Journal of Cranio-Maxillo-Facial Surgery 47 (2019) 158–164

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Reliable manifestations of increased intracranial pressure in patients with syndromic craniosynostosis

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ARTICLE INFO

Article history:
Paper received 9 April 2018
Accepted 15 October 2018
Available online 12 November 2018

Keywords:
Syndromic craniosynostosis
Crouzon syndrome
Increased intracranial pressure (ICP)

ABSTRACT

Purpose: Systematic examination of increased intracranial pressure (ICP) is important during the follow-up period after surgical repair of syndromic craniosynostosis. In these patients, postoperative progress can be unclear due to the involvement of multiple sutures and the high incidence of relapse due to the progressive nature of the disease and to genetic variability. In this study, we investigated the clinical manifestations of increased ICP in syndromic craniosynostosis patients before and after surgery.
Materials and methods: We collected pre- and post-operative data from patients with syndromic craniosynostosis from January 2004 and December 2014 on the clinical manifestations of increased ICP, namely, the presence of 1) subjective symptoms, 2) visual disturbances and papilledema, 3) thumb-printing phenomenon (beaten copper appearance) on skull x-ray, and 4) hydrocephalus on computed tomography.
Results: A total of 17 syndromic craniosynostosis patients were included in this study, and three distinct patterns of disease progress were noted. Among all patients who underwent cranioplasty, the significant finding with regards to clinical manifestations was amelioration of the beaten copper appearance on skull x-ray after surgery. Likewise, among patients with recurrent increased ICP during the postoperative follow-up period, numerous clinical manifestations were noted, including subjective symptoms (33.3%), papilledema (50%), ventricular dilation (66.6%), and a beaten copper appearance on skull x-ray (100%).
Conclusion: Close monitoring to detect increased ICP is important during follow-up of patients with syndromic craniosynostosis. Among non-invasive methods for indirectly assessing ICP post-operatively, a beaten copper appearance on skull x-ray may be a reliable indicator of increased ICP.

1. Introduction

Traditionally, the clinical manifestations of increased intracranial pressure (ICP), which are seen most often in the early years of life in patients with craniosynostosis, occur during the period of rapid brain growth. Clinical observation of increased ICP in these patients is an important indication for surgical intervention, such as release of abnormal sutures and remodeling/expansion of the cranial vault (Renier et al., 1982; Gault et al., 1992). In simple and non-syndromic forms of craniosynostosis in which the deformity is confined to the cranium, the effects of cranial expansion surgery on ICP are predictable to a certain extent. In contrast, the response to surgery is less certain in patients with syndromic craniosynostosis involving multiple sutures because of the progressive etiology and genetic variability of the disease, and there is a high rate of relapse in these patients (Thompson et al., 1997; Kim et al., 2017). In addition, progressive postnatal craniosynostosis, in which multiple-suture craniosynostosis develops postnatally despite the presence of normal sutures and skull shape during infancy, and secondary craniosynostosis, referring to post-surgical development of synostosis in previously opened sutures, are identified not infrequently among syndrome patients (Connolly et al., 2004; Kim et al., 2017). In some cases, persistent abnormal ICP may be adequately addressed through cranial expansion surgery or shunting (Thompson et al., 1997), highlighting the need for systematic and thorough examination to detect increased ICP.

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https://doi.org/10.1016/j.jcms.2018.10.021
1010-5182/

Direct measurement of ICP is too invasive for practical use in a clinical setting during routine follow-up (Wiegand and Richards, 2007). Using lumbar punctures as an alternative, indirect measurement of ICP has been introduced but tends to provide an overestimate, while other methods, such as evaluation of visual-evoked potentials and optic nerve sheath diameters, have not been fully developed (Wiegand and Richards, 2007; Cartwright and Igbaseimokumo, 2015). Thus, there are currently no non-invasive methods for accurately assessing ICP that can be used by surgeons during the follow-up period. Several reliable methods for assessing increased ICP clinically have been identified, including subjective signs and symptoms, ophthalmologic examination, and radiologic findings. However, previous studies have described outcomes following surgery in syndromic craniosynostosis, with most focusing on assessment of postoperative cranial shape based on the Cranial Index or Whitaker Classification and reporting surgical outcomes or reoperation incidence during the follow-up period. To the best of our knowledge, there have been no studies to date demonstrating the specific changes in clinical manifestations that occur in the context of increased ICP, which, in addition to esthetic considerations, is regarded as a critical factor in determining whether surgical intervention or re-intervention is required. Thus, in the present study, we investigated the clinical manifestations that occur in conjunction with increased ICP in syndromic craniosynostosis patients before and after surgery. In addition, we investigated whether any of the clinical manifestations evaluated during the postoperative follow-up period could serve as reliable markers of increased ICP, and reviewed the current literature.

