Letters to the Editor

NEUROSURGICAL FORUM

Raised intracranial pressure and nonsyndromic sagittal craniosynostosis

TO THE EDITOR: The recent paper by Wall et al.¹⁹ (Wall SA, Thomas GPL, Johnson D, et al: The preoperative incidence of raised intracranial pressure in nonsyndromic sagittal craniosynostosis is underestimated in the literature. *J Neurosurg Pediatr* 14:674–681, December 2014) on intracranial pressure (ICP) in a selected group of untreated children (mean age around 5 years) with sagittal synostosis ends with the recommendation that intraparenchymal ICP monitoring “should be considered and used routinely in all patients for whom a nonoperative course of management is proposed, no matter the nature or severity of the calvarial deformity.” As this represents a radical departure from the clinical practice of many, if not most, craniofacial units and because we fear the recommendation could lead to an epidemic of invasive monitoring (with its small but never absent risk of brain injury), we suggest that the following factors be considered.

Most importantly, their recommendation is associated with no identified benefit to the patients in their study. Not only do they state that “developmental delay was not significantly more common in patients with elevated ICP,” but they also reveal that “patients who manifested symptoms suggestive of raised ICP but who were found to have normal ICP on monitoring experienced an improvement or resolution of their symptoms over time.” There is no mention of what happened to those who did have abnormal ICP. In fact, the only support for their recommendation is their statement, “It remains reasonable to assume that continued chronically raised ICP in [sagittal craniosynostosis (SC)] is liable to curtail an individual’s neurocognitive development, even if it does not reliably cause a marked developmental delay and is not responsible for many of the developmental abnormalities seen in SC.” But is such an assumption in the absence of any supporting evidence “reasonable” enough to bear responsibility for one, possibly two, surgical interventions—one of which is a major cranial procedure?

Then there is the problem of what childhood ICP should be considered abnormal. The “true” level of childhood ICP remains, for obvious reasons, unknown. As Dominique Renier and his colleagues wrote in their classic 1982 paper,¹³ “The definition of ‘normal’ and ‘abnormal’ ICP recordings in children raises an initial problem.” Although the “Paris” range¹³ (< 10 mm Hg normal, 11–15

mm Hg borderline, and > 15 mm Hg raised) used here is most frequently accepted in craniofacial circles, a close reading of the 3 references^{5,9,17} used to support those values suggests the upper limit of their range could just as reasonably have been raised to 20 mm Hg.

Indeed, in a previous paper⁸ from Wall and colleagues’ unit (similar in its message but dealing with unicoronal synostosis), the authors state that “intracranial pressure was defined as elevated if the mean pressure was greater than or equal to 20 mm Hg.” It would be interesting to know their reasons for a change which, as they state in their *Discussion*, would reduce the number with raised ICP in their 39 monitored patients from 17 (44%) to 6 (15%)—and that’s without the 6 who were not monitored at all but were “well and asymptomatic when last reviewed.”

Their inclusion of “more than 3 B-type waves in a 24-hour period during sleep” as part of their classification of abnormal ICP is not helpful in the absence of any accompanying definition. “B” waves have had a checkered history since Lundberg first identified them in a study dealing predominantly with intracranial tumors in adults. Eide et al. pointed out⁷ (in a paper referenced by Wall et al.) that “the identification of B waves is subjective” and for that reason did not consider them useful in the diagnosis of raised ICP. In Renier et al.’s 1982 study,¹³ waves superimposed on a non-elevated baseline ICP (their “third type”) were dismissed as normal. In Wall et al.’s study,¹⁹ all 6 patients with 3 or more B-waves had baseline pressures of or below 15 mm Hg. Nevertheless, their presence was judged sufficiently abnormal to justify calvarial remodeling (surgical details not given despite some techniques producing a temporary rise in ICP).

The waves of increased ICP superimposed on an elevated baseline observed in children with syndromic/complex forms of craniosynostosis occur particularly during REM sleep—associated episodes of airway compromise. Although children with single suture synostosis are unlikely to be so affected, it does raise the question of what effect a “normal” degree of childhood adenotonsillar hypertrophy may have on ICP. To take an extreme example, it could be argued that any child (with or without craniosynostosis) who snores at night runs an ICP that, according to the criteria quoted in the authors’ study, would qualify them for cranial vault surgery. On a lighter note, the authors’ observation that raised ICP was seen less frequently in children with obvious scaphocephaly than in those in whom it was minimal or absent altogether might reflect no more than a tendency for the former to sleep more comfortably on their sides than their backs (when a vulnerable airway may be compromised).

There is indeed a small but definite incidence of papilledema-confirmed increased ICP in children with isolated sagittal synostosis.^{1,6,14,16} Its cause is unknown, but in the absence of other remediable factors (hydrocephalus, for example), it represents a proper indication for surgical intervention—usually a procedure designed to increase the cranial volume. None of the patients reported here had papilledema.

The authors state that “the sequelae of chronically raised ICP include visual loss and psychomotor impairment.” Visual loss due to papilledema—which, again, none of these patients had—is not in dispute. But with regard to possible brain effects, neither of their supporting references^{11,18} do more than repeat that statement. Pollack et al.¹¹ reference Renier and colleagues¹³ (plus a 1988 Paris review,¹² which added further numbers to the earlier paper) as their authority, whereas Vinchon et al.¹⁸ quote Connolly et al.,² who also do no more than refer back to Renier’s 1982 paper with its various pitfalls.

