The Course and Interaction of Ventriculomegaly and Cerebellar Tonsillar Herniation in Crouzon Syndrome over Time

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Background: Children with Crouzon syndrome have a higher incidence of cerebellar tonsillar herniation (TH) and ventriculomegaly than the general population, or children with other craniosynostosis syndromes.
Objective: This retrospective cohort study aimed to determine how ventriculomegaly and TH develop and progress over time, and determine associations between ventriculomegaly and TH in Crouzon patients, treated according to our center's protocol.
Methods: Fronto-occipital horn ratio (FOHR) and TH were determined over time using brain-imaging. These data were used to fit a mixed-model to determine associations between them, and with clinical variables, head-circumference, and lambdoid suture synostosis.
Results: Sixty-three Crouzon patients were included in this study. Preoperatively, 28% had ventriculomegaly, and 11% had TH ≥ +5mm. Postoperatively ventriculomegaly increased to 49%. Over time and with treatment, FOHR declined and stabilized around 5 years of age. TH ≥ +5mm increased to 46% during follow-up. FOHR and TH were associated: expected FOHR with a TH of either 0mm versus +8.6mm at 0 years: 0.44 versus 0.49, and at 5 years: 0.34 versus 0.38; 10% increase of FOHR was associated with 1.6mm increase in TH. Increased head-circumference was associated with increased FOHR. Lambdoid suture synostosis was associated with +6.9mm TH increase.
Conclusions: In Crouzon patients, FOHR was large at onset and decreased and stabilized with treatment and time. FOHR was associated with head-circumference and TH. TH was strongly associated with lambdoid suture synostosis and FOHR. Increased head-circumference was associated with an increased FOHR, and closed lambdoid sutures before 1 year of age were associated with a +6.92mm increase in tonsil position. *(Plast Reconstr Surg Glob Open 2022;10:e3979; doi: 10.1097/GOX.0000000000003979; Published online 24 January 2022.)*

INTRODUCTION

Crouzon syndrome is a type of syndromic craniosynostosis, with a prevalence of 0.1 per 10,000 live births.[1] There is

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a lot of overlap between patients with Crouzon and Pfeiffer syndrome, both in phenotype and genetic mutations; we therefore consider them to be a homogenous group of varying severity of the same genetic defect, and refer to them all as Crouzon patients. Crouzon syndrome is characterized by mutations in genes for fibroblast growth factor receptors type 1, 2, and 3.[2] Clinically, they often present with multiple suture synostosis, exorbitism, and midface hypoplasia. Crouzon syndrome has a wide spectrum of disease severity, ranging from a mild phenotype to a severe phenotype requiring multiple surgeries to treat intracranial hypertension (ICH), or conditions that cause ICH such as ventriculomegaly or obstructive sleep apnea (OSA).[3–7] Detecting and treating ICH is important because it can cause visual impairment and is thought to affect neurocognitive development.[8]

The wide range of severity and unpredictability of the outcome of surgical treatments in Crouzon syndrome can

make treating the individual Crouzon patient difficult. Unexpected problems that can occur are worsening of exorbitism, progressive expansion of ventricles after skull vault expansion, and recurrence of ICH soon after initial treatment.[7] This makes it difficult to decide which treatment is necessary at which moment. Repeat surgeries are related to hydrocephalus, cerebellar tonsillar herniation (TH), and their connection to ICH. Many theories have been postulated about the pathogenesis of TH and how it relates to ventriculomegaly.[9,10] Although there is no consensus about the sequence in which ventriculomegaly and TH occur, presence of either one is generally taken as a sign indicating a need for a closer follow-up.[7,11,12] This study has three main aims: (1) to determine how ventriculomegaly and TH develop and progress over time, (2) to determine how ventriculomegaly and TH relate to one another, (3) to determine which clinical traits, if any, are associated with TH or ventriculomegaly.

METHODS

The medical ethics committee of the Erasmus MC approved this study (MEC2017-1143). This retrospective study gives an overview of children with Crouzon syndrome treated at the Erasmus MC in Rotterdam, the Netherlands, Sophia Children's Hospital, the national referral hospital for patients with syndromic craniosynostosis. It serves an approximately 3.6 million national pediatric population.[13] Patients were included sequentially from June 1994 to October 2019, DNA analysis confirmed Crouzon syndrome.

As part of our clinical protocol,[4] we perform surgical vault expansion before 1 year of age. First choice is occipital expansion with springs, scheduled around the age of 5–6 months. If ventriculomegaly develops before this age, vault expansion is scheduled earlier. When hydrocephalus appears after vault expansion, a shunt or endoscopic third ventriculostomy (ETV) will be considered. If initial ventricular enlargement following a cranial vault expansion is not progressive, an expectant policy is followed. If ICH occurs, a second vault expansion is preferred over shunting. In general, a shunt is avoided before or shortly after cranial vault expansion to prevent skull growth reduction.

