


Metopic suture: formation and clinical implications – a review

Szew metopowy: powstawanie i obraz kliniczny

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Abstract

The timing of suture closure and clinical implications of the metopic suture are still unknown. Premature fusion, causing craniosynostosis, happens rarely, but it may result in serious complications, such as craniofacial dysmorphism and neurodevelopmental problems. The clinical significance of metopism is still uncertain. The aim of this study was to review the literature and identify uncertain aspects associated with the formation and clinical implications of the metopic suture. The review showed significant variations in the typical age of metopic suture closure reported in the literature (from five months to seven years). Premature fusion of the suture, usually occurring before birth, may cause skull deformity and developmental disorders. Aetiology is probably multifactorial. Craniosynostosis may result in different phenotypes, ranging from mild changes to trigonocephaly. Diagnosis is achieved based on physical examination and computed tomography scans. Treatment is surgical and aims to achieve two goals: correction of craniofacial dysmorphism and prevention of further complications. Persistence of the metopic suture is diagnosed based on computed tomography scans and is considered to be an anatomical variant. The metopic suture is clinically significant if premature fusion occurs, causing craniofacial and neurodevelopmental disorders. The timing of the closure of the suture, and the aetiology of craniosynostosis and metopism require further research.

Keywords: suture, craniosynostosis, metopic

Streszczenie

Czas zrośnięcia i znaczenie kliniczne szwu metopowego są nadal przedmiotem badań. Przedwczesne zrośnięcie szwu, powodujące kraniosynostozę, zdarza się rzadko, jednak może prowadzić do poważnych następstw. Znaczenie przetrwałego szwu metopowego nadal jest niejasne. Celem tego badania był przegląd literatury i identyfikacja niejasnych aspektów powstawania szwu metopowego oraz jego implikacji klinicznych. Przegląd ukazał duże rozbieżności w zakresie wieku, w którym zrasta się szew metopowy (5 miesięcy – 7 lat). Przedwczesne zrośnięcie szwu, najczęściej przed urodzeniem, może powodować deformację czaszki i zaburzenia rozwojowe. Etiologia jest prawdopodobnie wieloczynnikowa. Następstwa kraniosynostozy szwu metopowego bywają różnorodne: od delikatnych zmian po trigonocefalię. Diagnostykę stawiamy na podstawie badania klinicznego i badań obrazowych (badanie radiologiczne, tomografia komputerowa), a leczenie jest chirurgiczne i ma na celu poprawę wyglądu oraz zapobieżenie powikłaniom. Natomiast przetrwały szew metopowy (*metopism*) rozpoznajemy na podstawie badań obrazowych, a w literaturze najczęściej jest uznawany za wariant anatomiczny. Szew metopowy zyskuje znaczenie kliniczne, jeśli dojdzie do jego przedwczesnego zrośnięcia i powikłań z tym związanych. Określenie typowego czasu zrośnięcia, przyczyn kraniosynostozy i metopizmu wymaga dalszych badań.

Słowa kluczowe: szew, kraniosynostozy, metopowy

INTRODUCTION

The metopic suture is one of the primary sutures of the calvaria, and it fuses and disappears early in life. There is uncertainty regarding the age at which the metopic suture closes; according to different studies, it varies from five months to seven years (Vinchon, 2019). One study concerning the infant population in the United States found that fusion of the metopic suture started at three months and was completed by nine months of age (Chaisrisawadisuk et al., 2021). Lottering et al. (2016) reported that closure occurs between the 3rd and 17th month in male infants, whilst in female infants it is observed between the 5th and 15th month of life. Similar findings were observed in a study of the Australian population, with the typical age of closure ranging between three and 14 months (Teager et al., 2019). In a study of French infants, the closure of the metopic suture began at the age of five months and was completed at 10 months in the majority of cases (Vinchon, 2019). Rice (2008) suggests that fusion starts at 12 months, whereas the metopic suture is obliterated at seven years old. Consequently, significant variations in the typical age of metopic suture closure are reported in the literature. The metopic suture is clinically significant if it fuses prematurely, causing craniosynostosis, or if it persists, resulting in metopism (Vinchon, 2019).

