The Sutures of the Skull

Anatomy, Embryology, Imaging, and Surgery

Mehmet Turgut
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Editors
Mehmet Turgut
School of Medicine
Department of Neurosurgery
Aydın Adnan Menderes University
Efeler, Aydin
Turkey

Ahmet T. Turgut
Department of Radiology
Yüksek İhtisas University
Ankara
Turkey

R. Shane Tubbs
Departments of Neurosurgery
Neurology, Surgery, and Structural and
Cellular Biology
Tulane University School of Medicine
Center for Clinical Neurosciences
New Orleans, LA
USA

Aaron S. Dumont
Department of Neurosurgery
Tulane University
New Orleans, LA
USA

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Chapter 1
Introduction

Mehmet Turgut, R. Shane Tubbs, Ahmet T. Turgut, and Aaron S. Dumont

1.1 Introduction

One type of fibrous joint of the body is known as a suture (Figs. 1.1 and 1.2). These irregular and quite variable articulations are limited to the skull. Early anatomists and physicians have always been fascinated with these unusual bony features, especially those of the calvaria (Figs. 1.3, 1.4, and 1.5). The sutures are separated only by the so-called sutural ligament or membrane. These unique structures of the skull have been classified based on their appearance. Serrate sutures, such as the sagittal suture, have a sawtooth pattern (Figs. 1.6 and 1.7) and typically, are not deeply placed. Deeply placed sutures, such as most lambdoid sutures, are made of many tooth-like projections with free ends that generally become wider and are referred to as denticulate sutures. Williams and Warwick [1] have pointed out that these sutures provide a more effective interlocking between the adjacent bones as compared to serrate sutures. When a bone of the skull overlaps with adjacent bone in a bevel it is called a squamous suture (Fig. 1.8). These beveled edges can be ridged or serrated and in such cases, are referred to as a limbous suture. Lastly, if contiguous

M. Turgut (✉)
Department of Neurosurgery, Aydin Adnan Menderes University School of Medicine, Efeler, Aydin, Turkey

Department of Histology and Embryology, Aydin Adnan Menderes University Health Sciences Institute, Efeler, Aydin, Turkey

R. S. Tubbs
Departments of Neurosurgery and Structural and Cellular Biology, Tulane University, New Orleans, LA, USA

A. T. Turgut
Department of Radiology, Yüksek İhtisas University Faculty of Medicine, Ankara, Turkey

A. S. Dumont
Department of Neurosurgery, Tulane University, New Orleans, LA, USA

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Fig. 1.1 Beauchenne preparation of the human skull noting the articulations between many of the bones of the skull

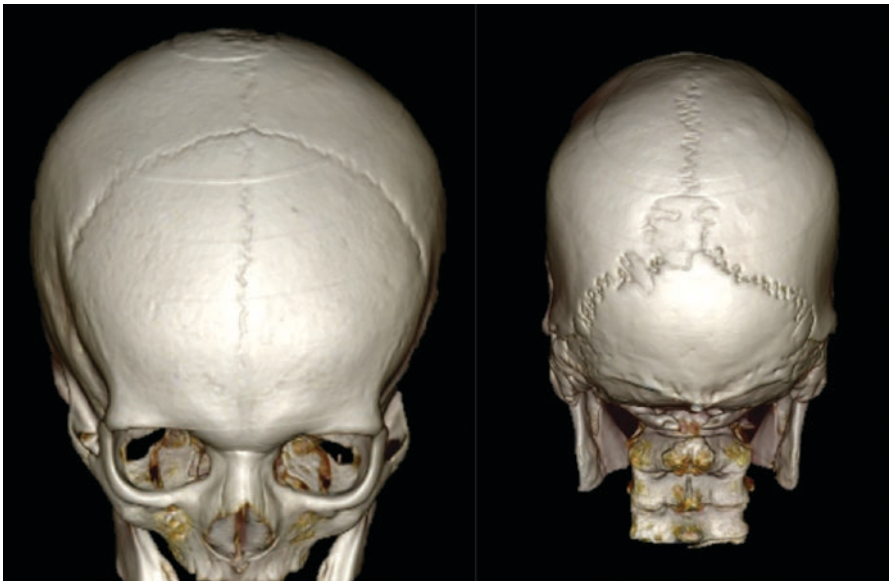

Fig. 1.2 3D reconstructed CT of the skull anterior and posterior views. The anterior view (left) illustrates the sagittal, coronal and metopic sutures. The posterior view (right) notes the sagittal suture and associated sutural bone and lambdoid sutures

surfaces have a simple apposition, they are called plane sutures and usually have an irregular or roughened edge such as the articulation between the palatine and zygomatic bones [2].

To our knowledge, this is the first text devoted entirely to the sutures of the skull. Chapters in this book cover the individual sutures e.g., those of the calvaria and skull base, embryological considerations, pathology, radiology and surgery. Our goal is to provide the reader with a comprehensive resource that can be consulted with any question related to these specialized joints of the skull.

Fig. 1.3 Drawings of the human skull illustrating the sutures of the calvaria from Johann Dryander's *Anatomia capitis humani* published in 1536

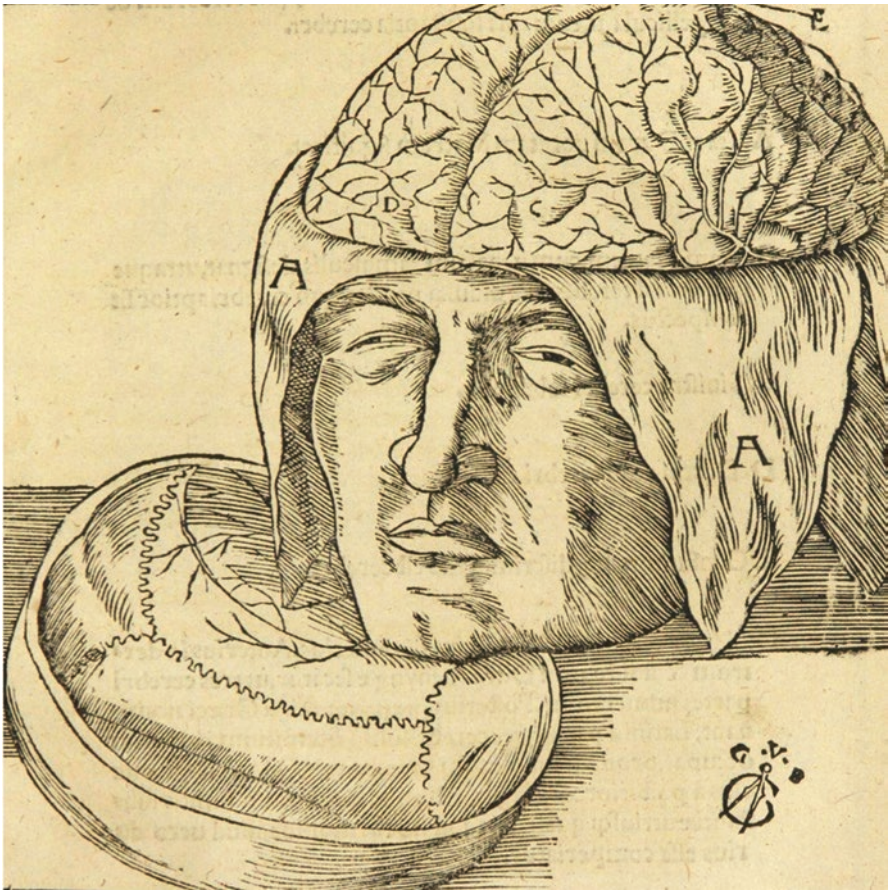

Fig. 1.4 Drawings of the human skull illustrating the sutures of the calvaria from Johann Dryander's*Anatomia capitis humani* published in 1536

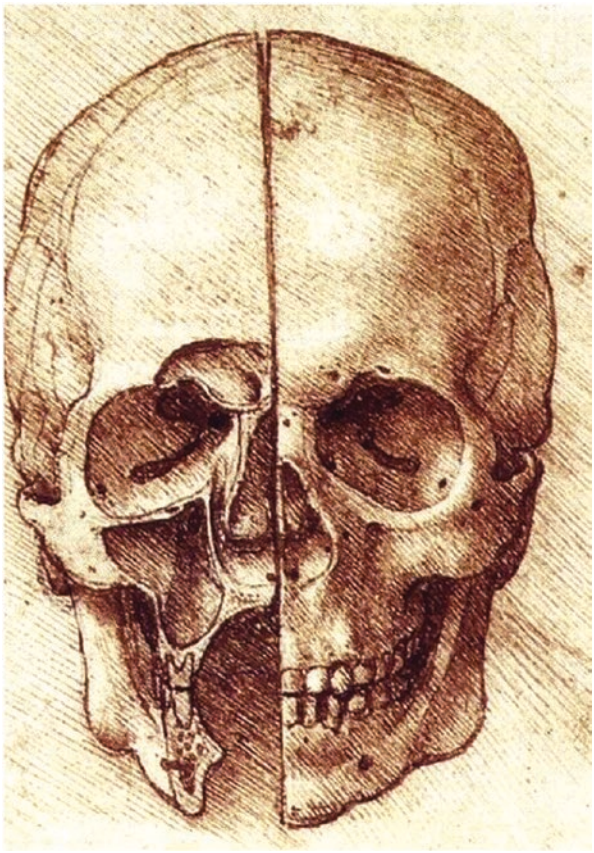

Fig.1.5 Drawing by Leonardo da Vinci (1452–1519) noting the coronal sutures

Fig. 1.6 Internal view of the right half of the sagittal suture from a disarticulated parietal bone

Fig. 1.7 External view of the right half of the sagittal suture from a disarticulated parietal bone

Fig. 1.8 External view of the right parietal part of the squamous suture from a disarticulated parietal bone

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Chapter 2
The Sutures of the Skull: A Historical Perspective

Nikolaos Ch. Syrmos, Vaitsa Giannouli, and Mehmet Turgut

2.1 Introduction

Skull sutures are essential anatomical and morphological elements of human skull structure. Moreover, they are important anthropologically for elucidating the evolution of mankind. They directly affect the growth of the human cranium and also specific brain development, but in addition they are relevant the evolution of the human central nervous system. The purpose of this study is to identify the most important historical perspectives on studies of the skull sutures [1–5].

2.2 Homer and Mythological Era

Hellenic Homer (Όμηρος) was the legendary author of the Odyssey (Οδύσσεια), the journey of Odysseus (Όδυσσέας) from Troy to his homeland Ithaca. He was also the author of another epic masterpiece, the Iliad (Ιλιάδα), the first documented civil war in human history, between two Hellenic populations (same language, same gods, same customs): Acheans (Αχαιοί) and Trojans (Τρώες). In his descriptions of war-related skull and cranial traumas in the Iliad, there is also a detailed mention of cranial sutures, providing evidence of the medical and anatomical knowledge of that time [1–7].

N. Ch. Syrmos (✉) · V. Giannouli
Aristotle University of Thessaloniki, Thessaloniki, Macedonia, Greece

M. Turgut
Department of Neurosurgery, Aydin Adnan Menderes University School of Medicine, Efeler, Aydin, Turkey

Department of Histology and Embryology, Aydin Adnan Menderes University Health Sciences Institute, Efeler, Aydin, Turkey

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2.3 Hellenic Hippocrates Era

Hellenic Hippocrates (Ιπποκράτης) of Kos (Κώς) (460–370 BCE), the first documented medical doctor and neurosurgeon in human history, together with his students, gave a detailed description of in skull and cranium anatomy in his marvelous books (Fig. 2.1) [4–9]. In particular, his work On Head Wounds (Περί των εν κεφαλή τραυμάτων), which has a total of 21 chapters, presents much information about elements of both craniology (Κρανιολογία) and cranial morphology (Μορφολογία). This book distinguishes various skull sutures types [5–11]:

- Back prominence type,
- T-type,
- H-type,
- X-type etc.

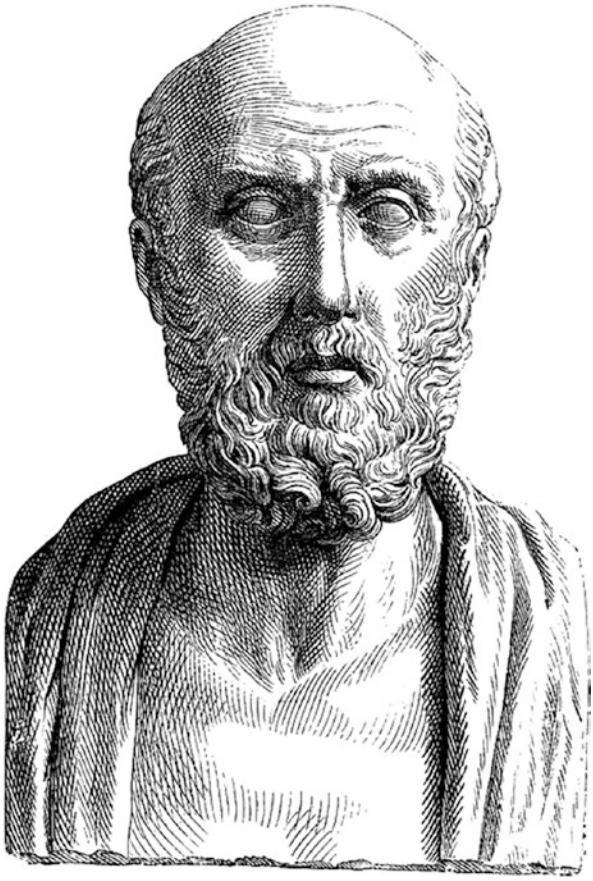

Fig. 2.1 Hippocrates (460–370 BCE)

His descriptive details of the thinner skull in the bregmatic cranial area are particularly interesting as evidence for the vulnerability of this part of the human body. All other areas of the skull are also discussed, in particularly the temporal region, the second thinnest part. He mentions its morphology; regarding its function, he notes it as the area where seizures develop. In addition he gives a detailed macroscopic view of structure and texture [6, 7, 12–15]. He also makes the first statement in history regarding skull and cranial anatomy in relation to anthropology: "*The heads of men are not all alike, nor are the cranial sutures arranged the same in all*". This statement is still valuable within the range of anthropology-related sciences [12–17].

The impact of Hippocrates on the ancient Hellenic world is reflected in many other neurosurgical operations and anatomical considerations within that world [14–19].

2.4 Other Ancient Hellenic Studies

Another important Hellenic (Asia Minor) physician, Herodotus (Ηρόδοτος) Halicarnassus (Αλλικαρνασσός), who lived between 484 and 425 BCE, managed to perform a study comparing skulls from Egypt and Persia (Fig. 2.2) [6–12]. He conducted an interesting experiment using stone impacts to verify the resistance of various cranial parts, observing the damage caused. Because the Egyptians used caps, their skulls were thicker than Persian ones on account of a physical compensatory mechanism [6–11, 13].

He wrote various books such as Histories (Ιστορίες), which dealt with the Persian Wars (Περσικοί Πόλεμοι), the attempts of the Persian Empire to conquer the separate Hellenic cities-states (Πόλεις-Κράτη). In particular, after the famous battle of Platea (Μάχη των Πλατεών) in central Greece, 479 BCE, where a Hellenic army lead by Pausanias managed to destroy the Persians under General Mardonius, he describes a skull with not a single suture, made by a unique type of bone [6–11, 14].

Aristotle (Αριστοτέλης), 384–322 BCE, was a Hellenic philosopher and polymath during the Classical period in Ancient Greece. He was born is Stagira, Macedonia. He was the teacher of Alexander the Great, 356–323 BCE, during the reign of his father, Phillip II of Macedonia. He was the first to mention the anatomical and skull differences between males and females [6–11, 15].

Galen of Pergamon (Πέργαμος) lived between 130 and 200 CE in the same geographical area as Herodotus, though later. Galen made the first attempt to categorize the clinical and pathological significance of morphological and cranial suture differences. He introduces the concept of craniosynostosis (Κρανιοσυνόστοση ή Κρανιοσυνοστέωση) for the first time by coining the term "oxicephaly" (Οξυκεφαλία). In his work De iuvamentis memborum, he clearly describes the cranial commissures (Fig. 2.3) [6–11, 16].

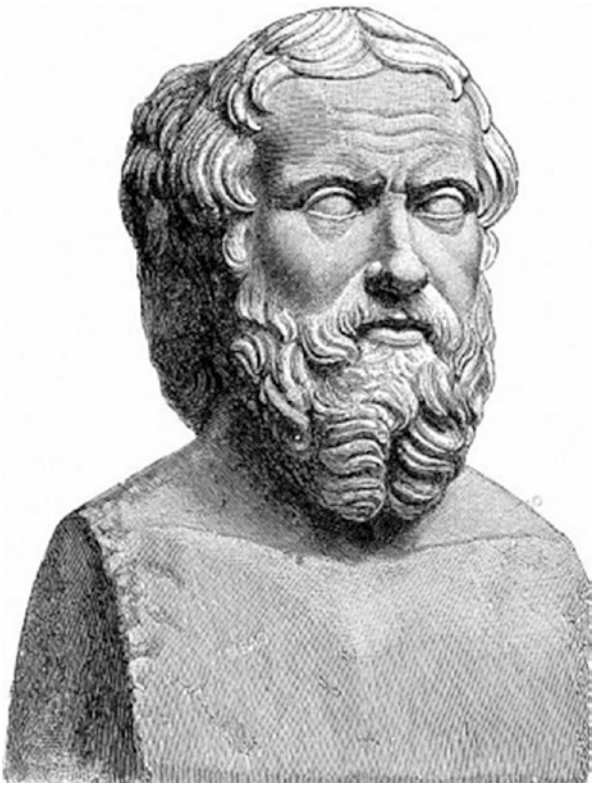

Fig. 2.2 Herodotus (484–425 BCE)

It is important to note that the Hellenic language and its spread, thanks to the conquests of Alexander the Great, gave rise to a great deal of terminology that has been used to the present day. The Latin-Italian terms that succeeded are also very descriptive and important for accuracy in anthropological and morphological studies [6–11, 17].

2.5 American-African and Mediorient Ancient Studies

Major civilizations also developed in other parts of the world: Central and Latin America, the North African and Mediterranean Area, and the Middle East (Maya, Incas, Aztecs, Zapotec, Minoans, Egyptians, Babylonians, Sumerians, Assyrians, Hittites, Persians, Jewish-Israelis, etc.) [6–12, 18]. They too developed knowledge of cranial sutures through the centuries, as revealed by various studies but mainly by paintings and other archeological findings, mainly to help them perform cranial

Fig. 2.3 Galen (130–200 CE)

neurosurgical procedures and also procedures related to religious acts, sacrifices etc. [1–5].

2.6 Arabic World

In his work Canon (Κανόνας), Avicenna, who lived between 980 and 1037 CE, describes the coronal suture for the first time, as "*An arc in whose center a perpendicular line has been set up*". He also studied the sagittal suture as "*The suture that divides the skull into two halves*". Avicenna identified the lambdoid suture as having

Fig. 2.4 Avicenna (980–1037 CE)

a form similar to the Greek letter Λ (Λάμδα) (Fig. 2.4) [6–11]. The Arabs also developed knowledge of anatomy and anthropology [1–5].

2.7 Medieval Times

During the medieval period, a great wave of knowledge spread over the whole European continent, especially in central countries such as Italy, France, Belgium, and Germany. All the sciences during this era were very active and at the same time educational for the European population. Many medical schools (such as Montpellier-France, Padova-Italy, and Bologna-Italy) were productive in the fields of human anatomy and physiology [6–11].

Medical literature, in combination with the anatomical dissections of that time, was invaluable for physicians studying the cranial sutures and achieving a better understanding of human morphology and function [6–11].

William of Saliceto (1210–1277) and his student Lanfranc of Milan (1250–1306) adopted the terms used by Avicenna to name the cranial bones and the skull sutures [6–11].

The Italian Mondino De Luizzi (1270–1326), from Bologna, Emilia Romagna, known as Mundinus, an innovative and provocative physician and anatomist, was also an innovative medical illustrator. He produced three-dimensional econographic studies of the skull (lateral, superior, posterior), pioneering work of its kind, and verified the locations of the cranial sutures exactly (Fig. 2.5) [6–11].

In France, Henri de Mondeville (1260–1320) and his student, Guy de Chauliac (1300–1368), proposed the cranial sutures as essential landmarks for performing accurate anatomical dissections. In Paris they studied thousands of skulls and they discussed the differences between males and females according to classical Aristotelian ideas and beliefs [6–11].

Leonardo da Vinci (1452–1519), the phenomenal scientist and artist, produced important and detailed descriptions of the skull sutures [6–11].

Berengario da Capri (1460–1530), another important anatomist and surgeon, noted for the first time that adhesion of the dura mater underlying the sutures of the cranium causes them not to be stronger than other areas [6–11].

Johann Dryander, a German physician, artist, scientist and anatomist from Marburg, lived between 1500 and 1560. He published an important 12-volume work, Anatomia Capitis Umani, with anatomical figures, in which he suggested that the frontal suture persists less in men than women [6–11].

Fig. 2.5 Mondino De Luizzi (1270–1326)

In Central Europe, Andreas Vessalius (1514–1564), a Flemish anatomist and physician, decided to follow Galen theory and attempt to reconcile morphology with function. He wrote the detailed masterpiece of his era, De humani corporis fabrica, to explain human body morphology thoroughly and show how it underpinned physiological functions (Fig. 2.6) [6–11, 18]. He attempted, not always with absolute success, to establish the most probable combinations among missing structures and relate them to cranial deformations. His most important contributions were his various graphical representations such as [6–11, 18]:

- Normal skull, normal sutures,
- Absence of coronal suture without causing bracycephaly (Βραχυκεφαλία),
- Absence of lambdoid suture without causing plagiocephaly (Πλαγιοκεφαλία),
- Replacement of both lambdoid and coronal sutures by a latero-lateral suture in turricephaly (Πυργοκεφαλία) cases,
- Sagittal suture missing, but no scaphocephalic (Σκαφοκεφαλία) shape.

He used his studies to relate such anatomical variations to normal or pathological function [6–11, 18].

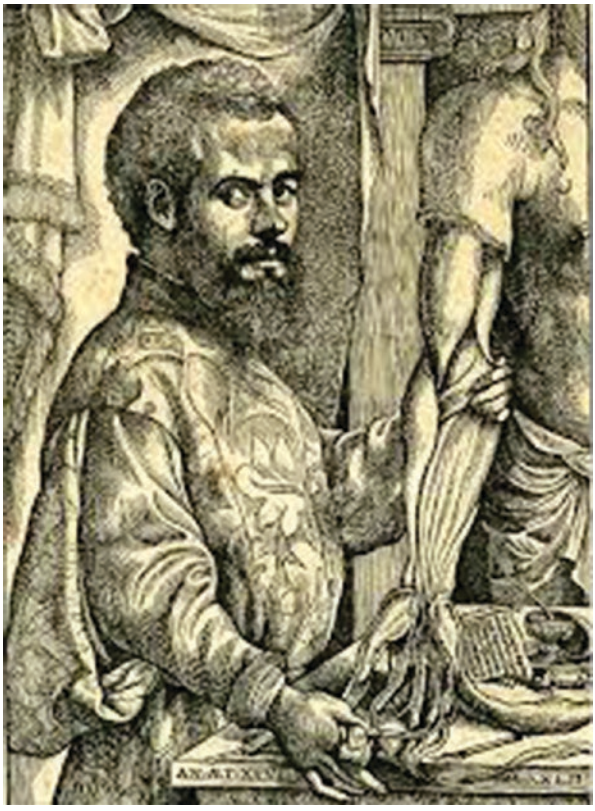

Fig. 2.6 Andreas Vesalius (1514–1564)

2.8 Nineteenth Century

Rudolph Virhow (1821–1902) was an outstanding scientist of his era. He was simultaneously physician, anatomist, pathologist and biologist despite having other duties such as politician, editor, writer and historian. He and the anatomist Adolph Otto (1786–1845) indicated the sutures as the main cause of craniosynostosis (Fig. 2.7) [10–13].

Odilon Marc Lanellongue, a French surgeon from Castera Verduzan, who lived between 1840 and 1911, was the first to describe performing a linear craniotomy for an operation mainly to preserve normal human brain growth [6–11]. Many surgeons of that time believed strongly in craniectomy as the appropriate treatment for craniosynostosis and other malformations related to the skull sutures. They had poor results and there were many early and late complications. Later, they changed their treatments to achieve better results and to optimize patient quality of life [6–11].

The medical illustrations together with the anatomical cadaveric procedures of this time greatly helped physicians to study the cranial sutures [6–11].

Fig. 2.7 Rudolph Virchow (1821–1902)

2.9 Modern Era

At the beginning of the twentieth century, neurosurgery became an autonomous medical and surgical discipline mainly thanks to the pioneering efforts of Harvey Cushing (1869–1939), the first modern neurosurgeon, and Walter Dandy (1886–1946), the first modern pediatric neurosurgeon, but also of other neurosurgeons all over the world [1–4, 6–11]. This first generation of pure neurosurgeons spent a lot of time studying the cranial sutures to improve surgeries for their patients. The introduction first of X-rays, and later of neuroimaging (CT and MRI), and nowadays of three dimensional (3D) imaging, were very important steps in improving the study of cranial sutures [13–17].

The development of other medical disciplines related to neurosurgery, such as neurology, pediatic neurology, neuroradiology, radiology, etc. were also a great help in improving understanding of the functions of the human cranial sutures. The development of pediatric neurosurgery by Antony J. Raimondi (1928–2000) during the 1970s as a subspecialism of adult neurosurgery was also a very important step [13–17].

The establishment of the European Society of Pediatric Neurosurgery (ESPN) and the International Society of Pediatric Neurosurgery (ISPN), together with the European Association of Neurosurgical Societies (EANS) and the World Federation of Neurosurgical Societies (WFNS), facilitates dialogue and knowledge growth among young neurosurgeons through courses and congresses. Neurosurgeons and pediatric neurosurgeons all over the world, such as Concezio Di Rocco (July 16, 1944) (Fig. 2.8), James T. Goodrich (1946–2020) and others,

Fig. 2.8 Concezio Di Rocco (July 16, 1944)

perform both classical and innovative techniques (endoscopic and others) to manage and treat craniosynostosis appropriately and effectively [13–17].

Nowadays, we also have 3D computer technology for performing accurate anatomical studies and also genetic insights into the development of the sutures, invlauable for predicting malformations from prenatal evidence and perhaps correcting them.

2.10 Conclusion

Through this historical study we infer the importance over the centuries of studies of cranial-skull sutures for improving understanding of the development and the anthropological and functional evolution of humankind. Furthermore, the same types of anatomical and morphological studies have helped greatly in establishing neurosurgery as a distinct medical discipline with useful approaches from related medical specialties and with the appropriate medical technology and upcoming new facilities.

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Chapter 3
Embryological and Histological Features of the Cranial Sutures

Servet Celik, Canberk Tomruk, Derya E. Tanriover, Yigit Uyanikgil, Okan Bilge, and Mehmet Turgut

3.1 Introduction

3.1.1 An overview of the Embryonic Development of the Skeletal System and Skull

The skeletal system develops in the embryo, originating from the neural crest and paraxial and lateral plaque parts of the mesoderm. From the paraxial mesoderm, tissue clusters develop as segments around the neural tube, known as somitomers in the head region and somites in the occipital region. The ventromedial parts of the somites form sclerotome and the dorsolateral parts form the dermomyotome. The sclerotome consists of mesenchyme, a loosely arranged tissue containing cells of different types. Mesenchymal cells can transform into fibroblasts, chondroblasts, or osteoblasts, with their various migration and differentiation capabilities. The parietal layer of the lateral plaque mesoderm also can form bone, not just sclerotome cells. In the lateral plate mesoderm, the bone parts of the extremities, the sternum, pelvis and shoulder arise in this layer, while cranial neural crest cells (CNC) turn

S. Celik · O. Bilge
Department of Anatomy, Ege University School of Medicine, Bornova, Izmir, Turkey

C. Tomruk · D. E. Tanriover · Y. Uyanikgil (✉)
Department of Histology and Embryology, Ege University School of Medicine, Bornova, Izmir, Turkey
e-mail: yigit.uyanikgil@ege.edu.tr

M. Turgut
Department of Neurosurgery, Aydin Adnan Menderes University School of Medicine, Efeler, Aydin, Turkey

Department of Histology and Embryology, Aydin Adnan Menderes University Health Sciences Institute, Efeler, Aydin, Turkey

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into mesenchyme, forming the bones of the face and skull. Somitomeres and occipital somites are also involved in forming the base of the skull. While most body bones are formed from cartilage originating from mesenchymal tissue (endochondral ossification), most of the skull bones are formed by direct differentiation of mesenchymal tissue (intramembranous ossification).

The skeletal structures of the skull develop from the embryonic mesoderm and the CNC, which originate from the neuroepithelium of the neural folds. CNC cells undergo epithelial-mesenchymal transition and migrate from their area of origin to the craniofacial regions [1]. CNC and mesodermal cells are highly plastic. Osteoblasts developed from CNC or mesoderm are functionally indistinguishable from each other. The functions of these cells can be shaped by inductive signals from the niche. Therefore, the niche including osteoblasts is more important than the niche of the CNC and mesenchymal cells. However, when the formation, migration, or proliferation of CNC cells is abnormal, the origin of the cells becomes important [2].

3.1.2 An Overview of Ossification in the Skull Bones

There are two types of bone formation in the head: endochondral and intramembranous ossification. Endochondral bone is formed from a hyaline cartilage precursor while intramembranous bone is formed by direct differentiation of mesenchymal cells to osteoblasts. Most of the skull bones are formed by intramembranous ossification. The subset of skull bones that supports the nasal sinuses, oral cavity, and pharynx and forms the face is called the '*viscerocranium*', and the part surrounding the brain is called the '*neurocranium*'. The neurocranium also consists of two parts; the base of the skull and the calvaria (skull vault). The bones of the skull base are formed by endochondral ossification and the cartilaginous joints between them are called synchondroses. The calvaria and facial bones are formed by intramembranous ossification [1, 3].

The bones of the skull consists of two parts: viscerocranial and neurocranial. The viscerocranial bones are of neural crest origin and are called facial bones. They originate from the first and second pharyngeal arches. The dorsal parts of the first arc-originated structures are responsible for forming part of the maxilla, zygomatic bone and temporal bone. The ventral parts contain Meckel's cartilage and ossify with the mesenchyme around it to form the mandible. The ear bones, malleus, incus and stapes, also originate from the dorsal end of the mandibular protrusion and the second pharyngeal arch, which ossifies during the fourth month, making them the first bones to ossify completely. The neurocranium can be examined in two parts: the membranous part forming the bones surrounding the brain, and the cartilaginous part forming the skull base.

The membranous part originating from the CNC and paraxial mesoderm ossifies and surrounds the brain. The needle-like bone spicules that it contains spread from the ossification centers to the surroundings. During this process, which continues

after birth, new layers are formed in the outer parts. These flat bones in the skull are separated from each other by limited connections consisting of connective tissue, called sutures. The origins of these connections differ; whereas the sagittal suture is of neural crest origin, the coronal suture is of paraxial mesoderm origin. Also, if the junction parts belong to more than two bones, they are found more broadly and are called fontanelles. The cartilaginous part of the skull ossifies endochondrally [4–6].

3.2 Development of Sutures

An adult has eight bones in her skull: one frontal, two parietal, two temporal, one ethmoid, one sphenoid, and one occipital. The numbers of these bones vary because of the ossification processes during development. Their borders make contact with each other by surfaces of fibrous tissue known as skull sutures, which differentiate from embryonic mesenchyme [7].

Intramembranous ossification begins from a center within vascularized mesenchyme or embryonic connective tissue and spreads to form the bone (Fig. 3.1). Thus, intramembranous ossification areas are formed. As ossification progresses, the bone areas come closer to each other, then sutures develop between them [6].

The sutures are not only joints between bones. They are also osteogenesis regions where osteoprogenitors proliferate, differentiate, and function on the bone margins. During the formation of a cranial suture, the osteogenic edges of the two bones involved, the mesenchymal tissue of the suture, the inner surface in contact with dura mater and the outer side in contact with pericranium, work together (Fig. 3.2b) [8]. These tissues of the suture complex interact to ensure proper formation of the suture or aperture throughout development. The cells in the middle of the mesenchymal tissue of the suture do not differentiate during bone formation, but those at the two osteogenic bone edges initiate intramembranous ossification and differentiate to osteoblasts. In order for the brain to continue growing in the skull cavity, the middle of this center must remain unossified, and the sutures forming between apposed bone edges must allow osteogenesis to continue with osteoblast formation.

Skull sutures are formed either by the direct joining or the overlapping of adjacent bones [7]. The sutures are usually of intramembranous ossification origin. However, the frontoethmoidal suture is formed by a combination of intramembranous and endochondral ossification [1].

The sutures and fontanelles have some degree of flexibility, as evidenced by the compression of the skull during birth. For structural and protective reasons, the sutures lose this limited mobility and become more rigid. This is accomplished by interlocking of the apposed bone margins and fusion along the suture.

In the human skull, the sutures are named metopic (between the frontal bones), sagittal (between the parietal bones), coronal (between the frontal and parietal bones), lambdoid (between the supraoccipital and parietal bones), and squamosal (between the parietal, temporal, and sphenoid bones) (Figs. 3.2, 3.3, and 3.4). Suture formation begins as these calvarial bones approach each other.

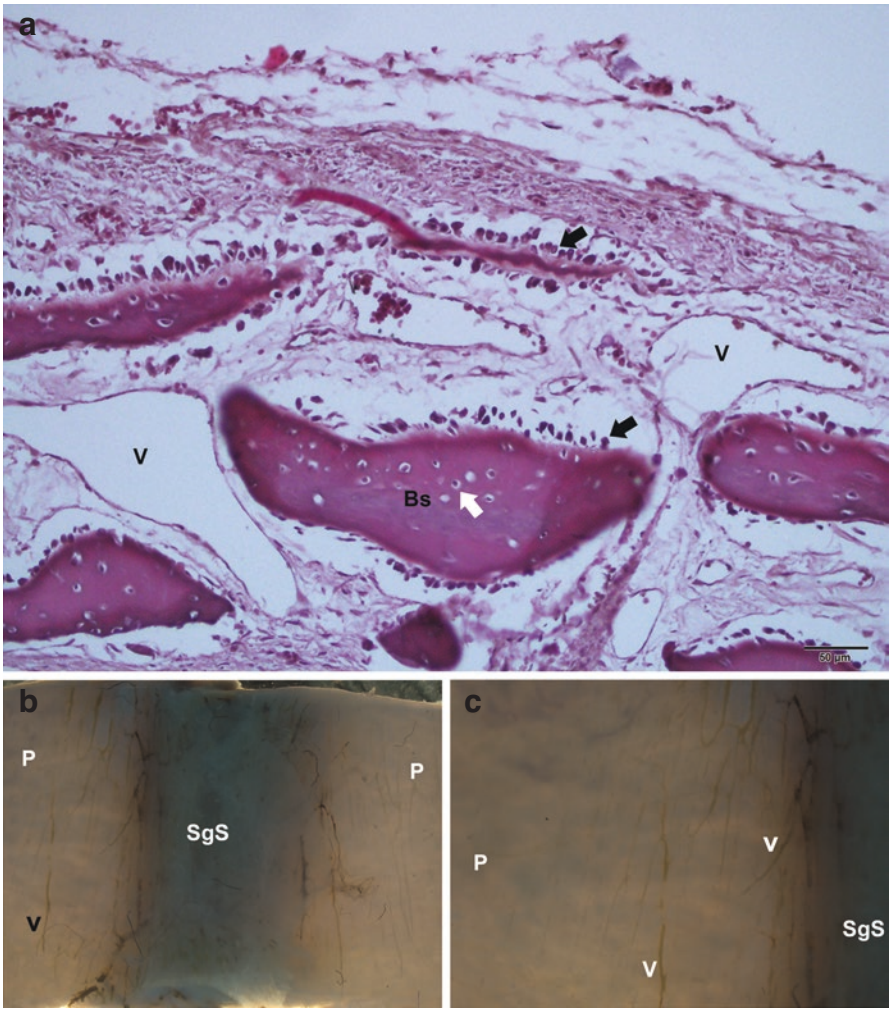


Fig. 3.1 Ossification of parietal bone in a 3.5-month fetus. (**a**) Histological view and (**b** and **c**) translumination stereomicroscopic view (Olympus SZ61, Olympus SC50, Japan) before histological sampling. Vessels in the bone tissue are seen extending radially from the ossification centers. (With permission of Ege University Faculty of Medicine Department of Anatomy). Abbreviations: Black arrow: Osteoblasts, Bs: Bone spicules, P: Parietal bone, SgS: Superior sagittal sinus, V: Vessel, White arrow: Osteocytes

During fetal life, the flat bones of the calvaria are separated by dense connective tissue membranes that form fibrous joints, calvaria sutures, and six large fibrous areas (fontanelles) where several sutures come together. The softness of the bones and the loose connections formed by the sutures allow the calvaria to change shape during childbirth. In areas where three or more bones come together in the calvaria, the sutures expand and become fontanelles. Fontanelles are larger than sutures

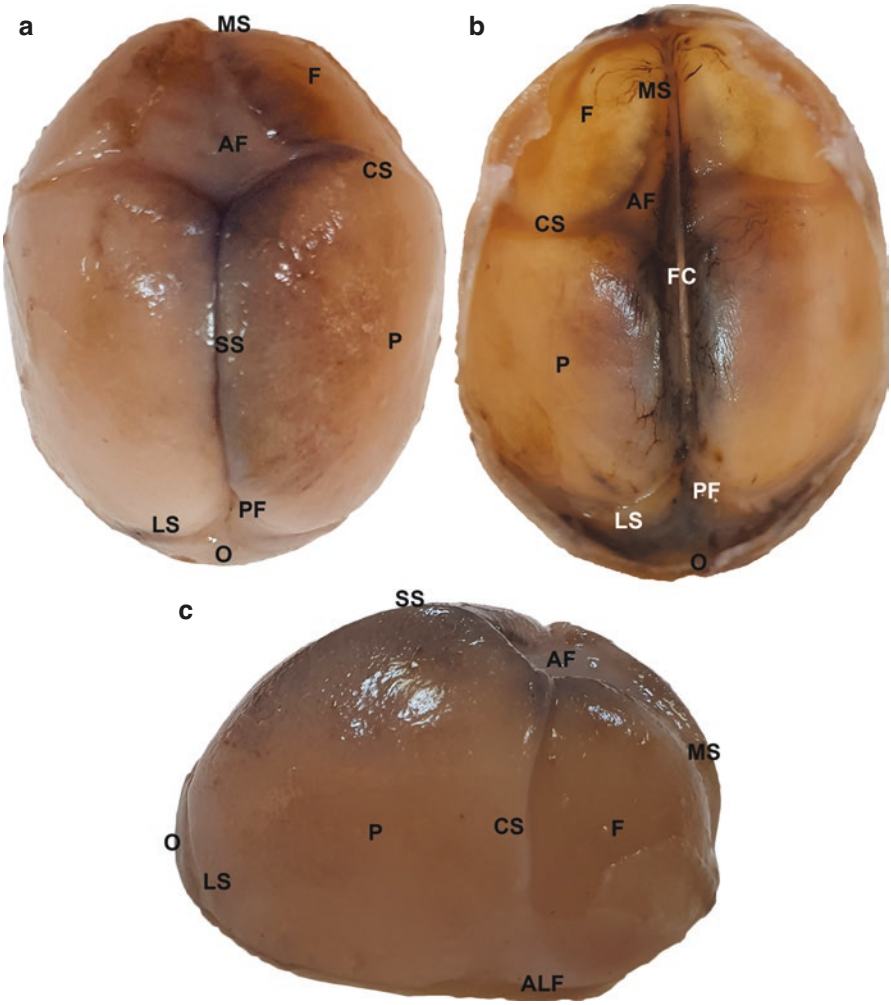


Fig. 3.2 The calvaria of a 3.5-month fetus. (**a**) Superior view of the calvaria after the scalp is removed. (**b**) Inferior view of the calvaria covered with cranial dura mater. (**c**) Lateral view of the calvaria. (With permission of Ege University Faculty of Medicine Department of Anatomy). Abbreviations: AF: Anterior fontanelle, ALF: Anterolateral fontanelle, CS: Coronal suture, F: Frontal bone, FC: Falx cerebri of cranial dura mater, LS: Lambdoid suture, MS: Metopic suture, O: Occipital bone, intraparietal part, P: Parietal bone, PF: Posterior fontanelle, SS: Sagittal suture

during birth, but the calvarial bones continue to grow postnatally and the fontanelles quickly shrink. Sutures and fontanelles are robust structures. They are flexible during birth to allow the calvaria to be temporarily compressed [1]. The fontanelles in a developing fetus are anterior, posterior, anterolateral and posterolateral.

