$), but fissure depth measurements were in the normal range ($p>0.05$). Also, the extra-axial fluid and the ventricular volume were increased (resp. p 0.0054 and p 0.0243). There was no difference in white matter or cerebellum volume ($p>0.05$). Conclusions Brain development in CDH fetuses around 28 weeks appears to be delayed. This is less prominent at 33 weeks. In addition, there was an increase in ventricular and extra-axial space volume in the third trimester.

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Running title:

Longitudinal brain development in CDH

ABSTRACT

Objective

To document longitudinal changes in brain development in fetuses with congenital diaphragmatic hernia (CDH).

Design

Retrospective cohort study

Setting

Single tertiary fetal surgery center

Population

Fetuses with isolated CDH and at least two MRI-examinations (n=42 fetuses). Fifty-six fetuses who underwent MRI for a condition not interfering with fetal brain development or fetuses from healthy volunteers served as controls.

Methods

Biometry included biparietal and fronto-occipital diameter, ventricular atrial width, transcerebellar diameter, head circumference and width of the extra-axial space. Cortical maturation was assessed using a qualitative and quantitative grading system. 3D volumes were segmented for white matter, intra-axial and extra-axial cerebrospinal fluid and cerebellum.

Main outcome measures

Brain development on MRI with subjective and objective assessment.

Results

The mean GA at first MRI was 28.0 ± 2.1 wks and at the second 33.2 ± 1.3 wks. The mean GA in controls was 30.7 ± 4.2 wks. At 28 weeks CDH fetuses displayed abnormal maturation grading ($p<0.003$) and fissure depth ($p<0.05$). By 33 wks, the brain grading indices were still abnormal ($p<0.01$), but fissure depth measurements were in the normal range ($p>0.05$). Also, the extra-axial fluid and the ventricular volume were increased (resp. p 0.0054 and p 0.0243). There was no difference in white matter or cerebellum volume ($p>0.05$).

Conclusions

Brain development in CDH fetuses around 28 weeks appears to be delayed. This is less prominent at 33 weeks. In addition, there was an increase in ventricular and extra-axial space volume in the third trimester.

Key words: congenital diaphragmatic hernia, magnetic resonance imaging, brain volume, segmentation, brain development, 3D volume

Tweetable abstract

Longitudinal brain development on MRI in CDH fetuses is significant altered compared to normal controls in the third trimester.

Introduction

Congenital diaphragmatic hernia (CDH) is a severe birth defect, occuring in approximately 1 in 3,000 live born neonates. [1]Despite optimal neonatal treatment, the disease is associated with high mortality and survivors often suffer short and long term morbidities.[1] These include respiratory, gastro-intestinal and neurologic impairments.[2]Neurodevelopmental delays, as well as behavioral difficulties have been linked to CDH in the past and certain risk factors have been suggested, including gestational age at birth, disease severity, associated anomalies, the requirement for extracorporeal membrane oxygenation and long stay in the neonatal intensive care unit. [2-5]

In infants with CDH, imaging studies have demonstrated several abnormalities including increased extra-axial space, delayed sulcation and white matter injury but the exact mechanisms remain unclear. As for other congenital malformations with an increased risk for neurodevelopmental abnormalities, parents may ask whether these are already present at the time of prenatal diagnosis, or they are more likely to be postnatally acquired. This will become even more important with the advent of effective fetal therapy [6, 7], which aims at fetuses with the more severe forms of CDH. For those parents and physicians likewise will want to understand whether brain development in CDH is already altered prenatally, and when present, if this would be severity dependent.[8] Currently, there is limited data on in utero brain development in CDH fetuses.

[8-10]. Radhakrishnan et al described enlargement of the extra-axial space and congestion of the venous sinuses in the third trimester. A further study reported a correlation between cerebellar and vermian dimensions and the severity of lung hypoplasia (evidenced by a lower fetal lung volume).[8] Recently, we described in a longitudinal ; study changes in cerebellar growth, and correlated this to disease severity; this study however was done by ultrasound.[5]

The objective was to describe brain development in CDH fetuses however using the gold standard imaging modality (MRI) to document cortical folding as well as the dimensions and volume of different brain structures in comparison to that in normal fetuses longitudinally during the second half of pregnancy.

