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Enlarged anterior cranial fossa and restricted posterior cranial fossa, the disproportionate growth of basicranium in Crouzon syndrome

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ABSTRACT

Crouzon syndrome patients develop normal intracranial volume and potential restricted posterior cranial fossa volume with growth. This study aims to trace the segmental anterior, middle and posterior cranial fossae volume, and structural morphology in these patients, in order to help discern more focused and individualized surgical treatment plan. Ninety-two preoperative CT scans (Crouzon, n = 36; control, n = 56) were included, and divided into 5 age related subgroups. CT scans were measured using Mimics and 3-matics software. Overall, Crouzon syndrome patients grew to a 27% ($p = 0.011$) increased anterior cranial fossa volume and a 20% ($p = 0.001$) decreased posterior cranial fossa volume, with normal middle cranial fossa and entire intracranial volume measurement. The posterior cranial fossa of Crouzon syndrome initially developed significantly reduced volume (19%, $p = 0.032$), compared to normals, from 6 months of age, and remained reduced thereafter. The 7.63 mm shortening of posterior cranial fossa length contributed most to the shortened entire cranial length (9.30 mm, $p = 0.046$). Although the entire cranial volume of Crouzon syndrome is normal overall, the segmental anterior, middle and posterior cranial fossae developed disproportionately. The early significant and lifelong restricted posterior cranial fossa addresses the importance of early posterior cranial expansion. Ideally expansion would have vectors in all three dimensions.

1. Introduction

Crouzon syndrome, with a frequency of 1 in 62500 newborns, is the most common form of syndromic craniosynostosis (Medicine, 2019). Multiple sutures synostoses are more commonly seen in Crouzon syndrome patients than other craniosynostoses, and this may limit the development of normal cranial capacity (Blount et al., 2007). The greater number of involved sutures, the higher risk of intracranial hypertension (Renier et al., 1982). Reduced overall intracranial volume, alone, seems insufficient to account for intracranial hypertension, because increased intracranial pressure could also be attributed to venous hypertension, obstructive sleep apnea, ventriculomegaly (hydrocephalus) (Bristol et al., 2004; Gault et al., 1992). However, Crouzon syndrome patients have a higher percentage of elevated intracranial pressure, suggesting an imbalanced relationship between the cerebral tissue and skull capacity.

Normal intracranial volume of Crouzon syndrome was observed in many studies, no matter whether these Crouzon syndrome patients were affected by one suture synostosis, multiple sutures or even progressive pansynostosis (Fok et al., 1992; Gault et al. 1990, 1992). A smaller posterior cranial fossa of syndromic craniosynostosis patients was first documented by Hoffman (Hoffman and Tucker, 1976). The restricted posterior cranial fossa could be a predisposing factor for cerebellar tonsillar herniation, which also distinguishes Crouzon syndrome from other craniosynostoses (Calandrelli et al., 2016; Cai et al., 2008). Moss (Moss, 1959) considered the anterior cranial base as the prime site of development of structural abnormalities in Crouzon syndrome; yet Burdi

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et al. (Burdi et al., 1986) speculated early fusion of the ethmosphenoid synchondrosis determined the craniofacial malformations in Crouzon syndrome. The role of the posterior cranial fossa anatomy was not been excluded as the major influencing factor.

The question that should be asked then is, could the local craniocerebral disproportion in the posterior cranial fossa be the decisive factor, resulting in the high occurrence rate of elevated intracranial pressure and Chari malformation in Crouzon syndrome (Rijken et al., 2015; Bristol et al., 2004)? If so, what is the development of anterior and middle cranial fossae like in this group of patients? Therefore, this study aims to investigate the temporal sequence of the development of segmental anterior, middle and posterior cranial fossae, using 3-dimensional volume and morphological measurements.

2. Material and methods

This is a retrospective study performed in accordance with the Institutional Human Investigation Committee (HIC 1101007932) of Yale university. Computed tomographic scans were obtained from all subjects without a history of any previous surgical intervention. **Caucasian** Crouzon syndrome patients and age- and gender-matched **Caucasian** controls without confounding disease were included. The CT scans were divided into 5 subgroups based on age: 0–6 months, 6 months to 2 years, 2–6 years of age, 6–18 years of age, and older than 18 years. Demographic information was tabulated.

Digital imaging and data were digitized and measured using Mimics (version 19.0; Materialise, Leuven, Belgium) and 3-matics software (version 11.0; Materialise, Leuven, Belgium). An interobserver analysis was performed in a series of test patients prior to the completion of data analysis, and the intraclass correlation coefficients were greater than 0.94. All the landmark points, generated lines, angles and volumes were measured twice by the same observer. The definitions of measurements were summarized (Table 1).

The cranial volume and segmented cranial fossa volume were measured as described in the flow chart (Fig. 1). The intracranial volume (ICV) was semiautomatically produced using the regional changes in growth with a preprogramed soft tissue Hounsfield threshold, using Mimics. Only the area internal to the cranial vault bone is included in the calculation of ICV. The volume of segmental anterior cranial fossa (ACF), middle cranial fossa (MCF) and posterior cranial fossa (PCF) were automatically calculated after the entire ICV was separated by defined planes (Lu et al., 2019c). The cranial fossae and upper cranial volume were first separated by a splitting plane (defined as a plane perpendicular to sagittal plane, at a point, one centimeter higher than the middle point of bilateral uppermost orbital rim points, and the internal occipital protuberance) (Iqbal et al., 2017; Fernandes et al., 2016; Kanodia et al., 2012), for the entire ICV. Subsequently, ACF, MCF and PCF were separated by the planes perpendicular to this splitting plane, at the posterior borders of the lesser wings of the sphenoid, and the superior border of the petrous temporal bone, respectively (Iqbal et al., 2017; Naran et al., 2017). Each segmental portion was manually inspected as well to ensure the integrity of the specific measurement landmarks of the individual cranial fossa.

Test of normality was produced using Shapiro–Wilk test (SPSS, v.24.0, IBM Corp., Armonk, NY). The type 3 t-test was used to compare measurements between Crouzon syndrome and controls in both age-subgroup analysis and overall comparison (Microsoft Excel, v.2016, Microsoft Corp., Redmond, WA). Pearson correlation coefficients were calculated to evaluate the correlation among the measured indicators (SPSS, v.24.0, IBM Corp., Armonk, NY). All statistical analyses were two-sided, statistical significance was set at $p < 0.05$. Measurements with correlation coefficients $r > 0.6$, were identified have a strong correlation.