EMBRYOLOGY AND HISTOLOGY OF METOPIC SUTURE

Formation of the frontal bone commences at the end of the 8th week of gestation through intramembranous ossification. At this point, two ossification centres appear symmetrically on each side of the midline. They are situated at the frontal tuberosities. Two secondary centres emerge two weeks later. Bone growth progresses significantly until the 18th week. By this stage, the space between the median margins of the two bone plates narrows, resulting in the formation of a tight strip of fibrous connective tissue that creates the metopic suture. As the bones continue to develop, the strip maintains a consistent width until the end of gestation (Rice, 2008).

Suture complex is formed from cells of the neural crest migrating between the brain and surface ectoderm. At the edges of these sutures, new bone is produced, stimulated by both osteogenic and extrinsic stimuli. The sutures remain unossified as long as bone continues to form along their edges, allowing for the expansion of the cranium (Ang et al., 2022).

Ossification is regulated by mesenchymal epithelium and dura mater. The epithelium secretes paracrine factors necessary for the onset of osteogenesis. However, they are not required to maintain the process of bone growth (Tyler and Hall, 1977). The dura mater regulates calvarial growth and prevents the restriction of suture closure. Studies have reported that soluble heparin binding factors from the dura

mater inhibit osteogenesis and may be capable of maintaining the presence of the cranial sutures (Opperman et al., 1993). These findings were supported by studies on rat models, which showed that suture patency varied depending on the dura mater-suture complex in different regions (Teager et al., 2019). Manzanares et al. (1988) studied the biology of the metopic suture and concluded that chondroid tissue was responsible for the growth of the two frontal bones towards each other and their fusion. The interdigitations of the sutural edges are formed by chondroid tissue and some of them are connected by thin bridges of chondroid tissue that pass through the sutural space. A nearly closed metopic suture consists of trabeculae of chondroid tissue, which are later substituted by lamellar bone. If the resorption processes are still active along the edges, the sutural space may be preserved. Therefore, the biology of chondroid tissue may be a determining factor in the closure of the metopic suture (Manzanares et al., 1988).

METOPIC CRANIOSYNOSTOSIS

Craniosynostosis refers to premature, pathologic ossification of one or more sutures (Karabagli, 2013). Metopic synostosis is defined as premature closure of the metopic suture, which can lead to growth restriction of the frontal bones, resulting in morphological deformity and neurodevelopmental problems (van der Meulen, 2012).

Premature fusion of the metopic suture typically occurs during the gestational period (Jimenez et al., 2018). However, as there is uncertainty in the literature regarding the physiological time of fusion of the metopic suture, caution is needed in the diagnosis, particularly in less severe phenotypes (van der Meulen, 2012).

There is a wide range of phenotypes among patients with metopic craniosynostosis. Typical morphological characteristics include the metopic ridge, trigonocephaly, reduced anterior cranial fossa, epicanthal folds, lateral orbital hypoplasia, hypotelorism, ethmoid hypoplasia, supraorbital retrusion, bitemporal indentation, and increased biparietal diameter (Hicdonmez, 2017; van der Meulen, 2012). However, some patients may present with the metopic ridge or only some of the listed characteristics. The metopic ridge is considered to be the mildest phenotype, which is not associated with trigonocephaly and requires no treatment. It is seen as a variant of norm, resulting from the physiological closure of this suture. Nevertheless, the cause of this ridge and why it occurs in some children and not in others remains unknown (Hicdonmez, 2017). Notably, patients with isolated metopic ridging have been found to have an increased incidence of orbitofrontal deformities, strabismus and amblyopia compared to the general paediatric population (Roider et al., 2021).

Considerations associated with a severe phenotype involve possibly reduced cranial volume, increased intracranial pressure, and neurodevelopmental problems. Although the anterior cranial fossa is reduced in volume, the overall

cranial volume is usually normal, probably due to compensatory growth of other bones. Reports of increased intracranial pressure (ICP), defined as ICP >15 mm Hg, exist in the literature, however these studies have been criticised for their methodology (namely, selection bias – patients with different craniosynostoses examined, brief measurement of ICP under general anaesthesia). In more recent studies, authors argue that the risk of increased ICP is small (Jaskolka, 2017). Increased ICP was reported in about 15–20% of patients with isolated craniosynostosis and in about 8–17% of cases of metopic synostosis (Campbell et al., 1995).

