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. 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. Given their findings, Renier et al. 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.

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 and NCI can be responsible for the NCI? Has the situation changed materially since Cohen and Persing wrote in 1996, “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, Renier et al. were careful to ring the conclusion that their results suggested “such a relationship, 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;26,36 2) hydrocephalus (the number so affected was not given in Renier et al.’s 1982 paper); 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.

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.” 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).”

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BROCA’S AREA
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. 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 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 1988 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 study 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 Fremming 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 colleagues 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 Marchac 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. 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.” 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, 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, and “no direct correlation exists between the degree of pressure elevation and the presence of headache”).

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