Monitoring Visual Function in Children With Syndromic Craniosynostosis

A Comparison of 3 Methods

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Objective: To compare visual acuity, optic disc appearance, and transient pattern reversal visual evoked potentials as markers of possible visual dysfunction in children with syndromic craniosynostosis.

Methods: Serial visual acuity, optic disc appearance, and pattern reversal visual evoked potential data were recorded in 8 patients with syndromic craniosynostosis before and after cranial vault expansion. The pattern reversal visual evoked potentials were analyzed using linear regression modeling, applied to the N80 to P100 amplitude.

Results: Serial optic disc appearances were available for all 8 patients and visual acuities for 7 patients. The visual acuity deteriorated in only 1 patient, improved in 4, and fluctuated in 2, before surgery. Of the 8 patients, 3 showed no papilledema in either eye at any time, 3 showed progressive bilateral swelling before surgery, and 2 exhibited only unilateral disc swelling. In all 8 patients, there was a trend for the N80 to P100 amplitude to decrease before surgery and to increase, in all but 2 patients, after surgery.

Conclusions: This study suggests that neither optic disc appearance nor visual acuity assessment alone is a reliable marker of potential visual dysfunction in children with syndromic craniosynostosis. It also suggests that the pattern reversal visual evoked potential can provide early evidence of visual dysfunction before vault expansion surgery in these children; this dysfunction may recover postoperatively.

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Craniosynostosis (CS) is the premature fusion of 1 or more cranial sutures during fetal development. Visual dysfunction is a complication in children with CS, which may be due to a combination of amblyopia, corneal scarring, and optic neuropathy. Optic neuropathy has been associated with an increased intracranial pressure (ICP) and has been traditionally evaluated by the presence of optic disc swelling, headaches, and vomiting, all of which may be unreliable or entirely absent. Intracranial pressure has been estimated to affect 13% of unisutural and 50% to 75% of multisutural CSs (which are more often seen in those with syndromic CS). Objective methods of documenting increased ICP include the following: lumbar puncture, which regularly requires a general anesthetic, and transcranial ICP bolt monitoring (tcICPm), an invasive procedure that requires a general anesthetic, with complications that can include intracranial hemorrhage and infection. A major factor in the decision of whether children with CS progress to undergoing tcICPm is deterioration in visual function. The morbidity and mortality associated with craniofacial surgery are still such that any ophthalmic findings that may lead to such surgery need to be robust and, ideally, detected early enough to allow possible reversal with intervention. Papilledema may not be evident in children with CS, even when an increased ICP is confirmed.

In infants, behavioral visual acuity tests are notoriously unreliable and further complicated by an improvement in performance and cooperation with age. By the time reproducible clinical behavioral measures of visual deterioration are obtained, irreversible damage may have already occurred. What is required is a reproducible noninvasive method of monitoring visual function. Visual evoked potentials (VEPs) provide a reproducible noninvasive method of monitoring neu-
Mursch et al\textsuperscript{16} reported pathological VEPs in 14 of 52 patients with CS had abnormal-flash VEPs, while larger stimuli\textsuperscript{17} and have been shown to be the only VEP measures used in this study to monitor visual function.\textsuperscript{15} Gupta et al\textsuperscript{15} reported that 11 of 66 patients with syndromic CS; these patients were under regular observation against months before and after craniofacial surgery. When for-\textsuperscript{†}These patients continued to deteriorate after craniofacial surgery.

Ethical approval of this hospital.

The threshold used to monitor visual function.