Methods

This is a retrospective cohort study including all consecutive fetuses, who were diagnosed with isolated CDH at the University Hospitals Leuven, Belgium, between January 2007 and May 2019 (n=283), and in whom at least two MRI examinations were available (n=48 fetuses). Isolated CDH was defined as the presence of normal prenatal genetic testing either conventional karyotyping or comparative genomewide hybridization array analysis[11] and the absence of a major structural anomaly. Fetuses with poor quality brain images due to motion artefacts were excluded (n=6). As controls, we used images from fetuses that underwent MRI imaging for an unrelated condition which was presumed not to involve with brain development, assessed between 20 and 37 weeks gestational age (GA) (n=26). The precise indications for MRI assessment are provided in table S1 and all brain examinations were reported as showing normal appearances for gestational age. We added to this control cohort additional fetal images (n=30) obtained by our collaborators from King's College London (Robert Steiner MRI Unit in Hammersmith Hospital, London, U.K.) between November 2007 and May 2013 on healthy pregnant women whom had normal neurodevelopmental follow up .[12] Selected patients were chosen to be equally distributed over the same gestational age period.

MRI examination

At the University Hospitals Leuven MRI was performed as being part of standard clinical care using a clinical 1.5 Tesla system (Siemens Aera; Siemens, Erlangen, Germany). Two small body coils were placed adjacent to each other over the maternal abdomen. The mother was positioned in the supine or left lateral decubitus position. Prior to September 2015, maternal sedation (flunitrazepam 0.5 mg per os 20 – 30 minutes prior to the examination) was used when GA was under 30 weeks, a practice that was since abandoned. [13, 14] . The protocol includes T2-weighted half-Fourier acquired single-shot turbo spin-echo (HASTE) sequences, obtained in three orthogonal planes relative to the fetal head (coronal ,axial and sagittal). Scanning parameters were echo time (TE) 133ms; repetition time (TR) 1,000ms; slice thickness (ST) 3.0–4.0mm; absence of intersection gap; and field of view (FOV) 300 x 300 - 380x380 mm. Fetal body imaging was performed with T2-weighted HASTE sequences, obtained in three orthogonal planes relative to the fetal body (coronal, axial and sagittal). Scanning parameters were TE 90ms; TR 1000ms; ST 3.0–4.0mm; absence of intersection gap; and FOV 300 x 300 - 380x380 mm. Parameters from the MRI examination in controls scanned at the Robert Steiner MRI Unit in Hammersmith Hospital, London, UK were similar and can be found in Kyriakopoulou et al.[12]

These examinations were performed using a 1.5 T MRI System (Philips Achieva; Philips Medical systems, Best, the Netherlands) with a 32-channel cardiac array coil. The mother was positioned in a left lateral tilt, no sedation was used. The images used for this study included T2-weighted images in transverse, sagittal, and coronal planes. T2-weighted Single Shot Turbo Spin Echo sequence was acquired using the following scanning parameters: TE = 160 ms, TR = 15,000 ms, ST 2.5 mm, slice overlap of 1.5 mm.[8]

Assessment of brain development and severity of pulmonary hypoplasia

Biometric measurements were made on standard T2-weighted images, and included brain and skull biparietal diameter (BPD) and fronto-occipital diameter (FOD), atrial width and transverse cerebellar diameter (TCD), measured following Garel et al. [13] (figure 1) Head circumference (HC) and extra-axial space percentiles were calculated according to Kyiakopoulou et al . [12] Fetal cortical development was scored using the grading

system described by Pistorius et al. [15] and measured following Egana-Ugrinovic et al.[16], which we have used and reported previously.[17] The following brain regions were scored subjectively (by D.E. supervised by M.A.): frontal, parietal, temporal, mesial, insular and occipital cortex. [15] Selected primary sulci and gyri were graded and/or measured, including the parieto-occipital fissure, the central, calcarine, superior temporal, cingulate sulcus and, for the opercularization, the Sylvian fissure.[15, 16] In addition to the Sylvian fissure depth, which reflects the distance between the inner part of the skull and the insular cortex, the insular depth was also measured, i.e. the distance from the midline to the insular cortex.[17] The sum of all the graded fissures provides a total grading score for the whole brain as well as for each hemisphere. [18]

