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ORIGINAL RESEARCH ARTICLE

Prevalence and treatment outcomes of hydrocephalus among children with craniofacial syndromes

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ABSTRACT

Introduction: Hydrocephalus is more common in patients with craniofacial syndromes (CS) relative to non-syndromic craniosynostosis, and the optimal management is challenging. This study examined the prevalence and treatment outcomes of hydrocephalus among children with CS.

Materials and methods: We performed a retrospective review of medical records for all children with established CS and registered in the Gothenburg Craniofacial Registry between 1975 and 2022. This review included analyses of data regarding patient demographics, radiological imaging, hydrocephalus treatment modalities, and shunt revisions.

Results: Eligible patients (n = 193) included those with CS, including Pfeiffer (n = 13), Crouzon (n = 57), Apert (n = 49), Muenke (n = 25), and Saethre–Chotzen (n = 49) syndromes. A total of 22 patients (11.4%) presented hydrocephalus requiring treatment [Pfeiffer, n = 8 (61.5%); Crouzon, n = 13 (22.8%); and Apert, n = 1 (2.0%)]. Nineteen (9.8%) patients underwent ventricular shunt insertion, and three (1.6%) underwent endoscopic third ventriculostomy as a first procedure. None of the Muenke or Saethre–Chotzen patients required hydrocephalus treatment. Seventeen (85%) patients with shunts required revision mainly due to shunt obstruction. Pfeiffer patients had the highest risk of both developing hydrocephalus requiring treatment and needing shunt revision ($p < 0.001$ and $p = 0.004$, respectively). Approximately 40% of patients with Pfeiffer, Crouzon, or Apert presented ventriculomegaly not requiring treatment.

Conclusions: Hydrocephalus requiring treatment is common in Pfeiffer and Crouzon patients but rare in Apert, Muenke, or Saethre–Chotzen syndrome. Shunt treatment is often associated with complications that require revisions, emphasizing the importance of distinguishing non-progressive ventriculomegaly from hydrocephalus requiring treatment.

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Introduction

Hydrocephalus is caused by disturbances of cerebrospinal fluid (CSF) circulation that leads to progressive ventricular dilatation and frequently requires surgical intervention. In children with craniosynostosis, hydrocephalus develops more commonly in those with craniofacial syndromes (CS) (12.1–15%) [1, 2] relative to non-syndromic craniosynostosis (0.28%) [1]. The need for treatment of hydrocephalus varies between different types of CS. Shunt-dependent hydrocephalus is more prevalent in Crouzon and Pfeiffer syndromes as compared with Apert syndrome [3, 4], where the enlarged ventricles are primarily stable [4]. To date, there have been no reports of shunt-dependent hydrocephalus in patients with Saethre–Chotzen or Muenke syndrome [3].

Increased intracranial pressure (ICP) in children with CS requires urgent detection to avoid negative consequences involving brain development and visual function. Premature fusing of sutures and hydrocephalus are two factors that contribute to increased ICP in CS and can be treated by either cranial vault expansion or ventricular shunting, respectively [5]. Hydrocephalus requiring treatment is mainly diagnosed according to the presence of progressive ventricular dilatation and symptoms of increased ICP [4]. However, in children with CS, it can be challenging to determine the presence of active hydrocephalus with progressive ventricular dilatation versus non-progressive ventriculomegaly, with the latter not necessarily requiring surgical treatment [3]. The pathogenesis of hydrocephalus in syndromic craniosynostosis is complex and multifactorial, resulting in several theories that alone fail to explain its mechanism in these children. Some theories include CSF disturbance due to brain malformation, venous sinus hypertension, small posterior cranial fossa volume (PCFV), or foramen magnum stenosis [3, 6].

Ventricular shunting has historically been considered the only appropriate treatment method for hydrocephalus in CS. An important potential problem with ventricular shunting in children is the risk of overshunting, which can negatively affect skull growth and potentially cause secondary synostosis [2]. A ventricular shunt can also cause other complications, including obstruction and infection, that require urgent surgical care with shunt revision [7]. There is growing evidence supporting endoscopic third ventriculostomy (ETV) as a treatment

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alternative for hydrocephalus involving an obstruction in children with CS. Therefore, some authors advocate ETV based on the high frequency of shunt failure [2, 3, 8].