Anterior fontanelle: The anterior fontanelle is also called the fonticulus major. It measures approximately 4 cm in the anteroposterior and 2.5 cm in the transverse

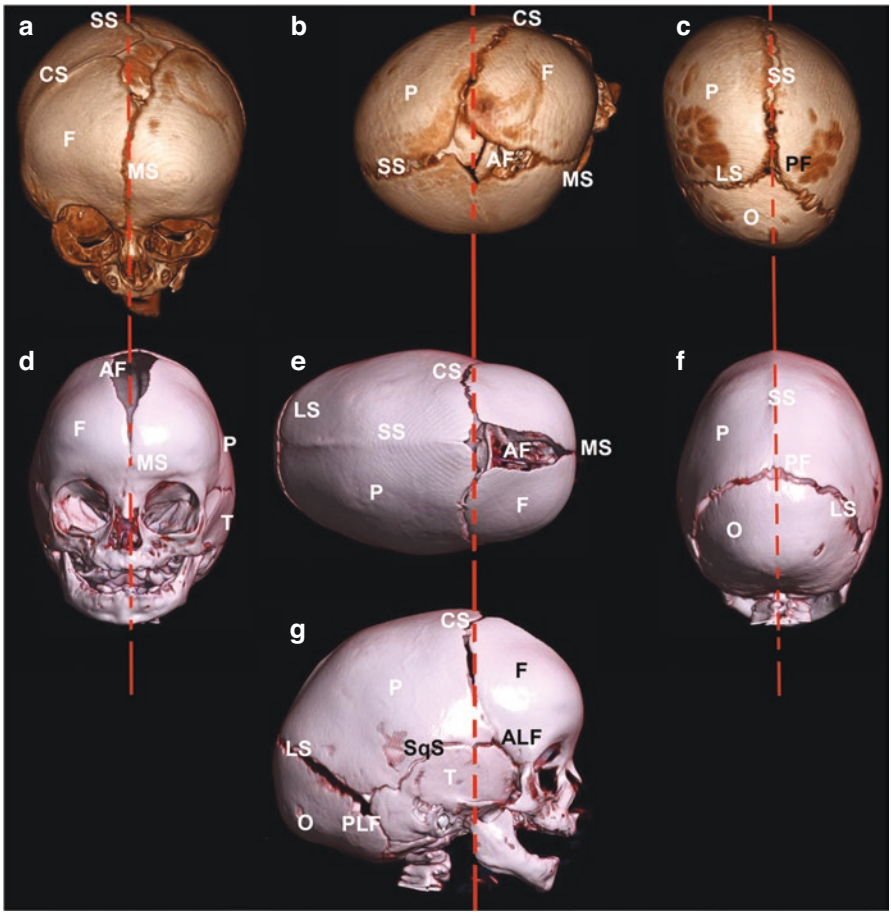


Fig. 3.3 CT 3D reconstructions of newborns with cranial suture and ossification anomalies. (**a**–**c**) Premature closure of right part of the coronal suture in 6-month-old child. (**d**–**g**) Premature closure sagittal suture in 4-month-old child. (Courtesy of Dr. Saim Kazan). Abbreviations: AF: Anterior fontanelle, ALF: Anterolateral fontanelle, CS: Coronal suture, F: Frontal bone, FC: Falx cerebri of cranial dura mater, LS: Lambdoid suture, MS: Metopic suture, O: Occipital bone, P: Parietal bone, PF: Posterior fontanelle, PLF: Posterolateral fontanelle, Red lines: Orientation lines for sutures, SqS: Squamous suture, SS: Sagittal suture, T: Temporal bone

dimension. This diamond-shaped, membrane-filled space is located between the anterior end of the sagittal suture and the frontal bone in the developing fetus. Its location is also the intersection of the metopic, coronal, and sagittal sutures. The anterior fontanelle, which initially has a membranous structure, usually fuses by the age of 18 months. Examination of it, where two parietal and two frontal bones come together, provides useful information about whether ossification is proceeding normally [1]. After the anterior fontanel closes, the sagittal and coronal sutures join at the same point. This junction point is called the bregma (Figs. 3.2, 3.3, and 3.4).

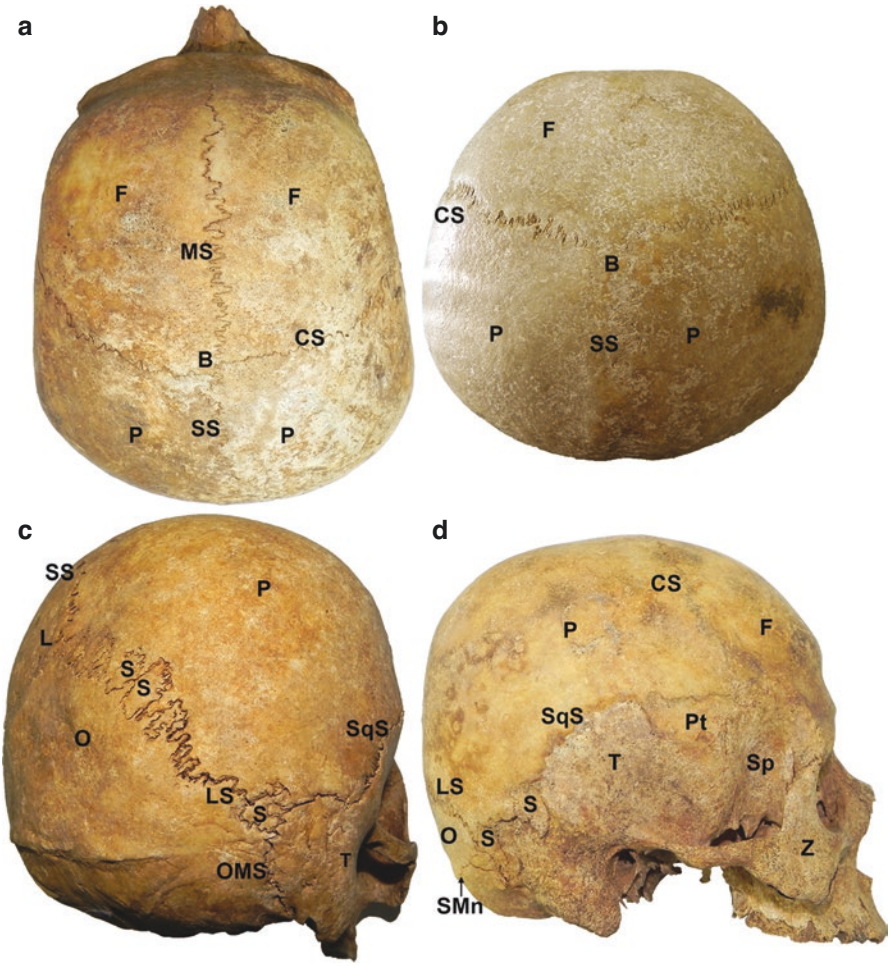


Fig. 3.4 Adult skulls with suture and ossification anomalies. (**a**) Complete persistent metopic suture from superior view. (**b**) Premature closure of sagittal suture results in formation of brachiocephalic cranium (superior view). (**c**) Multiple sutural bones in the lambdoid suture, right posterolateral view and (**d**) Multiple sutural bones including 'pterion ossicle', right lateral view. (With permission of Ege University Faculty of Medicine Department of Anatomy). Abbreviations: B: Bregma, F: Frontal bone, CS: Coronal suture, L: Lambda, LS: Lambdoid suture, MS: Metopic suture, O: Occipital bone, OMS: Occipitomasotid suture, P: Parietal bone, Pt: Pterion ossicle, S: Sutural bone, Sp: Sphenoid bone, SqS: Squamous suture, SMn: Sutura mendosa, SS: Sagittal suture, T: Temporal bone, Z: Zygomatic bone

Posterior fontanelle: this is also called the fonticulus minor. It is located between the posterior end of the sagittal suture and the occipital bone, at the intersection of the sagittal and the lambdoid sutures. This fontanelle is triangular and is smaller than the anterior fontanelle. Initially it has a membranous structure and it usually fuses by the age of 3–6 months [9]. After its closure, the sagittal and the lambdoid sutures on both sides are joined at a single point. This junction point is called the lambda (Figs. 3.2, 3.3, and 3.4).

Anterolateral (or sphenoidal) fontanelle: The anterolateral fontanelles are irregular in shape. They are located between the greater wing of the sphenoid bone, the squamous part of the temporal bone, the sphenoid angle of the parietal bone, and the frontal bone on both sides. The sphenoidal fontanelle is the next to close, around 6 months after birth. After it closes, neighboring bones form a H-shaped suture zone called the pterion. The pterion corresponds to the site of the anterolateral (sphenoidal) fontanelle in the neonatal skull (Figs. 3.2, 3.3, and 3.4).

Posterolateral (or mastoid) fontanelle: This is located between the mastoid angle of the parietal bone, temporal bone, and occipital bone. It closes 6–18 months after birth. After it closes, the point of suture intersection is called the asterion (Figs. 3.2, 3.3, and 3.4).

Thanks to these fontanelles and sutures, skull bones can overlap during childbirth, but their arrangement returns to normal postnatally. After birth, the skull bones continue to grow in parallel with the brain, and the sutures and some of the fontanelles remain membranous during this process.

3.3 Individual Bone Development and Ossification in Relation to Sutures

Sutures are fibrous joints between cranial bones and their formation depends on the ossification of those bones during development. Also, they are membranous or fetal cartilage into the seventh and eighth decades, changing constantly until the structure into bone. Sutures form between the cranium bones by ossification of their edges as they spread outwards. During fetal development, some sutures begin to form owing to ossification, and some arise as ossification continues postnatally. In both fetal and postnatal life, ossification and disruption of suture development can cause cranial deformities [10]. Craniosynostosis is the premature closure of sutures; late closure is called metopism. Craniosynostosis and metopism can lead to different head deformities that can be confused with trauma. Therefore, it is important to understand the ossification of cranial bones, the closure of the ossification centers and the times of suture formation. The ossification centers associated with the formation and ossification of sutures will be mentioned, but not the entire process of cranial bone development.

3.3.1 Ossification Centers in Neurocranial Bones

3.3.1.1 Frontal Bone

The frontal bone ossifies intramembranously from two primary ossification centers that Appear during the eighth week in utero, one near each frontal tuber. Ossification extends superiorly to form half of the main part of the bone; posteriorly to form the orbital part; and inferiorly to form the nasal parts [11, 12].

Numerical studies analyzing the ossification centers of skull bones are very rare owing to the limited availability of fetal material. A CT study of 18–30 week fetuses revealed the sizes of the primary ossification centers of the frontal bone. The mean vertical diameter of the primary ossification center in the squamous part of the frontal bone (or frontal squama) ranges from 20 to 33 mm. Its mean transverse diameter ranges from 18 to 30 mm. Its mean projection surface area ranges from 336 mm^2 at 18 weeks of gestation to 812 mm^2 at 30th weeks [13].

Two secondary centers for the nasal spine appear about the tenth year. Likewise, the nasal part and zygomaticus process also ossify from two separate secondary centers. *At birth,* the frontal bone has two parts. Between those parts is the metopic suture. The metopic suture starts to close after the first year and completely disappears by 7 years of age [9, 14]. At the age of eight, its upper part often fuses. But the metopic suture persists in a small percentage of individuals in various ethnic groups, and a partial or complete suture is seen in the frontal bone. This is called sutura frontalis (metopica) persistens (Fig. 3.4a) [12].

3.3.1.2 Parietal Bone

The parietal bone ossifies intramembranously from two centers. These ossification centers arise in the parietal tuber during the eighth week of intrauterine life. One is located above the other. They unite early and ossification subsequently radiates from the tuber towards the margins. Trabeculae radiate from the primary ossification center to the periphery of the parietal bone and take the form of a "coral reef" within the tuber [15]. The angles are therefore the last parts to be ossified, and fontanelles appear at these sites [5, 12]. In adults, the coronal, sagittal, lambdoid and squamous sutures surround the parietal bone. The coronal, sagittal, and lambdoid sutures start to fuse between the ages of 25 and 30 years [9, 14].

Because the two ossification centers ossify separately, accessory bones can appear in the parietal bone or the sutures surrounding it [16, 17]. An accessory suture in the parietal bone is rare, though it is more common in men. Such sutures in the parietal bone can be horizontal, vertical or obliquely oriented. Accessory sutures are usually bilateral, rarely one-sided. They often appears horizontally and divide the bone into two parts. An accessory suture extends anteriorly from the coronal suture to the lambdoid suture at the back [17].

Sutural bones can be seen in the sutures surrounding the parietal bone, but they are most common in the lambdoid suture (Fig. 3.4). Anteriorly, between the paired frontal and parietal bones, there is sometimes an accessory ossicle, osbregmaticum, either free or fused with one of the frontals or parietals [6, 12].

3.3.1.3 Occipital Bone

The ossification of the occipital bone is both membranous and cartilaginous. The superior part of the squamous part of the occipital bone in the fetus is called the interparietal part. Its inferior part extends to the posterior border of the foramen

magnum and is called the supraoccipital part. Between those parts lies the transverse occipital or mendosal suture. The other parts of the fetal occipital bones are two lateral (condylar) parts and the pars basilaris (basioccipital part). Between the supraoccipital and lateral parts on both sides is the sutura intraoccipitalis posterior. Between the lateral and basilar parts is the sutura intraoccipitalis anterior. The interparietal part ossifies intramembranously and other parts ossify intracartilaginously [6].

The interparietal part located above the highest nuchal lines develops into a fibrous membrane and ossifies from two centers (one on each side) from about the second fetal month. This part of the occipital bone can remain separate as the interparietal bone. The supraoccipital part ossifies from two centers that appear in about the seventh week and soon unite. The interparietal and supraoccipital parts unite during the third postnatal month but the line of their union is recognizable at birth [6].

The remainder of the cartilage of the occipital bone ossifies from five or six centers: two each for the lateral parts appear during the eighth week, and one or two for the basilar part appear around the sixth week. At birth, the occipital bone consists of four separate parts (one basilar, two lateral and one squamous). The squamous and lateral parts fuse during the second year. The lateral parts fuse with the basilar part during years three and four, but fusion can be delayed until the seventh year [18].

Persistence of the lateral portions of the transverse occipital sutures in adults is termed sutura mendosa (Fig. 3.4d). This starts from the lambdoid suture on both sides and represents the remnant of a transverse occipital suture. Its length ranges from 10.4 to 31.6 mm [19]. If the mendosal sutures on both sides fuse they form an interparietal bone (inca or intercalary or sutural bone). The interparietal or inca bones are bounded by the lambdoid suture and sutura mendosa (transverse occipital suture). An inca bone is rare (0.8–2.5%). Inca bones result from non-fusion of the multiple ossification centers in the interparietal part that ossifies intramembranously [20, 21].

In some cases, in addition to the primary ossification centers described above, separate ossification centers appear in the joints. In such cases, additional bones can be seen. These are usually symmetrical and are located around the sutura lambdoidea. They are called sutural or Wormian bones (Fig. 3.4c).

3.3.1.4 Temporal Bone

The four temporal components ossify independently. The squamous part is ossified in a sheet of condensed mesenchyme from a single center near the zygomatic roots, which appears in the seventh or eighth week in utero. The petromastoid part has several centers that appear in the cartilaginous otic capsule during the fifth month; as many as 14 have been described. These centers vary in order of appearance. Several are small and inconstant, soon fusing with others.

In the neonate, the petrous and squamous parts of the temporal bone are usually partially separated by the petrosquamous fissure, which opens directly into the mastoid antrum of the middle ear. Rarely, this fissure closes in infants during the first year; sometimes it remains unclosed up to the age of 19 years. It is a route for the spread of infection from the middle ear to the meninges.

3.3.1.5 Sphenoid Bone

Until the seventh or eighth intrauterine month, the sphenoid body has two parts, presphenoidal and postsphenoidal. The presphenoidal part is anterior to the tuberculum sellae and includes the lesser wings. The postsphenoidal part includes the sella turcica and dorsum sellae, and is integral with the greater wings and pterygoid processes.

Most of the sphenoid bone ossifies intracartilaginously. There are six ossification centers for the presphenoidal parts and eight for the postsphenoidal parts.

3.3.1.6 Ethmoid Bone

The ethmoid bone ossifies in the cartilaginous nasal capsule from three centers, one in the perpendicular plate and one in each labyrinth. The latter two appear in the orbital plates between the fourth and fifth months *in utero* and extend into the ethmoidal conchae. At birth, the labyrinths, although ill-developed, are partially ossified and partly cartilaginous. The perpendicular plate begins to ossify from the median center during the first year and fuses with the labyrinths early in the second year. The cribriform plate is ossified partly from the perpendicular plate and partly from the labyrinths. The crista galli ossifies during the second year. The parts of the ethmoid bone unite to form a single bone at around 3 years of age [5, 6].

3.3.1.7 Additional Ossification Center and Sutural (Wormian) Bones

In the developing fetus additional ossification centers can appear in or near sutures, giving rise to isolated sutural or Wormian bones. Those small irregularly-shaped bones are found in the cranial sutures (Fig. 3.4b). They also occur in fontanelles, especially the posterior fontanelle. Their size, shape, and number differ from skull to skull [22].

A sutural bone is occasionally present at the pterion or junction of the parietal, frontal, greater wing of the sphenoid, and the squamous portion of the temporal bone. It is called a “pterion ossicle,” “epipteric bone,” or “Flower’s bone” (Fig. 3.4d). Nayak and Soumya (2008) reported a case of three sutural bones at the pterion [23].

3.3.2 Ossification Centers of the Viscerocranial Bones

3.3.2.1 Maxilla

The maxilla ossifies intramembranously. It has two ossification centers and ossifies from the mesenchyme. One center is slightly above the canine fossa and the other is in the premaxilla region, where the incisors are located below. The maxillary ossification centers appear during the sixth week of intrauterine life. Ossification from the center in the canine fossa spreads to other parts of the maxilla. At the beginning of the third month (tenth week) in utero, the upper and lower ossification centers merge [24].

The suture between the ossification centers can persist, sometimes throughout life. In such cases, the incisive (premaxillary) suture is seen behind the incisors. It develops like a separate bone structure called the incisive bone, which is part of the incisors (Fig. 3.5). The incisive suture and incisive bone (premaxilla) make the number of ossification centers controversial. Some sources state that there is no separate ossification center in the premaxillary region [12]. Others state the ossification center in the canine fossa extends to the front premaxillary region [4].

3.3.2.2 Palatine Bone

The palatine bone ossifies intramembranously from a single center. This center is seen in the sixth to eighth weeks of intrauterine life and is located in the perpendicular plate. Ossification spreads from this center all over the bone [12].

The horizontal plates of both palatine bones that develop from the secondary raphe fuse in the midline during the tenth intrauterine week and form the posterior quarter of the hard plate. If this fusion does not occur, differently sized clefts can appear in the plate. In this condition, the median palatine suture can be completely or partly absent (Fig. 3.5) [4].

3.3.2.3 Os Zygomaticum

During the eight week in utero, the os zygomaticum usually ossifies from three centers, one in the lateral and the others in the orbital part. These centers fuse during the fifth intrauterine month. Rarely, a horizontally or vertically oriented accessory suture can be seen in the zygomatic bone between these two ossification centers after birth, and can divide the bone into two parts. Each part is called os Japonicum (Ainoicum). In such cases, the zygomatic bone is often in two parts, more rarely three. A multi-partite zygomatic bone (os Japonicum) is found in up to 3.8% [25].

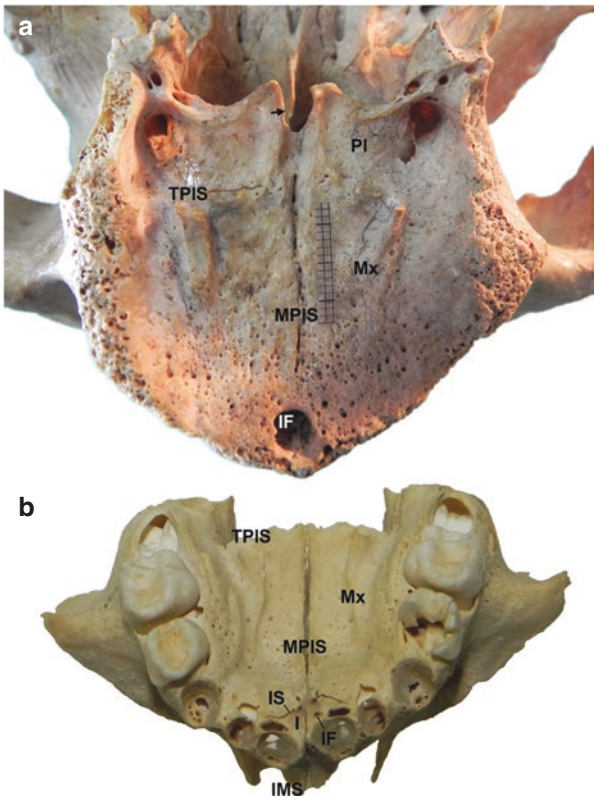


Fig. 3.5 Inferior view of palatal sutures. (**a**) Partial non-fusion of median palatine suture between palatine bones in adult cranium. (**b**) Incisive bone and separation on median palatine suture between alveolar processes of maxilla of three-year-old child. (With permission of Ege University Faculty of Medicine Department of Anatomy). Abbreviations: Black arrow: Fissure between palatine bones, I: Incisive bone, IF: Incisive foramina, IMS: Intermaxillary suture, IS: Incisive suture, MPlS: Median palatine suture, Mx: Palatine process of maxilla, Pl: Horizontal plate of palatine bone, TPlS: Transverse palatine suture

3.3.2.4 Vomer

The nasal septum is initially a plate of cartilage, part of which is ossified above to form the perpendicular plate of the ethmoid. Its anteroinferior region persists as septal cartilage. The vomer is ossified in a layer of connective tissue, which covers the cartilage posteroinferiorly on each aspect. At about the eighth week *in utero*, two centers appear flanking the midline, and in the 12th week they unite below the cartilage to form a deep groove for the nasal septum. Union of the bony lamellae progresses anterosuperiorly while the intervening cartilage is absorbed. By puberty, the lamellae are almost united, but evidence of their bilaminar origin remains in the everted alae and anterior marginal groove.

3.3.2.5 The Other Viscerocranial Bones

The inferior nasal concha is ossified from one center that appears at about the fifth month *in utero* in the inwardly curved lower border of the cartilaginous lateral wall of the nasal capsule. It loses continuity with the nasal capsule during ossification.

The lacrimal bone is ossified from a center that appears at about the 12th week in utero in the mesenchyme around the nasal capsule. In later life, the lacrimal bone is subject to patchy erosion. The nasal bone is ossified from a center that appears early in the third month in utero in the mesenchyme overlying the cartilaginous anterior part of the nasal capsule. The development and ossification of the mandible are very complex. However, since the mandible does not participate in suture formation, it will not be discussed here.

Many sutures between viscerocranial bones form the facial skeleton. They are named according to the bones between which they are located. In contrast to calvarial sutures, most facial sutures such as the frontomaxillary, nasomaxillary and zygomaticomacillary sutures remain until the seventh or eighth decade of life [26]. This is thought to be due to the mechanical tension applied to the upper part of the face through chewing. The intermaxillary suture starts to fuse between the ages of 30 and 35 years [27].

3.3.2.6 Histology of Cranial Sutures and Fontanelles

Histology of Sutures

The sutures consist of osteogenic cells, vascular structure and mesenchymal loose connective tissue [1, 28]. The intramembranous bone is formed from connective tissue. The bones of the skull such as the frontal, parietal, temporal, and the jaw are formed by this type of ossification. These bones are also called membranous bones. They develop as follows: the first mesenchymal cells gather around the vessels and proliferate. The gaps between them are filled with a soft matrix containing collagen fibers. Mesenchymal cells can transform into osteoblasts (Fig. 3.1), which differentiate into osteocytes by synthesizing intercellular substance and fiber. This area is called the ossification center. The bone formed is spongy (trabecular) and does not contain lamellae. Calcium-based structures have not yet collapsed and are called osteoid tissue (spicules). The process continues with new cells coming from behind where the osteoblasts around the vessels turn into osteocytes and empty them. Trabeculae grow and anastomose and the spongy bone tissue is shaped. In this type of ossification, the periosteum and endosteum are made by connective tissue that does not participate in ossification. The connective tissue in the intermediate cavities of the trabeculae also turns into the myeloid or hemopoietic tissue of the bone marrow.

The most widely accepted model of suture development is by Pritchard et al. [29]. They identified five separate layers: there are two cambial and two capsular layers of periosteum bone separated by a middle vascular layer. With maturation, the cambial layer develops as a single osteoblast layer. The capsular layer thickens and becomes parallel to the suture faces of the bones. The middle layer remains vascular. Osteonectin, a glycoprotein specific to bone, is located in the structure of the osteoid (bone spikes) that is both non-mineralized and mineralized in the osteogenic area. Osteoblasts synthesize type I collagen, but osteoprogenitor cells do not.

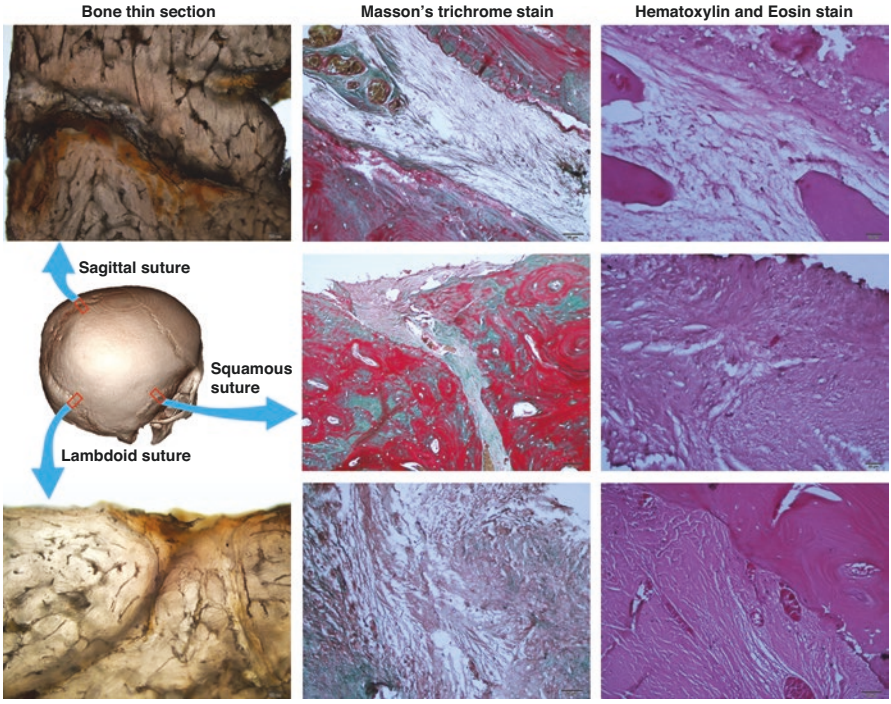


Fig. 3.6 Histological examination of sagittal, lambdoid and squamous sutures in unstained bone thin sections, and Masson's trichrome and Hematoxylin & Eosin stained sections. Histological preparation: From the skull of a 55-year-old man, 2 × 1 cm bone bands were removed from the sagittal, lambdoid and squamous sutures and immersed 20% formic acid for about 10 weeks to soften. Histological sections were checked once a week when softening was expected. Thick sections (1 mm) were taken from the lambdoid and sagittal sutures when they became sliceable. Similar sections could not be taken from the squamous suture owing to its anatomical condition. The thick sections were examined under a light microscope (Olympus BX51, Olympus C5050, Japan). Tissues samples were also taken by routine histological preparation and embedded in paraffin, and then 5 μm sections were cut with a Leica RM2145 microtome (Germany) and stained with H&E and Masson's trichrome. Sections taken from histological preparations of all three sutures were examined

Type V collagen, in contrast, is located proximally with the fibronectin in the apex the osteogenic areas around the osteoprogenitor cells [7].

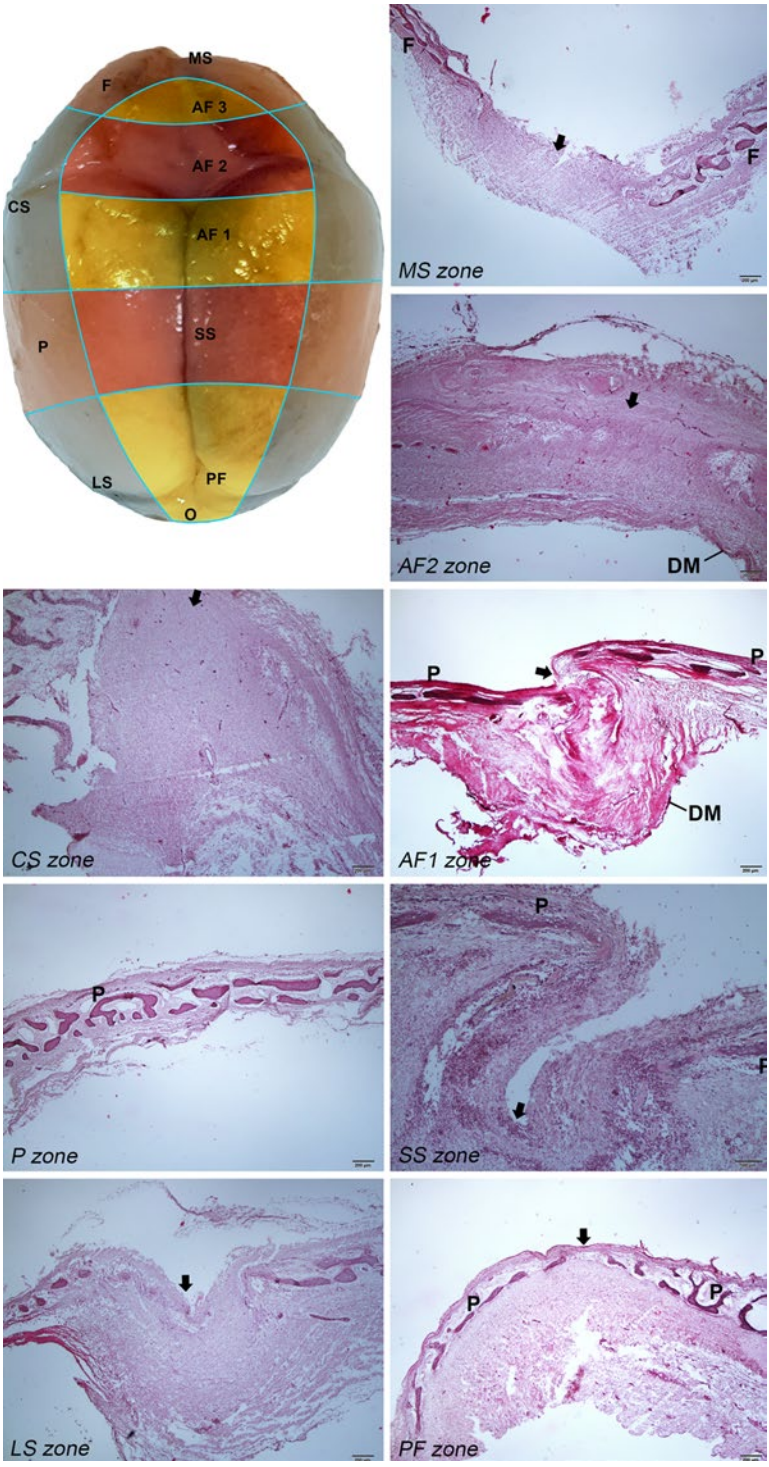
We have examined the bone structures surrounding the sutures histologically (Fig. 3.6). Fibrous connective tissue with dense type I collagen was observed in the sagittal and lambdoid sutures. This fibrous connective tissue is vascular. In addition to the collagen bundles in the sagittal and the lambdoid sutures there are a few connective tissue cells, along with proteoglycans, structural glycoproteins, and other elements of the ECM. The histological preparations show less ECM in the lambdoid suture. In the squamous suture there are dense collagen bundles and a small amount of ECM.

Histology of Fontanelles

Since the bones of the skull show membranous development, fontanelles were considered good indicators of intramembranous ossification. There is no bone precursor in the center of a fontanel. When the fontanel is cut transversely early in development, the skin, connective tissue and dura mater, respectively, are observed below. In an 8-week-old embryo, the skin comprises a monolayer of flat epithelial cells, which becomes a multi-layered epithelium with hair follicles by the 16th week. Towards the 19th week, the sebaceous glands begin to appear. At the 23rd week, small fat cell clusters begin to develop in the dermis. A continuous subcutaneous fat layer is formed by the 29th week. The collagen layer becomes slightly more dense as gestation proceeds. The dura, in contrast, consists of a single cell layer up to 28 weeks of pregnancy, when two cell layers become visible. The distribution of elastin in fontanels varies through pregnancy. It is first seen as widespread fibers around the dural vessels during week 16. A well-defined elastic lamina is formed in a fetus of 19 weeks. It can be defined as an elastic membrane structure by the 23rd week [30, 31].

When we dissected the 3.5-month-old fetus for this book chapter, we found the histological structure of the fontanelles to be as follows: condensed areas in the connective tissue structure containing stellate mesenchymal cells were observed in the middle part of the areas that showed intramembranous ossification and contained bone spicules. Mesenchymal connective tissue without significant stratification but containing scattered collagen bundles was observed in the anterior fontanelle area (Fig. 3.7).

Fig. 3.7 Histological examination of 3.5-month fetal calvarial sutures and fontanelles after scalp removed. MS zone: The metopic suture is apparent in the middle between the developing frontal bones. AF2 zone: Here the main part of the anterior fontanel and dense connective tissue is seen. AF1 zone: Section shows fusion of anterior fontanelle with anterior end of sagittal suture between slightly overlapping parietal bones. PF zone: The posterior fontanelle is seen between the developing occipital bones. CS zone: The lower part of the coronal suture. P zone: Ossification of the parietal bones is seen. LS zone: There is dense connective tissue in the lambdoid suture. Histological preparation: The calvaria of a 3.5-month fetus was removed for histological sampling. The zones of the calvaria were determined by examining the sutures and fontanelles. These zones were the metopic suture (MS) zone, the anterior fontanelle (AF) zone, the sagittal suture (SS) zone and the lambdoid suture (LS) zone in the midline. Lateral zones were the coronal suture (CS) zone, the parietal bone (P) zone and the posterior fontanel (PF) zone. Samples taken from the fixed cadaveric tissue were kept in 20% formic acid for one day and then subjected to routine histological preparation. Sections (5 μm thick) were taken from tissues embedded in paraffin with a Leica RM2145 microtome (Germany), stained with H&E and examined under a light microscope (Olympus BX51, Olympus C5050, Japan). Abbreviations: AF1, AF2 and AF3: Anterior fontanel parts, Black arrow: Side of suture or fontanelle on subfigures, CS: Coronal suture, DM: Dura mater (cranial), F: Frontal bone, LS: Lambdoid suture, MS: Metopic suture, O: Occipital bone, P: Parietal bone, PF: Posterior fontanel, SS: Sagittal suture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3.4 Molecular Mechanisms and Clinical Reflections in Sutural Development

Cranial suture fusion or suture aperture preservation is regulated by transcription factors, cytokines, growth factor receptors, and extracellular matrix molecules. Suture development is a complex process involving regulation of multiple genes. Fibroblast growth factors (FGF)/fibroblast growth factor receptors (FGFR), transforming growth factors (TGF), transcription factor twist (TWIST1), runt-related transcription factor 2 (RUNX2), fibrillin 1 (FBN1), bone morphogenetic proteins (BMP), msh homeobox 2 (MSX2) and neural EGFL like 1 (NELL-1) are the regulatory genes and signaling mechanisms involved in this process [32]. Defects in any of these mechanisms can lead to early suture fusion or craniosynostosis [33].

With early fusion of the sutures, normal growth of the neurocranium is arrested in some areas, while compensatory growth in other areas to accommodate the growing brain causes abnormal cranial development and severe deformity [9]. The pathophysiological development of craniosynostosis was first reported by Virchow in 1851 [34]. Craniosynostosis is divided into varieties according to the characteristic features of cranial growth resulting from the early fusion of different sutures. Two main groups can be considered, nonsyndromic and syndromic.

3.4.1 Nonsyndromic Craniosynostosis

Nonsyndromic craniosynostosis makes up nearly 80–85% of cases. Most craniosynostoses are in the sagittal, coronal, metopic and lamdoid sutures.

3.4.1.1 Sagittal Synostosis

This is the most common type, making up 40–55% of nonsyndromic craniosynostoses [9]. Coronal and metopic synostoses, respectively, are the next most common [35]. Early fusion of the sagittal suture arrests growth in the transverse direction and increases it in the anterior-posterior direction. The resulting characteristic “long boat” skull is called a scaphocephaly (Fig. 3.3d–g).

