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

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

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Abstract

Background

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

Methods

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

Results

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

Conclusions

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

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

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

Introduction

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

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

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

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

Methods

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

Study population

MRI scans from children with metopic synostosis for whom a surgical correction was considered were included over a period of two years (2018-2020). Surgery is only considered for moderate and severe presentation, mainly defined by the forehead shape in a bird eye's view and considered present if the lateral orbital rim is visible and the midline ridge is significantly prominent. This is illustrated by Birgfeld et al (2013) in Figure 5 .[14] Children were below 2 years of age at the time of the MRI brain study. The control group consisted of subjects undergoing MRI for clinical reasons. These subjects were included when the following conditions were met: 1) the subjects were found to have no neurological pathology of the head and neck area on imaging; 2) the subjects were free of any neurological or psychological morbidity on follow-up; and 3) the subjects' MRI data were of sufficient quality to be used for research.

MRI Acquisition

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

ASL Data Analysis

Data processing and evaluation was performed with the ExploreASL pipeline and it included the basic processing of ASL and M0 calibration images as described in the ExploreASL review paper[15]. T1-weighted images were excluded from the complete analysis due to insufficient differentiation between white and grey matter. This is common for the age group we studied due to incomplete myelination and it precluded successful segmentation and spatial normalization in part of the subjects. To be able to use the structural atlas of brain regions for the evaluation, the ASL images were directly aligned with the Montreal Neurological Institute (MNI) template. In this age group, the brain is of considerably different shape and size than the adult brain. Therefore, a dedicated template - UNC 0-1-2 Infant Atlases, the version for 1y - was used to replace the adult template.[16] The control images were not of high-enough contrast to allow alignment with the mean MNI T1-weighted image, therefore a registration of the individual CBF to a standard-space pseudoCBF, based on the GM and WM maps of the template, was performed.[17] Because of the relatively high amount of skull deformations in the patient group, rigid or affine registration was not considered sufficient for alignment of the individual data to the template. Therefore, an affine registration followed by nonlinear deformations using a linear combination of three dimensional discrete cosine transform (DCT) basis functions was used.[18]

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

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

Statistical Analyses

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

Results

Patient characteristics

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

Frontal lobe perfusion

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

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

Perfusion of other brain regions

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

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

Discussion

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

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

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

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

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

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

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

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

In this study segmentation was difficult which had an influence on the registration to the MNI atlases to assess CBF regionally. But we have used the registration of CBF to pseudoCBF that was shown by Mutsaerts in 2018.[17] On top of that, we managed to additionally use a low-degree-of-freedom non-linear component to improve the registration for the deformed skulls thus reaching a better registration. This was evaluated both visually and quantitatively, which is subject of another manuscript.

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

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

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

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

Conclusions

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

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Figure Legends

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Tables

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

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

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

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

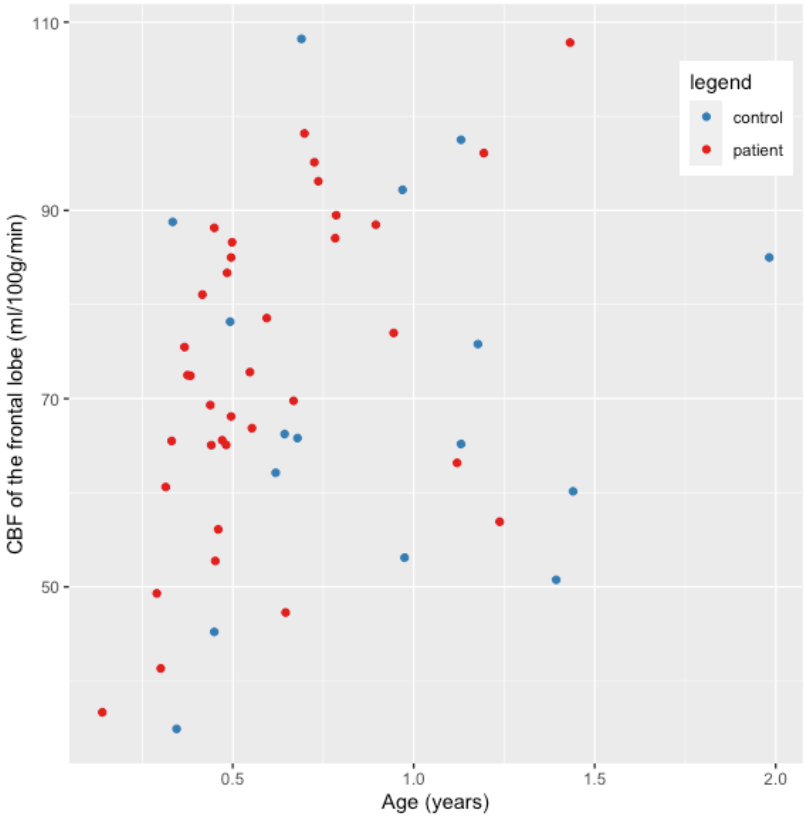

Table 3. Mixed model on the three levels of the frontal lobe using the Hammers Atlas (ml/100gr/min)

	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

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

	Trigonocephaly					Control				
Brain Region	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

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