CSs are rare conditions, making them challenging to study. Moreover, the treatment routines for children with CS vary between different countries and craniofacial centers. The vast majority of craniofacial surgical care for syndromic patients in Sweden (and earlier also other Nordic countries) has been performed at the Sahlgrenska University Hospital [9]. Therefore, the present study utilized access to an extensive database allowing international comparisons of patients with CS to evaluate the incidence and treatment outcomes of hydrocephalus in a large cohort of children with CS.

Materials and methods

Patients

This is a retrospective observational cohort study of children with CS using data extracted from the Gothenburg Craniofacial Registry. Children with a Swedish personal identity number – categorized as having Pfeiffer, Crouzon, Apert, Muenke, or Saethre–Chotzen syndrome – and registered between 1 January 1975 and 31 December 2021 in the Craniofacial Registry were included. Exclusion criteria included absence of accessible medical records. The primary outcome of this study was the frequency of hydrocephalus requiring treatment, with secondary outcomes being the number of and the reason(s) for shunt revision(s).

A medical record review was conducted to extract data related to ventricular shunting, its frequency, and indication(s) for shunt revision (obstruction, shunt infection, etc.). Background variables included sex, type of CS, and death during the study period. The medical record review was performed until 31 December 2023, enabling a possible follow-up of a minimum of 2 years.

Radiology

To assess the frequency of ventriculomegaly not requiring treatment, the latest available computed tomography or magnetic resonance imaging scans for untreated patients were examined. Radiological images were available for 101 patients not requiring treatment for hydrocephalus. Fronto-occipital horn ratio (FOHR) was estimated by one of the authors (TH), with FOHR ≥ 0.4 regarded as ventriculomegaly. Radiological statements alone were available for 51 patients. In these cases, ventriculomegaly was determined according to the assessment of the ventricles as enlarged. Records for 19 patients included neither images nor radiological statements.

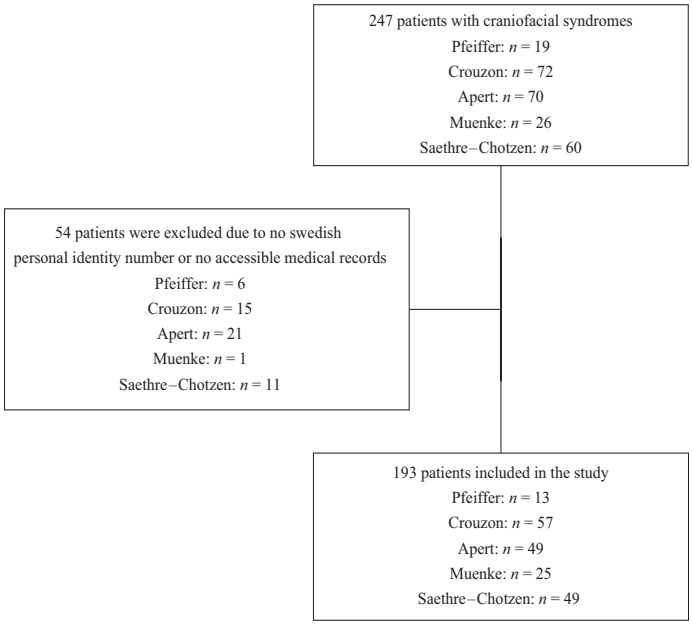

Figure 1. Flow chart describing the patients included in the study.

Statistics

Data were compiled using descriptive statistics. Categorical variables are described as numbers (n) and percentages (%), and continuous and discrete variables are described using medians and ranges. The chi-squared or Fisher's exact test was used to compare categorical variables. A Mann–Whitney *U* or Kruskal–Wallis test was used to compare continuous data between patient groups. Survival analysis was performed using Kaplan–Meier curves with a log-rank test. All statistical analyses were performed using SPSS (v.29; IBM Corp., Armonk, NY, USA).

Ethics

This study was approved by the Swedish Ethics Review Appeals Board (DNR; 57-2022/3.1). Patients and/or next of kin were informed about the study by an opt-out letter or telephone call. No patient declined participation.

Results

A total of 193 patients were included in the study (Pfeiffer, n = 13; Crouzon, n = 57; Apert, n = 49; Muenke, n = 25; and Saethre–Chotzen, n = 49) (Figure 1). Information regarding genetic testing was present for 124 patients. For 69 patients, diagnosis was based on clinical (phenotypic) findings. Ninety-eight (51%) patients were male and 95 (49%) female. Significantly, more males presented with Crouzon syndrome, and more females presented with Apert syndrome (p = 0.008). The median follow-up time was 18 years (range: 0–48 years). Nine patients (5%) died during the study period (Table 1).

