Noninvasive methods of detecting increased intracranial pressure

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Abstract The detection of elevated intracranial pressure (ICP) is of paramount importance in the diagnosis and management of a number of neurologic pathologies. The current gold standard is the use of intraventricular or intraparenchymal catheters; however, this is invasive, expensive, and requires anesthesia. On the other hand, diagnosing intracranial hypertension based on clinical symptoms such as headaches, vomiting, and visual changes lacks sensitivity. As such, there exists a need for a noninvasive yet accurate and reliable method for detecting elevated ICP. In this review, we aim to cover both structural modalities such as computed tomography (CT), magnetic resonance imaging (MRI), ocular ultrasound, fundoscopy, and optical coherence tomography (OCT) as well as functional modalities such as transcranial Doppler ultrasound (TCD), visual evoked potentials (VEPs), and near-infrared spectroscopy (NIRS).

Keywords Noninvasive intracranial pressure · Optical coherence tomography · Optic nerve sheath diameter · Papilledema · Transcranial Doppler ultrasound · Visual evoked potentials

Introduction

Elevated intracranial pressure (ICP) is a sign of numerous neurologic diseases and can have devastating consequences if diagnosis and treatment are delayed [1]. The onset of elevated ICP may be quite rapid such as with traumatic brain injury (TBI) or epidural hematoma. A more difficult diagnostic situation is when elevated ICP occurs insidiously over a long time interval such as may be the case in craniosynostosis, hydrocephalus, tumor, or idiopathic intracranial hypertension. Currently, evidence for an association between nonsymptomatic elevated ICP and neurocognitive delays in craniosynostosis is lacking [2]. However, intracranial hypertension associated with hydrocephalus or papilledema most likely requires surgical intervention. Thus, although the role of ICP in pediatric neurocognitive outcomes is actively debated, knowledge of ICP values and trends may still be useful for long-term monitoring and management of patients with a variety of neurological pathologies.

Certain symptoms such as headaches, vomiting, decreased consciousness, and visual changes are suggestive of increased ICP but sensitivity and specificity are low, and assessment in young children is difficult [3, 4]. The current gold standard for accurate ICP measurement is invasive placement of an external ventricular drain (EVD), which has the ability to both measure ICP as well as drain cerebral spinal fluid in an effort to lower ICP. However, EVDs have been associated with high rates of infection (up to 27%) [5–7], malposition (8.8%) [8], and hemorrhage (up to 18%) [8, 9]. An alternative to EVDs is the intraparenchymal ICP monitor, which measures the ICP within the brain parenchyma itself and is associated with reduced risks of hemorrhage and infection [8]. However, both EVDs and intraparenchymal ICP monitors involve an invasive procedure that requires hospitalization and typically 24–48 h of monitoring in the intensive care unit. Finally, placement of a measurement catheter may not always be possible due to the patient’s condition or lack of access to an experienced surgeon and appropriate facilities [1, 10].
The unreliability of clinical indicators and the invasive nature of intraventricular and intraparenchymal approaches have prompted a search for alternative noninvasive methods for measuring ICP. Modalities include computed tomography (CT), magnetic resonance imaging (MRI), transcranial Doppler ultrasound (TCD), and near-infrared spectroscopy (NIRS). The eye as an extension of the central nervous system (CNS) has been traditionally used as a monitor of ICP through the exam of the optic nerve head during dilated fundus examinations. The subjective nature of this assessment leads to variable or low reliability as a predictor of ICP [11–13]. These noninvasive modalities assess either the three-dimensional structure of the brain, skull, ventricles, optic disk, or optic nerve, or the function of cerebral blood flow or nerve conduction, each of which can be related to the ICP. Quantitative measures of visual function such as visual evoked potentials (VEPs) or retinal and optic nerve structure, such as ocular ultrasound and optical coherence tomography (OCT), have thus been used as alternative biomarkers for ICP.

The need for such noninvasive, objective measures of increased ICP is particularly acute in the pediatric setting where symptoms and clinical signs of increased ICP may be more difficult to interpret. The purpose of this work is to review the current literature on these emerging modalities and to compare their efficacy as noninvasive measures of ICP.

**Structural modalities**

**Computed tomography**

Head CT has become universally available as a diagnostic tool. Several CT findings that may correlate with increased ICP include thumb-printing, ventricle effacement, midline shift, and obliteration of the basal cisterns (Fig. 1). In a study of adult TBI patients by Toutant et al., 74% of patients with absent cisterns on CT had ICP values greater than 30 mmHg [14]. Eisenberg et al. found that midline shift, compression or obliteration of the mesencephalic cisterns, and the presence of subarachnoid blood were most significantly associated with abnormal ICP (measured as percent of time spent above 20 mmHg) and death in 753 adult TBI patients [10]. Similarly, using multiple regression analysis, Mizutani et al. looked at 39 CT parameters and found that the following contributed to the prediction of abnormal ICP: the appearance of cisterns, the size of a subdural hematoma, ventricular size, status of subarachnoid hemorrhage, status of cerebral contusion, magnitude of midline shift, and ventricular index [15]; they subsequently derived an equation to estimate ICP, which in 80% of cases was able to produce an estimated ICP value within 10 mmHg of the true ICP. Another study used an automated midline shift and blood and texture analysis algorithm to detect increased ICP in TBI patients with a sensitivity of 65% and specificity of 73% [16].