Table. Features of the 8 Patients With Syndromic Craniosynostosis

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Check, min\textsuperscript{*}</th>
<th>Syndrome</th>
<th>Gradient of Deterioration</th>
<th>Regression of VEP Data Points Before Surgery</th>
<th>Gradient of Recovery</th>
<th>Regression of VEP Data Points After Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 y 5 mo</td>
<td>50</td>
<td>Crouzon</td>
<td>−4.60</td>
<td>0.81</td>
<td>0.88</td>
<td>0.82</td>
</tr>
<tr>
<td>2\textsuperscript{†}</td>
<td>5 y 7 mo</td>
<td>25</td>
<td>Pfeiffer</td>
<td>−0.56</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>3</td>
<td>2 y 1 mo</td>
<td>50</td>
<td>Crouzon</td>
<td>−1.68</td>
<td>0.70</td>
<td>1.16</td>
<td>0.66</td>
</tr>
<tr>
<td>4</td>
<td>5 mo</td>
<td>50</td>
<td>Crouzon</td>
<td>−1.33</td>
<td>0.80</td>
<td>1.38</td>
<td>0.89</td>
</tr>
<tr>
<td>5</td>
<td>3 y 10 mo</td>
<td>100</td>
<td>Apert</td>
<td>−0.72</td>
<td>0.59</td>
<td>1.60</td>
<td>0.91</td>
</tr>
<tr>
<td>6</td>
<td>6 y 2 mo</td>
<td>50</td>
<td>Crouzon</td>
<td>−1.23</td>
<td>0.76</td>
<td>0.66</td>
<td>0.55</td>
</tr>
<tr>
<td>7\textsuperscript{†}</td>
<td>4 mo</td>
<td>12.5</td>
<td>Crouzon</td>
<td>−2.25</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>8</td>
<td>2 y 2 mo</td>
<td>100</td>
<td>Apert</td>
<td>−0.57</td>
<td>0.65</td>
<td>0.46</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Abbreviations: NA, no recordings were performed on this child after surgery; VEP, visual evoked potential.

**CLINICAL ASSESSMENT**

Visual acuity was measured with both eyes open and then, if possible, monocularly. Not all children allowed monocular acuity assessment and, therefore, the binocular acuity was plotted against months before and after craniofacial surgery. When formal visual acuity testing could be performed, a preferential looking technique (Cardiff acuity cards), a linear technique (Crowded LogMAR Kay Picture Test), a single-letter technique (Keeler LogMAR Crowded Test), and linear logMAR charts were used. All formal visual acuity measurements were recorded as logMAR equivalents. All children underwent an evaluation of exposure keratopathy using fluorescein eyedrops, and their optic discs were examined with an indirect ophthalmoscope using a 30-diopter lens after dilation with 1% cyclopentolate preservative-free eyedrops. The color of the optic discs and the presence of any swelling (and whether it was bilateral, unilateral, or sectorial) were noted. For graphical representation, the optic discs were classified on a scale from 1 to 6 (6 indicates no swelling; 5, congested; 4, mild swelling; 3, moderate swelling; 2, marked swelling; and 1, pallor). Where possible, a digital recording of the optic disc was made using a handheld digital camera (Nidek Inc, Chiyoda, Japan).

**ELECTROPHYSIOLOGICAL FINDINGS**

Transient prVEP recordings were performed (according to international recommendations\textsuperscript{19}) each time patients visited the department, leading up to and following surgery for CS.

In brief, the electroencephalogram was obtained using a 3-channel montage. The midline electrode was placed 3 cm above the inion at Oz and the lateral channels were positioned 4 cm along the Oz mastoid line (O1 and O2). All 3 electrodes were referred to Fpz, while the ground electrode was placed at POz. The electroencephalogram was amplified (×20 000) and digitized (analog to digital rate, 1.6 kHz), a specific period was chosen (−13 to 285 milliseconds), and data were averaged before being saved to a computer. The acquisition amplifier filters were set to a bandpass of 0.3 to 100 Hz. The electrodes were applied to the scalp using a conductive cream (Elefix; Ni-\textsuperscript{†}These patients continued to deteriorate after craniofacial surgery.

**METHODS**

Patients

We studied 8 patients (Table) with a confirmed diagnosis of syndromic CS; these patients were under regular observation by the Department of Ophthalmology, Great Ormond Street Hospital for Children NHS Trust. The study was performed under ethical approval of this hospital.