Brain Imaging

As per clinical protocol,[4] magnetic resonance imaging (MRI) exams were obtained at first presentation (usually before 1 year old), at 2 and 4 years old, and additionally when clinically indicated. All MRI data were acquired using a 1.5 Tesla MR Unit (General Electric Healthcare, Milwaukee, Wisc.). Images were aligned in sagittal and coronal planes using Philips 3D-modeling in Intellispace software, to ensure measurements were done consistently and in the correct plane.

Computed tomography (CT) scans were acquired using a multidetector CT-scanner (Siemens, Erlangen, Germany). Scan protocol parameters were set to obtain image quality required for clinical interpretation. Patients underwent at least one CT-scan during follow-up before surgery, to determine which cranial sutures were closed.

Takeaways

Question: How do ventriculomegaly and TH develop and progress over time?

Findings: A 10% increase in FOHR was associated with a +1.6 mm increase in tonsil position. Increased head circumference was associated with increased FOHR, and early closed lambdoid sutures were associated with a +6.92 mm increase in tonsil position.

Meaning: FOHR was large at onset and decreased and stabilized with treatment and time. FOHR was associated with head-circumference and TH. TH was associated with FOHR and early closed lambdoid sutures.

Additional CT-scans were done only when clinically indicated, to minimize radiation exposure.

Fronto-occipital horn ratio (FOHR) was used as parameter for ventricle size. FOHR is calculated as (frontal horn width + occipital horn width)/biparietal diameter*2, and gives a ratio of ventricle size that can be interpreted independent of age.[14,15] An FOHR ≥ 0.4 was considered ventriculomegaly. FOHR was determined on MRI or CT-scans. Children with hydrocephalus underwent VP-shunt/ETV.

The tonsil position was determined as the position of the lowest cerebellar tonsil in mm above (referred to as negative numbers) the foramen magnum (FM) or below the FM (TH, referred to as positive numbers; eg, tonsil position of 5 mm or more past the FM: TH ≥ +5 mm), and measured as a continuous variable. Increases in tonsil position referred to increasing downward movement of the cerebellar tonsils. Additionally, TH was divided into two categories: TH < +5 mm and TH ≥ +5 mm below FM.

Presence of abnormal venous anatomy was determined using MRI or CT-scans with angiography. We determined presence of occipital and mastoid emissary veins (0 = normal drainage pattern, 1 = abnormal emissary veins).

Clinical Measurements

Head-circumference was measured using the occipitofrontal circumference, which has shown to be a reliable indicator for intracranial volume.[16,17] Fundoscopy was performed to screen for ICH as determined by presence of papilledema. Patients were screened preoperatively, at the ages of 2, 4, and 6 years. Polysomnography was used to screen for the presence of OSA, using clinical in-house assessments, and ambulatory sleep studies. Obstructive apnea-hypopnea index (oAHI) was calculated as the number of obstructive and mixed apneas, or obstructive hypopneas with desaturation/arousal, divided by the total sleep duration of one night. The oAHI was used to classify patients in two categories: (1) no/mild (oAHI < 5), and (2) moderate/severe OSA (oAHI ≥ 5). Only head-circumference and early lambdoid suture closure were different on preliminary analysis between children with and without TH ≥ 5 mm and children with and without FOHR ≥ 0.4, and were used for further statistical analysis. Information about the timing and types of surgeries was collected.

Statistical Analysis

Relevant characteristics of the study population are summarized using mean and range, or when appropriate median an interquartile range (IQR), for continuous variables and counts and proportions for categorical variables. To give an overview of the data, we created a heatmap, in which patients were categorized into four groups based on the moment TH ≥ +5 mm developed: (1) patients who developed TH ≥ +5 mm before first vault expansion, (2) patients who had no TH ≥ +5 mm on first MRI, and later developed it, (3) patients who underwent first MRI at a late age and had TH ≥ +5 mm, and (4) patients without TH ≥ +5 mm. For each of these groups, the heatmap shows the frequency of patients with FOHR ≥ 0.4, lambdoid suture synostosis before 1 year of age, papilledema, venous emissary veins, and moderate/severe OSA.

