Pilot study of intracranial venous physiology in craniosynostosis

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OBJECTIVE In addition to craniocerebral disproportion, other factors, such as Chiari malformation type I, obstructive sleep apnea, and venous outflow obstruction, are considered to have a role in the occurrence of intracranial hypertension in craniosynostosis. This pilot study examined cerebral venous flow velocity to better characterize the complex intracranial venous physiology of craniosynostosis.

METHODS The authors performed a prospective cohort study of craniosynostosis patients (n = 34) referred to a single national (tertiary) craniofacial unit. Controls (n = 28) consisted of children who were referred to the unit's outpatient clinic and did not have craniosynostosis. Transfontanelle ultrasound scans with venous Doppler flow velocity assessment were performed at the first outpatient clinic visit and after each surgery, if applicable. Mean venous blood flow velocities of the internal cerebral vein (ICV_v) and the superior sagittal sinus (SSS_v) were recorded and blood flow waveform was scored.

RESULTS Preoperatively, SSS_v was decreased in craniosynostosis patients compared with controls (7.57 vs 11.31 cm/sec, p = 0.009). ICV_v did not differ significantly between patients and controls. Postoperatively, SSS_v increased significantly (7.99 vs 10.66 cm/sec, p = 0.023). Blood flow waveform analyses did not differ significantly between patients and controls.

CONCLUSIONS Premature closure of cranial sutures was associated with decreased SSS_v, but not ICV_v, indicating an effect on the superficial rather than deep venous drainage. Further Doppler ultrasound studies are needed to test the hypothesis that at an early stage of craniosynostosis pathology SSS_v, but not pulsatility, is abnormal, and that abnormality in both SSS_v and the superficial venous waveform reflect a more advanced stage of evolution in suture closure.

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KEYWORDS intracranial hypertension; craniosynostosis; Doppler ultrasound; superior sagittal sinus; cerebral venous drainage; craniofacial

CRANIOSYNOSTOSIS occurs in approximately 1 in 1500 births and results in abnormal shape of the cranium and increased risk of intracranial hypertension (ICHT).¹ In published series, the prevalence of ICHT ranges from 1% to 85%, and it is particularly high in syndromic cases of craniosynostosis.^{2,3,13,17} Historically, the development of ICHT in craniosynostosis was attributed solely

to skull growth restriction (i.e., craniocerebral disproportion).¹⁸ Now, however, the accumulated evidence suggests that other factors may also be relevant,^{5,6,8,9,19} including: cranial vault venous outflow obstruction, ventriculomegaly (or hydrocephalus if progressive), tonsillar herniation or presence of Chiari malformation type I, and obstructive sleep apnea (OSA). These pathophysiological features are

ABBREVIATIONS CSF = cerebrospinal fluid; ICHT = intracranial hypertension; ICP = intracranial pressure; ICV = internal cerebral vein; ICV_v = mean venous blood flow velocity of the ICV; MANOVA = multivariate analysis of variance; OFC = occipitofrontal head circumference; OSA = obstructive sleep apnea; P_{SSS} = SSS pressure; SSS = superior sagittal sinus; SSS_v = mean venous blood flow velocity of the SSS.

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rarely seen in single-suture craniosynostosis patients, and so we have to conclude that they are unlikely to account for the development of ICHT in such patients. In our previous work we have recognized a discrepancy in the rate of ICHT by suture involvement that is not readily explained by any of the mechanisms outlined above. For example, in cases of metopic suture synostosis, the rate of ICHT is low (1%–2%), irrespective of relatively small intracranial volume after surgery.^{2,12} The opposite is true in sagittal suture synostosis; that is, despite a relatively larger intracranial volume, ICHT is found in 6%–10% of patients.^{7,20}