3.4.1.2 Coronal Synostosis

Coronal synostosis accounts for 20–24% of nonsyndromic craniosynostoses. There are two types, bilateral and unilateral [9]. In bilateral early fusion of the coronal suture, growth is arrested in the antero-posterior direction and increased in the transverse direction. The resulting short wide head is termed brachycephaly (Fig. 3.4b). Anterior plagiocephaly results from unilateral early fusion of the

coronal suture. It entails nasal deviation and contralateral displacement of the anterior fontanelle (Fig. 3.3a–c).

3.4.1.3 Metopic Synostosis

Metopic synostosis accounts for 20–29% of nonsyndromic craniosynostoses. Studies have shown that its prevalence has increased [9]. Early fusion of the metopic suture causes the arrest of skull growth in the transverse direction anteriorly and increases growth in the anterior-posterior direction. The resulting skull pattern is termed trigonocephaly.

3.4.1.4 Lambdoid Synostosis

Lambdoid synostosis accounts for 0–5% of nonsyndromic craniosynostoses. It can be bilateral or unilateral. Bilateral early fusion of the lambdoid sutures results in bilateral flattening of the occipital and central posterior, bossing of the bitemporal, and widening of the posterior cranium. This is called posterior plagiocephaly. Bilateral lambdoid synostosis is less common than the unilateral form.

Unilateral lambdoid synostosis causes flattening of the unilateral occipital and contralateral forehead, anterior displacement of the ipsilateral ear and bossing of the ipsilateral frontal. This posterior oblique shape is called posterior plagiocephaly. There are synostoses in multiple sutures in 5–15% of nonsyndromic craniosynostoses [9].

Early fusion of three or more sutures is called pansynostosis. As a result of the bulging of the frontal and temporal bones, the skull shape becomes trilobular (a cloverleaf skull) [9]. The cloverleaf skull, or Kleeblattschädel, is a rare deformity resulting from premature fusion of multiple cranial sutures and is characterized by a trilobal skull with bossing of the forehead, temporal bulging, and a flat posterior skull [36–38].

3.4.2 Syndromic Craniosynostosis

Syndromic craniosynostosis accounts for approximately 15–20% of cases. There are many types such as Apert, Crouzon, Pfeiffer, Saethre-Chotzen, Craniofrontonasal, and Boston syndrome [39, 40]. The most common syndromic craniosynostoses, Apert and Crouzon syndromes, show autosomal dominant inheritance. Genetic analyses have indicated strong links between specific gene mutations and craniosynostosis [9]. In a cohort study involving craniosynostosis cases, 21% were diagnosed by genetics; 86% were single gene mutations and 15% were chromosomal anomalies.

3.5 Gene Mutations Associated with Craniosynostoses

The most common syndromic craniosynostosis is due to mutations in the *FGFR2* (32%) gene. Mutations in *FGFR3* (25%), *TWIST1* (19%) and *Ephrin-B1* (7%) are less frequent [41].

3.5.1 FGFR1, FGFR2 and FGFR3 Mutations

Mutations in the genes encoding FGFR1, FGFR2 and FGFR3, which make up the fibroblast growth factor receptor (FGFR) family, have been found in most syndromic craniosynostoses. These are receptor tyrosine kinases that are autophosphorylated by binding FGF, participating in a wide variety of cell functions and developmental processes including gastrulation, placenta and limb bud formation, organogenesis and bone ossification [9]. The best-known signal pathway for suture maturation and osteoblast differentiation is the FGFR pathway. FGFR mutations can activate the FGF/ FGFR pathway, changing the receptor activation level and ligand-receptor affinity, resulting in early suture closure. Also, the transcription factor required for osteoblast differentiation causes overexpression of *RUNX2*, leading to multisutural craniosynostosis [42–44].

Mutations of *FGFR1*, which is located on chromosome 8p, have been found to cause Pfeiffer and Jackson Weiss syndromes. Mutations of *FGFR2*, which is located on chromosome 10q, have been found to cause Crouzon, Jackson- Weiss, Apert, Pfeiffer, and Beare- Stevenson syndromes. Mutations of *FGFR3*, which is located on chromosome 4p, cause Crouzon syndrome with Acanthosis, Muenke syndrome, and thanatophoric dysplasia [9].

3.5.2 Transforming Growth Factor β (TGF β) Mutations

Transforming growth factor β (TGF β) is a superfamily of multipotential cytokines involved in various cellular processes. TGF β isoforms are effective in both cranial suture fusion and suture aperture preservation. In suture fusion, TGF β3 is inactive while TGF β1 and TGF β2 continue to be expressed. The opposite occurs in suture aperture preservation: TGF β3 is activated, TGF β1 and TGF β2 are suppressed. TGF β receptor-2 (TGF β R2) is released from the dura mater and cranial sutures. TGF β R1 and TGF β R2 mutations have been implicated in syndromic craniosynostoses. Bone morphogenetic proteins (BMP) are members of the TGF-β superfamily that are involved in many stages, including bone formation, skeletal shaping and limb development. BMP-2 and BMP-4 are released from the osteogenic bone edges of the cranial sutures; BMP-4 is also released from suture mesenchymal tissue and

the dura mater. TGF β and BMP affect suture formation through osteoblasts. TGF β3 and BMP3 release are associated with suture aperture preservation [45, 46].

3.5.3 Mutations of Transcription Factors

Mutations of transcription factors are also directly related to syndromic craniosynostoses. The best-known transcription factor associated with craniosynostosis is MSX2. This protein is important in osteoblast differentiation. Studies have revealed that MSX2 is required for normal suture fusion and skull mineralization. MSX2 is expressed in suture mesenchyme, where it binds to the promoter regions of the collagen type I and osteocalcin genes, inhibiting their transcription [28, 47].

3.5.4 TWIST1 (twist-related protein 1) Mutations

TWIST1 (twist-related protein 1) is another gene related to syndromic craniosynostoses. Heterozygous mutations in it cause Saethre-Chotzen syndrome [48]. *TWIST1* encodes a transcription factor in the basic helix-loop-helix family. It is thought to be pivotal in initiating bone cell differentiation and in regulating osteoblast proliferation and differentiation. TWIST1 binds to and negatively regulates *RUNX2*. Thus, it inhibits osteoblastic differentiation. As *TWIST1* is not expressed by mature osteoblasts, sutural mesenchymal cells that join the developing bones must stop its expression. Cells that over-express *TWIST1* remained undifferentiated, while cells that do not express it differentiate into a mature osteoblast-like state [9, 47, 49]. Sutures are stabilized by the combined functioning of osteoblasts and osteoclasts. The main regulators of osteoclasts are receptor activator of nuclear factor kappa-B ligand (RANK) and its stimulated active form, tumor necrosis factor receptor (TNFR)-associated factor 6 (TRAF6). RANK is a receptor in the tumor necrosis factor (TNF) signaling cascade. It regulates development and differentiation via osteoblasts and osteoclasts. Mice with RANK receptor deficiency have osteoclast deficiency, osteoporosis, and growth retardation in the skull [50].

Another important aspect of suture formation depends on the interaction between suture cells and the non-cellular niche or ECM. The ECM consists of glycosaminoglycans, proteoglycans, fibronectin, hyaluronic acid, collagen, and other glycoproteins. These molecules, differing in amounts among tissues and at different stages of development, provide adhesion, cell-to-cell communication, and cellular differentiation, which are important during craniofacial development [32]. The role of cell-ECM interactions in suture growth is elucidated by understanding of receptors and their involvement in craniofacial development. Intracellular signaling mechanisms often begin with protein-receptor interactions on the cell surface. Studies have revealed interactions between ECM molecules and the cytoskeleton [32]. Cells

respond to their surrounding ECM by binding directly via integrin receptors or proteoglycan receptors such as the syndecan family, known to function as heparin sulfate co-receptors in FGF signaling [32]. Integrin receptors, growth factor receptors and cytoskeleton binding proteins combine to form a complex structure called a focal adhesion. This protein complex connects the cell via the cytoskeleton to the ECM. Growth factor receptors express intrinsic kinase activity. Although integrins lack kinase activation, binding to ECM molecules triggers autophosphorylation of other proteins such as focal adhesion kinase, paxilline, Src, and integrin-linked kinase (ILK). ECM-cell receptor connections affect the expression of target genes by transferring signals from the cell membrane to the cytoplasm and nucleus. The ECM can be affected by deformation when under stress [32]. In vitro studies of fibroblast and osteoblast cultures from Apert and Crouzon syndrome cases showed that differences in the composition and distribution of the ECM caused variations in both osteogenic processes and cranial development, such as craniosynostoses. The balanced interaction among ECM, cytokines (e.g., interleukins), and growth factors (e.g., TGF-β and FGF2) regulates osteogenic events and cellular responses [32]. Fibroblasts from Apert syndrome cases synthesize more glycosaminoglycans than those from controls, and their cytokine production (IL-1 and IL-6) is unbalanced [32]. In addition, osteoblasts from Apert syndrome cases express more TGF-β1 than normal osteoblasts, and the addition of FGF2 causes a decrease in this TGF-β1 level [32].

Overall, the development of the adult skull is a rather complex process. In order to understand it thoroughly, it is necessary to understand the development of the head bones, the structure of the sutures between those bones, and the molecular biological basis of the processes involved. This understanding will elucidate the cranial anomalies and syndromes seen in the clinic.

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Chapter 4
Anatomy of the Sutures of the Calvaria

Katrina E. Bang, Stephen J. Bordes Jr, and R. Shane Tubbs

4.1 Introduction

The calvaria (from the Latin word *calvus,* meaning "bald") is the roof or dome of the skull and is formed by the frontal and occipital bones, and two parietal bones. Where these bones articulate with adjacent bones of the skull, they fuse together, forming a series of jagged fibrous joints that run across the skull and are known as the sutures of the calvaria. The sutures of the calvaria are destined to either completely fuse in early childhood or persist into adulthood via a series of highly regulated biochemical and mechanical processes [1–3]. Deviations from this process or its timeline can lead to pathological states that manifest clinically in the early stages of life [4]. This chapter will discuss the anatomy and clinical implications of the sutures of the calvaria and their related structures.

K. E. Bang
Department of Anatomical Sciences, St. George's University School of Medicine, Grenada, West Indies

S. J. Bordes Jr
Department of Anatomical Sciences, St. George's University School of Medicine, Grenada, West Indies

Department of Neurosurgery, Tulane University School of Medicine, New Orleans, LA, USA

R. S. Tubbs (✉)
Department of Neurosurgery, Tulane University School of Medicine, New Orleans, LA, USA

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4.2 Sutures of the Calvaria

4.2.1 Metopic Suture (Frontal)

The metopic suture (Figs. 4.1 and 4.2), also known as the frontal suture, is an unpaired fibrous joint on the anterior aspect of the calvaria that is found predominantly in infants and children. The suture forms between the paired frontal bones where it courses along the sagittal plane from the nasion to the anterior fontanelle [5]. The metopic suture is relatively narrow at term and typically fuses completely by the end of the second postnatal year [1]. Although, the suture has also been reported to persist into late childhood and even throughout life, as either totally, or partially persistent metopic sutures in up to 10% of adults [6–8]. Persistent metopic sutures, like accessory cranial sutures (Table 4.1), may be mistaken for skull fractures but are of no clinical significance [9]. Premature fusion, however, leads to a clinically identifiable pattern of cranial deformation known as trigonocephaly. Characterized by a triangular forehead, known as trigonocephaly. Trigonocephaly may occur as an isolated condition, or as part of a clinical syndrome [10].

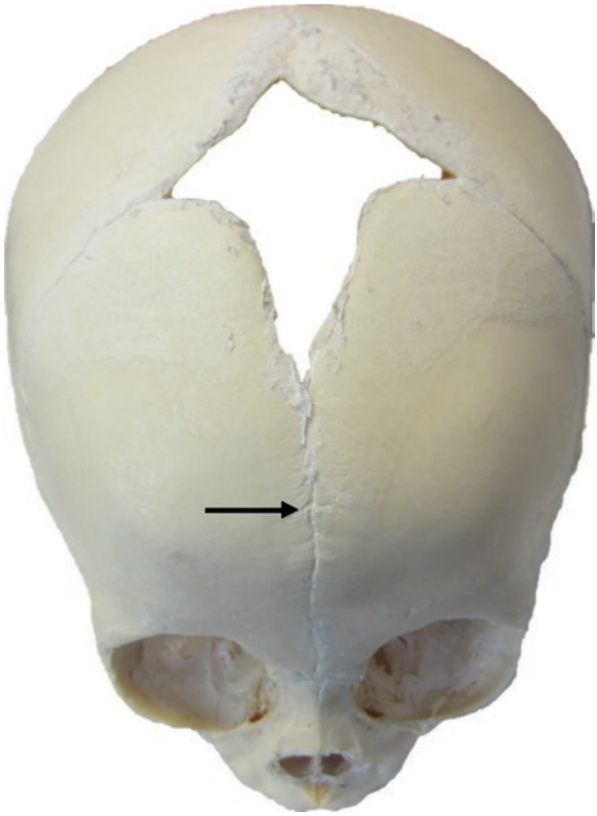

Fig. 4.1 Newborn skull with open anterior fontanelle and metopic suture (arrow)

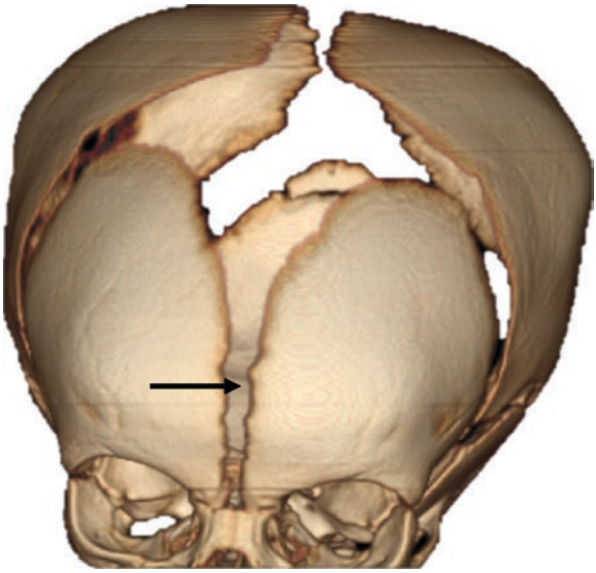

Fig. 4.2 Infant with hydrocephalus and metopic fontanelle (arrow)

Table 4.1 Comparison of key morphological differences between cranial fractures and accessory sutures on radiographic and CT imaging. Table compiled from [18, 21]

Differentiating Characteristics of Cranial Fractures vs. Accessory Sutures	
Fractures	Accessory Sutures
Sharp lucencies	Zig-zag pattern, interdigitations
Non-sclerotic edges	Sclerotic borders
Unilateral[a]	Bilateral
Asymmetric	Symmetric[b]
Healing or sclerosis within 2–3 months	No healing or sclerosis
High-Impact Cranial Fractures	
Cross suture lines	Do not cross suture lines
Span between major suture lines	Merge with major suture lines
Associated comminution & depression	No associated communition or depression
Soft tissue swelling, hematoma	No soft tissue swelling or hematoma
Fractures extending into major sutures[c]	*Accessory sutures extending into major sutures*
Widening intersection with major suture	No widening near intersection with major suture

[a]High-impact fractures may also present bilaterally
[b]Marked symmetry in accessory parietal bones [19]
[c]Major sutures include coronal, sagittal, lambdoid, and squamous

4.2.2 Coronal Suture

The coronal suture (Figs. 4.3, 4.4, and 4.5) is an unpaired suture on the anterior aspect of the skull that courses transversely between the paired frontal and parietal bones, then terminates at their intersection. The suture is of the squamous variety,

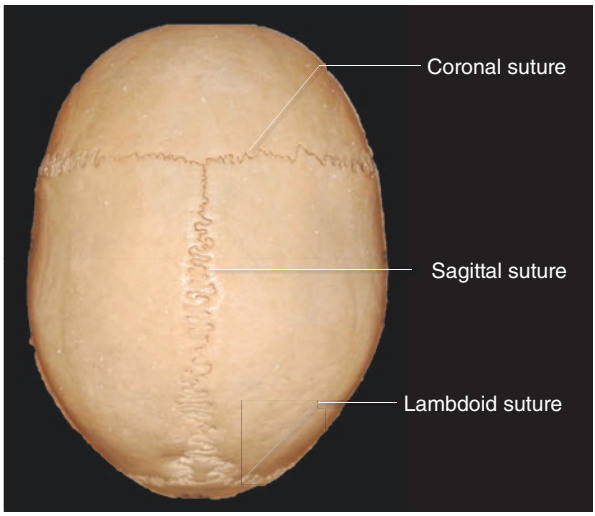

Fig. 4.3 Adult calvaria as seen from above

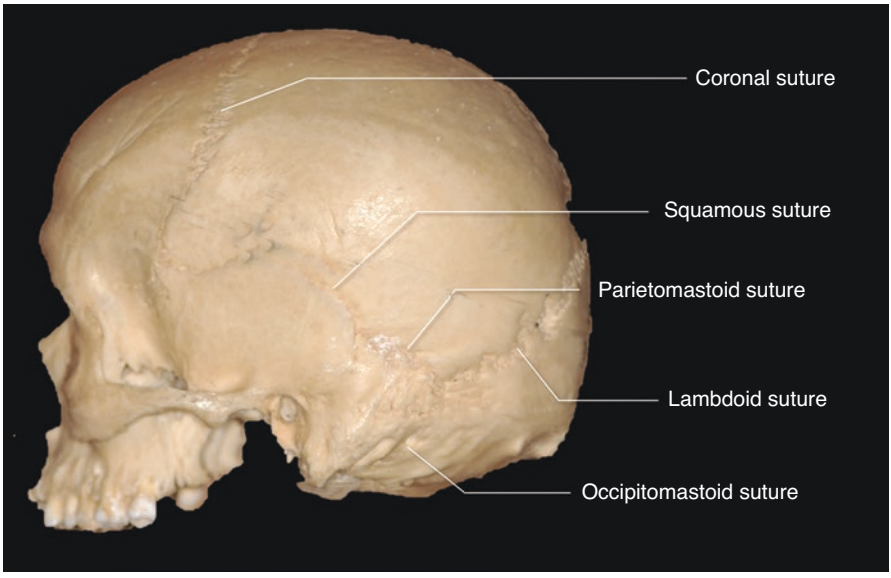

Fig. 4.4 Adult skull seen from a posterolateral view

meaning that the joint itself is formed by the overlap of sloped sections of adjoining bone fronts, and its fusion is regulated by signals from underlying dura [3, 11]. Suture closure begins at 24 months of age, reaching a maximum rate of fusion by the third decade of life, and continues to fuse beyond the sixth decade of life [9, 12]. Premature fusion of the coronal suture results in craniosynostosis and may occur unilaterally, resulting in anterior plagiocephaly, or bilaterally resulting in brachycephaly.

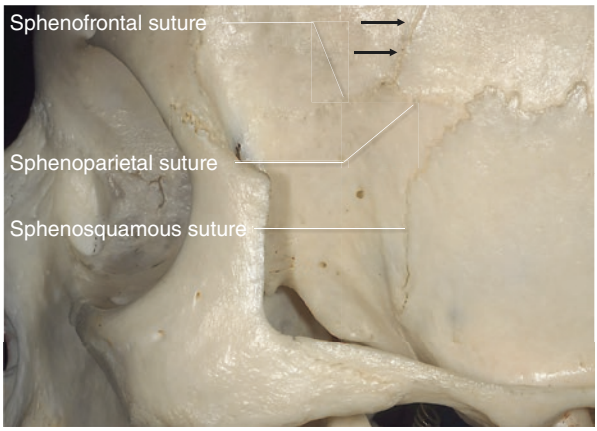

Fig. 4.5 Lateral aspect of the coronal suture at the pterion

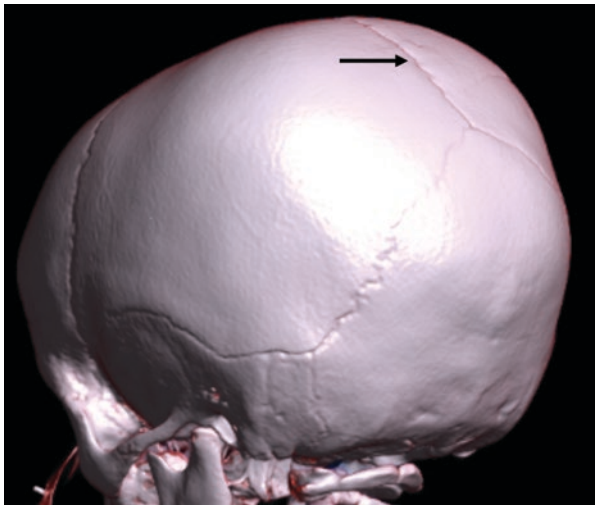

Fig. 4.6 3D CT noting the sagittal suture (arrow) and more posteriorly, the lambdoid sutures (not labeled)

4.2.3 Lambdoid Suture

The lambdoid suture (Figs. 4.6 and 4.7) is an unpaired suture on the posterior aspect of the calvaria that courses transversely between the parietal and occipital bones, and is continuous with the occipitomastoid suture. Like the coronal suture, the lambdoid suture is of the squamous variety. Suture closure begins at 26 months of age, with its rate of fusion reaching maximum by the third decade of life and continuing beyond the sixth decade of life [3, 9, 11, 12]. Premature fusion of the lambdoid suture may be unilateral, resulting in posterior plagiocephaly, or bilateral, resulting in posterior brachycephaly.

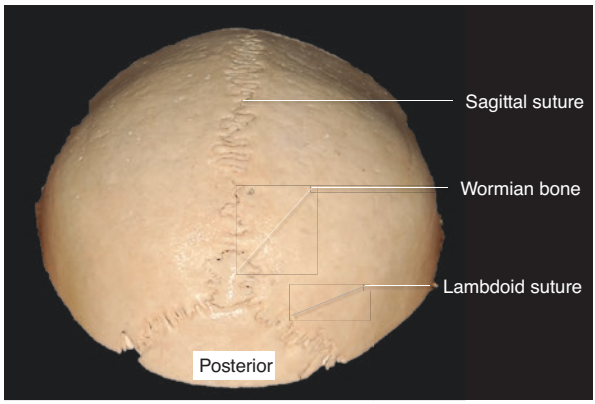

Fig. 4.7 Superior view of the calvaria noting a wormian bone between the sagittal and lambdoid sutures

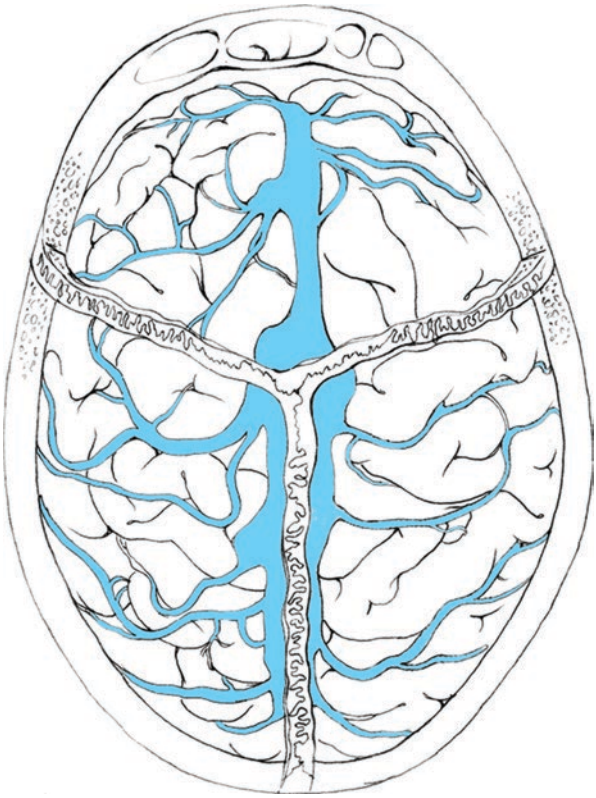

Fig. 4.8 Schematic drawing of the relationship between the coronal and sagittal sutures and the underlying superior sagittal sinus

4.2.4 Sagittal Suture

The sagittal suture (Figs. 4.6, 4.7, and 4.8) is an unpaired suture that runs along the superior aspect of the calvaria where it courses from its posterior articulation with the lambdoid suture, between the paired parietal bones, to its anterior articulation

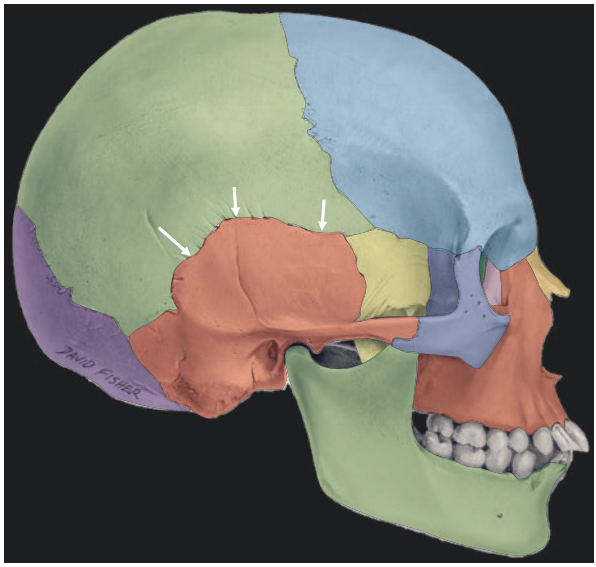

Fig. 4.9 Lateral view of the squamous suture. The temporal bone is colored red, the parietal bone green, the sphenoid bone yellow, and the occipital bone purple

with the coronal suture. The osteogenic fronts of the suture abut end-to-end, in a plane suture [3]. Suture closure begins at 22 months of age, with rapid rates of fusion in the third decade of life and continues into the sixth decade of life [12]. Premature closure of the sagittal suture results in scaphocephaly and has been found to be linked to inhibition of canonical Wnt signaling [13].

4.2.5 Squamous Suture

The squamous suture (Figs. 4.9 and 4.10), or squamosal suture, is a paired suture that runs along the lateral aspect of the head in the sagittal plane between the parietal and temporal bones. The suture courses posteriorly from the pterion to where it terminates on, and is continuous with, the parietomastoid suture [14]. Traumatic insult to the pterion, the weakest part of the skull, found in the temporal fossa approximately 2.6 cm behind and 1.3 cm above the posterolateral margin of the frontozygomatic suture, is associated with rupture of the middle meningeal artery and a subsequent epidural hematoma [15].

4.2.6 Accessory Parietal Suture

Accessory sutures are a rare type of suture that results from the formation of multiple osteogenic centers during embryogenesis and are most typically found in parietal and occipital bones [16]. Accessory parietal sutures are the most common type

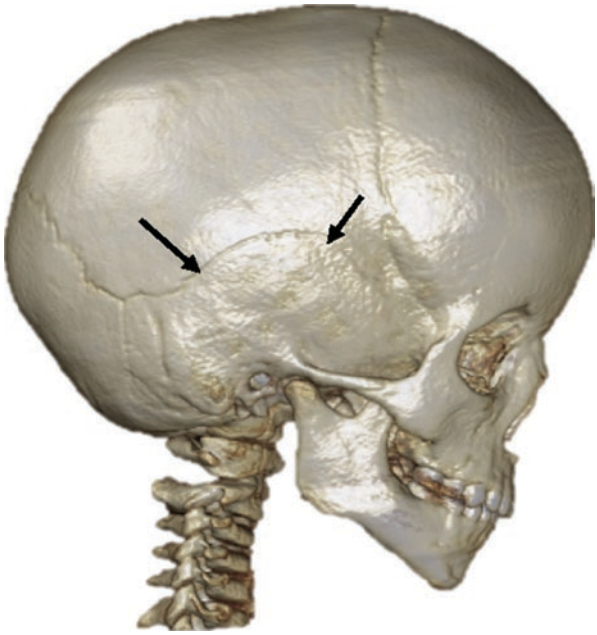

Fig. 4.10 3D CT of a child noting the squamous suture (arrows)

of accessory suture and their prevalence is estimated to be approximately 1 in every 4000 to 8000 individuals [8, 17]. The direction of the accessory suture in usually anterior-posterior, although superior-inferior and oblique directions have also been reported [8, 16, 18–20]. Accessory sutures are benign findings that are usually discovered incidentally. However, their presence may have more serious implications, such as in pediatrics, if diagnosticians misinterpret accessory sutures as signs of abuse and neglect [18, 21]. Fractures may be differentiated from accessory sutures by imaging and knowledge of general morphological features of each (see Table 4.1).

4.2.7 Wormian Bone

Wormian bones (Fig. 4.7), or sutural bones, are small bones of that develop within the calvarial mesenchyme, some distance from calvarial bones, and most commonly occur in the lambdoid suture. The presence of wormian bones has been linked to various pathological states such as cleidocranial dysplasia, osteogenesis imperfecta, hydrocephalous, hypothyroidism and lateral meningocele syndrome [14]. They occur more frequently in disorders that have reduced cranial ossification andhypotonia and are associated with deformational brachycephaly [22]. Larger-sized wormian bones are more common in cases of craniosynostosis and their relative location is associated with the affected suture [23]. Midline synostosis (of metopic and sagittal sutures) are associated with midline wormian bones, whereas unilateral

lambdoidal and coronal synostoses are associated with increased numbers of contralateral wormian bones [22].

4.3 Clinical Relevance

4.3.1 Fracture Versus Suture

In the instance of traumatic injury, it is important to distinguish sutural lines from traumatic cranial fractures, as the latter may necessitate immediate treatment [18, 20]. In the instance of high-impact cranial fractures, distinction between fracture and suture is rarely misinterpreted due to the nature of such an inciting event and the accompanying clinical evidence. However, in the case of accessory cranial sutures, most often found within the parietal and occipital bones, the delineation of fracture from suture is more subtle and may require a more intimate knowledge of the related anatomical differences [18]. Table 4.1 outlines major characteristics of both cranial fractures and skull sutures that may help the clinician to distinguish between the two on fluoroscopy and CT imaging.

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Chapter 5
Anatomy of the Sutures of the Skull Base

Stephen J. Bordes Jr, Katrina E. Bang, and R. Shane Tubbs

5.1 Introduction

The human cranium is comprised of calvarial, facial, and basal sutures, the majority of which are paired [1]. Sutures are made up of fibrous connective tissues that allow for flexibility and expansion of the skull, while preventing premature separation of bone [2]. Cranial sutures fuse once certain developmental milestones have been reached, which allows for natural childbirth and the expansion of the skull into the second and third decades of life [2]. In this chapter, we discuss the anatomy of the sutures of the cranial base, their clinical implications, and pathological variations.

5.2 Sutures of the Cranial Base

5.2.1 Occipitomastoid Suture

The occipitomastoid suture (Figs. 5.1 and 5.2), also known as the occipitotemporal suture, is a point of articulation between the squamous occipital bone and the mastoid portion of the temporal bone. This suture is continuous with the lambdoid suture and extends to the base of the skull [3, 4]. It typically fuses by age 16 years [3].

S. J. Bordes Jr · K. E. Bang
Department of Anatomical Sciences, St. George's University School of Medicine, Grenada, West Indies

R. S. Tubbs (✉)
Department of Anatomical Sciences, St. George's University School of Medicine, Grenada, West Indies

Department of Neurosurgery, Tulane University School of Medicine, New Orleans, LA, USA

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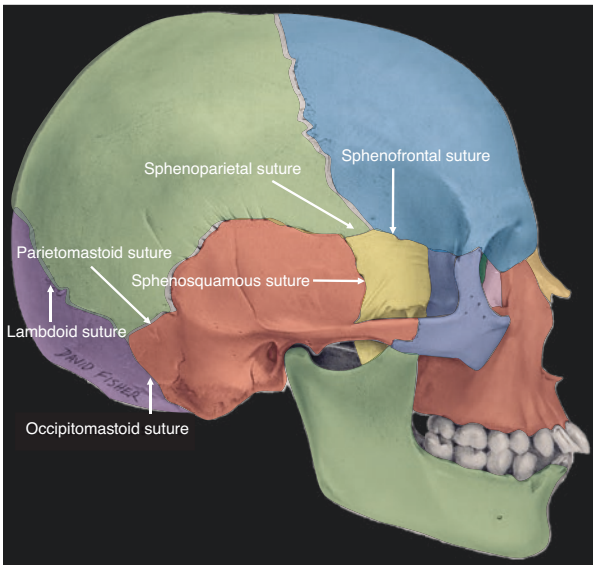

Fig. 5.1 Lateral image of the skull with many of the sutures of the skull base indicated. The frontal bone is colored blue, the parietal bone green, the occipital bone purple, the temporal bone red and the sphenoid bone yellow

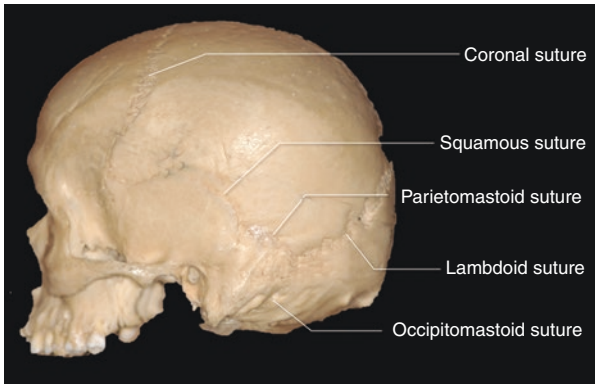

Fig. 5.2 Lateral skull specimen with many of the sutures of the skull base indicated

5.2.2 Parietomastoid Suture

The parietomastoid suture (Figs. 5.1 and 5.2) connects the temporosquamous and lambdoid sutures on either side of the cranium. The parietomastoid suture is short, nearly horizontal, and divides the mastoid process of the temporal bone from the mastoid angle of the parietal bone [3].

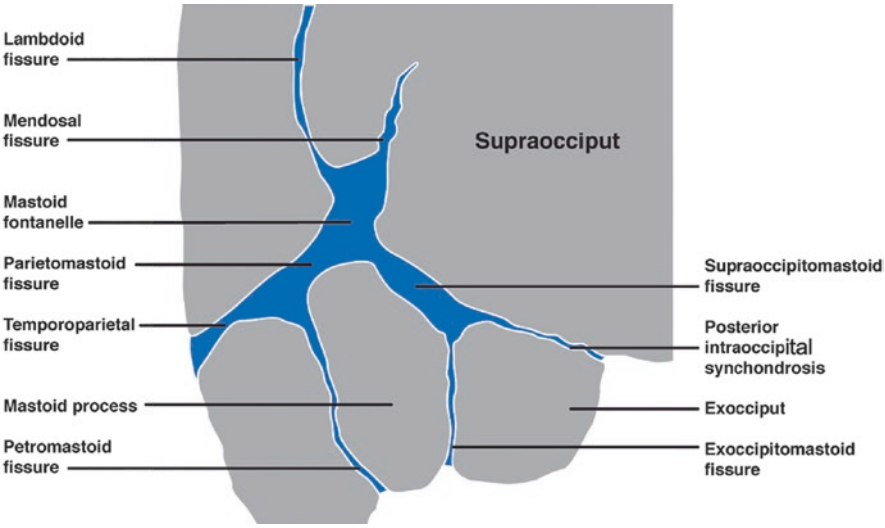

Fig. 5.3 Schematic drawing of the development of the sutures surrounding the left mastoid fontanelle (asterion)

5.2.3 Mendosal Suture

The mendosal suture (Fig. 5.3), or accessory occipital suture, originates above the asterion, a landmark found at the posterior end of the parietomastoid suture, and runs horizontally from the medial part of the lambdoid suture [5]. It is typically situated superior to the transverse sinus [5]. Closure of the mendosal suture is still debated but typically occurs between infancy and 10 years of age although it can persist into adulthood.

5.2.4 Sphenofrontal Suture

The sphenofrontal suture (Fig. 5.4) is a continuation of the coronal suture [4]. It is a transverse structure between the anterior margin of the lesser wing of the sphenoid- and the posterior margin of the horizontal orbital plates [3]. The suture can be further divided into medial and lateral aspects. The medial segment is part of the anterior cranial fossa and connects the lesser wing of the sphenoid bone with the frontal bone. This segment is relatively straight and horizontal. The lateral segment is part of the middle cranial fossa. It has a more complex shape as it connects the greater sphenoid wings to the frontal bone. Embryologically, the medial and lateral segments represent two different sphenofrontal sutures. The medial segment connects one bone of endochondral ossification with a bone of membranous ossification [6]. The lateral segment is a purely membranous articulation [6].

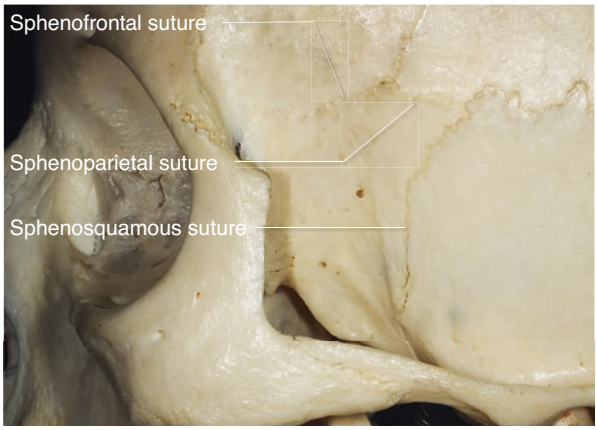

Fig. 5.4 Left lateral skull specimen with sutures near the pterion

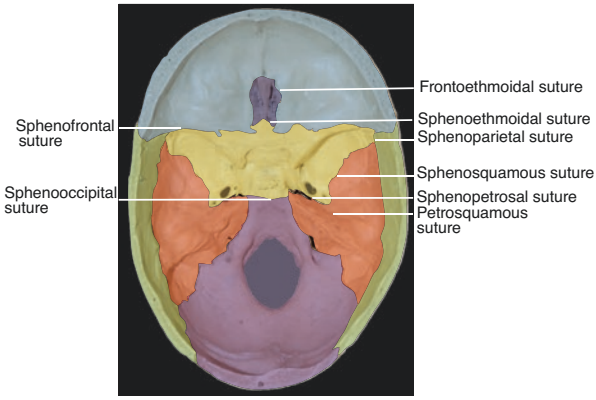

Fig. 5.5 Sutures of the skull base from an internal view

5.2.5 Sphenosquamous Suture

The sphenosquamous suture (Figs. 5.4 and 5.5), or squamomastoid suture, separates the sphenoid and squamous temporal bones. This suture runs vertically and inferior to the pterion. It is often mistaken for a cranial base fracture due to its anatomical location [3].

5.2.6 Sphenoethmoidal Suture

The sphenoethmoidal suture (Fig. 5.5) connects the medial margin of the lesser wing (orbital surface) of the sphenoid bone and posterior margin of the orbital plate of the ethmoidal labyrinth of the ethmoid bone. This suture forms in early childhood [7].