3D super-resolution reconstruction (SRR) volumes were created from the standard T2-weighted 2D stacks displaying the fetal brain, using NiftyMIC, a publicly available and state-of-the-art SRR algorithm.[19] The SRR volumes were automatically segmented for white matter, ventricular system (lateral ventricles, third ventricle, fourth ventricle and aqueduct) and the cavum septi pellucidi and cavum vergae, extra-axial space and cerebellum with manual correction when necessary (D.E. supervised by M.A). A deep learning algorithm for the automatic segmentation of white matter, ventricular system, and cerebellum was used for the first volumes that were processed.[20] As the number of volumes segmented for the extra-axial space increases, we trained a new deep learning-based segmentation algorithm[21] based on a partially supervised learning method that segments automatically white matter, ventricular system, cerebellum, and extra-axial space. These segmentations were used for volumetric analysis when the quality of the SRR volume allowed further analysis (determined by D.E. supervised by M.A. and L.F.). (Figure 2)

In all cases were the fetus underwent FETO the date of it was noted and the time interval between operation and second MRI was documented. The severity of the pulmonary hypoplasia in fetuses with CDH was assessed on MR images by measuring the right, left and total fetal lung volume (TFLV), the fetal body volume (FBV), liver position, intra-thoracic liver volume and thoracic volume, again measured manually (D.E. supervised by M.A.). From those, we calculated the O/E TFLV ratio[22] and the liver-to-thoracic volume ratio (LiTR).[23] The latter ratios provide biometric measurements in the index case, that are independent of gestational age and /or fetal weight.

Statistics

Data were analyzed with Prism for Windows version 7.0 (Graphpad Software, San Diego, CA, USA) and Analyze-it (Analyze-it for Microsoft Excel 4.81.4; Analyze-it Software, Leeds, UK). Data were checked for normality using the Shapiro Wilk test for normality. All data are expressed as mean +- standard deviation or median (interquartile range) depending on normality; sub classifications were illustrated as number (percentage). Regression analysis of the different variables (TCD, Skull and brain BPD, skull and brain FOD, atrial width, calculated HC and extra-axial CSF, total grading score and the different volumes) in normal fetuses allowed calculation of normal ranges for each parameter. Differences between the CDH population at the first and the second time point and the controls were studied with the Wilcoxon-Mann-Whitney test, using the observed/expected ratios, which controls for gestational age at imaging. To analyze the evolution over time, a Wilcoxon hypothesis test was performed on the difference in observed/expected ratio between the second and first time point. Correlations were assessed using Pearson's correlation coefficient and Bonferroni correction for multiple comparisons was made.

Results

Study population

Twenty-eight fetuses had left, 12 right and 2 bilateral CDH (n=42; Table 1). The mean GA at first MRI was 28.0 +- 2.1 weeks (median: 28.0; range: 22.4 – 32.0) and at the second 33.2 +- 1.3 weeks (median: 33.6; range: 29.9 – 35.0). The mean difference between the two measurements was 4.8 +- 1.9 weeks (range: 1.1 – 8.4). FETO was performed in 40 fetuses (95%) with a mean GA at FETO of 29.3 +-1.5 weeks (median: 29.4; range: 26.1-32.7). The mean number of days between FETO and second MRI was 26.45+-11.76. Balloon removal was performed at a mean GA of 33.5 +- 1.1 weeks (median: 33.9; range: 30.0 – 34.9). The mean GA in controls was 30.7 weeks +- 4.2 (median: 30.5; range: 20.6 – 37.7). SRR for volumetric analysis was

possible in 25 (60%) fetuses at the first time point, and 23 (55%) at the second time point. Further details of success rates for volumetric measurements at the first and second time point and numbers of available measures from paired data are displayed in table S2. In controls, 52 (93%) reconstructions were possible.

Measurement at first time point.