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in mesopic conditions to minimize distractions. The younger patients (below the age of 5 years) sat on a parent’s lap. Older patients were asked to fixate on a point at the center of the screen, while younger patients were encouraged to maintain fixation by one of the electrophysiologists orientating the child to the stimulus by using small toys. To maintain alertness and attention, the stimuli were alternated with cartoons. Fixation to the stimuli was monitored by closed-circuit television. The ongoing electroencephalogram during the recordings also enabled some assessment of alertness. Presentations of different stimulus check sizes (400-12.5 minutes) were used. The first stimulus provided in each case was our laboratory standard subtending 50 minutes. If a consistent response was obtained (evident in at least 2 of 3 runs), the check size was reduced until no reproducible response was evident. If no response to 50 minutes was obtained, the check size was increased until a reproducible response was recorded. The smallest test check to evoke a transient prVEP on the first visit was considered an individual patient’s threshold prVEP check size (Table). To monitor visual pathway function, the prVEPs evoked by this check size on subsequent visits were compared.

DATA PROCESSING AND STATISTICAL ANALYSIS

Data analysis involved measurement of the N80 to P100 amplitude of the prVEP from Oz in all patients on each visit to the department. The amplitude was measured over the serial visits and analyzed by fitting linear regression plots to individual patient data (amplitude against time plots). Regression data were calculated for periods of VEP deterioration and recovery. The quality of the models was determined by the adjusted $R^2$ statistic. Comparison of deterioration and recovery regression gradients was performed using the Wilcoxon rank sum test.

RESULTS

ELECTROPHYSIOLOGICAL FINDINGS

Serial binocular prVEPs were obtained for all patients. In all patients, the latency of the P100 component was within normal limits, while the N80 to P100 amplitude, although initially within normal limits, decreased before surgery (Figure 1 and Table). In 6 patients, regression models described the decrease and increase in the prVEP amplitude (regression of VEP data points before and after surgery, respectively) (Table). Comparison of the regression gradients showed a significant recovery of prVEP amplitude after surgery (Wilcoxon rank sum test $z=92.2, P=.03$). In 2 patients, the amplitude of N80 to P100 continued to decrease before further intervention, despite vault expansion surgery. The continuous decrease in amplitude of N80 to P100 after surgery in 1 patient (patient 2, previously described) suggested persistent increased ICP, prompting further imaging studies that revealed a blocked ventriculoperitoneal shunt. After shunt revision, the N80 to P100 amplitude improved (Figure 2). In the second patient (patient 7), the N80 to P100 amplitude also continued to decrease after vault expansion surgery. During this period, post-surgery sleep studies revealed periods of obstructive sleep apnea. Simultaneous monitoring of respiration levels, blood oxygen levels, and ICP during the sleep studies identified simultaneous periods of ICP spiking and obstructive sleep apnea. After intervention by continuous positive airway pressure followed by adenoidectomy and tonsillectomy, the amplitude of the prVEP increased.

OPTIC DISC APPEARANCE AND VISUAL ACUITY

Preoperative and postoperative visual acuities were available for 7 patients, while preoperative and postoperative optic disc appearance data were available for all 8 patients (Figure 3). All patients had adequate annotation of optic disc appearance preoperatively and postoperatively within their medical records. Five patients had digital images available before and after surgery, while 1 had only 1 data set preoperatively. None of the patients included in the study had any evidence of exposure keratopathy, and no patient had optic disc atrophy before surgery. Of the 8 patients, 5 (patients 1, 2, 4, 7, and 8) had equal and normal visual acuity in both eyes, 2 (patients 3 and 6) had mild unilateral decreased acuity, and 1 (patient 5) had severely decreased right eye acuity, thought to be due to dense strabismic and anisometropic amblyopia throughout the monitoring period. Visual acuity deteriorated before cranial vault expansion in a linear fashion in both eyes of 1 patient (patient 5). In 4 patients, the visual acuity was improving before surgery; and in 2 patients, it was fluctuating. In 3 patients (patients 3, 6, and 7), the optic discs of both eyes, based on clinical notes, were not swollen at any stage before surgery. After craniofacial surgery, optic discs remained unchanged in both eyes of 2 patients (patients 6 and 7) and in the left eye of the third patient (patient 3). The right eye of the third patient (patient 3) was mildly swollen after surgery. In 1 patient (patient 5), the left eye was not swollen before or after surgery. There was, however, progressive superior pole swelling of the right eye leading up to craniofacial surgery, which subsided postoperatively. In 3 patients (patients 1, 4, and 8), optic discs in both eyes became progressively swollen leading up to craniofacial surgery. In 2 patients (patients 4 and 8), both eyes recovered following surgery, while in 1 patient (patient 1), the optic discs remained swollen 6 months after surgery. In another patient (patient 2), the left and right eyes were mildly swollen before surgery. After surgery, the right eye swelling resolved, while the left eye remained swollen. However, analysis of serial digital images showed that the left eye disc head remained unchanged in appearance at any stage of treatment, suggesting the possibility of an anomalous disc.