To investigate the association between FOHR and tonsil position, head-circumference, and lambdoid suture synostosis before 1 year of age, we fitted a mixed-model assuming FOHR to follow a beta distribution conditional on the covariates. To allow for nonlinear trajectories over time, we included the children's age using natural cubic splines with three degrees of freedom. Because this leads to difficulties in interpreting the effects of age directly, the effect of age is displayed in figures to facilitate interpretation. Correlation between repeated measurements of the same child was taken into account by including a random (patient specific) intercept. An analogous model, but assuming a normal distribution, was fitted to investigate the association between tonsil position and FOHR, head-circumference, and lambdoid suture synostosis at the age of less than 1 year. Because FOHR, tonsil position, and head-circumference were measured at different time points, values of the independent variables had to be imputed at the time points the dependent variable was observed. To this end, we estimated both mixed-models in the Bayesian framework, which allowed us to simultaneously impute the missing observations by specifying additional mixed-models for each of the independent variables.

Specifically, the model for FOHR was estimated jointly with random intercept linear mixed-models (with natural cubic splines for age) to impute head-circumference and TH, and the model for TH was fitted jointly with a random intercept beta mixed-model for FOHR and a linear random intercept model for head-circumference (both with a natural cubic spline for age). We assumed vague priors for all parameters. Results of the Bayesian models are presented as posterior mean and 95% credible intervals (CI).

Table 1. Patient Characteristics

Crouzon patients	63
M:F	31:32
Age at presentation*	0.7 (0.2–2.9)
FOHR ≥ 0.4†	31 (18; 13)
TH ≥ +5 mm†	29 (6; 23)
FOHR ≥ 0.4 and TH ≥ +5 mm	18
Lambdoid suture synostosis <1 y of age	12
Head circumference < −1.0 SD	22
Papilledema	33
Moderate/severe OSA	18
Surgery	
No surgery	6
Patients that underwent a single surgery	19
Patients that underwent multiple surgeries	38
Types of surgeries	
Vault expansions‡	59 (46)
Fronto-orbital expansion	15
(Fronto-)biparietal remodelation	20
Occipital expansion classic/spring distraction	24
Midface surgeries‡	26 (18)
Combination vault expansion and midface surgery‡	25 (22)
FM decompressions‡	3 (3)
VP-shunts/ETV and revisions‡	47 (13)
VP-shunt§	8
ETV§	2
VP-shunt + ETV§	3
Endoscopic ventriculostomies‡	6 (4)

*Median age (interquartile range) in years.
†Values represent number of patients (number of patients in whom event occurred preoperatively; number of patients in whom event occurred postoperatively).
‡Number of surgeries (number of patients).
§Values represent absolute number of patients.
Values represent absolute numbers.
VP-shunt: ventriculoperitoneal shunt.

RESULTS

Patient Characteristics

Sixty-three Crouzon patients were included in this study, patient characteristics are presented in Table 1, and genetic changes are mentioned in Supplemental Digital Content 1 (**See table, Supplemental Digital Content,** which displays genetic changes present in this cohort of Crouzon patients.
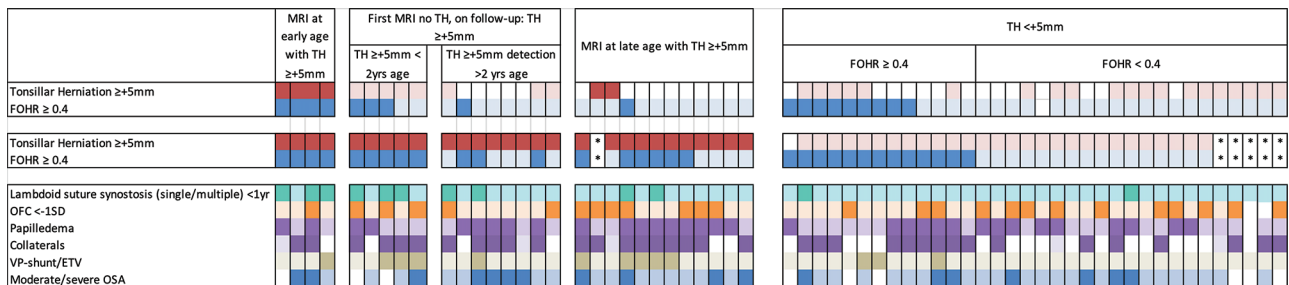

Fig. 1. Heatmap depicting attributes of the 63 Crouzon patients. Patients categorized by presence of TH ≥ +5 mm and/or FOHR ≥ 0.4 before, or after first surgical intervention. Presence of abnormalities in clinical attributes are also displayed. Of each color, the darker shade represents that the abnormalities are present, the lighter shade that the abnormalities are not present, blank squares represent missing values. *Patients who have not undergone skull vault surgery: therefore, only preoperative results displayed. FOHR: fronto-occipital herniation, yr(s): year(s), OFC: occipitofrontal circumference.

). Median age at presentation was 0.9 (IQR 0.2–3.0) years; median follow-up at study conclusion was 10.2 (IQR 4.3–15.7) years.