The biometry of the fetal brain (BPD, FOD and TCD) and skull (BPD and FOD) was not different between fetuses with CDH and those without. The extra axial space and atrial width in CDH fetuses were within the normal range, except for one fetus having mild ventriculomegaly (11 mm). The total brain cortical grading for fetuses with CDH was significantly lower than in controls ($p<0.003$). (Figure 3) When comparing the brain grading of each hemisphere, the difference was present on both sides (both $p<0.003$). The opercularization was delayed on the left side ($p=0.011$), but not on the right ($p=0.057$). There was a reduced depth of the parieto-occipital fissure ($p<0.003$ on the right and $p=0.003$ on the left), cingulate fissure (left and right $p<0.003$) but the depth of the calcarine fissure was normal on both sides ($p>0.05$) compared with controls. The Sylvian fissure was only just significantly deeper on the right ($p=0.042$), but not on the left ($p=0.055$) in fetuses with CDH. The insular depth in fetuses with CDH was within the normal range ($p>0.05$). There was no difference in volume of the total skull, extra-axial space, ventricular system, white matter or cerebellum between CDH fetuses and normal controls. (table S2)

Measurement and change at second time point.

At the second time point, most measurements were within the normal range, except for the atrial width ($p<0.003$), the ventricular volume ($p=0.024$) and the extra-axial space volume ($p=0.005$), which were larger than normal. The total brain cortical grading was lower than normal ($p=0.011$), on both sides ($p=0.019$ and $p=0.035$), and the opercularization was within the normal range ($p>0.05$). (Figure 4) The Sylvian fissure depth was deeper (both $p<0.003$) but all other fissures were comparable with controls . Compared to findings on initial scans, the atrial width increased further, the brain fissures which were initially less deep, measured within the normal range. The depth of the Sylvian fissure, which was normal earlier on, became abnormally deeper; also the left brain hemisphere cortical grading score was abnormal, but significantly less than at the first time point. Although the difference in brain scoring between the CDH population and the controls was smaller at the second time point, this was not significantly different from the first time point. (table S2)

Correlation with lung hypoplasia severity indicators

No correlation was found at either time-point between the liver-to-thorax ratio or o/e TFLV on one side, or the o/e total brain grading, o/e skull and brain FOD, o/e atrial width, o/e ventricular volume or o/e extra-axial space volume, o/e cerebellar volume or o/e total intracranial volume on the other side. No significant difference was found in the variables mentioned above when comparing fetuses with left and right CDH.

Discussion

Main findings

We found atypical brain morphology in fetuses with isolated CDH at 28 weeks of gestation, both on qualitative and quantitative scoring of different brain areas. By 33 weeks, the findings were less discrepant from those observed in normal fetuses. However, most fetuses (40/42, 95%) underwent FETO in between, hence severity of hypoplasia may be rather high and/or there may have been an effect of fetal surgery. We also found a significant increase in volume of extra-axial and ventricular fluid at 33 weeks of gestation in CDH.

Strengths

The strength of our study is that brain development was longitudinally documented with a qualitative and quantitative scoring methods. Second, we used a sophisticated segmentation technique [21]based on high-resolution 3D-volumes of the fetal brain.[19]

Limitations

We acknowledge several limitations. First, its retrospective design may result in selection bias as we included only cases with more than one good quality MRI examination. Second, as a fetal surgery center, the group of fetuses with severe hypoplasia is overrepresented; in addition most of them received a prenatal intervention, which changes the natural history [6, 7, 24]. Third, we have no standardized postnatal follow up information on these cases, as many patients do not deliver in our center.

Interpretation

On postnatal imaging, Danzer et al. reported a lower total maturation score in CDH infants after birth (6). Along the same lines, Lucignani et al reported reduced cortical maturation in extended brain areas of CDH newborns compared to healthy controls. [25] In earlier studies based on *prenatal* images, fetuses with CDH had brain sulcation scores, which are indicators of prenatal brain maturation, within the normal range between 20 and 37 weeks.[8, 26]One study on infants who had both pre- and postnatal imaging, reported signs of brain injury (e.g. hemorrhage, white matter injury, ...) on postnatal, *but not on prenatal MRI* . In that study , the injury score correlated with the degree of pulmonary hypoplasia, evidenced by the o/e TFLV.[26] Also, there was no indication of delayed sulcation in the prenatal period in those fetuses.