TRANSDURAL ICP MONITORING

Three patients (patients 2, 5, and 6) underwent tcICPm before surgery, confirming an increased ICP in all. One of these patients (patient 2) had anomalous optic discs, 1 (patient 5) only had unilateral papilledema, and 1 (patient 6) had no swelling of either disc. All 3 had an equivocal neurological examination. A further 3 patients had progressive optic disc swelling in 1 or both eyes, indicating the presence of increased ICP, negating the benefit of tcICPm. In another 2 patients, neuroimaging results suggestive of soft signs of craniocerebral disproportion.
together with other systemic clinical symptoms were believed to warrant surgical intervention rather than tCIPm.

CRANIOFACIAL SURGERY

All surgical procedures were performed to reduce increased ICP. All but 2 patients had posterior vault expansions; the remaining 2 patients (patients 6 and 7) had frontal monoblock advancements.

This study has shown that serial threshold prVEPs seem to provide a more robust and reproducible measure of

Figure 1. Transient visual evoked potential (VEP) N80 to P100 amplitude and visual acuity data points before and after surgery in patients 1 through 8 (A-H, respectively). The shaded area indicates the normal age-matched amplitude mean±SE. In B and G, the vertical dashed line indicates the time of an additional intervention (patient 2 [B] received a revised shunt, and patient 7 [G] received continuous positive airway pressure).
visual function than either optic disc appearance or visual acuity in a group of children with complex CS.

Preoperative and postoperative visual acuity data were inconsistent and sometimes misleading. Acuity actually improved in 4 children before craniofacial surgery despite the presence of clinical or tcICPm evidence of increased ICP. This is not surprising because there is a strong tendency in children for improvement with age in performance of visual acuity behavioral tasks.

Optic disc appearance also provided inconsistent and sometimes misleading findings. This is in agreement with previous reports that optic disc appearance is not always a reliable indicator of increased ICP in children with CS. We found that 7 (44%) of 16 eyes were not swollen at any stage, while 3 of the patients did not show any optic disc swelling in either eye. In the remaining 5 patients, the optic disc swelling was varied, including unilateral, bilateral, or sectorial swelling. The variable findings of optic disc appearance are difficult to explain, especially because we were able to take objective digital images of the optic disc appearance in addition to traditional indirect ophthalmoscopy. In 1 child (patient 2), serial digital images assisted in differentiating swollen discs from anomalous ones by removing interobserver description variability.

Despite a confirmed increased ICP on tcICPm, 1 child (patient 5) only had unilateral papilledema, while another child (patient 6) had no swelling but experienced pallor before surgery.

Our study revealed that serial threshold prVEP measures provide a reliable marker of progressive central visual dysfunction, manifesting as a gradual loss in the amplitude of N80 to P100 before vault expansion surgery.

Although it is well recognized that the major pattern reversal components are modulated by maturation, especially within the first 6 months of life, our labora-

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**Figure 2.** Serial pattern visual evoked potentials to 50-minute test checks in patient 4 (A), to 12.5-minute test checks in patient 7 (B), and to 50-minute test checks in patient 2 (C). CPAP indicates continuous positive airway pressure; and the shaded area of waveforms, the difference between baseline and serial responses in the P100 latency range. Negative numbers along the vertical axis signify before intervention, positive numbers, after intervention.
tory has shown that the prVEP P100 component to 100- and 50-minute checks has latencies within 10% of adult values by the age of 7 months; more important, only 2 children (patients 4 and 7) were younger than 7 months when first seen, and both of these children showed deterioration before surgery. Although amplitude has a higher intersubject variability compared with latency, studies demonstrate that intrasubject amplitudes measured over short-, medium-, and longer-term intervals are stable.