Hydrocephalus requiring treatment

Of the included patients, 22 (11.4%) developed hydrocephalus requiring treatment [Pfeiffer, n = 8 (61.5%); Crouzon, n = 13 (22.8%); and Apert, n = 1 (2.0%)]. Indication for hydrocephalus treatment was based on progressive ventricular enlargement accompanied by clinical evidence of raised ICP. None of the patients with Saethre–Chotzen or Muenke syndrome required treatment for hydrocephalus (p < 0.001) (Figure 2). First-line hydrocephalus treatment involved ventricular shunting for 19 (9.8%) patients, and three patients (Pfeiffer, n = 2; and Crouzon, n = 1) underwent ETV as a first-line treatment. One patient with Pfeiffer syndrome required a ventriculoperitoneal shunt (VP-shunt) following ETV surgery. At initial shunt insertion, a programmable valve was used in 13 patients, while in seven patients, a fixed pressure valve was used. The median ages at first hydrocephalus treatment were 4 months (Pfeiffer; range: 0–10 months), 10 months (Crouzon; range: 2–69 months), and 9 months (Apert) (p = 0.077, data not shown). Ten patients required hydrocephalus treatment before and 12 patients after any cranial vault surgery.

Separate analyses comparing Pfeiffer and Crouzon patients showed a higher frequency of hydrocephalus requiring treatment in those with Pfeiffer syndrome (p = 0.015) (Figure 2). Additionally,

Table 1. Patient characteristics

	Pfeiffer	Crouzon	Apert	Muenke	Saethre–Chotzen	*p*	Overall
No. of patients	13	57	49	25	49	—	193
Sex, *n* (%)							
[male and	6 (46)	39 (68)	16 (33)	13 (52)	24 (49)		98 (51)
female]	7 (54)	18 (32)	33 (67)	12 (48)	25 (51)	0.008	95 (49)
Deceased during the study period, *n* (%)	2 (15)	3 (5)	3 (6)	—	1 (2)	0.229	9 (5)

The chi-squared test was used to compare categorical variables.

Pfeiffer patients showed a significantly shorter time until first treatment relative to Crouzon patients [median age: 4 months (range: 0–10 months) vs. median age: 10 months (range: 2–69 months)] (p = 0.030, data not shown). Given the difference in follow-up length between patients, we performed survival analysis regarding risk of hydrocephalus requiring treatment, which revealed a higher risk for Pfeiffer relative to Crouzon patients (log-rank test $p < 0.001$) (Figure 3a).

Shunt revisions

Among patients requiring a shunt (n = 20), 17 (85.0%) (Pfeiffer, n = 7; Crouzon, n = 9; and Apert, n = 1) required a revision, with the median time to the first revision at 13 months (range: 0–197 months). Crouzon patients demonstrated a trend toward a longer time between shunt insertion and first shunt revision as compared with that for both Pfeiffer and Apert patients (p = 0.058). Similarly, significantly fewer Crouzon (1/9 patients) than Pfeiffer (5/7 patients) and Apert (n = 1) patients required shunt revision within 1 year after insertion (p = 0.024). A total of seven (35%) patients with a shunt required revision within 1 year (Table 2). There was no statistical difference regarding the need for shunt revision depending on whether a programmable valve was used at the initial shunt insertion (data not shown). Additional survival analyses to consider the different follow-up times for patients also showed a higher risk of needing and earlier performance of shunt revision for Pfeiffer as compared with Crouzon patients (p = 0.004) (Figure 3b). Shunt obstruction was the most common reason for the first shunt revision (n = 8; 47%), followed by infection (n = 5; 29%). The median number of shunt revisions was one (range: 1–11), with nine patients receiving one revision and eight undergoing two or more revisions (Table 2).