Conversely, this study demonstrates that CDH fetuses have indications of atypical brain development, i.e. there was a significant delay at 28 weeks and 33 weeks of gestation. By 33 weeks the quantitative scores were in the normal range. However, quantitative scoring was performed on primary and not on secondary sulci, limiting the detection of subtle folding abnormalities. [27] The *qualitative*scoring system we used, allows for a thorough scoring of brain sulcation throughout a wide GA range, as it evaluates the primary formation as well as the presence of secondary and tertiary sulcation.[15] We were not (yet) able to compare our morphologic findings with postnatal clinical neurobehavioral assessment. In CDH infants, 9% (4-14%) have abnormal opercularization, which translates later into language and speech abnormalities.[28] In our study, grading of the operculum was significantly lower at the first time point as well as at the second time point, although only left-sided. This may, at least in theory, have functional consequences: in earlier studies scores using the same system correlated well with the Neonatal behavioral Assessment Scale [29], albeit this was in fetuses with isolated non-severe ventriculomegaly or with late-onset growth restriction. (15, 23) On the other hand, one must take into account that any abnormality observed postnatally may as well have been acquired after birth.

The significant increase in volume of all fluid compartments at 33 weeks of gestation in CDH we observed, is in line with work of Radhakishnan et al. who reported enlarged extra-axial spaces in the third trimester.[8] Because fetuses had normal biometry of the cerebral hemispheres and lacked major parenchymal abnormalities, the authors questioned the clinical relevance of these findings.(7) One other study has reported lower cognitive scores and lesser language skills in children with larger extra-axial spaces. (6)

Irrespective of the functional impact, what would cause atypical brain folding as we observed in CDH fetuses, remains unclear. One factor may be a degree of hemodynamic dysfunction. We have previously reported a decline in the middle cerebral artery peak systolic velocity, hence in brain perfusion in fetuses with CDH .[5, 30] One may recognize similarities with circulatory disturbances in fetuses with congenital heart defects, which coincide with signs of abnormal brain development. In hypoplastic left heart syndrome (HLHS) a lower blood flow velocity has been associated with lower brain volume.[31, 32] Furthermore, fetuses with HLHS and other congenital heart defects display delayed brain maturation in the late second and early third trimester, and again, this has been linked to abnormal hemodynamics and oxygen delivery.[33] Lucigagni et al based actually support this theory to explain their recent findings of altered cortical maturation in CDH newborns.[25]

Abnormal extra-axial and intraventricular fluid volumes have been previously explained by a change in cardiac output in CDH caused by herniation of abdominal structures in turn leading to mild or moderate cardiac hypoplasia in left-sided CDH.[34] Also cardiac compression may compromise venous return. [2634] This may in turn cause venous congestion and lead to decreased CSF resorption, [35] and an overall increase of intracranial fluid. It may be useful to assess cardiac function and hemodynamics in more detail in fetuses with CDH to study whether there is a link with brain development.

Conclusion

In conclusion, we report delayed brain development in CDH fetuses around 28 weeks, which becomes less prominent at 33 weeks. This mandates further investigation into the sulcation pattern beyond 34 weeks in CDH fetuses, including quantitative methods, e.g. cortical folding pattern analysis[36], cortical thickness, local gyrification index[25], as well as earlier in fetuses not undergoing fetal therapy. We also observed an increase in extra-axial space and also in ventricular volume in the third trimester. Of note is that there was no correlation between brain development and the severity of lung hypoplasia in this highly selected group.

Tables and figures

Figure 1: T2- weighted images of the fetal brain in the coronal (A, B) and sagittal plane (C). Transverse cerebellar diameter (black line in A) and atrial width (white line in A) are shown. In B the biparietal diameter of the brain (white line) and the skull (black line) are illustrated. The fronto-occipital diameter of the brain (white line in C) and skull (black line in C) is measured as demonstrated.