2. Material and methods

After institutional review board approval, we retrospectively reviewed data from patients who were referred to our institution for evaluation and treatment of syndromic craniosynostosis during the period from January 2004 to December 2014, and for which at least 3 years of follow-up data was available. Patient medical records were reviewed for demographic data, medical/surgical history, age at presentation, classification of the craniofacial syndrome, involved suture(s), skull phenotype, presence of growth and developmental delays, presence of mid-face deformities, surgical data, and complications related to the initial operation.

2.1. Treatment and follow-up principles

All patients were examined by a multidisciplinary craniofacial team consisting of a neurosurgeon, plastic surgeon, ophthalmologist, pediatrician, and social worker. If surgery was indicated, patients underwent either cranial vault remodeling with bilateral fronto-orbital advancement (FOA) or distraction, performed by the senior author. Typically, we performed open osteotomy for synostosis correction and fixation with resorbable plate osteosynthesis; however, in a few cases, we used posterior distraction osteogenesis in order to minimize the extent of the procedure. When recurrence of increased ICP was identified during the follow-up period, surgical intervention took place in the form of a cranioplasty performed by a plastic surgeon, or an endoscopic third ventriculostomy (ETV) or ventriculo-peritoneal shunt (VPS) performed by a neurosurgeon. The specific intervention was determined by considering the patient's general condition and age.

2.2. Follow-up and assessment of clinical manifestations of increased ICP

Routine evaluation of syndromic craniosynostosis patients was performed based on the clinical manifestations of increased ICP, which included four categories: 1) presence of subjective symptoms, such as headache, vomiting, and irritability; 2) presence of visual disturbances or papilledema on ophthalmologic examination; 3) presence of a diffuse thumbprinting phenomenon (beaten copper skull) on skull x-ray; and 4) ventricular dilation or reduced intracranial volume on computed tomography (CT), which is indicative of hydrocephalus. After initial cranial vault expansion surgery or a neurosurgical procedure, patients were routinely followed up by a neurosurgeon and plastic surgeon approximately 6 and 12 months after the initial surgery and annually thereafter. Radiologic follow-up was performed using skull radiographs or CT with three-dimensional reconstruction in order to detect synostosis relapse and secondary synostosis, which was defined as closure of other sutures that were previously open after the initial cranial vault expansion (Kim et al., 2017). Patients who underwent surgical correction for increased ICP were classified into two groups: one consisting of patients with recurrent clinical manifestations related to increased ICP postoperatively, and the other consisting of patients without evidence of increased ICP and who displayed favorable postoperative progress.

3. Results

During the 10-year study period, a total of 17 syndromic craniosynostosis patients who met the inclusion criteria were identified at our institution. All except two patients (one with Pfeiffer syndrome and one with Saethre-Chotzen syndrome) were diagnosed with Crouzon syndrome. With respect to the involved sutures, 12 patients had pan-craniosynostosis, two patients had bilateral coronal synostosis, and the remaining three patients had unilateral lambdoid synostosis with or without sagittal involvement.