Pathologic morphology resulting from metopic synostosis indicates secondary brain malformation and possible neurodevelopmental problems. Patients with metopic craniosynostosis exhibit abnormalities such as smaller frontal lobes, widened precentral sulci, frontal subdural space distention, increased ventricular size, and anomalies of the corpus callosum and cerebellum. However, those abnormalities cannot be thoroughly explained by reduced anterior cranial fossa or increased intracranial pressure, which implies that brain malformations are at least partially independent of craniosynostosis (Jaskolka, 2017). What is more, some studies suggest that patients with metopic craniosynostosis suffer from speech disorders and behavioural problems. It has been speculated that those issues arise from frontal lobe compression and increased intracranial pressure. However, studies indicate that surgery, which is the treatment of choice for this condition, does not improve the neurological status of the patients. Furthermore, authors report that the severity of synostosis does not correlate with developmental deficits (Bajwa et al., 2013). These findings suggest that compression and intracranial pressure may not be the sole causes of these problems. Nonetheless, there are no standardised tools to assess the severity of metopic craniosynostosis and most of the studies have investigated a mixed group of subjects examined without a control group, so their results need to be interpreted with caution (Jaskolka, 2017).

EPIDEMIOLOGY

The general incidence of craniosynostosis is estimated at 0.6/1,000 live births. The incidence of metopic synostosis varies widely, ranging from approximately 1:700 to 1:15,000 newborns (Bajwa et al., 2013). Recently, its prevalence has increased, and it is currently reported as the second most common type of craniosynostosis, with an incidence rate of 1:5,000 (sagittal craniosynostosis being the most common). The male to female ratio is reported to be about 3:1 (Wójcicki and Prudel, 2019). Metopic synostosis may manifest as an isolated suture synostosis or be associated with other abnormalities or syndromes. Isolated metopic synostosis is more common, representing 78% of the cases according to Jaskolka (2017) and 65.4% in the study by Kini et al. (2010). Metopic synostosis can also occur as an associated feature in syndromes such as: Crouzon,

Saethre–Chotzen, Jacobsen, Haspeslagh, frontoocular, Opitz trigonocephaly C, Greig cephalopolysyndactyly deletion 9p, deletion 7p, deletion 13q and chromosome 2 pericentric inversion of 2p12–q14 (Ko, 2016; Linares Chávez et al., 2016).

AETIOLOGY

The cause of metopic craniosynostosis remains unknown. Studies have identified associations with genetic abnormalities, environmental factors, metabolic disorders, and intra-uterine constraint. Genetic mutations in *FREMI* or *T-GLI3* loss-of-function have been claimed to influence metopic synostosis in mouse models. Fibroblast growth factor (FGF) receptors, transforming growth factor β (TGF β), bone morphogenetic protein (BMP), and Wnt signalling pathways have been reported to be involved in the pathological ossification of the metopic suture (Jaskolka, 2017; Karabagli, 2013; van der Meulen, 2012). FGF2, BMP4, and TGF β are growth factors responsible for suture ossification. If TGF β signalling is lost, calvarian osteoprogenitor cells fail to develop, resulting in malformation of skull bones. Other studies have indicated that TGF β 1, TGF β 2 and TGF β 3 play a role in maintaining balance between the ossification process and suture closure. Loss of TGF β 2 activity prevents the fusion of sutures, whilst both lower and higher activity of TGF β 3 leads to premature suture closure. Increased TGF β 1 activity is also associated with an increased incidence of suture closure (Ang et al., 2022; Tyler and Hall, 1977). In addition, studies have suggested that *DLX5* and *DLX6* have a role in frontal and parietal bone growth. Mice models with double *Dlx5*^{-/-} and *Dlx6*^{-/-} mutations did not develop these bones (Rice, 2008). Another study investigated the gene expression profiles of suture cells in the metopic and other sutures. The findings revealed that gene expression in the metopic suture differed from that in other sutures. Furthermore, the gene expression profile of fused and unfused sutures varied among other sutures, but in the metopic suture, the profile remained consistent regardless of the fusion (Coussens et al., 2007). Examination of genes related to osteogenic and osteoinhibitory signals revealed the importance of *FREMI* gene mutations in human metopic craniosynostosis (Vissers et al., 2011). Hence, the aetiology of craniosynostosis is probably multifactorial.