However, despite the results of these studies, there also exists literature that questions the sensitivity of using CT to detect increased ICP. In a study conducted with adult trauma patients, Miller et al. examined ventricle size, sulci size, and gray/white matter differentiation. They found that these three parameters trended with ICP but were not able to reliably predict increased ICP. Using a logistic regression, they demonstrated a 4.9% increase in the prediction of high ICP, which allowed them to predict two more patients with high ICP than if they had not used the head CT [17]. Compared to the adult population, the evidence for using CT to detect abnormal ICP in children is less compelling. One of the CT findings thought to predict acute elevations in ICP is compressed or obliterated basal cisterns. However, Kouvarelis et al. found that the presence of open basal cisterns was only 58% specific in predicting ICPs less than 20 mmHg and thereby concluded that open cisterns should not provide assurance of normal ICPs in children [18]. In a study of 68 children with moderate to severe TBI, nine patients with normal CTs underwent invasive ICP monitoring due to clinical

**Fig. 1** Sagittal (a) and axial (b) head CT scans demonstrating thumb-printing, or increased convolutional markings of the inner table.
symptoms, and seven of these nine children had increased ICP [19]. Similarly, in a study with 34 children in nontraumatic comas, five out of seven patients with normal CTs developed ICPs greater than 20 mmHg within 36 h [20]; however, the correlation between CT findings and ICP in this study is difficult to state due to the fact that they were not measured simultaneously. Rather, patients were scanned, received treatment, and then began continuous ICP monitoring within 12 h of the CT scan.

Another use of head CT is in the evaluation of the optic nerve sheath diameter (ONSD). The optic nerve is an extension of the CNS so its investing sheath is continuous with the dura mater that surrounds the brain parenchyma. As such, any increased pressure in the subarachnoid space of the brain is transferred to the fluid in the subarachnoid space surrounding the optic nerve [21]. Due to this anatomical and physiological relationship, elevated ICP has been shown to cause distention of the optic nerve sheath and thereby, increase the optic nerve sheath diameter (ONSD). In a group of 57 adult TBI patients who had CT scans evaluating ONSD as well as invasively checked ICP values, there was a strong correlation between ICP and ONSD ($r = 0.74$) with AUC = 0.83 for detecting ICP > 20 mmHg. A 6.0 mm cutoff for the ONSD was used, which yielded a sensitivity of 97 %, specificity of 42 %, a positive predictive value (PPV) of 67 %, and negative predictive value (NPV) of 92 % [22].

Head CT is a quick, widely available, operator independent, and easily obtained exam that may be able to predict elevated ICP (Table 1). The literature demonstrates that it is most suited to identifying signs of elevated ICP in the most acute presentations (Table 2). However, its disadvantages include variable sensitivity and the exposure of the patient to ionizing radiation, the effect of which is of particular concern in the pediatric population because children are more radiosensitive and have a longer life expectancy compared to adults [23].

### Magnetic resonance imaging (MRI)

MRI is another imaging modality that has shown promise in the search for a noninvasive method of detecting elevated ICP. Several MRI-derived parameters have been proposed, including the elastance index, cerebral blood flow, and cerebrospinal fluid (CSF) velocity through the aqueduct. In addition, MRI has been used to measure the ONSD.

MRI data can be used to calculate changes in intracranial volume and pressure that occur with the cardiac cycle. The change in volume is derived from net transcranial CSF and blood volumetric flow rates, while the change in pressure is derived from the change in CSF pressure gradient calculated from CSF velocity. By definition, elastance ($E$) is the ratio of pressure change to volume change ($E = \frac{\Delta P}{\Delta V}$), so using the MRI-derived measurements, one can calculate an elastance index for the brain parenchyma. The exponential pressure-
volume curve for the brain introduced by Marmarous et al. states that at low ICP values, a small change in volume will cause a small change in pressure, whereas at high ICP values, a small change in volume will cause a large change in pressure; this relationship speaks to the high compliance (low elastance) of the brain at low ICPs and low compliance (high elastance) of the brain at high ICPs. Knowing this relationship between elastance and ICP, one can use the elastance index calculated from the MRI parameters to predict ICP [24, 25]. Alperin et al. found that the elastance index and invasively measured ICP values were highly correlated in five adult patients (r² = 0.965) [25]. Similarly, another study found that in children with hydrocephalus, shunt valve opening pressures and predictions of ICP based on MRI-derived elastance were positively correlated (Spearman ρ = 0.64) [26].

Another use for MRI to predict ICP involves the study of cerebral blood flow (CBF) as measured by MR angiography. In a study of infants with hydrocephalus, CBF was measured with MRA at the level of the internal carotid arteries and basilar artery both pre-shunt and post-shunt. The correlation coefficient between CBF and invasively measured ICP was r = −0.55 [27]. Furthermore, MRI has been used to look at CSF flow velocity through the cerebral aqueduct in patients with suspected normal pressure hydrocephalus [28]. The degree of agreement between ICP monitoring and MR dynamics was 82 %; sensitivity and specificity of CSF velocity for abnormal ICP were 90 and 50 %, respectively [29]. It has been proposed that both CBF and CSF flow velocities are decreased in settings of increased ICP due to decreased intracranial compliance [27, 28].