Based on the treatment and postoperative progress of these patients, we discerned three distinct groups. Specifically, Group A consisted of 8 (47.0%) patients diagnosed with syndromic craniosynostosis who showed definite manifestations of increased ICP, underwent cranial vault remodeling, and exhibited favorable progress without recurrent manifestations related to increased ICP up to 7 years postoperatively. Group B consisted of six (35.2%) patients with recurrent clinical manifestations of increased ICP during the post-operative follow-up period. Finally, Group C consisted of three (17.5%) patients with no definite manifestation of increased ICP initially despite a diagnosis of syndromic craniosynostosis with premature suture(s), and who underwent only surgical correction for a mid-face deformity, such as Le Fort III distraction osteogenesis (Fig. 1). Among patients who underwent cranioplasty (Groups A and B), the age at time of surgery ranged from 7 months to 11 years, 13 patients (92.8%) underwent conventional cranial vault remodeling, and one patient underwent posterior distraction osteogenesis (Table 1). Preoperatively, among the patients in Groups A and B who underwent cranioplasty, the rates of preoperative ventricular dilation, papilledema, and subjective symptoms, such as headache and irritability, were relatively low (11.7%, $n = 2$). Conversely, 100% of the patients in Groups A and B had a diffuse beaten copper appearance on skull x-ray preoperatively. During the post-operative period, the beaten copper appearance on skull x-ray disappeared for all patients in Group A. In addition, with respect to Group C patients, who did not need cranioplasties, there was no evidence of increased ICP clinically, with the exception of one patient with a mild beaten copper appearance in the posterior cranium.

In Group B, recurrence of increased ICP occurred at various times during the postoperative period, ranging from 6 months to 72 months. Two patients in Group B were positive for subjective symptoms, including headache and vomiting. Papilledema on

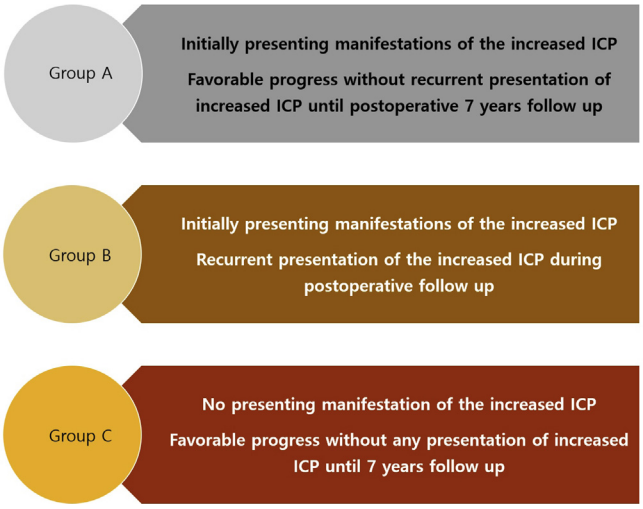

Fig. 1. Patient groups according to syndromic craniosynostosis disease progress.

ophthalmic examination was detected in 50% ($n = 3$) of patients, while ventricular dilation was seen in 66.6% ($n = 4$) of patients. All patients in Group B exhibited a diffuse beaten copper appearance on x-ray during the postoperative follow-up period. A total of 66.6% ($n = 4$) of Group B patients underwent re-operation, with one patient undergoing cranioplasty and the remaining three undergoing neurosurgical intervention to control the increased ICP. Two patients in Group B with a mild beaten copper appearance did not undergo re-operation because this mild manifestation was resolved within a few months. In addition, one-half of the Group B patients ($n = 3$) had secondary craniosynostosis at the time of presentation for recurrent increased ICP (Table 2).

3.1. Case presentation (patient no. 11, in Group B)

A 4-year-old boy visited our craniofacial center and was noted on clinical examination to have an obviously abnormal head shape with exophthalmos and mid-face deficiency characteristic of Crouzon syndrome. Preoperative CT confirmed pan craniosynostosis with mild ventriculomegaly, and skull x-ray revealed a severe beaten copper appearance. Mild papilledema was observed on ophthalmologic examination. At 48 months of age, a fronto-orbital bar advancement with bone flap repositioning was performed. The patient's early postoperative progress was favorable, without the occurrence of surgical complications, and there were no clinical manifestations of increased ICP, including a beaten copper appearance or papilledema, up to 5 years postoperatively. However, at the 6-year follow-up, a diffuse beaten copper appearance on x-ray was noted, accompanied by subjective symptoms, including headache and vomiting. On CT scan, persistent ventriculomegaly was noted and papilledema was also observed. The patient subsequently underwent an endoscopic third ventriculostomy (ETV) for decompression of the increased ICP. After the ETV, the subjective symptoms, papilledema, and diffuse beaten copper appearance on x-ray disappeared; however, the ventriculomegaly on CT scan continued to be present for up to 6 years post-ETV (Fig. 2).