Table 1: General characteristics of the congenital diaphragmatic hernia cohort.

Figure 2: T2-weighted images in the axial (A), coronal (B) and sagittal (C) plane illustrating automated segmentations of the extra-axial space (yellow), white matter (red), ventricular system (green) and cerebellum (blue).

Figure 3: Graphs demonstrating the observations in the normal population (black triangles) and CDH cohort at the first time point (white circles) of the total skull volume, total brain grading, extra-axial space volume, cerebellar volume, atrial width and ventricular volume. The trend line of the controls (full black line) and CDH population at time point 1 (dashed black line) is shown. The provided p-value is the significance level of the Wilcoxon-Mann-Whitney test. The 95% confidence interval (red lines) is also shown.

Figure 4: Graphs demonstrating the paired observations of the total skull volume, total brain grading, extra-axial space volume, cerebellar volume, atrial width and ventricular volume. The provided p-value is the significance level of the Wilcoxon-Mann-Whitney test comparing the observations at the second time point in fetuses with congenital diaphragmatic hernia compared to normal controls. The mean value of the control populations (full line) with the 95% confidence interval (dashed line) are also shown.

Table S1: Overview of indications for scanning the normal cohort.

Table S2: Number of fetuses available, mean and standard deviation and respective p-values of the Wilcoxon-Mann-Whitney test performed between the normal controls and fetuses with CDH at time point 1 and 2 respectively as well as of the Wilcoxon hypothesis test of the difference between time point 2 and 1.

Contribution to authorship

DE: Data acquisition, data analysis, interpretation of the data, drafting and revising manuscript

MA: Design of the study, data acquisition, data analysis, interpretation of the data, drafting and revising manuscript.

LVdV: Design of the study, data analysis, interpretation of the data, revising manuscript

LF: Data analysis, revising manuscript

PP: Data acquisition, revising manuscript

VK: Data acquisition, revising manuscript

LDC: Data acquisition, revising manuscript

FR: Data acquisition, revising manuscript

PD: Data acquisition, revising manuscript

TV: Data analysis, revising manuscript

MR: Data acquisition and analysis, revising manuscript

JD: Design of the study, data analysis, interpretation of the data, revising manuscript.

Ethics Approval

This study was approved by the Ethics Committee of the University Hospitals Leuven (S56786).

Disclosure statement:

The authors report no conflicts of interest

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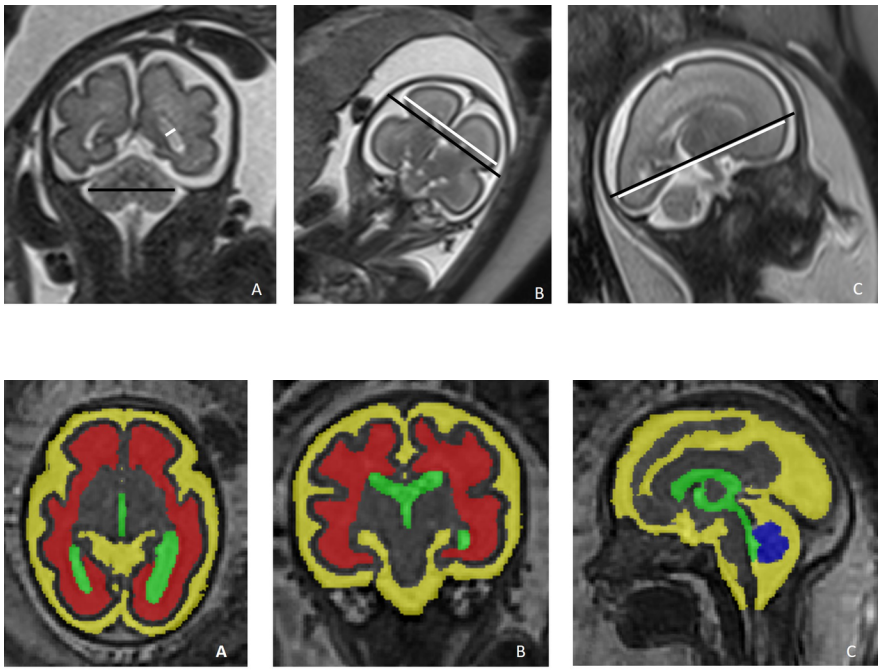