Given that only 6 patients had postoperative ICP monitoring, whether surgery actually lowered ICP in the remainder remains a matter of conjecture.

The authors quote Hanlo et al.¹⁰ in support of their statement that “in other pediatric neurosurgical conditions, elevated ICP has been correlated with impaired myelination and later poor neurodevelopmental scores.” But since the authors of that study looked at a condition (progressive hydrocephalus in infancy) with a very different mechanism for brain injury compared to craniosynostosis (and relied on anterior fontanelle tonometry to assess ICP), its relevance here is limited.

Finally, the authors quote 3 references^{3,4,15} in their statement that “several PET studies in children with isolated single-suture craniosynostosis have found areas of cerebral hypoperfusion associated with the stenosed suture, which resolved after corrective surgery.” In fact, only one of those references³ deals with PET scanning, and the other two refer to SPECT. A recent PubMed search failed to produce any other relevant PET studies.

In conclusion, we do not doubt that the content of Wall et al.’s paper is, in purely observational terms, correct; selected children with untreated sagittal synostosis of variable severity monitored at a mean age of around 5 years may be running ICPs at or above 15 mm Hg. What this means in terms of their cognitive development, however, is quite another matter. As the authors state, “The lack of a correlation between developmental delay and raised ICP found in the present study supports the hypothesis that there is no simple causal relationship between ICP and neurocognitive anomalies found in SC.” This leaves their recommendation that, in pursuit of essentially theoretical neurocognitive benefits, invasive ICP monitoring with a view to “calvarial remodeling” (with the attendant brain risks of both procedures) should be performed in all children whose parents have declined surgical intervention at least debateable—at worst dangerous.

Richard Hayward, FRCS(Eng)
Jonathan A. Britto, MD, FRCS(Plast)
David Dunaway FRCS(Eng)
Robert Evans, FRCS(Eng)

Noor ul Owase Jeelani, FRCS(NeuroSurg)

Dominic Thompson, FRCS(Eng)

Great Ormond Street for Children NHS Trust, London, United Kingdom

DISCLOSURE

The authors report no conflict of interest.

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Response

We have read with interest Professor Hayward and colleagues' letter and welcome their comments regarding our recent paper. They express concerns over the recommendation that ICP monitoring "should be considered and used routinely in all patients for whom a nonoperative course of management is proposed, no matter the nature or severity of the calvarial deformity." We would be interested to learn about the data from which the authors' suggest that our recommendation "represents a radical departure from the clinical practice of many, if not most, craniofacial units," as this would not be our experience. The basis for our recommendation was the observed high frequency of raised ICP in the series, in conjunction with the lack of a correlation between the severity of the calvarial deformity or clinical or radiological signs and the occurrence of raised ICP. Thus, clinical and radiological findings alone were not usefully predictive of an abnormal ICP, an observation that has been previously reported.⁴ In our current response, we will attempt to address the authors' comments and concerns with reference to the points they have raised.

In their first point, Professor Hayward and colleagues state that "their recommendation is associated with no identified benefit to the patients in their study." We agree that the paper does not detail the long-term outcomes of those patients who underwent ICP monitoring, nor does it compare them to a control population that did not have monitoring, as would be necessary to prove a benefit specific to that intervention. However, the goal of our study was not to assess the effectiveness of our management of elevated ICP in this cohort, once identified, but rather to investigate and report the incidence of abnormal ICP and its associations. The calvarial remodeling procedure performed in the patients in our study was designed to expand the calvarium (without increasing ICP) and correct the scaphocephalic deformity, when present. Following surgery, all patients were enrolled in a regular follow-up program, until they reached skeletal maturity. Although we did not specifically discuss the outcome of patients who had surgery for raised ICP but did not require further ICP assessment, we hoped that their satisfactory outcome was implied given our description of the other patients. Following calvarial expansion, in the absence of any clinical concern, we believed that no further ICP monitoring for confirmation of a normal ICP was indicated. This decision was based on our experience of the effectiveness of calvarial expansion in treating raised ICP in the craniosynostosis

population as a whole. This view is justified, in our opinion, given that no patient in whom postoperative ICP measurement had been performed exhibited an abnormal pressure profile. However, we accept the authors' point that this is not proof that calvarial expansion lowers ICP in all SC patients who have abnormal pressures prior to surgery. Nonetheless, we reiterate that the aim of our study was not to assess the effectiveness of calvarial expansion as a treatment for raised ICP in this population.

