Intracranial Pressure Patterns in Children with Sagittal Craniosynostosis

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Background: Elevated intracranial pressure (ICP) in sagittal craniosynostosis has a wide spectrum of reported incidence, and patterns are not well understood across infancy and childhood. Characterizing the natural history of ICP in this population may clarify risks for neurocognitive delay and inform treatment decisions.

Methods: Infants and children with sagittal craniosynostosis and unaffected control subjects were prospectively evaluated with spectral-domain optical coherence tomography from 2014 to 2021. Elevated ICP was determined based on previously validated algorithms using retinal optical coherence tomography parameters.

Results: Seventy-two patients with isolated sagittal craniosynostosis and 25 control subjects were evaluated. Overall, 31.9% (n = 23) of patients with sagittal craniosynostosis had evidence of ICP greater than or equal to 15 mmHg, and 27.8% (n = 20) of patients had ICP greater than or equal to 20 mmHg. Children with sagittal craniosynostosis younger than 6 months were more likely to have normal ICP (88.6% <15 mmHg; 91.4% <20 mmHg) than those aged between 6 and 12 months (54.5%, P = 0.013; 54.5%, P = 0.005) than those older than 12 months (46.2%, P < 0.001; 53.8%, P = 0.001). ICP was directly correlated with severity of scaphocephaly (P = 0.009). No unaffected control subjects at any age exhibited retinal thickening suggestive of elevated ICP.

Conclusion: Elevated ICP is rare in isolated sagittal craniosynostosis younger than 6 months, but it becomes significantly more common after 6 months of age, and may correlate with severity of scaphocephaly. (Plast. Reconstr. Surg. 154: 135e, 2024.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk, II.

Sagittal craniosynostosis often presents as an isolated, single-suture fusion without any associated syndrome. Nonetheless, it is associated with neurocognitive impairment in some patients, including early speech and language problems; subsequent literacy issues; and problems in related functions such as working memory, attention, and planning. Elevated intracranial pressure (ICP) may be partially implicated in these neurocognitive differences; however, there is a paucity of robust data demonstrating this relationship. Several reports have suggested that earlier surgical treatment is associated with improved neurocognitive outcomes in patients with sagittal craniosynostosis, which may partially be attributable to lower ICP at the time of treatment in younger patients.

There is limited understanding of the natural history of ICP in children with isolated sagittal craniosynostosis. Although funduscopic examination for papilledema is commonly deployed as a screening measure, it has poor sensitivity. Because direct ICP monitoring is invasive, it is not used routinely. Other noninvasive surrogates such as headaches, developmental delay, and radiographic findings have low specificity. The difficulties of measuring ICP may contribute to elevated ICP in nonsyndromic sagittal craniosynostosis.
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craniosynostosis being underestimated in the literature.\textsuperscript{18} Most importantly, no studies have evaluated ICP in children with craniosynostosis younger than 6 months.

Optical coherence tomography (OCT) of the peripapillary retina is a recently validated noninvasive, quantitative modality to assess ICP in pediatric patients with craniosynostosis.\textsuperscript{8,13} Because OCT can be deployed routinely in infants and children, it enables the incidence of elevated ICP to be assessed in a way not possible with conventional modalities.

The purpose of this study was to use OCT to assess the incidence of elevated ICP in infants and children with isolated sagittal craniosynostosis across various ages of treatment. We hypothesized that craniocerebral disproportion between the growing brain and constricted skull in younger infants is less pronounced and better compensated, and therefore, younger children will have lower ICP than older children.

**Patients and Methods**

Consecutive patients with isolated sagittal craniosynostosis were prospectively enrolled into an institutional review board–approved study using OCT to assess retinal parameters between 2014 and 2021. OCT measurements were obtained shortly after induction of anesthesia in patients undergoing surgical correction of craniosynostosis following the methodology outlined by Swanson et al. and Kalmar et al.\textsuperscript{8,13} OCT was performed in each eye using the Optovue device running iVue software (Optovue, Inc., Fremont, CA). OCT parameters included the maximal retinal nerve fiber layer thickness (MaxRNFL), maximal retinal thickness (MaxRT), and maximal anterior projection (MaxAP) using the OCT cross-section that corresponded most closely to the center of the optic disc. Segmentation boundaries, including the inner limiting membrane, retinal nerve fiber layer, and retinal pigment epithelium were automatically assigned by the software (Fig. 1).