3. Results

3.1. Demographic Data

A total of 92 computed tomographic scans were included (Crouzon, n = 36; control, n = 56). Age distributions were as follows: in Crouzon group, 0–6 months (n = 8, mean age of 0.27 ± 0.16 year); 6 months to 2 years (n = 5, mean age of 1.04 ± 0.29 years), 2–6 years of age (n = 6, mean age of 4.21 ± 1.17 years), 6–18 years of age (n = 6, mean age of 12.33 ± 4.59 years) and 11 patients older

Table 1
Definition of landmarks, cephalometric distances and angles.

Variable	Definition
Splitting plane	A plane perpendicular to sagittal plane and connected the point one centimeter higher than the middle point of bilateral uppermost orbital rim points and the internal occipital protuberance
Anterior cranial fossa depth	The farrest distance from the base of anterior cranial fossa to splitting plane
Middle cranial fossa depth	The farrest distance from the base of middle cranial fossa to splitting plane
Posterior cranial fossa depth	The farrest distance from the base of posterior cranial fossa to splitting plane
Anterior cranial fossa width	The distance between bilateral junctions of the posterior borders of the small wings of the sphenoid and temporal bone, measured on the splitting plane
Middle cranial fossa width	The farrest distance between bilateral middle cranial fossae wall, measured on the splitting plane
Posterior cranial fossa width	The distance between bilateral junctions of the arcuate eminence and petrous temporal bone, measured on the splitting plane
Anterior cranial fossa length	The distance from the point one centimeter higher than the middle point of bilateral uppermost orbital rim points to the center of sella
Middle cranial fossa length	The distance between the junction point of the posterior borders of the small wings of the sphenoid meets temporal bone, and ipsilateral junction point of the arcuate eminence meets petrous temporal bone, measured on the splitting plane
Posterior cranial fossa length	The distance between the center of sella and the internal occipital protuberance
Entire cranial length	The distance from the point one centimeter higher than the middle point of bilateral uppermost orbital rim points to the internal occipital protuberance
Anterior cranial fossa center angle	The angle between 2 planes follow bilateral posterior borders of the small wings
Middle cranial fossa center angle	The angle between a plane follow posterior borders of the small wing, and ipsilateral arcuate eminence and superior border of the petrous temporal bone
Posterior cranial fossa center angle	The angle between 2 planes follow bilateral arcuate eminence and superior border of the petrous temporal bone
Upper cranial height	The farrest distance between cranium to the splitting plane

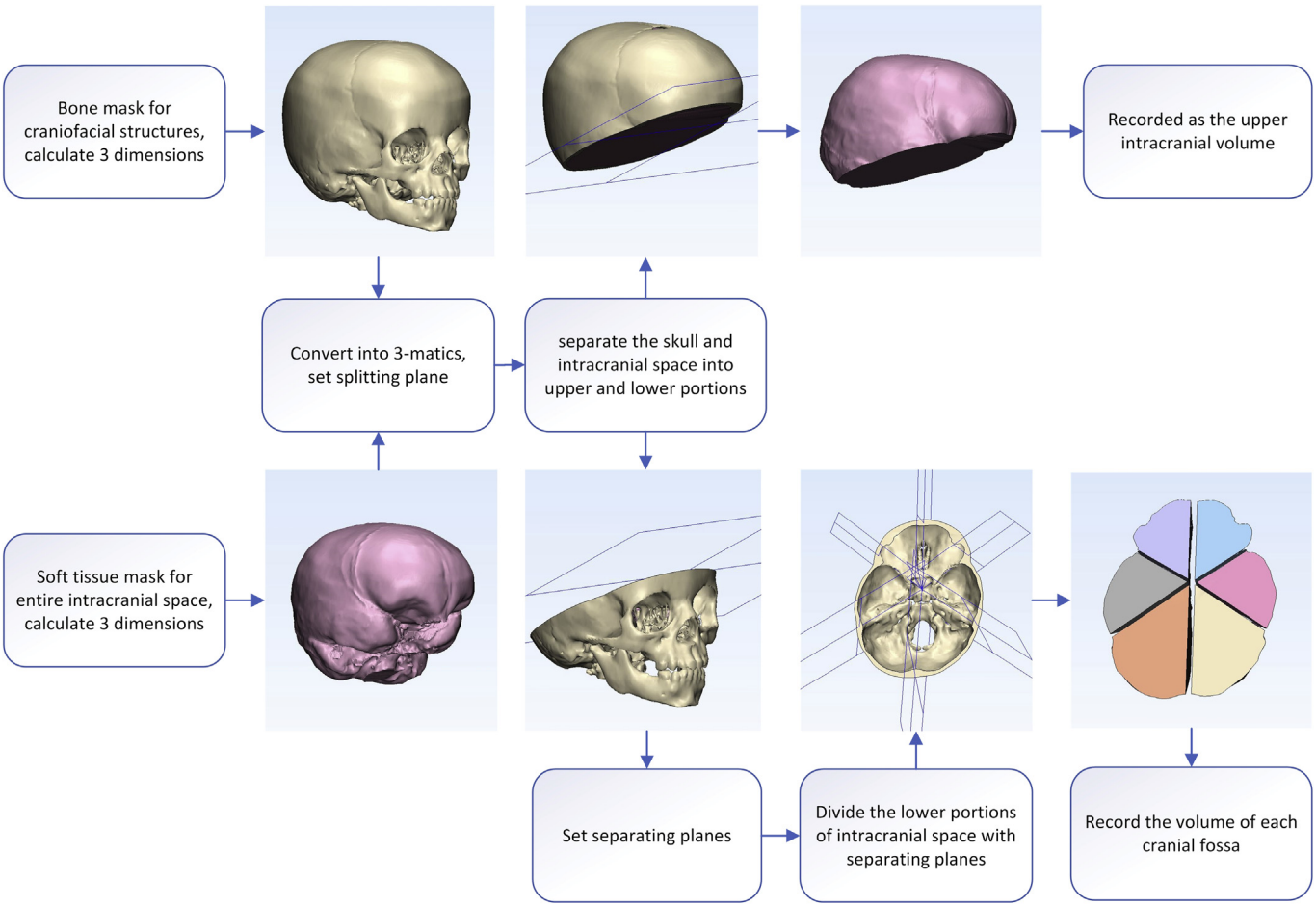

Fig. 1. The flow chart of measurement process of cranial volume and segmental cranial fossa volume.

than 18 years of age. The Crouzon group consisted of 12 males and 24 females, and in the controls were 21 males and 35 females ($p = 0.687$) (Table 2).