Ventriculomegaly and TH Development and Progress over Time

Figure 1 shows factors TH ≥ +5 mm and FOHR ≥ 0.4 preoperatively and postoperatively in the 63 children, categorized by the moment at which TH ≥ +5 mm occurred. In patients with both ventriculomegaly and TH ≥ +5 mm (n = 18), TH ≥ +5 mm was detected before ventriculomegaly occurred in one of 18 patients, TH ≥ +5 mm was detected after ventriculomegaly occurred in five of 18 patients, and TH ≥ +5 mm and ventriculomegaly were detected at the same time in 12 of 18 patients. In four patients TH ≥ +5 mm was detected after placement of a VP-shunt; in two patients TH ≥ +5 mm was detected after ETV. Thirteen patients underwent VP-shunting or ETV: 10 patients were initially treated with a vault expansion followed by VP-shunt, and in three patients the order of procedures was the other way around.

Patient-specific trajectories of FOHR and tonsil position are displayed in Figure 2. The trajectories show the distinct differences between patients in development and progress of FOHR and tonsil position.
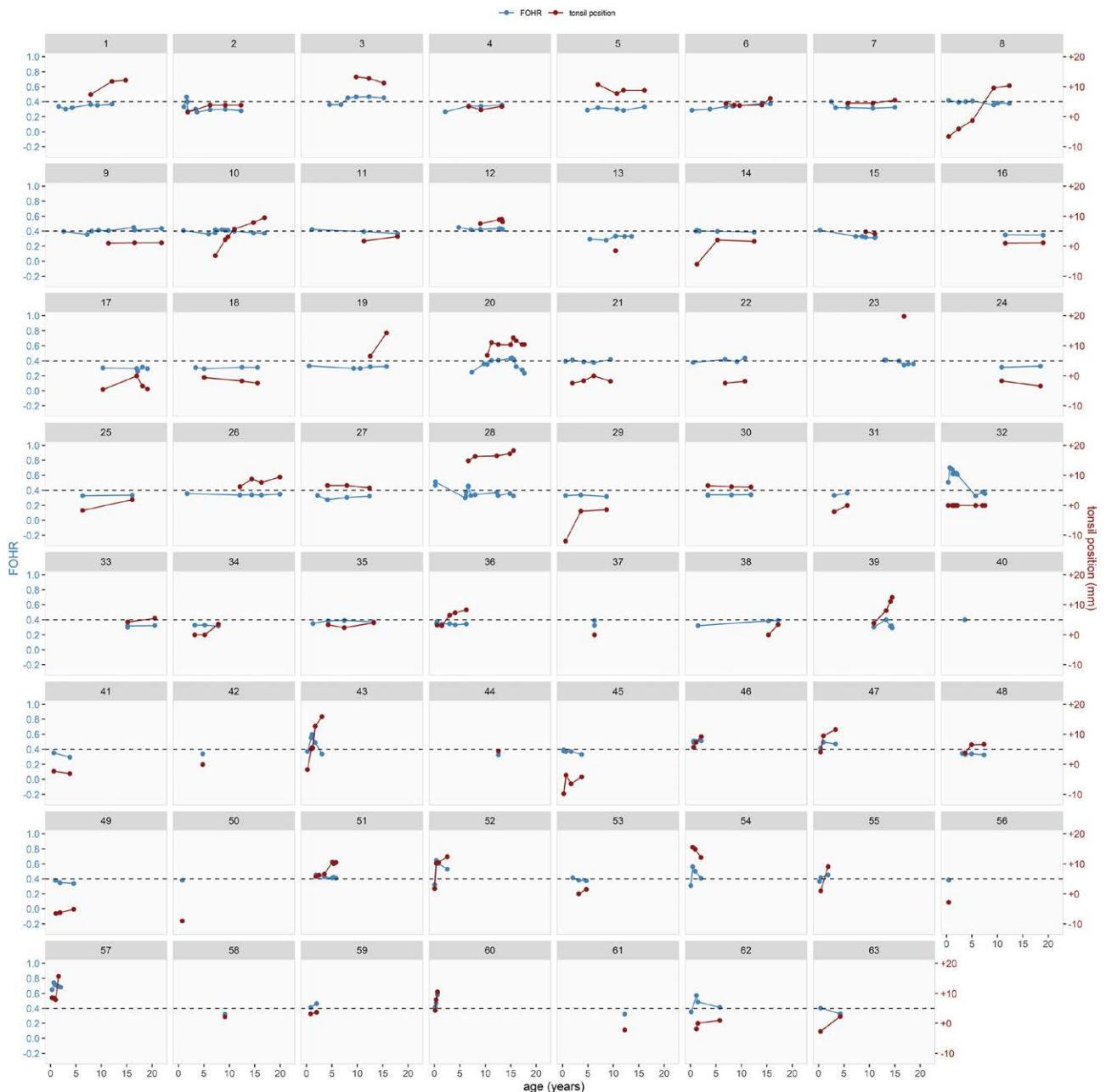

Fig. 2. Patient-specific trajectories depicting progression of FOHR and tonsil position over time. Y-axes (left for FOHR, and right for tonsil position) are adjusted so that FOHR values of 0.4 are aligned with a tonsil position of +5 mm.