Others may disagree with our strategy of operative intervention, but we would ask them to reflect on whether knowing that a child's ICP was abnormal would alter their management of that individual. Indeed, whether it is useful to know if a patient's ICP is raised rather depends on how one interprets the clinical significance of that information. We believe that chronically raised ICP in nonsyndromic single-suture craniosynostosis is likely to lead to long-term neurocognitive decline. The evidence surrounding this is mixed, as discussed in our paper, and is hampered by a scarcity of studies that have investigated long-term neurodevelopmental outcomes in patients with proven increased ICP who do not undergo corrective surgery. However, in a study published in 2005, Bellew and colleagues found that children with surgically uncorrected SC (a proportion of whom are likely to have abnormal ICP, given our own and others' data) had poorer neurodevelopmental outcomes than either their peers who had surgery or normal controls.² Although neurodevelopmental delay is very likely to be multifactorial in SC, it seems unreasonable to discount the contribution that chronically raised ICP might make, particularly when one considers its impact in other pediatric neurological conditions, albeit with different pathoetiologies. Furthermore, in nonsyndromic single-suture craniosynostosis patients who have had corrective calvarial surgery, we have observed that behavioral changes and a decline in academic attainment are often associated with raised ICP on intraparenchymal ICP monitoring. Following a calvarial expansion procedure designed to address their raised ICP, the patients' behavior usually improves and school performance ceases to decline.

Another point raised by Professor Hayward and colleagues, which we had believed we addressed in our paper, is what constitutes an abnormal ICP in childhood. Given the understandable lack of normative data, it is not surprising that the threshold defining raised ICP in children remains a topic of debate. With this in mind, we listed in Table 2 of our paper those patients whom we considered to have an abnormal ICP, giving sufficient information, we thought, for the readers to judge for themselves the incidence of raised ICP in the series, depending on their own belief as to where the threshold should lie. Even if one defines that threshold at 20 mm Hg and, for the sake of argument, includes in the series the 6 patients who were not monitored but were assumed (possibly incorrectly) to have normal ICP, then the incidence of raised ICP in the series is still 13% (6 of 45). Notably, 3 of the 12 non-scaphocephalic patients (25%) had nocturnal baseline ICPs of 20 mm Hg or greater. Of course, because other studies, including those from Professor Hayward and colleagues' own center,^{5,6} have defined the lower threshold of 15 mm

Hg, direct comparisons with those series are difficult to make if one applies a threshold of 20 mm Hg.

With respect to B-type waves, other authors support the inclusion of pressure waveforms in the evaluation of ICP normality in the craniofacial patient population, and we have found these to be a useful component of the evaluation.⁴ We are also cognizant of the complex interactions among venous pressure, sleep cycle, and respiration and their effects on ICP. In our opinion, pressure profiles assist, rather than hinder, the investigation and assessment of this often-demanding problem.

We infer from the correspondents' comments that they would support surgical intervention in the presence of papilledema given the likely risk of visual loss or neurocognitive decline. We would suggest, however, that ICP can be significantly raised in the absence of acute papilledema.⁷ In chronic cases, axonal swelling may subside, being replaced by more subtle examination features that may be missed in this age group. While pertaining to a different patient population, Acheson's review of idiopathic intracranial hypertension and visual function serves as a useful overview of ICP-related changes in the optic nerve and the potential pitfalls.¹

We agree with the authors' comments that Hanlo et al.³ and our own study populations have different underlying pathologies, but we contend that the correlation of abnormal ICP to neuroanatomical sequelae is relevant.

We certainly accept the authors' comments made regarding our citation of 3 references dealing with PET scanning. We would hope though that the accidental omission of the phrase "or SPECT" from our sentence would be readily apparent from the references cited in support.

If we are to resolve the key issue of what impact chronically raised ICP has in SC, then long-term studies of neurodevelopmental outcomes in non-operated SC patients with documented ICP are required. An adequately powered and controlled study should be able to demonstrate whether patients with an abnormal ICP suffer harm, and if so, what the pressure thresholds for such harm might be. Undoubtedly, undertaking such a study will prove challenging. Identifying the likely incidence of abnormal ICP in this cohort is a first step toward this. In the interim, we believe that existing evidence supports our practice of investigating ICP in patients with SC in whom nonoperative management is considered. In fact, we maintain that measuring ICP has significant potential benefits to patients in whom nonoperative management will be pursued. It not only enables one to identify patients with raised ICP who do not have clear clinical signs, but it also avoids unnecessary cranial vault surgery in patients in whom a clinical suspicion of raised ICP is in fact unfounded.

We hope that our response goes some way to addressing the concerns expressed by Professor Hayward and his colleagues. On reflection, our inclusion of the phrase "and used routinely" in our closing recommendation is open to misinterpretation and therefore would be better omitted. As with any invasive procedure, ICP monitoring should only be performed after careful consideration and following a detailed and frank discussion with the patients (when appropriate) and their guardians. However, given our data and experience, we continue to recommend considering

ICP monitoring in all patients for whom a nonoperative course of management is proposed, no matter the nature or severity of their calvarial deformity.

Steven A. Wall, FCS(SA)

Gregory P. L. Thomas, PhD, FRCS

David Johnson, DM, FRCS

Jo C. Byren, MRCGP

Jayarajnam Jayamohan, FRCS

Shailendra A. Magdum, FRCS

David J. McAuley, FRCS

Peter G. Richards, FRCS

Oxford University Hospitals NHS Trust, Oxford, United Kingdom

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Temporal evolution of medulloblastoma subgroups

TO THE EDITOR: We read with great interest the article by Shinojima et al.⁷ in which the authors describe a 13-year-old boy with a medulloblastoma containing cells representative of 2 distinct molecular subgroups: WNT and Group 3 (Shinojima N, Nakamura H, Tasaki M, et al: A patient with medulloblastoma in its early developmental stage. **J Neurosurg Pediatr** 14:615–620, December 2014). Using immunohistochemical staining for subgroup-specific markers in combination with fluorescence in situ hybridization (FISH) for chromosome 6, the authors identified a medulloblastoma in the early stages of tumorigenesis comprising individual cells that exclusively represent WNT or Group 3 medulloblastoma.