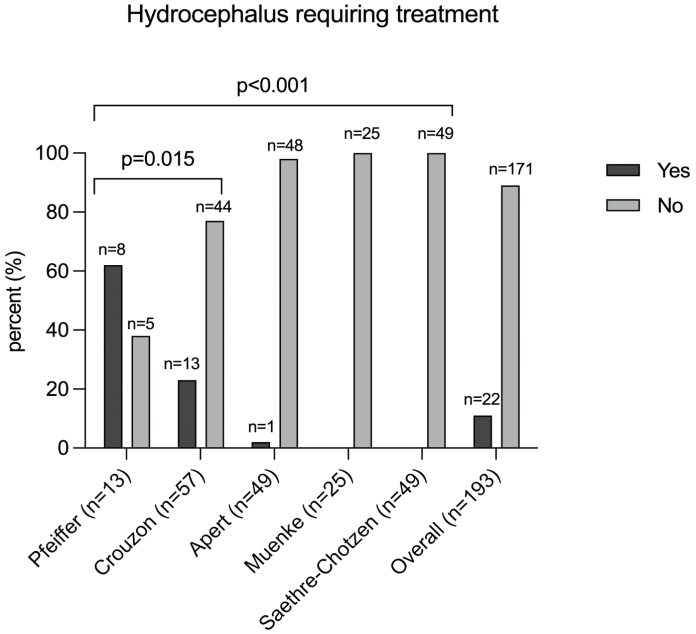

Figure 2. Frequency of hydrocephalus requiring treatment among patients presenting different types of CS. Fisher's exact test or the chi-squared test was used to analyze differences between groups.

Ventriculomegaly not requiring treatment

Medical records for 152 patients not requiring hydrocephalus treatment included radiological information. Ventriculomegaly (FOHR ≥ 0.4 or radiological diagnosis of enlarged ventricles) was described for 38 (25.0%) patients [Pfeiffer, n = 2/5 (40.0%); Crouzon, n = 16/37 (43.2%); Apert, n = 17/44 (38.6%); Muenke, n = 2/24 (8.3%); Saethre–Chotzen, n = 1/42 (2.3%)] ($p < 0.001$) (Figure 4).

Discussion

The findings of this retrospective cohort study illustrate the large variation between different types of CS regarding risk of developing hydrocephalus requiring treatment. Specifically, the results showed an overall risk of 11.4% with a much higher risk for patients with Pfeiffer or Crouzon syndrome relative to Apert, Muenke, or Saethre–Chotzen syndrome. For patients treated with ventricular shunting, revision was necessary in 85% of cases. Furthermore, 25% of patients (predominantly those presenting with Pfeiffer, Crouzon, or Apert syndrome) presented radiological findings of ventriculomegaly that did not require treatment.

Hydrocephalus develops more frequently in cases of syndromic craniosynostosis relative to non-syndromic craniosynostosis [1]. Reported frequencies of hydrocephalus in patients with CS range from 12.1% to 15% [1, 2], with higher frequencies observed in Pfeiffer (28–64%) [1, 10, 11] or Crouzon (9–26%) [1, 10, 12] patients relative to those presenting with Apert, Muenke, or Saethre–Chotzen syndromes [1, 3]. This is consistent with the present findings, which showed an 11.4% overall frequency of hydrocephalus requiring treatment (Apert, 2%; Crouzon, 22.8%; and Pfeiffer, 61.5%). Hydrocephalus treatment was not required for patients in our cohort with Muenke or Saethre–Chotzen syndrome, which is in line with previous studies [1, 13, 14].

A factor contributing to the variability in reported rates could involve the differing thresholds associated with treating hydrocephalus between centers. The variations in treatment regimens for hydrocephalus can be highlighted by the different frequencies described for shunt insertion in Apert patients [18.5–24.3% [15, 16] vs. 4–7% [17]], including studies reporting that ventricular shunting is rarely required in these patients [1, 18, 19]. In the present study, only one Apert patient required shunt insertion, confirming the rarity of hydrocephalus requiring treatment in these patients. Notably, among patients presenting with Pfeiffer, Crouzon, or Apert syndrome, approximately 40% were diagnosed with ventriculomegaly not requiring treatment. This emphasizes the importance of distinguishing non-progressive ventriculomegaly from hydrocephalus requiring treatment.

Timing and the number of fused sutures represent possible explanations for the differences in progressive hydrocephalus