In this context, clinical researchers have focused on cerebral venous drainage in craniosynostosis, albeit with few definitive studies. We know that there is an interaction between superior sagittal sinus (SSS) pressure (P_{SSS}) and intracranial pressure (ICP). For example, as early as 1984, Sainte-Rose et al. suggested that a rise in P_{SSS} due to obstruction resulted in a rise in ICP.¹⁹ We also know that the mean venous blood flow velocity of the SSS (SSS_v), measured using Doppler ultrasound in single-suture cases of craniosynostosis, differs from the norm.¹⁵ Last, we know that cranial venous drainage is different in craniosynostosis patients.^{6,9} Taking all of the above evidence together, we conclude that abnormality in cerebral venous dynamics is an important physiological feature of single-suture craniosynostosis. However, understanding the interaction between cerebral venous blood flow, cerebrospinal fluid (CSF) drainage, and ICP also requires consideration of anatomy. For example, the superficial venous drainage system, as reflected in the SSS, drains blood from the lateral aspects of the anterior portion of the cerebral hemispheres and collects CSF from the arachnoid granulations. The internal cerebral vein (ICV) is a component of the deep venous drainage system, and on each side of the brain it takes blood from the choroid plexus and thalamic and caudate nuclei. Therefore, in the current pilot investigation we have used Doppler ultrasound to examine cerebral venous flow velocity in the superficial and deep cerebral venous drainage systems to better characterize the complex intracranial venous physiology of craniosynostosis. Comparing both venous drainage systems enables us to examine the effect of craniosynostosis on the deep and superficial venous drainage system and, therefore, to evaluate the effect of corrective surgery on venous drainage and to identify possible targets to prevent ICHT.

Methods

This study was approved by our institution's medical ethics committee. Informed consent was obtained from all participants. Participants with syndromic and nonsyndromic craniosynostosis were recruited from craniosynostosis patients presenting to the Dutch craniofacial center in 2016. The healthy control group was also recruited at our center and comprised patients referred for nonsynostotic occipital plagiocephaly, metopic ridging, or nonsyndromic cleft lip.

Patient Management

Craniosynostosis patients were treated according to our

TABLE 1. Blood flow waveform categories as described by Ikeda et al.¹¹

Grade	Waveform
0	Steady waveform; constant perfusion speed
1	Fluctuating waveform; minimum speed is never less than half the maximum speed
2	Fluctuating waveform; minimum speed is less than half the maximum speed, but never drops to 0 cm/sec
3	Fluctuating waveform; minimum speed drops to 0 cm/sec

center's previously published treatment protocol.¹⁴ Briefly, this meant that fronto-orbital advancement and remodeling was performed between 9 and 12 months of age for the following indications: metopic synostosis, unicoronal synostosis, Saethre-Chotzen's syndrome, and Muenke's syndrome. Sagittal synostosis patients were treated with springs, which were inserted at 5–6 months of age and removed approximately 12 weeks later. Patients with lambdoid synostosis, Apert's syndrome, or Crouzon's syndrome were treated with posterior decompression with the use of springs at around 5–6 months of age (with the springs removed 12 weeks later).

Doppler Ultrasound Procedure and Analyses

Prospective, transfontanelle ultrasound scans with Doppler studies were performed using an Esaote MyLab Twice ultrasound scanner. Scans were carried out at the first outpatient clinic visit and follow-up evaluation after each surgery. Controls underwent only 1 ultrasound study at the time of presentation to the outpatient clinic. During the ultrasound procedure, patients were positioned either supine or with the head of the bed elevated to a maximum of 30°. Studies were carried out when a child was quiet and at rest. Data from agitated or crying children were excluded because of the influence of heart rate variability and raised intrathoracic pressure on measurement of SSS_v and mean venous blood flow velocity of the ICV (ICV_v).

ICV_v was measured in the sagittal plane using a convex ultrasound probe at 6.5 MHz (or at 4.5 MHz in those with larger skulls). As position and flow direction were the same in all patients and controls, we did not use any angle correction in the measurements. SSS_v was measured in the coronal plane using a linear probe (6.5 MHz frequency) and an angle of 30° to 45°. The Doppler range gate (2.2 mm) was constant in all measurements.

All ultrasound and Doppler data were obtained by one of two observers (M.J.C. or P.D.) and digitally stored. (The interobserver agreement for mean ICV_v and mean SSS_v , as assessed by intraclass correlation coefficient, was > 0.95.) The ICV blood flow waveform produced by spectral analysis using image-processing software (Esaote MyLab) was scored using a previously described categorization (Table 1).¹¹ Two observers (M.J.C. and R.d.G.) scored the waveform independently. Instances of disagreement between the scorers was resolved by open evaluation and agreed consensus. The evaluators' kappa statistics were 0.89 and 0.73 for the ICV and SSS waveforms, respectively.