Retinal parameter thresholds to detect elevated ICP above 15 mmHg and 20 mmHg were used based on previous investigations that used receiver operating characteristic curves.\textsuperscript{13} Retinal findings based on the lowest value from either eye of MaxRNFL greater than or equal to 159.8 μm and MaxAP greater than or equal to 129.1 μm were used as the threshold to define ICP elevation above 15 mmHg, which has been established to yield a sensitivity of 77.3% and a specificity of 95.0%.\textsuperscript{13} In addition, retinal findings based on the lowest value from either eye of MaxRNFL greater than or equal to 170.6 μm and MaxAP greater than or equal to 138.3 μm were used as the threshold to define ICP elevation above 20 mmHg, which has been established to yield a sensitivity of 90.0% and a specificity of 81.3%.\textsuperscript{13}

In subjects for whom intraoperative ICP monitoring was also used at the same time as their initial cranial vault procedure and OCT evaluation, these data were recorded and analyzed. ICP was measured using a subdural catheter with control for several variables including end-tidal carbon
dioxide, patient position, and timing after induction of anesthesia.\textsuperscript{8,13} This enabled continuous ICP data to be used in a subset of patients to assess its relationship to severity of scaphocephaly. Invasive ICP measurement was only performed in patients at risk for elevated ICP, whereas OCT was performed in all patients.

Subjects with a diagnosis of isolated sagittal craniosynostosis were included for analysis. Patients who had undergone any prior intracranial procedure (eg, cranial vault expansion, prior cerebrospinal shunt placement) were excluded to minimize potential confounding of these procedures relieving ICP elevations.

Unaffected control patients undergoing anesthesia for other indications unrelated to craniosynostosis (eg, nevus excision) were also included to assess retinal parameters. Control patients included similarly aged infants and a spectrum of older children. This enabled assessment of whether retinal thickness changes were influenced by older age, and the opportunity to test the reliability of our validated OCT parameters and potentially identify any false-positive cases.

Pearson chi-square test and Fisher exact test were used to compare categorical variables. Central tendency was reported using median and interquartile range (IQR). Bonferroni corrected pairwise comparisons were performed for any analyses across 3 or more groups. Linear correlations were reported using Pearson coefficient. \( P \) values were all two-tailed, and significance was set at the \( P < 0.05 \) level. Statistical analysis was conducted on SPSS version 27 (IBM Corp., Armonk, NY).

**RESULTS**

During the study interval, 72 patients underwent corrective surgery for sagittal craniosynostosis and met inclusion criteria, and there were 25 unaffected control patients who met inclusion criteria (Table 1). Patients with sagittal craniosynostosis had a median age of 6.5 months (IQR, 3.2 to 23.1 months), and unaffected control patients had a median age of 18.9 months (IQR, 9.9 to 75.7 months) (Table 1). Control patients were intentionally not age-matched to demonstrate that even at significantly older ages, unaffected control patients do not have thickening of retinal parameters.

Among patients with sagittal craniosynostosis, 48.6\% of patients (\( n = 35 \) of 72) were younger than 6 months, 15.3\% of patients (\( n = 11 \) of 72) were aged between 6 and 12 months, and 36.1\% of patients (\( n = 26 \) of 72) were 12 months or older (Table 2). These procedures represented the first cranial procedure for all patients, and none of these patients had any additional cranial suture fusion.