The current molecular classification of medulloblastoma takes into account 4 subgroups, each distinct in terms of prognosis and predicted therapeutic response.⁹ In keeping with their distinct molecular phenotypes, elegant murine models of medulloblastoma have recently implicated a unique cell of origin for each subgroup.^{1,2,4,6,10} Specifically, WNT-dependent medulloblastomas have been shown to arise from cells outside the cerebellum in the dorsal brainstem based on overlapping gene expression profiles between WNT medulloblastomas and a distinct hindbrain germinal zone located in the lower rhombic lip.¹ In contrast, Group 3 medulloblastomas have been derived from CD133+ cerebellar stem cells⁴ or Atoh1+ granule neuron precursors (GNPs).² Interestingly, while the cells used to establish GNP-driven Group 3 tumors were devoid of stem cell markers, Atoh1 expression was lost and a concomitant enrichment of stem cell markers such as CD133 was observed in the resultant tumors.² The subsequent identification of a cerebellar stem cell as a target for the initiation and propagation of Group 3 medulloblastoma is in keeping with the treatment-refractory, metastatic nature of these tumors.

Although current transgenic mouse models support regional differences in the cellular origin of each molecular subgroup, they may not accurately depict the dynamic cellular phenotypes that initiate and maintain sporadic de novo medulloblastoma as observed in humans.⁷ The presence of distinct WNT and Group 3 cells in a single tumor mass supports a framework that recognizes intratumoral heterogeneity as a natural component in the spatial and temporal evolution of medulloblastoma. The cancer stem cell hypothesis accounts for intratumoral heterogeneity by having a developmentally primitive cell at the apex of the hierarchy with a spectrum of more differentiated cells as one goes down this hierarchy.^{5,8} Accordingly, a medulloblastoma stem cell may represent a common cell of origin for all subgroups with subgroup-specific progenitors competing in a process of clonal selection in the early stages of tumor evolution to determine the dominant subgroup. Consequently, the current case may represent a critical stage in tumorigenesis in which the dominant subgroup has yet to be established.

Our proposed hypothesis for the temporal evolution of medulloblastoma subgroups as supported by this case report may not be effectively evaluated with current genomic platforms. Analyses of the bulk tumor are often based on tumors in which the dominant subgroup has already been established, which may further distort the identification of cells that compose a rare fraction of the bulk tumor such as medulloblastoma stem cells or ancestral nondominant subgroup clones.³ Such low-frequency cell populations may be functionally relevant in driving treatment failure, relapse, and poor overall survivorship; therefore, future murine models of medulloblastoma must reconcile our current limitations.

Branavan Manoranjan, BHSc^{1,2}

Sheila K. Singh, MD, PhD¹

¹McMaster Stem Cell and Cancer Research Institute, ²Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada

DISCLOSURE

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Response

We thank Mr. Manoranjan and Dr. Singh for their thoughtful comments on our case report in which we document the detection of a very small medulloblastoma harboring distinct WNT and Group 3 cells. Our findings suggest that early medulloblastoma is a heterogeneous tumor and that its growth requires clonal selection involving cell competition in which one subgroup of cells becomes the dominant population. They point out that findings on the different medulloblastoma subgroups using current murine models may not reflect human medulloblastoma. They addressed the cell of origin in the evolution of medulloblastoma from a retrograde perspective, based on our report and their earlier study of cancer stem cells.³ They offered the hypothesis that medulloblastoma stem cells are at the apex of the cell hierarchy in the tumor, are a common cell of origin for all medulloblastoma subgroups with subgroup-specific progenitors, and are implicated in the treatment-refractory, metastatic nature of medulloblastomas. Interestingly, Bandopadhyay et al.,² who established a cell line from a primary recurrent medulloblastoma after therapy, demonstrated that its gene profile was consistent with both Group 3 and Group 4 cells. Therefore, the first primary tumor before therapy was probably heterogeneous and contained a rare fraction of distinct subgroup

clones or medulloblastoma stem cells undetectable by current genomic platforms. Therapy may have induced iatrogenic cell competition that gave rise to cell populations such as a treatment-resistant Group 3 subgroup that became predominant and detectable. Therefore, new methods are needed for the detection of such rare cell fractions that may lead to treatment-induced therapy failure.

It has been suggested that cell competition, through which viable cells can be eliminated by neighboring cells, plays a role in organ development including organ size control, and that some molecules such as Myc are important for cell competition during organ development.^{1,4} We posit that cell competition also occurs in the course of medulloblastoma development and that without such competition the tumor may not grow. Consequently, the regulation of cell competition may facilitate the prevention and control of tumor growth. Detailed mechanisms underlying cell competition in the tumor remain to be identified, and new experimental models are needed to test our hypothesis of early medulloblastoma tumor heterogeneity and the role of cell competition in human medulloblastoma.

