Connecting raised intracranial pressure and cognitive delay in craniosynostosis: many assumptions, little evidence

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THE hypothesis that restricted skull growth is responsible for neurocognitive impairment (NCI) has a torrid history that can be traced back to the 19th century.²² However, not until 1982 did we see “modern” evidence coupling intracranial pressure (ICP) in children with craniosynostosis and NCI and supporting a causal relationship between the two in the literature.⁵⁶ Given their findings, Renier et al.⁵⁶ recommended that, especially in children with multisuture, complex, or syndromic forms of craniosynostosis, prophylactic vault expansion should be performed no later than the 1st year of life to avoid or at least minimize the degree of NCI for which raised ICP could be responsible—a policy followed by many craniofacial units to this day.⁶⁸

Although it has long been known that raised ICP, whatever its cause, can through optic atrophy lead to impaired vision and even blindness, how secure is the evidence that in the absence of hydrocephalus (whose well-recognized ill effects are not discussed further here) the elevations of ICP recorded in children with craniosynostosis can be responsible for the NCI? Has the situation changed materially since Cohen and Persing wrote in 1996,¹² “The premise that asymptomatic elevations of ICP in craniosynostosis are detrimental to normal intellectual development has been difficult to prove conclusively”? Indeed, in their classic 1982 paper,⁵⁶ Renier et al. were careful to ring the conclusion that their results suggested “such a relation-

ship, but [do] not prove it definitively” with the caveat that increased ICP and low IQ could be two consequences of a third variable.

The subject is of particular importance to the craniofacial surgeon because if the connection between raised ICP and the NCI of children with craniosynostosis lacks a secure evidence base, there exists the real possibility that patients may be subjected to unnecessary surgical procedures with their never-absent risks.

Renier et al.’s “Third Variables”

Several processes have the potential, alone or in combination, to impair neurocognitive function regardless of ICP. They include 1) the direct cerebral effects of any gene mutation or chromosomal abnormality;^{36,86} 2) hydrocephalus¹³ (the number so affected was not given in Renier et al.’s 1982 paper⁵⁶); 3) chronic airway obstruction;⁵³ 4) feeding difficulties and “failure to thrive”; 5) the developmental consequences of impaired vision and/or hearing; 6) low societal and familial expectations, including teasing;⁶⁴ and 7) the ill effects of previous surgical interventions, including those from anesthesia.⁵¹

Further complicating the issue is uncertainty over the normal range of childhood ICP. As Renier et al. also wrote in 1982, “the definition of ‘normal’ and ‘abnormal’ ICP recordings in children raises an initial problem.”⁵⁶ Although the range they proposed (normal < 10 mm Hg, borderline 11–15 mm Hg, and raised > 15 mm Hg) is the one most frequently accepted in craniofacial circles, a close reading of the 3 references they used to support those figures suggests that their upper limit could just as reasonably have been raised to 20 mm Hg. This increase is supported by Avery et al.’s observation, based on lumbar CSF opening pressures in 197 children between the ages of 1 and 18 years who had been investigated for non-CSF pressure-affecting conditions, that “the threshold for an abnormally elevated opening pressure, determined on the basis of the 90th percentile for all patients in the reference population, was 28 cm water (20.6 mm Hg).”⁵

What Evidence Links ICP to NCI in Children With Craniosynostosis?

Clinical Evidence

Clinical evidence of a causal link between ICP and NCI in children with craniosynostosis can conveniently be divided into the direct, which contains numerical data derived from ICP monitoring, and the indirect, which does not contain data derived from monitoring.

Direct Clinical Evidence

In their 1982 paper, Renier et al.⁵⁶ reported the results of ICP monitoring in 75 of 92 children with either single- or multiple-suture synostosis, 55 of whom had also undergone psychometric testing, and stated that “the IQ level decreased slightly when ICP increased” during both slow-wave and rapid eye movement (REM) sleep. An assertion that these frequently referenced findings were causally connected is, however, vulnerable to not only the qualifications already listed (the effects of one or more “third variables”) but also the following criticisms: 1) How the 75 of 92 children were selected for ICP monitoring and the 55 of 75 were selected for IQ testing is not stated. 2) There are no details on the type of synostosis (single vs multiple, for example) in the 55 children who had both their ICP monitored and their IQ measured. 3) The IQ was assessed by a variety of tests that depended on the subject’s age (42 of the original 92 children were 3 years old or younger; see Fig. 1 in Renier et al.⁵⁶) and whether there were “language difficulties.” 4) How many of the 55 children had hydrocephalus is not given.