Retinal parameter measurements demonstrated ICP less than 15 mmHg in 88.6\% of patients (\( n = 31 \) of 35) younger than 6 months. Compared with these children, significantly fewer patients aged between 6 and 12 months (54.5\%, \( n = 6 \) of 11; \( P = 0.013 \)) and 12 months or older (46.2\%, \( n = 12 \) of 26; \( P < 0.001 \)) had ICP less than 15 mmHg (Fig. 2). Retinal parameter measurements demonstrated ICP less than 20 mmHg in 91.4\% of patients (\( n = 32 \) of 35) younger than 6 months. Compared with these children, significantly fewer patients aged between 6 and 12 months (54.5\%, \( n = 6 \) of 11; \( P = 0.005 \)) and 12 months or older (53.8\%, \( n = 14 \) of 26; \( P = 0.001 \)) had ICP less than 20 mmHg (Fig. 3). Retinal parameters representing elevated ICP showed significant differences in pairwise comparison between various age cohorts (Table 3).

Despite unaffected control patients being significantly older than children with craniosynostosis (\( P < 0.001 \)), none of these control patients had retinal parameters suggesting ICP greater than or equal to 15 mmHg (\( n = 0 \) of 25) (Fig. 4) and none of these control patients had retinal parameters suggesting ICP greater than or equal to 20 mmHg (\( n = 0 \) of 25) (Fig. 5).

To assess ICP as a continuous variable, the subset of patients who had directly measured ICP were assessed with regard to severity of scaphocephaly.
### Table 2. Retinal Parameters by Age at Surgery

| Characteristic | Sagittal Craniosynostosis |  |  |  |  |
|---------------|---------------------------|---|---|---|---|
|               | Aged <6 mo (%) | Aged 6–12 mo (%) | Aged ≥12 mo (%) |  |
| No.           | 35 | 11 | 26 | 0.004 |
| MaxRNFL, μm   | 0.004 |  |  |  |
| Median        | 135 | 151 | 166 |  |
| IQR           | 120–157 | 126–191 | 1478–209 |  |
| MaxAP, μm     | <0.001 |  |  |  |
| Median        | 0 | 157 | 186 |  |
| IQR           | 0–53 | 27–273 | 71–287 |  |
| ICP ≥15 mmHg by OCT | 4 (11.4) | 5 (45.5) | 14 (53.8) | 0.001 |
| ICP ≥20 mmHg by OCT | 3 (8.6) | 5 (45.5) | 12 (46.2) | 0.002 |

**Fig. 2.** Proportion of patients with ICP above 15 mmHg as measured by OCT for patients undergoing surgery for sagittal cranioplasty. (Published with permission of Christopher L. Kalmar. Copyright © 2023 Christopher L. Kalmar, MD, MBA.)

**Fig. 3.** Proportion of patients with ICP above 20 mmHg as measured by OCT for patients undergoing surgery for sagittal cranioplasty. (Published with permission of Christopher L. Kalmar. Copyright © 2023 Christopher L. Kalmar, MD, MBA.)
ICP was never checked directly in patients younger than 6 months, but was obtained by means of durotomy in 25 older patients. Directly measured ICP was inversely correlated to cephalic index \((P = 0.009; \rho = -0.530)\), such that patients with more severe scaphocephaly had higher ICP.

### Table 3. Retinal Parameters by Age at Surgery Bonferroni Pairwise Comparisons

| Sagittal Craniosynostosis | Aged <6 mo | Aged 6–12 mo | Aged ≥12 mo | \(P\) |
|----------------------------|------------|--------------|-------------|------|
| No.                        | 35         | 11           | 26          |      |
| MaxRNFL                    |            |              |             |      |
| Aged <6 mo                 | Aged 6–12 mo |              |             | 0.290|
| Aged 6–12 mo               | Aged ≥12 mo |              |             | NS   |
| Aged <6 mo                 | Aged ≥12 mo |              |             | 0.003|
| MaxAP                      |            |              |             |      |
| Aged <6 mo                 | Aged 6–12 mo |              |             | 0.027|
| Aged 6–12 mo               | Aged ≥12 mo |              |             | NS   |
| Aged <6 mo                 | Aged ≥12 mo |              |             | <0.001|
| ICP ≥15 mmHg by OCT        |            |              |             |      |
| Aged <6 mo                 | Aged 6–12 mo |              |             | 0.039|
| Aged 6–12 mo               | Aged ≥12 mo |              |             | NS   |
| Aged <6 mo                 | Aged ≥12 mo |              |             | 0.001|
| ICP ≥20 mmHg by OCT        |            |              |             |      |
| Aged <6 mo                 | Aged 6–12 mo |              |             | 0.015|
| Aged 6–12 mo               | Aged ≥12 mo |              |             | NS   |
| Aged <6 mo                 | Aged ≥12 mo |              |             | 0.002|