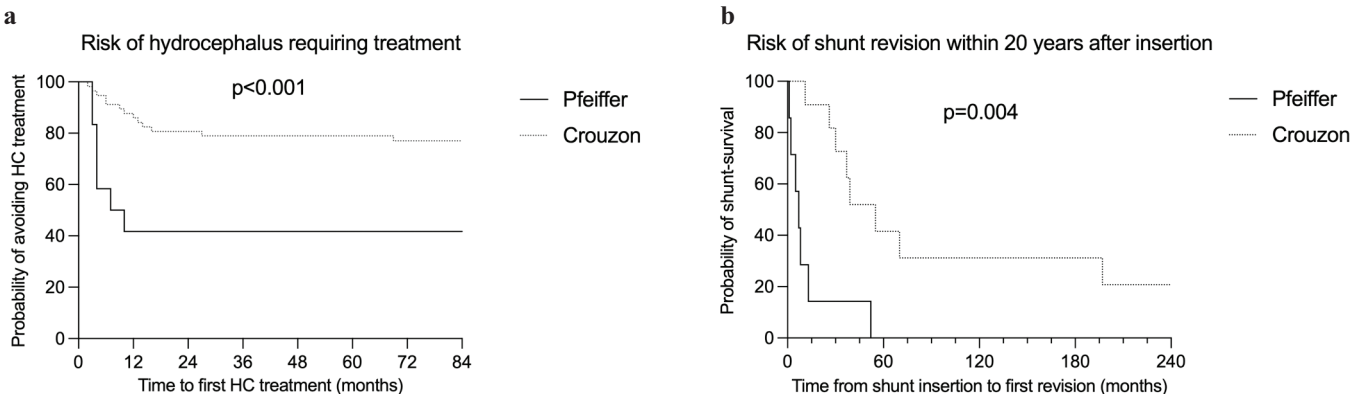

Figure 3. Kaplan–Meier curves describing the differences between patients with Pfeiffer or Crouzon syndrome in terms of the risk of requiring (a) hydrocephalus treatment and (b) shunt revision.

observed between the different CS types [20]. In patients with Apert syndrome, the lambdoid sutures fuse at an older age as compared with Pfeiffer or Crouzon syndrome [20], resulting in a PCFV closer to normal in patients with Apert syndrome and a smaller PCFV in those with Pfeiffer or Crouzon syndrome. Fusion and the involvement of the sagittal suture and the cranial base also occur later in Apert syndrome as compared with Crouzon syndrome. These outcomes can lead to more severe venous hypertension and more significant mechanical obstruction of CSF outflow in Crouzon and Pfeiffer syndromes relative to Apert syndrome and accompanied by subsequent development of progressive hydrocephalus. Moreover, venous hypertension combined with a higher number of open sutures might explain why ventriculomegaly is mostly non-progressive in patients with Apert syndrome [1, 4].

Revisions due to shunt complications are common in the pediatric population, especially among newborns [21]. Mechanical malfunctions (e.g. obstruction) are the most common cause of shunt revision, followed by infection [22–24]. However, there are few studies on shunt complications among patients with CS. Reported frequencies of shunt failure within the first year after initial shunt insertion in pediatric populations range from 17% to 26% [25, 26]. In the present study, shunt failure was observed in 35% of the cohort within the first year after shunt insertion. Of those receiving shunts (n = 20), 17 patients (85%) required a median of one revision (range: 1–11). The most common cause for shunt revision was obstruction (47%), followed by infection (29%), which is in line with findings from previous reports. Furthermore, the present results indicated that patients with Pfeiffer syndrome showed the highest risk for early shunt failure. Generally, reported frequencies of shunt complications vary greatly but are consistent with our findings, which confirmed shunt complications as a significant problem requiring additional surgeries and hospitalization for these children.

Although ventricular shunting is traditionally used to treat hydrocephalus in CS, recent studies suggest ETV as an alternative treatment method for hydrocephalus involving an obstructive factor for children with CS [2, 27]. Di Rocco et al. [2] noted a preference for ETV, as it allows preservation of CSF as a driving force for skull expansion and reduces the risk of infection. Additionally, Bonfield et al. [27] reported similar revision rates for ETV and VP-shunt, concluding that both treatments are acceptable. However, both of these studies generated conclusions concerning use of ETV in CS patients according to outcomes in relatively small patient cohorts. In the present study, only three patients underwent ETV, with one subsequently requiring a shunt. It is possible that additional patients in the present cohort may have benefited from ETV. Similarly, it is possible that several of the patients with CS and hydrocephalus have an obstructive component resulting from structural crowding in the posterior fossa due to a small PCFV and/or the presence of a Chiari I malformation [4, 27, 28]. However, the pathogenesis of hydrocephalus in CS can be multifactorial [3], and sometimes, there might be elements of both obstructive and communicating compartments that further complicating treatment decisions.

In this study, 12 patients underwent a cranial vault procedure before hydrocephalus treatment, while 10 patients had the procedure thereafter. Given the high frequency of shunt revisions, it is important to consider whether a cranial vault procedure as an initial intervention could potentially defer or even avoid the need for CSF diversion.

