Child's Nervous System (2020) 36:535–544
https://doi.org/10.1007/s00381-019-04448-x

ORIGINAL ARTICLE

Intracranial pressure patterns in children with craniosynostosis utilizing optical coherence tomography

Jordan W. Swanson[1] · Wen Xu[1] · Gui-Shuang Ying[2] · Wei Pan[2] · Shih-Shan Lang[3] · Gregory G. Heuer[3] · Scott P. Bartlett[1] · Jesse A. Taylor[1]

Received: 25 January 2019 / Accepted: 19 November 2019 / Published online: 17 December 2019

Abstract

Background Better understanding the incidence and patterns of elevated intracranial pressure (ICP) in patients with craniosynostosis may facilitate more timely intervention to alter neurocognitive outcomes. Spectral-domain optical coherence tomography (OCT) of the retina can non-invasively diagnose elevated ICP, and has demonstrated high sensitivity and specificity among patients with craniosynostosis. This study sought to characterize patterns of elevated ICP among patients with craniosynostosis.

Methods Quantitative retinal parameters were prospectively assessed in both eyes of patients with craniosynostosis using spectral-domain OCT. Based on retinal OCT thresholds associated with elevated ICP (> 15 mmHg), subjects were assigned an OCT diagnosis of elevated or non-elevated ICP which was analyzed relative to clinical characteristics and craniosynostosis patterns.

Results Eighty subjects (aged 0.2–18 years) with craniosynostosis were enrolled; among these, 67 (84%) were nonsyndromic. OCT evaluation was performed at initial vault expansion in 56 (70%) patients. Among this subset, 27 (48%) patients had papillary changes suggestive of elevated ICP, reflecting a 44% incidence in nonsyndromic and 83% in syndromic patients. The median age at initial vault expansion was higher among those with elevated ICP (11.1 months) than those without (7.8 months; $p = 0.04$.) Multi-suture synostosis was associated with changes consistent with elevated ICP in 9 (75%) patients compared with 18 (41%) with single suture synostosis ($p = 0.05$).

Conclusions OCT of the retina produces a potentially sensitive indicator of ICP in craniosynostosis patients. Elevated ICP may be associated with number of involved sutures and older patient presentation, and refining appropriate "cutoffs" will be important as the technology becomes more widespread.

Keywords Craniosynostosis · Optical coherence tomography (OCT) · Intracranial pressure · Noninvasive retinal imaging · Papilledema

Introduction

Surgical management of patients with craniosynostosis is guided both by functional and aesthetic objectives. An increasing body of evidence suggests that elevated intracranial pressure (ICP) may be quite prevalent in patients with craniosynostosis [1–4], may not correlate with phenotypic presentation [5], and may recur following surgery [6]. Studies of traumatic brain injury find that neurocognitive outcomes are improved when ICP is within normal limits [7–9]. Likewise, earlier and more extensive surgical expansion in patients with craniosynostosis may be associated with improved neuropsychological outcomes [10, 11], which might in part be mediated by prevention or alleviation of elevated ICP [2]. Nonetheless, the relationships between craniosynostosis patterns, neurocognitive pathophysiology, and intracranial

Jordan W. Swanson and Wen Xu contributed equally to this work.

✉ Jesse A. Taylor
taylorj5@email.chop.edu

[1] Craniofacial Surgery Center and Division of Plastic Surgery, The Children's Hospital of Philadelphia and the University of Pennsylvania, Philadelphia, PA, USA

[2] Scheie Eye Institute and the Department of Ophthalmology, Perelman Center for Advanced Medicine and the University of Pennsylvania, Philadelphia, PA, USA

[3] Division of Neurosurgery, The Children's Hospital of Philadelphia and the University of Pennsylvania, Philadelphia, PA, USA

pressure are incompletely understood, as are their roles in determining the optimal type and timing of surgery. Reliable detection of elevated ICP could enable better understanding of this disease process and the impact of different interventions, as well as facilitate earlier diagnosis and treatment in individual patients, potentially improving long-term neurologic and cognitive outcomes.

However, conventional methods of detecting elevated ICP are often equivocal or invasive [12]. Classic symptoms such as headache, behavior changes, or vomiting are unreliable, particularly among infants and children [13]. Fundoscopy for optic atrophy or papilledema is subjective, with low inter-clinician agreement and only 10–40% sensitivity, often detecting only late manifestations of severely-elevated ICP [14–16]. Optic nerve sheath diameter (ONSD) and transcranial ultrasonography show potential for diagnosing severely-elevated ICP, but seem best suited to detect acute fluctuations in evolving conditions [17–20]. ONSD ultrasonography showed a sensitivity of only 11% in patients with craniosynostosis [21, 22]. In contrast, direct transcranial ICP monitoring is invasive, associated with complications such as infection and hemorrhage, and typically requires 24–48 h of sedation [23–25]. An ideal measure of ICP would be sensitive, noninvasive, and could be performed serially over time to monitor changes.

Spectral domain optical coherence tomography (SD-OCT) uses noninvasive laser interferometry to quantitatively image the retina with micron-level resolution, and is increasingly used by ophthalmologists to diagnose retinal disorders [26–30]. We recently used OCT to perform retinal evaluations in a prospective cohort of children aged 2 months–18 years with craniosynostosis, as well as a positive control cohort of children with hydrocephalus, and a negative control cohort of children who were healthy [31]. In the first two cohorts, intracranial pressure was also measured directly. In multivariate analysis among cohorts, three OCT parameters (maximal retinal nerve fiber layer (RNFL) thickness, maximal retinal thickness, and maximal anterior retinal projection) each correlated significantly with ICP. Using cut points derived from the negative control cohort, OCT parameters yielded 89% sensitivity and 62% specificity for detecting elevated ICP, with high intra-grader and inter-grader agreement. OCT outperformed conventional clinical measures of ICP, which had low sensitivity (11–42%).

In this study, we aim to apply this novel methodology to examine trends in ICP elevation among a large cohort of patients with craniosynostosis, using SD-OCT as the method of detecting elevated ICP.