Relation between Ventriculomegaly and TH

The results of the mixed-model for FOHR are shown in Table 2. The odds ratio refers to the change in the ratio FOHR/(1-FOHR) that is associated with a 1-unit change in a covariate. Table 2 shows that progress of tonsil position is associated with an increase in FOHR (tonsil position: odds ratio = 1.02 (95% CI[1.01–1.03]).

Figure 3 displays the expected FOHR and corresponding 95% CIs across age for different scenarios with respect to tonsil position, head-circumference and closed lambdoid sutures at the age of less than 1 year. It shows that FOHR starts high during the first 1.5 years of life, declines with treatment and time, and from the age of 5 years remains relatively stable. Figure 3A displays the expected FOHR in two scenarios where tonsil position is either 0 mm (first quartile in observed data; Q1) or +8.6 mm (third quartile in observed data; Q3). The other variables were set to the median (head-circumference: 0.51 SD) and reference category (lambdoid sutures: open). It visualizes the difference in FOHR associated with tonsil position at Q1 and Q3: at age 0 an FOHR of 0.44 (Q1 range 95% CI band: [0.42–0.47]) versus 0.49 (Q3 range 95% CI-band: [0.45–0.52]), and at age 5 years an FOHR of 0.34 (Q1 range 95% CI-band [0.33–0.36]) versus 0.38 (Q3 range 95% CI-band [0.36–0.41]).

Results of the mixed-model for tonsil position are given in Table 3. Ten percentage-point higher FOHR was associated with a +1. 597 mm increase in tonsil position (95% CI[0.410–3.047]). Figure 4 visualizes the estimated development of tonsil position over time for different scenarios with regard to FOHR values, head-circumference, and closed lambdoid sutures at the age of less than 1 year. It presents a steep increase in tonsil position during the first 2.5 years of life, after which it slows down. Figure 4A shows the expected tonsil position in two scenarios, where FOHR is either 0.33 (Q1) or 0.41 (Q3), and shows an overlap between their 95% CIs. Again, for these scenarios, the other independent variables are set to median or reference values.

Closed Lambdoid Sutures and Head-circumference

Figure 3B, C display the corresponding plots of FOHR for the scenario in which head-circumference varies between its Q1 and Q3, and lambdoid suture closure at the age of less than 1 year is present, or not present. Increase in head-circumference was associated with an increase in FOHR (see Table 2, head-circumference: odds ratio = 1.102 (95% CI[1.063–1.140]). There was no clear evidence for differences in FOHR depending on whether patients presented with closed lambdoid sutures at the age of less than 1 year.

Figure 4B, C shows the corresponding effects on tonsil position for the scenarios in which head-circumference varied between Q1 and Q3, and lambdoid suture closure before 1 year of age was present or not present. Table 3 shows that there was no evidence for an association between tonsil position and head-circumference. Closed lambdoid sutures before 1 year of age were associated with a +6.990 mm increase in tonsil position (95% CI [3.614–10.276]).

DISCUSSION

In this study focusing on ventriculomegaly and TH in children with Crouzon syndrome, we have identified three main findings. First, we aimed to determine how ventriculomegaly and TH develop and progress over time. We found that ventriculomegaly is present in 29% at onset, the prevalence increases to 49% shortly after skull expansion, mostly in the first 1.5 years, then declines and normalizes over time and following treatment, remaining relatively stable from 5 years of age onward. TH is present in 11% at onset, with time and despite treatment (ie, vault expansion, ETV, or VP-shunting), prevalence increases to 46%, with the biggest increase happening in the first 2.5 years. Second, we aimed to determine how ventriculomegaly and TH relate to one another. We found that FOHR and tonsil position were associated, and that a 10% increase in FOHR was associated with a +1.6 mm increase in tonsil position. Third, we aimed to determine which clinical traits (if any) were associated with TH or ventriculomegaly. We found that FOHR is associated with head-circumference but not with closed lambdoid sutures before 1 year of age, and TH is associated with closed lambdoid sutures before 1 year of age, but not with head-circumference.