NS, not significant.

**Fig. 4.** (Above) Age versus MaxRNFL measurements labeled by thresholds for ICP 15 mmHg. (Below) Age versus MaxAP measurements labeled by thresholds for ICP 15 mmHg. (Published with permission of Christopher L. Kalmar. Copyright © 2023 Christopher L. Kalmar, MD, MBA.)
Retinal parameters for patients with sagittal craniosynostosis with directly measured ICP showed substantial differences compared with control patients (Fig. 7).

**DISCUSSION**

This study used OCT to evaluate ICP in a broad sample of infants and children undergoing initial treatment for sagittal craniosynostosis and...
yielded several novel findings. First, the vast majority—approximately 90%—of patients with sagittal craniosynostosis who were evaluated before age 6 months showed no retinal findings of elevated ICP. Second, approximately half of patients developed elevated ICP exceeding 20 mmHg after 12 months of age. Third, severity of scaphocephaly was significantly associated with degree of ICP elevation. These findings are likely generalizable as demonstrating the natural history of ICP progression in patients with sagittal craniosynostosis.

Elevated ICP in craniosynostosis is most likely caused by craniocerebral disproportion between a growing brain and constricted skull, which may be implicated in neurodevelopmental differences. In early brain growth, compensatory perpendicular dysmorphic changes, cerebrospinal fluid dynamics, widening of unaffected sutures, and other factors may initially buffer ICP and cerebral impact of this constriction. This may explain why younger children appear to have a lower incidence of elevated ICP than older children with craniosynostosis.

Premature fusion of the sagittal suture is the most common form of craniosynostosis, yet the incidence of elevated ICP in this population remains poorly understood, especially among nonsyndromic patients who undergo early intervention. Studies have shown that among isolated forms of craniosynostosis, sagittal craniosynostosis has the highest ICP elevation. However, these were direct ICP measurements, potentially biased by being measured in older children. In some studies, selection bias may reflect sampling to favor...
those who were suspected to have high ICP to warrant invasive measurement. Most importantly, there are no known studies addressing the incidence of elevated ICP in children younger than 6 months. OCT technology allowed our team to assess elevation of ICP in children undergoing surgery for sagittal craniosynostosis across various age ranges, including those younger than 6 months.

Previous literature suggests that 30% to 40% of syndromic patients and 15% to 20% of nonsyndromic patients with craniosynostosis exhibit elevated ICP. A major limitation to understanding patterns of ICP in this population arises from the difficulty in its measurement. Invasive ICP monitoring is considered the standard method for evaluation of ICP, but risks and costs preclude its routine use; therefore, studies based on such methodology likely exhibit selection bias. Historical reports may underestimate the true incidence, because many studies used papilledema on funduscop y as the surrogate for elevated ICP, which is known to have low sensitivity.

Indeed, studies that use direct ICP monitoring report rates of 31% to 44% among nonsyndromic patients, but these studies may actually overestimate the true incidence by predominantly sampling patients with increased risk. Given the noninvasive nature of OCT, use of this technology allowed us to test all patients with sagittal craniosynostosis regardless of perceived risk, thus eliminating the selection bias of previous studies. This study demonstrated that patients with sagittal craniosynostosis had an overall incidence of 28% (n = 20 of 72) for elevated ICP above 20 mmHg.

