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1 **Cerebral blood flow of the frontal lobe in untreated children with trigonocephaly vs healthy controls:**
2 **an arterial spin labeling study**

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22 **Key words:** ASL, trigonocephaly, brain, perfusion, CBF, craniosynostosis

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25

26 **Abstract**

27 **Background**

28 Craniofacial surgery is the standard of treatment for children with moderate to severe trigonocephaly.
29 However, assessing the risk of suboptimal neurodevelopment and added value of surgery is difficult in
30 individual cases. In this study we aim to address the hypothesis that brain development is restricted in
31 trigonocephaly patients by investigating cerebral blood flow in the frontal lobe.

32 **Methods**

33 Between 2018 and 2020, we prospectively included trigonocephaly patients for whom a surgical
34 correction was considered in an MRI study measuring cerebral perfusion with arterial spin labeling (ASL).
35 The mean value of cerebral blood flow (CBF) in the frontal lobe was calculated for each subject and
36 compared between the trigonocephaly patients and healthy controls.

37 **Results**

38 MRI scans of 36 trigonocephaly patients (median age 0.5y, IQR 0.3, 11 females) were included and
39 compared with 16 controls without cerebral pathology (median age 0.83y, IQR 0.56, 10 females). The
40 mean CBF values in the frontal lobe of the trigonocephaly patients (73.0 ml/100g/min) did not appear to
41 be significantly different in comparison with controls (70.5 ml/100g/min, $p = 0.6479$). The superior,
42 middle, and inferior part of the frontal lobe showed no significant differences either.

43 **Conclusions**

44 Before surgery, the frontal lobe of trigonocephaly patients aged under 18 months old has a normal CBF.
45 In addition to the previously reported very low prevalence of papilledema or impaired skull growth, this

46 finding further supports our hypothesis that craniofacial surgery for trigonocephaly is rarely indicated
47 for signs of raised intracranial pressure.

48

49 **Key words:** trigonocephaly, craniosynostosis, brain perfusion, cerebral blood flow, , frontal lobe, arterial
50 spin labeling, ASL

51

52 **Introduction**

53 Trigonocephaly is the second most common form of non-syndromic craniosynostosis, with prenatal
54 closure of the metopic suture.¹ Patients present within a sliding scale of severity in phenotype,
55 depending on the timing of suture closure. It still remains a subject of discussion, which degree of
56 severity is clinically relevant for a surgical indication. Nowadays, patients with moderate and severe
57 phenotypes undergo surgical correction of the frontal bones and supra orbital rims aiming for
58 unrestricted brain development, to reduce the risk of neurodevelopmental disorders, and improved
59 esthetics. However, preoperatively less than 2% of the trigonocephaly patients have papilledema as a
60 sign of intracranial hypertension.² Moreover, preoperative trigonocephaly patients show a completely
61 normal intracranial volume in comparison to healthy aged-matched controls.³ Lastly, it was shown that
62 patients with trigonocephaly are at risk of developing mental deficiencies/disorders, behavioral
63 problems, delays in speech and language, irrespective of having undergone surgery.^{4,5} Taking all the
64 above together, it remains unknown what the added value of surgery is in trigonocephaly with respect
65 to future brain development.

66 The exact mechanism of the association between trigonocephaly and suboptimal neurodevelopmental
67 outcome is not fully understood.⁶ Although some have suggested that brain development is impaired as
68 a result of the synostosis, others hypothesize the increased prevalence of neurodevelopmental
69 disorders in these patients is caused by an intrinsic brain disorder. The former hypothesis of brain
70 development restriction due to synostosis could be reflected in altered cerebral blood flow (CBF).⁷⁻¹⁰
71 Brain perfusion in trigonocephaly patients was examined previously with single-photon emission
72 computed tomography (SPECT) and a lower perfusion was reported in the frontal lobe preoperatively
73 compared to postoperatively and to the rest of the brain.^{9,10} These two studies offered, however,
74 qualitative evaluation of relative perfusion values only. Over the last decade, more advanced imaging

75 techniques have been developed to measure cerebral perfusion, hence, this original claim was not
76 reassessed yet. Arterial spin labeling (ASL) Magnetic Resonance Imaging (MRI) is a technique that
77 provides injection-free measurements of absolute brain perfusion with quantitative accuracy
78 comparable to that of PET.¹¹ ASL has previously been used for several pediatric applications, but
79 craniosynostosis patients might present a further challenge given the skull deformations of these
80 patients.^{8 12, 13}