Naoki Shinojima, MD, PhD

Hideo Nakamura, MD, PhD

Jun-ichi Kuratsu, MD, PhD

Kumamoto University Hospital, Kumamoto, Japan

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Intracranial pressure and sagittal craniosynostosis

TO THE EDITOR: We read with interest and concern the paper by Wall et al.⁷ summarizing their finding of intracranial pressure (ICP) monitoring in patients with radiological sagittal suture synostosis who had presented for unrelated reasons in early childhood (Wall SA, Thomas GPL, Johnson D, et al: The preoperative incidence of raised intracranial pressure in nonsyndromic sagittal craniosynostosis is underestimated in the literature. *J Neurosurg Pediatr* **14**:674–681, December 2014). Of the 39 patients, 17 were found to have “raised ICP” and were subjected to calvarial remodeling based solely on the fact that

the ICP number was high without establishing the relationship of high ICP to any symptoms.

In our review of the literature, we have not found any controlled studies investigating ranges of normal and high ICP in pediatric patients. We believe that the generally used reference ranges for pediatric ICP may be from numbers mentioned in publications by R. A. Minns⁶ in the 1980s, without studies backing them up. Furthermore, critical ICPs cannot be deduced from pressure readings alone. Cerebral perfusion pressure (CPP) is also an important parameter. Since there is no clearly defined measure of high ICP in the literature, in this article the authors chose to define raised ICP as ICP persistently higher than 15 mm Hg or the presence of 3 B waves in a 24-hour period. This is referenced to a review written by the senior author (P.R.) himself,⁸ which is then referenced to articles by Lundberg et al. from the early 1960s.^{3–5}

These articles were from the pre-CT era and report on adult patients who had clear clinical symptoms of increased ICP unlike those in the series reported by Wall et al. In fact, Lundberg et al.³ state at the beginning of Chapter 12 of their thesis on normal ventricular fluid pressure that “Since the main indications for continuous VFP [ventricular fluid pressure] control were a space occupying lesion and intracranial hypertension, the present series does not include any cases that can with certainty be regarded as normal in respect of central nervous system. One case, where the VFP was recorded graphically can, however, be regarded as probably representative of a normal VFP.” While these papers gave us a significantly improved understanding of the patterns of ICP waveforms in symptomatic adult patients with raised ICP along with clinical symptoms and intracranial lesions, these data cannot be extrapolated to the asymptomatic pediatric patients with no intracranial pathology on whom Wall et al. report in their series.

It is well known that B waves occur in healthy individuals. Most of the work defining criteria for what constitutes pathological B waves has been done on symptomatic adult patients with normal-pressure hydrocephalus, shunt-treated hydrocephalus, or head injuries. While there continues to be some controversy as to what constitutes abnormal B waves in symptomatic adults, the authors have not given adequate justification by means of appropriate references for considering the presence of 3 or more B waves in a 24-hour period to be abnormal. Six of their patients had ICPs of 15 mm Hg or less but were subjected to a major cranial vault reconstruction based on the undefined criterion of B waves. Subjecting asymptomatic children without papilledema to a major cranial vault reconstruction without a scientific basis does not seem justifiable.

Increased ICP can cause problems in a number of ways. Focally raised pressure in its extreme form may lead to brainstem herniation and death. Increased ICP can stretch and distort sensitive basal or tentorial dura mater and cause symptoms such as headaches or vomiting from distortion of the brainstem. Increased pressure can lead to progressive papilledema and vision loss. Finally, high ICP from hydrocephalus or a normal ICP with increased brain compliance in normal-pressure hydrocephalus can distort periventricular fibers, which can result in symptoms ob-

served in those patient populations. In patients with all of these conditions, we strongly feel that surgical intervention is required. However, none of the patients that Wall et al. present in their series had these problems, and in our opinion surgery may not have been necessary (except in the patients with significant scaphocephaly, in whom the surgery is justifiable for cosmetic reasons).

Understandably, very high ICP beyond the autoregulation capacity of the brain can compromise cerebral perfusion. In adults this generally does not happen until the pressure reaches a threshold of about 40 mm Hg. Even so, some patients with pseudotumor cerebri and ICPs in this range can function normally with no symptoms other than headaches. In children with severe traumatic brain injury, an ICP greater than 20 mm Hg and a CPP of less than 40 mm Hg has been recommended as a threshold for instituting treatment (Level III recommendation).² As the authors rightly pointed out, if this ICP criterion were to be used, only 4 of the 39 patients would qualify as having elevated ICP. Of these 4 patients, only one was developmentally delayed and none of them were symptomatic or had papilledema. Does the mere presence of increased pressure in an asymptomatic patient without papilledema justify a major cranial vault expansion?

Presumably, chronically altered cerebral perfusion in a developing brain may have consequences such as developmental or psychomotor retardation. Wall et al. have used this as a leaning post to justify surgery in their patients. However, their own data do not support this. They very clearly state in their paper that the “high ICP” had no relationship to the patients’ presenting symptoms or developmental delay in their patient population. They further establish by way of references that there is no evidence to support improvement in neurodevelopment outcomes after corrective surgery.

The first tenet of medicine is “to do no harm.” Six of the 18 patients became symptomatic (4 of 14 who were asymptomatic developed symptoms) or remained symptomatic (2 of 4 who were symptomatic remained symptomatic after surgery) after the calvarial reconstruction. One patient, in fact, had a decline in academic performance after surgery. Wall et al. take refuge in the fact that their patients’ ICPs had normalized and, therefore, ignore the consequences. Nevertheless, in our opinion the surgery did more harm to these patients, and the good that Wall et al. intended is not reflected in any of the results.