3.2. Case presentation (patient no. 13, in Group C)

A 4-year-old boy visited to our institute with complaints of exophthalmos and mid-face deficiency characteristic of Crouzon syndrome, who had not undergone previous surgery. Although CT confirmed pan craniosynostosis, there was no definite manifestation of increased ICP, such as subjective symptoms, abnormal presentation on ophthalmologic examination, a diffuse beaten copper skull on skull x-ray, or ventricular dilation on CT scan. These facts, in addition to the patient's relatively favorable head shape, indicated that there was no need for surgical correction of the cranial vault. During the follow-up period, increased ICP was not observed. At 8 years of age, the patient underwent surgical correction for a mid-face deformity via Le Fort III osteotomy and distraction osteogenesis. Postoperative examination revealed a continued excellent facial shape without evidence of increased ICP symptoms through 8 years of follow-up after surgery (Fig. 3).

4. Discussion

In syndromic craniosynostosis, there is a great variation in the dysmorphology within and between patients, including between affected individuals from the same family. This disease and its heterogeneity are known to be the result of predetermined events

Table 1
Demographic and pre-operative data and age at the time of primary surgery for all patients.

No.	Sex	Syndrome	Involved sutures	Group	Subjective symptoms (headache, irritability)	Papilledema	Diffuse beaten copper appearance	Ventricular dilation	Type of cranioplasty	Age at surgery (months)
1	F	Crouzon	Total	A	−	−	++	−	FOA & cranioplasty	72
2	M	Crouzon	Total	A	−	−	++	−	FOA & cranioplasty	48
3	F	Crouzon	Uni-lambdoid and uni-coronal	B	−	−	+	−	FOA & cranioplasty	7
4	M	Crouzon	Bi-coronal	B	−	−	++	−	FOA & cranioplasty	10
5	F	Saethre-Chotzen	Bi-coronal	A	−	−	+	−	FOA & cranioplasty	16
6	M	Crouzon	Total	A	−	−	++	−	FOA & cranioplasty	91
7	F	Crouzon	Total	A	−	−	+	−	FOA & cranioplasty	132
8	M	Crouzon	Total	A	−	−	++	−	FOA & cranioplasty	22
9	F	Crouzon	Total	A	−	−	++	−	FOA & cranioplasty	48
10	M	Crouzon	Total	B	−	+	++	++	FOA & cranioplasty	36
11	M	Crouzon	Total	B	−	+	++	+	FOA & cranioplasty	47
12	M	Crouzon	Uni-lambdoid	B	+	−	++	−	FOA & cranioplasty	12
13	M	Crouzon	Total	C	−	−	−	−	N/A	N/A
14	M	Crouzon	Total	C	−	−	−+	−	N/A	N/A
15	M	Crouzon	Total	C	−	−	−	−	N/A	N/A
16	F	Pfeiffer	Total	B	+	−	+	−	Posterior D.O.	12
17	M	Crouzon	Sagittal and lambdoid	A	−	−	+	−	Cranioplasty	12

F = female; M = male.

Table 2
Postoperative progress for six patients after primary cranial correction who presented with clinical manifestations of recurrent increased intracranial pressure (ICP) and underwent a secondary surgery.

Patient no.	Onset of recurrent symptoms (postoperative months)	Secondary craniosynostosis	Subjective symptoms	Papilledema	Diffuse beaten copper appearance	Ventricular dilation	Reoperation	Type of reoperation
3	24	+	−	−	Mild (resolved)	−	No	N/A
4	24	+	−	−	Mild (resolved)	−	No	N/A
10	48	−	−	−	Severe	+	Yes	FOA
11	72	−	+	+	Severe	+	Yes	ETV
12	16	+	−	+	Severe	+	Yes	VPS
16	6	−	+	+	Severe	+	Yes	VPS

FOA = fronto-orbital bar advancement.