Patients and methods

Subjects

Patients aged 0–18 years with a diagnosis of craniosynostosis were prospectively enrolled from the Craniofacial Surgery clinic at The Children's Hospital of Philadelphia (CHOP), between September 2014 and November 2015. Written informed consent for all subjects and assent for subjects over the age of 7 years were obtained, and procedures were approved by The Children's Hospital of Philadelphia Institutional Review Board (IRB 13-010131). Patients were candidates for study participation if they were scheduled to undergo a procedure under general anesthesia, and were willing to also undergo SD-OCT eye examination. The study was designed with intent for consecutive patient enrollment, which was carried out subject to availability of the OCT machine and technician. Patient records were reviewed for demographic information, diagnosis, and previous surgical history.

Spectral domain optical coherence tomography

OCT Scan

Subjects underwent OCT evaluation under general anesthesia, in the supine position, and prior to commencing the surgical procedure (Fig. 1). An ophthalmic speculum was introduced to retract upper and lower eyelids, balanced salt solution was used to irrigate each eye, and the head was deviated 10° ipsilateral to the eye undergoing examination. Portable OCT imaging (iVue, Optovue, Fremont, CA; software version 3.2) was performed by capturing two scans with the optic nerve head (ONH) and 3-D disc imaging protocols in each eye. Total scan time was approximately 7 min.

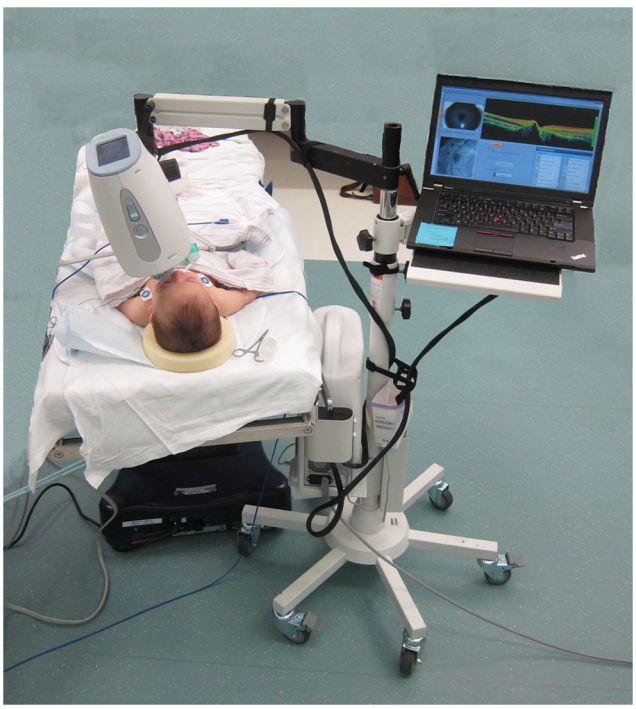

Fig. 1 Optovue iVue optical coherence tomography unit, in use performing retinal imaging on an infant under sedation prior to cranial vault expansion

Post-scan processing

From the ONH scan, the average peripapillary RNFL thickness, optic disc area, and optic disc volume were calculated automatically. On the 3D scan, the iVue software performs automatic segmentation of the inner limiting membrane (ILM), RNFL, and retinal pigmented epithelium (RPE) [32]. The single OCT cross-section corresponding to the center of the optic disc was selected for each eye, and the ILM served as the most vitread reference for the following 3-D disc scan parameters: maximal RNFL thickness, maximal retinal thickness, and maximal anterior projection (Fig. 2). Maximal RNFL thickness was defined as the maximal distance between the ILM and the posterior boundary of the RNFL on the previously determined OCT cross-section centered on the optic disc. Maximal retinal thickness was defined as the length of a line that extends from the maximal ILM elevation to a perpendicular intersection with the segmentation boundary of the RPE as it connects the nasal and temporal sides of the neural canal. Finally, maximal anterior projection was measured perpendicularly from a ray bridging the peripapillary ILM anteriorly to the point of maximal ILM elevation. The relative position of each segmentation boundary was exported as raw data (Microsoft Excel v 14.4.7; Redmond, WA). Cross-sections were exported as bitmap files and images analyzed (Image-J, National Institutes of Health, Bethesda, MD). The SD-OCT image acquisition protocol has been described previously [31].

ICP classification based on OCT parameters

An SD-OCT diagnosis of elevated ICP was made in any subject for which the maximal RNFL thickness exceeded 207 μm or the maximal anterior retinal projection exceeded 159 μm in either eye. These cutoff points were established previously and corresponded to the 97.5th percentile of healthy control patients; and did not vary significantly based on subject age [31]. These cutoff points would be expected to detect elevated ICP (above 15 mmHg) with 89% sensitivity and 62% specificity.

Statistical Analysis

Patient characteristics and craniosynostosis patterns were compared between subjects with and without elevated ICP, cross-sectionally, and longitudinally. Cross-sectionally, two sample t test was used to compare any difference in means, Wilcoxon rank sum test for medians, chi-squared test for proportions, and when frequency count was too low (< 5), Fisher exact test was used. Longitudinally, among patients with multiple OCT assessments corresponding to multiple surgical procedures, we used paired t test for comparing means and Wilcoxon signed rank for comparing medians, and repeated measures logistic regression were used to evaluate factors for their association with elevated ICP. All statistical analyses were performed with the use of SAS v 9.4 (SAS Institute Inc, Cary, NC), and p value < 0.05 (without correction for multiple comparisons) was considered statistically significant.

Results

Study subjects

Eighty infants and children (0.2–18 years) with craniosynostosis enrolled in and completed the study; 25 (31%) were female and 55 (69%) male. The median age at the time of SD-OCT examination was 11.4 months (interquartile range 5.7–46.0 months). The majority of subjects (67, 84%) were non-syndromic, with sagittal synostosis (n = 27) diagnosed most frequently (Table 1). Of the 13 subjects with syndromic craniosynostosis, 4 (30%) had Apert syndrome. Among all 80 subjects, SD-OCT diagnosis of elevated ICP was made in 36 (45%).