3.2. Overall analysis

Overall, Crouzon syndrome patients grew a 27% ($p = 0.011$) increased anterior cranial fossa volume and a 20% ($p = 0.001$) decreased posterior cranial fossa volume. This was accompanied by a normal middle cranial fossa and entire intracranial volume (Fig. 2, Table 3). The lengths of anterior, middle and posterior cranial fossa were all reduced, by 4.23 mm ($p = 0.012$), 5.26 mm ($p = 0.010$) and 6.43 mm ($p = 0.035$), respectively, resulting in a 11 mm ($p = 0.010$) shortening of the entire cranial anteroposterior length. The depths of the cranial fossae were changed from anterior to posterior as well. The anterior cranial fossa was deepened by 16% ($p = 0.003$), the depth of middle cranial fossa depth is normal, and the posterior cranial fossa was more shallow by 6% ($p = 0.032$). The widths of all fossae were normal in overall.

3.3. Correlation analysis

The correlation between occipitofrontal circumference and intracranial volume of Crouzon syndrome is similar with normals ($r = 0.880$ vs. $r = 0.898$, both $p < 0.001$) (Fig. 3). The reduced posterior cranial fossa volume is a higher contributor to the reduced intracranial volume of Crouzon syndrome ($r = 0.701$, $p < 0.001$), than anterior and middle cranial fossae volume ($r = 0.646$, $p < 0.001$, and $r = 0.538$, $p = 0.001$) (Fig. 4). In normal individuals, the posterior cranial fossa volume has an almost equal correlation with its length ($r = 0.921$, $p < 0.001$), depth ($r = 0.894$, $p < 0.001$), and width ($r = 0.879$, $p < 0.001$). However, in Crouzon syndrome, the correlation between the posterior cranial fossa volume, and all its three dimensions, was reduced ($r = 0.629$, $r = 0.704$ and $r = 0.763$ for length, depth and width, respectively), suggesting an anomalous malformation. The volume of anterior and middle cranial fossae have higher correlations to their depths ($r = 0.880$ and $r = 0.847$, both $p < 0.001$) in Crouzon syndrome. However, in normal individuals, the volume of middle crania fossa is more closely related to its length ($r = 0.852$, $p < 0.001$) (Table 4, Fig. 5).

3.4. Age subgroup analysis

Before 6 months of age, the cranial fossae volume and morphology measurements of Crouzon were divergent from controls, but they still were within normal ranges. The relatively significant changes were the increased anterior cranial fossa volume, and the decreased posterior cranial fossa volume, by 11% and 8%, respectively (Fig. 6).

From 6 months to 2 years of age, the posterior cranial fossa initially developed significantly reduced volume by 19% ($p = 0.032$) compared with normals, and remain reduced into adulthood by 16% ($p < 0.001$). The reduced cranial fossa volume was attributed to

Table 2
Demographic information of Crouzon syndrome and controls.

Age Group	Crouzon	control	p value
0–0.5			
Number	8	9	
Age ± SD (years)	0.27 ± 0.16	0.24 ± 0.14	p = 0.742
Sex			
Male	4	4	p = 0.832
Female	4	5	
0.5–2			
Number	5	10	
Age ± SD (years)	1.04 ± 0.29	1.08 ± 0.35	p = 0.812
Sex			
Male	2	3	p = 0.739
Female	3	7	
2–6			
Number	6	8	
Age ± SD (years)	4.21 ± 1.17	4.49 ± 0.99	p = 0.647
Sex			
Male	2	4	p = 0.568
Female	4	4	
6–18			
Number	6	12	
Age ± SD (years)	12.33 ± 4.59	12.39 ± 4.11	p = 0.980
Sex			
Male	3	7	p = 0.763
Female	3	5	
18–62			
Number	11	17	
Age ± SD (years)	35.55 ± 11.08	31.79 ± 13.57	p = 0.431
Sex			
Male	1	3	p = 0.522
Female	10	14	
0–62			
Number	36	56	
Age ± SD (years)	13.82 ± 16.37	13.18 ± 15.14	p = 0.851
Sex			
Male	12	21	p = 0.687
Female	24	35	

its 10% (p = 0.035) narrowed width, and 9% (p = 0.075) shortened anteroposterior length during this timeframe. This 7.63 mm shortening of posterior cranial fossa length contributed most to the shortened, entire intracranial length (9.30 mm, p = 0.046). Both shortened lengths remain into adulthood, by 6.97 mm (p = 0.019) and 13.68 mm (p < 0.001), respectively. The center angle of anterior cranial fossa was increased by 8.35° (p = 0.017), describing to the enlargement of anterior cranial fossa volume (40%, p = 0.385), during this timeframe.

From 2–6 years of age, the occipitofrontal circumference was reduced by 6% (p = 0.031) when compared with normals, at 2 years of age, and remained reduced through 18 years of age (7%, p = 0.002). The reduced length of anterior cranial fossa reached statistical significance (6.42 mm, p = 0.011) at this time period, from the initially slight increase (4.54 mm, p = 0.155) before 6 months of age, and remained shortened thereafter.

After 6 years of age, the center angle of middle cranial fossa was 8.07° less (p = 0.020), when compared to normal, resulting a 14.24 mm shortened middle cranial fossa length (p < 0.001), accompanying a 13.15-degree (p = 0.014) greater posterior cranial fossa center angle.

In adulthood, the anterior cranial fossa depth and width were increased 28% (p = 0.008) and 6% (p = 0.047) respectively, resulting in increased anterior cranial fossa volume (p = 0.007). However, the depth of posterior cranial fossa was reduced by 8% (p = 0.001) (see Table 5).

