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FOCUS SESSION

Pathology in metopic synostosis

Pinar Karabagli

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Abstract Premature closure and subsequent ossification of the metopic suture results in triangular head shape called trigonocephaly and is characterized by a midline metopic ridge, frontotemporal narrowing, and an increased biparietal diameter. Trigonocephaly is the second most frequent type of craniosynostosis. It can be isolated and associated with other congenital anomalies without any known syndrome, or occurs as part of a multiple malformation syndrome. Improvement in treatment is directed by a thorough understanding of the basic pathology of this condition. This review aims to provide an overview of metopic synostosis by correlating what is known about pathogenesis and pathology of this entity.

Keywords Trigonocephaly · Metopic suture · Pathology · Craniosynostosis

Introduction

Craniosynostosis (CS) is a premature, pathologic ossification of one or more sutures [1, 2]. Premature closure and subsequent ossification of the metopic suture results in triangular head shape called trigonocephaly. Trigonocephaly is the second most frequent type of craniosynostosis (incidence, 1:5,200).

During development, the calvarial bones are separated by non-ossifying mesenchyme, and bone margins and mesenchyme form a flexible fibrous union called suture. The active sites of bone deposition or the regions of growth exist at the cranial suture [3]. The metopic suture separates the frontal bones and is the first suture to close physiologically, starting at as early as 3 months and generally being completely fused at the age of 8 months [4].

Premature closure of the sutures was first described by Hippocrates and Galen. Sommering, in 1791, noted abnormalities of bone growth at suture lines in this condition. In the nineteenth century, important ideas were expressed by Otto, Virchow, Minchin, Lannelongue, and Lane [3, 5]. In 1851, Virchow noted that compensatory expansion in the skull occurred to accommodate the growing brain. He observed that the growth in the skull was restricted perpendicular to the suture line but increased parallel to it [3, 4, 6].

Trigonocephaly is characterized by a midline metopic ridge, frontotemporal narrowing, and an increased biparietal diameter and is often accompanied by compensatory changes accommodating the decrease volume of the anterior cranium by means of secondary increases in height or width of the posterior cranium (Fig. 1) [6–8]. Trigonocephaly can be isolated and associated with other congenital anomalies without any known syndrome, or occur as part of a multiple malformation syndrome [7, 9, 10]. Isolated metopic synostosis commonly represents only an esthetic anomaly, rarely associated with intracranial pathology and mental retardation [11, 12]. Severe mental retardation, which may occur in some patients with trigonocephaly, is not due to isolated craniostenosis but rather to associated developmental defects of the brain [13].

Histomorphology and development

Understanding the development of a skull deformity requires an understanding of normal cranium development and morphology. Neocranium is embryologically divided into the vault (calvarium) formed from membranous bone, and the basicranium formed in the cartilage. The initial neocranium development depends on the formation of the brain and its surrounding membranes including dura. Brain absence has

P. Karabagli (✉)
Department of Pathology, Faculty of Medicine, Selcuk University, Candir mah. Candir sok. Hazal sitesi No. 24/C, 42090 Meram, Konya, Turkey
e-mail: pinarkarabagli@yahoo.com

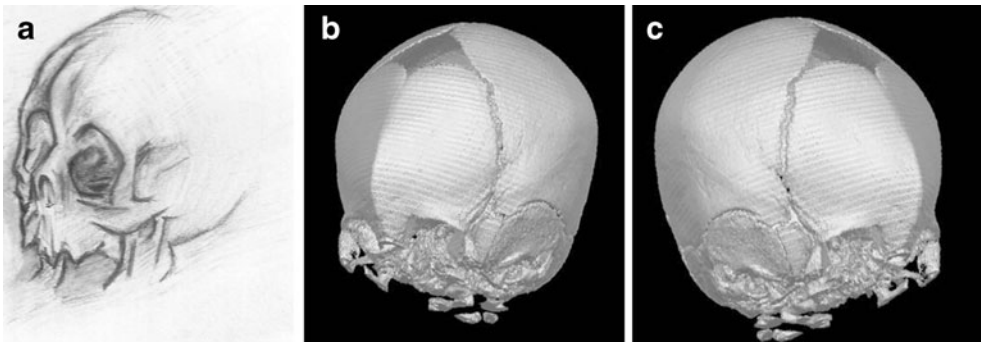

Fig. 1 **a** Metopic synostosis with trigonocephaly. **b**, **c** Three-dimensional computed tomography scan demonstrating the classical triangular shape of the frontal bones associated with metopic synostosis and ectocranial ridging

been shown to cause "acalvaria" [6]. Cranial bones develop within a fibrous membrane termed the "ectomeninx." With enlargement of the bone fields, a wedge-shaped proliferation of precursor cells termed the "osteogenic front" develops at periphery [14, 15]. When two osteogenic fronts get closer to one another, a cranial suture develops. Cohen suggests that an end-to-end presentation is related to the equal pressure being exerted on midline development (metopic, sagittal), in contrast to unequal pressures placed on overlapping sutures [5, 16, 17].