The same group of authors returned to the subject in 1988⁵⁵ when the total number of children studied had risen to 358 (an increase due, in particular, to the number of children with sagittal synostosis increasing to 118 from 25 in 1982) and when 8 children with hydrocephalus were excluded. Two hundred fifty-eight children underwent psychological testing via a similar variety of methods (again, selection criteria were not stated). Only baseline pressures were discussed, and although the observation of an association between elevated ICP and lower IQ in older children was again cautiously advanced (“seems likely”) on the basis that children who had undergone surgery earlier had a better cognitive outcome than those who had undergone surgery later (see below), no functional benefit from surgical intervention was observed.

Since then we have been unable to find clinical studies causally linking overnight monitored levels of ICP to NCI in children with craniosynostosis. Although Eide et al.’s 2002 study²⁰ included “delayed psychomotor development” among their patients’ symptoms and signs, the authors were careful to point out that “the aim of this study was neither to explore the possible normal distribution of ICP elevations nor to explore possible clinical consequences of sustained intracranial hypertension.”

In a smaller study Eide and Fremming¹⁹ did compare pre- and postoperative ICP monitoring in 15 patients with “a tentative diagnosis of craniosynostosis with or without a hydrocephalic component.” But their uneven patient mix (5 cases also had shunts) coupled with a lack of detail about postoperative courses (outcome information limited

to “good” in 12 of 15 cases) limits the usefulness of their study to this analysis.

In 2007 Eide and colleagues¹⁸ returned to the subject because, as they stated in their introduction, they had found ICP monitoring to be of “questionable value” in craniosynostosis. Included in their retrospective analysis of ICP monitoring in 65 children were 18 patients with craniosynostosis, 10 of whom were subsequently “treated”; the remaining 47 patients had either hydrocephalus or benign intracranial hypertension, and details of the sutures involved in the craniosynostosis group were not given. The authors generally concluded that “the mean ICP wave amplitude (not mean ICP) was increased in those that improved from clinical symptoms/findings after treatment,” but the lack of precise information about the selection and management of the children studied makes it impossible to draw particular conclusions about the level of ICP, if any, that may be harmful to a child with craniosynostosis.

Another way to clinically demonstrate a causal link between ICP-monitored increased ICP and NCI is to look for evidence of symptomatic improvement following procedures aimed at reducing that pressure, for example, as seen in hydrocephalus following shunt insertion. However, in an expanded 1988 study of ICP monitoring in children with craniosynostosis, Renier and Marchac⁵⁵ observed no functional benefit from surgery, concluding for their 66 patients with “North African oxycephaly” (a conveniently stereotyped combination of bicoronal and sagittal synostosis) that “operations were likely to stop the worsening of the mental impairment, but did not seem to correct already impaired intelligence” and that “surgery does not improve the [IQ] once it is already impaired.”

A similar conclusion was drawn by Arnaud et al.⁴ in a study of “mental outcome” in 99 children with “isolated” brachycephaly, a proportion of whom had the *FGFR3* mutation and less than half of whom had both pre- and postoperative evaluations; these children were surgically treated “to prevent mental impairment caused by the intracranial hypertension,” although no ICP details were given. “Surgery did not improve a child’s mental status but may prevent deterioration in mental function.”⁴ Indeed the strongest predictor of postoperative mental outcome was a child’s preoperative evaluation ($p < 0.0001$).

Indirect Clinical Evidence

Effects of ICP-Lowering Procedures. Improvement in NCIs following ICP-lowering surgery even when monitoring has shown raised ICP has already been discussed. Nevertheless, there can be few craniofacial surgeons who have not listened with satisfaction to parental reports of a gratifying leap in their child’s development following some form of intervention designed to lower ICP even in the absence of monitoring confirmation that the ICP was elevated. Such surgery may have been performed when the clinical evidence of increased ICP was strong (in the presence of papilledema,⁷⁶ for example) or weak (in the presence of behavior changes or headaches, for example; both can be absent in children with syndromic synostosis even when ICP is known to be high,⁷ and “no direct correlation exists between the degree of pressure elevation and the presence of headache”⁶⁵).