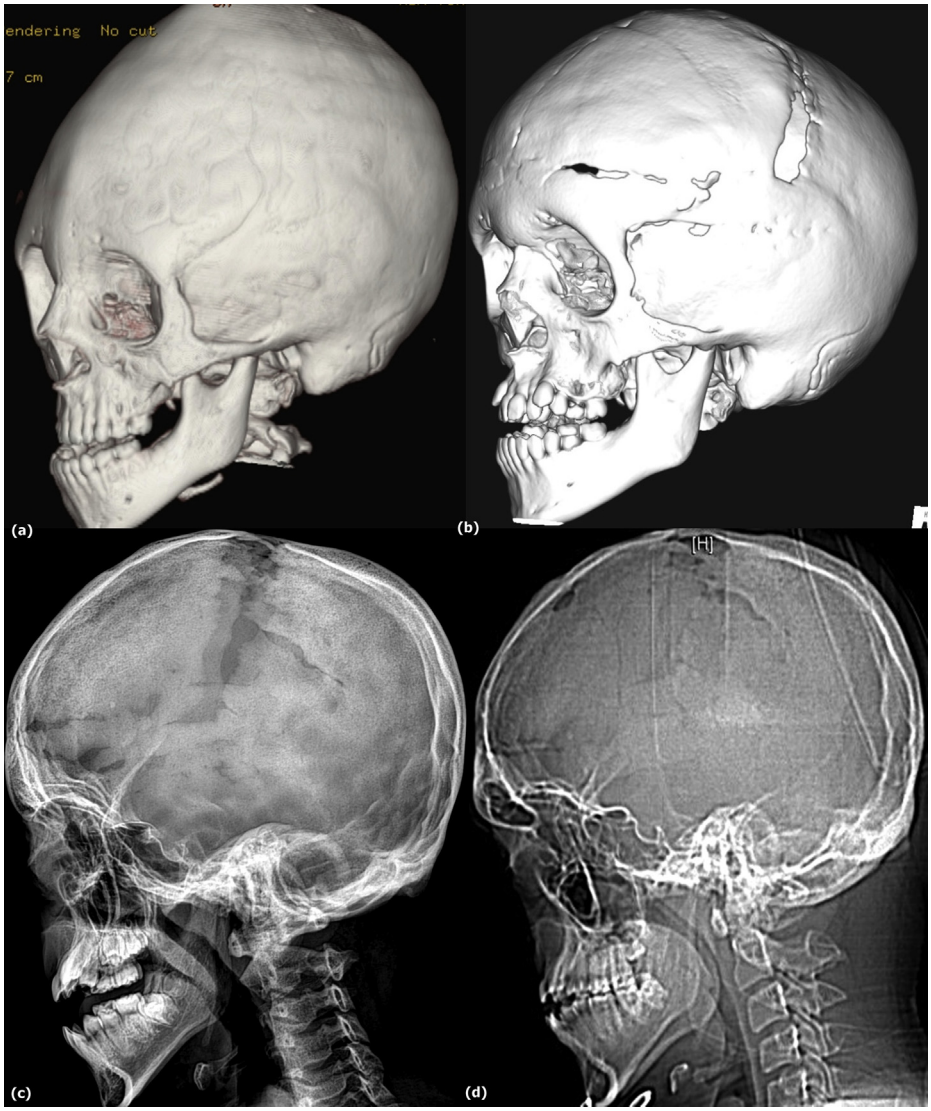

Fig. 2. Case presentation. (a) Preoperative CT scan demonstrating a diffuse beaten copper appearance. (b) Five-year postoperative follow-up CT showing favorable progress and (c) recurrent beaten copper appearance 6 years postoperatively. (d) Disappearance of the beaten copper appearance 6 years after an endoscopic third ventriculostomy.

that occur early in fetal development, most probably due to the phenotypic effects of different mutations, tissue-specific expression of different FGFR isoforms or other modifying factors, and possibly environmental factors (Melville et al., 2010). Furthermore, it was recently reported that syndromic patients can have a variable disease course, as well as a variable initial presentation. Consistent with this observation, we identified three distinct groups of syndromic patients according to their disease course. The first group (Group A) exhibited definite clinical characteristics of syndromic craniosynostosis with clinical manifestations of increased ICP preoperatively, and exhibited favorable post-operative progress. In Group A, the number of involved sutures varied from one to all, and the age when patients were diagnosed and underwent surgery also varied considerably, with some patients presenting early in life (<4 years, 37.5%) and others later (>4 years, 62.5%).