The most widely accepted view of a suture structure was initiated by Pritchard et al., who investigated the development and structure of a variety of sutures in available fetal, young, and adult material of six species. He described two cambial layers, two capsular layers of periosteum, and a middle vascular layer (Fig. 2). All these layers had, at one time or another, been described by previous authors, but no author seems to have recognized them all [18, 19]. With maturation, cambial layers decrease to a single layer of osteoblasts, the capsular layers thicken, and the middle layer becomes more vascular [20].

Manzanares et al. have confirmed the presence of two distinct tissue types along the edges of the metopic suture: secondary cartilage and chondroid tissue, basing on human autopsy material [19]. Secondary cartilage observed in the metopic sutural edges in different stages of an endochondral ossification. The histological characteristics of secondary cartilage as have already been described by Trevisan and Scapino: it consists of very abundant, large, and rounded cells which are disseminated in a scanty matrix [19, 21]. It appears after the formation of the chondrocranium, which is considered to be primary cartilage. The study has revealed that secondary cartilage clearly undergoes endochondral ossification, and secondary cartilage formation is not an important stage for sutural closure, which occurs later. Manzanares et al. have also observed that the edges of the metopic suture are composed of chondroid tissue throughout the period of sutural development. They have proposed that the chondroid tissue is directly responsible for the growth of each frontal bone toward the other and constitutes the first bridge of union between these two bones. A nearly closed metopic suture consists of large trabeculae of chondroid tissue that is progressively replaced by lamellar bone. At this stage, a sutural space can be actively maintained by resorption along the edges that preserve a discontinuous sutural gap [19]. Chondroid is a tissue that differs from both cartilage and bone. It has already been observed in some limited areas such as the mandible, the clavicle, and the cranial vault [19, 22]. It has ultrastructural characteristics similar to those bones and cartilages, and it directly differentiates from mesenchyme [23]. Finally, its matrix contains collagen type I, as is found in bone, and collagen type II, as in cartilage [22].

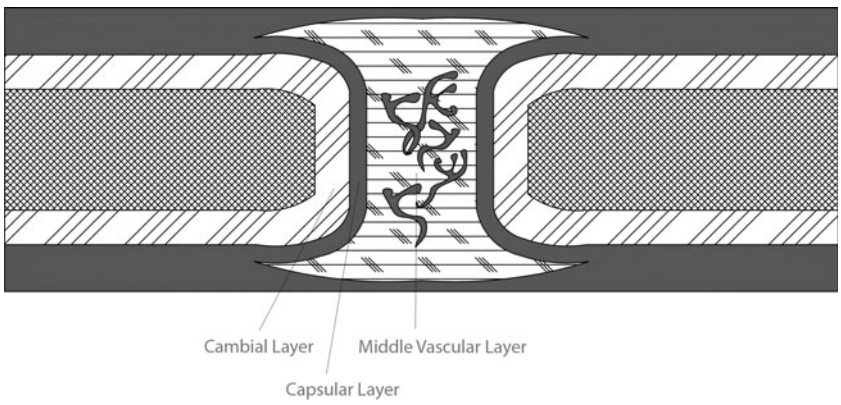

Fig. 2 Histology of a suture

Immunohistochemical analyses examined the distribution and patterns of sutural extracellular matrix in different studies. Studies have revealed that the fibronectin has been observed along the apical edge of osteogenic front associated with osteoprecursor cells. Therefore, fibronectin was associated with cell migration, perhaps facilitating osteoblast migration and proliferation in the suture area. Osteonectin was observed in deposits in both nonmineralized and mineralized areas of the osteogenic front [14–16]. Various subtypes of collagen were also found within sutures at various stages of development in mice. Type V collagen was associated with the early osteoprecursor cells at the osteogenic front in a pattern similar to fibronectin. In contrast, type I collagen was found within the osteoid, associated with well-differentiated osteoblastic cells but not with osteoprecursor cells of the osteogenic front. Type III collagen was linked to the periods of rapid suture growth [14, 24, 25]. Of the cartilage proteins, the 59 kDa protein, bone sialoproteins (BSP) I and II, and osteopontin (os I) were clearly labeled along the sutural bone margins. Proteoglycan S1 (PG-S1) was detected primarily at the sutural edge. The moderate and late occurring presence of the 58 kDa cartilage–extracted protein at the sutural region during the postgrowth period may indicate the potential importance of cartilaginous tissue in sutural closure [19, 20].