OCT findings during initial intracranial procedure

Fifty-six (70%) subjects underwent initial intracranial surgery at time of OCT; 24 (30%) were undergoing a repeat intracranial procedure. Among those receiving initial intracranial surgery, median age was 9.3 months with a range from 2.6 months to 8.5 years. Twenty-seven (48%) of the 56 subjects presented with OCT-defined elevated ICP (Table 2). Twenty-two (44%) of 50 subjects in the nonsyndromic group had elevated ICP, whereas 5 (83%) of the 6 subjects in the syndromic group had elevated ICP (p = 0.10). At the time of initial surgery, patients with elevated ICP were older (median 11.1 months (IQR 5.8–22.9)) compared with those without elevated ICP (7.8 (3.5–10.1) months, p = 0.04) (Fig. 3).

Among nonsyndromic patients, approximately 40% of patients with metopic or sagittal synostosis and 60% of patients with unicoronal or multi-suture synostosis patterns exhibited elevated ICP (Table 2). However, no single suture type conveyed significantly disproportionate risk of elevated ICP in this sample of nonsyndromic patients (p = 0.72). Among syndromic patients (n = 6), multiple-involved sutures trended toward increased risk of elevated ICP. On pooled analysis, involvement of multiple (2 or more) sutures regardless of syndromic status was associated with elevated ICP in 9 (75%) of patients compared with 18 (41%) with single suture synostosis (p = 0.05).

OCT findings during subsequent surgical procedures

Fourteen subjects underwent OCT evaluation both at an initial intracranial procedure and then again at a subsequent

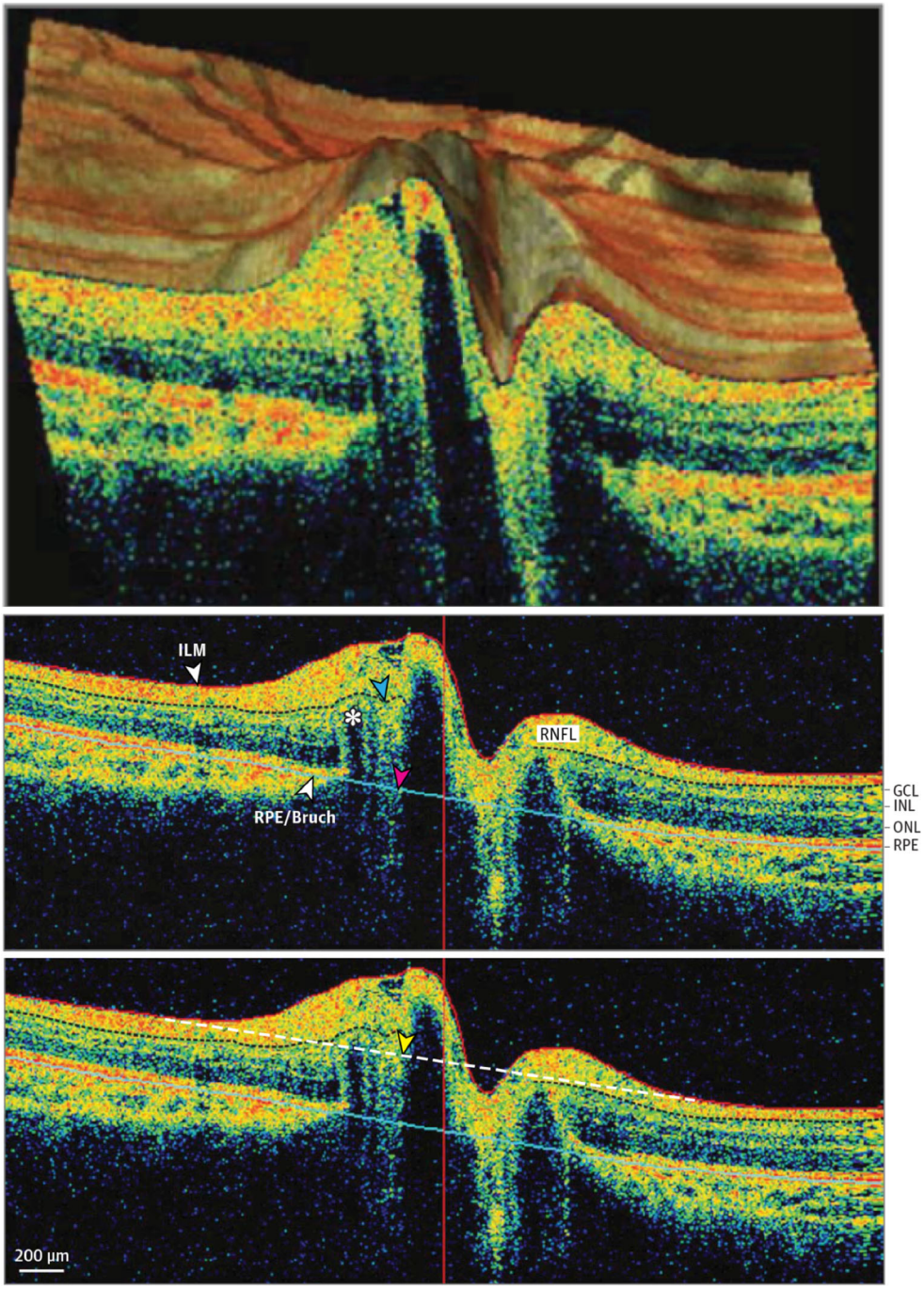

Fig. 2 Key OCT parameters corresponding to intracranial pressure. An axial cross-section through the center of the **a** optic disc enables analysis of **b** RNFL thickness (width between the inner limiting membrane (ILM; red line) and blue arrowhead, which corresponds to the surface of the ganglion cell layer, GCL) and retinal thickness (width between the ILM and red arrowhead, which corresponds to the surface of the retinal pigmented epithelium (RPE) and Bruch's membrane), as well as **c** anterior retinal projection (width between the ILM and yellow arrowhead on the dotted white line), which is a vector connecting the posterior-most ILM adjacent to either side of the optic disc. The asterisk in B indicates vascular elements causing posterior shadowing. Inner nuclear layer (INL), outer nuclear layer (ONL). Reprinted by permission from *JAMA Ophthalmology*