TABLE 2. Preoperative baseline characteristics and mean blood flow velocities

Variable	Mean $\pm$ SEM (no. of measurements)			
	Nonsyndromic Craniosynostosis	Syndromic Craniosynostosis	All Craniosynostosis Patients	Controls
Age in mos	4.04 $\pm$ 0.57 (28)	2.71 $\pm$ 0.72 (6)	3.81 $\pm$ 0.49 (34)	6.04 $\pm$ 0.42 (28)
OFC*	+0.62 $\pm$ 0.24 (28)	-0.32 $\pm$ 0.79 (6)	+0.45 $\pm$ 0.24 (34)	+0.15 $\pm$ 0.25 (22)
SSS _v in cm/sec	7.80 $\pm$ 0.51 (23)	6.66 $\pm$ 0.71 (6)	7.57 $\pm$ 0.44 (29)	11.31 $\pm$ 1.06 (26)
ICV _v in cm/sec	10.00 $\pm$ 0.34 (22)	8.57 $\pm$ 0.76 (5)	9.74 $\pm$ 0.33 (27)	9.68 $\pm$ 0.29 (26)

* OFC in standard deviations compared to the national normal values.

Statistical Analyses

The sample size for our pilot study was based on previous guidelines¹⁶ and our center's medical ethics committee's recommendations. The statistical analyses assumed normal distribution for ICV_v and SSS_v data. A multivariate analysis of variance (MANOVA) test was performed to assess the effect of craniosynostosis on SSS_v and ICV_v. The chi-square test was used for assessment of waveform categorical data. Finally, in the comparisons of pre- to postoperative change, we used the preoperative data along with the data from after the last (or most recent) operation. Post hoc nonparametric testing (Kruskal-Wallis or Wilcoxon signed-rank test) was performed when appropriate.

Results

We recruited 34 craniosynostosis patients, including 14 patients with sagittal synostosis, 11 with metopic synostosis, 2 with unicoronal synostosis, 1 with lambdoid synostosis, 1 with Saethre-Chotzen's syndrome, 3 with Muenke's syndrome, and 2 with Crouzon's syndrome. Postoperatively, we were able to obtain ultrasound scans in 22 (65%) of these 34 patients (8 with sagittal suture synostosis, 9 with metopic synostosis, 1 with lambdoid synostosis, 1 with Saethre-Chotzen's syndrome, 2 with Muenke's syndrome, and 1 with Crouzon's syndrome). The control group comprised 28 patients (24 with nonsynostotic occipital plagiocephaly or metopic ridging, 2 with cleft lip, and 2 unaffected twin siblings of craniosynostosis patients).

None of the patients with craniosynostosis had papilledema at the time of initial assessment. One patient with Muenke's syndrome developed papilledema after the preoperative ultrasound study, and for this reason she underwent posterior cranial vault decompression. Additionally, 1 patient with Crouzon's syndrome developed papilledema after the first ultrasound. At the time of the postoperative ultrasound study the papilledema was resolving in both cases but had not completely disappeared. None of the other patients had papilledema at the postoperative assessment.

Preoperative ICV_v and SSS_v

Table 2 summarizes the initial findings in the 3 study groups (patients with nonsyndromic or syndromic craniosynostosis and controls). The age distribution differed significantly between groups (Kruskal-Wallis test, $p < 0.001$). Post hoc testing showed no significant difference with regard to age at ultrasound between the syndromic and nonsyndromic craniosynostosis groups (Mann-Whitney

U-test, $p = 0.24$), but it did show a significant difference between the nonsyndromic group and controls (Mann-Whitney U-test, $p = 0.001$). There was no significant between-groups difference in occipitofrontal head circumference (OFC) (ANOVA, $p = 0.20$).

We performed a MANOVA analysis to test whether there were significant differences with regard to venous flow velocity between craniosynostosis patients and controls, correcting for age at ultrasound and OFC. This analysis showed significantly lower venous blood flow velocity in the SSS_v in craniosynostosis patients compared with controls (Table 3). Age at ultrasound and OFC were not significant contributors to this effect. Additional testing did not show statistically significant differences between nonsyndromic and syndromic craniosynostosis patients after correction for age at ultrasound and OFC.

Venous Blood Flow Waveform

Preoperative cerebral venous blood flow waveform scores are shown in Table 4. The chi-square test did not show any significant differences in distribution among the different groups for the 2 measurements.