81 The aim of this study is to reassess the previous claims of perfusion changes in craniosynostosis subjects
82 to gain more insight into the hypothesis of brain restriction by investigating cerebral blood flow by
83 acquiring ASL MRI brain scans of young children with trigonocephaly preoperatively and of aged-
84 matched healthy controls. Brain perfusion will be assessed in several brain regions focusing mostly, due
85 to the shape of the skull in trigonocephaly patients as well as the increased prevalence of behavior and
86 cognitive disorders, on the frontal lobe. Based on the very low prevalence of papilledema or impaired
87 skull growth in trigonocephaly compared to other craniosynostosis patients, we hypothesize that there
88 are no abnormalities in frontal lobe perfusion in the first two years of life.^{2, 3}

89

90 **Methods**

91 The Ethics Committee of the Erasmus Medical Center approved this prospective imaging study in patients
92 with trigonocephaly (METC-2018-124), which is part of an ongoing work at the Dutch Craniofacial Center.

93

94 **Study population**

95 MRI scans from children with metopic synostosis for whom a surgical correction was considered were
96 included over a period of two years (2018-2020). Surgery is only considered for moderate and severe
97 presentation, mainly defined by the forehead shape in a bird eye's view and considered present if the
98 lateral orbital rim is visible and the midline ridge is significantly prominent. This is illustrated by Birgfeld
99 et al (2013) in Figure 5.¹⁴ Children were below 2 years of age at the time of the MRI brain study. The
100 control group consisted of subjects undergoing MRI for clinical reasons. These subjects were included
101 when the following conditions were met: 1) the subjects were found to have no neurological pathology
102 of the head and neck area on imaging; 2) the subjects were free of any neurological or psychological
103 morbidity on follow-up; and 3) the subjects' MRI data were of sufficient quality to be used for research.

104

105 **MRI Acquisition**

106 All brain MRI data were acquired with a 1.5T scanner (GE Healthcare), including pseudocontinuous ASL
107 sequences with the following imaging parameters: 3D FSE spiral readout with a stack of 8 spirals and 3
108 averages, TR 4604 ms, TE 10.7 ms, voxel size 3.75 x 3.75 x 4.0 mm³, axial field of view 24.0 cm, number
109 of slices, labeling duration 1450 ms, post-labeling delay (PLD) 1025 ms, background suppression, and
110 M0-scan acquisition for calibration. This protocol was identical in both trigonocephaly patients and
111 controls. Both groups underwent deep sedation or anesthesia during the MRI procedure, which included
112 using sevoflurane or propofol.

113

114 **ASL Data Analysis**

115 Data processing and evaluation was performed with the ExploreASL pipeline and it included the basic
116 processing of ASL and M0 calibration images as described in the ExploreASL review paper¹⁵. T1-weighted
117 images were excluded from the complete analysis due to insufficient differentiation between white and
118 grey matter. This is common for the age group we studied due to incomplete myelination and it
119 precluded successful segmentation and spatial normalization in part of the subjects. To be able to use
120 the structural atlas of brain regions for the evaluation, the ASL images were directly aligned with the
121 Montreal Neurological Institute (MNI) template. In this age group, the brain is of considerably different
122 shape and size than the adult brain. Therefore, a dedicated template - UNC 0-1-2 Infant Atlases, the
123 version for 1y - was used to replace the adult template.¹⁶ The control images were not of high-enough
124 contrast to allow alignment with the mean MNI T1-weighted image, therefore a registration of the
125 individual CBF to a standard-space pseudoCBF, based on the GM and WM maps of the template, was
126 performed.¹⁷ Because of the relatively high amount of skull deformations in the patient group, rigid or
127 affine registration was not considered sufficient for alignment of the individual data to the template.
128 Therefore, an affine registration followed by nonlinear deformations using a linear combination of three
129 dimensional discrete cosine transform (DCT) basis functions was used.¹⁸

130 The CBF has been quantified according to the consensus paper by Alsop et al.¹⁶ Whole brain and regional
131 CBF were evaluated in both hemispheres taken together and superior, middle, and inferior levels of the
132 frontal lobe. There were large shape and size differences in the population due to age and disease.
133 Therefore, we chose to evaluate the mean CBF values in the native space of each subject to avoid effects
134 of interpolation and voxel size change. The anatomical ROIs were taken from Hammer's atlas in the MNI
135 space and transformed to the subject's space using the previously obtained transformation for the
136 spatial normalization.¹⁹ Mean CBF values were investigated as well for the following brain regions:

137 Frontal lobe, Occipital lobe, Parietal lobe, Temporal lobe, Insula, Cerebellum, Caudate, Putamen, and
138 Thalamus.

139

140 **Statistical Analyses**

141 Statistical analyses were performed using R Version 1.1.442 Parametric statistics were used when the
142 distribution of the data did not violate assumptions of normality.²⁰ Linear mixed models were used to
143 compare the mean CBF in the frontal lobe in trigonocephaly patients vs controls. To confirm the validity
144 of our data, we normalized CBF data of the frontal lobe by occipital lobe data, using the ratio of frontal
145 lobe/occipital lobe. We compared this ratio of frontal lobe/occipital lobe between patients and controls
146 by using a T-test. In addition, we assessed the ratio of the spatial coefficient of variation, a measure of
147 global spatial signal distribution, between the frontal lobe and occipital lobe, comparing the ratios
148 between patients and controls using a T-test.

149

150

151 **Results**

152

153 **Patient characteristics**

154 Thirty-six patients with trigonocephaly with a median age of 0.50 years (IQR 0.30) and sixteen control
155 subjects with a median age of 0.83 years (IQR 0.56) were included in this study as presented in **Table 1**.

156

157 **Frontal lobe perfusion**

158 By mixed model, **Table 2** demonstrates that there is no significant difference in the mean perfusion of
159 the frontal lobe between trigonocephaly patients (73 ml/100 g/min) and controls (70.5 ml/100 g /min, p
160 = 0.6479).The mean perfusion was compared between the two groups. **Table 3** shows the mean
161 perfusion for three levels of the frontal lobe - the superior, middle, and inferior level. None of these
162 three levels was significantly different between the patient and control groups.

163 To account for possible variation in labelling efficiency, we chose the occipital lobe as a reference region
164 for normalization. We compared the CBF ratio of frontal lobe / occipital lobe between patients and
165 controls, where we found no significant difference between the groups (p=0.10). In addition, we
166 compared the ratio of the spatial coefficients of variation of the frontal lobe/occipital lobe for patients
167 and controls. Again, we found no significant difference between the groups (p=0.091). To demonstrate
168 the range of values, the mean CBF of the frontal lobe for each individual in our cohort is shown in **Figure**
169 **1**.

170

171 **Perfusion of other brain regions**

172 We assessed the CBF of several brain regions (Frontal lobe, Occipital lobe, Parietal lobe, Temporal lobe,
173 Insula, Cerebellum, Caudate, Putamen, and Thalamus) in trigonocephaly patients as compared to

174 controls, using anatomical structural atlas. We observed no significant difference in trigonocephaly
175 patients as compared to controls for these regions. The CBF values are summarized in supplemental
176 **Table 4.**

177

178 **Discussion**

179 The aim of this study was to investigate CBF in the frontal lobe of patients with trigonocephaly as
180 compared to age-matched controls. Our study suggests that there is no significant difference in CBF in
181 trigonocephaly patients as compared to healthy controls. This is consistent with our research hypothesis
182 that there are no abnormalities in frontal lobe perfusion in trigonocephaly patients aged from 0-18
183 months. This matches the previous findings of a very low risk to develop raised intracranial pressure in
184 the first 18 months of life in trigonocephaly patients and the fact that trigonocephaly patients have
185 normal intracranial volume compared to controls without cerebral pathology.^{2,3}

186 Currently, patients with a moderate or severe phenotype of trigonocephaly undergo surgery with the
187 aim to reduce restriction of the brain that might cause raised intracranial pressure and hereby improve
188 brain and neurocognitive development as well as to improve aesthetic outcome.

189 However, the functional indication and the efficacy of surgical correction of trigonocephaly has been
190 under debate among craniofacial surgeons since a few years. It is unclear if premature closure of the
191 metopic suture restricts brain development mechanically, especially of the frontal lobe, and whether
192 craniofacial surgery has a positive effect. The neurocognitive findings reported in older children with
193 treated trigonocephaly might represent an intrinsic brain disorder which is not improved with surgery.²¹

194 Our current finding of equal CBF in trigonocephaly patients before surgery and that of control patients
195 suggests the metopic synostosis does not impair CBF in the forebrain below the age of 18 months, and
196 thus supports the hypothesis of intrinsic brain problems rather than that of mechanical restriction of
197 brain development.

198 In line with the theory that trigonocephaly is mainly an inborn brain disorder are recent studies which
199 have shown that some genetic mutations found in patients with trigonocephaly overlap with patients
200 with developmental delay disorders.⁶ Further studies into the microstructure of the brain, using for

201 example diffusion tensor imaging are required to further clarify brain development in trigonocephaly
202 patients and understand the underlying pathophysiology.