surgical procedure during the study period, at a median 2.6 months later (Table 3). Three (21%) were syndromic, and 11 (79%) were nonsyndromic. Treatment was with distraction osteogenesis in 9 patients (64%), cranial springs in 3 patients (21%), and open cranial remodeling in two patients (14%). In most patients, the subsequent procedure was for distractor or spring removal. Seven (50%) had SD-OCT diagnosis of elevated ICP at initial treatment; among these 4 (57%) showed retinal findings consistent with non-elevated ICP at subsequent OCT evaluation, and 3 (43%) showed findings consistent with persistent elevated ICP. Among the seven patients with SD-OCT diagnosis of non-elevated ICP at initial treatment, one (14%) showed signs of elevated ICP on the subsequent OCT evaluation. In univariate analysis, neither the length of time interval between assessments (OR 1.28, 95% CI 0.54–3.04, $p = 0.58$), the age at initial procedure (OR 1.01, 95% CI 0.99–1.03, $p = 0.45$), nor craniosynostosis pattern ($p = 0.49$) was associated with apparent persistence of elevated ICP in this small sample.

Table 1 Characteristics of study subjects (n = 80)

		Nonsyndromic (n = 67)	Syndromic (n = 13)	Overall (n = 80 patients)
Sex	Female	18 (26.9%)	7 (53.8%)	25 (31.3%)
	Male	49 (73.1%)	6 (46.2%)	55 (68.7%)
Age (months)	Mean (SD)	37.2 (53.3)	58.6 (72.2)	40.7 (56.8)
	Median (Q1, Q3)	10.7 (5.2, 43.0)	22.9 (14.1, 59.1)	11.4 (5.7, 46.0)
	< 6 months	19 (28.4%)	2 (15.4%)	21 (26.3%)
	≥ 6, < 12 months	19 (28.4%)	1 (7.7%)	20 (25.0%)
	≥ 12, < 24 months	7 (10.4%)	4 (30.8%)	11 (13.8%)
	≥ 24 months	22 (32.8%)	6 (46.2%)	28 (35.0%)
Diagnosis	Metopic	19 (28.4%)	0 (0.0%)	
	Unicoronal	7 (10.4%)	1 (7.7%)	
	Sagittal	27 (40.3%)	0 (0.0%)	
	Lambdoid	3 (4.5%)	0 (0.0%)	
	Multi-suture	11 (16.4%)	4 (30.8%)	
	Bicoronal	0 (0.0%)	8 (61.5%)	
Syndrome	Apert		4 (30.8%)	
	Pfeiffer		1 (7.7%)	
	Meunke		2 (15.4%)	
	Saethre-Chotzen		2 (15.4%)	
	Crouzon		2 (15.4%)	
	Treacher-Collins		1 (7.7%)	
	Other		1 (7.7%)	
First cranial expansion	Yes	50 (74.6%)	6 (46.2%)	56 (70.0%)
	No	17 (25.4%)	7 (53.8%)	24 (30.0%)
ICP status	Non-elevated	40 (59.7%)	4 (30.8%)	44 (55.0%)
	Elevated	27 (40.3%)	9 (69.2%)	36 (45.0%)

Clinical indicators of elevated ICP

Among 80 subjects with craniosynostosis in this study, signs, and symptoms of papilledema on fundoscopy, headaches, and CT findings of "copper beaten" cranial bone or ventricular effacement were found to demonstrate poor sensitivity (6–29%) for detecting elevated ICP (defined based on OCT criteria) (Table 4). Three representative subjects are shown in Fig. 4.

Discussion

Elevated intracranial pressure (ICP) is increasingly implicated as a potential pathophysiologic factor in patients with craniosynostosis [1–4], yet the relationship among craniosynostosis patterns, ICP, and neurocognitive impairment remains poorly understood. A central challenge has been assembling meaningful ICP data, given the heterogeneity of clinical presentations and limitations of established methods to detect ICP, particularly in children. This study surmounted conventional barriers to evaluating ICP by employing OCT across a large sample of patients with craniosynostosis and utilizing two key OCT parameters that have been previously validated to detect elevated ICP in children and infants with 89% sensitivity and 62% specificity [31].

Three core findings emerged from this study. First, we found that at the time of initial cranial expansion, 44% of nonsyndromic patients and 83% of syndromic patients presented with OCT-defined peri-papillary changes consistent with elevated ICP, rates exceeding those previously reported. Second, the median age at initial vault expansion was significantly higher among those with elevated ICP (11.1 months) than those without (7.8 months). Third, multi-suture synostosis was associated with changes consistent with elevated ICP twice as frequently (75%) as single suture synostosis (41%).

We identified changes consistent with elevated ICP in 44% of nonsyndromic and 83% of syndromic patients, rates which may exceed historically-quoted rates of 15–20% in nonsyndromic patients and 30–40% in syndromic patients [2, 33]. Historical reports may underestimate the true incidence, because findings of papilledema on direct fundoscopy—the traditional diagnostic exam for elevate ICP—have a sensitivity of only 10–30% [14–16, 31]. Indeed, studies that utilize direct

Table 2 Patterns of elevated ICP among patients undergoing initial intracranial procedure (n = 56)

		Elevated ICP (n = 27 patients)	Non-elevated ICP (n = 29 patients)	P value
Sex				0.08
	Female	11 (68.8%)	5 (31.3%)	
	Male	16 (40.0%)	24 (60.0%)	
Age	Mean (SD)	18.2 (19.6)	13.4 (20.9)	0.38
	Median (Q1, Q3)	11.1 (5.8, 22.9)	7.8 (3.5, 10.1)	0.04
	< 6 months	7 (33.3%)	14 (66.7%)	
	≥ 6, < 12 months	9 (50.0%)	9 (50.0%)	
	≥ 12, < 24 months	5 (71.4%)	2 (28.6%)	
	≥ 24 months	6 (60.0%)	4 (40.0%)	
Suture Status				0.05
	Single suture	18 (41%)	26 (59%)	
	Multi-suture	9 (75%)	3 (25%)	
Nonsyndromic		22 (44%)	28 (56%)	
	Metopic	6 (40%)	9 (60%)	0.72
	Unicoronal	3 (60%)	2 (40%)	
	Sagittal	9 (43%)	12 (57%)	
	Lambdoid	0 (0%)	2 (100%)	
	Multi-suture	4 (57%)	3 (43%)	
Syndromic		5 (83%)	1 (17%)	
	Single suture	0 (0.0%)	1 (100.0%)	0.17
	≥ 2 suture	5 (100.0%)	0 (0.0%)	