The commonly drawn conclusion is that such improvements are evidence that the ICP must have been both raised and responsible for any preoperative issues. Perhaps, but such anecdotal evidence—in the absence of input from independent developmental pediatricians and/or neurologists—should be treated with caution as it could represent no more than the normal stepwise pattern of childhood development bolstered by the placebo effect of a major cranial procedure and the possible cognitive bias of surgeons assessing their own results.

Early Versus Late Studies. Much clinical evidence, both direct and indirect, put forward to support a causal link between the deleterious effect of raised ICP and the NCIs of children with craniosynostosis (complex^{4,54,55} and single suture⁵²) has depended on the different outcomes in children surgically treated “early” (usually under 1 year) compared with those surgically treated “late”—the assumption being that if the early cohort has the better outcome, the difference must be attributable to the preventative effects of their earlier surgery, with the late cohort having been exposed to a longer period of raised ICP. For example, according to some authors, “the younger the patient is at the time of surgery, the better the results,”⁵⁵ and even if NCI does not improve, at least “surgery halts this regression (due to raised ICP).”⁵⁵

The vulnerability of the early versus late argument lies in its dependence on the 2 cohorts being identical in all respects except their age at surgery. But assuming that the children are undergoing surgical treatment at a similar interval following their presentation to the craniofacial unit, there exists the strong possibility that the indications for their referral will not have been the same. For example, the early children are likely to have been first identified and then referred because of the severity of their phenotype, while the late children may not have attracted concern until some other problem arose, for example, a delay in their development. Such a difference will clearly impact the incidence of developmental issues in the late cohort regardless of whether such problems could have been avoided by earlier surgery and thus will account both for the failure of surgery to improve cognitive outcome and for the fact that the strongest predictor of postoperative mental outcome is a child’s preoperative evaluation.⁴

The possibility of this error was recognized by Bottero et al.⁸ in their study of cognitive outcome in metopic synostosis, which promoted a beneficial relationship between NCI and age at surgery: “It is possible that developmental delay in itself may have resulted in parents seeking medical attention and this causing bias in the present study.”

Selection bias may have also influenced the results of a large study of children with Apert syndrome⁵⁴ that pointed to a better cognitive outcome not only for those undergoing cranial vault surgery early as opposed to late, but also for those not previously institutionalized.

That is not to say that early surgery has no effect on the NCI outcome in children with craniosynostosis, merely that early versus late surgery evidence is open to questions that can only be satisfactorily answered by matching the children with their reasons for presentation and by using age-matched control children without synostosis, as

has been done for children with single-suture synostosis (SSS).^{51,67,70,81}

“Theoretical” Evidence

Studies of Cerebral Blood Flow

The hypothesis that any ill effects of non-hydrocephalus-associated raised ICP are mediated through a state of relative ischemia secondary to impaired perfusion accounts for the large number of published studies on cerebral blood flow (CBF) in children with craniosynostosis—and the variety of techniques that have been employed. In the absence of the more direct methods available in the experimental situation, various substitutes (proxies) have been used, but the results to date have not proved helpful in reliably identifying states of significant underperfusion. Such indirect methods include transcranial Doppler (TCD) ultrasonography,^{34,35,50,84} single-photon emission computed tomography (SPECT),^{11,15,60–62} perfusion-weighted MRI (unpublished data, Paternoster et al., 2013),^{42,73} near-infrared spectroscopy,⁴⁷ and positron emission tomography (PET).¹⁴ Case numbers are small, however, and the results do not provide convincing evidence of reductions in CBF that can be linked to NCI. Only Horínek et al.,³⁴ in their investigation of 21 children with scaphocephaly (without ophthalmic or radiological evidence of raised ICP), attempted to link various TCD-derived blood flow velocity indices to actual ICP measurements (recorded as lumbar puncture [LP] pressures) but they found no such correlation, leading them to conclude that TCD “is not a reliable tool in predicting abnormal LP values.” Near-infrared spectroscopy is a promising method, but in Martini et al.’s⁴⁷ recent study in 22 children (aged 3–12 months) with a variety of nonsyndromic suture fusions, the possible presence of raised ICP preoperatively was inferred from hemodynamic changes observed during and after surgery rather than diagnosed clinically or from actual measurement.

