Child's Nervous System (2019) 35:329–335
https://doi.org/10.1007/s00381-018-3957-9

ORIGINAL PAPER

Physiologic closure time of the metopic suture in South Australian infants from 3D CT scans

Sophie Jane Teager[1] · Sarah Constantine[2] · Nicolene Lottering[3] · Peter John Anderson[1,3,4]

Received: 28 February 2018 / Accepted: 19 August 2018 / Published online: 14 September 2018

Abstract
Metopic synostosis is a craniofacial condition characterised by the premature fusion of the metopic suture. This early fusion restricts frontal bone growth [17] and has significant impacts on the developing infant during a critical phase of rapid growth and development [4]. Diagnosis of the condition is usually achieved by clinical assessment, followed by a three-dimensional computed tomography (3D CT) scan, verifying premature metopic suture fusion.

Purpose This retrospective study aims to investigate the timing of metopic suture fusion in the developing infant in an Australian subpopulation.

Methods The study evaluates metopic suture fusion in 258 cranial 3D CT scans of children aged 0–24 months over a 5-year period (2011–2016), scanned at Women's and Children's Hospital.

Results The findings suggest that the age range over which physiologic metopic suture fusion occurs is larger than previously reported.

Conclusions The approximate range for physiologic fusion was found to be 3–19 months and patients with fusion within this range can be considered normal. Complete suture fusion is expected by 19 months. Additionally, results indicate suture fusion prior to 3 months is abnormal and diagnostically indicative of metopic synostosis.

Keywords Craniosynostosis · Metopic synostosis · Trigonocephaly · Suture biology

Introduction

In Australia, approximately 1 in every 2000–2500 births are affected by the congenital craniofacial abnormality known as craniosynostosis [5]. This condition involves the premature fusion of one or more of the cranial sutures resulting in deformational growth of the cranium and abnormal head shape. In the case of metopic synostosis, the metopic suture is prematurely fused resulting in restricted frontal bone growth and *trigonocephaly* or triangular head shape [17]. Metopic synostosis has an incidence of 1 in 15,000 births making it the third most frequent single suture craniosynostosis (Fig. 1).

Metopic synostosis has significant impacts on the developing infant during a critical phase of rapid growth and development [17]. Consequences can include elevated intracranial pressure [19], learning disability and behavioural abnormality [16] as well as impacts on the aesthetics of the head and face of varying degrees of severity. Restriction of frontal growth results in a triangular or wedge-shaped head, decreased distance between the orbits (hypotelorism) and a prominent frontal ridge, all of which can have a negative impact on the child in a psychosocial context. The effects of metopic synostosis on cognitive ability are widely contested, with some studies reporting that infants with metopic synostosis can demonstrate mild developmental delays [3], whilst others report the mental development of affected children to be within the normal range [7].

Metopic synostosis can present either as part of a syndrome [12] or as an isolated non-syndromic anomaly, this non-syndromic form of craniosynostosis represents approximately 85% of cases [6]. The exact aetiology of non-syndromic