Understandably, the Oxford craniofacial group is exploring reasons, other than for cosmesis, to justify surgery in patients with sagittal craniosynostosis. A previous publication from the Leeds craniofacial service seemed to suggest that at 5 years of age (mean age 64.9 months) patients who have undergone surgery in infancy do better in motoric function compared to the results of preoperative assessment at a mean age of 7.4 months.¹ The unbalanced comparison was made to patients who did not undergo surgery, were a year and a half younger (mean age 42.9 months), and had an initial assessment at mean age of 15 months. Not surprisingly the p value was significant in the surgically treated group. Numerous other papers show conflicting results. If surgery were to be so successful in improving the neurocognitive outcome, we are certain that

studies would have shown a definitive outcome. Wall et al. have acknowledged this controversy and appropriately referred to it in their article.

While we are not opposed to the authors’ presenting their data, we certainly take objection to their suggestion that asymptomatic patients with mild or no scaphocephaly with sagittal craniosynostosis and no papilledema be subjected to a major cranial vault reconstruction without there being any objective evidence of its benefits. Our main concern is that aggressive surgeons will misquote this article in their own defense at conferences and in publications for years to come.

Sandeep Sood, MD
Neena Marupudi, MD, MD
Abilash Haridas, MD
Steven D. Ham, DO

Children’s Hospital of Michigan, Detroit, MI

DISCLOSURE

The authors report no conflict of interest.

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Response

We have read with interest Dr. Sood and colleagues’ correspondence regarding our recent paper published in this journal and welcome the opportunity to further discuss our study.

While we agree that there is a relative lack of normative data for ICP in infancy and childhood, the literature regarding ICP in craniosynostosis has long considered

an ICP of 10 mm Hg or below to be normal, between 10 and 15 mm Hg to be borderline, and above 15 mm Hg to be raised.^{6,15–18} These thresholds, which more closely reflect adult parameters, are greater than those proposed by Minns (upper limits of normal: 3.5 mm Hg in neonates, 5.8 mm Hg in infants, and 6.4 mm Hg in children)¹¹ and were adopted by earlier authors as a discriminator of surgical need.¹⁶ It may be argued that these parameters are unduly low. However, the single largest body of evidence regarding treatment of raised ICP comes from studies of acute brain injury, an admittedly very different pathology. Pediatric and adult brain trauma guidelines indicate that there is reasonable (Level III) evidence for instituting treatment of an ICP of 20 mm Hg or greater,^{3,8} and an “even lower threshold may physiologically make sense for infants and young children.”¹⁸

In craniosynostosis, there is evidence of harm occurring at the parameters as currently defined. In a 1996 study, Tuite and colleagues investigated the correlation between papilledema and ICP and found that of the 15 children with papilledema whom they identified, 9 (60%) had an overnight sleeping mean ICP of between 15 and 20 mm Hg.¹⁷ Moreover, 2 patients (13.3%) had papilledema with a borderline ICP between 10 and 15 mm Hg. This last finding suggests that, in some patients at least, an ICP classified as “borderline” is sufficiently high to cause pathological signs. Therefore, how is one to distinguish between patients in this borderline group? We believe that pressure waveform evaluation is informative.

Abnormal ICP waves are recognized to occur during sleep in both syndromic and nonsyndromic craniosynostosis (summarized by Tamburrini et al. in 2005).¹³ Thompson and colleagues described waves that were characterized by an abrupt increase in mean ICP and wave amplitude which was sustained for up to 30 minutes before waning towards the baseline. These occurred at regular intervals throughout sleep.¹⁶

Renier et al. describe two pathological wave types occurring during rapid eye movement (REM) sleep. The first was a plateau wave with sudden onset and an abrupt termination. The second also had a fast onset, but with a gradual return of the ICP to baseline.¹² Both were characterized by an elevation in mean ICP, with superimposed phasic variations. The mean duration of these waveforms was 11 minutes. Renier also identified a nonpathological third type that presented on a background of a normal baseline ICP; this type was characterized by increased phasic activity, but without an elevation of the mean ICP during the episode.

More recently, Eide and colleagues investigated the frequency and extent of ICP elevations during sleep in a retrospective study of 121 consecutive craniosynostosis patients.⁵ They concluded that a qualitative assessment of ICP elevations greater than 20 mm Hg (typically between 20 and 40 mm Hg) was a more sensitive guide to intracranial hypertension, particularly in borderline cases, than mean ICP.