Autoregulation

The brain has no capacity to store glucose and to function properly requires a constant supply of oxygenated, glucose-laden blood to match its changing metabolic needs. This supply is protected against variations in both arterial blood pressure (ABP) and ICP by the physiological processes of autoregulation. Therefore, the question is whether cerebral autoregulation is effective over the range of ICPs (baseline and plateau waves) observed in children with craniosynostosis.

Baseline pressure can be thought of as a “steady state” upon which plateau waves of higher ICP are superimposed. Contributors to an elevated baseline in craniosynostosis include, in the absence of hydrocephalus, craniocerebral disproportion (particularly for those younger than 1 year^{24,63}) and chronic venous hypertension (with or without an obstructed airway).^{23,30,57,59} Studies that quote mean baseline levels^{20,56,75} report pressures that rarely rise above 20 mm Hg—the level below which pediatric intensivists aim to keep their head-injured patients’ ICP.²⁵ In a study on the effect of raised ICP (and airway obstruction) on the cerebral perfusion pressure (CPP) of children with syndromic craniosynostosis,³¹ 2 patients had baseline pressures of around 26 mm Hg during quiet sleep (see their Fig. 2), while the

remaining patients all had baseline pressures below 20 mm Hg. Although plateau waves may rise to double the baseline ICP, available evidence suggests that it is unusual for their height to exceed 50 mm Hg ("In children evaluated for . . . craniosynostosis, ICP elevations of 50 mm Hg or above are seldom observed";²⁰ see also Figs. 6, 8, and 9 in Renier et al.⁵⁶ and Fig. 1 in Renier and Marchac⁵⁵).

In Renier et al.'s 1982 study,⁵⁶ the plateau waves rose to a mean of 48 mm Hg in patients with an already elevated baseline ICP (2 of the 75 patients with peaks of 70 mm Hg, 1 with a peak of 60 mm Hg, and the rest with a peak of or below 50–55 mm Hg; see Figs. 8 and 9 in Renier et al.⁵⁶). Whittle et al.⁸⁵ illustrated a rise to around 50 mm Hg in a child with multiple suture closures and the recurrence of raised ICP despite previous ICP-lowering surgery. In our study of CPP,³¹ ICP during active sleep rose to as high as 56 mm Hg in 2 patients. The remaining 9 patients had pressures that rose to between 26 and 50 mm Hg.

Is cerebral autoregulation active in children with craniosynostosis and raised ICP, and can it "cope" with the pressures quoted above? Several pieces of evidence (summarized here) suggest the answer to both questions is yes.

Lundberg's original proposition—that the rapid rise and subsequent resolution of plateau waves in patients with raised ICP due predominantly to brain tumors were the result of an unstable "cerebrovascular control system" ("The autoregulation of the cerebral blood flow may cause a lot of havoc if the capacity for spatial buffering is impaired."⁴⁶)—has since been confirmed experimentally by, among others, Rosner and Becker,⁵⁸ who showed that the presence of plateau waves is itself an indication of a functional autoregulation system. Of particular relevance to patients with craniosynostosis was their observation that such plateau waves could be precipitated by hemodynamic events on the venous as well as the arterial side of cerebral circulation. Rosner and Becker⁵⁸ also suggested that as long as ICP did not rise above the normal cerebral autoregulatory range (as confirmed by the presence of plateau waves), any accompanying fall in CBF would be slight, describing it as "relatively normal."

Although most studies of cerebral autoregulation have concentrated on the response to fluctuations in BP as opposed to ICP, "compensation for changes in perfusion pressure due to changes in ICP is similar to that due to changes in arterial pressure. However the lower limit for autoregulation may be lower in the case of elevated ICP."⁹

Although recorded decreases in CPP to as low as a mean of 32.6 mm Hg in a study of children with syndromic craniosynostosis³¹ might imply that the limits of autoregulation had been exceeded, the lack of any compensatory rise in BP ("elevations of ABP appeared modest and remained within the normal limits for age") suggests that the limits had not been exceeded. Cerebral vasodilation, as well as the increase in cerebral blood volume for which it is responsible (the final common pathway for ICP plateau waves whatever the underlying pathology), is in craniosynostosis a primary rather than a secondary phenomenon due to the rise in PaCO₂ (hypercapnia) related to the airway obstruction that occurs particularly during REM, or active, sleep.²⁶ The extreme sensitivity of the cerebral arterioles to such alterations in PaCO₂ ("cerebral blood flow

increases linearly by 2%–4% per mm Hg PaCO₂ within the range of 25–75 mm Hg, making PaCO₂ the most potent physiologic cerebral vasodilator"⁷⁷) is a further indication of a functioning autoregulatory system.