4. Discussion

Intracranial volume of normal individuals has been documented in previous studies(Dekaban, 1977; Sgouros et al., 1999; Abbott et al., 2000; Lee et al., 2010). Although detailed measurement methods are not exactly consistent, the result of intracranial volume in this study are consistent with previous studies (Table 6). Crouzon syndrome patients have a higher risk of elevated intracranial pressure, likely in part, due to the multiple vault suture and base synchondroses fusion in early youth (Kreiborg et al., 1993). In agreement with previous studies, the overall intracranial volume of Crouzon syndrome is within normal limits (Fok et al., 1992; Gault et al. 1990, 1992), in both overall group comparison between Crouzon patients and normals, and the age subgroup analysis. However, 92% (33 of 36) of Crouzon patients, in this study, presented with multiple suture synostosis. However, the development

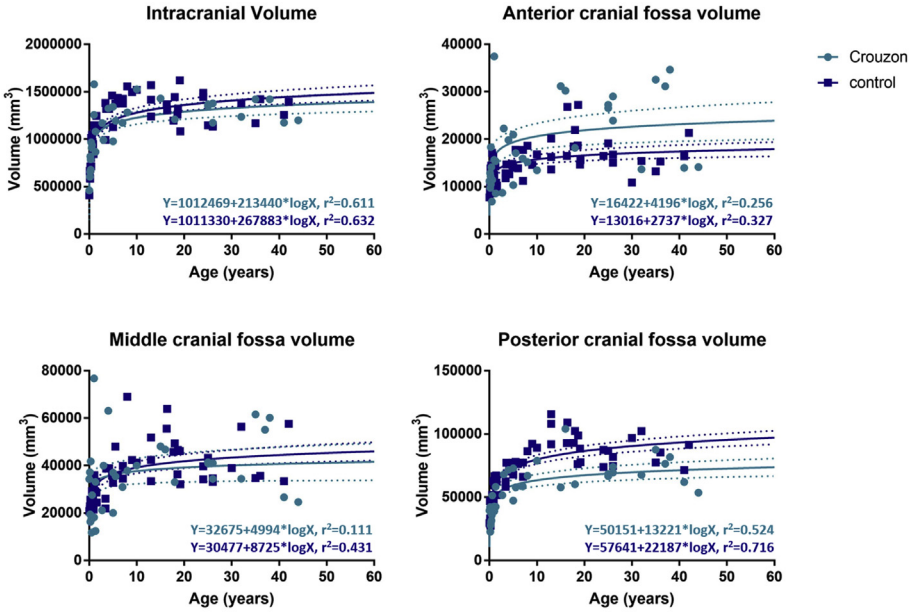

Fig. 2. The growth curves of intracranial volume, anterior, middle and posterior cranial fossa volume in both Crouzon syndrome and controls.

Table 3
Overall analysis results in the full age range (0–62 years of age) of Crouzon syndrome compared to controls.

Index	Crouzon, n = 36		Control, n = 56		T test	change %
	Ave	STD	AVE	STD	p	
Anterior cranial fossa (ACF)						
ACF volume	18758.83	8358.94	14785.41	4011.57	0.011*	27%
ACF depth	20.00	5.00	17.23	2.26	0.003**	16%
ACF width	100.13	12.92	97.05	9.61	0.224	3%
ACF length	63.13	6.69	67.36	9.06	0.012*	−6%
ACF center angle	115.73	8.30	114.24	7.55	0.387	1%
Middle cranial fossa (MCF)						
MCF volume	35456.07	15096.97	36119.61	11138.22	0.821	−2%
MCF depth	27.71	5.26	28.44	3.71	0.470	−3%
MCF width	121.96	17.17	125.95	13.57	0.243	−3%
MCF length	73.73	8.46	78.99	10.62	0.010*	−7%
MCF center angle	68.86	4.51	70.95	3.94	0.026*	−3%
Posterior cranial fossa (PCF)						
PCF volume	57513.62	18408.28	71990.24	21969.12	0.001**	−20%
PCF depth	30.61	4.58	32.73	4.43	0.032*	−6%
PCF width	114.52	20.37	118.28	13.83	0.335	−3%
PCF length	87.08	14.47	93.51	13.32	0.035*	−7%
PCF center angle	107.06	7.74	103.67	5.82	0.029*	3%
Overall morphology						
Intracranial volume	1120923.32	277400.27	1180534.88	282210.07	0.331	−5%
Circumference	489.74	61.61	515.28	66.71	0.069	−5%
Upper volume	904551.09	232615.54	935604.50	229814.83	0.541	−3%
Upper height	87.02	9.27	84.60	7.74	0.207	3%
Entire cranial length	150.08	17.99	161.08	21.75	0.010*	−7%

* $p < 0.05$.
** $p < 0.01$.

of segmental anterior, middle and posterior cranial fossae follow different patterns.

The anterior cranial fossa volume of Crouzon syndrome was found have a significant initial enlargement overall, which is mainly contributed to by its depth and width. Calandrelli et al. proposed that the synostosis around the coronal ring caused the reduction in the growth of surrounding structures (Calandrelli et al., 2014). Therefore the enlarged anterior cranial fossa may be an effective compensatory development, at least early on. It may not only compensate for the coronal synostosis, but also to the inherent genetic bone growth malformations effective elsewhere (base and face) in Crouzon syndrome. This finding supports the concept that posterior cranial distraction is helpful in addressing the need for anterior cranial volume, although the anterior cranium may not be operated upon (Jong et al., 2012).

Specifically, this enlarged anterior cranial fossa seems to have 2 different pathologic phases. Before 6 months of age, all the depth, width and length of anterior cranial fossa measurements were normal. This suggests the anterior cranial fossa may not limit the growth of brain during this time period. Especially, the normal length of anterior cranial fossa, suggests, theoretically, the Crouzon patients may do not need anterior cranial advancement during this time.

However, after 2 years of age, the normal development of anterior cranial fossa in Crouzon syndrome was reduced. The

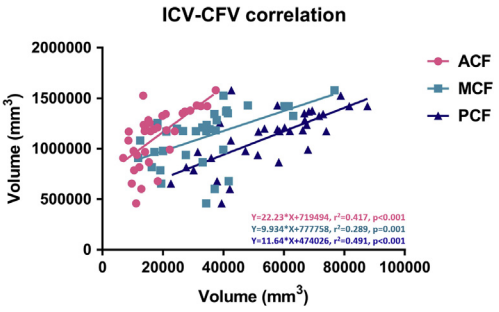

Fig. 4. The correlation of intracranial volume against anterior, middle and posterior cranial fossa volume of Crouzon syndrome.

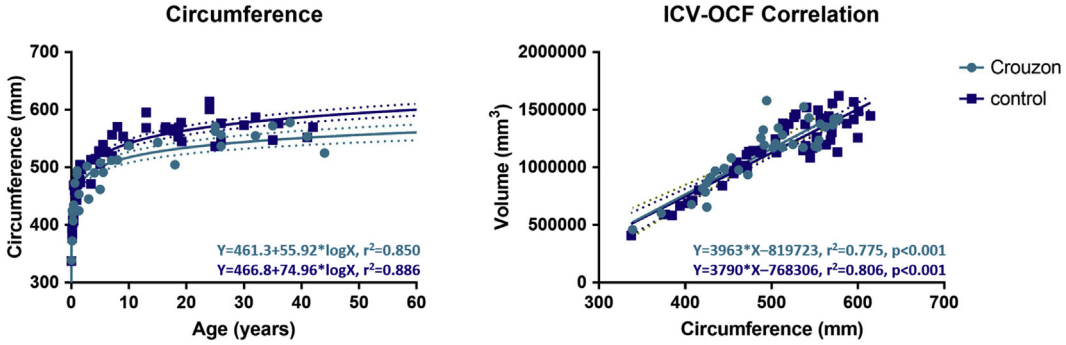

Fig. 3. The growth curves of occipitofrontal circumference and its correlation against intracranial volume in both Crouzon syndrome and controls. The circumference of Crouzon syndrome parallel to normals.