Group B consisted of patients with recurrent clinical manifestations of increased ICP during the post-operative follow-up period

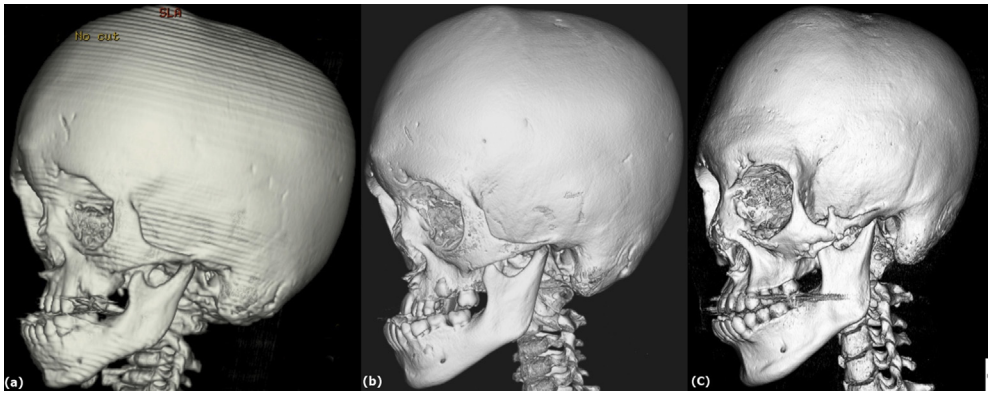

Fig. 3. Case presentation. (a) Initial CT scan demonstrating favorable head shape and the pan-craniosynostosis without a definite beaten copper phenotype. (b) Preservation of a favorable head shape without presentation of increased ICP until 8 years of age. (c) Postoperative view demonstrating excellent mid-facial shape at the 8-year follow-up visit after Le Fort III osteotomy and distraction osteogenesis.

despite having received adequate surgical correction as in Group A. Consistent with this observed population, a previous study also described recurrence of increased ICP after surgery among a few cases of patients with various degrees of syndromic craniosynostosis (Pollack et al., 1996). Finally, Group C consisted of patients with mild syndromic characteristics but no clinical manifestations related to increased ICP (17.5%, $n = 3$) and who underwent surgery for correction of mid-face deformities, such as Le Fort III distraction osteogenesis. A similar group of patients had been observed previously, indicating that not all children with syndromic craniosynostosis will develop raised ICP, not all who do need vault expansion to reduce it, and prophylactic treatment will not necessarily prevent recurrence (Hayward et al., 2016).

Although there were no cases of delayed manifestation of increased ICP in the present study, a previous study reported that some syndromic patients have minimal deformities after premature closure of sutures and live without symptoms of increased ICP early in life. These patients can be left untreated initially, but should remain under regular observation, as they may later present with unexpected clinical and laboratory findings of increased ICP (Martinez-Lage et al., 1999). Although not included in the present study, patients with progressive postnatal craniosynostosis, characterized as a normal suture and head shape with only mid-face manifestations of syndromic craniosynostosis at birth and who present with delayed and progressive pan-craniosynostosis with clinical manifestations of increased ICP developing with time, have been evaluated previously (Connolly et al., 2004). In addition, several authors have identified patients with synostosis of other sutures that were previously patent before synostosis correction, and have referred to this condition as 'secondary craniosynostosis.' Secondary craniosynostosis occurs more frequently in syndromic patients than in non-syndromic patients, with an incidence ranging from 10.8% to 36.8% (Kim et al., 2017). Taken together, these observations suggest that syndromic craniosynostosis patients can have a variable disease progress and clinical manifestations.