Given the heterogeneity of age at treatment in this cohort, and the clear relationship between age and intracranial hypertension that this data establishes, an additional key finding is the natural progression of ICP elevation as a function of time in patients with craniosynostosis. ICP elevation jumps from less than 10% for patients younger than 6 months, to approximately 50% of patients older than 12 months. This suggests that there are substantial physiologic changes in patients younger than 6 months versus those older than 12 months with craniosynostosis. Further research will be needed to elucidate this key age period from the standpoint of neurocognitive sequelae, bone stability, and growth, in addition to ICP changes.

Debate continues regarding threshold of ICP that is considered elevated. Minns argued that various upper normal limits of ICP exist on an age-based spectrum (eg, 3.5 mmHg in neonates, 5.8 mmHg in infants, 6.4 mmHg in children, and 15.3 mmHg in adolescents and adults). Several centers including ours have argued that the conventional 15-mmHg threshold may encompass patients in the upper limits of normal, and instead have posed 20 mmHg as a more appropriate cutoff. We have used both thresholds in this study, and interestingly found few patients to have retinal OCT correlates corresponding to this borderline 15- to 20-mmHg range. An even more salient finding of this study was that the retinal thickening and anterior projection (Figs. 4, below, and 5, below) of nearly all patients with sagittal synostosis across all age ranges exceeded these retinal parameters compared with healthy control patients. There are two potential explanations for these findings: (1) that most patients with sagittal synostosis have retinal thickening as a de novo finding unrelated to ICP, which is not known to be reported; or (2), more plausibly, that most patients with sagittal synostosis, even those not meeting conventional thresholds of elevated ICP, have retinal thickening suggesting ICP chronically elevated above healthy controls.

The fundamental question of the degree and duration of ICP elevation, whether it depends on age, and how it relates to neurocognitive impairment in children with sagittal craniosynostosis is unable to be addressed by this study. Renier et al. presented some of the earliest evidence of a potential association between elevated ICP and poor neurocognitive outcomes in patients with craniosynostosis, and further showed that surgical intervention can lead to normalization of ICP. Nonetheless, Hayward et al. thoughtfully discuss shortcomings of this and other studies purporting a relationship between elevated ICP and neurocognitive impairment. Few studies exist in this space because of the aforementioned challenges in ICP measurement, compounded by those of neurocognitive assessment. A recent systematic review suggests that although intelligence improvements may be affected by earlier surgery and may be mediated by alleviation of ICP, deficits in speech, language, motor, and attention appear to persist regardless of timing of surgery. More recent studies have attempted to pinpoint the optimal timing for surgical intervention and the optimal surgical approach. Patel et al. found that surgery before 6 months of age led to improved neurodevelopmental outcomes.
as measured by locomotor function.35 Further studies are needed to clarify these findings, and if verified, identify whether ICP or other variables are the primary mediating factors.

Multiple factors must be considered when weighing early intervention with strip craniectomy and spring-mediated cranioplasty or molding orthosis versus whole-vault cranioplasty for children with sagittal craniosynostosis.36–40 This study using OCT technology concluded that elevated ICP appears to be very uncommon when minimally invasive surgical correction is undertaken earlier than 6 months of age, whereas children older than 6 months have a significantly higher likelihood of elevated ICP. We believe that this adds to the potential advantages of earlier intervention in patients who present in the first 6 months of life, acknowledging the importance of further research to clarify the relationship between ICP and neurocognitive outcomes. Our center typically recommends spring-mediated minimally invasive vault expansion in patients presenting before 4 months of age and conventional open vault remodeling at 9 months of age for those who present later. Based on these data, we are now discussing open vault remodeling earlier than 9 months of age for patients who present with severe scaphocephaly.