Table 4
Correlation analysis results of anterior, middle and posterior cranial fossa volume to the depth, width, length and center angle, in both Crouzon syndrome and controls.

Index	Crouzon			
	Depth	Width	Length	Center angle
Anterior cranial fossa				
Pearson r	0.880	0.831	0.476	0.411
P value	<0.001**	<0.001**	0.003**	0.013*
Middle cranial fossa				
Pearson r	0.847	0.801	0.494	−0.427
P value	<0.001**	<0.001**	0.002**	0.009**
Posterior cranial fossa				
Pearson r	0.704	0.763	0.629	0.240
P value	<0.001**	<0.001**	<0.001**	0.159
Index	control			
	Depth	Width	Length	Center angle
Anterior cranial fossa				
Pearson r	0.7255	0.677	0.608	0.327
P value	<0.001**	<0.001**	<0.001**	0.014
Middle cranial fossa				
Pearson r	0.835	0.762	0.852	0.361
P value	<0.001**	<0.001**	<0.001**	0.006**
Posterior cranial fossa				
Pearson r	0.894	0.879	0.921	−0.524
P value	<0.001**	<0.001**	<0.001**	<0.001**

* $P < 0.05$.
** $P < 0.01$.

length of anterior cranial fossa became significantly shortened, associated with ethmosphenoid, intersphenoidal and sphenofrontal synchondroses, all had reduced growth (Matras et al., 1977). This was also documented in a group of Crouzon syndrome patients aged from 5 to 7 years by Carinci et al. (Carinci et al., 1994), and in 6 months–11 years of patients by Matras et al., (1977) Meanwhile, the lower position of ethmosphenoid synchondrosis was also confirmed by Grayson et al. and Burdi et al. (Grayson et al., 1985; Burdi et al., 1986), which mirrors increased anterior cranial fossa depth.

Therefore, anterior cranial vault advancement alone, with the goal to provide more intracranial space for the brain development, may not be the ideal step to reshape the fronto orbital region in early infants (Posnick et al., 1995; Lu et al., 2019b).

The volume of middle cranial fossa in Crouzon syndrome is normal, although with a twisted shape in older patients, (i.e. a deepened and shortened form). The normal middle cranial fossa volume distinguishes Crouzon syndrome from another GFR2 mutation craniosynostosis syndrome, Apert syndrome. The Apert syndrome develops significantly restricted middle cranial fossa volume across all the observed timeframes, from 3 days to 26 years of age (Lu et al., 2019b). Therefore, the normal middle cranial fossa volume of Crouzon syndrome in this study, distinguishes itself from Apert syndrome, where the restricted anteroposterior length of middle cranial fossa is an intrinsic feature of the Apert patient skull.

The smaller posterior cranial fossa has been observed in many previous studies (Calandrelli et al., 2016; Cai et al., 2008), and is further supported by this study. Coll et al., however, documented in a group of Crouzon patients, with mean age of 8.5 months, that they had normal posterior cranial fossa volume (Coll et al., 2016). The data in this study shows the significantly restricted posterior cranial fossa, developed between 6 months and 2 years of age, which could explain the discrepancy with previous studies as they are generally younger at the time of measurement. On the other hand, the posterior fossa volume was found to be greater in male versus female Crouzon patients, with greater gender difference than normals (Fig. 7 more details will be presented in an ongoing study).

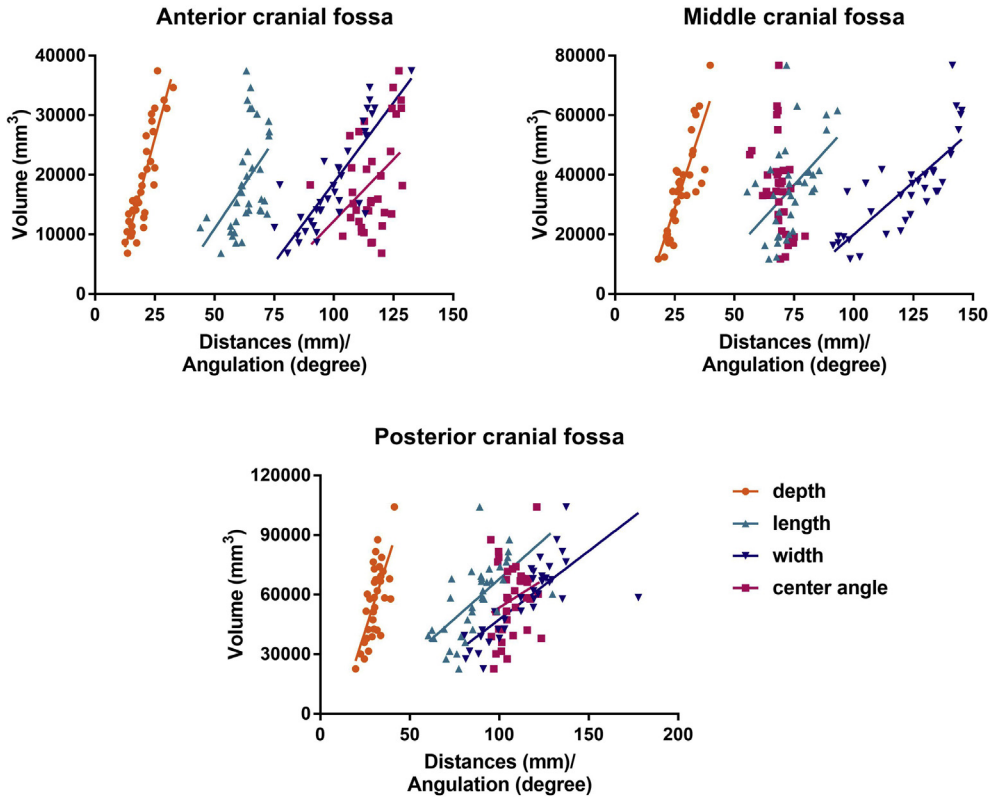

Fig. 5. The correlation of anterior, middle and posterior cranial fossa volume of Crouzon syndrome against with corresponding anteroposterior length, depth, width and center angle.