An important finding from this study is that serial recordings are required to document visual deterioration. This

Figure 3. Optic disc appearance before and after surgery in patients 1 through 8 (A-H, respectively). In B and G, the vertical dashed line indicates the time of an additional intervention. Mark indicates marked swelling; Mild, mild swelling; Mod, moderate swelling; and Not, not swollen.


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is because the amplitudes and latencies recorded in the first study for each child were initially within the normal clinical range. The trends in serial prVEPs identified in the present study were clear, and inspection of our results indicates that serial recordings at intervals of 2 to 4 months would be sufficient to identify functional deterioration.

All children underwent surgery to relieve increased ICP. This was documented in 3 children using tcICPm, while the remaining 5 had clinical and radiological evidence causing a significant suspicion of increased ICP. Because 6 children had improved prVEP measures after surgery and the remaining 2 had improved prVEP measures after a second intervention to lower ICP, the decrease in the amplitude of N80 to P100 may be because of increased ICP, in keeping with data in previous studies. 27-30

A decrease in prVEP amplitude with increased ICP may be because of a combination of optic nerve and occipital lobe compromise, owing to edema and/or hyponxia.

The subarachnoid space of the brain is continuous with the optic nerve sheath, and pressure transmitted to the optic nerve during episodes of increased ICP may impede axoplasmic transport, causing intra-axonal edema in the area of the optic disc, which causes it to swell (papilledema). If persistent papilledema occurs, secondary ischemia can result in anterior optic nerve or visual pathway dysfunction. During increased ICP, impairment of the blood supply to the optic nerve (eg, via the ophthalmic artery) or optic radiations (posterior cerebral arteries) can ultimately lead to hyponxia. The effects of edema and hyponxia have the potential to adversely affect central nervous system function and can lead to visual loss in patients with optic neuropathy (because of chronic papilledema) 31,32 or optic tract involvement. 33 While serial measures of prVEP provided convincing evidence of central visual dysfunction in our patients, there were 2 children who continued to demonstrate deterioration in prVEP amplitude after vault expansion surgery, and this indicated a persisting hyponxic or edematous compromise. In one child, this was because of a ventriculoperitoneal shunt blockage (previously reported). 3 The other child (patient 7) who had continued deterioration after vault expansion, ICP measurements were normal and it was postulated that obstructive sleep apnea was the cause because there was a recovery of VEP amplitude following continuous positive airway pressure and adenoidectomy and tonsillectomy. There have been many reports of visual compromise secondary to obstructive sleep apnea in adults, 34,35 and recently, similar findings were reported in a child with CS (not in this study). 36 The evidence from these 2 children highlights the need for serial prVEP studies before and after interventions to monitor visual pathway function.

This study has demonstrated that progressive visual dysfunction in patients with complex CS is most reliably detected using serial recordings of the prVEP, while visual acuity in young children and optic disc appearance alone are not. More important, the visual dysfunction identified by the decrease in amplitude of the threshold prVEP N80 to P100 component is recoverable after surgical intervention to normalize the increased ICP. Based on the findings of this study, we recommend that children with complex forms of CS (including syndromic) should have regular-pattern VEP assessments to detect early visual pathway compromise not otherwise detected by visual acuity or optic disc assessment.

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Author Contributions: Drs Liasis and Nischal had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

REFERENCES


**Archives Web Quiz Winner**

Congratulations to the winner of our March quiz, K. N. Poornesh, MS, DNB, FRCS Ed, Department of Ophthalmology, Ipswich Hospital, Ipswich, England. The correct answer to our March challenge was tuberous sclerosis. For a complete discussion of this case, see the Clinicopathologic Reports, Case Reports, and Small Case Series section in the April ARCHIVES (Mennel S, Hausmann N, Meyer CH, Peter S. Photodynamic therapy for exudative hamartoma in tuberous sclerosis. *Arch Ophthalmol.* 2006;124:597-599).

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