✉ Sophie Jane Teager
sophie.teager@sa.gov.au

1 School of Dentistry`, The University of Adelaide, Adelaide, South Australia, Australia

2 Department of Medical Imaging, Women's and Children's Hospital, North Adelaide, Australia

3 School of Medicine, University of Adelaide, Adelaide, Australia

4 Australian Craniofacial Unit, Adelaide, Australia

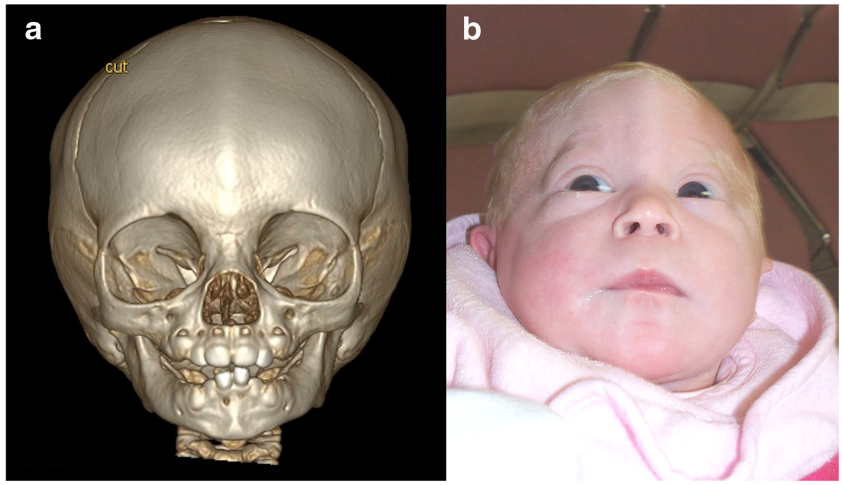

Fig 1 **a** 3D CT scan showing metopic synostosis in frontal view **b** shows the characteristic clinical appearance of metopic synostosis with a prominent frontal ridge, hypotelorism and trigonocephaly (courtesy of the ACFU)

metopic synostosis is undefined; however, current literature points towards a multifactorial aetiology in which genetic abnormalities combine with various epigenetic and environmental factors to affect suture development [2]. The current literature reports several main mechanisms, which may contribute to the development of metopic synostosis, namely altered suture biology resulting in acceleration of physiologic fusion mechanisms, malformation of the bone, malformation of the brain and obstetric issues relating to cranial compression and fetal head immobilisation in late stage pregnancy [8, 11]. Recent studies suggest a variety of proteins and transcription factors are involved in the development of metopic craniosynostosis, including FGRF2, TGFB, RUNX2 and BMP [9]. With the advent of new genomic technologies, such as genome-wide association studies advances have been made regarding the genetics of both sagittal and coronal non-syndromic craniosynostosis [6], an encouraging sign that similar advances will soon be made with relation to metopic non syndromic craniosynostosis. It has been suggested that metopic synostosis has a stronger genetic component than its sagittal suture counterpart with up to 10% of patients displaying familiar recurrence [10].

Three-dimensional computed tomography (3D CT) plays a vital role in the diagnosis of metopic synostosis. Objectivity in the analysis of 3D CT scans via 2D and 3D vector measurements has historically been challenging; however, the development of more refined assessment techniques, such as point cloud representation and 3D stereophotogrammetry are improving our assessment of 3D CT and allowing for more reproducible analyses to be made [13]. Currently, there is discrepancy in the literature regarding the precise physiologic closure time of the metopic suture. Two recent studies assessing American infants report physiologic fusion to occur between 6 and 8 months [20] and 3 and 9 months [18] respectively. Both studies are based on a relatively small sample size and denote suture as either open or closed. Another recent study reports physiologic suture fusion to occur between 2 and 14 months, a much wider range than previously reported; the study evaluated 337 patients and denoted patent, partially fused and complete fusion of the suture [1].

This study aims to determine the age range for physiologic closure of the metopic suture in Australian infants, which may then act as a baseline for comparison during the clinical diagnosis of metopic synostosis and to guide appropriate treatment for each patient.

Methods

Cranial 3D CT scans of patients aged 0–24 months who presented to the Women's and Children's Hospital in Adelaide over the period of 2011–2016 were retrospectively accessed. These patients had been referred for a cranial 3D CT for a variety of reasons, including paediatric trauma ($n = 145$), investigation of non-trauma related intracranial pathology ($n = 92$) and to investigate potential craniosynostosis ($n = 21$).

Strict exclusion criteria were implemented to remove all patients with conditions related to suture development and fusion. A total of 336 patients were excluded from the study. The exclusion criteria included patients with craniosynostosis; patients with other craniofacial abnormalities; patients with syndromes, which have a craniofacial component; patients with intracranial pathology including subdural haematomas or collections; patients with hydrocephalus or a VP shunt; patients with brain malformation; patients with intracranial neoplasm and patients who had suffered trauma to the frontal region. Patients who were deceased were also excluded.Table 1

All scans were undertaken on the GE Healthcare, CT750 HD multislice CT scanner. Scans were performed using a helical scan mode, with an average kilovolt of 100 and milliamperes of 80–350 depending on patient size. Images were reconstructed at slices of 0.625 mm with bone, soft tissue and

3D reconstructions. Images were viewed using Carestream VuePACS Version 11.3.2.