ICP measurement show higher incidence. Renier et al. found a 31% incidence of preoperative intracranial hypertension in a heterogenous group of craniosynostosis patients via direct ICP monitoring [1], Tuite et al. [14] employed direct subdural ICP measurement and identified a rate of elevated ICP of 34% in children with non-syndromic craniosynostosis, and Wall et al. [2] found a 44% rate among older sagittal synostosis patients not suspected to have elevated ICP. Our distribution of cases closely reflects accepted prevalence rates [34], suggesting selection bias to be a minimal confounder. This incidence is an interesting finding given that our sample reflects patients generally undergoing surgery at what we consider optimal age, although some were older children.

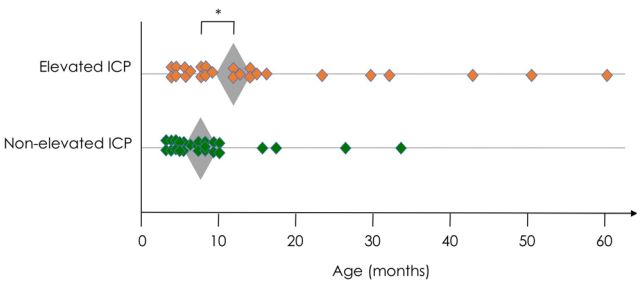

Fig. 3 ICP status as measured by OCT, as a function of time at initial cranial vault expansion surgery. Median age 11.1 months among those with elevated ICP, 7.8 months among those without elevated ICP

Jeelani and colleagues at Great Ormond Street Hospital have questioned whether 20 mmHg may be a more appropriate cutoff for abnormally elevated ICP [35], given some of the original data cited by Renier [1]. Avery et al.'s finding that the 90th percentile of lumbar puncture opening pressure among children was 28-cm water (20.6 mmHg) might also support this cutoff [36]. Increasing the cutoff to 20 mmHg would decrease our reported incidence of elevated ICP considerably, perhaps more in line with other published literature. However, Minns review of all studies before 1990 in which ICP had been objectively measured found upper normal limits of 3.5 mmHg in neonates, 5.8 mmHg in infants, 6.4 mmHg in children, and 15.3 mmHg in adolescents and adults [37]. This more closely matches the clinical experience of our pediatric neurosurgical team, who consider an ICP of > 10 mmHg in children to be highly unusual. Further, in the previous study validating OCT as a measure of ICP in children, retinal changes in craniosynostosis were distributed along a spectrum of severity, which deviated qualitatively from normal controls even with ICP well below 15 mmHg [31]. This study was underpowered to clearly show differences in raised ICP among different synostosis patterns, although with further data these may become apparent. The purpose of this study is not to comment on currently held standards of what constitutes "high", or "abnormal", ICP; that stated, OCT may provide a non-invasive, readily available, means by which we gain

Table 3 Patterns of elevated ICP among patients with serial OCT evaluation (n = 14)

		Initial intracranial procedure (n = 14)	Subsequent OCT evaluation (n = 14)
Age	Mean (SD)	41 (32)	44 (32)
	Median (Q1,Q3)	8.4 (3.3, 100.8)	11.0 (6.4, 104.1)
Syndromic status	Nonsyndromic	11 (79%)	11 (79%)
	Syndromic	3 (21%)	3 (21%)
ICP Status	Elevated	7 (50%)	4 (29%)
	Non-elevated	7 (50%)	10 (71%)
Procedure	Cranial distraction	9 (64%)	0
	Cranial spring	3 (21%)	0
	Distractor/spring removal	0	12 (85%)
	Other	2 (15%)	2 (15%)

further insight into patterns of ICP in the craniosynostosis population, thereby, gaining a better understanding of it as a pathophysiological mechanism behind neuropsychological findings.

As for timing of elevated ICP in patients with craniosynostosis, we found that the median age at initial vault expansion was significantly higher among those with elevated ICP (11.1 months) than those without (7.8 months). This supports the concept that ICP continues to increase in craniosynostosis patients until the cranial vault is surgically expanded. It may also support the hypothesis that elevated ICP may in part mediate the onset of neurocognitive impairment, given the parallel findings by Persing et al. that showed improved neurocognitive outcomes in patients with sagittal synostosis when surgical treatment is earlier and more extensive [10, 11]. Findings about onset of ICP elevation must be weighed with other factors when considering the optimal timing for first cranial expansion procedure. While operating earlier may be associated with lower rates of intracranial hypertension and improved neurocognitive outcomes, it may also come with increased peri-operative risks as well as an increased risk for needing additional surgery later in childhood [10, 11, 38–40]. It remains to be seen whether and how increased rates of ICP elevation in children undergoing later cranial vault expansion correlate clinically with neurocognitive differences and relevant long-term outcomes [41]. There may also be intrinsic patient mechanisms that compensate for increasing ICP, such as a persistent or enlarged open fontanelle. Although not assessed in this study, this would be an interesting area of future research.

We also found that synostosis involving more than one major suture was associated with elevated ICP nearly twice as frequently (75%) as single suture synostosis (41%). Similarly, the frequency of raised ICP was nearly twice as high in syndromic (83%) compared to nonsyndromic (44%) patients. This further strengthens the evidence that certain phenotypic patterns are more frequently associated with raised ICP [14]. Nonetheless, the Oxford Unit reported a high frequency of raised ICP in patients with unicoronal synostosis and mild phenotypic features leading to clinician and/or parental reluctance to proceed with surgical expansion [5]. This suggests that ICP status may not correlate with phenotype, or more specifically may be elevated even without overt signs or symptoms. Given that raised ICP was elicited so frequently (41%) in the relatively lower-risk patients with single-suture synostosis, it is far from clear if this group can really be treated as less severe from a clinical management standpoint.