The prevalence of 49% of ventriculomegaly is in line with the reported prevalence of 30%–70% in children with Crouzon syndrome.[18–20] The prevalence of 46% of patients with TH ≥ +5 mm is similarly in line with reported

Table 2. Mixed-model for FOHR

	OR	95% CI 2.5%	97.5%
Intercept	0.756	0.677	0.845
Age at measurement*			
Tonsil position	1.021	1.012	1.030
Head circumference†	1.102	1.063	1.140
Closed lambdoid sutures <1 year	1.103	0.971	1.266
Expected FOHR at 0 and 5 years by specific covariate values‡			

Tonsil Position§	Expected FOHR	95% CI	
Age 0 Q1: 0.0	0.442	0.415	0.470
Q3: +8.6	0.486	0.449	0.524
Age 5 Q1: 0.0	0.343	0.327	0.360
Q3: +8.6	0.384	0.363	0.405
Head-circumference†			
Age 0 Q1: −0.66	0.434	0.403	0.467
Q3: 1.39	0.484	0.452	0.516
Age 5 Q1: −0.66	0.336	0.317	0.355
Q3: 1.39	0.382	0.362	0.400
Closed lambdoid sutures <1 year			
Age 0 open	0.462	0.431	0.493
Closed	0.487	0.456	0.518
Age 5 open	0.361	0.345	0.378
Closed	0.385	0.355	0.415

*The nonlinear effect of age at measurement was used in the model, but cannot be represented by a single parameter estimate and the corresponding estimates do not have direct clinical interpretation.
†In SD.
‡The other covariates were set to reference/median values (tonsillar position: +3.88 mm, head- circumference: 0.51 SD, lambdoid suture: open).
§Values represent tonsil position in mm relative to the FM, where tonsillar herniation past the FM is represented as positive numbers, and a position above the FM as negative numbers.
OR: odds ratio; Q1: first quartile in observed data; Q3: third quartile in observed data.
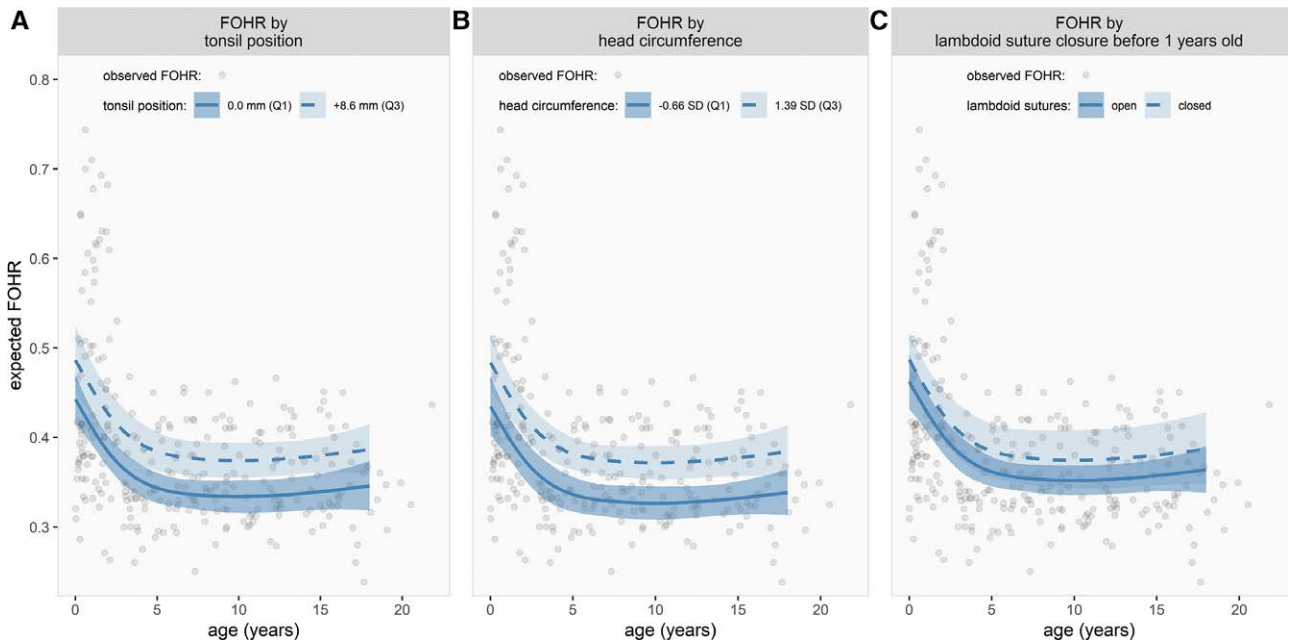
Fig. 3. Expected FOHR across age by 3 different covariate values. Expected FOHR and corresponding 95% CI across age, by specific covariate values: FOHR by tonsil position (A); FOHR by head circumference (B); FOHR by lambdoid suture closure before the age of 1 year (C). Variables that are not shown in a particular panel were set to reference/median values (tonsillar position: +3.88 mm, head-circumference: 0.51 SD, lambdoid suture: open).