3D CT scan evaluation

The scans were assessed and analysed by a single examiner noting the following: (1) metopic suture patency as either patent, partially fused or fused; (2) direction of suture fusion; (3) age of the patient at the time of scan; (4) gender; (5) the reason for the scan and (6) the patency of the anterior fontanel. Anterior fontanel patency and/or notching was considered as a separate finding and did not have any bearing on the classification of suture patency. Inter-operator reliability was then verified by a second blind observer.

Definitions for suture patency

Patent metopic suture (Fig. 2) This is an observable patent suture line extending to the entire distance from the glabella to the anterior fontanel.

Partially fused metopic suture (Fig. 3) This is a suture line which is *partially* observable between the glabella and the anterior fontanel, i.e. line is observable at the anterior fontanel but is not observable at the glabella.

Fused metopic suture (Fig. 4) A fused metopic suture is non-distinguishable suture line—complete obliteration of the metopic suture between the glabella and anterior fontanel.

Lottering's cranial ossification scoring system

In addition to our classification of cranial ossification (patent, partially fused, fused), each patient was graded according to Lottering's cranial ossification scoring system (see Fig. 2 in *[14]*) [14]. In our assessment, measurements of the fibrous tissue interfaces separating the frontal bones were not possible; thus, all patent sutures were classified as stage I or II inclusively. Partially fused sutures were classified as stage III and fused sutures as stage IV as per the criteria below:

Stage I. Fibrous tissue interface separating left and right frontal bones is ≥ 2 mm in width.
Stage II. Commenced fusion: Fibrous tissue interface is present; however, sections of the suture are closed or if distinct separation of the frontal halves, the width is < 2 mm.
Stage III. Complete fusion: complete ossification of tissue interface; remnant of suture may be present.
Stage IV. Obliterated: suture line is obliterated.

Table 1 The reasons for obtaining each CT scan used in the study and the corresponding number of patients

Reason for CT scan	No. of patients
Trauma	146
Investigative/diagnostic	46
Acute abnormal neurology	22
Suspected craniosynostosis	21
Soft tissue lesions	17
Episodes of apnoea	4
Postoperative	2

Results

Of the 594 patients between the ages of 0–24 months who had a cranial CT scan at the Adelaide Women's and Children's Hospital between 2011 and 2016, 258 aligned with our strict inclusion criteria and were eligible for inclusion within this study. When separated by age, the study population included 29% between 0 and 4 months ($n = 74$), 22% between 4 and 8 months ($n = 58$), 19% between 8 and 12 months ($n = 48$), 10% between 12 and 16 months ($n = 26$), 12% between 16 and 20 months ($n = 30$) and 9% between 20 and 24 months ($n = 22$). Of the 258 patients, 42% were females and 58% were males as illustrated in Fig. 5.

Of the 258 CT scans evaluated for metopic suture patency, 113 were patent with a mean age of 4 months, 35 were partially fused with a mean age of 8.2 months and 110 were fused with a mean age of 14.6 months. The earliest evidence of suture fusion commencing was 2.4 months with the earliest complete fusion at 3.4 months. The latest fully patent suture identified was at 18.6 months. All patients greater than

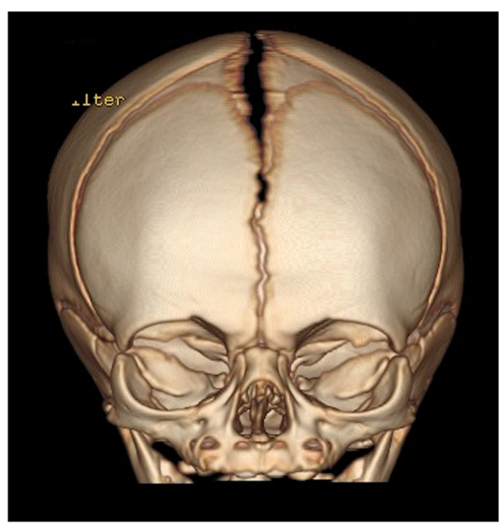

Fig 2 A 3D CT scan of a patent metopic suture in a 25-day-old patient, the entire length of the metopic suture from glabella to the anterior fontanel can be clearly seen