Although there are contradictions in the current literature regarding the timing of physiological closure of the metopic suture, recent radiographic studies have shown that the metopic suture begins to close as early as 3 months and generally being completely fused at the age of 8–9 months [3, 4, 26]. However, approximately 10 % of the population have patent metopic suture [27].

Pathology

The cerebral pathology of trigonocephaly is very poorly documented. Currarino and Silverman have reported on an autopsy performed on a neonate with severe simple trigonocephaly. The brain, though small, (260 g; mean weight for age, 335 g) was said to have no abnormality, though the histological findings were not described [28].

Histologic studies of craniosynostotic sutures have demonstrated that the synostosis usually begins at a single focal point, and then spreads along the suture through distinct zones of alteration [16, 29–34].

Albright and Byrd evaluated gross and microscopical pathology of skull sutures affected by craniosynostosis. They examined 19 specimens, two of which had metopic synostosis from 18 neonates and infants. The metopic specimens had a prominent external ridge of bone. Their internal surfaces were smooth, and suture was visible in the superior positions (Fig. 3). Microscopically normal cranial bone with normal osteoclastic activity was observed in these sections. In the areas of maximum clinical abnormality, every specimen demonstrated complete fusion, with no microscopic evidence of a suture. It affected only one region of the suture, and no foci of bone formation were evident in the suture distant to the fused portion. Areas of fusion, sutural narrowing, and normal suture were demonstrated in the metopic specimens. In metopic and coronal specimens, suture in the superior portions was normal and was narrowed by having encroachment in the middle portions; there was fusion in the inferior portions. The findings indicate that fusion progresses along the suture. The entire suture ultimately becomes ossified. Therefore, they have demonstrated that craniosynostosis is characterized by obliteration of sutures by progressive fusion of adjacent calvarial bones. The pathological findings did not demonstrate "closure" of normal suture unlike previous definitions of craniosynostosis as premature suture closure [29]. When craniosynostosis occurs, midline sutures (sagittal and metopic) tend to have much more ridging than nonmidline sutures [5, 16].

Regelsberger et al. evaluated histomorphological findings of sagittal sutures of nine infants with isolated, nonsyndromic synostosis. Combined analyses at cellular, material, and structural levels of the sutures suggested that the bone segments in fused sutures were associated with different stages in the course of normal osteogenesis (Fig. 4) [35].

While these authors have provided important data on synostotic suture pathology, a number of studies have been performed by small and etiologically heterogeneous postnatal samples, limited histologic-site sampling along the affected suture, and the lack of appropriate age-matched control sutures for comparisons [16].

Trigonocephaly mostly occurs as isolated cranial defect; however, it may be associated with a number of cerebral, cardiac, urogenital, and limb anomalies in a clinically and genetically heterogeneous group of syndromes [36, 37]. Patients with metopic synostosis have been found to display central nervous system anomalies as frontal subdural space distention, corpus callosum anomalies, Dandy–Walker anomaly, mega cisterna magna, progressive microcephaly, abnormally small frontal lobes, and widened precentral sulci [10, 37, 38].

Pathogenesis

The pathogenesis of metopic synostosis, as with other craniosynostosis, appears to be multifactorial and is not completely understood. Premature synostosis may simply reflect an acceleration or alteration of normal physiologic sutural maturation and closure mechanisms [16]. Metopic synostosis most likely results from many different pathologic processes. Intrauterine constraint may alter the position of the ossification centers, which has been proposed as a theory for the pathogenesis of craniosynostosis. Graham and Smith described two cases of trigonocephaly considered to be due to fetal constraint [39]. Intrauterine constraint as a cause of craniosynostosis is

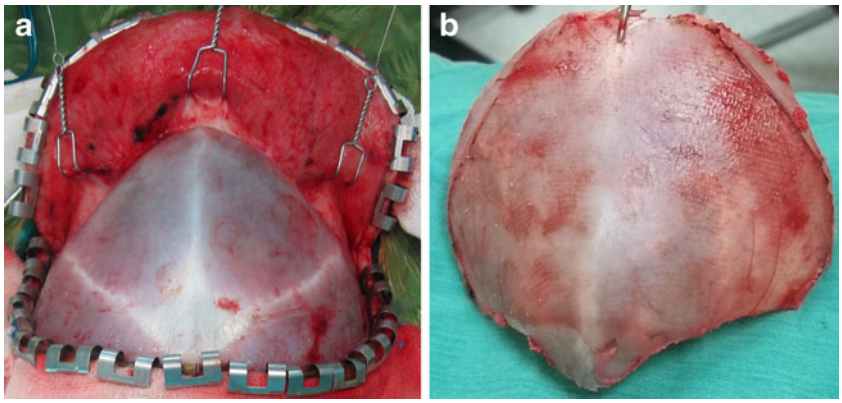

Fig. 3 **a** Intraoperative photograph showing a superior view of the frontal bone via a bicoronal scalp flap. Complete absence of the metopic suture is noted. **b** Both frontal bones have been removed en bloc due to the extent of deformity

also supported by Smartt et al., proving the principle in a mouse model [40].