An additional consideration favoring the routine use of OCT technology for ICP monitoring is the high rate of postoperative intracranial hypertension (ICH) described by Thomas et al. in 2015.41 Their study analyzed 217 children retrospectively after sagittal craniosynostosis operation for an average of 86 months and found a 6.9% incidence of elevated ICP following corrective surgery. They found postcorrection ICH to be significantly more common in patients who underwent surgery at younger than 9 months and who underwent strip craniectomy compared with subtotal vault reconstruction. OCT technology will potentially also allow longitudinal evaluation of elevated ICP even after children have undergone successful corrective surgery for craniosynostosis. Numerous reports attest to more extensive normalization of head shape afforded by subtotal calvarial reconstruction,42 and increased brain growth velocity in the first year of life.43 Thomas et al. also note the poor sensitivity and specificity of clinical symptoms and radiographic signs for detection of ICH in their sample and advocate for routine formal monitoring.41,44,45 OCT technology may help fulfill this need without a requirement for invasive ICP monitoring or unreliable clinical monitoring, providing sensitive and specific indicators of ICP that can be measured on a routine basis.15 However, further study of OCT validity and reliability in the postoperative period is necessary to better clarify its utility in this way.

Although some could contend that retinal parameters might increase as children grow older, our control cohort unaffected by craniosynostosis continued to demonstrate minimal retinal thickening throughout childhood. All these unaffected control patients had retinal parameters below our previously validated cutoffs to diagnose elevated ICP of 15 mmHg and 20 mmHg, despite being significantly older. This underscores that retinal parameters are not becoming thicker simply because of age.

Limitations

The findings of this study need to be viewed in the context of several limitations. First, general anesthesia is known to influence ICP, and we therefore attempted to control for end-tidal carbon dioxide, timing of measurement relative to the beginning of the case, and to ensure a stable ICP waveform. We are unable to comment on the impact of OCT measurements with and without anesthesia, but we anticipate that this will have minimal effect on OCT measurements, because OCT captures chronic ICP elevations rather than momentary ICP elevations. Second, OCT technology for noninvasive ICP monitoring in clinical settings requires patients to keep still with their eyes focused straight ahead for the few moments that are required to obtain measurements. As a result, our center must use sedation in patients younger than 3 years to obtain OCT; however, new OCT technology and techniques show feasibility to image infants in the clinic setting.39,40 Third, this study was performed at a single institution on a single OCT device. Some might argue that absolute measurements between OCT devices are unreliable; therefore, we have used the same OCT device over the past 5 years of this study at this institution. Fourth, the time course for developing elevated OCT parameters with elevated ICP remains unknown. Our study assumes that patients generally develop sagittal craniosynostosis at similar times in their lives, and that older age represents a longer duration with the abnormality, which contributes to elevated ICP and thus increased OCT parameters. Fifth, perhaps greater severity of scaphocephaly is simply a surrogate for greater duration of time with elevated ICP, and thus our findings of increased OCT parameters are not caused by severe scaphocephaly per se; rather, they might
simply be caused by longer duration with sagittal craniosynostosis. Sixth, OCT is unable to provide a real-time surrogate for ICP; rather, OCT is most useful to demonstrate chronic elevations of ICP. Previous unpublished experiments in our laboratory demonstrated that retinal parameter thickening because of elevated ICP continues to persist for several months after resolution of ICP to normal levels. As such, OCT is unable to provide definitive postoperative assessment of normalized ICP. Nevertheless, our study demonstrates that earlier treatment for children with craniosynostosis might help avoid predisposing their developing brain to elevated ICP. Further study of the relationship between ICP and neurocognitive outcomes will help clarify the importance of ICP in determining the optimal timing and technique of treating craniosynostosis.

CONCLUSIONS

Nearly all patients undergoing early surgical treatment for sagittal craniosynostosis younger than 6 months do not have elevated ICP by OCT measurement, whereas patients undergoing surgical treatment for sagittal craniosynostosis after 6 months of age are significantly more likely to have elevated ICP. Further research is needed to understand whether and how ICP elevations relate to neurocognitive outcomes.

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DISCLOSURE

The authors have no financial or nonfinancial conflicts of interest to disclose.

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