Finally, among our subset of patients who had follow-up OCT imaging approximately 3 months after cranial expansion, we were surprised that nearly half of patients had retinal findings suggestive of persistently elevated ICP. Based on our study methodology, it is not possible to distinguish whether

Table 4 Association between clinical findings and elevated ICP (n = 80 patients*)

Sign/symptom	Elevated ICP	Sign/symptom present	Sign/symptom absent	P value
Papilledema	Yes	2 (6%)	31 (94%)	0.22
	No	0 (0%)	37 (100%)	
Headaches	Yes	6 (27%)	16 (73%)	1.00
	No	7 (29%)	17 (71%)	
CT thumb printing	Yes	10 (28%)	26 (72%)	1.00
	No	9 (25%)	27 (75%)	
CT ventricular effacement	Yes	4 (11%)	32 (89%)	1.00
	No	3 (17%)	33 (83%)	

*Not all 80 patients had clinical evaluations of every sign and symptoms

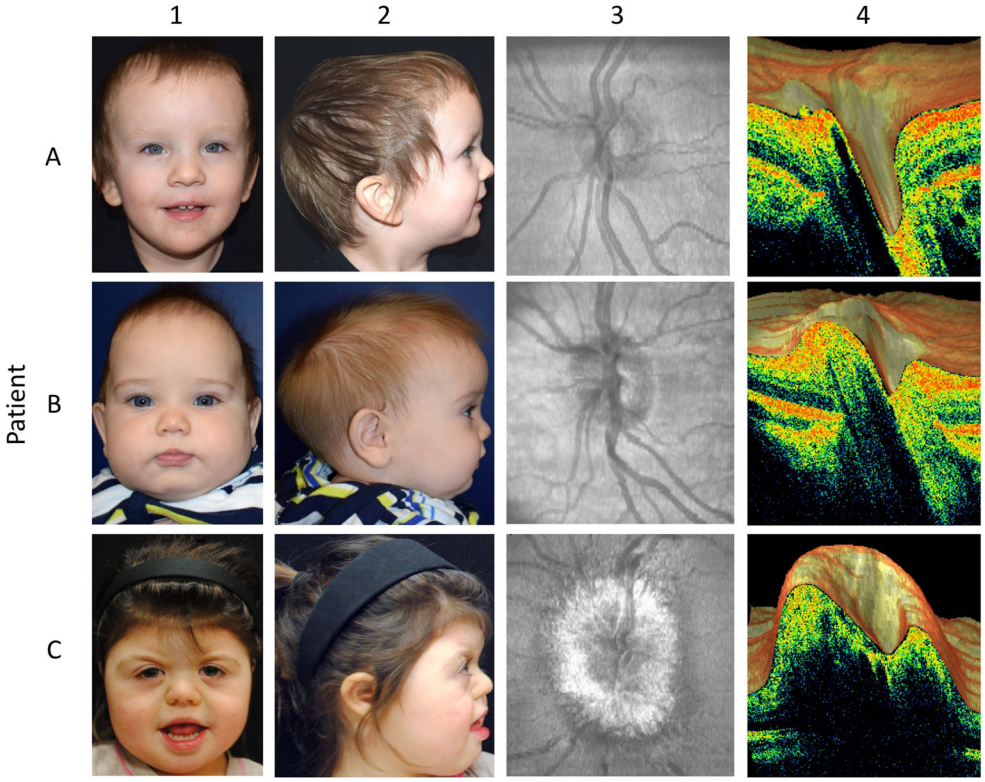

Fig. 4 Reference cases of fundoscopy and OCT findings in patients with craniosynostosis. Columns show pre-operative anteroposterior (1) and lateral (2) clinical photographs, retinal fundoscopic images (3), and OCT 3-d reconstruction images of the optic nerve disc for three patients with craniosynostosis. Patient A is a 6 month old male with metopic synostosis, no papilledema detected on funduscopic exam, OCT imaging showing no optic disc elevation or thickening, and a direct ICP measurement of of 9 mmHg. Patient B is an 11 month old male with sagittal synostosis, no papilledema detected on funduscopic exam, OCT imaging which shows retinal thickening and elevation, and a direct ICP measurement of 18 mmHg. Patient C is a 3 year old female with Saethre-Chotzen syndrome and bicoronal synostosis, with papilledema noted on fundoscopy, OCT findings of retinal thickening and elevation, and direct ICP measurement of 16 mmHg

these retinal findings were due to ICP that remained elevated, or due to retinal thickening that persisted in the absence of raised ICP – due to persistent edema, fibrosis, or a lack of distensibility. The latter possibility is an area of emerging research [42]. It is unclear whether the new finding of elevated ICP on follow-up examination represents uncorrected ICP, a delay in normalization of the retina, or an OCT reading error. The impact of surgical treatment on ICP has been rarely reported [43]. The Oxford Craniofacial Unit reported an elevated ICP frequency of 7% among nonsyndromic sagittal craniosynostosis patients in whom there was clinical suspicion of elevated ICP, at a mean 4 years postoperatively [43]. Postoperative ICP elevation was more common in the cohort treated with strip craniectomy at a younger age as opposed to calvarial remodeling at an older age. Unfortunately, this subgroup sample size was too small to explore associations between persistence of raised ICP and type/timing of surgery or underlying craniosynostosis diagnosis. Regardless, it suggests the possibility of persistently elevated ICP and the importance of future investigations in this area.

This prospective study has several notable limitations. First, although the sample size was relatively large, the heterogeneity of craniosynostosis presentation patterns and diversity of techniques employed at our institution precluded associations being drawn between raised ICP and individual synostosis patterns or type or timing of surgery with adequate power. Second, the methodology utilized by this study [31], while validated in a comparable patient population with high intra- and inter-rater reliability, is relatively novel and may be further refined with time. Further, given its high sensitivity but lower specificity, our OCT methodology may result in a higher rate of false positives than other methods with lower sensitivity and higher specificity. Finally, the sample was limited to subjects under general anesthesia; in the future, assessing patients in the clinic—likely feasible in those over 5 years of age—will diversify the sample [44]

Conclusion

Many factors and data inform the decision to expand or remodel a child's cranial vault. Among these factors, assessing the presence of elevated ICP—not to mention its present or future impact on neurological function—is challenging and

often incomplete. OCT enables a detailed examination of the optic nerve head, and provides a potentially sensitive indicator of ICP elevation in craniosynostosis patients. By cautiously applying this new methodology to a relatively large cohort of such patients, this study suggests that ICP may be associated with number of involved sutures and older patient presentation. Continued research to further validate OCT as a tool, refine "cut-off" thresholds of abnormalcy that likely result from elevated ICP, understand the processes through which the retina normalizes after intracranial surgery, and how to apply this data to clinical decision-making will all be critically important as the technology becomes more widespread.