Hayashi et al.²⁸ used a qualitative CT-derived method for assessing CBF in 5 adults (including 2 with idiopathic intracranial hypertension [IIH], a condition with interesting parallels to craniosynostosis) and recorded plateau waves with pressures of 74–90 mm Hg. However, CBF fell by a more limited 20%–30%, demonstrating how even at levels of ICP that exceed those reported for craniosynostosis, cerebrovascular autoregulation was able to mitigate much of their potential effect.

A case report⁴⁰ of PET studies performed in an adult with IIH showed that during plateau waves that rose as high as 88 mm Hg ($\pm$ 7 mm Hg), there was no reduction in CBF despite marked decreases in CPP (and no compensatory elevations in mean BP).

Experimental evidence in primates suggests that CBF (measured by xenon clearance) remains constant up to ICP levels of 50 mm Hg³⁷ and even 60 mm Hg³⁸ because of a mixture of systemic vasoconstriction (that elevated mean ABP) and cerebral vasodilation—in other words, an effective autoregulatory system.

In brief, the evidence (clinical, experimental, and theoretical) does not support the hypothesis that the levels of baseline ICP and plateau waves observed in patients with craniosynostosis exceed the limits of a normal autoregulatory system—assuming that the various genetic mutations associated with this condition have not had a direct effect upon it.

Venous "Back Pressure"

It is theoretically possible that the increased venous back pressure that is an important contributor to nonhydrocephalus-associated raised ICP in children with craniosynostosis could affect cerebral perfusion and impair cerebral function independent of any rise in ICP, for which it is also responsible. Such ill effects are well recognized with, say, aneurysms of the great vein of Galen when it can be responsible for diffuse subcortical white matter calcification and atrophy as well as reduced diffusion in areas of acute ischemia or infarction.⁶ In that situation, however, the brain's venous system is exposed to actual or near arterial pressures, whereas in complex craniosynostosis it can be assumed that venous back pressure will be similar to that observed in achondroplasia and venous sinus thrombosis—associated IIH (see below).

The effect of extracranial venous obstruction on intracranial venous pressure was investigated in 15 anesthetized children without craniosynostosis and again in 8 when they were awake.²⁷ Following bilateral internal jugular vein compression (mimicking skull base venous outflow obstruction), sagittal sinus pressure (SSP) rose to 26 mm Hg in awake supine children, decreasing to 17 mm Hg when the children were upright (details taken from Fig. 4 in Grady et al.²⁷). These results are similar to those described by Sainte-Rose et al.,⁵⁹ who, in 4 children with either craniosynostosis or achondroplasia in whom angiography had demonstrated obstruction to cranial venous outflow, recorded SSPs of around 25 mm Hg.

Given the common contribution of venous hypertension to the raised ICP observed in children with achondroplasia and benign intracranial hypertension or IIH (conditions not associated with NCI; see below) as well as those with complex or syndromic craniosynostosis, it appears unlikely that the levels recorded are sufficient to adversely affect cognitive function.

Age-Related Susceptibility of the Brain

Although it is often stated that the plasticity of the young brain allows it to “cope” with injuries capable of producing significant deficits in older children, this may not be so.⁷⁸ The age-related susceptibility of a child’s brain has been well demonstrated recently in a large retrospective study³ that recorded the particular vulnerability of the brain of children younger than 3 years to a variety of insults, including ischemia and trauma. This supports Hebb’s hypothesis³² that “an early injury may prevent the development of some intellectual capacities that an equally extensive injury, at maturity, would not have destroyed. Some types of behaviour that require a large amount of brain tissue for their first establishment can then persist when the amount of available tissue has been decreased. More fibres are necessary (for the first establishment of an assembly) than for its later function.”