Like head CT, MRI can also be used to measure the optic nerve sheath diameter (ONSD). Geeraerts et al. demonstrated a positive correlation between MRI-derived ONSD and invasively measured ICP (r = 0.71), and using a 5.82 mm cutoff, they determined that the ability of ONSD to detect ICP > 20 mmHg was excellent with AUC = 0.94 and NPV of 92 % [30, 31]. Interestingly, a comparison of CT to MRI concluded that the two modalities produce comparable measurements of ONSD [32].

MRI has the potential to noninvasively measure ICP based on parameters such as flow velocities, intracranial elastance, and ONSD. However, disadvantages of this method include its relatively higher cost, lack of portability, and long examination time requiring high patient compliance and sedation in young children.

**Ocular ultrasound**

Although CT and MRI have been used to measure ONSD, the most widely studied modality for measuring ONSD is ocular ultrasound. Greater resolution and detail are the obvious advantages of this modality compared to CT and MRI. Several studies have correlated ultrasound-derived ONSD values with CT or MRI signs suggestive of increased ICP (Fig. 2). Shirodkar et al. found ONSD cutoffs (4.6 mm for females; 4.8 mm for males) that had a sensitivity between 84.6 % (females) and 75 % (males) and a specificity of 100 % (both genders) for the detection of MRI signs of elevated ICP, such as midline shift, edema, and effacement [33]. Similarly, a study of 24 adult patients compared ONSD by ocular ultrasound to CT findings of midline shift, sulcal effacement with significant edema, third ventricle collapse, and hydrocephalus, and using a cutoff of 5.0 mm, they achieved a sensitivity of 100 %, specificity of 75 %, PPV of 95.4 %, and NPV of 100 % [34]. There have also been a number of studies that compared ocular ultrasound-derived ONSD with ICP measured by LP opening pressure or invasive monitoring. In the adult population, the literature shows evidence for cutoff values ranging from 4.1 to 5.7 mm, which are associated with 74.1 to 100 % sensitivity and 74 to 100 % specificity [35, 36]. Interestingly,

| Table 2 Detection of acute vs. chronic ICP elevation by noninvasive modalities |
|--------------------------------------------------|--------------------------------------------------|
| **Acute findings of elevated ICP** | **Chronic findings of elevated ICP** |
| CT | • Obliteration or compression of the basal cisterns | • Thumb-printing |
| | • Ventricle effacement | • Ventricle effacement |
| MRI | • Increased elastance index | • Increased elastance index |
| Ocular ultrasound | • Increase in optic nerve sheath diameter | • Increase in optic nerve sheath diameter |
| Fundoscopy | • Likely normal | • Optic disk swelling |
| | | • Blurred disk margin |
| OCT | • Unknown | • Increase in RNFL thickness |
| | | • Increase in TRT |
| TCD | • Increase in PI | • Increase in PI |
| VEP | • Prolongation of peak latencies | • Prolongation of peak latencies |
| NIRS | • Decrease in cerebral oxygenation | • Decrease in cerebral oxygenation |
one study demonstrated that changes in ONSD appear quite rapidly after the onset of elevated ICP. In that study of 18 adult TBI patients, Maissan et al. investigated the effects of acute ICP changes on ONSD by measuring ONSD before, during, and after tracheal manipulation, which is known to increase ICP [37]. They found that ONSD increased with tracheal manipulation and immediately returned to baseline once manipulation was stopped. On the other hand, one study found that although there was a correlation between ONSD and ICP, no single cutoff value could be used as a suitable diagnostic tool to predict ICP [38]. Another study of 10 adult trauma patients using a cutoff of 6.0 mm demonstrated 36% sensitivity and 38% specificity, and thereby concluded that ONSD measured by US is not a useful tool for predicting ICP [39]. Table 3 enumerates a list of ONSD studies, modality of measurement, cutoff values, and relevant statistics.

A challenge associated with this modality is the presence of inter-individual variability. A Chinese study with 279 adults found an optimal cutoff of 4.1 mm, which is at least 0.5 mm lower than any other study. Furthermore, interpreting ONSD measurements in children provides an additional challenge in that ONSD tends to increase with age [40]. One normative study claims that ONSD values greater than 4.0 mm in infants less than 1 year and 4.5 mm in older children should be regarded as abnormal [41]; similarly, a study of 483 children determined the upper limit of normal to be 4.5 mm based on neurological examination, imaging, and/or clinical follow-up [42]. These studies demonstrate that sophisticated normative data that allows for differences in age, gender, race, and comorbidities do not exist.

ONSD measured by ocular ultrasound has the potential to be a powerful tool in the noninvasive detection of elevated ICP. A common concern regarding ultrasound techniques is operator variability. A study by Ballantyne et al. measured both intra- and inter-observer variation when measuring ONSD in 67 healthy adults [43]; they found that with three independent observers, the median intra-observer variation was ±0.1 mm with 5th–95th centile values of ±0–0.4 mm, and the median inter-observer variation was ±0.2–0.3 mm with 5th–95th centile values of ±0–0.7 mm. Therefore, they concluded that with standardization of technique, operator variability can be minimized. Overall, ONSD as measured by ocular ultrasound involves little risk to the patient, is relatively inexpensive, quick to use, portable, and generally provides values that correlate well with ICP.