5.2.7 Sphenoparietal Suture

The sphenoparietal suture (Figs. 5.4 and 5.5) is a small articulation between the sphenoid and parietal bones. It is one of the sutures that comprises the pterion.

5.2.8 Petrosquamous Suture

The petrosquamous suture (Fig. 5.5) can be found in the middle cranial fossa. This suture is an articulation between the petrosal and squamous parts of the temporal bone. It overlies the eustachian tube and forms Koerner's septum, also known as the internal petrosquamous lamina [8].The superior tympanic artery, a branch of the middle meningeal artery, passes through the petrosquamous suture [8]. This suture may also contain the petrosquamous sinus and is important to note during otolaryngologic surgery [9].

5.2.9 Sphenopetrosal Suture

The sphenopetrosal suture (Fig. 5.5), or sphenopetrosal fissure, is located in the middle cranial fossa. It is an articulation between the greater sphenoidal wing and the petrous portion of the temporal bone.It originates at the level of the mandibular fossa and runs anteromedially along the petrous temporal bone [10]. The suture forms the posterior portion of foramen lacerum, which is posterior to foramen ovale and anterior to the carotid canal [10].

5.2.10 Sphenooccipital Suture

The sphenooccipital suture (Figs. 5.5, 5.6, and 5.7) refers to the junction between the basiocciput and basisphenoid, which together form the clivus. Current data suggest that sphenooccipital synchondrosis is heavily influenced by pubertal hormonal changes, with girls reaching closure 1–3 years earlier than boys [7]. As a result, degree of closure can be used to reliably predict age in teenagers and young adults [11–14].

5.2.11 Frontoethmoid Suture

The junction between the ethmoid bone and frontal bone is the frontoethmoid suture (Fig. 5.5). In the anterior cranial fossa, this junction is centrally located.

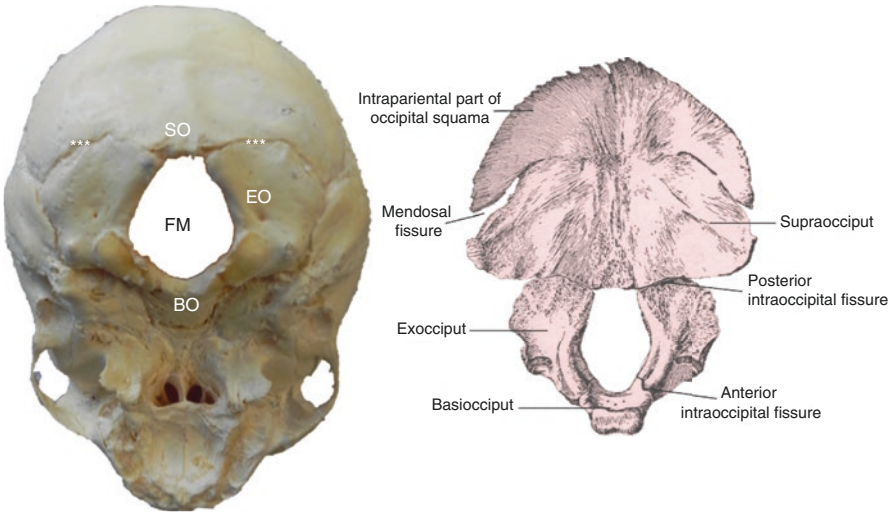

Fig. 5.6 Inferior view of a fetal skull noting the supraocciput (SO), exocciput (EO), basiocciput (BO), foramen magnum (FM), and posterior intraoccipital fissure (asterisks)

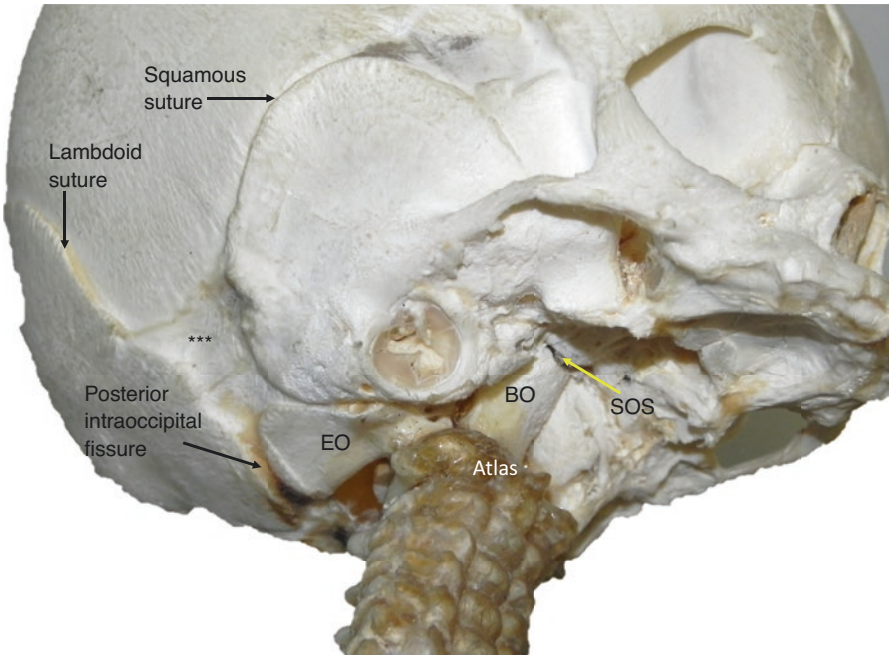

Fig. 5.7 Right lateral view of the skull with various sutures indicated. The asterion (asterisks), exocciput (EO), basiocciput (BO), and sphenooccipital synchondrosis (SOS) are seen

5.3 Clinical Relevance

5.3.1 Craniosynostosis

Craniosynostosis is the premature fusion of one (simple) or multiple (compound) sutures [2]. While coronal and lambdoid synostosis are most common, skull base sutures are also often involved. For example, sphenofrontal synostosis occurs and may be confused with coronal synostosis [2, 4]. Physical signs of sphenofrontal involvement include a downward deviation of the supraorbital margin and tip of the nose toward the affected side [4]. Complications include increased intracranial pressure, facial asymmetry, and malocclusion [2].While craniosynostosis may be influenced by a variety of factors, FGFR gene coding is thought to be responsible for a majority of cases [1].

5.3.2 Basal Cranial Fractures

Basal sutures can often resemble cranial fracture lines as can basal fissures, foramina, and neurovascular channels [9, 15]. Knowledge of suture anatomy allows individuals to rule out skull fractures. Additionally, basal fractures can result in widened, diastatic sutures [15]. A diastatic suture should raise suspicion for fractures elsewhere.

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Chapter 6
Anatomy of the Sutures of the Face

Joe Iwanaga

6.1 Introduction

The sutures of the face are mostly paired sutures, except the median palatine, intermaxillary, and internasal sutures. Many of them are located in and around the orbit and are related to facial fractures and surgery of the orbit. In this chapter, we discuss the anatomy of the sutures of the face and its clinical implications.

6.2 Sutures of the Face

6.2.1 Frontonasal Suture

The frontonasal suture (Figs. 6.1 and 6.2) connects the nasal margin (medial half) of the squamous part of the frontal bone and superior margin of the nasal bone. The frontonasal suture is continuous with the frontomaxillary suture, which normally courses across the top of the bridge of the nose [1]. Alesbury et al. [2] suggested that the frontonasal suture is not a strong predictor of closure patterns, but the direction of its fusion was endocranial to ectocranial. The thickness of the nasal bone on this suture is thicker than the lower part of the nasal bone.

J. Iwanaga (✉)
Department of Neurosurgery, Tulane University School of Medicine, New Orleans, LA, USA

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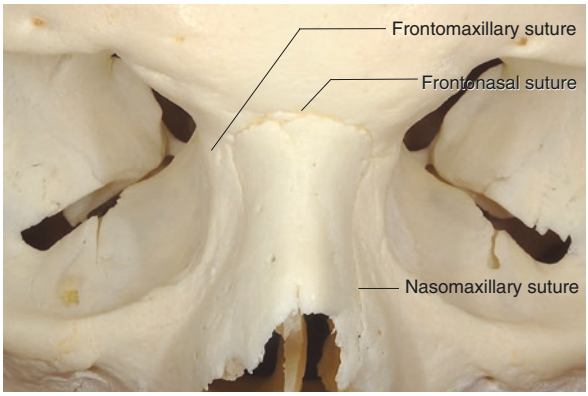


Fig. 6.1 Anterior view of the nose

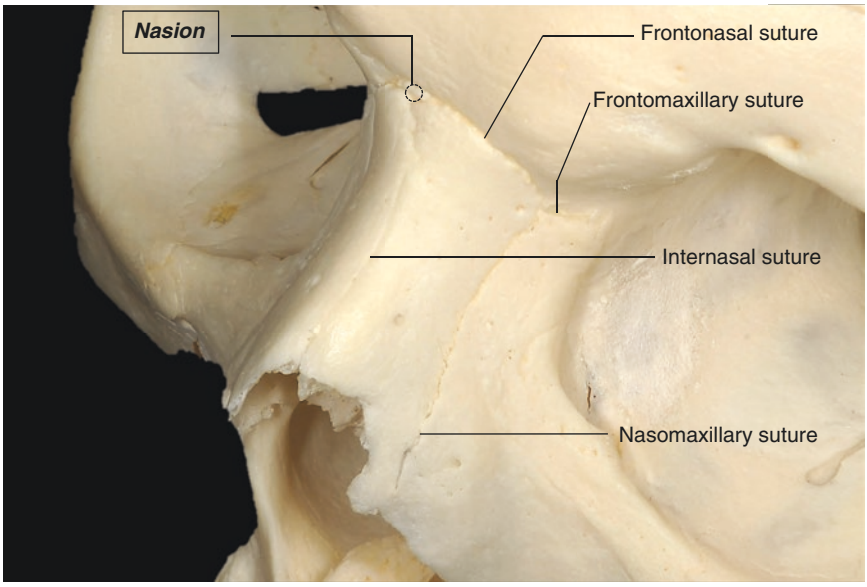


Fig. 6.2 Oblique view of the nose

6.2.2 Frontoethmoidal Suture

The frontoethmoidal suture (Figs. 6.3 and 6.4) connects the medial margin (larger posterior portion) of the orbital surface of the frontal bone and the superior margin of the orbital plate of the ethmoidal labyrinth of the ethmoid bone. The positional relationship between the frontoethmoidal suture and ethmoidal foramina is a landmark for medial orbital wall surgery, as this anatomy is crucial for controlling epistaxis.

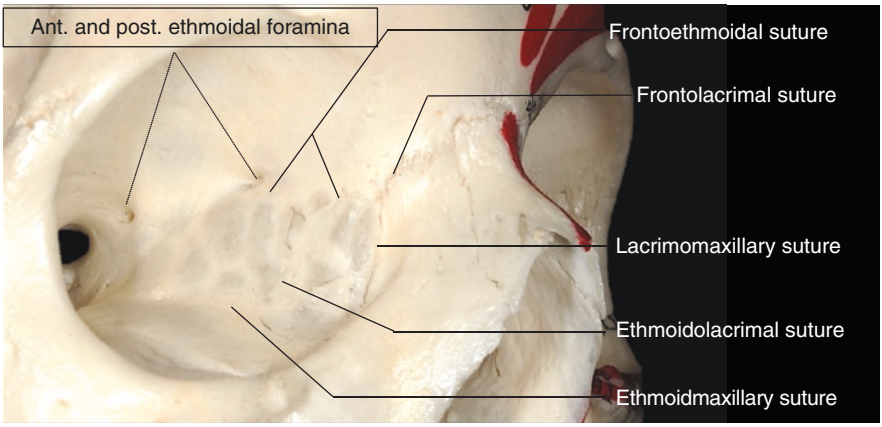
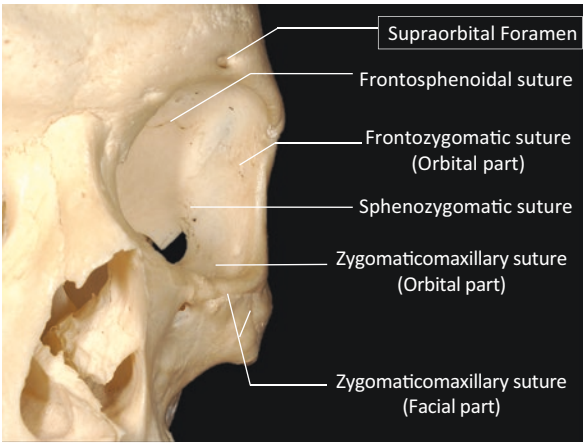


Fig. 6.3 Lateral view of the medial wall of the orbit

Fig. 6.4 Medial view of the lateral wall of the orbit



The ethmoidal foramina have been believed to be located on the frontoethmoidal suture. However, recent studies revealed the incidence of the anterior ethmoidal and posterior ethmoidal foramina located off the suture is 3.7–62% and 2–12.5%, respectively, and the distance from the frontoethmoidal suture to the anterior ethmoidal foramen and posterior ethmoidal foramen is 1.0–4.0 mm and 2.0–12.5 mm, respectively [3, 4].

While the ethmoidal roof directly attaches to the medial orbital wall, the frontoethmoidal suture is used as a surgical landmark to limit the superior border for bone removal during medial orbital wall decompression procedures. Bone removal above the frontoethmoidal suture may cause cerebrospinal fluid (CSF) leakage [5, 6].

6.3 Frontolacrimal Suture

The frontolacrimal suture (Fig. 6.3) connects the medial margin (smaller anterior portion) of the orbital surface of the frontal bone and the superior margin of the lacrimal bone.

6.3.1 Frontomaxillary Suture

The frontomaxillary suture (Figs. 6.1 and 6.2) connects the nasal margin (lateral half) of the squamous part of the frontal bone and superior margin of the frontal process of the maxilla.

6.3.2 Frontozygomatic Suture

The frontozygomatic suture (Figs. 6.4, 6.5, and 6.6) connects the zygomatic process of the squamous part of the frontal bone and frontal process of the zygomatic bone. According to Kokich [7], the frontozygomatic suture undergoes synostosis during the eighth decade of life. The surfaces of the frontozygomatic suture become increasingly irregular with aging [7].The frontozygomatic suture has been used as a

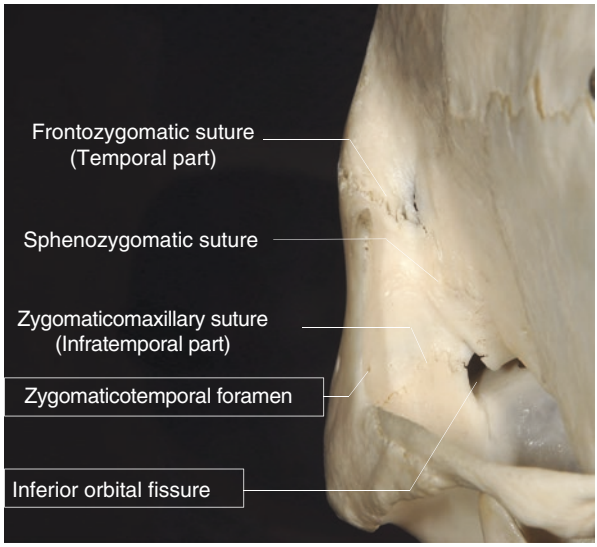


Fig. 6.5 Posterior view of the anterior part of the temporal and infratemporal fossae

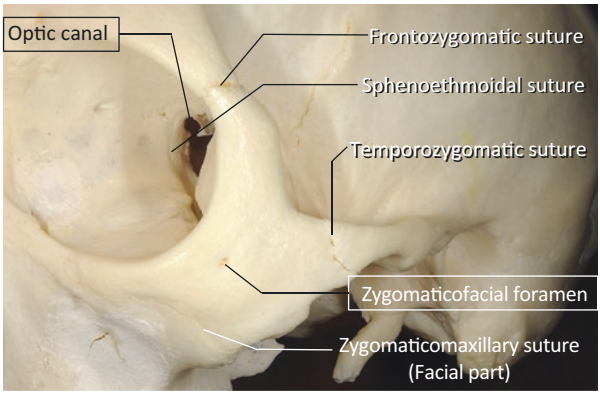


Fig. 6.6 Lateral view of the zygoma

reference point to measure the distance to the midpoint of the superior orbital fissure, which ranged from 34–38 mm [8–10]. This distance is suggested to be a safe working space when the lateral wall of the orbit is dissected. When a supraorbital orbitozygomatic craniotomy is performed, the periorbita must be freed along the superolateral orbit. Typically, the frontozygomatic suture limits the lateral exposure, while the supraorbital notch (foramen) limits the medial exposure. The periorbital dissection is best initiated adjacent to the lacrimal gland, which is just medial to the frontozygomatic suture [11].

6.3.3 Zygomaticomaxillary (infraorbital) Suture (Facial, Orbital, and Infratemporal Parts)

The zygomaticomaxillary suture (facial part) (Figs. 6.4 and 6.6) connects the inferior margin of the lateral surface of the zygomatic bone and the superior margin of the zygomatic process of the maxilla.

The zygomaticomaxillary suture (orbital part) (Fig. 6.4) connects the medial margin of the orbital surface of the zygomatic bone and the lateral margin of the orbital surface of the zygomatic process of the maxilla.

The zygomaticomaxillary suture (infratemporal part) (Figs. 6.5 and 6.7) connects the medial margin of the temporal surface of the zygomatic bone and the lateral margin of the infratemporal surface of the zygomatic process of the maxilla.

According to a recent CBCT study reported by Angelieri et al. [12], no fusion of the zygomaticomaxillary suture was observed in patients younger than 10 years old, and the fusion is assessed mainly in patients older than 15 years old. Great variability of the fusion is observed from 10 to 15 years old.

Most facial sutures remain open until late adulthood due to mechanical strains via masticatory forces on the upper face. For example, the nasomaxillary, frontomaxillary, and zygomaticomaxillary sutures do not begin to fuse until the seventh or eighth decade of life [13].

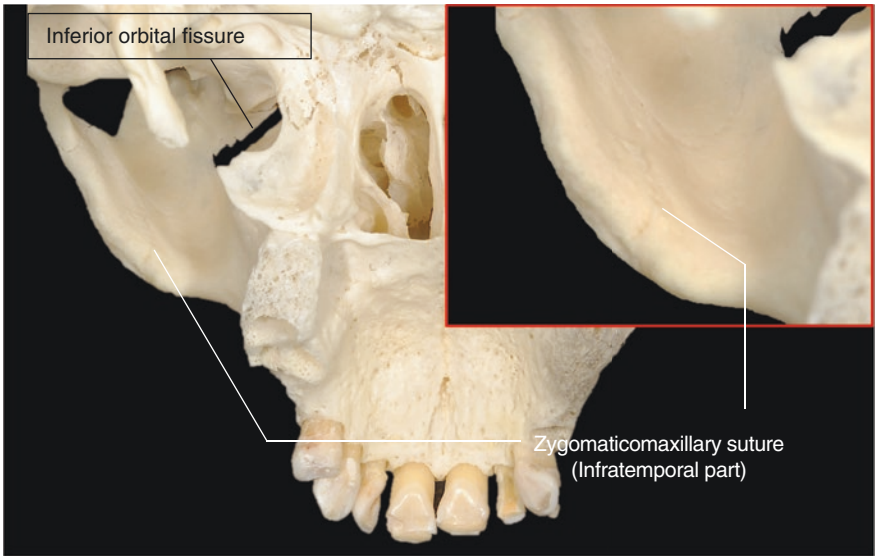


Fig. 6.7 Posterior view of the zygomatic arch

Classification of the shape of the zygomaticomaxillary suture is often applied in forensic assessment of ancestry. Earlier studies reported higher frequencies of "curved" sutures in Caucasians and higher frequencies of "angled" sutures in Native Americans [14]. Sholts and Wärmländer[15] classified these sutures into three types, i.e., curved, angled, and straight.

6.3.4 Ethmoidomaxillary Suture

The ethmoidomaxillary suture (Fig. 6.3) connects the inferior margin of the orbital plate of the ethmoidal labyrinth of the ethmoid bone and the medial margin (larger posterior portion) of the orbital surface of the body of the maxilla.

6.3.5 Nasomaxillary Suture

The nasomaxillary suture (Figs. 6.1 and 6.2) connects the lateral margin of the nasal bone and the anterior margin of the frontal process of the maxilla. The nasomaxillary arch and nasal bones form the arch of the external nose.

6.3.6 Internasal Suture

The two nasal bones (medial margins) articulate at the midline to form the internasal suture (Fig. 6.2). The junction of the internasal and frontonasal sutures is called the *nasion*.

6.3.7 Sphenozygomatic Suture

The sphenozygomatic suture (Figs. 6.4 and 6.5) connects the zygomatic margin (anterior margin of the orbital surface) of the greater wing of the sphenoid bone and the posterior margin of the orbital surface of the zygomatic bone. The sphenozygomatic suture runs up the lateral wall of the orbit from the anterior edge of the inferior orbital fissure [16]. According to Rohner et al. [17], the sphenozygomatic suture is a key site for osteosynthesis of the orbitozygomatic complex in panfacial fractures. By using the sphenozygomatic suture for the fixation, three-dimensional stability can be improved.

6.3.8 Lacrimomaxillary Suture

The lacrimomaxillary suture (horizontal part) connects the inferior margin of the lacrimal bone and the medial margin (small anterior portion) of the body of the maxilla.

The lacrimomaxillary suture (perpendicular part) (Fig. 6.3) connects the anterior margin of the lacrimal bone and the posterior margin of the body of the maxilla.

6.3.9 Ethmoidolacrimal Suture

The lacrimoethmoidal suture (Fig. 6.3) connects the posterior margin of the lacrimal bone and the anterior margin of the orbital plate of the ethmoidal labyrinth of the ethmoid bone. Kim et al. [18] investigated the orbital lines using plain radiographs and CT revealing that the anterior lamina papyracea line which is seen as the inner line of the medial orbital wall corresponds to the lacrimoethmoidal suture.

6.3.10 Intermaxillary Suture (Facial Part)

The intermaxillary suture (Fig. 6.8) runs anteriorly from the anterior to the incisive fossa to the anterior nasal spine in the midline (between the right and left central incisors).

6.3.11 Temporozygomatic Suture

The temporozygomatic suture (Fig. 6.6) connects the zygomatic process of the temporal bone and the temporal process of the zygomatic bone.

6.3.12 Palatomaxillary Suture (Nasal Part)

The palatomaxillary suture (nasal part) connects the anterior margin of the perpendicular plate of the palatine bone and posterior part of the body of the maxilla.

The palatomaxillary suture (orbital part) (Fig. 6.9) connects the anteroinferior margin of the orbital process of the perpendicular plate of the palatine bone and the medial margin (smaller posterior portion) of the orbital surface of the body of the maxilla.

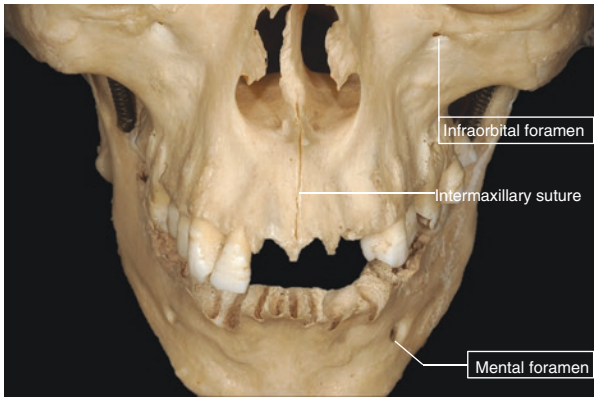


Fig. 6.8 Anterior view of the maxilla

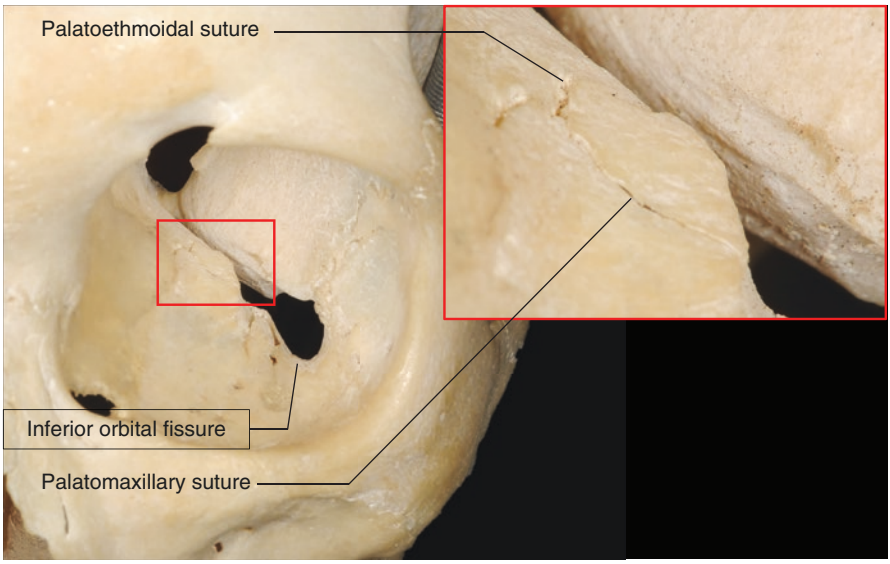


Fig. 6.9 Anterior view of the inferior wall of the orbit

6.3.13 Lacrimoconchal Suture

The lacrimoconchal suture connects the medial part of the inferior margin of the lacrimal bone and lacrimal process (superior margin) of the inferior nasal concha.

6.3.14 Palatoethmoidal Suture

The palatoethmoidal suture (Fig. 6.9) connects the superoanterior margin of the orbital process of the perpendicular plate of the palatine bone and the inferior margin (smaller posterior portion) of the orbital plate of the ethmoidal labyrinth of the ethmoid bone.

6.3.15 Sphenovomerine Suture

The sphenovomerine suture connects the body of the sphenoid bone and posterosuperior margin of the vomer.

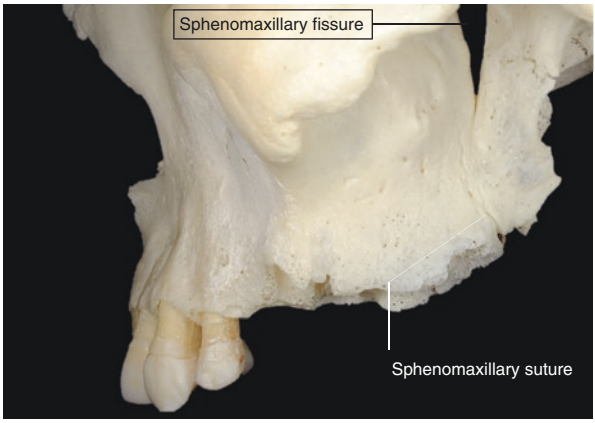


Fig. 6.10 Lateral view of the sphenomaxillary junction

6.3.16 Sphenomaxillary Suture (Pterygomaxillary Suture)

The sphenomaxillary suture (Fig. 6.10) connects the posterior portion of the maxillary tuberosity and the anterior border of the pterygoid process of the sphenoid bone. The sphenomaxillary suture is separated when osteotomy on the maxilla, such as Le Fort osteotomy and the surgically assisted rapid maxillary expansion procedures are performed.

6.3.17 Sphenoethmoidal Suture

The sphenoethmoidal suture (Fig. 6.6) connects the medial margin of the lesser wing (orbital surface) of the sphenoid bone and posterior margin of the orbital plate of the ethmoidal labyrinth of the ethmoid bone.

6.3.18 Incisive Suture

The incisive suture separates the anterior part of the bony palate (upper incisors area) from the rest of the palate [19]. The incisive suture is at the junction of the primary palate and lateral palatal shelves (palatal processes of the maxilla).

6.3.19 Median Palatine Suture

The median palatine suture (Fig. 6.11) runs posteriorly from the incisive fossa to the posterior nasal spine in the midline. The median palatine suture becomes

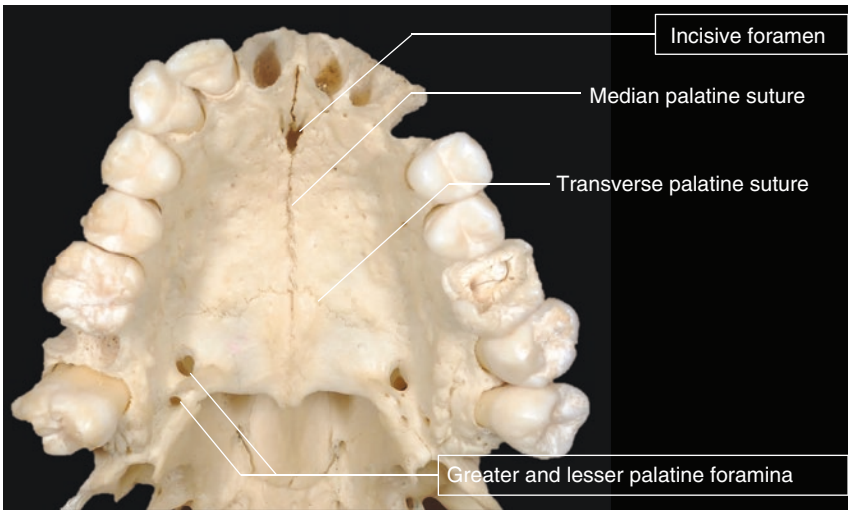


Fig. 6.11 Inferior view of the bony palate

evident at ten and a half weeks. In the coronal plane, the median palatine suture in infancy and childhood is Y-shaped and T-shaped, respectively, due to the relationship among the vomer and palatal shelves. Growth at the median palatine suture ceases between 1 and 2 years old. The median palatine suture begins to fuse between the ages of 15 and 35 years [20]. Obliteration of the median palatine suture may start in adolescence, but the timing and degree of the complete fusion is variable and rarely seen in patients younger than 30 years old [21].

6.3.20 Transverse Palatine Suture

The transverse palatine suture (Fig. 6.11) runs between the posterior margin of the palatine process of the maxilla and anterior margin of the horizontal plate of the palatine bone. It appears horizontally in the posterior part of the bony palate.

6.4 Clinical Relevance

6.4.1 Cleft Palate

Embryologically, mistiming or failure of fusion of the paired palatine at the palatal-shelves (median palatine suture in adults) leads to a cleft palate.

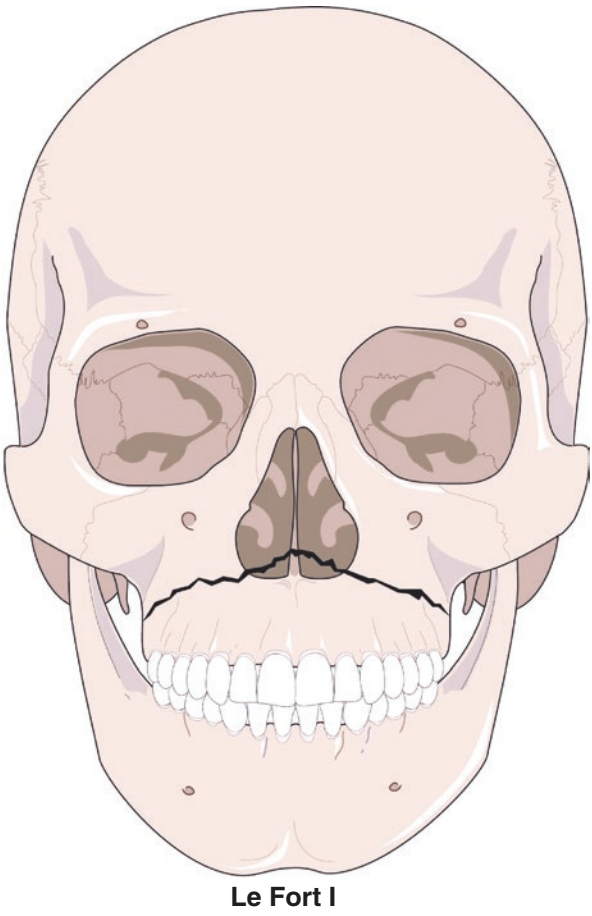


Fig. 6.12 Le Fort I fracture

6.4.2 Fractures Related to Sutures of the Face

6.4.2.1 Le Fort I Fracture

A Le Fort I fracture (Fig. 6.12) is a horizontal maxillary fracture that separates the upper teeth from the upper face. A fracture line passes through the upper alveolar ridge, lateral nose and inferior wall of the maxillary sinus.

6.4.2.2 Le Fort II Fracture

A Le Fort II fracture (Fig. 6.13) is a pyramidal-shaped fracture, with the frontonasal suture at its apex, and teeth at the pyramid base. The fracture arch passes through the posterior alveolar ridge and lateral walls of the maxillary sinuses. The

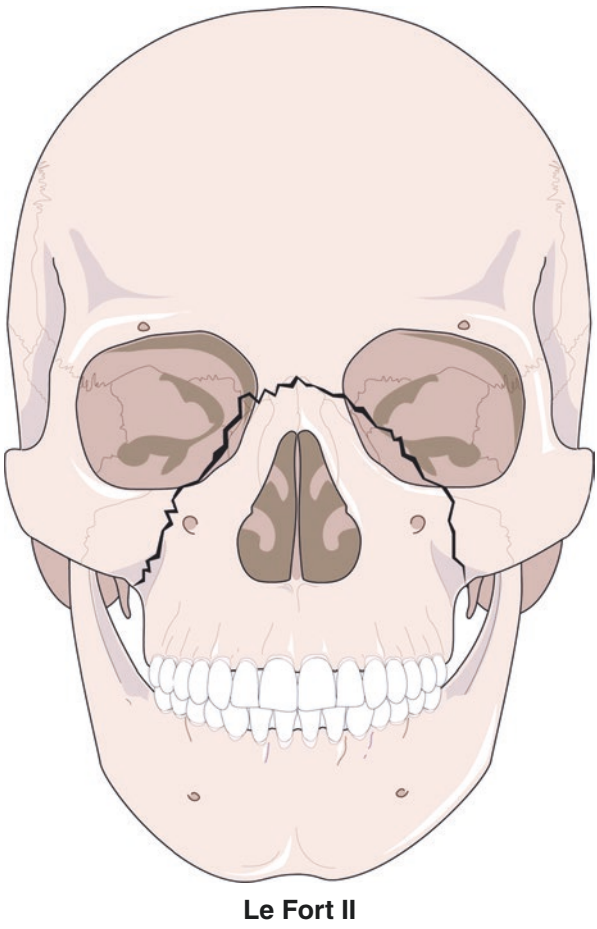


Fig. 6.13 Le Fort II fracture

infraorbital margin and nasal bone's uppermost fracture line can pass through the frontonasalsuture or the frontomaxillary suture.

6.4.2.3 Le Fort III Fracture

A Le Fort III fracture (Fig. 6.14) results in craniofacial disjunction. The transverse fracture line passes through the frontonasal suture, frontomaxillary suture, orbital wall, and zygomatic arch/frontozygomatic suture.

6.4.2.4 Naso-orbitoethmoid Fracture (NOE Fracture)

The NOE fracture includes the nasal, orbital, and ethmoid bones and the frontal process of the maxilla. This can be missed when concurrent with an orbito-zygomatic fracture and is classified into types I, II, and III.

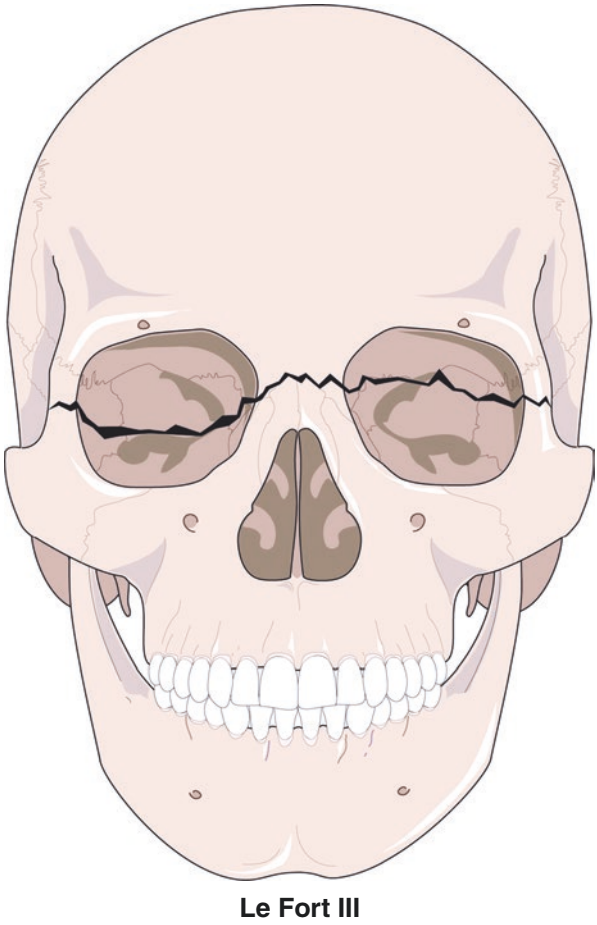


Fig. 6.14 Le Fort III fracture

6.4.2.5 Zygomaticomaxillary Complex Fracture (ZMC Fracture)

A ZMC fracture is defined as the osseous disruption of the malar eminence at four buttresses: zygomaticomaxillary, temporozygomatic, frontozygomatic, and sphenozygomatic sutures. This fracture is the second most common fracture of the face after nasal bone fractures [22].

6.4.2.6 Orbital Fractures

Orbital fractures include the floor, medial wall, roof, lateral wall, and combined fractures. Any sutures in the orbit can be disrupted by orbital fractures.

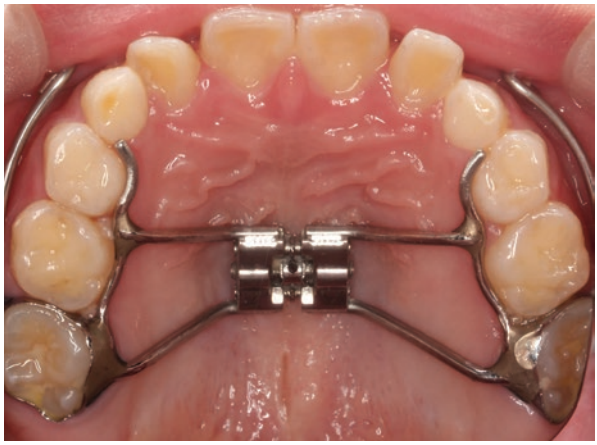


Fig. 6.15 Rapid maxillary expansion (Courtesy of Dr. Morita)

6.4.3 Rapid Maxillary Expansion

Rapid maxillary expansion (RME) is one of the orthodontic treatments that spreads the median palatine suture by placing lateral forceson to the bony palate from the midline (Fig. 6.15). A computed tomography (CT) study by Ghoneima et al. [23] revealed that the RME produced significant increases in the internasal, maxillonasal, intermaxillary, frontomaxillary, and frontonasal sutures, while the frontozygomatic, temporozygomatic, zygomaticomaxillary, and pterygomaxillary sutures did not show significant changes.