In our study of children with Apert syndrome, raised ICP was identified at an average age of 18 months in the 20 children who developed it.⁴⁸ In our study of Crouzon syndrome, raised ICP requiring some form of intervention occurred in 30 of 49 children at an average age of 1 year, 5 months (range 4 months–6 years, 4 months), with recurrence most likely in those in whom the rise was first diagnosed at under 1 year of age.¹ Ten of the 11 children in Gonzalez et al.’s study on the interaction between ICP and respiratory obstruction were younger than 3 years—3 were under 1 year of age.²⁶ Of the 21 children in our study on anomalous venous drainage in children with craniosynostosis and raised ICP, only 4 were over 3 years old—and 6 were under 1 year.⁷⁴ These are ages when (particularly during the 1st year) there is in progress the combination of rapid myelination, dendritic arborization, and synaptogenesis responsible for the most rapid period of brain growth.

It is also possible that at just these ages the brain could be particularly vulnerable to reductions of oxygen tension. In our study of ICP in 11 patients with upper airway obstruction, however, the mean oxygen saturation (SaO₂) was 96% (SD 1.9%) in quiet sleep and 95% (SD 2.2%) in active sleep, although in the 8 children with moderate or severe upper airway obstruction, dips in SaO₂ tended to be deeper and more frequent.²⁶

It appears unlikely that age-related vulnerability in children with craniosynostosis is related to age-related variations in autoregulation. According to one study, “data from healthy anesthetized children suggest that CO₂ vaso-reactivity is higher in children than in adults.”⁷⁷ In a study that used TCD ultrasonography during low-dose sevoflurane anesthesia to investigate cerebral autoregulation in 52 children ages 6 months–14 years and compared it to that in 12 adults, Vavilala et al.⁸⁰ found “no age-related differences in autoregulatory capacity [and] no differences in autoregulatory capacity between children and adults.” In

a complementary study⁷⁹ (this time in 53 children ages 6 months–14 years) of the lower limits of autoregulation as well as autoregulatory reserve, the authors concluded that “increasing age appears to confer some margin of safety against cerebral hypoperfusion,” but they attributed this to “physiologically normal age-related increases in MAP [mean arterial pressure]” rather than any age-related variability in autoregulatory abilities.

Raised ICP and Cognitive Function in Related Conditions

The pathophysiological processes underlying the elevations of ICP in patients with, for example, craniocerebral trauma, tumor, or ischemia are not the same as those responsible for non-hydrocephalus-related elevations occurring in craniosynostosis. For example, in craniosynostosis the brain and its vascular system have not undergone any damage (direct or indirect), there are no mass-related forces acting upon them, and (assuming the relevant mutation has no effect upon the cerebral vasculature) there is normal cerebral autoregulation.

To examine further the link between ICP and NCI, it is therefore instructive to examine 2 other conditions in which the pathophysiological processes responsible for elevating ICP overlap with those found in craniosynostosis, in particular, anomalous intracranial venous drainage^{23,57,59,74} and upper airway obstruction²⁶ during REM, or active, sleep: IIH and achondroplasia.

Idiopathic Intracranial Hypertension

A major sinus obstruction was present in 50% of children in a recent study¹⁷ of pediatric patients with IIH. Although ICP can reach levels that, if not relieved, can cause papilledema leading to optic atrophy and severe visual loss, impaired cognitive function has not been described.^{2,44,66,69,87} That is not to say that IIH arising in childhood does not affect NCI—it may not have been looked for, as it has been in a study (in adults) by Yri et al.,⁸⁸ who found that “patients with IIH performed significantly worse than controls in four of six cognitive domains. . . . Despite marked improvement in ICP (measured at LP) and headache, re-examination showed persistent cognitive dysfunction 3 months after diagnosis and start of treatment.” It could also be relevant that the median age of the children in the pediatric IIH study¹⁷ was 12.4 years (range of 0.6–17.1 years), whereas raised ICP in children with craniosynostosis tends to occur much earlier (as detailed above).

The lack of a recorded connection between ICP and NCI in the many studies of children with IIH does suggest, however, that the level of ICP needed for the production of papilledema lies below the level with the potential to affect the brain.