**Fundoscopy**

Papilledema, defined as optic disk edema due to increased ICP, diagnosed on fundoscopic examination is widely used as a clinical indicator of increased ICP. It is a subjective measure that can be divided into six grades as described by Frisén [44], with grade 0 denoting a normal optic disk and grade 5 denoting a severe degree of optic disk edema (Fig. 3). In the literature, the sensitivity of papilledema for increased ICP ranges from 14 to 40% [11, 12]. Steffen et al. showed that in 37 patients with acute elevated ICP due to hemorrhage or trauma, papilledema was an uncommon occurrence [45]; this, however, may be related to the pathophysiology of papilledema, and perhaps the duration of elevated ICP was insufficient to cause clinically apparent papilledema.

Papilledema has also been tested in clinical situations in which ICP is more chronically elevated. In a group of adults with idiopathic intracranial hypertension (IIH; formerly known as pseudotumor cerebri), 5.7% did not have papilledema [46]. In another study of 85 adult patients with chronic headache, 15% had ICP > 18.4 mmHg and no evidence of papilledema [47]. The results for the pediatric population are more variable. Two studies of children with IIH showed that 17.8–48% of patients did not demonstrate papilledema on exam [48, 49].

Fundoscopic exam to detect papilledema has long been a mainstay for diagnosing elevated ICP noninvasively and can be performed relatively quickly and easily. Best diagnostic
<table>
<thead>
<tr>
<th>Study</th>
<th>Imaging modality</th>
<th>Patient type</th>
<th>Study size (n)</th>
<th>ONSD cutoff</th>
<th>Invasive ICP measurement</th>
<th>Relevant statistics</th>
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</table>
| Sekhon et al. 2014 [22]    | CT              | Adult TBI patients                               | 57             | 6.0 mm      | Yes                     | r = 0.74, p < 0.001
|                            |                 |                                                  |                |             |                         | AUC = 0.83
|                            |                 |                                                  |                |             |                         | Sensitivity 97%
|                            |                 |                                                  |                |             |                         | Specificity 42%
| Geeraerts et al. 2008 [30]| MRI             | Adult TBI patients                               | 38             | 5.82 mm      | Yes                     | r = 0.71, p < 0.0001
|                            |                 |                                                  |                |             |                         | AUC 0.94
|                            |                 |                                                  |                |             |                         | Sensitivity 97%
| Shirodkar et al. 2014 [33]| Ultrasound      | Adults with signs of increased ICP              | 60             | 4.6 mm (female) | No. compared to MRI findings suggestive of increased ICP | r = 0.74, p < 0.001
|                            |                 |                                                  |                | 4.8 mm (male) |                         | Sensitivity: 84.6 % females, 75 % males
|                            |                 |                                                  |                |             |                         | Specificity: 100 % both genders
| Cammarata et al. 2011 [108]| Ultrasound      | Adult trauma patients                            | 11             | N/A         | Yes                     | Sensitivity 100%
|                            |                 |                                                  |                |             |                         | Specificity 75%
| Qayyum et al. 2013 [34]   | Ultrasound      | Adults with signs of increased ICP              | 24             | 5.0 mm      | No. compared to CT findings suggestive of increased ICP | Sensitivity 100%
|                            |                 |                                                  |                |             |                         | Specificity 90.4%
|                            |                 |                                                  |                |             |                         | PPV 95.4%
|                            |                 |                                                  |                |             |                         | NPV 100%
| Nabetta et al. 2014 [38]  | Ultrasound      | HIV+ adults with suspected cryptococcal meningitis | 81             | 5.0 mm      | Yes                     | Sensitivity 95%
|                            |                 |                                                  |                |             |                         | Specificity 92%
| Wang et al. 2015 [35]     | Ultrasound      | Adults with signs of increased ICP              | 279            | 4.1 mm      | Yes                     | Sensitivity 95%
|                            |                 |                                                  |                |             |                         | Specificity 92%
| Soldatos et al. 2008 [109]| Ultrasound      | Adults with brain injury                         | 50             | 5.7 mm      | Yes                     | r = 0.68, p = 0.002
|                            |                 |                                                  |                |             |                         | Sensitivity 74.1%
|                            |                 |                                                  |                |             |                         | Specificity 100%
| Maissan et al. 2015 [37]  | Ultrasound      | Adult TBI patients                               | 18             | 5.0 mm      | Yes                     | Sensitivity 94%
|                            |                 |                                                  |                |             |                         | Specificity 98%
| Amini et al. 2013 [36]    | Ultrasound      | Adult nontrauma patients at risk for increased ICP | 50             | 5.5 mm      | Yes                     | Sensitivity 100%
|                            |                 |                                                  |                |             |                         | Specificity 100%
| Strumwasser et al. 2011 [39]| Ultrasound    | Adult trauma patients                            | 10             | 6.0 mm      | Yes                     | AUC 0.36
|                            |                 |                                                  |                |             |                         | Sensitivity 36%
|                            |                 |                                                  |                |             |                         | Specificity 38%
| Korber et al. 2005 [42]   | Ultrasound      | Children (mean age 7.5 years) with suspected increased ICP | 483           | 4.5 mm      | No                      | Normal ICP mean diameter: 3.4 mm ± 0.7 mm
|                            |                 |                                                  |                |             |                         | Increased ICP mean diameter: 5.6 mm ± 0.9 mm
| Ballantyne et al. 1999 [41]| Ultrasound      | Children with no concern for increased ICP      | 102            | 4.0 mm (<1 year) | No                     | Mean ONSD: 3.08 mm ± 0.36 mm
|                            |                 |                                                  |                | 4.5 mm (>1 year) |                         | r² = 0.48 for ONSD and age relationship

*a Invasive ICP measurement denotes intraventricular catheter, intraparenchymal device, or lumbar puncture*
yield is obtained by binocular biomicroscopic examination of the optic nerve with the use of a slit lamp which limits its use to cooperative and often only ambulatory patients. The literature shows that this exam is much less sensitive than other tests.