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Chapter 7
Normal Growth of the Sutures of the Skull

Rosalinda Calandrelli, Fabio Pilato, Gabriella D'Apolito, Marco Panfili, and Cesare Colosimo

7.1 Suture and Synchondroses of the Skull: Identification

At the end of the embryonic stage, the ossification fronts of the bones of the calvaria and skull base are separated by non-ossified tissue barriers, known as sutures and synchondroses and these structures allow the skull to change shape and grow according with brain development [1].

Sutures are joints composed of bands of fibrous connective tissue that link the ossifications fronts of the flat bones. The synchondroses are immovable joints, composed of hyaline cartilage between the two articular surfaces [2–5]. The identification of sutures and synchondroses reveals the functional importance of the four "sutural arches". The sutures of the vault, named major sutures, and those of the base, named minor sutures, along with three synchondroses make the sutural arches of the skull. Minor sutures and synchondroses are the extension of the vault sutures towards the skull base [3].

The sagittal arch is composed of sagittal and metopic sutures (major sutures) and frontoethmoidal (fe) sutures (minor sutures). The coronal arch consists of the coronal sutures of both sides (major sutures). The extension of each coronal suture toward the skull base is divided into an anterior and a posterior branch. The anterior branch (AB) is composed of the frontosphenoidal (fs) sutures (minor sutures) and the ethmoidosphenoidal (es) synchondrosis, whereas the posterior branch (PB)

R. Calandrelli (✉) · G. D'Apolito · M. Panfili · C. Colosimo
Department of Radiology and Neuroradiology, Oncological Radiotherapy and Hematology-Diagnostic Imaging Area, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Catholic University, Rome, Italy
e-mail: rosalinda.calandrelli@policlinicogemelli.it

F. Pilato
Unit of Neurology, Neurophysiology and Neurobiology, Department of Medicine, Università Campus Bio-Medico di Roma, Rome, Italy

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consists of the sphenoparietal (spa) and sphenosquamous (ss) sutures (minor sutures) as well as the sphenopetrosal (sp) synchondrosis. The lambdoid sutures (major sutures) extending to the minor sutures of the skull base, including the occipitopetrosal or occipitomastoid sutures (op=om) and the sphenooccipital synchondrosis (so) make the lambdoid arch. The parietosquamosal arch consists of the parietosquamous (ps) and parietomastoid (pm) sutures. Only three out of seven synchondroses of the skull base belong to the four "sutural arches" of the skull (es, sp, so). The other four synchondroses (anterior intraoccipital =ioa, posterior intraoccipital =iop, temporooccipital/petrooccipital synchondroses=to/po, anterior intrasfenoidal synchondrosis=isa) which belong to skull base, do not make up the sutural arches [3, 6, 7].

The minor sutures/synchondroses coursing in the anterior cranial fossa (ACF) are frontoethmoidal sutures (fe), frontosphenoidal (fs) sutures and ethmoidosphenoidal (es) synchondrosis. The fe sutures belong to the sagittal arch, while the others belong to the coronal arch AB. The minor sutures/synchondroses coursing in the middle cranial fossa (MCF) are sphenosquamous sutures (ss), sphenoparietal sutures (spa), the sphenopetrosal synchondrosis (sp) and the anterior intrasfenoidal synchondrosis (isa); the first three belong to PB of the coronal arch. The minor sutures/synchondroses coursing in the posterior cranial fossa (PCF) are occipitopetrosal or occipitomastoid sutures (op=om), the sphenooccipital synchondrosis (so), anterior intraoccipital synchondrosis (ioa), posterior intraoccipital synchondrosis (iop) and temporooccipital/petrooccipital synchondroses (to/po); the first and second belong to the lambdoid arch. The parietomastoid sutures (pm) mark the boundary between the MCF and the PCF [8] (Fig. 7.1).

7.2 Sutures and Synchondroses Are Cranial Growth Centers: Formation and Development

7.2.1 Skull Development: Role of Sutures and Synchondroses

The growth of the cranial base occurs by expansion of cranial base synchondroses mainly through the intrinsic growth capability of the cartilaginous synchondroses, rather than a response to external stimuli [5].

On the other hand, postnatal growth of the cranial membranous bones occurs through sutures and in response to the growing brain which sends signals by means of the dura mater [9].

The sutures and synchondroses represent the main sites of bone growth and they need to remain in an unossified state during the skull growth [4]. The overall skull shape is the result of these bone formation processes along the suture and synchondoses margins [10]. In particular, skull growth follows these steps of increasing for each dimension: (1) in width primarily through major sutures of the skull; (2) in length due to the growth of the cranial base through synchondroses; (3) in height due to the activity of the parieto-squamous sutures [11].

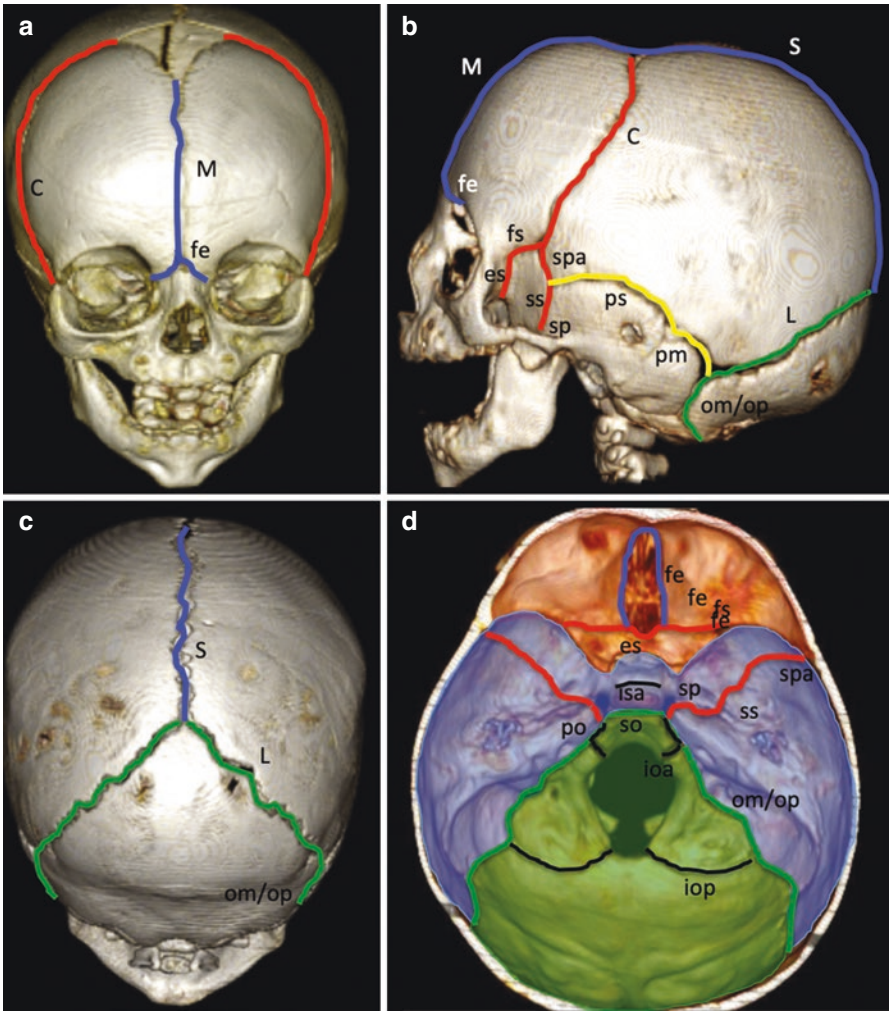

Fig. 7.1 Representative scheme of sutural arches and of the cranial fossae. 3D CT: (**a**) frontal view; (**b**) lateral view; (**c**) posterior view, (**d**) skull base view. *Sagittal arch* is shown in blu (**a**, **b**). Major sutures: sagittal (S) and metopic (M) sutures; minor suture: frontoethmoidal (fe) sutures. *Coronal arch* is shown in red (**a**, **b**). Major sutures: coronal sutures (C). AB: frontosphenoidal (fs) sutures (minor suture) and ethmoidosphenoidal (es) synchondrosis. PB: sphenoparietal (spa) and sphenosquamous (ss) sutures (minor suture) and sphenopetrosal (sp) synchondrosis. *Lambdoid arch* is shown in green (**b**, **c**). Major sutures: lambdoid sutures (L); minor sutures: occipitopetrosal or occipitomastoid sutures (op=om) and spheno-occipital synchondrosis (so). *Parietosquamosal arch* is shown in yellow (**b**). Major sutures: parietosquamous (ps) sutures; minor suture: parieto-mastoid (pm) sutures. *Anterior cranial fossa* (ACF) is shown in red: fe, fs and es course in ACF. (**d**). *Middle cranial fossa (MCF*) is shown in purple: ss, spa, sp. and isa course in MCF (**d**). *Posterior cranial fossa* (PCF) is shown in green: op/om, so, ioa, iop and to/po course in PCF (**d**)

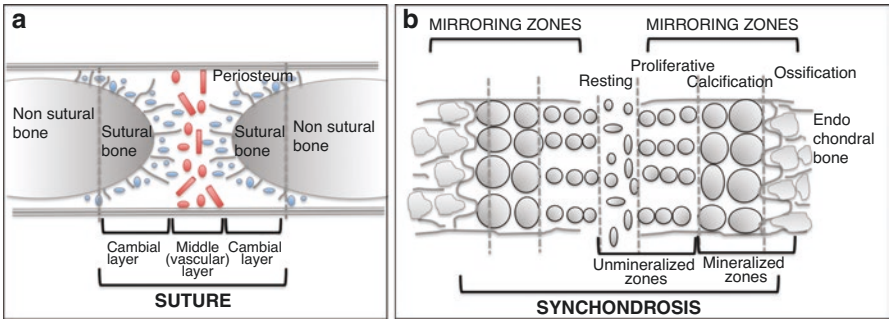

Fig. 7.2 Schematic representation of a suture (**a**) and a synchondrosis (**b**). Sutures are composed of a cambial layer with numerous osteoblasts and a vascular middle layer (non-osteogenic). The sutural cambial layer is continuous with the periosteum of the bones. The mineralized tissues directly bordering the sutures are referred to sutural bone or sutural mineralized tissues.The mineralized tissues that are more distant from the sutural borders are referred to 'non-sutural' bone (or 'non-sutural' mineralized tissues). Skull bones and their sutures are linked together by dense regular connective tissues mostly composed of collagen fibers. Synchondroses are composed of different cellular zones: one central resting zone and mirroring proliferative, calcification (hypertrophied cartilage) and ossification zones. The resting and proliferative zones are unmineralized (formed of hyaline cartilage), and the calcification/hypertrophied cartilage and ossification zones are mineralized. Endochondral bone is present on the two borders of synchondroses. This figure is a schematic reproduction of the drawings of Pritchard et al. [12] and Opperman et al. [5]

7.2.2 Histology

It is important the distinction between sutures and synchondroses because the embryological origins and histologies of these articulations are different.

Sutures are composed of: (1) the periosteum of the two separated membranous bones (each having a cambial layer containing collagenous fibers, osteoprogenitor cells and osteoblasts, and a rarely observed capsular layer composed mostly of collagenous fibers, small blood vessels and fibroblasts); and (2) a middle layer that is non-osteogenic and composed mostly of collagens fibers, mesenchymal cells, fibroblasts and blood vessels. They are encapsulated in dense fibrous connective tissues called uniting layers [2, 4, 12].

Synchondroses can be described as two epiphyseal growth plates positioned back to back with one common resting zone and mirroring proliferative zones (where cellular divisions occur), hypertrophied cartilage/calcification zones and ossification zones [2, 13] (Fig. 7.2).

7.2.3 Stages of Sutural Growth and Closure

In the skull, the processes of sutures development and fusion are controlled by a complex interaction among genetic, biochemical and environmental factors that regulate bone formation and resorption during prenatal development and infancy [1, 14].

In particular, these complex regulatory mechanisms determine the time and location of suture formation during prenatal development, the sutural growth and closure patterns during infancy and adulthood [1].

All factors that regulate suture development have not been definitely understood yet; however, some studies have demonstrated that three sequential events are important to set these processes.

The first event is the formation of the primary ossification centers of the plat bones driven by the concentrations of two molecules (BMP2 and Noggin), controlling the differentiation of mesenchymal cells into osteoblasts (approaching stage; Fig. 7.3a) [15]. In this stage dura mater is not required to induce initial overlap of the bone fronts during their development [4].

The second event is bone growth and suture formation (meeting stage; Fig. 7.3b); it is mainly regulated by the concentrations of transforming growth factor beta three (TGF-β3) and transforming growth factor beta two (TGF-β2). The former, promoting adjacent mesenchymal cells differentiation into osteoblasts at these sites, have an osteoinductive role while TGF-β3 inhibiting the differentiation of mesenchymal cells into osteoblasts at the bone fronts, have a osteoinhibitory role [16–20]. The presence of dura mater is required both for suture formation and stabilization: the former by permissing osteogenic signal and the latter by inhibiting osteogenic signals [4, 21].

In particular, the ossification centers gradually expand and give rise to the paired parietal, frontal, temporal and the unpaired supraoccipital, ethmoidal and interparietal bones (membranous ossification). With increased growth, the opposing borders of the primordial cranial bone meet, forming thin areas with sustained osteoproliferative capacity called cranial sutures. The site of suture formation corresponds to the location of major dural reflection [11].

The formation and growth of a suture is a combination of (1) deposition of osteoid at the sutural margins, (2) surface apposition and resorption (remodeling) of the bone by direct osteoblastic and osteoclastic activities, and (3) centrifugal displacement by the expanding brain [11]. The growth of the sutures is unidirectional and follows the natural growth curve; in particular the growth rate is extremely rapid during the first few years of life but slows down dramatically by the age of 6–7 years [11].

The third event rules the sutural morphological changes leading, through the process of suture interdigitation, to the physiological fusion. Stages of suture interdigitation in infancy are achieved through two uncoupled processes: suture width reduction by the overall radial bone growth and a local interaction between bone formation and resorption processes taking place at opposing bone fronts. The former is controlled by TGF-β3 and TGF-β2 concentrations, whereas the latter by the action of Wnt and Sclerostin molecules along the sutures (growing and fusion stages; Fig. 7.3c, d) [1]. Hence, interdigitation process is dependent on Wnt and Sclerostin concentrations along the sutures, where high Wnt concentrations (low Sclerostin) induce bone formation by inducing mesenchymal cells differentiation into osteoblasts and low Wnt concentrations (High Sclerostin) promote bone

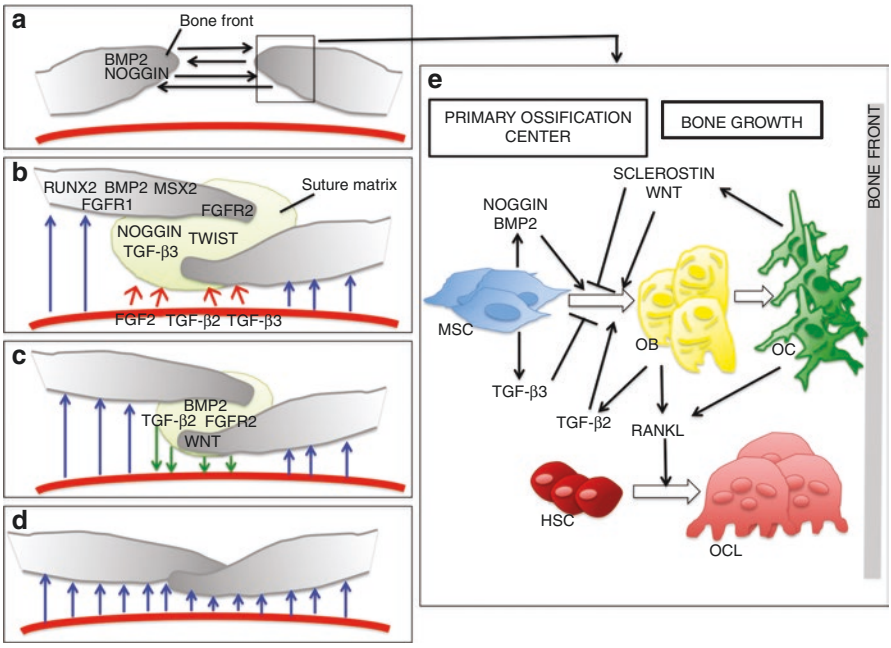

Fig. 7.3 Schematic representation of sutural formation, growth and fusion. Principal molecules involved in these processes. (**a**) Approcching stage. Inductive signals (black arrows) from the approaching bone fronts (gray area) are indipendent from dura mater (red line) and allow the bone fronts to grow and overlap. (**b**) Meeting stage. Once the bone fronts have overlapped one another, a signal (red arrows) from the dura mater maintains the presence of the newly formed suture (light yellow area). Osteogenic signals from the dura (blue arrows) cause also the growing of the bones. Open suture shows the presence of Twist, Noggin, and Tgf-3 in the suture matrix (light green area), Fgfr2 in the edges of the bone fronts (gray regions), Runx2, Bmp2, Msx2, and Fgfr1 in the bones (light gray area), and Fgf2, Tgf-2, and Tgf-3 in the dura mater (red line). (**c**) Growing stage. The suture, once stabilized, signals the local underlying dura (green arrows) not to produce osteogenic signals. Fusing suture shows down regulation of Twist, Noggin, and Tgf-3, and upregulation of Bmp2, Tgf-2, and Fgf2 in the remnants of suture matrix (light green area). (**d**) Suture obliteration. When the osteoinhibitory signals from the suture end, the osteogenic signals from the dura allows the growh of the bone fronts and the suture obliteration. (**e**) Detail of molecular processes at the bone front. MSC: Mesenchimal Stromal Cells; OB: Osteoblasts OCL: Osteoclasts; OC: Osteocytes; HSC: Hematopoietic Stem Cells; ➔ indicates activation; ⊣ indicates inibition. MCS produce NOGGIN, BMP2 and TGF-β3; OB produce TGF-β2 and RANKL; OC produce SCLEROSTIN and WNT

resorption by promoting osteoclastogenesis at opposing bone front sites [22–25]. Moreover, resorption events have been also associated with the concentration of receptor activator of nuclear factor kappa-B ligand (RANKL), a protein required for osteoclast differentiation, expressed by both osteocytes alone and active osteoblasts on the bone front where bone formation takes place [23, 26]. The bone deposition and resorption at the suture margins may vary, not only between various sutures but also on opposite sides of or along the same suture.

The resulting patterns of bone formation and resorption, together with the effects of TGF-β2 TGF-β3, progressively decrease the width of the sutures, generate interdigitated sutures until the sutures fully ossify. In most cases, the suture interdigitation process begins at 12 months of age and the continuous narrowing of the suture proceeds, variably, throughout the infancy until adulthood [1].

The sutural closure happens by fusion of the sutural bone fronts in sutures [4]. Closure of the sutures progressed slowly from the internal side to the external surface [27]. The fusion of the sutures is mainly regulated by the dura mater, which interacts with the overlying tissues of the cranial vault. In this phace the dura mater provides many important regulators of growth, such as intercellular signals, mechanical signals, and cells which undergo transformation and migrate to the suture. In particular the absence of osteoinhibitory signals from the suture allow the underlying dura mater to remain continuously osteogenic resulting in osseous obliteration of the suture [4].

The mode of sutural fusion mostly is made via 'normal' intramembranous ossification or via chondroid bone formation, an intermediate tissue between bone and cartilage. After fusion, the 'suture' is called synostosis [12, 28].

7.2.4 Synchondroses Growth and Closure

The growth of the synchondroses has the peculiar characteristic of being bidirectional as a consequence of its mirroring layers [5]. Synchondroses of the skull base grow through chondrocyte proliferation and differentiation processes and gradual osseous transformation contributing principally to growth length of the chondrocranium. Chondrocytes in growth plates are continuously supplied by the differentiation and proliferation of chondrocytes in the reserve and proliferative zones, while terminally differentiated hypertrophic chondrocytes are removed at the chondro-osseous junction by apoptotic cell death. The balance between the addition and removal of chondrocytes as well as matrix production and degradation determine the synchondroses growth. Once expansion occurs within the cartilage, the hyaline cartilage is replaced by bone via endochondral bone formation or sometimes by fibrocartilage [29]. In particular, in the peripheral portion of synchondrosis (at the chondro-osseous junction), osteoblasts and blood vessels invade the area of cartilage. The resting and proliferative layers within the synchondrosis gradually decrease, leading to a relative narrowing of the growth center [13].

A review of the literature reveals significant gaps in knowledge about the cranial base synchondroses, with very few publications in recent years using molecular biological tools to study the factors influencing their development, growth and closure [5]. Synchondrosal growth and ossification are regulated by a complex series of molecular interactions**.** An essential regulator of endochondral bone growth is fibroblast growth factor receptor (Fgfr). Fgfr is preferentially expressed in proliferating and prehypertrophic chondrocytes and in epiphyseal growth plates, regulating chondrocyte differentiation and proliferation. Fgfr and MAPK signaling in

chondrocytes regulate also synchondrosis closure, osteoblast differentiation and bone formation. Other molecules are important because contribut to synchondroses growth and ossification processes. Parathyroid-hormone-related peptide (PTHrP) stimulates chondrocyte proliferation and inhibits chondrocyte hypertrophy. Indian hedgehog (Ihh) controls both chondrocyte proliferation and hypertrophy through molecular circuitry with PTHrP and parathyroid hormone receptor (PTHR) [30]. Transforming growth factor beta (Tgf-) stimulates chondrocyte differentiation, while plays a role in inhibiting chondrocyte proliferation, hypertrophy and mineralization [31].Vegf promotes vascular invasion. Bone morphogenetic proteins (Bmps) stimulate chondrocyte differentiation, hypertrophy and mineralization whereas Bmps antagonists (Noggin, Gremlin and Chordin) inhibit bone formation [32]. The regulation of Vegf, Bmps and Bmp antagonists are at least partially mediated by the MAPK pathway [13] (Fig. 7.4).

7.3 Assessment of Sutures and Synchondroses Growth: Role of CT and MRI

7.3.1 CT and MRI: What Is the Best Technique?

Although histologic examination remains the gold standard to asses the growth status of suture and synchondrosis, non-invasive diagnostic imaging methods as MRI and CT are usuful tools to evaluate their patency or closure. The width of sutures and synchondroses, as well as the consistent change of signal or density from cartilage or to bone tissue allow to understand their growth or fusion status.

High resolution CT with three-dimensional (3D) shaded-surface volume-rendered (VR) CT images, using a surface rendering software, is the best technique because it provides a rapid overview of the sutures and synchondroses allowing appreciation of their course, margin linearity, separation, and symmetry [33]. In children the use of the iterative reconstruction technique, such as the Adaptive Statistical Iterative Reconstruction (ASIR) or SAFIRE (Sinogram affirmed Iterative Reconstruction), is mandatory for low-dose scanning; the use of lens protection systems (ODM, Xcare) and the use of dose modulation systems (e.g. Auto mA, smartmA, Care Dose 4D) are highly recommended [34, 35].

The levels of radiation exposure (DLP) useful to visualize both major and minor skull base sutures/synchondroses are estimated between 420 and 550 mGy*cm [8].

2D MPR images allow to better evaluate the degree of sutural gap while volume rendering images seems to be more straightforward than MPR or MIP in assessment of sutural overall course and morphology because they show bone surface anatomy [36]. To correctly visualize the sutural width, the threshold chosen for 3D reconstructions should be set to the lowest level that permits avoidance of soft-tissue visualization from the thinnest structures of the facial bones. Generally, threshold values ranging from 120 HU for younger patients to 150 HU for older patients are

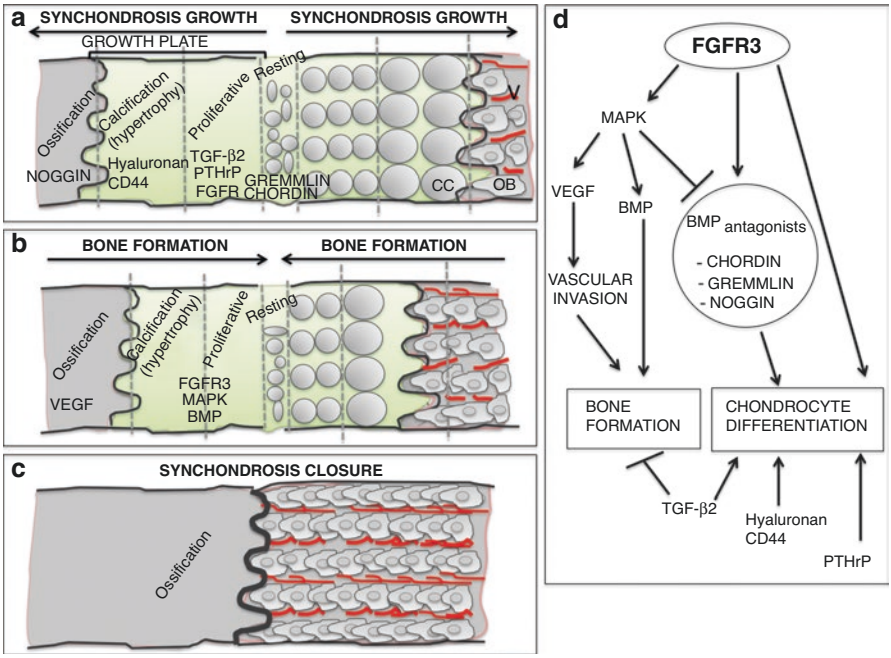

Fig. 7.4 Schematic representation of sinchondrosys growth and fusion. Principal molecules involved in these processes. CC: chondrocytes; OB: osteoblasts; V: blood vessels; green shaded area: growth plate of synchondrosis; grey shaded area: ossification front. (**a**, **d**) Snchondrosal growth. Chondrocyte differentiation from the resting zone stimulates chondrocytes proliferation. Fgfr (in proliferating and prehypertrophic chondrocytes and in epiphyseal growth plates) regulates chondrocyte differentiation and proliferation. Parathyroid-hormone-related peptide (PTHrP) stimulates chondrocyte proliferation, mantaining the endochondral growth plate at a costant width. Transforming growth factor beta (TGF-β) stimulates chondrocyte differentiation, while plays a role in inhibiting chondrocyte proliferation, hypertrophy and mineralization. Hyaluronan and CD44 (in the hypertrophic zone) NOGGIN (in the prehypertrophic zone), GREMMLIN and CHORDIN (in the resting zone) contribute to synchondrosal growth. (**b**–**d**) Synchondrosal ossification. Osteoblasts and blood vessels invade the cartilage, while the resting and proliferative layers within the synchondrosis gradually decrease until to complete closure of synchondrosis and ossification of its borders. Fgfr by MAPK pathway regulate also synchondrosis closure. Increased FGFR3 induces increased secretion of BMP ligands (BMPs), decreased secretion of BMP antagonists (noggin, gremmlin, chordin) and upregulation of VEGF promoting vascular invasion, bone formation and fusion of ossification centers

adequate. The width of a suture on 3D reconstruction may be considerably altered when different thresholds are selected. An increase or reduction in threshold value can show the sutures as artifactually "open" or "close" [37].

MRI offers a potential non-ionising alternative to CT, but, in infants, routine sequences have been shown to be less reliable than CT imaging in the identification of the cranial sutural/synchondrosis course, patency and closure [38].

"Black Bone" MRI is a good alternative to CT in the identification of normal and prematurely fused cranial sutures both in 2D and 3D imaging. "Black Bone" MRI

uses novel gradient echo parameters, optimized to minimize soft tissue contrast, enhancing the bone-soft tissue boundary. This is achieved by using 3D volume acquisition, a short TE, TR, and low flip angle [39].

7.3.2 CT and MRI: Sensitivity and Specificity

Both CT and MRI show a good sensitivity and specificity, in the assessment of synchondrosal status. The large size of synchondroses, as well as the consistent change of signal (or density) from cartilage to bone tissue account for this result.

However, not all synchondroses may be assessed equally well; the sphenoethmoidal synchondrosis has a lower sensitivity compared to spheno-occipital and intersphenoidal synchondrosis in both CT and MRI.

Concerning the assessment of suture status CT correctly identifies a cranial suture as open (high sensitivity) and closed (high specificity) even if the correct identification of minor skull sutures is more difficult and requires experienced radiologists.

On the other hand, MRI shows a moderate sensitivity to identify an open suture and a low specificity for the assessment of sutural closure. However Eley et al. reported a major sensitivity to demonstrate patent cranial vault sutures using Black Bone MRI sequence [39]. On the other hand, the low specificity to assess sutural closure can be attributed to the small size, width and course of the examined structures.

Beyond size and morphology, the variability between the observers both on CT and MRI indicates that assessment of sutures is also experience dependent [40].

7.3.3 Assessment of Sutures Growth on CT

On CT, an open synchondrosis or suture is shown as a hypodense zone between well-defined hyperdense borders of the calvaria or cranial base bones. Partial closure is shown as a non-continuous hypodense zone due to the presence of bone-isointense bridges. A complete closure is shown as the absence of hypodense zone between sclerotic borders while a synostotic suture or synchondrosis causes the disappearance of sclerotic margins [40] (Figs. 7.5 and 7.6).

7.3.4 Assessment of Sutures Growth in MRI

On T2 weighted images MR, an open suture is shown as a hypointense signal with interruption of the hyperintense calvarial bone marrow signal. A closed suture is shown as a lack of a hypointense signal within the hyperintense bony structures.

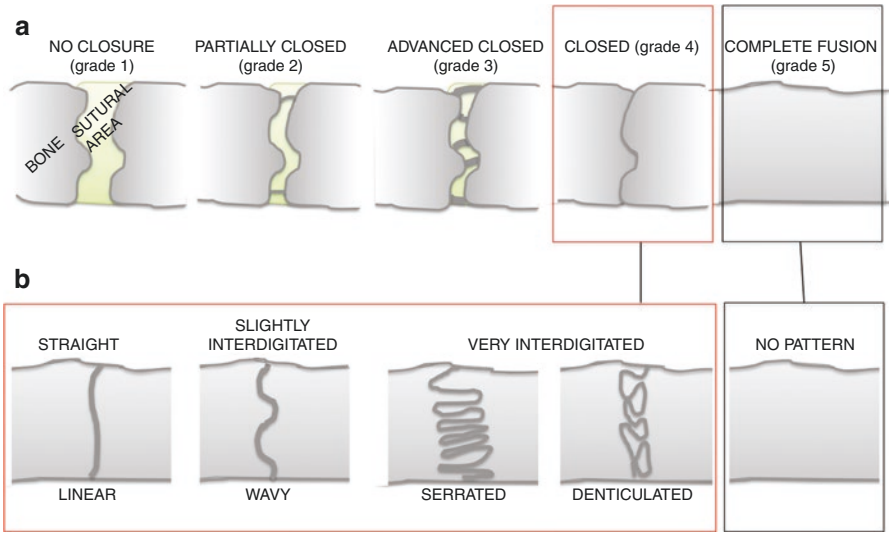

Fig. 7.5 Sutural area morphology. *Degree of sutural closure* (**a**). Suture is considered open if bone fronts are clearly separate along their margins of contact (grade 1); partially closed if bone fronts are still separate but are significantly closer to each other than in the previous state and some areas are indistinct or suspicious for bony bridging (grade 2); advanced closure if bony bridging are clearly identified in some parts of the suture (grade 3); closed if the bone fronts are conjoined into a single unit with sutural visible line (grade 4); completely obliterated when there is absolutely no trace of the suture line (grade 5). *Degree of interdigitation and sutural patterns* (**b**). Straight line (linear, end-to-end, butt, flat, or plane), slightly interdigitated (wavy), very interdigitated (serrated and denticulated) and patternless

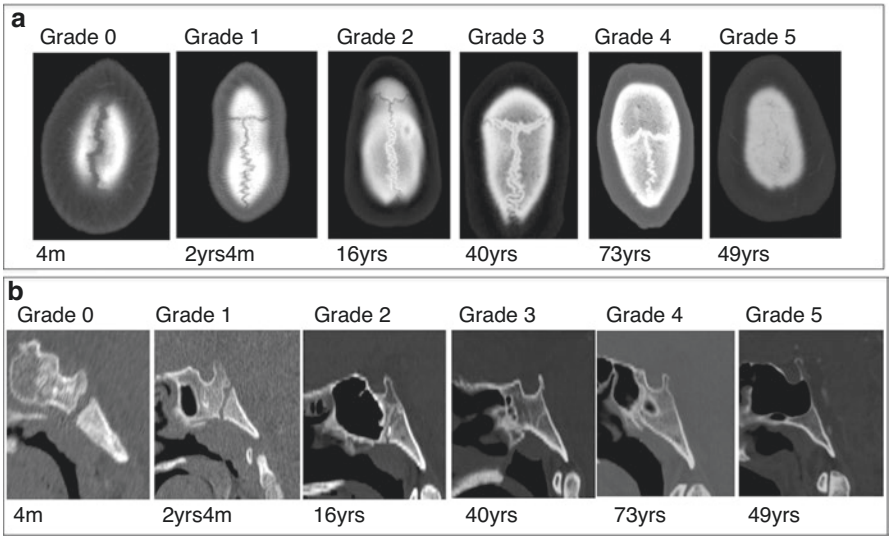

Fig. 7.6 Representation of closure degree of sagittal suture (**a**) and spheno-occipital synchondrosis (**b**) on CT images. Note the closure progression from birth to adulthood age

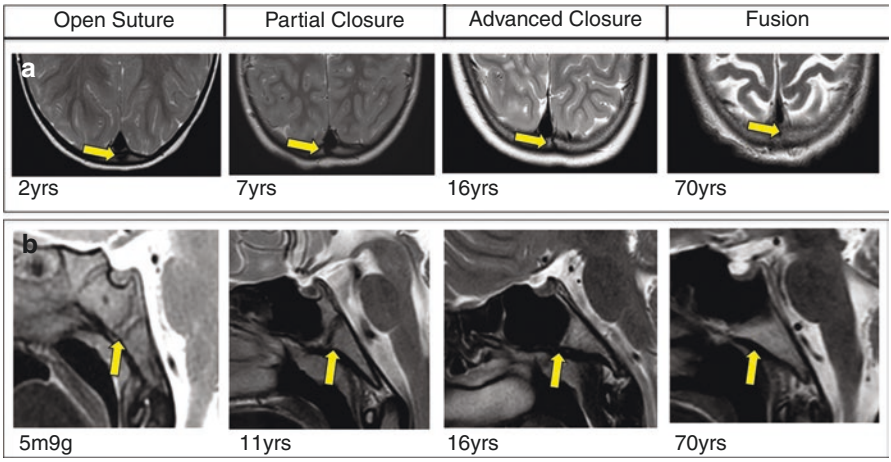

Fig. 7.7 Representation of growth status of sagittal suture (a) and spheno-occipital synchondrosis (**b**) on T2-weighted MRI. Note the closure progression from birth to adulthood age

An open synchondrosis is based on the presence of a broad hyperintense signal zone (cartilage) with well-defined, hypointense borders (endplates). A closed synchondrosis is based on the obliteration of the edges of the synchondrosis, replacement of cartilage and development of a continuous isointense signal from the bone marrow cavity. At the beginning, the cartilage disappears and the two hypointense endplates are in contact; the total absence of the hypointense signal of endplates defines the late phase of ossification.

Partial closure is defined as bony bridges within the suture or synchondrosis, visible as a partial hypointense signal of a suture within the hyperintense bone, or as a hypointense signal within the hyperintense cartilage signal of the synchondrosis [38, 41].

On "Black Bone" MRI the patent cranial sutures are seen as areas of increased signal intensity, making them distinct from the surrounding signal void of the bone. With increasing age, the increased signal intensity disappears; this represents the normal progression toward the closure of cranial suture appearance [39] (Figs. 7.5 and 7.7).

7.4 Plastic Changes of Sutural Area During Closure and Fusion Processes

Each suture or synchondrosis may be coded according to its degree of closure and its degree of interdigitation. During the closure process cranial sutures/synchondroses exhibit morphological changes going from straight lines (end-to-end, butt, flat,

or plane) to an interdigitated and beveled (or overlapping) patterns until, with progressive interlocking of the two margins of the suture, the interdigitations disappear, the bone fronts fuse and the suture is often replaced by bone marrow and blood vessels [42, 43].

In the view of Moss and Young, all sutures initially have end-to-end forms but with increasing age the bony sutural surfaces become more irregular because of an increase in number and length of the bony interdigitations [43, 44].

7.4.1 Grading System of Closure

The degree of sutural/synchondrosis closure refers to the reduction of width of the gap seen between adjacent bones leading to the sutural/synchondrosis fusion. The term 'closed' is a pure radiologic description of the condition in which two or more adjacent bones meet with each other without any patency in their borderline with or without ossification. The term 'fused' means status of ossified suture among closed sutures [36].

A grading system for sutural and synchondrosal closure assessed on CT scans was introduced by Madeline and Elster [45].

Grade 1: No closure along the whole length; all margins of the suture are clearly defined and separated on all parts.

Grade 2: Partial or intermittent closure; some parts are suspicious of bony bridging, but the mean part is still clearly defined and separated.

Grade 3: Advanced closure; bony bridging can be clearly identified in some parts of the suture or synchondrosis.

Grade 4: Complete fusion of the suture/synchondrosis with remaining sclerotic margins.

Grade 5: No sclerotic margins are present.

The time course leading to the ossification process and the duration of these grades are heterogeneous both for each sutures/ synchondrosis and along the entire length or depth of the suture/synchondrosis [46] (Table 7.1 and Figs. 7.5 and 7.6).

Table 7.1 Grading system for sutural and synchondrosal closure assessed on CT (Madeline and Elster)

Grade	
1	NO CLOSURE along the whole length; all margins are clearly defined and separated.
2	PARTIAL OR INTERMITTENT CLOSURE; some parts are suspicious of bony bridging, but the mean part is still clearly defined and separated.
3	ADVANCED CLOSURE; bony bridging can be clearly identified in some parts of the suture or synchondrosis.
4	COMPLETE FUSION with remaining sclerotic margins.
5	COMPLETE FUSION without sclerotic margins.

7.4.2 *Degree of Interdigitation: Sutural Patterns*

Sutures are coded according to their morphology and sinuosity and they depend on their degree of interdigitation. Interdigitations development depend mainly on the activity of osteoblasts and osteoclasts. Over time, the bony sutural surfaces become more irregular because of an increase in number and length of the bony interdigitations [47].