Table 3. Mixed-model for Tonsil Position

		95% CI	
	Estimate	2.5%	97.5%
Intercept	−11.616	−17.882	−6.232
Age at measurement*			
FOHR: Per 10% increase	+1.597	+0.410	+3.047
Head circumference†	−0.424	−1.569	+0.303
Closed lambdoid sutures	+6.990	+3.614	+10.276
< 1 year			

Expected tonsil position at 0 and 5 years by specific covariate values‡			
FOHR	**Expected Tonsil Position**	**95% CI**	
Age 0 Q1: 0.33	−6.558	−9.048	−4.020
Q3: 0.41	−5.279	−7.233	−3.088
Age 5 Q1: 0.33	+1.518	+0.190	+3.185
Q3: 0.41	+2.798	+1.347	+4.597
Head-circumference†			
Age 0 Q1: −0.66	−5.431	−7.459	−3.120
Q3: 1.39	−6.295	−9.017	−3.648
Age 5 Q1: −0.66	+2.646	+0.929	+4.801
Q3: 1.39	+1.781	+0.269	+3.517
Closed lambdoid sutures			
<1 year			
Age 0 Open	−5.920	−8.086	−3.585
Closed	+1.079	−2.497	+4.496
Age 5 Open	+2.157	+0.878	+3.806
Closed	+9.156	+6.105	+12.155

*The nonlinear effect of age at measurement was used in the model, but cannot be represented by a single parameter estimate and the corresponding estimates do not have direct clinical interpretation.

†In SD.

‡The other covariates were set to reference/median values (FOHR: 0.37, head circumference: 0.51 SD, lambdoid sutures: open).

Q1: first quartile in observed data; Q3: third quartile in observed data.

Values represent tonsil position in millimeters relative to the FM, where tonsillar herniation past the FM is represented as positive numbers, and a position above the FM as negative numbers.

prevalence of 38%–70% in Crouzon patients.[21,22] In the majority of our patients, ventriculomegaly preceded the development of TH. However, our cohort shows different orders of occurrence of ventriculomegaly and TH, which illustrates the unpredictable nature of developing ventriculomegaly and/or TH.

In line with studies that have shown that premature closure of the lambdoid sutures is associated with development of TH ≥ +5 mm,[23,24] we found a strong association between closed lambdoid sutures within the first year of life and a +6.990 mm increase in tonsil position (95% CI [3.614–10.276]). We found no evidence for an association between tonsil position and head-circumference.

A study by Coll et al[20] showed a statistically significant association between the presence of hydrocephalus and TH in Crouzon patients, as determined by a chi-square test. This study expands on that finding by demonstrating that a 10% increase in FOHR was associated with a +1.6 mm increase in tonsil position.

Many theories have been postulated to explain hydrocephalus in syndromic craniosynostosis.[18,25] However, to date, no unifying theory has been able to explain all variations of manifestations of hydrocephalus and TH.[11,26] In Crouzon patients, there have been big differences in the prevalence of hydrocephalus and TH ≥ +5 mm on their own, but also in how often they occur together between studies using single time-point measurements and serial measurements.[20,23]