DIAGNOSIS

Patients with metopic craniosynostosis often develop trigonocephaly, which is present at birth and does not improve. Since this dysmorphology is pathognomonic for metopic craniosynostosis, diagnosis can often be made from physical examination and medical history. However, milder phenotypes (e.g. metopic ridge without severe trigonocephaly) may present a diagnostic challenge. Computed tomography (CT) scans combined with clinical and radiological analysis may help to reach a diagnosis. Characteristic features

for metopic craniosynostosis seen on CT scans include a closed metopic suture with an ectocranial ridge and endocranial notch. Other findings may include pulled anterior fontanelle, straight lateral frontal bone which is displaced posteriorly and tangential to the midorbit or medial to the midorbit, upsloping lateral orbital rim, interorbital narrowing, and narrowing of the upper orbital width. Authors in the literature have proposed various measurements aiding in the diagnosis and assessing the indications for surgery, yet there is no standardised protocol. It appears that the interfrontal angle is one of the most commonly measured parameters, and a value greater than or equal to 118° was suggested as an indication for treatment in uncertain cases (Jaskolka, 2017).

TREATMENT

There are no clear guidelines regarding the indications for and timing of surgery. Literature reports provide no evidence for the benefits of treatment.

The goals of the surgical treatment include the prevention or limitation of neurodevelopmental deficits and correction of craniofacial dysmorphology. Controversies arise with milder phenotypes, as there is no standard of acceptable dysmorphology, whereas craniofacial surgery carries various risks (Jaskolka, 2017).

Severe phenotypes of metopic craniosynostosis are currently treated using two techniques: endoscopy-assisted suturectomy followed by postoperative cranial orthotic therapy, or fronto-orbital advancement combined with anterior cranial vault reconstruction. Both techniques aim to correct trigonocephaly by removing the fused suture, expansion of frontal bones, correction of associated deformities, and remodelling and advancement of the supraorbital band (Jaskolka, 2017; Wójcicki and Prudel, 2019).

Endoscopy-assisted suturectomy is a relatively new technique, which requires a smaller incision, but its long-term results are yet unknown. This approach also requires an earlier intervention, which may result in poorer neurodevelopmental outcomes due to the side effects of anaesthesia. Another concern is postoperative helmet therapy, which requires compliance (Jaskolka, 2017). However, the first reports of follow-up several years after surgery show better aesthetic results than in patients after open surgery, and proper brain development (Jimenez et al., 2018). On the other hand, open surgery has been performed for years and is considered to be safe. Larger incision, risk of relapse, blood transfusion, longer hospitalisation and thus higher costs are drawbacks of this method (Jaskolka, 2017). Long-term complications include showing the boundaries of the osteotomy and plates, wires, screws used during the procedure, and the development of turricephaly (Jimenez et al., 2018). Both techniques have low morbidity (Wójcicki and Prudel, 2019).

Regarding the timing of the intervention, there seems to be a consensus in the literature that open surgery after six

months of age is associated with less complications, whereas the endoscopic technique has better outcomes when it is performed earlier, before the age of four months (Jaskolka, 2017). However, there are reports of poor postoperative outcomes (poor bone growth, relapse) after early surgery in the long-term follow-up (Bajwa et al., 2013). It is generally accepted that any intervention should be carried out before the first year of life (Wójcicki and Prudel, 2019).

Surgical outcomes are determined either by the cosmetic result or the need for further surgery (for example, using the Whitaker classification) (Whitaker et al., 1987). However, cosmetic outcomes are not standardised and may differ among surgeons, patients, and their families. The concept of assessing the need for another intervention is valid, but does not take into account various other reasons which are not directly associated with craniosynostosis (e.g. infection, leak of cerebrospinal fluid) (Jaskolka, 2017).

METOPISM

Metopism, defined as the persistence of the metopic suture over the usual age of closure, is considered as a variant of norm. It is not certain after what age the presence of the metopic suture should be considered as metopism. Vinchon in his study on the French population concluded that metopism occurred as early as after 12 months, whilst an Australian study considered that metopism was present if the metopic suture persisted after 24 months of age (Chaisrisawadisuk et al., 2021; Vinchon, 2019).

Lottering et al. developed a staging system for the fusion of the metopic suture (stages 1–4) based on the progression of ossification. Open suture means that the fibrous tissue interface width separating the left and right frontal bones is equal or greater than 2 mm (1). Commenced fusion (2) occurs when there is still fibrous tissue present, however the separation of the frontal halves is less than 2 mm or the sections of the suture are closed. When the ossification of fibrous tissue is complete, the fusion is complete (3), and if the suture line is obliterated, then the metopic suture is obliterated (4) (Lottering, 2016). The authors found the metopic suture at stage 1 in 4.8% of males and females, and obliteration of the metopic suture in 88.8% of patients (males and females) (Chaisrisawadisuk et al., 2021).