The suture patterns seen in the ectocranial and endocranial surfaces are the result of the interdigitation process observed on a large number of sutures in human skeletons [27]. Suture patterns are individual like finger ridges; each suture has a complexity of large numbers of serrations, denticulations and the irregularities with a very high degree of randomness resulting in an almost infinite diversity of suture patterns. Chandra Sekharan classified suture patterns into 10 types [48] but other authors simplifyed the classification of sutural area morphology into a total of five types: straight when it is linear, wavy when it is undulated, serrated when it is tooth like, denticulated when its terminal ends are expanded or fan like and patternless when it reveals evidence of fusion with interdigitations disappearance. The first 4 patterns proved to be signs of closed suture while the last one is a sign of sutural fusion [49, 50].

Suture patterns are plastic during the juvenile stage and they undergo significant remodeling during growth into adulthood. It indicates that the growth and remodeling of the cranial sutures causes alterations in the sutural morphology; the onset of adulthood is suggested as the age for stabilization of suture patterns [50].

Although CT imaging allows a better accuracy in the assessment of overall sutural morphology, influenced both by the sutural patterns seen in the ectocranial and endocranial surfaces, to date, there was lack of uniformity in the assessment of the radiological suture pattern. Broadly serrate type suture is the most predominant pattern in juvenile skulls while denticulate type is the most predominant pattern in adult skulls. However, different morphologies can be observed not only among the sutures but also within the same suture [43] and it might depend on the time course of sutural closure (Figs. 7.5 and 7.8; Table 7.2).

Minor sutures and synchondroses patterns are lacking in literature probably because of their course and reduced length.

7.5 Sutures Fusion: Process and Timing

For an early diagnosis of skull deformity, it is important to know not only the timing of complete fusion of the cranial sutures but also the sequential closure process itself [36].

Most reports describing physiologic suture closure observed only the time of completion of suture closure defined as completely fused sutures or suture closure grade 4. Quantitative degree of closure according to the age has not been fully

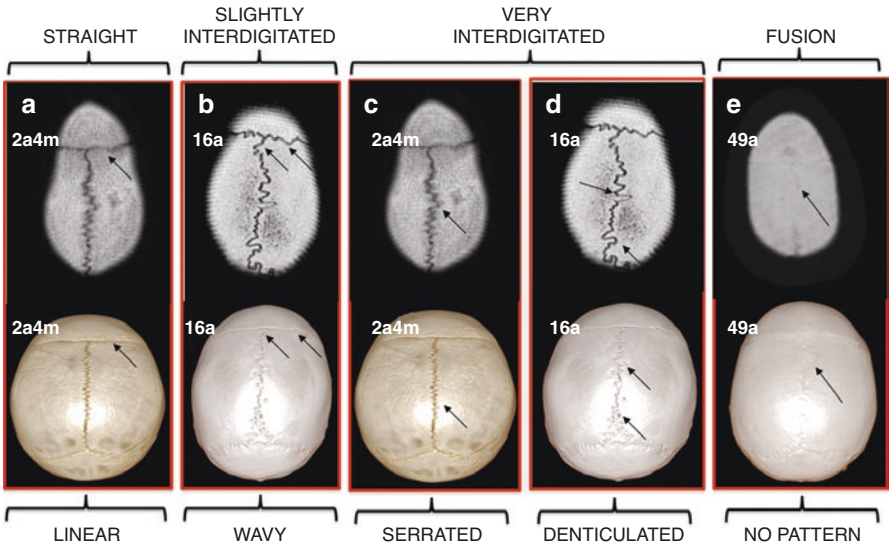

Fig. 7.8 Degree of interdigitation and representation of sutural patterns of sagittal and coronal sutures on 2D and 3D CT. Note the increasing in number and length of the bony interdigitations with increasing age during the sutural closure process (**a**–**d**) until the fusion process (**e**)

Table 7.2 Spectrum of suture patterns observed during growth from adolescence age to adulthood age

	Sutural pattern		
Suture	Adolescence	Early/middle adulthood	Late adulthood
Metopic	No pattern	No pattern	No pattern
Sagittal	Wavy	Wavy/serrated/ denticulate	Serrated/denticulate/no pattern
Coronal	Linear/wavy	Wavy/serrated	Serrated/no pattern
Lambdoid	Linear/wavy/ serrated	Wavy/serrated/ denticulate	Serrated/denticulate/no pattern
Parieto-Squamous	Linear/wavy/ serrated	Wavy/serrated/ denticulate	Serrated/denticulate/no pattern

Aging is associated with increasing suture complexity but different morphologies may exist within a given suture

described yet, especially for sutures which usually complete their ossification process at adulthood [36, 51].

There is a variability in the timing of closure among different sutures and synchondrosis beginning from the birth until adulthood to approximately 30–40 years of age [36]. Moreover, previous studies have demonstrated that closure began at different times on the endo- and ecto-cranial surfaces because the closure progresses slowly from the internal side to the external surface [27]. The use of CT provides more details and it is more accurate for the assessment of timing course of closure and fusion.

Specifically the metopic suture normally ossifies between 3 and 11 months [52]; normal closure of the metopic suture begins at the level of the frontal eminences and proceeds superiorly to the bregma. A small supranasal portion of the metopic suture remains unobliterated until the sixth year of life, although some parts of the suture may persist into adult life [53]. All the other vault sutures (sagittal, coronal and lambdoid) normally do not fuse until adult life, at approximately 30–40 years of age; there is a sequence to cranial suture closure, beginning with the sagittal suture, then the coronal suture, the lambdoid suture and finally the squamosal suture soon after [27].

The average width of the sagittal suture at birth is 5.0 mm ± 0.2, narrowing significantly to 2.4 mm ± 0.1 by 1 month of age and narrowing further over time.

The closure of sagittal suture begins in adolescence at the point of intersection with the lambdoid suture and continues anteriorly; typically it is completed between 21–30–years of age but sometimes finishes at middle adulthood [54].

The average width of the coronal sutures at birth is 2.5 mm ± 0.1, narrowing significantly to 1.3 mm ± 0.1 by 1 month of age. Similar to the sagittal suture, the coronal suture remains unfused throughout childhood, its closure begins in adolescence, typically it is completed by 24 years of age but it may last until 38 years. The fusion of these sutures usually begin inferiorly and proceed superiorly to the bregma [33, 54].

The lambdoid suture remains open during childhood, begins to close in adolescence and typically close between 26 and 40 years of age [33]. The closure of parieto-squamosal suture begins at 30 years and it is reported not completely close until 60 years of age [55–57].

Among minor sutures/synchondroses of ACF, the closure of frontoethmoidal sutures occurs by 7 years of age, the closure of sphenoethmoidal suture begins at about 2 years and it reaches a grade 4 of fusion by the age of 15 years. The narrowing of frontosphenoidal sutures begins after 6 months whereas closure begins at 5 years and it becomes completely fused in all patients older than 15 years. Residual sclerosis along both the frontosphenoidal and sphenoethmoidal sutures is commonly seen throughout adolescence [58].

Among minor sutures/synchondroses of MCF, the closure of sphenoparietal (spa) and sphenosquamous sutures typically occurs by 6 years of age but it can take more time until 10 years, closure of parieto-mastoid sutures may take until 60 years of age, whereas closure of anterior intrasfenoidal synchondrosis begins at about 1–2 months reaching a grade 5 of fusion by age 3–5 months and sphenopetrosal (sp) synchondrosis remains cartilaginous and mobile throughout entire life [58].

Among minor sutures/synchondroses belonging to PCF, the closure of occipito-mastoid sutures typically begins approximately between 16 and 22 years of age and it ends at around 80 years. Posterior synchondroses show a global scheme of ossification: it starts from posterior interoccipital synchondroses (PIOS), followed by anterior interoccipital synchondroses (AIOS), spheno-occipital synchondrosis (SOS) and finally it ends with petro-occipital synchondroses (POS). The closure of posterior intra-occipital synchondrosis begins by 1st-2nd year and it ends by 4th-7th year, the anterior intra-occipital synchondrosis begins to ossify by 1st-2nd year

and it ends by 7th-10th year; the fusion of the spheno-occipital synchondrosis occurs between the 17th and 20th year, while the temporo-occipital or petro-occipital synchondroses exhibit residual cartilage throughout adolescence [45, 58] (Fig. 7.9 and Table 7.3).

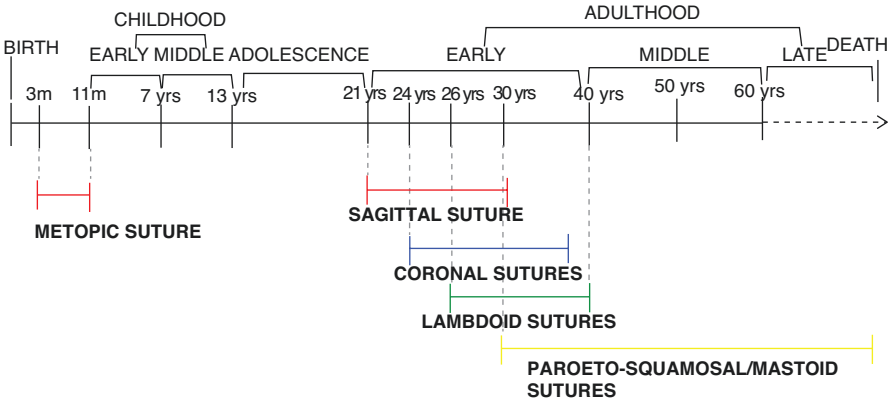

Fig. 7.9 Time course of major sutures fusion. Red: sutures of the sagittal arch; blue: sutures of coronal arch; green: sutures of lambdoid arch; yellow: sutures of parietosquamosal arch

Table 7.3 Timing course of minor sutures and synchondrosis fusion

SUTURAL ARCHES	MINOR SUTURES/SYNCHONSDROSES	GRADE 2	GRADE 4-5
SAGITTAL ARCH	Frontoethmoidal sutures	3 months	3-7 years
CORONAL ARCH	Sphenoethmoidal sutures	1-2 years	15 years
	Frontosphenoidal sutures	2-4 years	15 years
	Sphenoparietal and sphenosquamous sutures	2-7 years	7-10 years
	Sphenopetrosal synchondrosis	No evidence of fusion life time	
	Anterior intrasphenoidal synchondrosis	1 month	3-5 years
PARIETO-SQUAMOSAL ARCH	Parieto-mastoid sutures	30 years	60 years
LAMBDOID ARCH	Occipito-mastoid sutures	16-22 years	80 years
	Posterior intra-occipital synchondrosis	1-2 years	4-7 years
	Anterior intra-occipital synchondrosis	1-2 years	7-10 years
	Spheno-occipital synchondrosis	5-7 years	17-20 years
	Temporo-occipital or petro-occipital synchondrosis	2-5 years	No fusion life time

Red: sutures belonging to anterior cranial fossa; blue: sutures and synchondroses belonging to middle cranial fossa; green: sutures and synchondroses belonging to posterior cranial fossa

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Chapter 8
Variations in Sutural Anatomy of the Skull

Peter C. Oakes and R. Shane Tubbs

The human skull is composed of numerous sutures (*L. sutura*, seam), including those of the face, basal skull, and calvaria (Fig. 8.1). The majority of these sutures are paired and fusion of these sutures are often delayed until after birth, providing an opportunity for skull growth, and perinatal malleability while passing through the birth canal. Understanding the possible variations of sutural patterns is important for multiple reasons including the following: adjusting their use as a reference point during surgery, indications of other underlying pathology, and possibly most importantly, distinction of sutural variants from traumatic skull fractures [1]. This chapter seeks to address the most common variations in sutural anatomy, and their clinical importance.

P. C. Oakes (✉)
Department of Internal Medicine, Louisiana State University School of Medicine, New Orleans, LA, USA

R. S. Tubbs
Department of Neurosurgery, Tulane Center for Clinical Neurosciences, Tulane University School of Medicine, New Orleans, LA, USA

Department of Neurology, Tulane University School of Medicine, New Orleans, LA, USA

Department of Structural and Cellular Biology, Tulane University School of Medicine, New Orleans, LA, USA

Department of Surgery, Tulane University School of Medicine, New Orleans, LA, USA

Department of Neurosurgery and Ochsner Neuroscience Institute, Ochsner Health System, New Orleans, LA, USA

Department of Anatomical Sciences, St. George's University, Grenada, West Indies

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Fig. 8.1 Disarticulated coronal and sagittal sutures

8.1 Metopic Suture Variations

The metopic suture is located between the two frontal bones prior to their fusion (Fig. 8.2). Persistence of this suture beyond infancy is termed metopism (Fig. 8.3), and is seen in differing frequencies depending on the patient's genetic make-up (8.7% in Caucasians, 5.1% of Asians, 1.2% of sub-Saharan Africans) [2]. Some have considered a persistent metopic suture as a dominant Mendelian trait [3]. The extent of metopic suture persistence is very variable. Partial persistence of the suture occurs most often in the inferior portion of the frontal bone [4]. Occasionally, an inverted Y shaped sutural pattern has been observed in those with metopism. The persistent suture can deviate to one side and when present, is often associated with small frontal sinuses [3]. Emissary foramina might be found along the obliterated metopic suture and arachnoid pits might be found along the internal surface of the region of the metopism.

The timing of the closure of this suture has also been well documented. In one study, it was found that all subjects over the age of 16 months had achieved fusion of this suture, with the median age for commencing fusion at 5 months, and completion of fusion at approximately 8 months [3]. There is some discrepancy in whether there is a sex imbalance in this condition, as some report the occurrence as equal and others an increased frequency in males [1, 4].

The persistence of this suture has been associated with several disease processes. Rarely, persistence of this suture has been found concomitantly with partial or

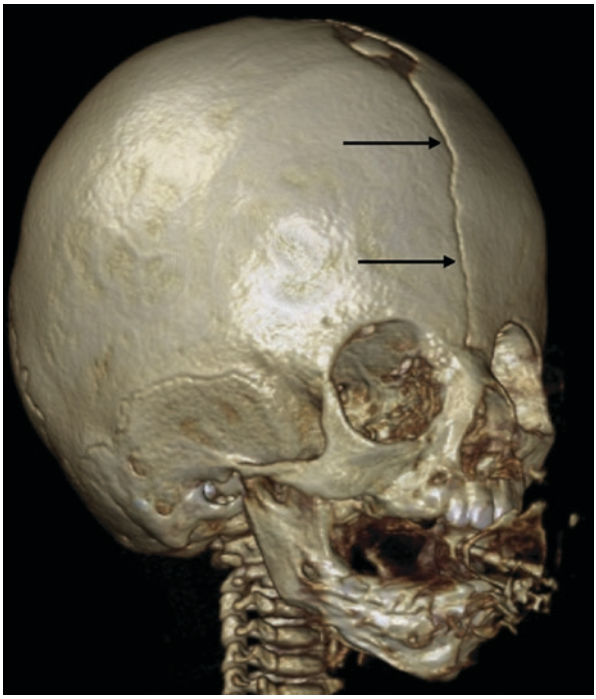

Fig. 8.2 Child with bilateral coronal synostosis and persistent metopic suture (arrows)

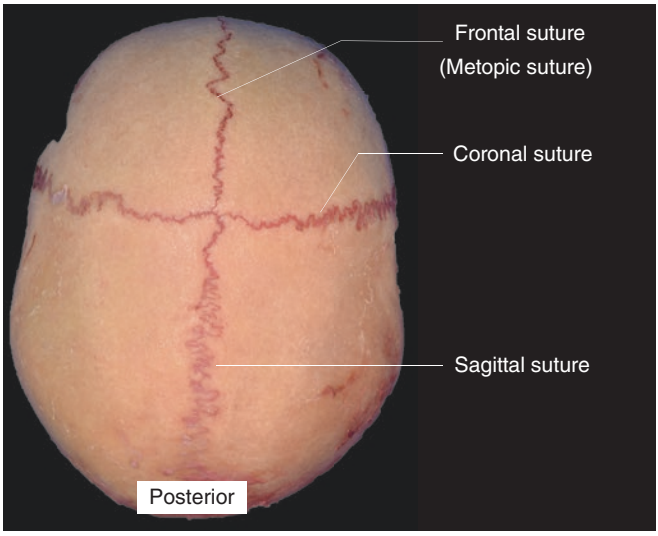

Fig. 8.3 Persistent metopic suture in an adult

complete absence of the clavicle in a condition known as cleidocranial dysostosis [2]. In this condition, there are often many wormian bones noted in the metopic suture as well with some often found at the junction of the suture and nasion [1]. Additionally, other hypostotic traits such as tympanic dehiscence have been noted

in the presence of metopism [1]. The suture is also disproportionately (18%) present in children with intellectual disabilities, but its persistence does not correlate with the presence of hydrocephalus [1].

A short vertical or transverse suture may be seen just inferior to the frontal tuberosities and these are thought to represent a remnant of the metopic fontanelle [3]. The metopic fontanelle can persist into childhood in association with cleidocranial dysostosis.

Metopic ridges (Fig. 8.4) should be distinguished from persistent metopic sutures. These bony protuberances are common in infancy and in most children, disappear. In some, however, these ridges are persistent due to metopic synostosis and can result in trigonocephaly.

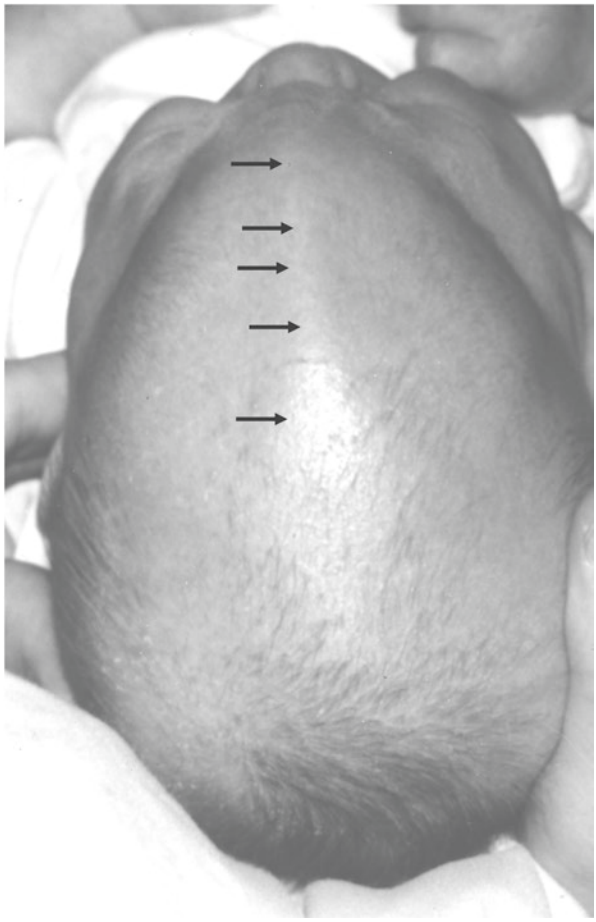

Fig. 8.4 Metopic ridging in an infant (arrows)

8.2 Epipteric Bone

This bone found at the pterion (junction of the parietal, frontal, sphenoid, and temporal bones) has a wide variety of shapes and sizes [4]. These bones are also known as pterion ossicles, epipteric bones, or Flower's bones) [4]. One further subclassification of this bone is into either a complete or true epipteric bone (os epiptericum verum) which touches all four of the previously mentioned bones, or an incomplete or spurious epipteric bone (os epiptericum spurium) which does not share a border with all four of these bones [1]. The presence of this bone is increased in females, and has been noted to occur more unilaterally than symmetrically [1]. This bone is also observed more frequently in those with an Inca bone than in patients who do not possess the structure [1].

8.3 Coronal Suture

The coronal suture forms the posterior border of the frontal bone and the anterior border of the parietal bones, with the junction of all three termed the bregma where occasionally bones can form instead of the anterior fontanelle (Fig. 8.5). Bregma ossicles are positively related to the presence of sagittal and lambdoid ossicles [1]. The coronal suture can have simple and complex forms (Fig. 8.6).

8.4 Interparietal Bone

In rare circumstances, the parietal bones will fail to fuse completely [2]. This can be accompanied by the presence of an Inca bone (also known as an interparietal bone or Goethe's ossicle) or a preinterparietal bone (Fig. 8.7) [2]. The Inca bone gains its name from the triangular design often noted in that of Incan architectural design. It is a rare finding, with occurrence ranging from 0.8% to 2.5 % [4]. One study found that the interparietal bone had an approximate incidence of 1.6%, being singular in 0.4% of people and multiple in 1% [2]. The preinterparietal bone was present in 0.8% of subjects, being single in 0.4% of patients and multiple in 0.4% as well [2]. Occasionally, the parietal bone is composed of two parts divided by a horizontal suture termed the subsagittal suture or accessory intraparietal suture. If this horizontal suture occurs, it more often occurs bilaterally than unilaterally, but when it does occur unilaterally, it is more often on the left side [1]. An even more rare variation is a vertical division of the parietal bone into three or four smaller bones [2]. If this occurs, there is often an os bregmaticum (Fig. 8.8) or os pterion that forms in the

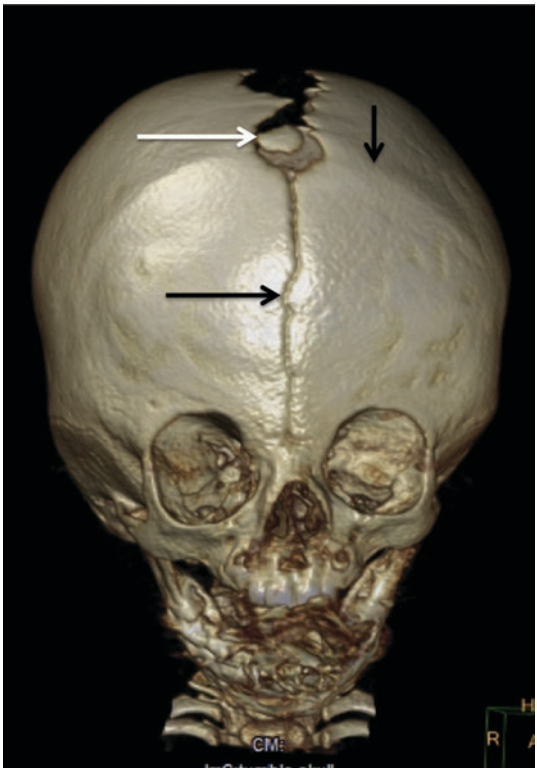

Fig. 8.5 Child seen in Fig. 8.2 who also has a sutural bone (white arrow) at the anterior fontanelle. The synostotic left coronal suture is seen at the vertical black arrow and the persistent metopic suture at the horizontal black arrow

Fig. 8.6 Skull with artificial cranial deformation noting a simple (black arrows) and complex (white arrows) parts of the left coronal suture

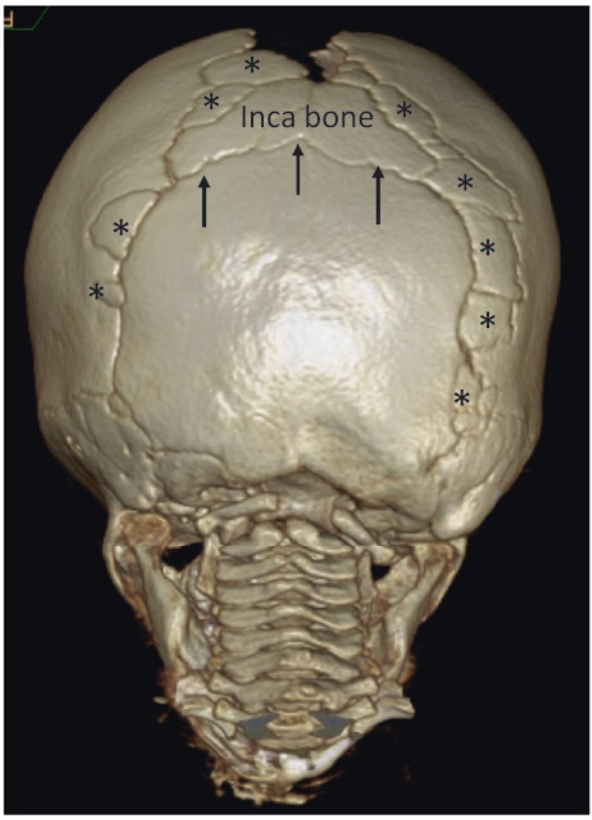

Fig. 8.7 Posterior view of the skull on 3D CT noting a transverse occipital suture (black arrows), Inca bone, and many sutural bones (asterisks) within the sagittal and lambdoid sutures

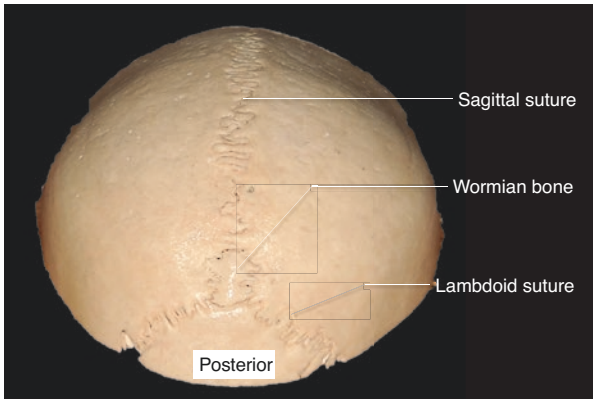

Fig. 8.8 Sutural bone at the junction between the sagittal and lambdoid sutures

space of the anterior fontanelle and may fuse with one of the parietal of frontal bones. Finally, an oblique accessory suture in the location of the bregma, lambda, or asterion is also possible [1]. The frequency of this split parietal bone is quite low however, with no frequency above 1% reported [1].

When a division of the parietal bone occurs, there are numerous associated anomalies that have an increased likelihood to occur. Hydrocephalus and dystosis cleidocranialis is seen with an increased frequency. Other anatomical variations include the presence of numerous ossa suturarum, persistence of other sutures including the metopic or mastoid sutures, a sutura mendosa, and obliteration of normally observed sutures.

8.5 Sagittal Suture Variations

The sagittal suture is located between the two parietal bones, and there are some rare variations that can occur in this anatomy. One is the presence of a sagittal ossicle. This is a rare finding, however when it does occur, the structure often stretches out along the entire sagittal suture. This occurs more frequently in women, and in young adults when compared to the elderly [1]. The sagittal suture can be absent without signs of sagittal synostosis (Figs. 8.9, 8.10, 8.11, and 8.12).

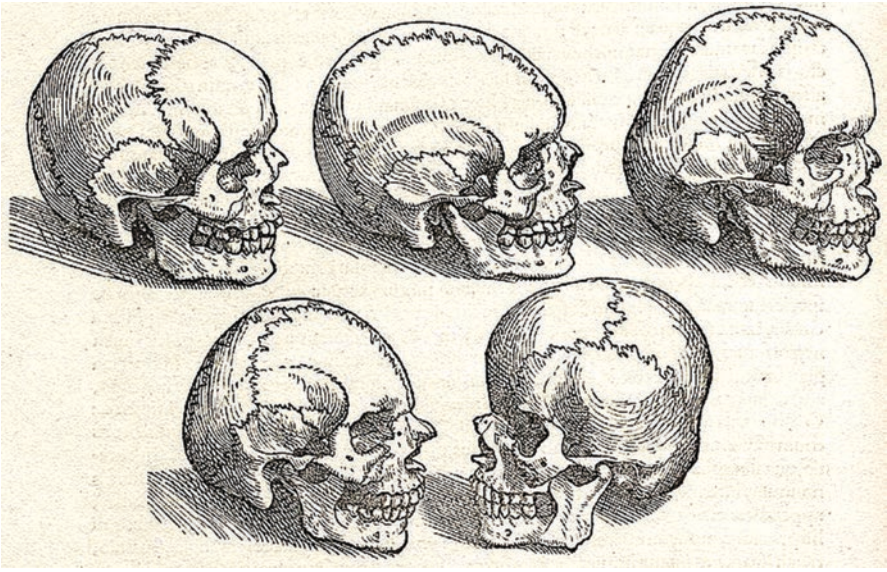

Fig. 8.9 Vesalius' drawing illustrating skull and sutural variants. Note the upper middle image with no coronal sutures and continuation of the sagittal and metopic sutures, the lower left image with metopism, and the lower right image with a parasagittal suture

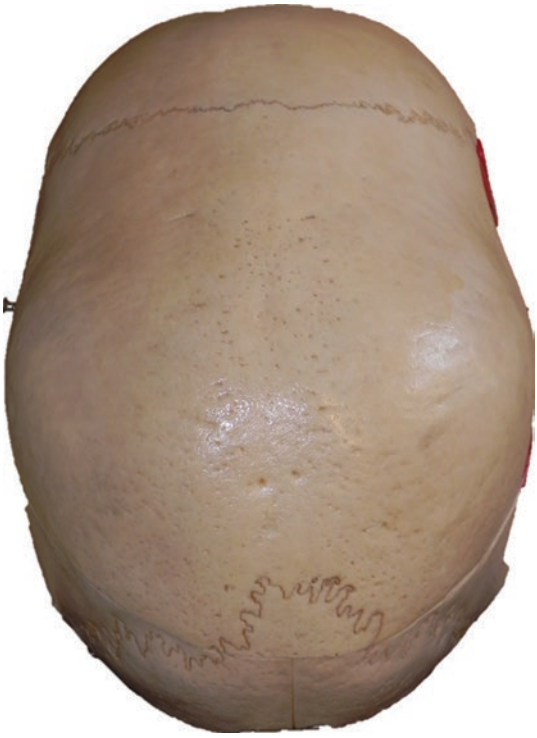

Fig. 8.10 Adult skull with absence of the sagittal suture but without scaphalocephaly

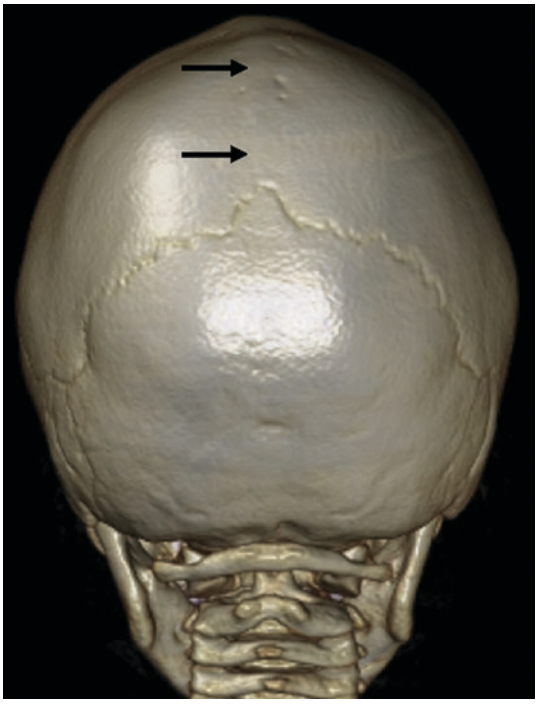

Fig. 8.11 3D CT of a child noting absence of the sagittal suture (arrows)

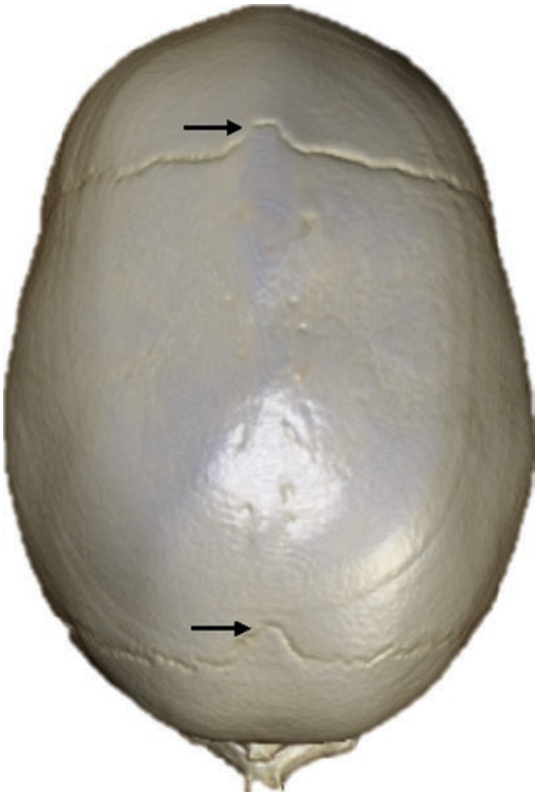

Fig. 8.12 Absence of the sagittal suture with unusual anterior deflection of the coronal suture (upper arrow). The lower arrow marks the midline portion of the lambdoid suture

One case report found the instance of an extension of the sagittal suture into the occipital bone with subsequent synostosis (Fig. 8.13) [5]. The first report of its kind in the literature, the article further stated that the child had bifrontal bossing and premature closure of the anterior fontanelle. At the age of 2 months, her head circumference was >95th percentile, without any elongation of the skull, but with the presence of biparietal narrowing. One additional finding noted was the thickening of the lambdoid sutures, which possessed increased ridging when compared to those of other children [5].

An extremely rare paramedian longitudinal suture also known as the parasagittal suture has been reported [6]. In fact, Vesalius depicted this variant suture (Fig. 8.9). Lang illustrated a case of this suture with associated metopic suture and multiple sutural bones [6].

The sagittal suture may be seen to be out of alignment with a metopic suture when the latter is present i.e., misalignment of metopic and sagittal sutures [7]. The sagittal suture may present with a simple or complex form i.e., linear versus zig-zag. Posteriorly, the suture may deviate significantly to one side.

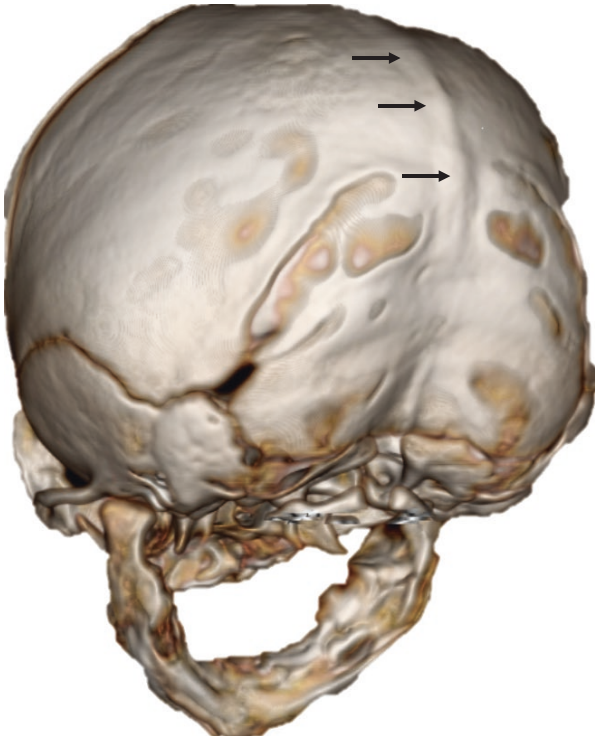

Fig. 8.13 Sagittal synostosis (arrows) extending posteriorly into the occiput

8.6 Variation in the Sutures of the Temporal Bone

The variations of the squama temporalis can range from its being absent from a patient's skull to being bipartite to divided into up to four parts [2, 7]. The anterior edge of the squama may form a bony growth that projects into the space between the sphenoid and parietal bones, reaching all the way to the frontal bone [2]. Another aberrant finding that is sometimes seen is the persistence of the suture between the squama and the mastoid process into adulthood [2]. The temporal squama can be partially bipartite (Fig. 8.14) resultingin extension of the sphenofrontal sutures [7].

The petrosquamous suture, another component of the temporal bone, has been noted to persist into adulthood in some individuals. This can sometimes occur in the form of either a complete or incomplete horizontal suture, or even more rarely, a vertical suture which when present, gives the appearance of a "divided mastoid" (Fig. 8.15) [7]. An incomplete division is more frequent, and often occurs in the setting of multiple wormian bones [4].

The squamomastoid suture is a component of the petrosquamous suture [1]. Disappearance of this structure occurs in 3.85% of children by age one, 53.9% at age two, and in two thirds of older adolescents [1]. Persistence of the suture has

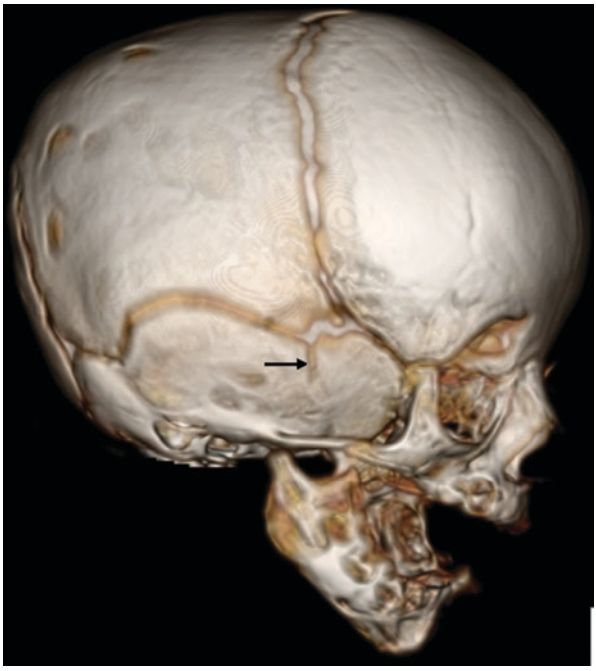

Fig. 8.14 Bipartite right temporal bone (arrow)

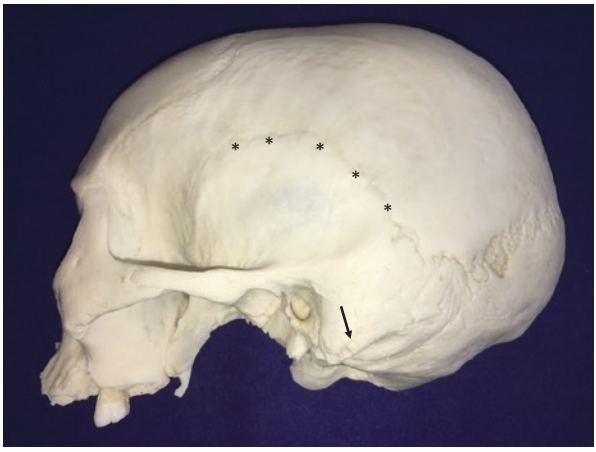

Fig. 8.15 Flattened left squamosal suture (asterisks) and "split" mastoid process (arrow)

been reported from 1.5% to 5.7%, and in very rare cases, this has been reported to allow direct infection from the tympanic antrum [1]. The suture is also an important landmark for surgery involving the facial nerve. The literature is divided on whether there is a higher prevalence in males or equal presence in both sexes; however, when it does occur, it is usually found bilaterally. In the case of unilaterally, the left side seems more affected [1].