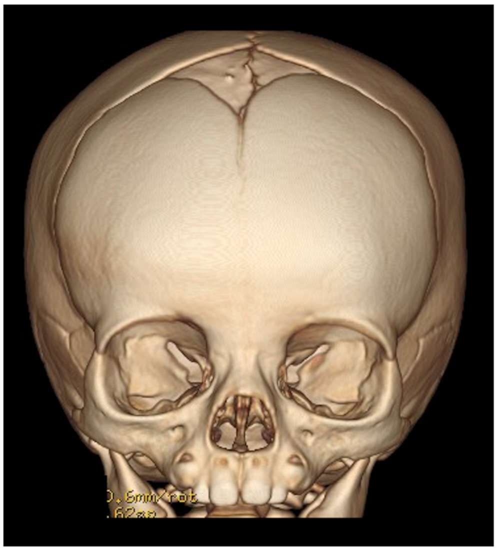

Fig 3 A 3D CT scan of a partially fused metopic suture in a 8-month-old patient. The suture line has ossified at glabella but is still observably patent towards the anterior fontanel

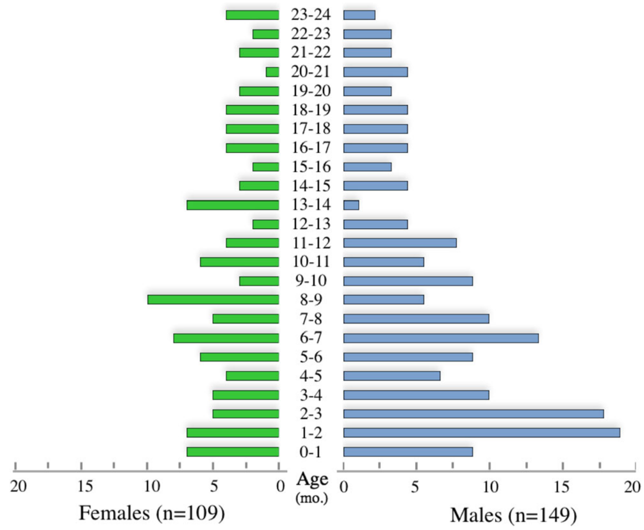

Fig 5 Distribution of patients according to their age group and sex. All age groups are depicted in months

19 months of age demonstrated complete metopic suture fusion. A cumulative probability curve for the commencement and completion of metopic suture fusion can be seen in Fig. 6 as per the data from Tables 2 and 3.

The recent study by Lottering et al. in 2016 [14] aimed to provide probabilistic information allowing age estimation of modern Australian children. The authors achieved this by developing reference tables from which age of a child could be estimated from various cranial variables, e.g. fusion of individual cranial sutures. The authors make direct mention of the use of these tables for forensic age estimation and for use in missing persons' scenarios; for these cases, they recommend the use of a 68% credible interval (CI) at first, as a 95% CI may be too wide. The accuracy of these reference tables was observed in our study by comparing the age estimation from metopic suture fusion and anterior fontanel fusion against our specific population group of modern Australian children. Table 4 shows the age estimation from the reference tables according to a 95% credible interval. The right column lists the percentage of patients from our study for which the age estimation was correct. We have compared both the 68 and 95% CIs to confirm the postulation by Lottering et al. [14] that a 68% CI increases the likelihood of unintentionally eliminating possible identifications. We can see from the comparison that a 98% CI aligns much more closely with our data set and that the age estimation was reasonably accurate with > 90% of patients being predicted correctly in stage III and IV of metopic fusion and for all stages of anterior fontanel fusion in males.

Fig 4 A 3D CT scan of a fused metopic suture in a 21.5-month-old patient. The suture line has completely ossified from glabella to the anterior fontanel

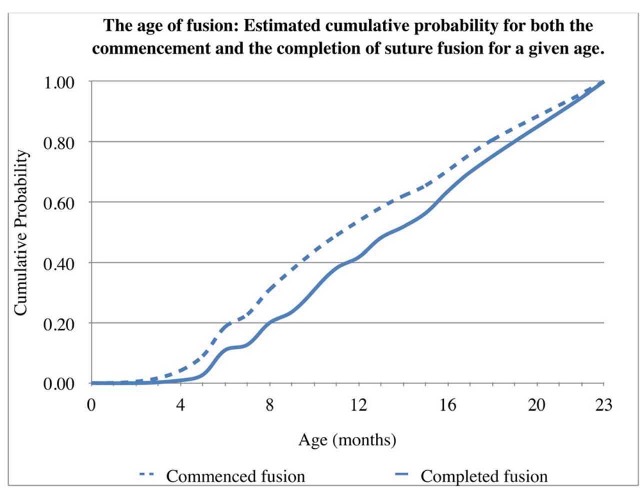

Fig 6 Estimated cumulative probability curve for both the commencement and the completion of suture fusion for a given age (months)