Chaisrisawadisuk et al. (2021) found that among their subjects the frequency of persistent metopic suture at Lottering stage 1 was 4.8%, whereas 1.6% and 4.7% of the patients were classified as Lottering stages 2 and 3, respectively.

AETIOLOGY

Several theories about the causes and relevance of metopism have been put forward. Among the proposed causative factors for metopism one finds: stenocrotaphy, plagiocephaly, brachycephaly, encephalic pressure, diminution of muscular pressure, endocrine dysfunction, atavism, heredity, and heredo-specific factors (Ashley-Montagu, 1937).

It is suggested that the presence of the metopic suture at birth is connected with cranial moulding during delivery and it is considered to be an adaptation to solve the “obstetric dilemma”. It is related to the problem of delivering the baby with a huge brain with the constraints of the pelvis adapted to bipedalism. This hypothesis is corroborated by the high incidence of delivery complications which occur during the birth of children with metopic suture synostosis (Vinchon, 2019).

EPIDEMIOLOGY

Metopism seems to be present in the minority of the population, yet its prevalence varies across ethnic groups.

The incidence of metopism by gender also varies among studies. Vinchon showed that the prevalence appeared to be greater in females (3.8% in females compared to 1.8% in males), although the findings of the study were not always statistically significant (Vinchon, 2019). In contrast, Singh et al. (2017) found that in Indian population metopism was more common in males (18.75%) than females (6.25%). Chaisrisawadisuk et al. (2021) reported no difference in the incidence by gender in the Australian population.

CLINICAL SIGNIFICANCE

Metopism is considered to be a normal variant. Its morphological and clinical implications are not known, with some authors assuming that as a variant of norm, it does not have any. Closure of the suture is associated with the overall development and takes part in the growth of the cerebrum in humans (Vinchon, 2019).

Studies have found that metopism is associated with range of midline closure defects, such as cranium bifidum, dorsonasal dermal fistula, suprasellar teratoma, dermoid cyst of the glabella, cleidocranial dysostosis, hypertelorism, and facial cleft (Chaisrisawadisuk et al., 2021; Vinchon, 2019). It has also been observed that persistent metopic suture is commonly found in some of the congenital disorders involving impaired bone formation. Furthermore, the coincidence of supernumerary cranial bones (Wormian bones) and metopism has been reported. These bones arise either as a result of additional ossification centres or the non-fusion of ossification centres (Nikolova and Toneva, 2023). It is suggested that metopic crania have a distinctive cranial morphology, with greater inter-frontal and inter-orbital breadths, and are associated with supernumerary calvarial bones, underdeveloped frontal sinuses and remnants from embryonic sutures (Nikolova et al., 2016, 2019). There is also a case report showing the presence of metopism and atlas occipitalisation in one individual without any evident signs of a general disorder (Nikolova and Toneva, 2023). It was suggested that the concurrent presence of metopism and frontal sinus aplasia was caused by elevated intracranial pressure during the first years of development (Nikolova et al., 2018). The coincidence of atlas occipitalisation and

persistent metopic suture does not seem to have one cause and represents some sort of aberration, either congenital or developmental (Nikolova and Toneva, 2023).

The implications of metopism are not clear. It appears to be relevant in forensic medicine and anthropometry, and it seems to play a role in shock absorption, possibly cushioning the severity of head trauma (Nikolova et al., 2016). However, other studies suggest that it does not have any clinical implications. Thus, coincidence with midline closure defects and reported distinctive cranial morphology require further investigation.

CONCLUSIONS

The review of the literature on the metopic suture has highlighted numerous uncertainties regarding the timing of the physiological closure, genetic and other factors that regulate this process, indications for treatment, the best management of metopic craniosynostosis, and the significance of metopism. The accessibility of CT imaging may drive further research into the timing of suture closure. Different results of studies involving diverse populations suggest that the process may be population-specific. In terms of the indications and treatment of craniosynostosis, doubts regarding milder phenotypes should be assessed on a case-by-case basis, while the results of the two common techniques should be compared in studies with long-term follow-up. Further research is essential to determine the clinical significance of metopism.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the content of this publication and/or claim authorship rights to this publication.

Author contribution

Original concept of study: MLP. Collection, recording and/or compilation of data: MLP, AC. Analysis and interpretation of data: MLP, AC, KZ. Writing of manuscript: MLP, AC. Critical review of manuscript: MLP, KZ, KW, DJJ. Final approval of manuscript: MLP, KZ, KW, DJJ.

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