Acknowledgements The authors wish to thank Lawrence O. Lin, MS, for his graphic design contribution, and Tomas S. Aleman, MD, Grant T. Liu MD and William R. Katowitz, MD of the Division of Ophthalmology at the Children's Hospital of Philadelphia, for their essential contributions to study conception and design.

Funding information This study was supported by the National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS) UL1TR000003, the NIH National Eye Institute (NEI) K12EY015398-10, 2-P30-EY01583-26, the Center for Human Appearance at the University of Pennsylvania, Research to Prevent Blindness, Foundation Fighting Blindness, Hope for Vision, Macula Vision Research Foundation, Pennsylvania Lions Sight Conservation and Research Foundation, Mackall Trust Funds, and the Foundation Fighting Blindness for equipment acquisition, research assistance and biostatistical support.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Renier D, Sainte-Rose C, Marchac D, Hirsch JF (1982) Intracranial pressure in craniostenosis. *J Neurosurg* 57(3):370–377
2. Wall SA, Thomas GPL, Johnson D, Byren JC, Jayamohan J, Magdum SA, McAuley D, Richards PG (2014) The preoperative incidence of raised intracranial pressure in nonsyndromic sagittal craniosynostosis is underestimated in the literature. *J Neurosurg Pediatr* 14(6):674–681
3. Gault DT, Renier D, Marchac D, Jones BM (1992) Intracranial pressure and intracranial volume in children with craniosynostosis. *Plast Reconstr Surg* 90(3):377–381
4. Thompson DN, Harkness W, Jones B, Gonsalez S, Andar U, Hayward R (1995) Subdural intracranial pressure monitoring in craniosynostosis: its role in surgical management. *Childs Nerv Syst* 11(5):269–275
5. Eley KA, Johnson D, Wilkie AOM, Jayamohan J, Richards P, Wall SA (2012) Raised intracranial pressure is frequent in untreated non-syndromic unicoronal synostosis and does not correlate with severity of phenotypic features. *Plast Reconstr Surg* 130(5):690e–697e
6. Spruijt B, Joosten KFM, Driessen C, Rizopoulos D, Naus NC, van der Schroeff M, Wolvius EB, van Veelen M, Tasker RC, Mathijssen IM (2015) Algorithm for the management of intracranial hypertension in children with syndromic craniosynostosis. *Plast Reconstr Surg* 136(2):331–340
7. Becker DP, Miller JD, Ward JD, Greenberg RP, Young HF, Sakalas R (1977) The outcome from severe head injury with early diagnosis and intensive management. *J Neurosurg* 47(4):491–502
8. Marshall LF, Smith RW, Shapiro HM (1979) The outcome with aggressive treatment in severe head injuries. Part II: acute and chronic barbiturate administration in the management of head injury. *J Neurosurg* 50(1):26–30
9. Chesnut RM, Temkin N, Carney N, Dikmen S, Rondina C, Videtta W, Petroni G, Lujan S, Pridgeon J, Barber J, Machamer J, Chaddock K, Celix JM, Cherner M, Hendrix T, Global Neurotrauma Research Group (2012) A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med* 367(26):2471–2481
10. Patel A, Yang JF, Hashim PW et al (2014) The impact of age at surgery on long-term neuropsychological outcomes in sagittal craniosynostosis. *Plast Reconstr Surg* 134(4):608e–617e
11. Hashim PW, Patel A, Yang JF, Travieso R, Terner J, Losee JE, Pollack I, Jane J Sr, Jane J Jr, Kanev P, Mayes L, Duncan C, Bridgett DJ, Persing JA (2014) The effects of whole-vault cranioplasty versus strip craniectomy on long-term neuropsychological outcomes in sagittal craniosynostosis. *Plast Reconstr Surg* 134(3):491–501
12. Pollack IF, Losken HW, Biglan AW (1996) Incidence of increased intracranial pressure after early surgical treatment of syndromic craniosynostosis. *Pediatr Neurosurg* 24(4):202–209
13. de Jong T, Bannink N, Bredero-Boelhouwer HH et al (2010) Long-term functional outcome in 167 patients with syndromic craniosynostosis; defining a syndrome-specific risk profile. *J Plast Reconstr Aesthet Surg* 63(10):1635–1641
14. Tuite G, Chong WK, Evanson J, Narita A, Taylor D, Harkness WF, Jones BM, Hayward RD (1996) The effectiveness of papilledema as an indicator of raised intracranial pressure in children with craniosynostosis. *Neurosurgery.* 38(2):272–278
15. Nazir S, O'Brien M, Qureshi NH, Slape L, Green TJ, Phillips PH (2009) Sensitivity of papilledema as a sign of shunt failure in children. *J AAPOS* 13(1):63–66
16. Rangwala L, Liu G (2007) Pediatric idiopathic intracranial hypertension. *Surv Ophthalmol* 52(6):597–617
17. Teismann N, Lenaghan P, Nolan R, Stein J, Green A (2013) Point-of-care ocular ultrasound to detect optic disc swelling. *Acad Emerg Med* 20(9):920–925
18. Bolesch S, von Wegner F, Senft C, Lorenz MW (2015) Transcranial ultrasound to detect elevated intracranial pressure: comparison of septum pellucidum undulations and optic nerve sheath diameter. *Ultrasound Med Biol* 41(5):1233–1240
19. Kimberly HH, Shah S, Marill K, Noble V (2008) Correlation of optic nerve sheath diameter with direct measurement of intracranial pressure. *Acad Emerg Med* 15(2):201–204
20. Dubourg J, Javouhey E, Geeraerts T, Messerer M, Kassai B (2011) Ultrasonography of optic nerve sheath diameter for detection of raised intracranial pressure: a systematic review and meta-analysis. *Intensive Care Med* 37(7):1059–1068
21. Driessen C, Bannink N, Lequin M, van Veelen M, Naus NC, Joosten KF, Mathijssen IM (2011) Are ultrasonography measurements of optic nerve sheath diameter an alternative to funduscopy in children with syndromic craniosynostosis? *J Neurosurg Pediatr* 8(3):329–334
22. Driessen C, van Veelen M-LC, Lequin M, Joosten KFM, Mathijssen IMJ (2012) Nocturnal ultrasound measurements of optic nerve sheath diameter correlate with intracranial pressure in children with craniosynostosis. *Plast Reconstr Surg* 130(3):448e–451e
23. Kristiansson H, Nissborg E, Bartek J, Andresen M, Reinstrup P, Romner B (2013) Measuring elevated intracranial pressure through