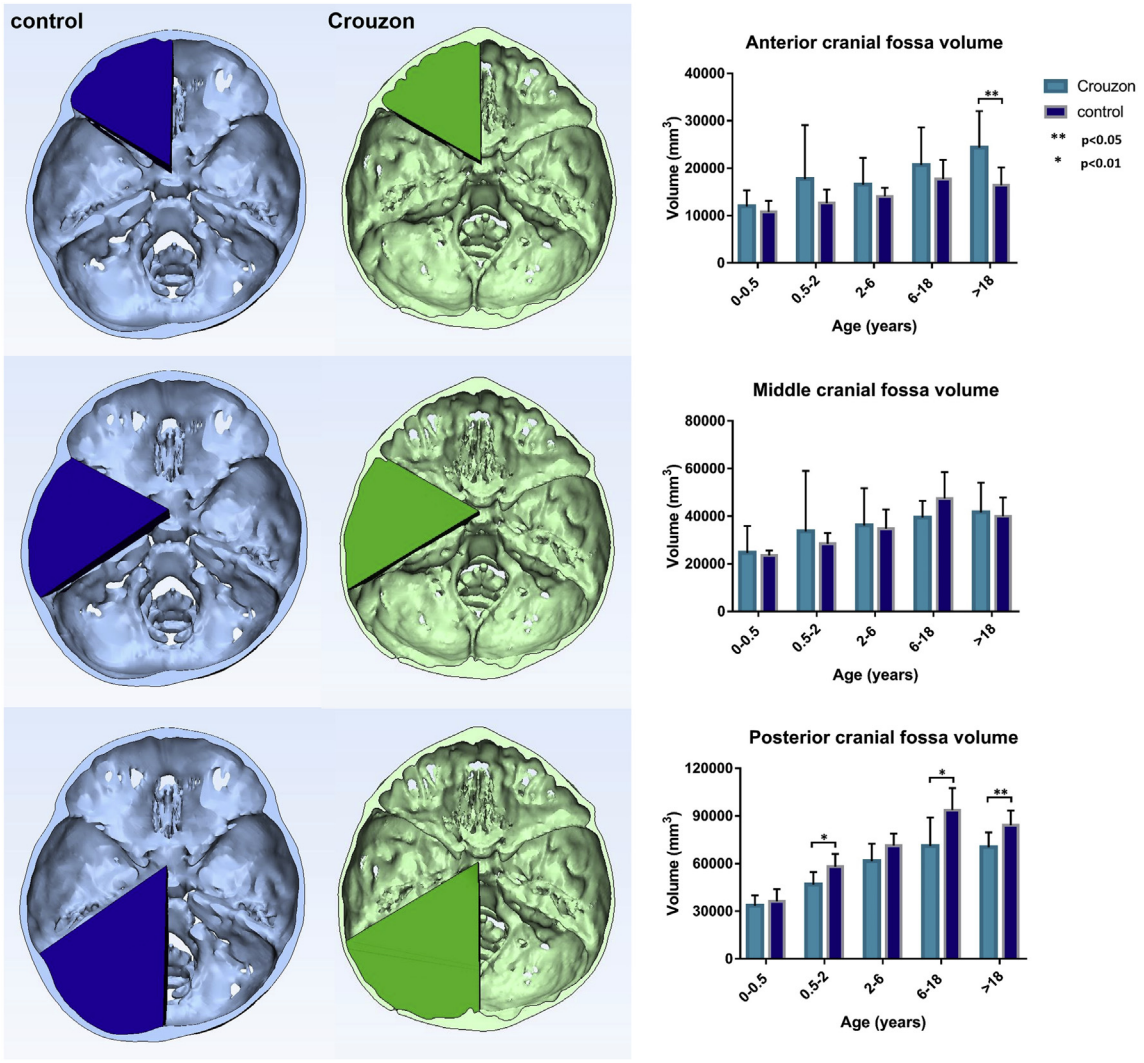

Fig. 6. The volumes of segmental anterior, middle and posterior cranial fossa of Crouzon syndrome compared with normals, in 5 age subgroups.

Therefore, if the included Crouzon syndrome subjects were dominated by patients younger than 6 months of age, or female patients, it could be more difficult to document a significant reduction of the posterior cranial fossa volume in this specific age group.

The posterior cranial fossa volume in Crouzon is more correlated with its width, rather than the almost balanced correlation of synchronously increased width, length and depth in normals. This may be explained by the early moderating growth of noted anteroposterior length. The length of posterior cranial fossa in Crouzon syndrome passes its fast growth period, earlier than normals (Fig. 8). Posterior fossa length reduction could be caused by both the premature fused lambdoidal sutures and other minor sutures around posterior cranial fossa (Kreiborg, 1981; Kreiborg and Bjork, 1982; Peterson-Falzone et al., 1981; Carinci et al., 1994), such as the parieto-squamosal arches (Calandrelli et al., 2014; Runyan et al., 2017). The anteriorly and inferiorly rotated clivus, i.e. the kyphotic cranial base angulation, however could be due to other features. An anterior growth vector, such as the compensatory growth for the limited posterior growth of occipital bone, which is inadequate to accommodate the growing cerebellum could be one of those factors (Moss, 1959; Lu et al., 2019a; Fearon, 2017; Tokumaru et al., 1996). This is also supported by the study of Bauder et al., in that posterior vault distraction osteogenesis can increase cranial base angulation, and at the same time increase posterior cranial volume (Bauder et al., 2015).

Posterior cranial fossa volume is abnormal in Crouzon patients just after birth, although it fails to reach statistical significance before 6 months. The reduced volume is comprised of a reduced depth, width and anteroposterior length, which suggests the desirability of posterior cranial expansion of Crouzon syndrome. This is not limited to only the anteroposterior linear distraction, but also mediolateral and vertical dimensions as well. All need to be addressed, in order to provide more space for posterior cranial fossa neural structures and improve entire cranial capacity.(Serlo et al., 2011; Choi et al., 2012; Senda et al., 2018; Nov 27. [Epub ahead of print]).

As a limitation of this study, the associated cranial vault synostosis pattern was not described. Crouzon syndrome is often associated with multiple sutures synostoses, and the suture pattern may change with growth. The order and rate of the involved sutures with synostosis likely impact the temporal progression and ultimate morphology (Carinci et al., 2005). Therefore, the initial associated synostosis pattern of Crouzon syndrome patients may vary with time, related to skull malformation, and individual suture abnormalities. The interaction between Crouzon syndrome and combined synostosis (additive effect or neutralization) needs more

Table 5
Age subgroup analysis results in Crouzon syndrome compared to controls.