Hormonal, pharmaceutical, and genetic factors have also been reported to contribute to the physiological closure of sutures. Thyroid hormone replacement therapy in case of hypothyroidism has been shown to cause metopic synostosis [41]. There are some evidences relating maternal exposure to Valproate [10, 42].

Maintenance of suture patency depends on regulating a complex array of factors that may work within the same pathways or independently of one another. It is known that MSX2 expression is regulated by BMP-4 and that these factors regulate FGF-2 mediated reactions, including TWIST expression and TGF-β2 production [43–45]. TWIST in turn regulates FGFR expression [46, 47]. Several of these factors have no known mutation associated with craniosynostosis [27].

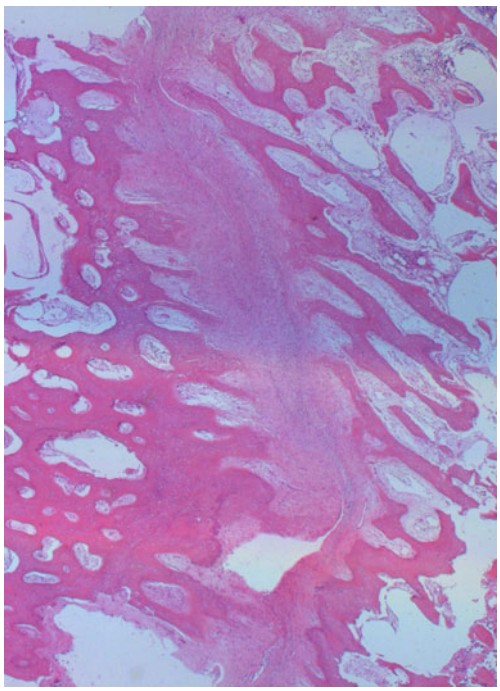

Fig. 4 Early calvarial encroachment into the metopic suture (H&E X 25)

Tartaglia et al. investigated the possible FGFR involvement in nine patients with isolated metopic synostosis, and they found that none of these patients showed mutations in canonical FGFR hot spots. The findings indicated that the isolated premature closure of the metopic suture was not associated with mutational FGFR hot spots [36, 48]. A study in individuals with either syndromic or nonsyndromic metopic craniosynostosis found no pathologic mutations in FGFR1, CER1, or CDON, suggesting that analysis of these genes was not warranted in persons with these findings [49].

Understanding of the pathogenesis of craniosynostosis including the gene defects requires a genetic animal model with primary craniosynostosis and molecular techniques [16].

Alazami et al. demonstrated expression of FREM1 in the developing midface by whole mount in situ hybridization in normal mice on 11.5th embryonic day consistent with the midfacial phenotypes seen in both BNAR and FREM1 trigonocephaly [50].

Recently, Vissers et al. reported that expression of FREM1 mRNA existed in the developing interfrontal suture, and these findings were also validated by immunohistochemical detection of FREM 1 protein within the sutural mesenchyme as well as in the dura mater and pericranium prior to the initiation of the posterior frontal suture on postnatal day 7. Therefore, they speculated that the expression of FREM1 within the intrasutural mesenchyme would be consistent with the role in modulating FGF or other growth factor availability. They provide evidence that FREM1 mutations are associated with trigonocephaly, and they presented the FREM1 mouse as a new animal model for trigonocephaly [2].

Veistinen L et al. showed that Gli3 loss-of-function ($Gli3^{Xt\text{-}J/Xt\text{-}J}$) mice exhibit ectopic ossification in the interfrontal suture, and in the most severe cases, the suture fuses already prior to birth [51].

Lajeunie et al. showed hereditary proof in 5.6 % of their diseases [10]. Metopic synostosis can also occur as an associated feature in some craniosynostotic syndromes such as Frontoocular, deletion 9p, deletion 7p, deletion 13q, the syndromes of Jacobsen, Frydman, Crouzon, Saethre–Chotzen, Haspeslagh, Opitz trigonocephaly C, and Greig cephalopolysyndactyly and

chromosome 2 pericentric inversion of 2p12-q14 [4, 8, 37, 51–58].

Conclusion

Trigonocephaly is associated with a remarkable incidence of intracranial abnormalities and neuropathology. The development of trigonocephaly is associated with many different pathologic processes of metopic suture. The etiology of metopic synostosis, as with other craniosynostosis, is unknown. With the advances in suture biology, molecular genetics and pathology will further contribute to the treatment of these anomalies.

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