Table 2 The estimated cumulative probability that a patient of a certain age group will have commenced fusion (PF, partially fused; F, fused)

Age group (months)	Total patients	No. patients who have commenced fusion	Estimated cumulative probability
0–1	15	0	0.00
1–2	24	0	0.00
2–3	21	1	0.01
3–4	14	2	0.02
4–5	10	3	0.04
5–6	14	7	0.09
6–7	20	14	0.19
7–8	14	6	0.23
8–9	15	12	0.31
9–10	11	8	0.37
10–11	11	10	0.43
11–12	11	8	0.49
12–13	6	6	0.53
13–14	8	8	0.59
14–15	7	5	0.62
15–16	5	5	0.66
16–17	8	8	0.71
17–18	8	8	0.77
18–19	8	6	0.81
19–20	6	6	0.85
20–21	5	5	0.88
21–22	6	6	0.92
22–23	5	5	0.96
23–24	6	6	1.00

Table 3 The estimated cumulative probability that a patient of a certain age group will have completed fusion (F, fused)

Age group (months)	Total patients	No. patients with completed fusion	Estimated cumulative probability
0–1	15	0	0.00
1–2	24	0	0.00
2–3	21	0	0.00
3–4	14	1	0.01
4–5	10	0	0.01
5–6	14	2	0.03
6–7	20	9	0.11
7–8	14	2	0.13
8–9	15	8	0.20
9–10	11	4	0.24
10–11	11	8	0.31
11–12	11	8	0.38
12–13	6	4	0.42
13–14	8	7	0.48
14–15	7	4	0.52
15–16	5	5	0.56
16–17	8	8	0.64
17–18	8	7	0.70
18–19	8	5	0.75
19–20	6	6	0.80
20–21	5	5	0.85
21–22	6	6	0.90
22–23	5	5	0.95
23–24	6	6	1.00

Discussion

Historically, the physiologic timing of metopic suture fusion has been highly contested and varied throughout the literature. Two most recent studies on the timing of normal metopic suture fusion report a relatively narrow age range of 6–8 months [20] and 3–9 months [18] respectively.

Our study establishes a much wider age range for physiologic closure of the metopic suture at 3–14 months. This age range is largely in keeping with findings from a recent study by Bajwa et al. [1] [1] who reported physiologic suture fusion between the ages of 2–14 months. This wider age range than previously reported in the literature may relate to the assessment of a multi-ancestral population group with greater socio-economic variation than in previous studies. In contrast to current literature on this topic, our study considered the fusion of the anterior fontanel *separately* to the fusion of the metopic suture. Of the 110 patients in our study whose metopic suture was completely fused, 72% of them had a patent anterior fontanel; thus, the patency of the anterior fontanel was considered separately and did not have an impact on the classification of metopic suture fusion. In current literature, study populations have included children in the UK and the USA. Our study is unique in its evaluation of the *Australian* population, and as the Women's and Children's Hospital is a quaternary referral centre, a broad ethnic diversity was afforded within our study population. From our observational statistics, it was found that female patients tend to fuse slightly earlier than male patients, a finding that is supported in the literature [1]; however, no quantitative statistical analysis was carried out to investigate for a statistically significant difference between the sexes.

Our study corroborates the findings of a modern Australian study on Queensland infants, in which Lottering et al. [14] [14] aimed to estimate the age of clinical patients based on the stages of fusion of the metopic suture and anterior fontanel. Despite this, not being the intended use for the reference tables, our comparison illustrates close alignment between the reference tables and our study population of a similar demographic. The estimates are more accurate in stages III and IV and generally more accurate for the male population. It has been stated by Lottering et al. [14] [14] that this is not the intended use of the tables and nor do they claim that age estimation from a single cranial site to be accurate; however,