Index	0–0.5				T test	0.5–2				T test	2–6				T test
	Ave	STD	AVE	STD	p	Ave	STD	AVE	STD	p	Ave	STD	AVE	STD	p
Anterior cranial fossa (ACF)															
anterior AVE	11951.36	3384.85	10795.45	2308.21	0.432	17692.68	11430.66	12664.59	2833.93	0.385	16513.29	5719.07	14035.17	1822.27	0.347
anterior depth AVE	17.14	4.13	15.96	1.67	0.470	18.56	4.37	15.90	1.95	0.253	18.62	3.96	16.88	1.97	0.354
anterior width	84.63	6.60	82.20	9.87	0.557	101.21	18.55	92.51	4.56	0.357	97.88	4.61	98.12	6.70	0.937
Anterior'-S′	55.30	7.04	50.76	5.02	0.155	61.87	5.61	63.38	2.91	0.595	62.60	3.60	69.02	4.34	0.011*
anterior angle	108.00	8.60	110.65	6.49	0.490	118.86	5.14	110.52	4.57	0.017*	114.33	4.01	115.47	6.15	0.683
Middle cranial fossa (MCF)															
middle AVE	24628.19	11278.31	23522.85	2096.77	0.792	33618.43	25407.61	28429.85	4536.23	0.673	36120.83	15659.33	34759.84	8069.79	0.851
middle depth AVE	26.99	7.66	25.71	2.08	0.660	27.69	7.64	25.63	2.19	0.584	27.48	5.28	27.70	2.77	0.931
middle width	98.37	6.84	103.87	10.40	0.214	113.77	17.43	117.77	7.59	0.645	125.81	10.04	127.72	7.00	0.700
middle length AVE	63.94	4.80	63.11	5.40	0.744	69.32	2.48	72.32	4.01	0.100	75.51	4.19	77.54	6.82	0.505
middle angle AVE	72.94	3.61	71.50	4.01	0.449	69.93	3.56	70.39	2.59	0.804	69.38	3.34	68.97	4.78	0.852
Posterior cranial fossa (PCF)															
posterior AVE	33428.02	6566.00	36229.28	7770.66	0.433	46734.83	7946.99	58054.38	8110.75	0.032*	61561.40	10851.49	71331.62	7565.19	0.094
posterior dept AVE	26.22	4.59	26.82	3.31	0.767	30.26	3.43	30.01	2.26	0.891	31.12	4.86	32.75	2.44	0.476
posterior width	88.68	6.77	93.69	8.91	0.209	100.31	8.15	111.38	6.27	0.035*	115.07	6.54	120.73	5.99	0.127
posterior'-s'	70.42	7.67	70.85	6.00	0.899	78.10	7.14	85.74	4.91	0.075	87.43	9.20	93.61	5.07	0.180
posterior angle	106.13	9.20	106.35	4.26	0.953	102.08	7.69	108.70	3.23	0.127	106.91	4.74	106.60	5.98	0.915
Overall morphology															
total volume	734145.79	167497.07	686781.46	165755.61	0.568	1144105.27	285056.75	1071271.01	119170.82	0.609	1166343.19	156747.19	1301533.03	161359.54	0.143
Circumference	406.25	33.38	399.55	35.21	0.693	466.56	28.10	471.95	18.60	0.711	483.15	24.38	513.99	20.15	0.031*
Upper volume	594130.64	192261.39	545686.31	149522.63	0.575	948013.37	250299.59	872973.37	107964.39	0.551	937952.17	132856.30	1061279.76	146067.51	0.127
upper height	75.32	10.18	72.71	6.83	0.551	92.72	9.39	84.40	5.08	0.121	88.62	2.37	88.98	4.67	0.852
anterior'-posterior'	125.83	12.38	121.66	10.35	0.467	140.15	7.29	149.45	6.75	0.046*	150.26	10.86	162.66	8.56	0.045*

Index	6–18				T test	18+				T test
	Ave	STD	AVE	STD	p	Ave	STD	AVE	STD	p
Anterior cranial fossa (ACF)										
anterior AVE	20694.46	7905.86	17716.51	4058.15	0.417	24363.38	7693.85	16429.32	3741.63	0.007**
anterior depth AVE	19.46	4.18	17.66	2.51	0.362	23.77	5.20	18.55	1.98	0.008**
anterior width	109.04	8.40	105.12	5.08	0.329	107.28	8.38	101.38	3.64	0.047*
Anterior'-S′	66.87	3.73	72.19	2.44	0.015*	67.64	3.90	74.29	4.23	<0.001**
anterior angle	122.32	7.88	116.96	11.13	0.258	117.11	7.60	115.85	6.06	0.648
Middle cranial fossa (MCF)										
middle AVE	39450.66	7003.41	47448.28	11026.19	0.082	41624.71	12495.83	39955.07	7847.62	0.698
middle depth AVE	29.12	2.81	31.29	4.31	0.220	27.60	3.60	29.89	2.93	0.094
middle width	132.21	7.04	137.02	6.13	0.188	135.15	7.73	133.79	4.98	0.612
middle length AVE	74.87	4.96	89.11	6.10	<0.001**	81.27	7.70	84.86	5.86	0.205
middle angle AVE	63.73	5.99	71.81	4.97	0.020*	67.91	1.68	71.32	3.39	0.002**
Posterior cranial fossa (PCF)										
posterior AVE	71085.20	17980.02	93650.58	13860.50	0.027*	70319.32	9335.76	84140.35	9224.58	<0.001**
posterior dept AVE	34.10	5.59	37.06	3.69	0.276	31.79	1.45	34.38	2.40	0.001**
posterior width	136.54	21.26	128.40	5.31	0.396	127.47	5.93	127.07	5.33	0.857
posterior'-s'	100.08	15.58	103.52	6.73	0.624	95.99	7.50	102.96	6.26	0.019*
posterior angle	112.58	9.05	99.43	4.07	0.014*	107.06	6.59	100.92	5.36	0.019*
Overall morphology										
total volume	1323798.06	149957.65	1409338.65	119309.38	0.298	1290065.10	106168.77	1294459.19	152255.33	0.932
Circumference	521.98	17.12	563.77	20.69	0.002**	555.96	16.32	568.40	23.31	0.117
Upper volume	1081294.40	125428.29	1091707.90	132693.22	0.882	1022744.00	68462.39	1014162.74	141454.03	0.838
upper height	91.70	6.69	87.04	5.74	0.218	90.25	2.68	87.39	5.73	0.099
anterior'-posterior'	165.57	10.24	176.21	5.45	0.052	163.68	5.02	177.35	9.06	<0.001**

* $P < 0.05$.
** $P < 0.01$.