Optical coherence tomography (OCT)

Optical coherence tomography (OCT) uses interferometry to obtain micron-resolution images of the optic disk based on the variation the different reflectivities of each of the retinal layers. There are two main types of OCT, time domain OCT (TD-OCT) and spectral domain OCT (SD-OCT); the major difference between the two lies in the way in which information is processed as it is reflected and returned to the detector [50]. While TD-OCT uses a photodetector in the detector arm, the newer SD-OCT uses a spectrometer which allows for much faster acquisition of images with increased lateral resolution as well as for online imaging processing resulting in a remarkable increase in resolution [50]. A typical SD-OCT exam comprises of directing the light beam onto the optic disk and capturing an image that can then be analyzed manually or automatically by built-in software typically embedded within the OCT instruments (Fig. 4). By providing a detailed examination of the retina and optic nerve head, equivalent in many ways to an in vivo, noninvasive biopsy, OCT has been shown to be a valuable tool in the diagnosis and monitoring of a number of pathologies, including glaucoma [50, 51], macular degeneration [52], papilledema [53], and optic neuropathy in older children with craniosynostosis [54].

There are a number of parameters that can be studied on the OCT-acquired image of the retina, including peripapillary retinal nerve fiber layer (RNFL) thickness, total retinal thickness (TRT), macular thickness, and optic nerve head height and volume. Normative data for some of these parameters have been obtained in adults and children. Gabriele et al. described RNFL thickness at different points on the retina of healthy adults [55], while Varma et al. looked specifically at adult Latinos and concluded that peripapillary RNFL and macular thickness decrease with age but do not vary with gender [56]. Normative data for children have also been partially established. A Turkish study looked at children ages 6–16 years and determined that peripapillary RNFL, macular thickness, and macular volume were not correlated with age, spherical equivalence, or axial length (cornea-retina distance) [57]. A similar study in Hong Kong children ages 6–17 years showed that while age did not significantly affect OCT measurements, axial length demonstrated a negative correlation with RNFL thickness [58]. Another normative study of North American children ages 5–15 years found that macular thickness varied with age; meanwhile, RNFL thickness did not correlate with age but in general, tended to be greater in the pediatric population [59]. Importantly, the North American study reported a 95 % success rate in obtaining high-quality OCT images in children ages 5 and above without sedation, which is significant given that the successful use of OCT requires reasonable patient compliance. In comparison to the other normative studies, El-Dairi et al. found that in 286 healthy children ages 3–17 years, OCT measurements actually varied with three different factors: race, axial length, and age [60]. Of note, normative OCT values for infants and young children less than 3 years old have not been extensively

Fig. 3 Fundoscopic image of an optic disk with grade 3 papilledema. Adapted from Wall et al. [106]

Fig. 4 Optical coherence tomography (OCT) image at the level of the optic nerve head
studied. Determining universal normative values for children is an ongoing challenge, but interestingly, a study by Sasapin et al. found that OCT parameters did not change significantly in healthy children followed over a 4-year time span [61], suggesting that OCT may be useful for long term monitoring regardless of generalizable normative data.

A complex interplay exists between OCT parameters, papilledema, and ICP. The correlation between OCT and Frisen grading for papilledema has been demonstrated in several studies [62–64]. One study found a positive correlation between Frisen grading and RNFL thickness with \( r = 0.7952 \) [63]. Taking it one step further, Vartin et al. looked at both RNFL thickness and peripapillary total retinal thickness (TRT) and concluded that TRT is a more sensitive indicator for mild papilledema [62]. Meanwhile, Scott et al. found that in 36 patients with papilledema, both RNFL thickness and TRT correlated well with Frisen scores with \( r = 0.85 \) and \( r = 0.87 \), respectively. However, they determined that with higher-grade abnormalities, TRT may show more proportional change per change in degree of disk edema, which would make TRT a more favorable parameter to study when dealing with more extreme pathology. They hypothesized that “this disproportional increase of TRT above that of the RNFL represents fluid from neurosensory retinal detachment in the peripapillary retina” [64].

There have also been a few studies looking at the relationship of OCT to ICP. Kaufhold et al. found that the OCT parameter optic nerve head volume (ONHV) was actually a better measure of ICP compared to RNFL thickness with AUC = 0.835 and AUC = 0.464, respectively [65]. The major flaw with their study, however, is that the ICP measurements were acquired from lumbar puncture (LP) opening pressures that were performed anytime within 0 to 24 months of the OCT scan, which in some cases, resulted in a large time gap between ICP and OCT measurements. Another study of patients with newly diagnosed IIH compared RNFL thickness and TRT with LP opening pressure and found that including these parameters in multiple regression models to detect ICP \( > 25 \) cmH\(_2\)O (\( \sim 18.4 \) mmHg) improved the AUC from 77.1 to 86.9 [66].