All 3 groups viewed such ICP elevations or waveforms to be pathological because they occurred most frequently, for the longest duration, and at the greatest amplitude when the sleeping baseline ICP was greater than 15 mm

Hg, less frequently with a borderline ICP, and most rarely when the ICP was less than 10 mmHg.^{5,15,16}

We observe similar waveforms in our own practice. These B-type waves present as rises in mean ICP, with levels between 20 to 50 mm Hg that are typically sustained for at least 5 to 10 minutes, and often longer.¹⁹ Eide and colleagues criticized the identification of B waves in the literature as being subjective, as various authors defined the waves differently, resulting in contention as to what frequency should be considered normal.⁵ We agree with Eide et al. and believe that the problem lies chiefly with the difficulty inherent in capturing and effectively analyzing waveforms of short duration (particularly with older ICP monitoring techniques and systems). In our view, a minimum of 5 minutes' duration is necessary to reliably identify a change in the mean ICP and thus distinguish between pathological and likely nonpathological waveforms (similar to Renier's third type).¹²

We do observe B-type waves, as we describe, occasionally in patients with a sleeping ICP baseline value of 10 mm Hg or less. In 118 ICP recordings performed between 1994 and mid-2012 in our unit, from both preoperative and postoperative sagittal craniosynostosis patients (unpublished data, but including this study's cohort), up to 2 B-type waves were recorded in 23% of patients with an ICP of 10 mm Hg or less. These waves tended to be of lower amplitude and shorter duration than those in patients with higher sleeping ICP baselines. Of those children with an ICP between 10 and 15 mm Hg, 52% had at least 1 B-type wave, with 21% experiencing 4 or more. In the 15–20 mm Hg group, B-type waves were recorded in 83%, with 4 or more occurring in 58%.

Our choice of a threshold of 4 B-type waves or more is based on Renier et al.'s observation that pathological waveforms occurred between 4 to 8 times during sleep at night.¹² They believed that this frequency reflected periods of REM sleep, a hypothesis that had been proven in earlier studies of hydrocephalus and was tested by themselves in 8 patients. Our own observations from combined sleep studies and ICP monitoring support this theory. In the 118 monitoring procedures discussed above, only 1 patient had more than 7 abnormal waves. Of course, the choice of 4 or more waves (i.e., greater than 3, not 3 or more, as Dr. Sood and colleagues suggest) is somewhat arbitrary, as the choice of any threshold is. However, allowing for variations in non-REM–REM cycle length between infants and older children, this threshold should capture most REM periods over a night's sleep, with the view that abnormal wave activity should be observed occurring in most, if not all, REM episodes.

Sood and colleagues rightly draw attention to the importance of CPP. However, the data present in the craniosynostosis literature relating to this are scant. One small study of 11 children published by Hayward and Gonzalez in 2005 demonstrated that CPPs fell dramatically with episodes of raised ICP during REM sleep.⁷ Although all patients in the study had complex craniosynostosis, and most had sleep apnea (which is not the case in sagittal craniosynostosis), there is certainly no good evidence that CPP is not adversely affected by episodes of raised ICP in sagittal craniosynostosis, such as we describe.

Naturally, the interpretation of an ICP recording is not simply a matter of identifying the baseline and counting abnormal waveforms. Other factors that contribute to raised ICP need to be sought and investigated—obstructive sleep apnea being a case in point.

We are concerned that Dr. Sood and his colleagues have interpreted our paper as an argument for corrective surgery in all cases of raised ICP, as defined by the criteria discussed above. This is not the case. The core argument of the paper is based on the finding that in older patients presenting with sagittal craniosynostosis, such as the study cohort, abnormal or raised ICP is relatively common and cannot be accurately predicted by clinical or radiological findings alone. It is for this reason that we advocate the consideration of intraparenchymal ICP monitoring for all patients in whom surgery is not planned.

As Sood et al. acknowledge, 4 (10%) of 39 patients in whom ICP was measured had a sleeping baseline ICP greater than 20 mm Hg, and we would draw the authors' attention to another 2 children with a mean baseline of 20 mm Hg (see Table 2), 15% of the study cohort in total. Even if one accepts Sood and colleagues' proposition that calvarial expansion should only be undertaken in the presence of papilledema (if head shape is aesthetically acceptable), we would still ask them to reflect on whether the knowledge that such a patient had a nocturnal ICP baseline of 20 mm Hg or above would alter their ongoing management of that child. In our study, half of the 6 patients with mean nocturnal ICP values of 20 mm Hg or greater had mild scaphocephaly, and the remainder were not scaphocephalic. These are the very patients whose morphological abnormalities may well be sufficiently mild to not warrant surgery on esthetic grounds alone, and thus they may well be discharged or seen in clinic only occasionally. Not discharging these patients, or instituting more frequent in-depth follow-up and ophthalmological assessments in the light of ICP findings would constitute a change of management.

The complication rate of intraparenchymal ICP monitoring is low, with a relatively benign profile in our experience and that of others.⁵ We are therefore of the opinion that, even accepting the most conservative definition of what sleeping baseline constitutes raised ICP (> 20 mm Hg), the balance of risk is in favor of monitoring.

As this study was not designed to investigate outcomes of our treatment protocols, we did not discuss in the paper our own approach to the surgical treatment of patients with raised ICP. In our unit, ICP data form only part of the evidence considered by the multidisciplinary team (MDT) when planning patient care. Raised ICP, as we have defined it, is not an absolute indication for calvarial expansion.