Table 6
Intracranial volume of normal individuals previous and present studies.

Author	Dekaban (1977)	Sgouros et al. (1999)	Abbott et al. (2000)	Lee et al. (2010)	Present study
Study year	1977	1999	2000	2009	2019
Number	1058	68	157	143	56
Method	Mathematical formulas, based on x-ray	Birmingham software, based on MR	Persona software, based on CT scans	ImageJ software, based on CT scans	Mimics and 3-matics software, based on CT scans
ICV(ml)	mean	mean ± SD	range	mean	mean ± SD
0–6m	608.55	599.75 ± 190.90	494.0–909.1	744.80	686.78 ± 165.755
6m-2y	990.04	1055.33 ± 99.73	1024.9–1304.7	**7–12mo**: 939.67 **13–30mo**: 1117.52	1071.27 ± 119.17
2–6y	1228.55	1299.71 ± 246.34	1191.2–1427.8	**31–60mo**: 1271.29	1301.53 ± 161.36
6–18y	1399.16	1424.56 ± 139.13	1298.7–1472.9	**>61mo**: 1414.44	1409.34 ± 119.31

exploration. Therefore, a study which mainly focuses on individual types of suture fusion could be more helpful in developing a more complete understanding of potential mechanisms, as we investigate the comprehensive relationship between Crouzon syndrome genetic abnormalities and synostosis.

In summary, for the surgical approaches of patients with Crouzon syndrome, the posterior cranial expansion is ideally performed at a young age. Theoretically, it may be more effective, if the vectors are provided in multiple dimensions: anteroposterior, mediolateral and vertical directions. This more completely simulates the natural expansion pattern of posterior cranial fossa in normal individuals, producing a more balanced expansion pattern. However, the anterior cranial expansion is not as influential in Crouzon patients, especially younger than 2 years of age, if providing more space for brain development, is the main purpose of the intervention. However, for older Crouzon children, teenagers and adults, in order to normalize appearance and breathing and eating functions, it may be beneficial.

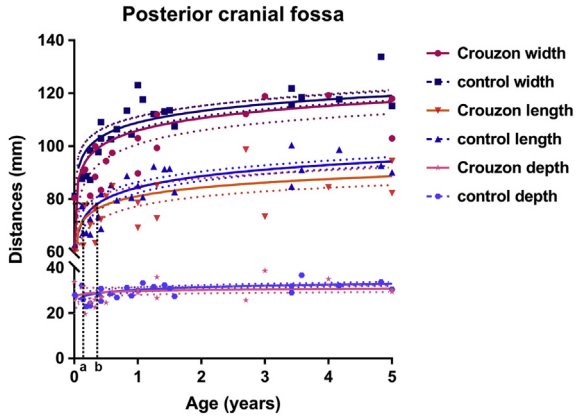

Fig. 8. The growth curves of width, length and depth of posterior cranial fossa. The length of posterior cranial fossa in Crouzon syndrome passes its fast growth period (point a), earlier than normals (point b).

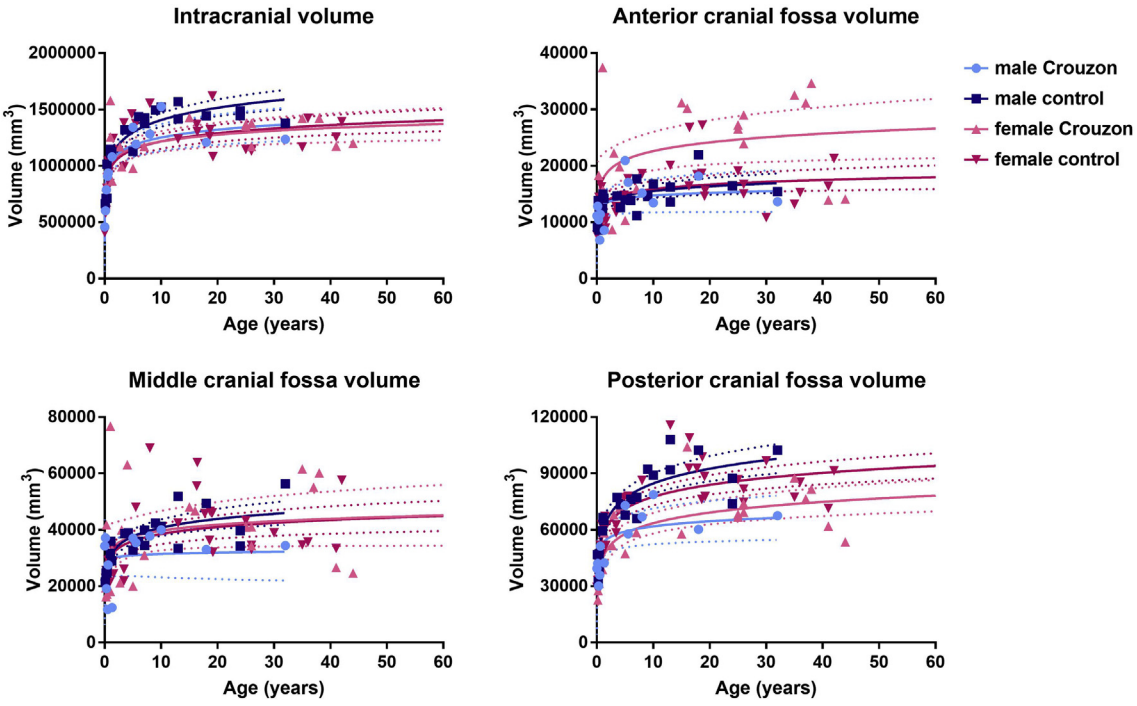

Fig. 7. The differences between gender, in the growth curve of segmental anterior, middle and posterior cranial fossa of Crouzon syndrome, compared with normals.

5. Conclusion

Although the entire cranial volume of Crouzon syndrome is normal overall, the segmental anterior, middle and posterior cranial fossae developed in a disproportionate manner. The enlarged anterior cranial fossa, at least temporally, reduces the necessity of anterior cranial advancement for Crouzon infants in the short term. The significant and lifelong restricted posterior cranial fossa speaks to the importance of posterior cranial expansion, early and multidimensionally, to be of greater benefit in Crouzon patients.

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