The above results highlight that close, long-term monitoring is warranted for the group of patients with a confirmed syndromic diagnosis regardless of treatment. In particular, a wait-and-see approach before any surgical intervention has recently been suggested to be important in syndromic patients, and strict compliance with follow-up and adherence to a validated increased ICP screening tool with excellent sensitivity and specificity are needed. Thus, identifying increased ICP is critical not only to the decision-making process for primary intervention, but also for follow-up in patients postoperatively and those being managed conservatively with observation (Wiegand and Richards, 2007). As shown in previous studies, long-term follow-up is especially essential in syndromic craniosynostosis patients, and clinical indicators for determining the presence of increased ICP are keenly needed in practice because these patients potentially have up to 5-fold higher risk of delayed presentation for increased ICP when compared with that of non-syndromic patients (Foster et al., 2008). Unfortunately, to the best our knowledge, specific guidelines for the long-term management of these syndromic craniosynostosis patients are not well established. Furthermore, prior studies have included various kinds of craniosynostosis, making it difficult to generalize those results to specific syndromic patients.

Direct measurement of ICP through placement of a device within the cranial cavity and transduction of the pressure is the most objective and accurate method to determine intracranial pressure. However, there are many risks associated with invasive procedures involving the insertion of an object into the brain, as well as the accompanying anesthesia. Furthermore, interpretation of ICP values as 'normal' and 'abnormal' can be ambiguous due to several factors, including measurement method, age, patient positioning during measurement, clinical background, symptomatology (injury, trauma, or elective measuring), and type of anesthetic agent used during the procedure (Wiegand and Richards, 2007). Indeed, the range of normal ICP values can vary between infants and adults, and normal ICP has not yet been precisely defined in younger patients.

Clinical assessment can give surgeons a better idea of the actual ICP (Wiegand and Richards, 2007); however, it remains undetermined as to what set of physical manifestations can serve as a reliable and predictable way to detect increased ICP. Generally, indirect methods for assessing increased ICP include clinical manifestations, such as subjective signs and symptoms, ophthalmologic examination, and radiologic findings. The subjective symptoms of increased ICP include chronic headache, vomiting, and irritability. Clinically speaking, it is difficult to recognize a significantly increase in ICP based on the presence of these subjective symptoms alone, as they tend to be vague. In addition, many patients are too young to verbally complain of headaches, but may exhibit episodic screaming and/or head-banging, which is suggestive of increased ICP. It can be difficult to differentiate between benign childhood headaches and those that could represent increased ICP requiring surgical treatment. Furthermore, these subjective symptoms usually appear later in the disease, and thus their incidence at the time

of diagnosis is relatively low. Indeed, one study reported that no direct correlation exists between the degree of increased ICP and the presence of headaches (Silberstein and Marcelis, 1992). In our study, only two patients exhibited irritability during preoperative assessment, and it remains unclear whether these symptoms were caused by increased ICP. Furthermore, the classic symptoms of vomiting and altered mental status were typically absent in our patients.

Papilledema, defined as optic disk elevation and blurred margins on ophthalmologic examination, is considered one of the more reliable clinical manifestations of increased ICP (Tuite et al., 1996a). However, in one study investigating the association between ICP and papilledema in 122 children, the presence of papilledema was a specific (98%) indicator of increased ICP, but its sensitivity was age-dependent, being positive in only 22% of patients under 8 years of age (Tuite et al., 1996a). The presence of intracranial hypertension without papilledema has been reported in other studies (Marcelis and Silberstein, 1991). That is, the absence of papilledema does not necessarily speak to whether or not ICP is elevated. This result was consistent with the findings of our study in which only two (14.2%) patients had papilledema out of a total of 14 individuals with other clinical manifestation of increased ICP on preoperative assessment and three (50%) patients with recurrent presentation of increased ICP postoperatively.