Postoperative Blood Flow Velocity

Preoperative and postoperative cerebral venous blood flow velocities of the SSS were gained in 15 patients: 4 patients with scaphocephaly, 6 with trigonocephaly, 1 with lambdoid synostosis, 1 with Crouzon's syndrome, 1 with Saethre-Chotzen's syndrome, and 2 with Muenke's syndrome. A related-samples Wilcoxon signed-rank test showed a significant increase in SSS_v postoperatively (median 7.25 cm/sec [IQR 6.75–8.95 cm/sec] vs 10.20 cm/sec [IQR 8.95–12.20 cm/sec], $p = 0.023$). The ICV_v remained unchanged (median 9.90 cm/sec [IQR 7.95–10.98 cm/sec] vs 10.15 cm/sec [IQR 8.00–11.35 cm/sec], $p = 0.68$). Fig.

TABLE 3. MANOVA correcting for age at time of ultrasound and OFC

Variable	Mean $\pm$ SEM		F	df	p Value
	Craniosynostosis	Controls			
SSS _v	7.37 $\pm$ 0.33	11.51 $\pm$ 1.13	7.253	1	0.009*
ICV _v	9.74 $\pm$ 0.34	9.30 $\pm$ 0.30	0.180	1	0.612

df = degree of freedom.

Velocities are presented in centimeters/second. Design: intercept + age at ultrasound + OFC + craniosynostosis. Adjusted $R^2 = 0.25$.

* Statistically significant.

TABLE 4. Distribution of preoperative blood flow waveform grades in patients with nonsyndromic or syndromic craniosynostosis and controls

Variable	Nonsyndromic Craniosynostosis	Syndromic Craniosynostosis	Controls
ICV			
Grade 0	5	0	3
Grade 1	17	5	23
Grade 2	0	0	0
Grade 3	0	0	0
Total	22	5	26
SSS			
Grade 0	7	1	5
Grade 1	12	4	19
Grade 2	4	1	2
Grade 3	0	0	0
Total	23	6	26

Values are numbers of patients. The preoperative venous blood flow waveform grades are based on the scoring system described in Table 1. No significant differences were found for ICV ($p = 0.77$) or SSS waveform ($p = 0.62$) using the chi-square test.

1 shows patient-specific pre- to postoperative change of the SSS_v .

Discussion

This study assessed cerebral venous blood flow velocity and blood flow waveform in patients with craniosynostosis compared with controls using Doppler ultrasound. Before surgery, patients with craniosynostosis showed lower SSS_v compared with controls, that increased postoperatively. There was no difference in ICV_v at any time, and blood flow waveform characteristics were similar in both cases and controls.

Previous studies have reported on the interaction between hydrocephalus and hydrodynamic and hemodynamic pressures (i.e., raised ICP and P_{SSS}) in various patient groups.^{10,15,16,19} For example, in children with achondroplasia and hydrocephalus, cine phase-contrast MRI shows reduced SSS_v .¹⁰ Hirabuki et al. hypothesized that the reduced cerebral venous blood flow, as indicated by reduced SSS_v , was the result of venous outflow obstruction.¹⁰ In our current findings, we have taken measurements from both the superficial and deep cerebral venous drainage systems as a test of the anatomy before and after any potential point of venous constriction or compression. The resulting data indicate that premature closure of cranial sutures may, in itself, be related to decreased SSS_v and thus reduced cerebral venous drainage from the superficial system, i.e., at a point proximate to the confluence of the straight sinus and SSS. In contrast to these observations, Mursch et al. found higher SSS_v in craniosynostosis patients;¹⁵ it should, however, be noted that their measurements were made at the site of venous constriction/compression. Of interest, de Souza and Pinto showed that the diameter of the SSS is related to sagittal suture growth.⁴ These findings, together with our own, strengthen the hypothesis that cerebral venous out-

flow obstruction due to venous constriction or compression is caused by the presence of a synostotic suture. Consistent with this idea is our observation that decreased SSS_v is also found in single-suture craniosynostosis patients (Table 2); until now, cerebral venous hypertension has been considered an attribute of syndromic craniosynostosis.^{6,9} In fact, we think that this physiology may be important in the etiology of ICHT in unsutural craniosynostosis patients, particularly as OSA, Chiari malformation type I, and hydrocephalus are not found in this patient group. Furthermore, the postoperative increase in SSS_v may also reflect that venous obstruction/compression caused by the synostotic suture has been relieved and resistance into venous outflow in the superficial drainage system has been lowered. Since we only performed postoperative analyses in 15 patients, these findings should be confirmed in a larger study.