Table 2. Frequency of shunt insertion and revision.

	Pfeiffer (n = 7)	Crouzon (n = 12)	Apert (n = 1)	p	Overall (n = 20)
Median age at shunt insertion, months [range]	4 [0, 10]	10 [2, 69]	9	0.09	6 [0, 69]
Shunt revision, n (%)	7 (100)	9 (75)	1 (100)	0.31	17 (85)
Median time between initial shunt insertion and the first shunt revision, months [range]	7 [1, 52]	37 [0, 197]	1	0.058	13 [0, 197]
VP-shunt failure within 1 year after initial shunt insertion, n (%)	5 (71)	1 (8)	1 (100)	0.024	7 (35)
Median no. of shunt revisions [range]	2 [1, 9]	1 [1, 6]	3	—	1 [1, 11]
Reason for the first shunt revision, n (%)					
Obstruction	6 (86)	2 (22)	—	—	8 (47)*
Shunt infection	—	4 (44)	1 (100)		5 (29)
Other	1 (14)	3 (33)	—		4 (24)**

Comparisons between groups were performed using the Kruskal–Wallis test for continuous data and the chi-squared test for categorical data.

VP-shunt, ventriculoperitoneal shunt.

*3 patients had proximal obstruction, 2 distal obstruction, and 3 obstruction at an unspecified location.

**Including 1 patient with failure of peritoneal cerebrospinal fluid absorption, 2 with slit ventricles, and 1 with uncertain cause of shunt failure.

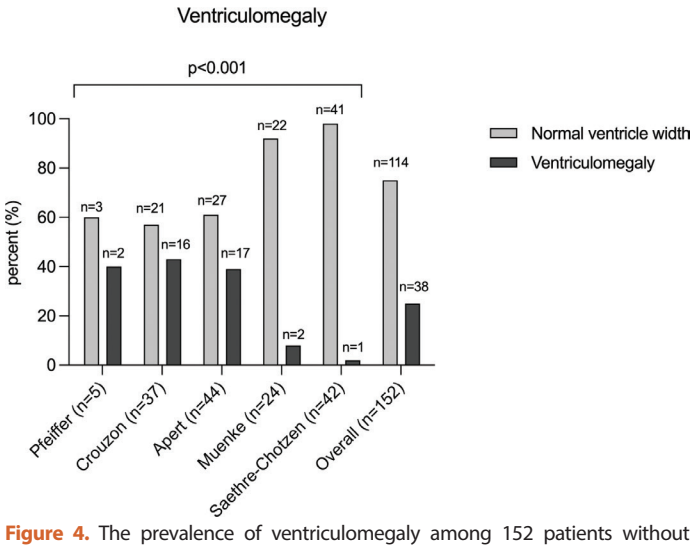

Figure 4. The prevalence of ventriculomegaly among 152 patients without hydrocephalus requiring treatment and in whom assessment of ventricle width was possible. The chi-squared test was used to analyze differences between groups.

Although a particular strength of this analysis is the relatively large patient cohort, this study does have some limitations. Due to the retrospective nature of the study, information concerning patient diagnosis and treatment was limited to the documentation available in medical records and the Gothenburg Craniofacial Registry. Because different centers in Sweden use separate systems for updating medical records, relevant information regarding shunt insertion and revision may be either missing or described differently. Moreover, genetic analyses were present in only 64% of cases, resulting in possible misclassification of some patients. Although children with Apert syndrome can be easily diagnosed according to phenotype [6], accurate diagnosis is more challenging for other syndromes. Furthermore, due to variations in follow-up time, it may be that some patients with shorter follow-up will develop hydrocephalus requiring treatment and/or shunt complications. To address this, we added survival analyses with Kaplan–Meier curves to illustrate the risk over time for these events.

Conclusion

Hydrocephalus requiring treatment is a common finding in children with Pfeiffer or Crouzon syndrome but rare for those diagnosed with other CS types. In those requiring shunt insertion, revision is a frequent event that requires additional hospitalization for these children. Therefore, distinguishing non-progressive ventriculomegaly from hydrocephalus requiring treatment is important in order to avoid unnecessary shunt operations. Given the high risk of such complications, children with CS and obstructive hydrocephalus should be considered for ETV as an alternative treatment method.

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Declaration of interest statement

The authors have no potential conflicts of interest, including financial interests, activities, relationships, or affiliations, to disclose.

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