In this report, the great variation in sequence in which ventriculomegaly and TH ≥ +5 mm can occur is exemplified in our relatively large and homogenous group of only Crouzon patients with repeated measurements. Our study showed patients who start with TH ≥ +5 mm and develop
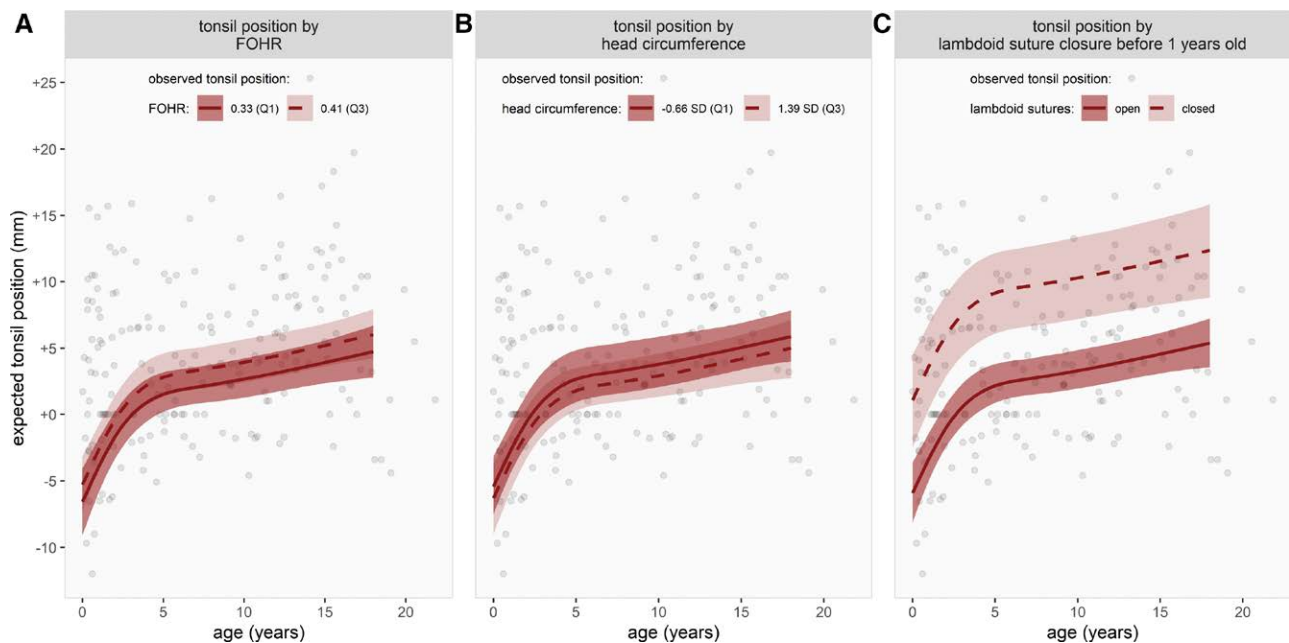
Fig. 4. Expected tonsil position across age by 3 different covariate values. Expected tonsillar position and corresponding 95% CI across age, by specific covariate values: Tonsil position by FOHR (A); Tonsil position by head circumference (B); Tonsil position by lambdoid suture before the age of 1 year (C). Variables that are not shown in a particular panel were set to reference/median values (FOHR: 0.37, head-circumference: 0.51 SD, lambdoid sutures: open).

ventriculomegaly (n = 1), but also those who start with ventriculomegaly and develop TH ≥ +5 mm (n = 5), those in whom ventriculomegaly and TH ≥ +5 mm are detected at the same time (n = 12), those who start with ventriculomegaly and never get TH ≥ +5 mm (n = 13), and those who have TH ≥ +5 mm and never develop ventriculomegaly (n = 11). These variations exemplify why it is so difficult to predict at onset which clinical course an individual patient will follow and shows the need for individual treatment plans for Crouzon patients.

Figures 3 and 4 show that although FOHR is high at onset, it declines and remains stable from 5 years of age onward. Tonsil position, on the other hand, continues to increase even after the age of 5 years, when FOHR remains stable. This could indicate that TH ≥ +5 mm on its own does not contribute to ventriculomegaly in Crouzon patients. This is supported by our finding that only one in 18 patients who eventually developed both TH ≥ +5 mm and ventriculomegaly developed TH ≥ +5 mm before developing ventriculomegaly. Furthermore, because TH ≥ +5 mm rarely causes neurological deficits, we should question how much of the treatment protocol should be focused on treating/stabilizing TH.[11,27,28]

Recent studies show a relationship between ventriculomegaly and increased diffusivity values in white matter tracts of the corpus callosum and cingulate gyrus.[29] This is associated with internalizing and externalizing behavior, showing the importance of treating ventriculomegaly at onset in Crouzon patients.[30,31]

This study's first limitation is its retrospective aspect. Over time a shift occurred in the availability of brain imaging material. Starting in 2007, we implemented a protocol, including MRI assessment before surgery. Patients who were treated before this time underwent only CT imaging;

thus, tonsil position before surgery could not be determined. Most of these patients underwent MRI assessment after first vault surgery.

The second limitation is that we did not have a control group of patients who did not undergo surgical intervention because we aimed to operate on all children before 1 year of age. We therefore cannot determine what changes in FOHR or tonsil position are due to natural progression or due to iatrogenic effects. Similarly, in our small group of patients who underwent VP-drain/ETV, some showed increase in TH; we could not determine if this was despite VP-drain/ETV, or if this was due to iatrogenic effects. These could be topics of interest for future studies.

In conclusion, we found that FOHR was large at onset and that treating ventriculomegaly gives a decrease and stabilization in FOHR over time. FOHR and tonsil position were associated, and a 10% increase in FOHR was associated with a +1.6 mm increase in tonsil position. Increased head-circumference was associated with an increased FOHR, and closed lambdoid sutures before 1 year of age were associated with a +6.92 mm increase in tonsil position. Overall, the more common sequence is first occurrence of ventriculomegaly, followed by TH, although we cannot claim a causal relationship.

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