With respect to radiologic monitoring, there are two main findings seen in association with increased ICP. First, hydrocephalus (ventriculomegaly) on CT is defined as the presence of any enlargement or prominence of the lateral or third ventricles. Acute intracranial catastrophes caused by increased ICP can lead to obliteration of the basal cisterns or vault sulci, resulting in ventriculomegaly. A CT finding of ventricular dilation has a high reported sensitivity (99.1%) for increased ICP, but also a high false-positive rate (Hirsch et al., 2000). In our series, all four cases of recurrent increased ICP requiring reoperation presented with ventriculomegaly, although this finding persisted on follow-up CT scan despite normalization of ICP following revisional surgery. Thus, the presence of ventriculomegaly may be a useful screening modality for the primary detection of increased ICP, but may have limited utility for detecting increased ICP during follow-up. In addition to CT findings, the presence of a beaten copper appearance on skull x-ray is regarded as a highly specific manifestation of increased ICP due to the continuous pulsatile pressure exerted on the cranium by the brain, which causes remodeling of the inner cranium, especially in children less than 18 months of age (Tuite et al., 1996b). While convolution markings can be observed in normal development during the period of rapid brain growth—before 8 months of age and between 3 and 5 years of age—they are more likely to be mild or present in the posterior cranium compared to the characteristic diffuse beaten copper appearance that occurs much more frequently in patients with craniosynostosis. Indeed, a matched case–control study investigating the correlation between ICP and the presence of a beaten copper cranium reported that ICP was greater when a “diffuse” beaten copper appearance on skull x-ray and CT, erosion of the dorsum sellar, and suture diastasis were present (Tuite et al., 1996b). Based on our preoperative assessment series, 14 (100%) patients required primary surgical correction for increased ICP and presented with a diffuse beaten copper appearance on initial skull x-ray. Another important finding of our study was the resolution of the beaten copper appearance after primary surgical correction for increased ICP. In addition, the reappearance of the beaten copper phenotype after primary cranioplasty developed in all patients with clinical manifestations of recurrent increased ICP. We suggest that this result supports the high sensitivity of the diffuse beaten copper appearance as a marker for ICP during the postoperative follow-up period. Further supporting the usefulness of the diffuse beaten copper skull sign for detecting ICP, none of the children in Group C, which consisted of patients only under observation without surgical correction of the cranium, had this finding on initial presentation or during the follow-up period. Therefore, although decisions regarding reoperation should not be based solely on the presence of a beaten copper phenotype, we suggest that a diffuse beaten copper appearance has clinical significance as a marker for monitoring increased ICP. Likewise, changes on x-ray may potentially provide clinicians indirect evidence for the recovery from or recurrence of increased ICP. Furthermore, this method utilizes simple x-ray imaging, which affords several benefits, including decreased invasiveness, ease and simplicity of use, and lower morbidity compared to CT due to a lower radiation dose.

There were several limitations of this study. First, due to its retrospective nature, there were some limitations inherent in our study design, such as recording bias. Second, the study size was relatively small. Larger, prospective studies with age-matched patients will be needed to better address the issues raised in this study. Finally, although it is beyond the scope of this study, the purported causal connection between increased ICP and cognitive delay has not been proved, as several other factors, including underlying genetic defects, hydrocephalus, chronic airway obstruction, and developmental consequences of impaired vision or hearing, are capable of affecting neurologic cognitive impairment (Hayward et al., 2016). Based on this, there exists the real possibility that patients may be subjected to unnecessary surgical procedures primarily or secondarily with their never-absent risks. Furthermore, reliable clinical manifestations affecting all neurologic cognitive functions, which could differ from those that we studied, should be further investigated in the future.

5. Conclusion

In conclusion, we noted that patients with syndromic craniosynostosis have variable disease courses, and have higher rates of increased ICP compared to non-syndromic patients, indicating the importance of close, systematic monitoring of increased ICP during follow-up. Among non-invasive methods for indirectly assessing increased ICP in craniosynostosis patients, a beaten copper appearance on x-ray accurately reflected changes in ICP in these patients, and thus this sign may be a simple and more reliable indicator of ICP during the follow-up period than other clinical manifestations due to their variability. The combination of beaten copper appearance on skull x-ray with other clinical assessments may improve the detection of increased ICP, although the sensitivity and specificity of this approach remain unclear.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding

There were no funding sources for this study.

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