Table 4 A table illustrating the predicted age estimates (95% CI, 68% CI) from the stage of fusion of the metopic suture and anterior fontanel as per Lottering et al.'s reference tables separated by gender. The percentage of patients in the current study's population group who aligned with this predicted age range is listed in the third and fifth columns

Male				
Stage of metopic suture fusion	Predicted age 95% CI (months)	Patients that within the predicted age range (%)	Predicted age 68% CI (months)	Patients that within the predicted age range (%)
Stage I or II	< 5.2	77	< 2.52	49
Stage III	0.85–17.2	95	1.75–8.10	60
Stage IV	> 3.37	100	> 7.65	82
Stage of anterior fontanel fusion		Patients that aligned with the predicted age range (%)		Patients that aligned with the predicted age range (%)
Patent	< 15.48	90	< 6.23	53
Fused	> 10.15	96	> 15.18	70
Female				
Stage of metopic suture fusion	Predicted age 95% CI (months)	Patients that within the predicted age range (%)	Predicted age 68% CI (months)	Patients that within the predicted age range (%)
Stage I or II	< 5.13	66	< 3.07	45
Stage III	1.42–15.15	93	2.48–8.47	67
Stage IV	> 5.1	100	> 10.16	76
Stage of anterior fontanel fusion		Patients that aligned with the predicted age range (%)		Patients that aligned with the predicted age range (%)
Patent	< 16.54	84	< 7.16	44
Fused	> 15.12	82	18.99	45

it does offer an interesting comparison between the two Australian studies.

In addition to the timing of suture fusion, the direction of suture fusion was also observed with all sutures found to be commencing at glabella and progressing towards the anterior fontanel. Some studies support this finding of commencement of suture fusion occurring at Naseon; however, Bajwa et al. reported that fusion can commence at any point in the inferior one third of the suture. Our study does not corroborate this finding but supports the general notion that suture fusion progresses in a "zip-like" fashion towards the anterior fontanel [15, 20, 1].

This study aims to develop a baseline age range, during which physiologic metopic suture fusion occurs; however, further research comparing the observed suture on cranial 3D CT and the actual pathology found at time of surgery would strengthen the literature in this area and allow refinement of an observational classification system for metopic suture fusion from cranial 3D CT.

Conclusions

Our study suggests that the age range over which metopic suture fusion occurs is larger than previously reported. The results indicate an approximate range of 3–19 months for physiologic metopic suture fusion; patients within these parameters can be considered normal. Complete suture fusion is expected by 19 months. Suture fusion prior to 3 months is considered to be abnormal and diagnostically indicative of metopic craniosynostosis. It is important to note that radiographic evaluation along is not suggestive enough to warrant early or immediate surgery, and clinic factors must also be considered in the diagnosis of metopic synostosis.

Acknowledgements The authors would like to thank the Australian Craniofacial Unit and Women's and Children's Medical Imaging Unit for their assistance in providing patient records and their ongoing support throughout this study. In addition, the authors are grateful for the support of the Women's and Children's Health Network Human Research Ethics Committee for providing ethical approval for the study (Audit 838A, 2016). Written informed consent was obtained from the form parent/LAR of the patient for publication of any accompanying images (Fig. 1b).

Author contributions S.J. Teager: project development, data collection, data analysis and manuscript writing

S Constantine: data analysis and interpretation

N Lottering: data analysis and manuscript editing

P J Anderson: project development, manuscript editing

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Bajwa M, Srinivasan D, Nishikawa H, Rodrigues D, Solanki G, White N (2013) Normal fusion of the metopic suture. J Craniofac