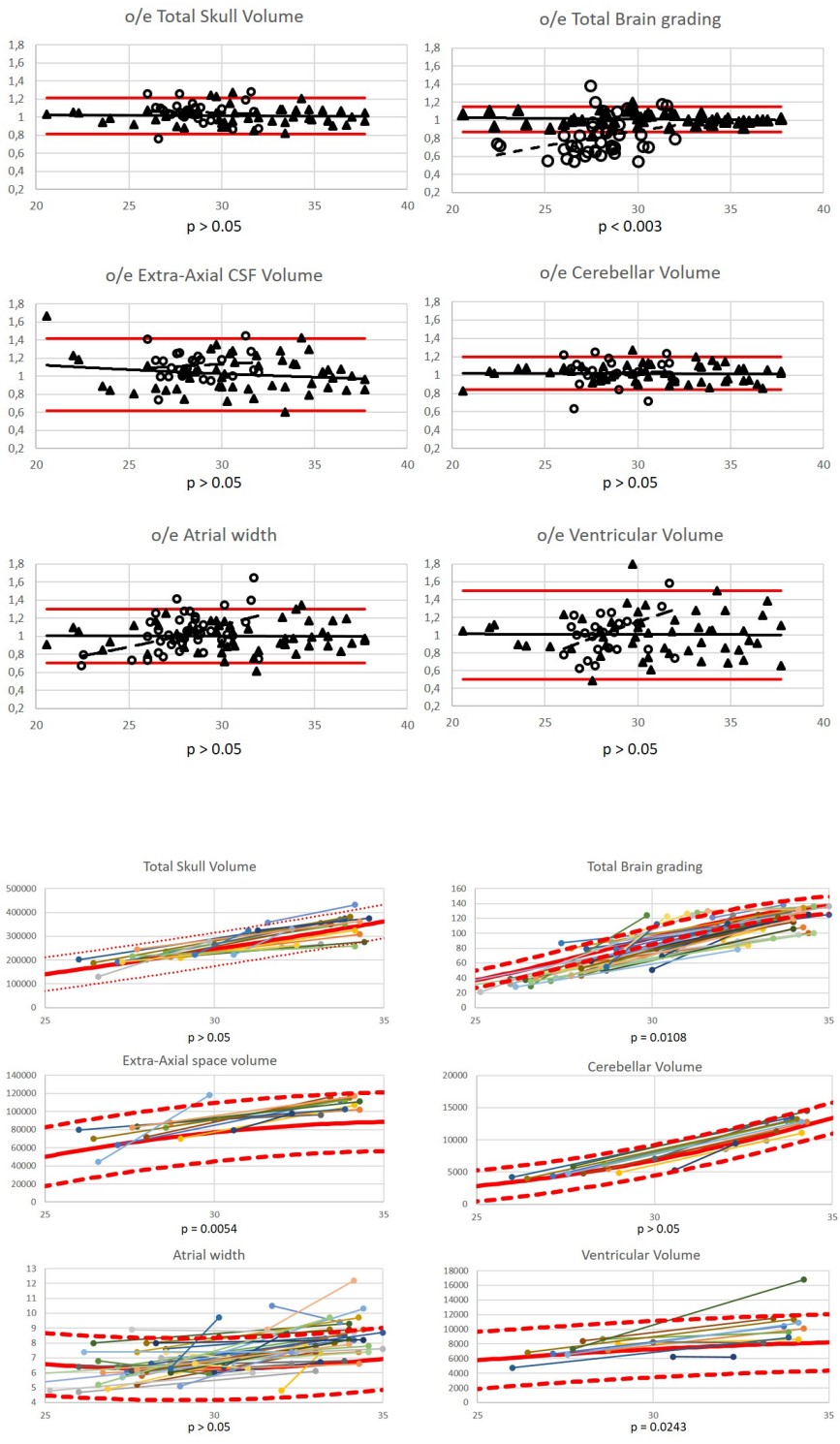

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