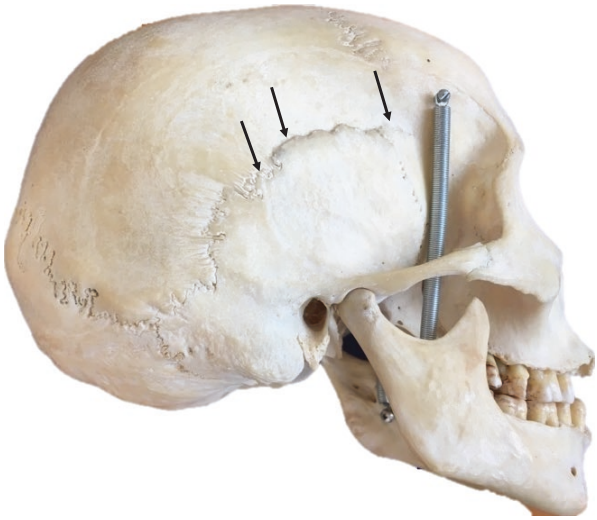

Fig. 8.16 Elevated right squamosal suture (arrows)

The squamosal suture can be flattened and indistinct (Fig. 8.15) or raised and more prominent (Fig. 8.16).

8.7 Lambdoid Suture Variations

The patterns of the lambdoid suture are often the most diverse of anywhere on the skull [1]. Lambdoid ossicles, or bones that occur within the sutures themselves, occur relatively frequently throughout the entire length of these sutures and in fact, sutural bones occur most frequently in the lamboid suture (Fig. 8.7) [3]. Interestingly, the sutural bones here can involve only one table of the calvaria. Most authors report that such ossicles occur more frequently in males, and in a symmetric fashion with either no preference of laterality when unilateral or a slight tendency to occur more on the right [1]. These ossicles are observed more frequently in the presence of an Inca bone than without the structure [1]. The lambdoid suture may present with a simple or complex form i.e., linear versus zig-zag (Figs. 8.7 and 8.10).

The asterion is a region of the skull defined by the parietomastoid, occipitomastoid, and lambdoid sutures, and in terms of calvarial bones, between the superoposterior mastoid, and lateral portion of the squama of the temporal bone [1]. Ossicles in this location have been found to be hereditary in nature. In terms of epidemiology, males of sub-Saharan African descent have been demonstrated to have an increased incidence of these ossicles. In the event there is only one such ossicle, there is no clear preference of laterality [1].

8.7.1 Os Incae

As mentioned previously, the Inca bone (Fig. 8.7) occurs in an interparietal location, and can be further subdivided. In the event that the transverse suture runs through the occipital squama at the level of the highest nuchal line, any portion superior to this border is termed a complete Inca bone. In the event that one or more vertical sutures subdivide the bone, the result is a bipartite, tripartite, or multipartite Inca bone [1]. In the event of a transverse occipital suture, a partial Inca bone is expected. The presence of this bone is most often attributable to genetic inheritance, with a calculated penetrance of approximately 50% [1]. Between the sexes, the bone is seen more frequently in males than females, and occurs more often in a "classical" than mentioned "variations." [1] Its presence indicates failure in the fusing of the occipital squamae [1].

8.8 Mendosal Suture

The lateral edges of the transverse occipital sutures may persist beyond infancy in an anatomical variation that has been termed the mendosal suture (Fig. 8.17). It is this suture that continues on to form the intraparietal bone described above as the Inca bone. It most frequently traces its origins from the asterion (68% frequency), below the asterion (21% frequency), or in very rare cases, above it [1]. Most often, it is located above the transverse groove of the occipital squama [1]. The length of this structure usually is 30 mm or less [1]. In its course, it has never been seen to intersect with the occipital squama [1]. Presence of this suture beyond the age of

Fig. 8.17 Fetal skull with right mendosal suture (black arrow), right lambdoid suture (blue arrow), and asterion (asterisk)

two is required before referring to the structure as the mendosal suture [1]. There is no increased frequency in one gender when compared to the other, and there is no preference of laterality when it occurs asymmetrically [1].

8.9 Os Japonicum

The occurrence of a splitting of the zygomatic bone either completely or incompletely into two parts has been termed the os japonicum due to the frequency with which it is seen in those of Japanese descent (7%) versus those of descent from other parts of the world (2.5–6.5%) [1, 2]. The occurrence of this variation is increased in females when compared to males [4]. The fissure splitting the bone in two may occur in a vertical, horizontal, oblique, and arched fashion, with horizontal being the most common and partial division occurring more frequently than complete [1, 4]. If the os japonicum does occur, it is most often bilateral, and if unilateral, there is no predominance of left over right or vice versa [1]. This bone may even consist of three entities, but this is much less common [2, 4].

8.10 Infraorbital Suture

If present, this suture will travel the length of the orbital canal. It tends to run either on the orbital or facial portion of the canal. If on the facial surface, it tends to run vertically, transversely upwards, or medially [1]. At times, and dependent on the distance of the infraorbital suture from the zygomaxillary suture, the infraorbital suture will join with the zygomaxillary suture in the direction of the infraorbital margin or contact it at one point. Most individuals will have experienced obliteration of this suture in the sixth to eighth decade of life [1]. Females reportedly have a higher occurrence of this suture, and it occurs most often symmetrically [1].

8.11 Transverse Palatine Suture

There is a great deal of diversity in the course of the transverse palatine suture. The suture itself may run transverse or in a convex manner either anteriorly, or more rarely, posteriorly [1]. The most frequent of these is the convex anterior, and the other two have approximately equal incidence [1]. Asymmetry has also been observed, with interposition of maxilla's posterior interpalatine process in some cases [1]. In females, a convex anterior course is noted more frequently, with males having a higher occurrence of a straighter suture [1].

8.12 Miscellaneous Sutural Variations

There are numerous variations in the sutural anatomy of the sub-calvarial skull. The inferior portion of the vomer has been observed to directly abut the intermaxillary suture at times [2]. It has also been seen to participate with the palatine bones to form the hard palate of the mouth [2]. Between the ethmoid and maxillary bones, there is a suture in which a hiatus can be seen that allows communication between the orbital and nasal cavities. The intranasal suture has been noted to be absent when fusion of nasal bones occurs, or it can be divided into multiple parts [2, 4]. A supranasal suture may be present and related superiorly to a persistent metopic suture [7].The lacrimal bone has been observed to be subdivided into various components, at times to the point that it takes the appearance of a net rather than a solid bone [4]. Ossicles can be often found around its periphery. The mandible's coronoid and condylar processes are rarely observed to be joined by a suture of the ramus, each termed sub-coronoid and sub-condyloid sutures, respectively [2]. The zygomaticomaxillary suture can be oriented diagonally and have a straight appearance [7]. The frontozygomatic suture may contain an accessory suture [7]. There may be a frontotemporal suture. A vertical suture can exist rarely in the occipital bone through the external occipital proturbarnce [7]. The sphenooccipital synchondrosis (Fig. 8.18) may be remain open or a trace of it might be visible.

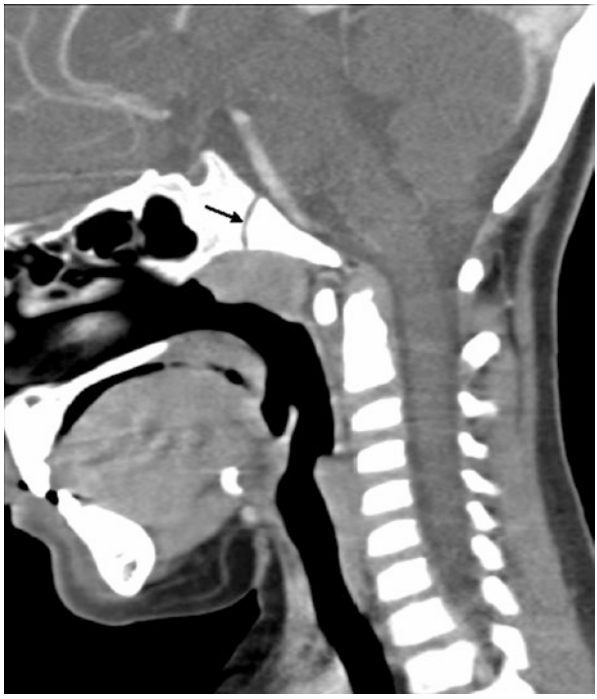

Fig. 8.18 Sagittal CT of an child illustrating the sphenooccipital synchondrosis (arrow)

8.13 Conclusion

Appreciation of the variations of sutures in the human skull allows insight into certain potential problems, among these are: first and foremost, mistaking a skull variation for a fracture. Secondly, awareness of any variation in the skull preoperatively allows for perioperative adjustment of operative plans as well as adjustment of landmarks in the face of such variation.

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Chapter 9
Metopism: Anatomical, Clinical and Surgical Aspects

Hakan Çakın and Saim Kazan

9.1 Introduction and Terminology

The flexible fibrous joints (*sutures*) located between the bones of the skull that surround the brain have two major functions during and after birth. First, during childbirth, they allow the bones in the calvarial roof to cross over each other, except for the bones around the synchondrotic type joints in the skull base, and this helps delivery by reducing the head circumference. Secondly, they allow the skull to grow as the brain increases in volume postpartum. These sutures slowly close at different times after birth. During infancy, the *metopic suture* closes first and disappears naturally; other sutures close much later. However, the metopic suture sometimes does not close during infancy and continues to the sagittal midline, like a joint separating the frontal bone into two symmetrical halves. The presence of the metopic suture in an adult cranium is commonly known as a '*persistent metopic suture'* or '*median frontal suture'* and is considered a normal variant. It can be found as an incomplete (partial) or a complete type. The presence of a complete metopic suture in the adult cranium is called '*metopism*' (Fig. 9.1). Crania with metopic sutures are also referred to as '*crania metopica'* or '*crania bifida'* [1]. The term '*metopic'* means *'in the middle of the face',* from the Greek; *'metopon'* means *'forehead'* [2, 3]. Metopism has anthropological, developmental, and clinical significance [1, 3].

H. Çakın · S. Kazan (✉)
Department of Neurosurgery, Akdeniz University Medicine Faculty, Antalya, Turkey

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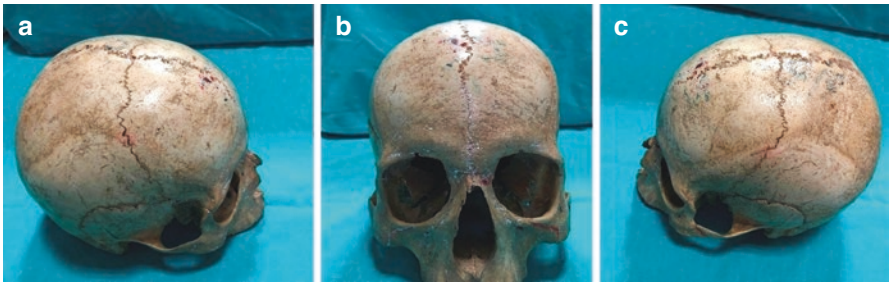

Fig. 9.1 Metopism, persistent complet type metopic suture in an adult skull. In complete type metopic suture, the suture extends from the bregma to the nasion. Right lateral (**a**), frontal (**b**) and left lateral (**c**) views

9.2 Epidemiology

The frequency of metopism differs among geographic populations and between the sexes. Its prevalence is 0.12% in the Malawian skull and 12.8% in the Medieval Oslo skull [1, 4]. Its frequency is reported as 7–10% in Europeans, 4–5% in Asians, 1% in Africans, and 1% in Australians, but some recent studies show the upper and lower limits differ when populations are evaluated individually [5, 6]. For instance, while the frequency of metopism among European populations is given as 7–8%, it is 14.9% in French and Swiss populations and 10.70% among Italians; it is given as 4–5% among Asians, it is 9.1% in the Japanese [7]. These results fall outside the given intervals. Indeed, there can be differences even within the same nation; for example, while the frequency of metopism in Brazil was found to be 2.75%, it was 7.04% among South Brazilians [8]. Researchers attribute this difference to the migration of a large group of Europeans to the south of Brazil. On this basis, it appears that genes are important for the frequencies of metopism among different populations.

Eroğlu et al. [5] examined 487 adult crania aged between 16.5 and 65 years. The skeletons belonged to individuals from twelve different Anatolian populations. They lived in different areas in Anatolia during different historical periods from the Neolithic to the first quarter of the twentieth century. Metopism was not related to cranial form or sex in those populations. In her study, the frequency of metopism in ancient Anatolia ranged from 3.3% to 14.9%, and she commented that this range shows that the inhabitants of Anatolia have been open to gene flow in both the past and the present.

The frequency of metopism differs between the sexes according to the literature. Its prevalance has been reported as between 0.32% and 23.6% in females and between 1.56% and 17.8% in males. da Silva et al. [9] examined 134 skulls, 13 of which had persistent metopic sutures; 61.5% were male and 38.5% female. In some studies, females had significantly higher frequencies of metopism. In contrast, in the Marciniak and Nizankowsky's study, the frequency of metopism was significantly higher in Polish men than women [10]. When all populations are considered

together, the frequency of metopism is 2% higher among females, but this is not statistically significant [5].

9.3 Etiology

All questions regarding metopism focus on why the two halves of the frontal bone do not merge [5]. According to Scheuer et al., the question is: why does the interfrontal suture not merge in a small group of people while it happens in the vast majority of individuals at an early age [11]? Researchers think that the frontal bone is very important for connecting the facial bones to the neurocranial skeleton owing to its morphology and position; therefore, they suggest that the early closing of the metopic sutures, as a result of the finalization of growth in the ethmoid centers, serves to provide maximum stability in the fronto-ethmoidal-nasal suture system [5]. Nevertheless, early closure of the metopic suture (metopic synostosis) can result in serious deformity of the orbital walls and other cranial areas, but metopism is not associated with such deformities.

Vinchon [12] claims on the basis of data from comparative anatomy and paleoanthropology that postnatal persistence of the metopic suture in early hominid species resulted from the risk of dystocia caused by the closed pelvis associated with bipedalism. The predisposing factors for metopism include abnormal growth of the cranial bones, growth retardation, hydrocephalus, heredity and heredo-specific factors, sexual influence, plagiocephaly, stenocrotaphia, scaphocephaly, mechanical causes and hormonal dyfunction [6, 13–15].

The mechanism or etiology of metopic synostosis is still uncertain. However, studies indicate a multifactorial etiology; genetic abnormalities combine with various epigenetic and environmental factors to affect suture development. According to the current literature, several main mechanisms such as bone malformation, brain malformation, obstetric issues causing cranial compression, and fetal head immobilization during late stage pregnancy can change suture biology and fusion development and could also cause metopic synostosis. Many researchers have studied the cellular mechanisms related to sutural growth and fusion. Recent studies show that particular proteins and transcription factors are related to the development of metopic craniosynostosis, including FGFR2, TGBF, RUNX2 and BMP [15].

Manzanares and colleagues found two distinct tissue types along the edges of the metopic suture: secondary cartilage and chondroid tissue [16]. The secondary cartilage appears after the chondrocranium, which is accepted as primary cartilage. It undergoes endochondral ossification with no evidence of direct transformation into chondroid bone and it is not involved in sutural fusion. Manzanares et al. also showed that the edges of the metopic suture are composed of chondroid tissue throughout the period of sutural development [16]. The secondary cartilage in the sutural area allows for passive growth of the frontal bones and is not involved in sutural fusion; it is eliminated by endochondral ossification. The chondroid tissue is responsible for the growth of the frontal bones toward each other and for the first

bridge uniting them. The trabeculae of the chondroid tissue are replaced by lamellar bone as the metopic suture is almost closed. At this stage, continued resorption of new bone along the edges can keep the suture open. Manzanares et al. [16] claimed that this active resorbtion continues from birth to the 17th month of neonatal life in the metopic suture, but Weinzweig et al. [17] reported that it finishes much earlier, enabling the metopic suture to fuse normally by 6–8 months of age. Chaoui et al. examined second and third trimester fetuses by three-dimensional sonography and reported pathological changes in the metopic sutures of 11 fetuses at 17–32 weeks [18]. In those fetuses with abnormal metopic sutures there were other midline abnormalities such as holoprosencephaly, abnormal corpus callosum, or Dandy-Walker malformation.

The metopic suture is reported to remain a suture throughout life in certain circumstances. According to the literature, it persists in adult skulls because of genetic influences. It is not an abnormality, but a consequence of the brachycephalization process, i.e. shortening of the skull. This process has continued from paleolithic times to the present [14].

9.3.1 Anatomical Aspects

The frontal bone is a median and symmetrical bone that occupies the most anterior part of the cranium, forming the forehead (Fig. 9.2). It forms joints with the parietal, ethmoid, sphenoid, nasal, zygomatic, lacrimal, and maxillary bones, thus contributing towards uniting the neurocranium and viscerocranium. The first ossification

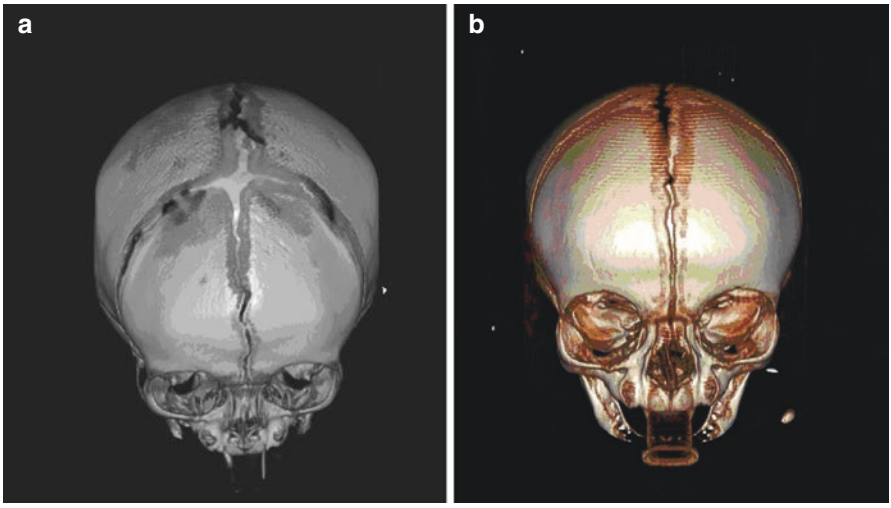

Fig. 9.2 The 3D cranial CT images of a 2-month-old female with a suspicion of premature closure in sutures (**a**) and a 6-month-old female with a head injury (**b**). Metopic sutures that are not fully closed are clear in both cases

centers appear between the sixth and seventh weeks of intrauterine life, and from these the frontal bone begins to grow and develop. In three-dimensional sonography of normal fetal frontal bones and the metopic suture, Faro et al. [19] reported that radial bone expansion begins during the second trimester and the metopic suture starts to close from the glabella to the anterior fontanel during the third trimester.

The metopic suture is a dentate type and leads from nasion to bregma. It normally begins to fuse from the nasion, progressing towards the superior end on the anterior fontanel (Fig. 9.3). Nevertheless, it begins to disappear on the frontal tuber and progresses in both directions. The suture is located almost in the middle of the two frontal bones. It first becomes apparent at the end of the second month of fetal life. It usually closes during the first or second year of life, but the literature reports cases that do not close until 8 years old. There are disagreements among studies about the closure time of the metopic suture. Vu et al. [20] found that the earliest time of metopic suture closure was 3 months of age (33%; 4:12); at 5 and 7 months of age, there is closure in 59% (13:22) and 65% (15:23) of children, respectively. There is no easy way to determine the time of suture closure during neonatal life.

The metopic suture can be complete or incomplete. In the 'complete' type, the suture extends from the bregma to the nasion. If the suture does not extend over this entire distance and occupies only a small area between these two points, it is considered 'incomplete'. Incomplete metopic sutures can be divided into two subclasses: 'nasion incomplete type' and 'bregma incomplete type', depending on the site from which they arise. The nasion incomplete metopic suture type is also described as a linear type, V-shaped and U-shaped (Fig. 9.4). Singh et al. [6] examined 80 crania and found 2.5% complete type and 11.25% incomplete type metopic sutures.

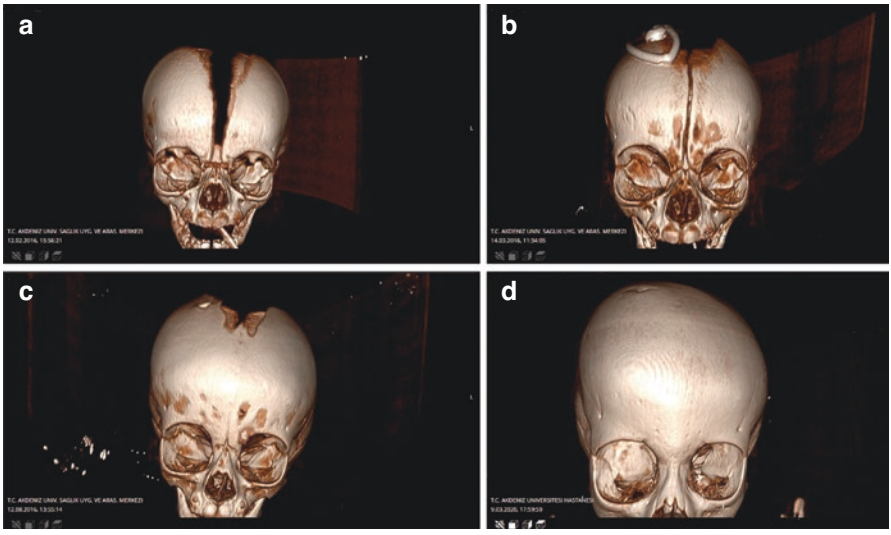

Fig. 9.3 The cranial 3D CT images of a female patient aged 2 (**a**), 3 (**b**), 6 months (**c**) and 4 years (**d**) who we followed up due to premature posthemorrhagic hydrocephalus (a permanent vp shunt performed after temporary subgaleal shunt). It can be seen that the metopic suture was mostly closed at 6 months of age and no longer remains at the age of 4

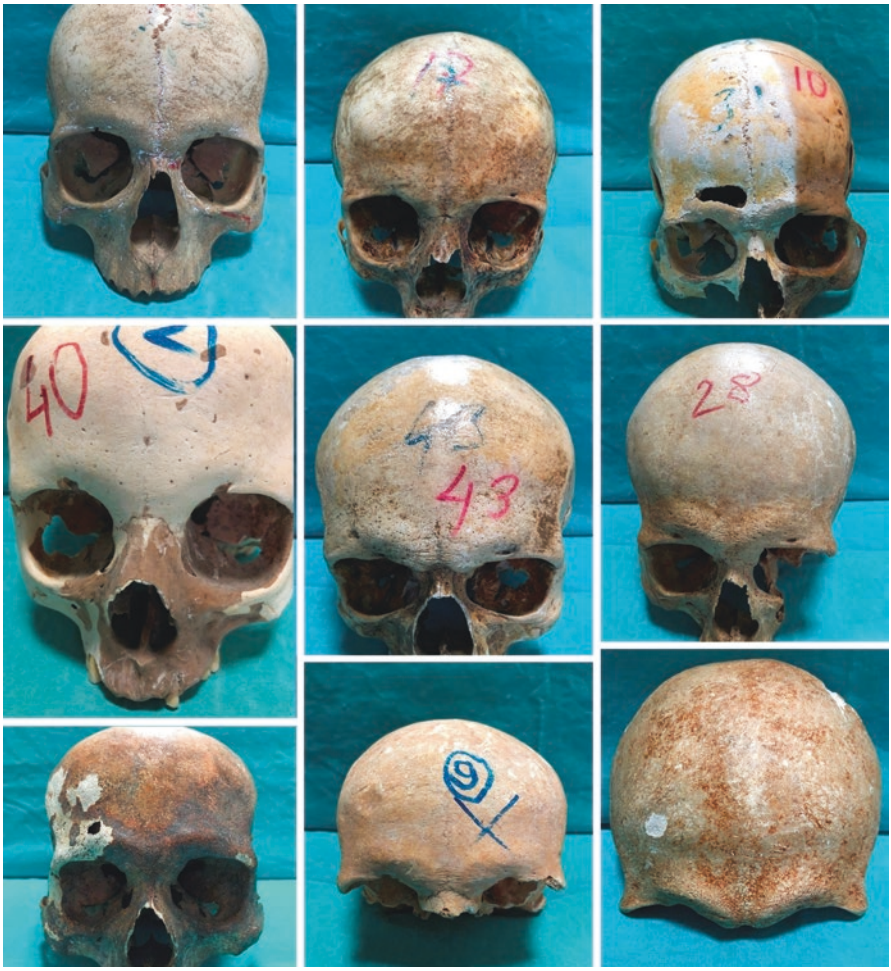

Fig. 9.4 Skulls showing different types of metopic suture

9.4 Relationship Between Metopism and the Frontal Sinus

The frontal bone is described as pneumatic because it has a cavity called the frontal sinus. This cavity is usually radiologically invisble during the first year of life. During childhood, the development of the frontal sinus is influenced by osteoclastic activity in the region of the ethmoidal cells, the two sides developing independently. The morphology of the frontal sinus differs among individuals (Fig. 9.5). During adolescence or early adulthood, the frontal sinuses are fully mature and their sizes and contours remain constant thereafter. Since the radiographic morphology of the frontal sinus is highly distinctive, it is very useful for human identification in complex cases [10, 13, 21, 22].

Studies show that persistence of the metopic suture can prevent frontal sinus development. This is based on the fact that frontal bone growth is necessary for frontal sinus development; it is probably a feedback mechanism. If the frontal bones fail to connect, the metopic suture could become permanent, and the frontal sinuses cannot develop or they develop late. Some studies have confirmed this hypothesis. While the frontal bones and metopic suture develop during intrauterine life, the frontal sinuses appear during the fifth or sixth years postnatally. In view of this time line, it is interesting that there is a connection between these two anatomical

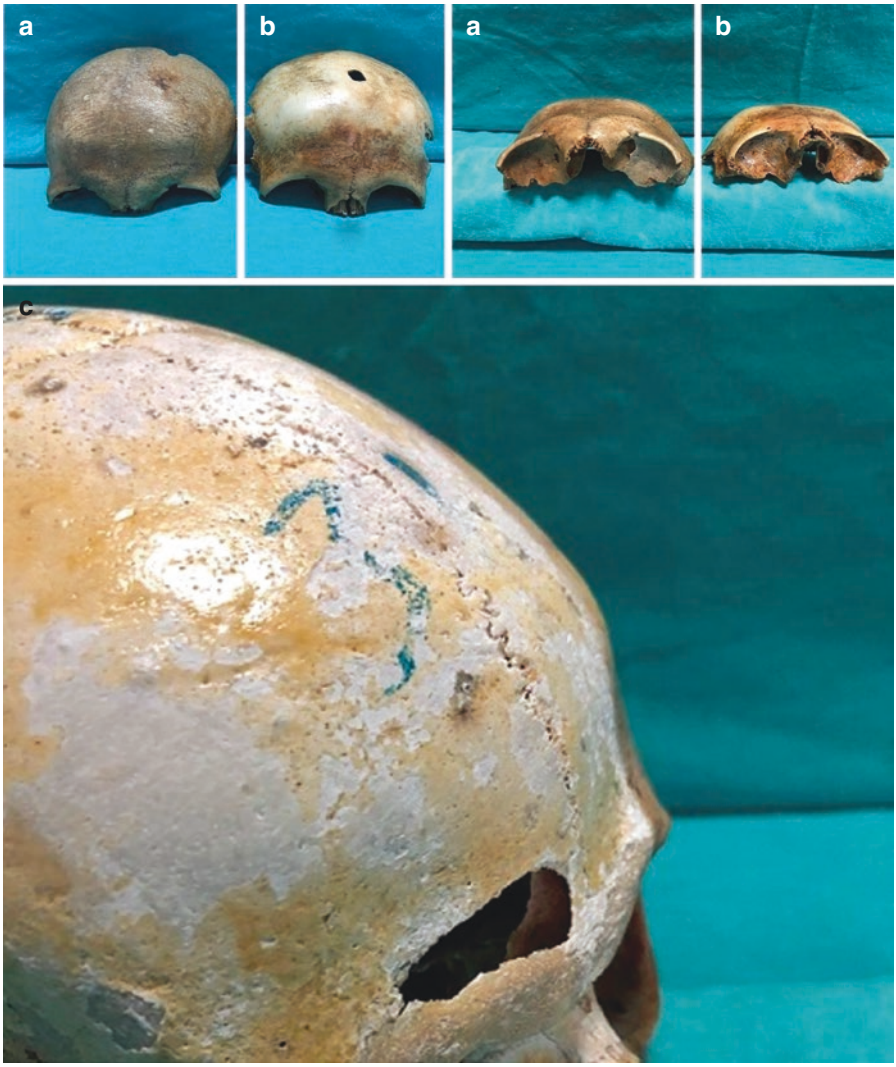

Fig. 9.5 Samples showing the relationship between the metopic suture and frontal sinus. Normal (**a**) and hypoplastic (**b**). Frontal sinuses are seen in the upper frontal bones with partial metopic sutures. Permanent metopic suture and large right frontal sinus on the skull (**c**)

structures. According to this hypothesis, a persistent metopic suture cannot affect frontal sinus development [10, 22] (Fig. 9.5).

However, there is still no consensus about the correlation between frontal sinus development and late closure of the metopic suture. Bilgin and colleagues examined 631 CT and MRI images of patients to evaluate persistent metopic sutures [21]. Sixty-one of the cases revealed persistent metopic sutures (9.7%), and 15 (2.4%) had a persistent metopic suture associated with an atrophied frontal sinus. Among those 15 cases, the frontal sinus atrophy was bilateral in six. There is no significant correlation between metopism and the development of the frontal sinus. Also, when a metopic suture persists, the frontal sinus develops separately on each side, not connecting on the midline, and this can be used to differentiate a persistent metopic suture from a cranial fracture. Bilgin et al. [21] and Nikolova et al. [13] reported that persistence of the metopic suture leads to dominant pneumatization of the left side of the frontal sinus and also underdevelopment or absence of the right side. This condition results in a greater risk of injury to the left sinus than the right during supraorbital craniotomy.

Phylogenetically, the frontal sinus is present only in African great apes and humans. Metopism never occurs in other primates. Thus, investigations of the prevalance of agenesis of the frontal sinus among subjects with metopic sutures have potential applications in human identification in forensic medicine. More specifically, agenesis of the frontal sinuses is important for post-mortem forensic investigations [10, 13, 22].

9.4.1 Clinical Aspects

Sutures are important for the growth of the skull and the brain within it. Persistence of the metopic suture is not necessarily pathological, but its anatomy and incidence are clinically important. Metopism is also significant for paleodemography and in forensic medicine [3].

The metopic suture can be misdiagnosed as a fracture in head injury patients [1, 23]. On X-ray, the sclerotic borders enable the distinction to be made. This helps the radiologist and neurosurgeon to diagnose and treat a head injury patient and is also helpful during frontal craniotomy surgery. This is important because such a misdiagnosis can lead to wrong therapies and unnecessary interventions. Neurosurgeons want to know all about the anatomical configurations of the skull before cranial surgery. A persistent metopic suture should be revealed prior to a frontal craniotomy. Sometimes, X-rays can show a linear fracture better than other tests, so meticulous radiographic examinations including X-rays and 3-dimensional CT should be performed to ensure the correct diagnosis. Some clinical situations can coexist with metopic sutures: visceral inversion, cleft lip, cleft palate, frontal sinus variation, cretinism, abnormal intelligence, and wormian bones [1]. The sutures can be prominent in such diseases as hydrocephalus, cerebritis, brain neoplasms, metastases, leukemia, lymphoma, and increased intracranial pressure. There is no significant relationship between metopic sutures and frontal sinusitis or other frontal sinus pathologies in the literature [21].

Metopic synostosis is the second most common type of craniosynostosis. It can be part of a syndrome such as Crouzon or Saethre-Chotzen, or it can occur nonsyndromically [15, 24–26]. A diagnosis of metopic synostosis is suspected by physical examination and confirmed by radiography. Metopic synostosis is characterized by restricted growth of the frontal bones, resulting in a prominent midline ridge with a triangular forehead and bitemporal narrowing and occipitopariteal widening, the condition described as '*trigonocephaly*' [24, 26]. The calvaria try to compensate for metopic synostosis, resulting in characteristic orbital dysmorphology, with depression of the superolateral orbital rims and ethmoidal hypoplasia; this is called *orbital hypotelorism* (Fig. 9.6).

Trigonocephaly has become more prevalent during recent years. Researchers say that this malformation is the second most frequent isolated craniosynostosis, with an incidence approaching one per 5000 live births [25]. The female to male ratio is 1:3.

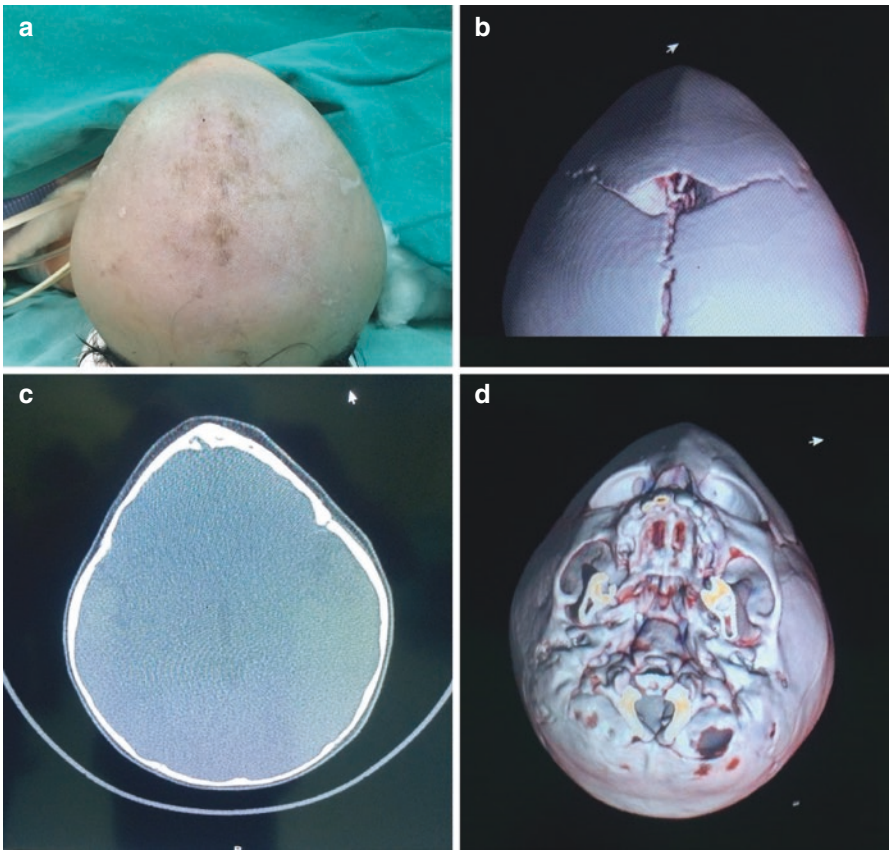

Fig. 9.6 Intraoperative view, demonstrating the characteristic features of a patient with metopic craniosynostosis (**a**). 3D CT reconstruction from the top, demonstrating the characteristic features of a patient with metopic craniosynostosis (**b**). Axial CT slice, demostrating a patient with a prominent metopic ridge and bitemporal narrowing (**c**) 3 D CT reconstruction of the same case demonstrating orbital hypotelorism with a prominent metopic ridge from the ventral view (**d**)

A positive family history is found in 6.8% of patients. The pan-European study in 1997–2006 in which 3240 patients were operated on in seven craniofacial centers revealed that the incidence of isolated suture craniosynostosis was 23%, but other publications from North America reported incidences as high as 27% and 31%. There are multiple explanations for the etiology of trigonocephaly, including increasing maternal and paternal age, changes in prenatal folic acid intake, an increase in syndrome-associated subtypes, and a possible correlation with small uterine anatomy and other deformations. Subjective assessment of moderate and mild subtypes can be related to over-diagnosis and over-treatment for trigonocephaly. Unlike metopic synostosis, trigonocephaly is associated with a high incidence of neurodevelopmental problems. Children with this condition show delayed speech and language development, and cerebral function disorders associated with frontal lobe dysfunction [27]. MRI reveals both cortical and subcortical brain dysmorphology that cannot be completely explained by the abnormal cranial shape (Fig. 9.7).

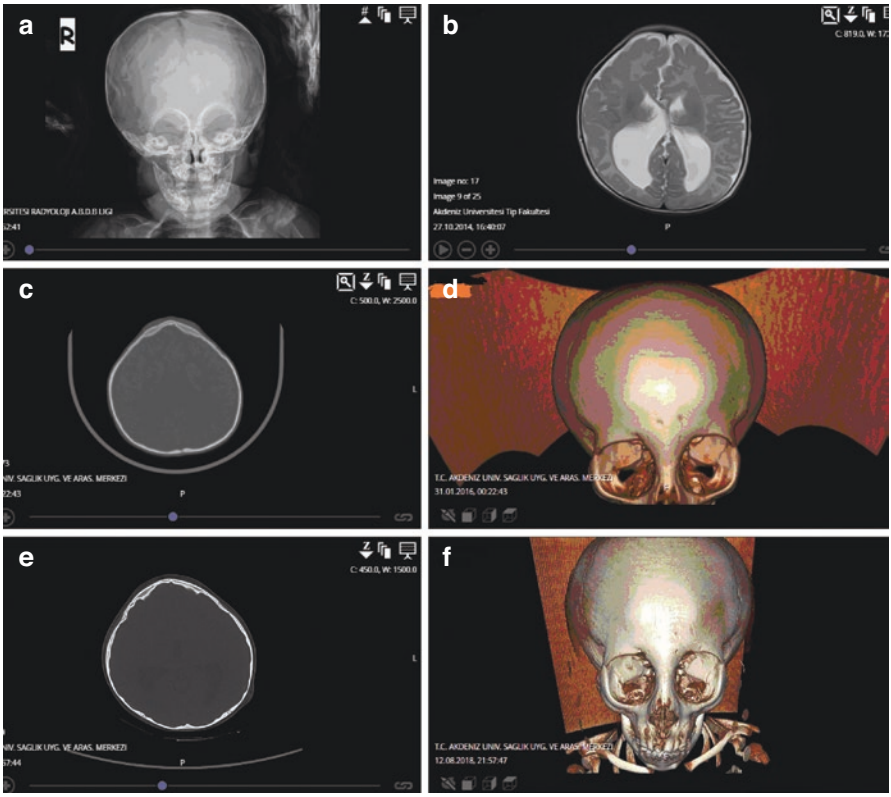

Fig. 9.7 The mild trigonocephalic appearance was present in the physical examination of the case, who was diagnosed with hydrocephalus in the intrauterine period and was born with C/S. There was no clinical or radiological findings about high intracranial pressure. Hypotelorism was prominent on the AP cranial radiography (**a**). There was corpus callosum dysgenesia, colpocephaly and ventricular deformation in cranial MRI (**b**). The cranial axial and 3D CT images of 3 month of age case who we did not performed surgery (**c**, **d**). The cranial axial and 3D CT images of 4 years old case who we did not performed surgery (**e**, **f**)

Small frontal lobes, widened precentral sulcus, frontal subdural space, ventriculomegaly and corpus callosum and cerebellar dysmetria are other structural abnormalities. The pre- and post-operative brain volumes of metopic synostosis patients show no change: gray matter, white matter, and regional and total volume remain similar [15, 24–26].