However, we do not believe that papilledema must be present before surgery is undertaken when the ICP is abnormal. Papilledema appears to be a relatively late sign of raised ICP in younger children. Abnormalities of the visual pathway (as elicited by pattern reversal visual evoked potentials), which correct following surgery, have been identified in the complete absence of papilledema.^{9,10} Tuite et al. found that only 20% of children aged 1–8 years with an ICP of greater than 15 mm Hg had papilledema, yet it was present in all of their older patients with ICPs over the same threshold.¹⁷ The authors hypothesized that difficulties

in examining younger children or protective anatomical differences may account for this aged-related discrepancy. However, it is also possible that over time ICPs that remain elevated through childhood may eventually lead to papilledema in nearly all cases, albeit via an indolent course. It is worth noting that of the 15 patients with papilledema in their study, only 3 exhibited other symptoms of raised ICP. Also, in longstanding papilledema, axonal swelling may subside, being replaced by more subtle examination features,¹ which might be missed in children who are poorly compliant with ophthalmological examination.

Given that papilledema undoubtedly represents harm, waiting to intervene until it is present does not adhere to the maxim of “do no harm.” Indeed, this approach is not dissimilar to a physician declining to treat a patient's raised blood pressure until a cardiac event or a cerebrovascular accident has happened, on the grounds that such outcomes do not eventuate in all patients with a similar blood pressure.

Sood and colleagues suggest that surgical intervention caused harm to the patients in this study. While we do not doubt that calvarial expansion procedures do risk harm in the immediate operative period, we reject their suggestion that the limited outcomes we reported (by way of explanation as to why some patients had further postoperative ICP monitoring) were caused by the surgical procedure itself. Firstly, those episodes occurred on average more than 3 years after surgery. Secondly, as others and we have reported,^{4,5} many of the symptoms of raised ICP are subtle and nonspecific, having a variety of potential medical, developmental, and psychosocial causes. Nothing in our follow-up and investigation of those patients indicated that surgery was a cause.

We do hypothesize that chronically raised ICP during childhood is likely to reduce the eventual intellectual attainment of affected individuals. The evidence for this is mixed, as we discussed. We would suggest, though, that just as papilledema is more common with raised ICP with increasing age and is likely to be preceded by more subtle abnormalities of the visual pathways, so effects impacting other white matter pathways, which are less directly amenable to assessment, might also occur in parallel. It is not a surprise that studies have yet to conclusively test this hypothesis. Most children presenting with sagittal craniosynostosis undergo surgery within the first 18 months of life. If neurocognitive sequelae represent a gradual phenomenon that emerges over the 1st decade or more, then one would not expect to see any clear effect of early surgery within the treated group. One might observe differences in comparison with a control cohort of patients who were not surgically treated, but such groups are rare and would require follow-up over many years. Further, if patients with raised ICP are a minority within a cohort, any more subtle loss of function they suffer may well be obscured by the noise of the group as a whole.

What is more, most investigators that look at neurocognitive development surrounding surgery tacitly assume that the surgical procedure effectively treats raised ICP, when present. There is significant variation in surgical techniques in sagittal craniosynostosis, and, with the notable exception of the Paris group at the Necker Hospital for

Sick Children,^{2,12} most have not looked at ICP profiles in postoperative patients. Our own recently published work on this topic showed that there was a marked difference in the postoperative incidence of abnormal ICP between the two surgical techniques employed in that study.¹⁴

In view of the variety of potential causes of developmental delay, we would not expect to identify a clear correlation between it and raised ICP in our study. However, we do consider that developmental delay, where it is progressive or without a clear cause, in the presence of raised ICP is an indication to undertake a procedure designed to correct the ICP.

Sood and colleagues accept operative intervention “in the patients with significant scaphocephaly, in whom the surgery is justifiable for cosmetic reasons.” We suggest that the evidence for surgery on cosmetic grounds alone in craniosynostosis is limited and no better than that for ICP. What aesthetic threshold should one observe? If one applies the logic of their argument regarding ICP to aesthetic indications, then one should defer any surgical intervention until the patient encounters psychosocial difficulties, such as bullying and stigmatization, with its resulting psychological sequelae.

In the cohort of this study, patients were considered for surgery on a case-by-case basis, taking into account ICP findings, any symptoms or signs of raised ICP, developmental delay, radiological evidence, the extent of cranial deformity (when present), comorbidities, and parental wishes. When the ICP was elevated above 15 mm Hg, and more so at 20 mm Hg or greater, concerns regarding future visual deterioration and neurocognitive development came to the fore in the MDT decision-making process. The limits of our current understanding of these issues and the surrounding evidence were openly discussed with the patient’s family. At lower baseline pressures, which we still viewed to be elevated because of the presence of abnormal waveform activity, the nature of the scaphocephalic deformity, developmental delay, and any other symptoms carried more weight. Although every child with an elevated ICP in this study underwent surgery, there are other patients with different single-suture craniosynostoses under our care and similarly raised ICPs who have not had surgery, but continue to be managed expectantly, because of a different balance between risks and benefits in the MDT’s judgment.

Arguments over the precise indications for surgical intervention should not detract from the core message of our paper that intracranial ICP monitoring is a safe and important step towards the better management of this group of patients.

Steven A. Wall, FCS(SA)
 Gregory P. L. Thomas, PhD, FRCS
 David Johnson, DM, FRCS
 Jo C. Byren, MRCP
 Jayaratnam Jayamohan, FRCS
 Shailendra A. Magdum, FRCS
 David J. McAuley, FRCS
 Peter G. Richards, FRCS

Oxford University Hospitals NHS Trust, Oxford, United Kingdom

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