In regard to the characteristics of the cerebral venous waveform in craniosynostosis, Mursch et al. previously reported that such patients had different SSS pulsatility measurements (i.e., pulsatility index and resistance index).¹⁵ We could not reproduce these findings when using a system of scoring venous blood flow waveform profiles. Taken together with the above discussion of SSS_v , this observation suggests that we may have been seeing patients early in the course of uncorrected natural history; that is, at an early stage of pathology when there is premature suture fusion with an effect on SSS_v but pulsatility remains unchanged. The state in which craniosynostosis influences both SSS_v and SSS waveform pulsatility most likely represents a more severe or later stage.

There are some limitations in this study that need to be considered. First, we have little comparative data. Even though the cranial venous outflow of patients with craniosynostosis has been a subject of research over the past decade, we have only one quantitative study of SSS_v , until now. The present study was designed as a pilot project to explore potential effects of craniosynostosis on the superficial and deep cerebral venous drainage systems, and we hope that our findings will stimulate research in other clinical centers. Second, in accordance with our institution's medical research ethics advice for pilot studies, we could only recruit up to 15 patients in each diagnostic group, which, at this preliminary stage, limits the generalization of our findings. Third, postoperative analyses were limited by the presence of closure of the anterior fontanelle—the radiological “window” for examining the SSS and ICV. We have no control over this limitation, but in the future dynamic cerebral MR venography may provide useful information. Fourth, flow velocity is not equal to flow volume. In this study we showed that there is a lower flow velocity in the SSS, but it is not yet proven that this also means a lower flow volume. However, we do believe a lower flow velocity is more likely to represent a lower flow volume in this case, especially given the flow velocity increase postoperatively. Last, technical components of Doppler ultrasound studies have the potential to add to variability, e.g., angle of insonation, patient activity, and positioning. We have limited these potential technical effects by standardizing our approach and excluding data that are inadequate (e.g., because patients were restless or moving).

FIG. 1. Preoperative to postoperative change in superior sagittal sinus flow velocity of the patients. Each black line indicates the data from 1 patient. The red squares represent point data from controls. See text for details. Figure is available in color online only.

Therefore, considering the results of the present study and the above limitations, our hypothesis is that cerebral venous drainage and outflow has a role in the etiology of ICHT, even in single-suture craniosynostosis patients. This finding should be confirmed in future studies, which should also explore potential differences between the different types of craniosynostosis. It would also be interesting to test whether patients with an affected suture in the midline (i.e., metopic or sagittal synostosis) show a more profound effect of suture closure on SSS_v compared with the other subtypes of craniosynostosis. In addition, the effect of surgery should be evaluated, especially the possible hierarchy in severity (i.e., closed suture with decreased SSS_v vs decreased SSS_v with abnormal venous waveform).

Conclusions

This pilot study of cerebral venous outflow patterns in craniosynostosis patients shows that premature closure of cranial sutures is associated with decreased SSS_v, but not ICV_v—that is, an effect on the superficial venous drainage rather than deep venous drainage. Further Doppler ultrasound studies are needed, not only to confirm the current findings, but also to test the hypothesis that at an early stage of craniosynostosis pathology SSS_v is abnormal while pulsatility is normal, and that abnormalities in both SSS_v and the superficial venous waveform reflect a more advanced stage of evolution in suture closure.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Cornelissen, Doerga, Lequin, Govaert, Mathijssen, Dudink, Tasker. Acquisition of data: Cornelissen, de Goederen, Doerga, Cuperus. Analysis and interpretation of data: Cornelissen, de Goederen, Dudink, Tasker. Drafting the article: Cornelissen, de Goederen, Tasker. Critically revising the article: Doerga, Cuperus, van Veelen, Lequin, Govaert, Mathijssen, Dudink, Tasker. Reviewed submitted version of manuscript: Doerga. Statistical analysis: Cornelissen, de Goederen, Tasker. Administrative/technical/material support: Cuperus, van Veelen, Lequin. Study supervision: van Veelen, Lequin, Mathijssen, Tasker.

Supplemental Information

Previous Presentations

Portions of this paper were previously published in Dr. Cornelissen's thesis, "Unisutural craniosynostosis: simple or complex?" submitted as partial fulfillment of the PhD degree conferred on October 13, 2017, by Erasmus University, Rotterdam, The Netherlands.

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