noninvasive methods: a review of the literature. *J Neurosurg Anesthesiol* 25(4):372–385
24. Raboel PH, Bartek J, Andresen M, Bellander BM, Romner B (2012) Intracranial pressure monitoring: invasive versus non-invasive methods-a review. *Crit Care Res Pract* 2012:950393
25. Wiegand C, Richards P (2007) Measurement of intracranial pressure in children: a critical review of current methods. *Dev Med Child Neurol* 49(12):935–941
26. Skau M, Yri H, Sander B, Gerds TA, Milea D, Jensen R (2012) Diagnostic value of optical coherence tomography for intracranial pressure in idiopathic intracranial hypertension. *Graefes Arch Clin Exp Ophthalmol*:567–574
27. Yri HM, Wegener M, Sander B, Jensen R (2011) Idiopathic intracranial hypertension is not benign: a long-term outcome study. *J Neurol* 259(5):886–894
28. Kaufhold F, Kadas EM, Schmidt C, Kunte H, Hoffmann J, Zimmermann H, Oberwahrenbrock T, Harms L, Polthier K, Brandt AU, Paul F (2012) Optic nerve head quantification in idiopathic intracranial hypertension by spectral domain OCT. *PLoS One* 7(5):e36965
29. Aleman TS, Soumittra N, Cideciyan AV et al (2009) *CERKL* mutations cause an autosomal recessive cone-rod dystrophy with inner retinopathy. *Investig Opthalmol Vis Sci* 50(12):5944
30. Heidary G, Rizzo JF Use of optical coherence tomography to evaluate papilledema and pseudopapilledema. *Semin Ophthalmol* 25(5-6):198–205
31. Swanson JW, Aleman TS, Xu W, Ying GS, Pan W, Liu GT, Lang SS, Heuer GG, Storm PB, Bartlett SP, Katowitz WR, Taylor JA (2017) Evaluation of optical coherence tomography to detect elevated intracranial pressure in children. *JAMA Ophthalmol* 135(4):320–328
32. Curcio CA, Messinger JD, Sloan KR, Mitra A, McGwin G, Spaide RF (2011) Human chorioretinal layer thicknesses measured in macula-wide, high-resolution histologic sections. *Invest Ophthalmol Vis Sci* 52(7):3943–3954
33. Tamburrini G, Caldarelli M, Massimi L, Santini P, Di Rocco C (2005) Intracranial pressure monitoring in children with single suture and complex craniosynostosis: a review. *Childs Nerv Syst* 21(10):913–921
34. Selber J, Reid RR, Chike-Obi CJ, Sutton LN, Zackai EH, McDonald-McGinn D, Sonnad SS, Whitaker LA, Bartlett SP (2008) The changing epidemiologic spectrum of single-suture synostoses. *Plast Reconstr Surg* 122(2):527–533
35. Hayward R, Britto J, Dunaway D, Jeelani O. Connecting raised intracranial pressure and cognitive delay in craniosynostosis: many assumptions, little evidence. Journal of Neurosurgery: Pediatrics. 2016 Aug 1;18(2):242–50
36. Avery RA, Shah SS, Licht DJ, Seiden JA, Huh JW, Boswinkel J, Ruppe MD, Chew A, Mistry RD, Liu GT (2010) Reference range for cerebrospinal fluid opening pressure in children. *N Engl J Med* 363(9):891–893
37. Minns RA (1984) Intracranial pressure monitoring. *Arch Dis Child* 59(5):486–488
38. Thomas GPL, Johnson D, Byren JC, Judge AD, Jayamohan J, Magdum SA, Richards PG, Wall SA (2015) The incidence of raised intracranial pressure in nonsyndromic sagittal craniosynostosis following primary surgery. *J Neurosurg Pediatr* 15(4):350–360
39. Gospe SM, Bhatti MT, El-Dairi MA (2017) Emerging applications of optical coherence tomography in pediatric optic neuropathies. *Semin Pediatr Neurol* 24(2):135–142
40. Utria AF, Lopez J, Cho RS, Mundinger GS, Jallo GI, Ahn ES, Kolk CV, Dorafshar AH (2016) Timing of cranial vault remodeling in nonsyndromic craniosynostosis: a single-institution 30-year experience. *J Neurosurg Pediatr* 18(5):629–634
41. Layliev J, Gill R, Spear M, Cifuentes J, Wang L, Kelly KJ (2016) The optimal timing for primary cranial vault reconstruction in nonsyndromic craniosynostosis. *J Craniofac Surg* 27(6):1445–1452
42. Pagnoni M, Fadda MT, Spalice A et al (2014) Surgical timing of craniosynostosis: what to do and when. *J Cranio-Maxillofacial Surg* 42(5):513–519
43. Kapp-Simon KA, Speltz ML, Cunningham ML, Patel PK, Tomita T (2007) Neurodevelopment of children with single suture craniosynostosis: a review. *Childs Nerv Syst* 23(3):269–281
44. Chang RO, Marshall BK, Yahyavi N, Sharma A, Huecker J, Gordon MO, McClelland C, van Stavern G (2016) Neuroimaging features of idiopathic intracranial hypertension persist after resolution of papilloedema. *Neuroophthalmology*. 40(4):165–170