Achondroplasia

During their early years, children with achondroplasia (like many synostosis-related syndromes also due to a mutation in the *FGFR* “cascade”—*FGFR3*¹⁶) can run elevated ICP (including plateau waves) due to a combination of venous hypertension and upper airway obstruction.^{39,59,71} It is not, however, a condition associated with impaired cognitive development. “Children with achondroplasia usually have normal intelligence unless there are neurologic

complications related to hydrocephalus, head injury, or impaired respiratory function such as sleep apnea with hypoxemia.”⁷³ Indeed, any delay in their language development is more likely attributable to the middle ear problems to which they, like children with syndromic synostosis, are particularly vulnerable.¹⁰

Although a small proportion of children develop hydrocephalus sufficient to require some form of CSF diversion (ventriculoperitoneal shunting or endoscopic third ventriculostomy),^{43,72} most do not.

In summary, any elevation in nonhydrocephalus-related ICP falls below levels sufficient to impair either vision or NCI in children with achondroplasia.

Linking NCI to the Ophthalmic Effects of Raised ICP

It would greatly assist the management of the child with craniosynostosis if, given the uncertainties over the possible harmful cerebral effects of (nonhydrocephalus-related) raised ICP, clinicians could use the ICP level capable of producing papilledema as the threshold above which intervention should be considered. This would allow such decisions to be made on ophthalmic grounds alone in the knowledge that the brain would also be protected.

Evidence for what this level is can, in fact, be extracted from a study by Tuite et al.⁷⁶ that investigated the sensitivity (low for children under the age of 8 years) and specificity (high at all ages) of papilledema as an indicator of raised ICP (using the 1982 “Paris” criteria⁵⁶) in children with craniosynostosis. In 15 children with papilledema (out of a total of 122), baseline sleeping pressures ranged from 13 to 24.8 mm Hg, with an average of 17.5 ± 3.2 mm Hg. Similar figures were reported by Eide et al.,¹⁸ who found “a significantly higher mean ICP in those with papilledema (12.1 vs 10.4 mm Hg).” These results fit with the observations of Walsh et al.,⁸³ who simultaneously performed funduscopy and measured lumbar CSF pressure in patients with normal ICP. Retinal venous pulsations, a presumed precursor of papilledema,⁴⁹ ceased when CSF pressure exceeded 15 mm Hg.

Unfortunately, the assumption that an ICP capable of producing papilledema is the same as that with the potential to harm the brain fails to take into account the very different pathophysiological mechanisms involved,^{29,45} the variable anatomy of the optic nerve sheath, and the effects of (mutated) *FGFR2* receptors described within it⁴¹ and, of course, its low sensitivity in children under the age of 8 years.

In brief, although the presence of papilledema is always an indication for considering some form of ICP-lowering intervention, its absence (particularly in children under 8 years of age) tells us nothing further about whether (in the absence of hydrocephalus) an ICP considered to be elevated as a result of ICP monitoring is or is not capable of putting the neurocognitive development of the child with craniosynostosis at risk.

Discussion

It would appear that there has been little change in our knowledge of the causal connection between ICP and NCI

in children with craniosynostosis since Cohen and Persing’s 1998 statement¹² quoted in the introduction. This does not mean that, because such a connection is difficult to disentangle from the effects of the many other factors capable of affecting the NCI of children with, in particular, syndromic craniosynostosis, it does not exist. Indeed, given its plausibility as a hypothesis, one could reasonably argue that in the absence of more definite evidence either way, it is in the best interest of affected children to assume that it does. However, this does not mean that the topic should not be subjected to critical scrutiny, especially since the many uncertainties we have described could make patients vulnerable to the potentially injurious effects of both overdiagnosis and overtreatment.

A definitive resolution of these uncertainties could only come from a prospective study (incorporating matched controls) of children with syndromic and/or complex forms of craniosynostosis similar to those described for SSS. But given the small number, phenotypic variability, and complexity of so many complicating “third variables,” such a study is unlikely ever to be performed, and thus the craniofacial community will continue to look for clinical guidance based on the linking together of often small observational studies in the hope that a more securely evidence-based management algorithm will eventually emerge.

From a practical point of view, however, what weight should be given to a nonhydrocephalus-associated baseline ICP of 20 mm Hg and intermittent rises to (say) 30 or so mm Hg in the absence of ophthalmic compromise and/or a tense and bulging fontanelle (or craniectomy defects) recorded in a child 3–4 years old with Crouzon syndrome who presents with such low-specificity symptoms as headache and behavior change? The evidence reviewed here suggests that when counseling parents in such a situation, the fragility of the evidence that a never-risk-free vault-expanding operation will not only relieve symptoms but also “protect the brain” against future pressure-induced ill effects should be made clear and the professional advice tempered accordingly.