203 The previous imaging SPECT studies in trigonocephaly patients had different findings.^{9, 10} This can be
204 explained by different methodology, we used a quantitative methods instead of the qualitative
205 comparison. Also, the studies have reported some left-right asymmetry and none of that was visible in
206 our subjects despite that the ASL signal is usually very stable across the hemispheres.²² At last, Shimoji et
207 al had a different age range (1-9 year).⁹

208 As the largest ASL study of healthy children to date, Carsin-Vu et al showed a mean perfusion of 54.6
209 mL/100gr/min and of 68.4 mL/100gr/min in the frontal lobe of 6 -11 months (n=4) and 12-23 months
210 (n=14) old healthy children respectively, which is roughly similar to our results.²³ The differences are
211 likely to stem from differences in the methodological issues of brain region definition (e.g. manual or
212 automatic ROIs), different ASL sequences types (pulsed, pseudocontinuous), and different ASL
213 acquisition parameters. As the range of our cohort in figure 1 is shown, we expect that age will not have
214 had a significant effect on our results. Due to our limited sample size we did not conduct additional
215 analyses on age and its correlation with cerebral perfusion.

216
217 In this study segmentation was difficult which had an influence on the registration to the MNI atlases to
218 assess CBF regionally. But we have used the registration of CBF to pseudoCBF that was shown by
219 Mutsaerts in 2018.¹⁷ On top of that, we managed to additionally use a low-degree-of-freedom non-
220 linear component to improve the registration for the deformed skulls thus reaching a better registration.
221 This was evaluated both visually and quantitatively, which is subject of another manuscript.

222

223 Our study has several limitations. First, our study focusses on a limited number of patients. Therefore,
224 establishing that there is no difference in CBF between trigonocephaly patients and controls with
225 certainty remains difficult. We demonstrated that the range of CBF in both trigonocephaly patients and
226 controls is similar to the range found in previous studies. In our cohort there was no significant
227 difference between mean CBF of the frontal lobe in trigonocephaly patients as compared to controls.
228 We tested these results by both checking the CBF ratio of frontal lobe/occipital lobe in patients as
229 compared to controls and by establishing the ratio of spatial coefficients of variation of the frontal
230 lobe/occipital lobe in patients vs controls, where both tests showed no significant difference. Still, large
231 cohort studies and therefore standardized CBF values in pediatric patients are missing. ASL studies
232 focusing on clinical relevance of differences in CBF range are required for the pediatric setting.

233

234 Second, we were unable to obtain exact-aged matched healthy controls, due to ethical constraints on
235 subjecting healthy children to the anesthesia required for undergoing MRI examination, solely for
236 research purposes. Our control group therefore consisted of patients who underwent MRI examination
237 for clinical reasons, where MRI and clinical course showed no cerebral pathology. Patients with
238 trigonocephaly tend to go younger to MRI because of the visibility disorder which could develop later in
239 life. This age difference might have produced an additional mean CBF difference of -0.3, 0.12, -0.06
240 mL/100g/min (for the three presented models) between the groups, which would have then even
241 reduced the group difference or not change it significantly.²³

242 Third, we did not differentiate between gray and white matter when evaluating the mean regional CBF
243 due to the absence of T1-weighted image segmentation. Instead, the mean parenchymal CBF was
244 assessed per region. Gray matter perfusion is around 2 times higher than white matter perfusion in
245 pediatric populations and joint evaluation of gray matter and white matter signals can bias the CBF
246 analysis if gray matter and white matter volumes differ significantly between groups.²³⁻²⁵ However, such

247 volumetric difference between GM and WM is not expected, so we estimate that this had no influence.
248 More advanced analysis that uses T2w and DTI images to aid the segmentation and study the partial
249 volume corrected gray matter CBF is however planned.²⁶ As the study of Carsin-Vu et al among pediatric
250 patients found no difference in CBF between patients of a different sex or the use of different types of
251 anesthesia, we did not take these factors into account in our analysis.²³

252

253 **Conclusions**

254 In conclusion, our finding of a normal CBF in untreated trigonocephaly patients under the age of 18
255 months as compared to controls supports a more conservative approach to prevent potential
256 overtreatment of patients with trigonocephaly. In addition to the previously reported very low
257 prevalence of papilledema or impaired skull growth, this finding further supports our hypothesis that
258 craniofacial surgery for trigonocephaly is rarely indicated for signs of raised intracranial pressure.