Surg 24:1201–1205. https://doi.org/10.1097/SCS.0b013e31829975c6
2. Boyadjiev SA, International Craniosynostosis C (2007) Genetic analysis of non-syndromic craniosynostosis. Orthod Craniofac Res 10:129–137. https://doi.org/10.1111/j.1601-6343.2007.00393.x
3. Cohen SR, Maher H, Wagner JD, Dauser RC, Newman MH, Muraszko KM (1994) Metopic synostosis: evaluation of aesthetic results. Plast Reconstr Surg 94:759–767
4. Da Costa AC, Anderson VA, Savarirayan R, Wrennall JA, Chong DK, Holmes AD, Greensmith AL, Meara JG (2012) Neurodevelopmental functioning of infants with untreated single-suture craniosynostosis during early infancy. Childs Nerv Syst 28:869–877. https://doi.org/10.1007/s00381-011-1660-1
5. Di Rocco C, Velardi F, Ferrario A, Marchese E (1996) Metopic synostosis: in favour of a "simplified" surgical treatment. Childs Nerv Syst 12:654–663
6. Flaherty K, Singh N, Richtsmeier JT (2016) Understanding craniosynostosis as a growth disorder. Wiley Interdiscip Rev Dev Biol 5:429–459. https://doi.org/10.1002/wdev.227
7. Kapp-Simon KA, Figueroa A, Jocher CA, Schafer M (1993) Longitudinal assessment of mental development in infants with nonsyndromic craniosynostosis with and without cranial release and reconstruction. Plast Reconstr Surg 92:831–839 discussion 840-831
8. Kim HJ, Rice DP, Kettunen PJ, Thesleff I (1998) FGF-, BMP- and Shh-mediated signalling pathways in the regulation of cranial suture morphogenesis and calvarial bone development. Development 125:1241–1251
9. Kosty J, Vogel TW (2015) Insights into the development of molecular therapies for craniosynostosis. Neurosurg Focus 38:E2. https://doi.org/10.3171/2015.2.FOCUS155
10. Lattanzi W, Barba M, Di Pietro L, Boyadjiev SA (2017) Genetic advances in craniosynostosis. Am J Med Genet A 173:1406–1429. https://doi.org/10.1002/ajmg.a.38159
11. Lattanzi W, Bukvic N, Barba M, Tamburrini G, Bernardini C, Michetti F, Di Rocco C (2012) Genetic basis of single-suture synostoses: genes, chromosomes and clinical implications. Childs Nerv Syst 28:1301–1310. https://doi.org/10.1007/s00381-012-1781-1
12. Lee HQ, Hutson JM, Wray AC, Lo PA, Chong DK, Holmes AD, Greensmith AL (2012) Changing epidemiology of nonsyndromic craniosynostosis and revisiting the risk factors. J Craniofac Surg 23:1245–1251. https://doi.org/10.1097/SCS.0b013e318252d893
13. Lloyd MS, Buchanan EP, Khechoyan DY (2016) Review of quantitative outcome analysis of cranial morphology in craniosynostosis. J Plast Reconstr Aesthet Surg 69:1464–1468. https://doi.org/10.1016/j.bjps.2016.08.006
14. Lottering N, MacGregor DM, Alston CL, Watson D, Gregory LS (2016) Introducing computed tomography standards for age estimation of modern Australian subadults using postnatal ossification timings of select cranial and cervical sites. J Forensic Sci 61(Suppl 1):S39–S52. https://doi.org/10.1111/1556-4029.12956
15. Manzanares MC, Goret-Nicaise M, Dhem A (1988) Metopic sutural closure in the human skull. J Anat 161:203–215
16. Sidoti EJ Jr, Marsh JL, Marty-Grames L, Noetzel MJ (1996) Long-term studies of metopic synostosis: frequency of cognitive impairment and behavioral disturbances. Plast Reconstr Surg 97:276–281
17. van der Meulen J (2012) Metopic synostosis. Childs Nerv Syst 28:1359–1367. https://doi.org/10.1007/s00381-012-1803-z
18. Vu HL, Panchal J, Parker EE, Levine NS, Francel P (2001) The timing of physiologic closure of the metopic suture: a review of 159 patients using reconstructed 3D CT scans of the craniofacial region. J Craniofac Surg 12:527–532
19. Wall SA, Thomas GP, Johnson D, Byren JC, Jayamohan J, Magdum SA, McAuley DJ, Richards PG (2014) The preoperative incidence of raised intracranial pressure in nonsyndromic sagittal craniosynostosis is underestimated in the literature. J Neurosurg Pediatr 14:674–681. https://doi.org/10.3171/2014.8.PEDS1425
20. Weinzweig J, Kirschner RE, Farley A, Reiss P, Hunter J, Whitaker LA, Bartlett SP (2003) Metopic synostosis: defining the temporal sequence of normal suture fusion and differentiating it from synostosis on the basis of computed tomography images. Plast Reconstr Surg 112:1211–1218. https://doi.org/10.1097/01.PRS.0000080729.28749.A3