There are 2 clinical situations for which this question has particular relevance: the policy of recommending some form of vault expansion at presentation for all children with syndromic craniosynostosis and the use of routine ICP monitoring for all children with unsutural synostosis whose parents have declined reconstructive surgery on primarily appearance-changing grounds.”^{21,82}

Routine Vault Expansion for Syndromic Craniosynostosis

The causative role of increased intracranial pressure . . . has led to a policy of early intervention before 1 year of age.⁴

The justification for this policy is that even if ICP is not raised when the child first presents, its increase can be predicted with sufficient certainty to justify early (usually in children under 1 year of age) intervention—or if the syndrome is not usually associated with raised ICP (Saethre-Chotzen and Muenke syndromes, for example), a fronto-orbital reconstruction will “cover” that rare possibility while hopefully providing long-term cosmetic benefits.

The problem with any prophylactic intervention is that

to demonstrate its benefit, it is necessary to know when the event to be avoided would otherwise have occurred—and then (after the necessary length of time has elapsed) to show that surgery (say) has significantly reduced its incidence.

But not all children with syndromic or complex forms of craniosynostosis will develop raised ICP, not all who do need vault expansion to reduce it, and prophylactic treatment will not necessarily prevent recurrence. In our study of Crouzon syndrome, 19 (39%) of 49 children did not develop raised ICP while under regular observation in our unit.¹ Of those who did (at an average age of 1 year, 2 months), 16 had a single episode while 14 had multiple episodes. The causes of a first episode (as reflected in their management) were hydrocephalus in 8 patients and airway obstruction in 3; in the remaining 19 patients, the presumptive diagnosis was venous hypertension. Causes (excluding shunt blockage) of recurrent raised ICP were venous hypertension in 5 patients and upper airway obstruction in 1. A second recurrence due to venous hypertension (2 patients) and a combination of venous hypertension and airway obstruction (1 patient) was seen in 3 patients. In our study of Apert syndrome, raised ICP was identified at an average age of 18 months in 20 of 24 children, leaving 4 in whom a policy of “routine” vault expansion would have been unnecessary (at least in terms of ICP control).⁴⁸

ICP Monitoring of Children With SSS

We do not intend to air here the arguments for and against the possible contribution of raised ICP to the incidence of cognitive impairment in children with neither mutational nor chromosome-related SSS, except to state that such a connection has yet to be confirmed by age-matched control studies and that much of the evidence advanced in favor of such a connection has relied on evidence derived from early versus late studies whose weakness has already been discussed.

However, it has been suggested that children with either sagittal synostosis⁸² (in a study in which ICP was considered raised if it was > 15 mm Hg) or unicoronal synostosis²¹ (when ICP was considered raised if it was > 20 mm Hg) whose parents have declined surgical intervention should, even in the absence of papilledema, have mandatory ICP monitoring with a view to calvarial remodeling when the ICP was found to be raised.

Given that neither invasive ICP monitoring nor calvarial surgery is free of small but quantifiable risks to the brain and that a study on sagittal synostosis⁸² (in which the mean age of the patients was 56 months) reported no benefits from intervention, such a policy would appear vulnerable to challenge for several reasons, including uncertainty over not only the natural range of childhood ICP but also what danger, in the absence of papilledema, a baseline pressure of 15–20 mm Hg actually represents.

Conclusions

Given that the “natural” range of childhood ICP (which may well extend to 20 mm Hg) and the particular pattern of the pathophysiology responsible for elevating ICP in craniosynostosis both remain unknown, the evidence that

levels frequently accepted as elevated can be responsible (in the absence of hydrocephalus) for cognitive impairment is weak at best. In addition, not all children with syndromic or complex forms of craniosynostosis have raised ICP, and for those who do, intervention to reduce it does not always require vault expansion. As a consequence, the present level of uncertainty should always be made clear when the relative benefits and risks of an ICP-lowering surgical procedure are discussed with the parents of a child with craniosynostosis, and the arguments in favor of routine vault expansion for children presenting with syndromic or complex forms of craniosynostosis, or of ICP monitoring for children with SSS whose parents have declined surgical intervention, are open to serious question.

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Disclosures

The authors report no conflict of interest.