259

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261 **Disclosure:** none

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318

319

320 **Tables**

321

322 **Table 1.** Patient Characteristics

	Trigonocephaly	Controls
n	36	16
f:m	11:25	10:06
median	0.50	0.83
IQR	0.30	0.56

323

324 **Table 2.** Mixed model on the perfusion of the frontal lobe using the structural atlas (ml/100gr/min)

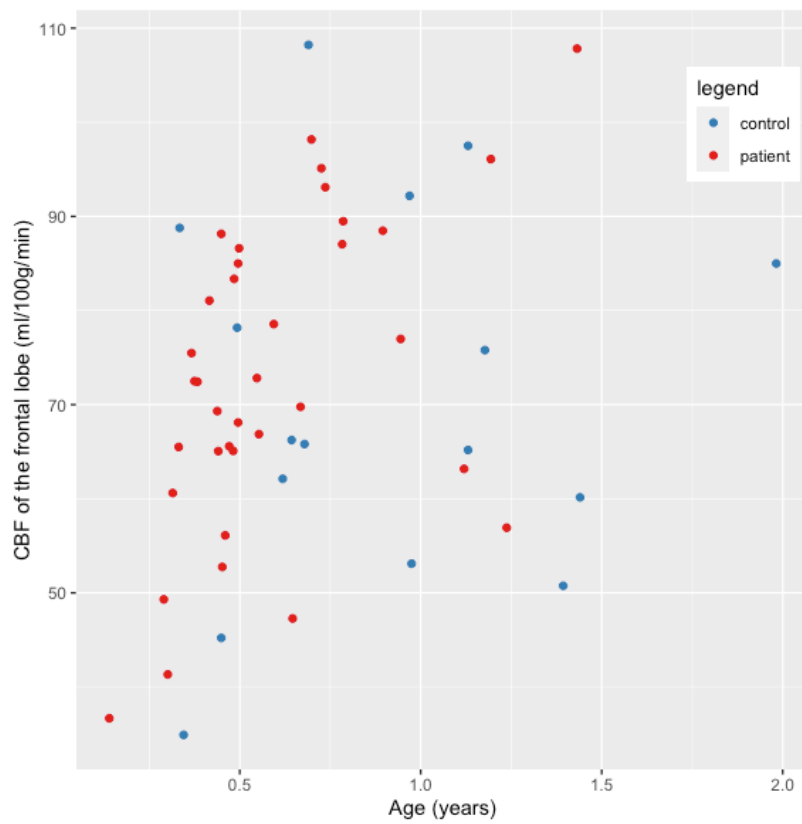
	Trigonocephaly				Control				p-value
	mean	SE	lower.ci	upper.ci	mean	SE	lower.ci	upper.ci	
Frontal lobe	73.0	2.97	67.0	78.9	70.5	4.45	61.6	79.4	0.6479

325

326

327

328 **Figure 1.** Mean CBF (ml/100gr/min) of the frontal lobe in trigonocephaly patients and controls over time
329 (age in years)



330

331

332 **Table 3.** Mixed model on the three levels of the frontal lobe using the Hammers Atlas (ml/100gr/min)

	Trigonocephaly				Control			
	mean	SE	lower.ci	upper.ci	mean	SE	lower.ci	upper.ci
Frontal lobe superior	70.9	2.90	65.1	76.7	68.2	4.34	59.5	76.9
Frontal lobe middle	68.4	3.09	62.2	74.6	70.1	4.63	60.8	79.4
Frontal lobe inferior	76.8	2.9	70.9	82.6	75.9	4.5	66.8	84.9

333

334

335 **Supplemental table 4.** Perfusion per brain region from the structural atlas in ml/100gr/min

Brain Region	Trigonocephaly					Control				
	mean	sd	se	lower.ci	upper.ci	mean	sd	se	lower.ci	upper.ci
Frontal	72.97	16.77	1.98	69.03	76.91	70.51	19.97	3.53	63.31	77.71
Occipital	80.32	20.95	2.47	75.40	85.25	71.60	18.20	3.22	65.04	78.16
Parietal	77.49	18.37	2.16	73.18	81.81	72.94	17.35	3.07	66.68	79.20
Temporal	71.90	15.91	1.88	68.16	75.64	69.93	19.87	3.51	62.77	77.10
Insula	79.93	15.96	1.88	76.18	83.68	73.34	21.95	3.88	65.43	81.25
Cerebellum	73.96	15.67	1.85	70.28	77.64	66.47	21.88	3.87	58.58	74.36
Caudate	63.25	14.04	1.65	59.95	66.55	56.20	15.61	2.76	50.57	61.83
Putamen	78.93	15.20	1.79	75.36	82.50	70.88	25.23	4.46	61.79	79.98
Thalamus	93.24	25.25	2.98	87.30	99.17	80.03	28.15	4.98	69.88	90.18