Finally, a couple of studies have studied the relationship of OCT parameters with both papilledema and ICP. The OCT Sub-Study Committee for the NORDIC Idiopathic Intracranial Hypertension Study Group found that OCT parameters (RNFL thickness, TRT, ONHV) were significantly correlated with both Frisen grade and ICP measured by LP opening pressure, but that the correlation was stronger with the former \( (r > 0.76) \) and weaker with the latter \( (r > 0.24) \) [67]. In another study, OCT and papilledema were compared head to head in a group of 20 patients with confirmed elevated ICP via LP opening pressure. Direct ophthalmoscopy and fundus photography detected 80 and 70 %, respectively, while the OCT parameters of peripapillary average retinal thickness and peripapillary RNFL thickness detected 90 and 85 %, respectively [68], demonstrating that perhaps OCT may be a more sensitive indicator of elevated ICP compared to papilledema.

In general, OCT is a promising technology that may be useful in the noninvasive detection of elevated ICP. Further inquiry should be performed to determine the best parameters to measure as well as to increase our knowledge of normative values. By allowing a detailed quantitative examination of the optic disk, it is a technological leap from fundoscopy. Current evidence suggests that OCT parameters may be a more sensitive indicator of increased ICP compared to fundoscopy and therefore may be able to detect changes in the eyes related to ICP before they become apparent on routine ophthalmological exam [68]. Additionally, OCT machines are reasonably priced, portable, can provide quantitative measurements, and do not involve ionizing radiation, and therefore, would be safe to be used as a long-term monitoring and screening tool in both the adult and pediatric populations.

### Functional modalities

#### Transcranial Doppler ultrasonography (TCD)

TCD is an ultrasound technology that looks at blood vessel flow velocities in order to predict ICP. The relationship between ICP and TCD flow variables was first described by Klingelhofer in 1988 and relies heavily on cerebral hemodynamics [69]. Physiologically, as ICP increases, diastolic flow velocity is reduced to a greater degree compared to systolic flow velocity, which results in an increased pulse peak between diastole and systole. The Gosling pulsatility index (PI) is defined as \( PI = \frac{FV\text{peak systole} - FV\text{peak diastole}}{FV\text{peak systole}} \) [70]. Therefore, a rise in ICP leads to increases of both pulse peak and PI. One important detail to note is that although flow velocities are affected by the angle of insonation, PI is a ratio and thus not affected, making it a more robust predictor of ICP [71]. A standard TCD exam consists of finding an adequate acoustic window in the temporal bone with the ultrasound probe and using Doppler technology to measure flow velocities (Fig. 5).

Current clinical pathologies for which TCD can be used, as determined by the American Academy of Neurology (AAN), include sickle cell stroke, angiographic vasospasm, intracranial steno-occlusive disease, and cerebral circulatory arrest. TCD has also been used for monitoring during cerebral thrombolysis, coronary artery bypass grafting, and carotid endarterectomy [72].

Various studies have compared TCD measurements to ICP measured invasively or with LP opening pressure. Ragauskas et al. found that TCD was a superior indicator of ICP \( > 14.7 \) mmHg compared to ultrasound-measured
ONSND; ONSD with a cutoff value of 5.0 mm yielded a sensitivity of 37.0 %, specificity of 58.5 %, and AUC = 0.57, while TCD demonstrated a sensitivity of 68.0 %, specificity of 84.3 %, and AUC = 0.87 [73]. A number of studies have found that PI and ICP are highly correlated with correlation coefficients ranging from 0.89 to 0.938 [74, 75]; similarly, Hunter et al. found that the change in ICP was correlated with the change in PI before and after CSF withdrawal in patients with suspected idiopathic intracranial hypertension (p = 0.004) [76]. Using PI cutoff values ranging from 1.26 to 1.335, several studies determined that PI could predict elevated ICP values with 80–88.5 % sensitivity and 90–97 % specificity [75, 77, 78].

Although it seems that PI is a good predictor of increased ICP with high sensitivity and specificity, there is opposing evidence as well. One study stated that although PI seems to correlate with ICP trends (e.g., higher PI in hydrocephalus patients vs. normal controls), an exact noninvasive measurement of ICP by TCD is unlikely [79]. Likewise, Zweifel et al. found that the diagnostic value of PI to assess ICP has an overall AUC = 0.62 for ICP > 15 mmHg and AUC = 0.74 for ICP > 35 mmHg [80]; from these data, they concluded that the relationship between PI and ICP is strong for highly elevated ICP but weak for marginally elevated ICP, thereby making PI an unreliable diagnostic tool in the range of ICP for which a noninvasive method would be most essential. Another limitation of TCD is that physiologic variations can have profound effects on the ICP-PI relationship. Behrens et al. found that variations in vessel compliance, autoregulation, and arterial pressure can all confound the ICP prediction [81]. In terms of using TCD for long-term monitoring, a study of infants with hydrocephalus showed that PI correlated well with ICP immediately before and after shunt procedures, but the ICP-PI relationship was not maintained at long-term follow-up [82]. This may be due to changes in brain compliance associated with chronically abnormal intracranial pressures. One other consideration when using TCD is that the technology relies on the presence of an adequate temporal bone acoustic window, which is not present in all patients. In the Behrens study, two out of ten patients were unable to complete testing due the absence of an acoustic window through which TCD measurements could be made [81].

Generally, TCD-derived parameters such as PI seem to be correlated with invasively measured ICP values. Possible disadvantages of TCD include the confounding effects of various physiologic differences (e.g., arterial pressure) and pathologic differences (steno-occlusive vessel disease) on TCD measurements as well as the need for an adequate acoustic window and interpretation by experienced sonographers [83].

**Visual evoked potentials (VEPs)**

VEPs are the summed electrical signals produced in the occipital lobe in response to visual stimuli. There are many components to VEP waveforms, including number of positive or negative waves, latency of these waves from time of stimulus, and shape of the waveform. The peaks of the VEP are named P or N, indicating positive or negative deflection, with a number subscript, indicating the average peak latency following the time of stimulus [84]. VEPs provide an overarching picture of the status of the visual system from optic nerve to primary visual cortex. Obtaining a VEP tracing involves placing standard EEG electrodes on the patient’s scalp and recording the summed signals as various types of visual stimuli are presented to the patient. Current applications of VEPs include the management of optic nerve pathologies and the monitoring of brain activity during select surgeries [85].

Studies of children with hydrocephalus have demonstrated that progression of their intracranial pathology is associated with concurrent changes in the shapes and latencies of their flash VEP (F-VEP) waveforms, and treatment with shunt placement leads to F-VEP normalization [86, 87]. Specifically, Sjöström et al. found that the P’ (P prime) latency was disproportionately prolonged just prior to surgical

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*Fig. 5 Transcranial Doppler ultrasound waveforms. a Patient with bacterial meningitis with CSF pressure of 37 cmH₂O and PI = 1.46 (upper) on day 1 of treatment and CSF pressure of 16 cmH₂O and PI = 1.12 (lower) on day 5 of treatment. b Transcranial Doppler spectra possibilities at varying pulsatility indices (PI). Adapted from Alvarez-Fernández et al. [107] and Wakerley et al. [78].*
intervention and normalized following the surgery [88]. As an explanation for these changes, Fichsel postulated that the alterations in VEP were produced by the effects of enlarging ventricles on the visual radiation pathways in the brain [87].

In addition to being correlated with high ICP disease processes, VEPs and specifically the N2 latency have also been compared directly to invasively measured ICP values. Several studies have reported a positive correlation between ICP and F-VEP N2 wave latency with correlation coefficients ranging from 0.83 to 0.84 [89, 90]. Similarly, Gumerlock et al. found that a F-VEP N2 latency >80 ms linearly corresponded to an ICP > 20 cmH2O [91].

The potential variability in VEPs within and between individual patients is an important source of debate. A longitudinal study that recorded monthly F-VEPs for up to 4 months in children has demonstrated that although there seems to be significant inter-individual variability in N2 latency, it is similar within individuals across time; these data suggest that N2 latency may be useful for the long-term monitoring of children at risk of elevated ICP [92]. On the other hand, Andersson et al. showed that in healthy adults tested on three different occasions with F-VEP, there was significant intra- and inter-individual variability in N2 and P2 latencies, amplitudes, and overall waveform shape [93].

In terms of emerging technologies, multifocal VEPs, which involve using hundreds of stimulations presented close in time, may provide a more detailed look at the visual pathways [85, 94]. However, the same questions regarding inter- and intra-individual variability will undoubtedly arise. As for the currently available literature on VEP and its use in ICP measurement, the majority of the studies have employed F-VEP rather than patterned VEP. It has been shown that patterned VEP displays less inter-individual variability and thus, may be preferable for determining ICP [95]. However, compared to F-VEP which can be performed easily on most patients, patterned VEP measurement necessitates an awake and attentive patient who can fixate on the stimulus as instructed and therefore would be difficult to do with younger children and patients with altered mental status [85]. Another consideration is that VEPs are affected by anesthesia since they are a measure of brain electrical activity; therefore, their use in trending ICP would be somewhat limited in sedated and intubated patients [93].

**Near-infrared spectroscopy (NIRS)**

First described by Franz Jobcis in 1977 [96], NIRS is a noninvasive optical technique that utilizes light in the near infrared spectrum. In between source and detector, the light can be scattered and absorbed by chromophores, leading to a certain amount of attenuation that can then be used to derive the ratio of oxyhemoglobin to deoxyhemoglobin and therefore calculate the tissue oxygen saturation in the local area [97]. The majority of NIRS cerebral oximeters currently on the market comprise of a combination light source and sensor pad that is applied to the patient’s head and connected to a monitor that displays regional saturation values calculated from proprietary algorithms. Most current clinical use of NIRS is for monitoring during cardiac and vascular procedures as well as in the care of TBI patients [97].

In order to understand the use of NIRS in studying ICP and brain injury, one must first have knowledge of the concepts behind cerebrovascular reactivity and specifically the pressure reactivity index (PRx). PRx is a correlation coefficient between simultaneous measures of ICP and arterial blood pressure (ABP) and is therefore reflective of the reactivity of vessels to changes in ABP [98]. Several studies have shown that a positive value for PRx is correlated with higher ICP and poorer long-term outcomes. Czosnyka et al. studied 82 patients with brain injuries and found that a positive PRx correlated with high ICP (r = 0.366; p < 0.001), low admission GCS score (r = 0.29; p < 0.01), and poor outcome at 6 months after injury (r = 0.48, p < 0.00001), and therefore concluded that although they were unable to use PRx to predict an exact ICP, it does have some cumulative and prognostic implications [98]. Similarly, another study found that a value of PRx > 0.35 was associated with over 50% mortality rate at 6 months following TBI [99]. An interesting use of PRx was demonstrated by Steiner et al., who studied 114 TBI patients who had continuous mean arterial pressure and ICP monitoring. With these values, they were able to determine an optimal cerebral perfusion pressure (CPP) for each patient, which was defined as the CPP at which PRx reached its minimal value. At 6 months post-injury, Glasgow outcome scale results showed that patients managed at the CPP closest to the calculated optimal CPP had the best outcomes [100].

Although PRx seems to correlate with ICP and can be prognostically significant, its calculation requires invasive ICP measurement, so by definition, it cannot be a noninvasive indicator of elevated ICP. There is a potential to use NIRS parameters combined with ABP measurements to noninvasively estimate ICP by creating a new index that is similar to PRx. Lee et al. postulated that the same blood changes that cause ICP shifts would also induce changes in the relative total hemoglobin. They defined hemoglobin volume index (HVx) as the correlation coefficient between simultaneous measures of relative total hemoglobin (rTHb), obtained by NIRS, and arterial blood pressure (ABP) [101]. By measuring rTHb, ABP, and ICP simultaneously in a piglet experimental model, they determined that HVx correlated with PRx (r = 0.73) [101]. In a similar study, Zweifel et al. defined total hemoglobin reactivity (THx) as a moving correlation coefficient between total hemoglobin index, obtained by NIRS, and ABP [102]. PRx and THx were significantly correlated within individuals (r = 0.49, p < 0.0001) and between individuals (r = 0.56, p = 0.0002). They also went one step further and used THx to calculate optimal CPP, which showed significant agreement with the optimal CPP determined using PRx [102].
In addition to being tested against PRx, NIRS-derived parameters have also been directly compared to various values of ICP and changes in ICP. One study used NIRS to calculate regional cerebral oxygenation (rSO2) in patients with ICP > 25 mmHg and patients with ICP < 25 mmHg [103]. They found that rSO2 values were significantly lower in patients with elevated ICP and concluded that NIRS may noninvasively detect impaired cerebral microcirculation in patients with increased ICP. A second study looked at six comatose children in whom phenylephrine injections were used to temporarily manipulate BP and ICP. Continuous MAP, ICP, and NIRS monitoring showed a significant correlation between cerebral hemoglobin saturation changes measured by NIRS and ICP changes ($r = 0.82, p < 0.001$) [104].

In summary, several studies have shown that NIRS-derived indices of cerebrovascular reactivity seem to be correlated with ICP and long-term patient outcomes after TBI [102–104]. Currently, NIRS has not been used to predict exact ICP measurements but further research into this modality is required in order to make any relevant conclusions regarding its use as a noninvasive detector of increased ICP.

**Conclusion**

In this review, we have outlined the current state of both structural (CT, MRI, fundoscopy, OCT, and ONSD) and functional (TCD, VEP, NIRS) noninvasive methods of detecting elevated ICP (Tables 4 and 5). Some modalities such as NIRS have been shown to just trend with ICP while modalities like ocular ultrasound and TCD have demonstrated high sensitivity and specificity for predicting clinically important elevations in ICP. Additionally, while CT, ocular ultrasound, TCD, VEP, and NIRS may be able to detect acute ICP changes, fundoscopy and OCT may be better suited for examining ICP trends and detecting insidious rises in ICP. In terms of the pediatric population, there is some data available for CT, ocular ultrasound, fundoscopy, OCT, and VEP, but factors such as patient cooperation and need for sedation should be considered.

At our high-volume craniofacial referral center, we regularly utilize noninvasive methods of ICP measurement. Almost all craniosynostosis patients undergo routine fundoscopic examination by an experienced pediatric ophthalmologist both preoperatively and during routine follow-up. Additionally, children who experience any clinical symptoms of elevated ICP undergo fundoscopic examination and often go on to require 24–48 h of intraparenchymal ICP monitoring in the intensive care unit. However, due to the low sensitivity of papilledema and the invasiveness of intraparenchymal monitoring, a dilemma exists in the management of a patient who has clinical symptoms but no papilledema. Should the patient be observed, undergo invasive ICP monitoring, or undergo surgical cranial expansion? As a result of the problems posed by relying on only fundoscopy and intraparenchymal monitoring, we have decided to explore
the use of OCT in detecting elevated ICP. As a noninvasive modality, OCT can be used preoperatively in the clinic for older children and during sedation for CT or MRI for younger children and infants. Additionally, if validated, OCT could be used to observe children in the immediate postoperative time period as well as during their yearly follow-up visit. Due to its noninvasiveness and higher sensitivity, OCT may be able to bridge the gap between fundoscopy and intraparenchymal monitoring in the care of patients with craniofacial anomalies. As we work on validating the OCT parameters, we hope to further incorporate OCT as a noninvasive measure of ICP into our craniofacial practice.

Overall, challenges of almost all techniques discussed include obtaining a reliable set of normative data for a population diverse in race, gender, and age, as well as reducing intra- and inter-individual variability, which may not be universally possible. In addition, within each modality, one must determine the most indicative parameter to study as well as establish the best cutoff points for the continuous parameters. Other considerations include examination time, ease of use, cost of equipment, and cost of personnel and training (Online Resource 1 for cost estimates). At present, no single method has prevailed, so further research is required in order to find and optimize a noninvasive method of measuring ICP that is reliable, easy to use, and cost-effective.
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