In clinical practice, besides metopic synostosis, there is a group of children with only a metopic ridge in the frontal midline [2, 28–30]. This can be palpated during examination. The ridge starts from the nasofrontal suture and extends towards the anterior fontanel. Children with a metopic ridge have no features characteristic of trigonocephaly such as hypotelorism or orbital dismorfism (Fig. 9.8). According to Hopper and colleagues [31], metopic ridging is a variant of the metopic suture. Birgfeld et al. [24] reported that the palpable ridge forms physiologically during metopic suture closure and is often confused with premature closure of the metopic synostosis. In the relevant literature, there is no clear definition of metopic suture pathologies.

It is reported that metopic synostosis can be a familial and inherited facial morphology, with no clinical significance in its mildest form. Metopic synostosis and trigonocephaly are not similar clinical entities; the former is a prominent ridging of the metopic suture without features of trigonocephaly. It is a nonsurgical metopic ridge. The definition of trigonocephaly is a surgical form of metopic synostosis. Metopic synostosis is a suture pathology, but trigonocephaly is a clinical problem (Fig. 9.9). Weinzweig et al. [17] reported that an endocranial ridge was rare in synostotic patients, but a 'metopic notch' was diagnostic of premature suture fusion; it was seen in 93% of synostotic patients but in no nonsynostotic patients. In addition to the typical clinical and radiological findings, this radiological finding could help in the differential diagnosis between metopic synostosis and metopic ridge. Corrective surgical intervention is not applicable to simple metopic synostosis children without the typical clinical or radiological features of trigonocephaly.

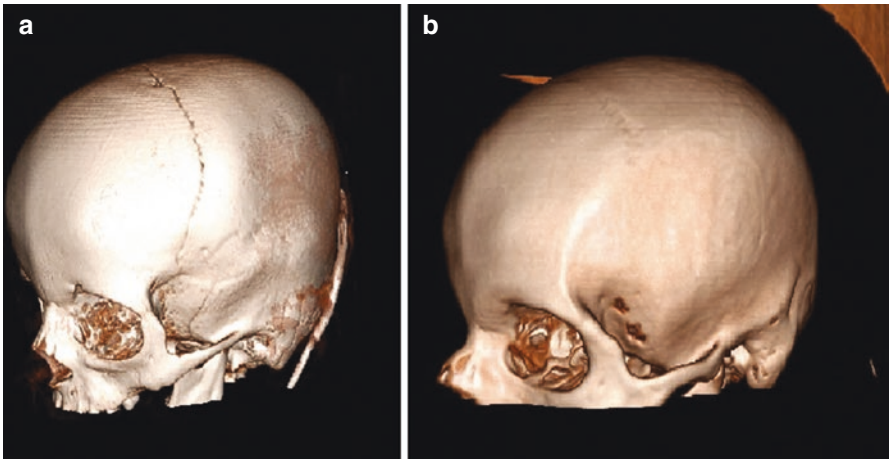

Fig. 9.8 Metopic ridge. 3 years old male case (left sided vp shunt). Partially closed metopic suture and metopic ridge (**a**). 23 year old female case. The metopic ridge in posttraumatic 3D cranial CT reconstruction (**b**)

Fig. 9.9 8 years old male case. An unoperated patient. Mild trigonocephalic appearance on physical examination

9.4.2 Surgical Aspects: Metopic Synostosis—Trigonocephaly

Normally, the metopic suture closes in children during their first year of life, but there are a few exceptions. It is very important to determine whether surgical intervention is necessary in early stage or suspected trigonocephaly cases. Overgrowth of the posterior biparietal bones and perisutural region (bifrontal narrowing) can be a compensatory mechanism and also an early warning sign for trigonocephaly. Unfortunately, there are no subjective analyses or objective measurements for the severity of trigonocephaly [32]. Indications for surgery for craniosynostosis include esthetic reasons and making adequate space for normal brain growth; these indications also cover trigonocephaly. The aim of esthetic correction is social and psychological improvement in the child's life. Increased intracranial pressure (ICP) is an absolute indication for craniosynostosis surgery. However, the risk for increased ICP is very low in metopic synostosis. Surgical methods and techniques for correcting craniosynostosis-related skull deformities have evolved, but there is no consensus about which surgical technique is best. At the moment, the most popular surgical techniques are fronto-orbital advancement with anterior cranial wall reconstruction, or minimally invasive anterior wall recontruction using endoscopy combined with cranial orthotic therapy. The aims of surgery are to correct hypotelorism and the trigonocephalic deformity, and also to regulate pterional and frontozygomatic connections, and to improve lateral and superior orbital rim projections and the forehead contour [25, 26, 33, 34].

Surgical craniosynostosis procedures are usually safe but intervention should only be undertaken if necessary. There are some arguments about the cosmetically acceptable level of craniofacial dysmorphology and who should decide it. The best way to decide the surgery is open and honest discussion between the surgeon and family regarding risks and benefits. The other indication for surgical treatment is to prevent limited neurodevelopment; but does surgical treatment of metopic synostosis affect neurodevelopment? This is not clear in the literature, but some researchers have said that cranial bone expansion prevents, limits, or even treats neurodevelopmental delay in patients with metopic craniosynostosis [27, 35].

The timing of the operation should also be planned carefully, as the procedures in infants tend to be less invasive. Endoscopic techniques show the best performance by 3–6 months of age [26]. Open cranial procedures are usually delayed until 6–12 months because patients undergoing operations before the age of 6 months often need revision surgery. The complication and mortality rates in trigonocephaly surgeries are very low. However, there are still complications in surgery such as subgaleal hematoma, cerebrospinal fluid leakage, infections, and dural injuries.

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Chapter 10
Skull Sutures as Anatomical Landmarks

Abdelmonem Awad M. Hegazy

10.1 Skull Sutures

The skull comprises two main parts: the neurocranium (bones surrounding the brain) and the viscerocranium (bones of the face); each is made of individual bones. The skull contains 22 bones in total; all are firmly interconnected in adults by immobile fibrous joints called sutures. The exception is the single bone of the lower jaw called the mandible, which articulates with the skull at a pair of mobile synovial 'temporomandibular' joints. The sutures are not straight lines, but are twisted to interlock the juxtaposed bones, increasing protection for the enclosed brain. In newborns, the bones are not firmly interconnected but are separated by wide fibrous areas at the suture sites to allow mobility and approximation of the bones, in ordeer to decrease the size of skull during birth and to permit the brain to grow, especially during the first year of life. The areas where more than two bones meet are much wider, forming what are called fontanelles. The fontanelles vary in size; the largest is the anterior fontanelle.

10.2 Calvarial Sutures

These are sutures in the top part of the neurocranium. They include:

A. A. M. Hegazy (✉)
Anatomy and Embryology Department, Faculty of Medicine, Zagazig University, & College of Biotechnology, Misr University for Science and Technology (MUST), Zagazig, Egypt

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10.2.1 Coronal Suture

This extends in a coronal plane at the top of the skull. It passes from side to side separating the two parietal bones posteriorly from the frontal bone anteriorly. Its name derives from the Latin word "corona" meaning a crown. The point of meeting of the coronal suture with the sagittal suture is called the *bregma*. The suture extends caudally on each side of the skull to reach the point of the pterion.

The suture is covered on the top of the skull by the epicranial aponeurosis, and on either side by the temporalis muscle. The part covered externally by the muscle is related internally to the anterior branch of the middle meningeal artery ascending from the point of the pterion [1]. The suture can contain *sutural bones*, also called *wormian bones*; these are small accessory bones [2] (Fig. 10.1).

The coronal suture is easily palpable throughout the scalp and easily identified in lateral view skull X-rays and CT. There is a close craniocerebral relationship. However, an occupying lesion inside the cranial cavity could alter this relationship. Therefore, the precentral gyrus is identified exactly by CT scans and intraoperative stimulation of the cortical strip [3]. The suture could be used as a landmark for identifying the frontal horn of the lateral cerebral ventricle for neurosurgical ventriculostomy cases. It has been concluded that the coronal suture lies about 12 cm from the nasion, and the point of drainage is 3 cm lateral to the midline [4].

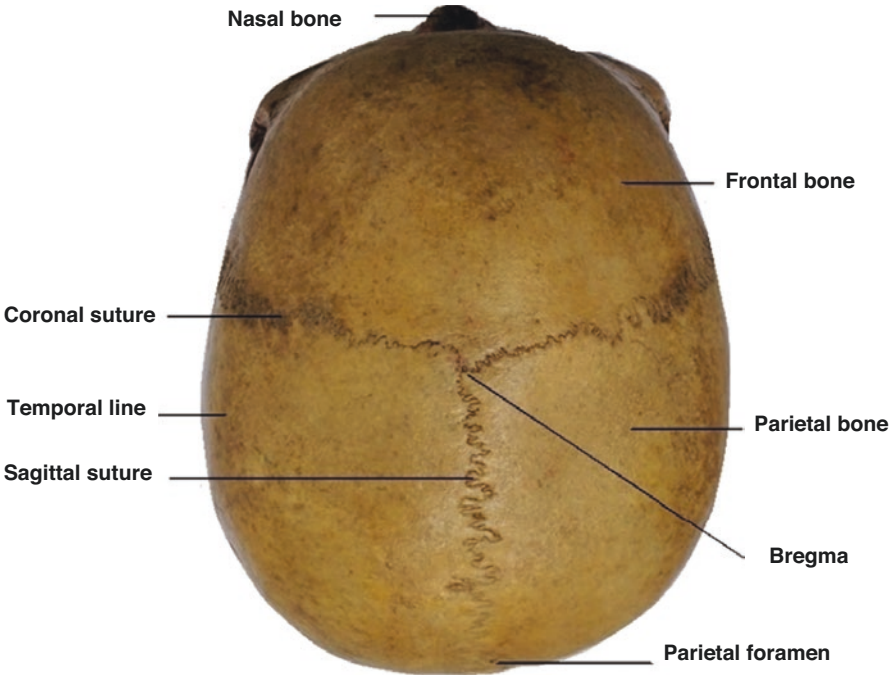

Fig. 10.1 Photograph of the superior view of the skull showing bones and sutures

10.2.2 Sagittal Suture

The sagittal suture extends over the top of skull in the midsagittal plane between the two parietal bones. It extends from the bregma, its meeting with coronal suture, to reach the lambdoid suture. Its name originates from the Latin word "sagitta" meaning arrow. Three landmark points characterize the sagittal suture: the bregma at its anterior end, the vertex at its middle and the lambda at its posterior end. The vertex is the highest point on the vault of the skull (Figs. 10.1 and 10.2). The suture represents an important landmark for the middle portion of the superior sagittal sinus, which runs on the internal aspect of the skull dome (Fig. 10.3). However, it can deviate slightly in some cases, by less than 1 cm to the right, to accommodate its common tendency to drain into the right transverse sinus [5]. The position of the sinus underlying the sagittal suture makes it prone to injury during a midline surgical approach, especially craniotomy. This inadvertent injury to the sinus can lead to severe bleeding that is difficult to control. Therefore, in craniotomy, caution is essential to avoid injury to the sinus when procedures are

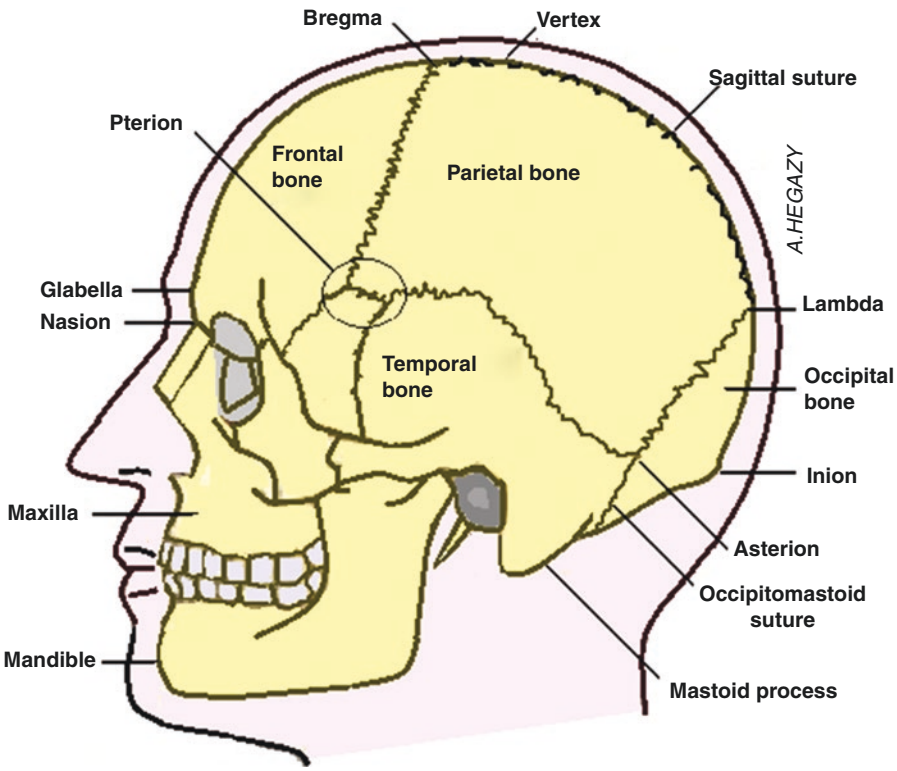

Fig. 10.2 Diagram showing lateral view of the skull and outer landmark points

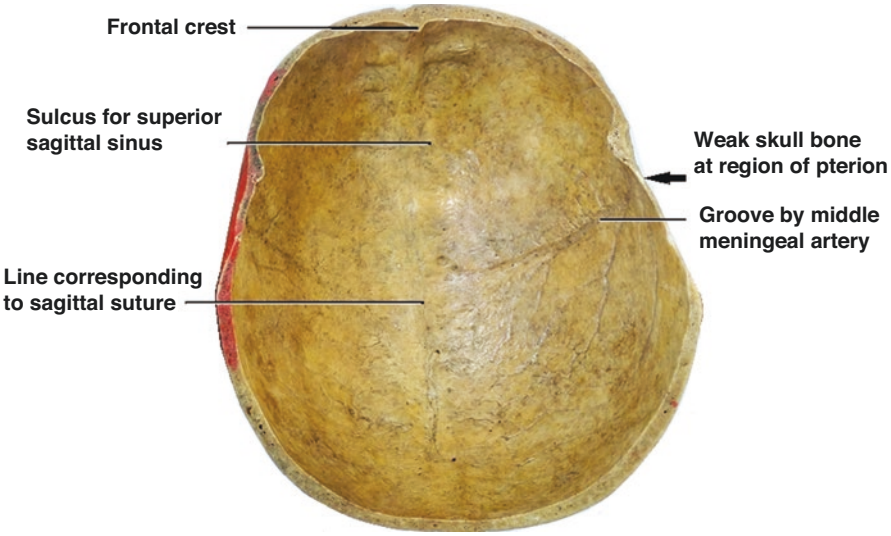

Fig. 10.3 Photograph of the inner surface of the vault of the skull showing the sulcus for the superior sagittal sinus and bone grooving for the middle meningeal artery

performed 10 mm on either side of the midline [6]. The part of the suture lying opposite an imaginary line connecting the two parietal foramina is called the *obelion*. This point represents a landmark for the site of onset of occlusion of the superior sagittal sinus [7].

The suture is about 5.0 mm wide in newborns, diminishes markedly to about 2.5 mm at 1 month, and decreases progressively to close completely at the age of 21–30 years. The closure extends anteriorly from its junction with the lambdoid suture [8].

10.2.3 Lambdoid Suture

This is an inverted V-shaped suture extending on the posterior aspect of the skull. Its apex joins the posterior end of the sagittal suture. From the point of the apex, it runs downwards and laterally on both sides, dividing the occipital bone from the parietal bone on either side. It takes its name from the Greek letter "lambda" (Λ). It continues below with the *occipitomastoid suture*.

There can be small sutural bones at any suture or fontanelle site; however, they are most common in the lambdoid suture (Fig. 10.4) [2]. Finding these bones within a suture is considered normal; however, an increase in their number could indicate underlying pathology. They can be formed as a result of extra-ossification centers appearning in the connective tissues of the membranes between the bones of the skull at sutures and fontanelles [9].

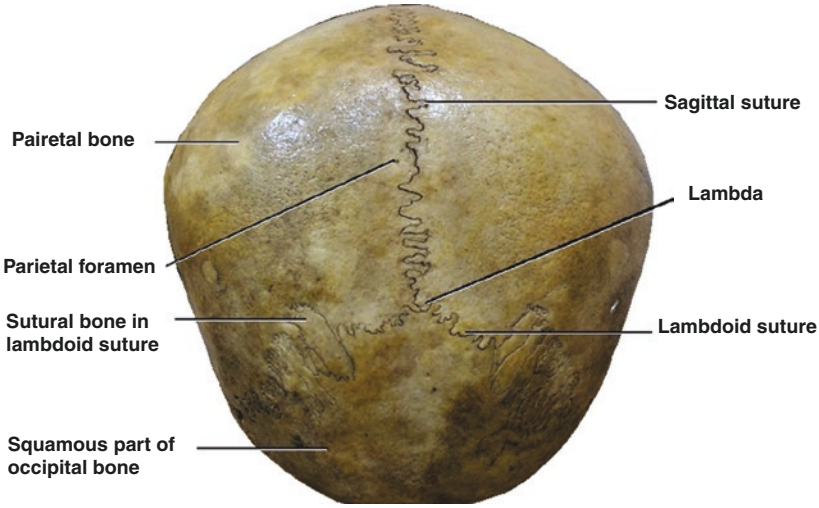

Fig. 10.4 Photograph of the posterior view of the skull showing bones and sutures

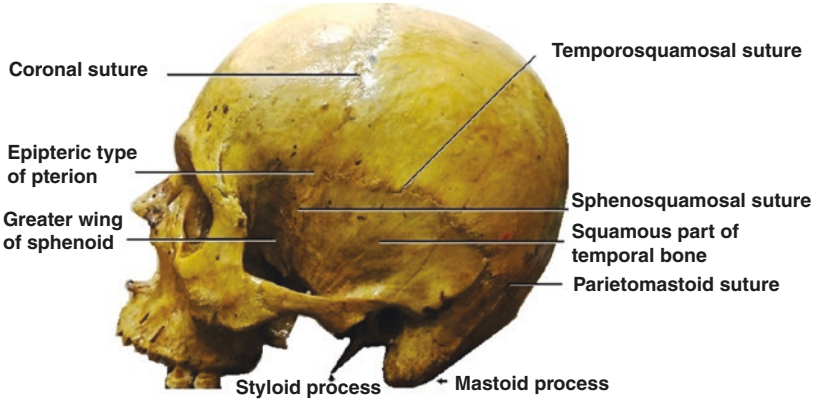

Fig. 10.5 Photograph of the lateral view of the skull showing the squamosal suture and epipteric type of the pterion

10.2.4 Squamosal Suture

This joins the squamous part of the temporal bone to the parietal bone above and the greater wing of the sphenoid anteriorly on the lateral side of the skull. It bounds the squamous part of the temporal bone so it is also called the squamous suture. It comprises two parts: the *temporosquamosal suture*, arching horizontally, and the *sphenosquamosal suture*, extending vertically. The temporosquamosal suture extends from the pterion posteriorly to reach the parietotemporal (parietomastoid) suture, while

the sphenosquamosal passes from the pterion inferiorly to the base of the skull, separating the temporal bone from the greater wing of the sphenoid (Fig. 10.5) [8].

The squamosal suture can be used as a landmark for approaches to the middle cranial fossa in craniotomy. An optimum approach can be found by following the squamosal suture two-thirds anterior or one-third posterior to a horizontal line extending above the external acoustic meatus (Fig. 10.6) [10]. Moreover, the supramastoid crest extends posteriorly, angulating upwards to meet the posterior end of the squamosal suture. This crest forms a surface landmark for the middle cranial fossa at the tegmen tympani. It bounds a slight depression below it called the suprameatal or MacEwen's triangle (Fig. 10.7), which forms the lateral wall of the mastoid cells and is bounded below by the suprameatal crest. It forms a surgical guide for the mastoid antrum [11].

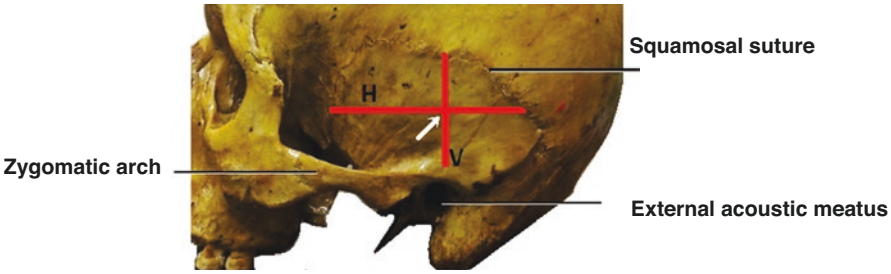

Fig. 10.6 Photograph of lateral skull surface showing the squamosal suture and two lines drawn on the temporal bone outer surface to identify the point (arrow) of the middle cranial fossa approach lying at the crossing of the vertical line (V) and horizontal line (H) at the junction of the anterior two-thirds with the posterior third

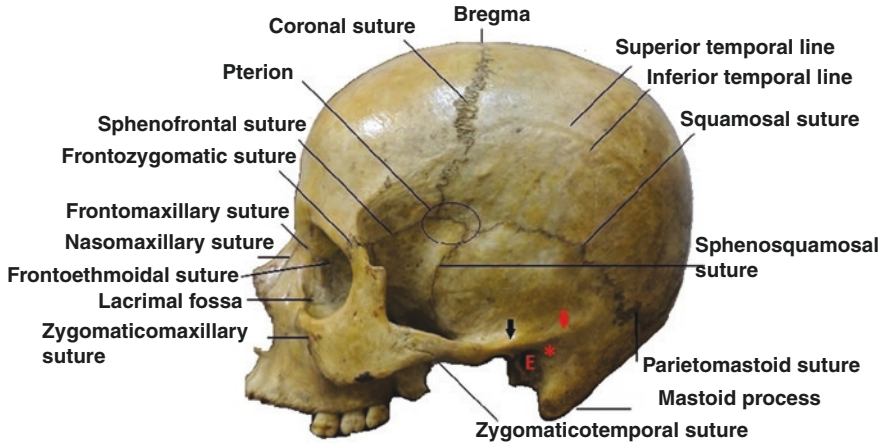

Fig. 10.7 Photograph of the lateral view of the skull showing the suprameatal (MacEwen's) triangle (*), supraarticular crest (black arrow), supramastoid crest (red arrow) and external acoustic meatus (E)

10.2.5 Occipitomastoid Suture

This is also called the occipitotemporal suture and connects the occipital bone to the mastoid part of the temporal bone. It meets two other sutures, the lambdoid and parietomastoid, at the asterion. It represents the lower continuation of the lambdoid suture, extending downwards to the base of the skull (Fig. 10.2). The clinical importance of this suture is that it can be misinterpreted in CT scans as a fracture in the base of the skull. Such misinterpretation can be avoided through identification of the symmetrical suture on the other side and the upward extension of the suture [8]. It remains partially open until adolescence (the 15+ and 18+ age ranges in males and females, respectively), when it completely closes [12].

10.2.6 Parietomastoid Suture

This is a nearly horizontal suture at the posterior end of the squamosal suture connecting it with the lambdoid suture. It lies between the parietal bone and the mastoid part of the temporal bone (Fig. 10.5).

10.2.7 Frontal Suture

This is also called *metopic suture*. The term 'metopic' is derived from a Greek word meaning the middle of the face. The suture bisects the frontal bone into two halves during the fetal and infantile periods (Fig. 10.8). It usually disappears within the first to second year of life but can persist up to 7 years. The fusion starts from below at the nasion, proceeding upwards to the anterior fontanelle. It rarely persists in adults, extending from the nasion anteriorly to the bregma upwards and posteriorly; this is called *metopism*. Its persistence could be related to a defect in bone growth or pathologies such as hydrocephalus; it can be misinterpreted as a fracture during clinical investigation [13]. Many cases close at 3 months of age, and this should not be considered a metopic synostosis [14].

10.3 Facial Sutures (Fig. 10.9)

These are sutures joining the bones of the face, including:

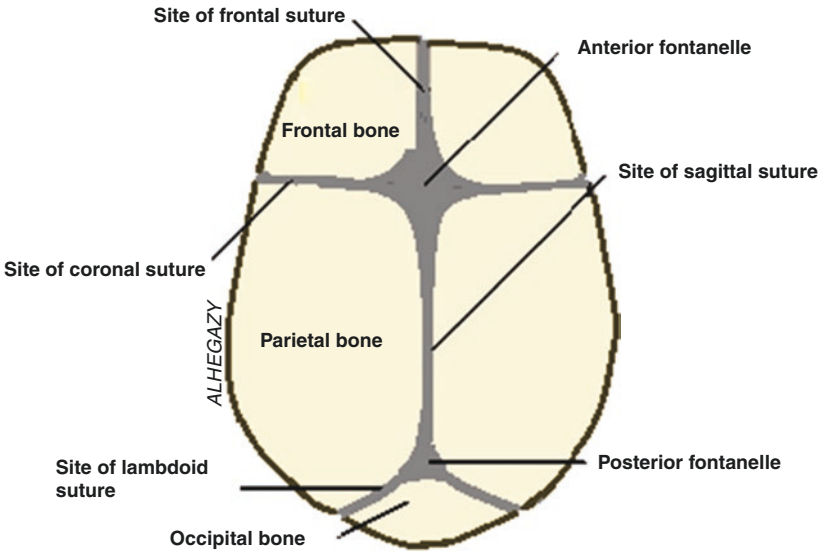

Fig. 10.8 Diagram showing the superior view of a newborn skull

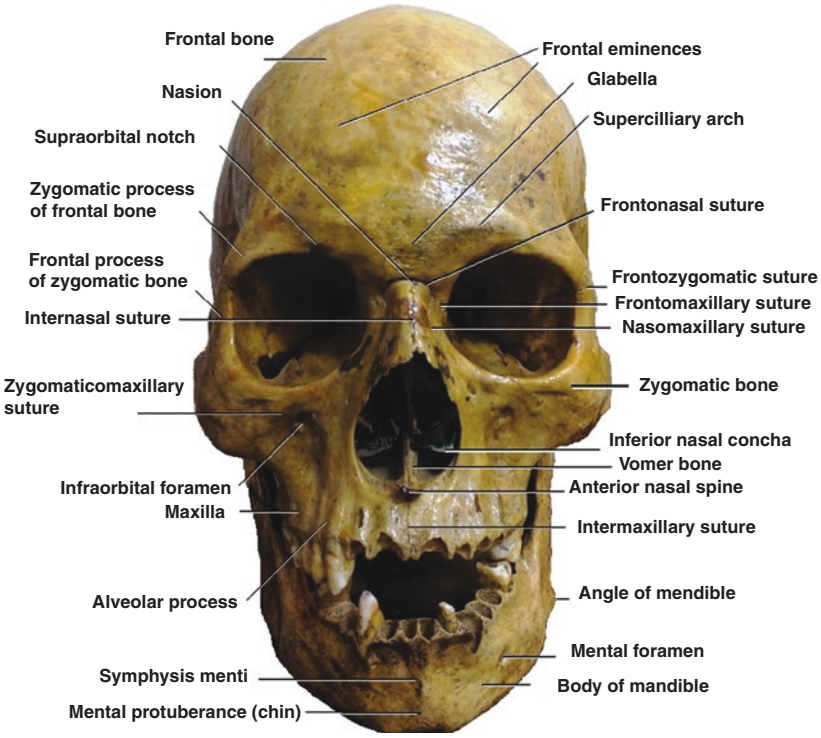

Fig. 10.9 Photograph of the anterior view of the skull showing facial skeleton (viscerocranium)

10.3.1 Frontozygomatic Suture

This joins the frontal and zygomatic bones. It is easily palpated lateral to the eye. Therefore, it represents an important landmark for surgical operations on the orbit. The midpoints of the superior orbital fissure, the fossa for the lacrimal gland, the lateral aspect of the optic canal and the inferior orbital fissure, are at about the following distances from the suture: 37.7mm, 17.5 mm, 44.9 mm and 33.4 mm, respectively [15]. These dimensions can vary according to gender, race and side [16]. On the other hand, the frontozygomatic suture helps to identify the position of the pterion, which is located about 3 cm behind it [17]. The distance from the center of this suture to the point of the pterion can be used to define the inferior border of the frontal cerebral lobe for deeper brain surgical approaches [18].

10.3.2 Frontomaxillary Suture

This joins the frontal bone (its maxillary process) to the maxillary bone (its frontal process). It can be palpated at the lateral end of the deep nasal bridge, along the frontonasal suture [19].

10.3.3 Frontonasal Suture

This is the suture joining the frontal and the two nasal bones. It is situated above the nose at its root and below the glabella, which is a median elevation connecting the two superciliary arches. The nasion is the central point of the suture, lying at its meeting with the internasal suture [20]. It represents an important cephalometric landmark [21]. Superciliary arches or ridges, one on each side, are prominent bulging arches above the orbit overlying the underlying frontal air sinuses within the frontal bone [22].

10.3.4 Temporozygomatic Suture

The temporozygomatic suture is situated on the anterior third of the zygomatic arch; it connects the temporal bone through its zygomatic process to the zygomatic bone through its temporal process. Therefore, the zygomatic arch is formed by two processes and can be located in relation to the floor of the middle cranial fossa [23].

All ‘three’ temporal rami of the facial nerve cross superficial to the zygomatic arch, deep to the subcutaneous tissue and the temporozygomatic fascia. The most posterior ramus of the temporal nerve lies 1.68–2.49 cm in front of the external acoustic meatus with a mean of 2.12 ± 0.21 cm [23, 24].

10.3.5 Zygomaticomaxillary Suture

This is the suture joining the maxilla to the zygomatic bone below the orbit. It participates in most cases of zygomaticomaxillary complex fractures, the second most common type of face fracture following nasal fracture, and the second most common fracture after the mandible subjected to surgical interference [25]. The complex can include four anatomical articulations. In addition to the zygomaticomaxillary suture, it can also include the zygomaticofrontal, zygomaticosphenoid and zygomaticotemporal sutures. Fractures of it can lead to widening of the opening of the orbit with enophthalmos [26].

10.3.6 Nasomaxillary Suture

This is a small suture on the side of the nasal bone connecting it to the frontal process of the maxillary bone at the medial aspect of the orbit.

10.3.7 Sphenofrontal Suture

This suture joins the frontal bone anteriorly to the sphenoid bone posteriorly. It is important because it connects the intra-membranous ossified "frontal" part to the intra-cartilaginous ossified "sphenoid" part. This suture fuses at about 15 years of age. It comprises two portions: the lateral sphenofrontal suture and the medial orbitosphenofronal suture. The lateral part lies between the frontal bone and the greater wing of the sphenoid on the lateral aspect of the skull (Fig. 10.7). In contrast, the medial part is situated at the base of the skull between the lesser wing of the sphenoid and the orbital part of the frontal bone (Fig. 10.9) [27].

10.3.8 Sphenozygomatic Suture

This suture joins the greater wing of the sphenoid to the zygomatic bone, lying on the lateral wall of the orbit. It can be used as a guide for proper reduction of zygomatic bone fractures [28].

10.4 Skull Point Landmarks

10.4.1 Bregma

The bregma is the point at which the sagittal suture meets the coronal suture anteriorly. It represents the site of the anterior fontanelle during the fetal and infantile periods (Figs. 10.1, 10.2, 10.7, and 10.8) [29].

The anterior fontanelle is the largest fontanelle in newborns, measuring about 4 cm antero-posteriorly and 2.5 cm from side to side. It closes at about the age of 12–18 months. It is diamond-shaped, being situated at the meeting of four sutures: frontal (metopic) anteriorly, sagittal posteriorly, and coronal on each side. This fontanelle is of clinical importance. During labor, its palpation per vaginal examination helps in locating the head of the fetus. During the neonatal and infantile periods, its state can help in diagnosing various conditions, such as a bulge in cases of meningitis or increased intracranial pressure, a depression in case of dehydration and delayed closure, and denting in clinical disorders including achondroplasia, hypothyroidism and Down syndrome [29]. Moreover, this fontanelle forms an access approach to the veins inside the cranium [30]. Specimens of cerebrospinal fluid (CSF) can be obtained through the anterior fontanelle when indicated by inserting a long needle into the subarachnoid space, or even from the lateral ventricle [22].

The bregma and the coronal suture can be identified by finger palpation. The bregma is situated about 124.3 ± 6.9 mm from the nasion [31]. The bregma point has been noted as an important landmark for identifying the central cerebral gyri. The precentral, central and postcentral sulci lie about 26.8; 47.8 and 60.6 mm, respectively, behind it [32].

10.4.2 Lambda

This is the point where the sagittal suture meets the lambdoid suture posteriorly. It represents the site of the posterior fontanelle during the fetal and early infantile periods (Figs. 10.2, 10.4, 10.8, and 10.10) [33]. Its distance from the highest point of the sagittal suture (called the vertex) is about 100.7 ± 5 mm in females and 109.5 ± 8 mm in males [34]. At the lambda point, the superior sagittal sinus could be exposed through a small gap made in the sagittal suture [6]. The superior sagittal sinus lies directly beneath the lambda in only about 25% of cases; in others, it is shifted slightly to right side of the midline by about 5.7 mm [35].

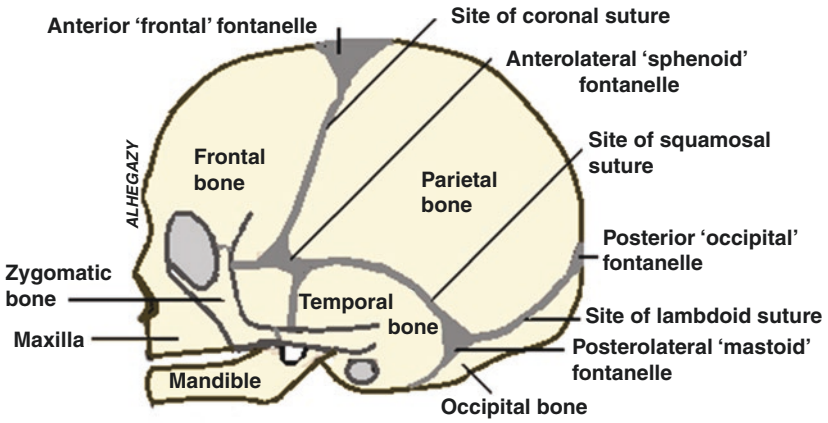

Fig. 10.10 Diagram showing lateral view of a newborn skull

10.4.3 Pterion

The pterion is an important craniometric point for both anthropological and radiological investigations. It lies at the meeting of four bones; frontal, parietal, temporal and the greater wing of the sphenoid. It is an H-shaped suture. It represents the meeting of five sutures: a horizontal limb formed from the sphenoparietal suture; an anterior limb consisting of the coronal suture above and the sphenofrontal suture below; and a posterior limb formed from the squamosal and sphenosquamosal sutures (Fig. 10.7). The horizontal suture is located between the antero-inferior angle of the parietal bone above and the upper border of the greater wing of the sphenoid below. Therefore, this commonest form is called a sphenoparietal pterion [36]. There can be other anatomical variations at the pterion, including a meeting of only two or three bones, a meeting of the four bones at one point (stellate type), and the epipteric type, in which there are sutural bones in the horizontal limb of the H-shaped pterion (Fig. 10.5) [37, 38]. The pterion represents the site of the anterolateral fontanelle, also called the sphenoid fontanelle in infants (Fig. 10.10). This fontanelle closes at about the 6th month after birth [33].

The pterion is located about 4.0 cm above the mid-point of the zygomatic arch and about 3–3.5 cm behind the frontozygomatic suture [22, 39]. In clinical practice, it can be roughly defined as a shallow hollow two finger-breadths above the zygomatic arch and one thumb-breadth behind the frontozygomatic suture [36].

It is also important as the weakest part of the wall of the skull that protects the anterior branch of the middle meningeal artery running on its inner aspect inside the cranial cavity (Fig. 10.3). This weak area is prone to fracture; skull trauma can injure the artery, with subsequent intracranial extradural hemorrhage leading to hematoma formation. Therefore, the location of the pterion is important for

evacuation of extradural hematomas. Moreover, the pterion represents an important surgical landmark for defining such brain regions as Broca's area and the frontal cerebral lobe. It can also be used as a pterional approach for surgery on the intracranial optic nerve and to manage aneurysms of the middle cerebral artery. An oblique line extending from the pterion to the frontozygomatic suture corresponds to the inferior border of the frontal cerebral lobe. Also, the posterior end of this line corresponds closely to the anterior end of the lateral cerebral sulcus. The motor speech 'Broca's' area lies about a finger-breadth above the posterior end of the previous line on the left side [36].

10.4.4 Asterion

This is the meeting point of three sutures; lambdoid, occipitomastoid and parietomastoid. It lies at meeting of three bones: occipital, parietal and the mastoid part of the temporal bone (Fig. 10.2). Its name comes from the Greek word "astērion" meaning star. It is visible when uncovered from the scalp tissues [40]. It is the site of the posterolateral fontanelle, called the mastoid fontanelle in infants (Fig. 10.10). The fontanelle closes at 6–18 months of age [33].

The asterion is a useful surgical landmark for the posterior cranial fossa approach. Its position corresponds to the transverse-sigmoid hinge of the intracranial venous sinuses in most cases [41]. Location of the asterion is important for drilling a primary burr hole in the cerebellopontine angle approach. A 2 cm diameter hole can be made with maximum safety and visualization of structures at the cerebellopontine angle if it is located at the midpoint between the asterion and the tip of the mastoid process [42]. The mastoid process is a projection from the temporal bone extending downwards and forwards behind the auricle. It appears by the third year of life, probably due to the pull of the sternocleidomastoid muscle attached to it [22].

10.4.5 Inion

This is the point where the external occipital protuberance projects most at the back of the skull (Figs. 10.2 and 10.11). The inion is used to estimate the proper posterior cranial approach to avoid injuring the nearby transverse intracranial venous sinus (Fig. 10.12). The safest midline approach for infratentorial supracerebellar regions is through a burr hole about 10 mm below the inferior nuchal line. This line is located 12.7–37.7 mm below the projecting inion. Injury to the transverse sinus can be avoided through the previous approach [43]. Another study showed that the insertion of the semispinalis capitis in the area between the superior and inferior nuchal lines corresponds to the internal location of the transverse sinus [44].

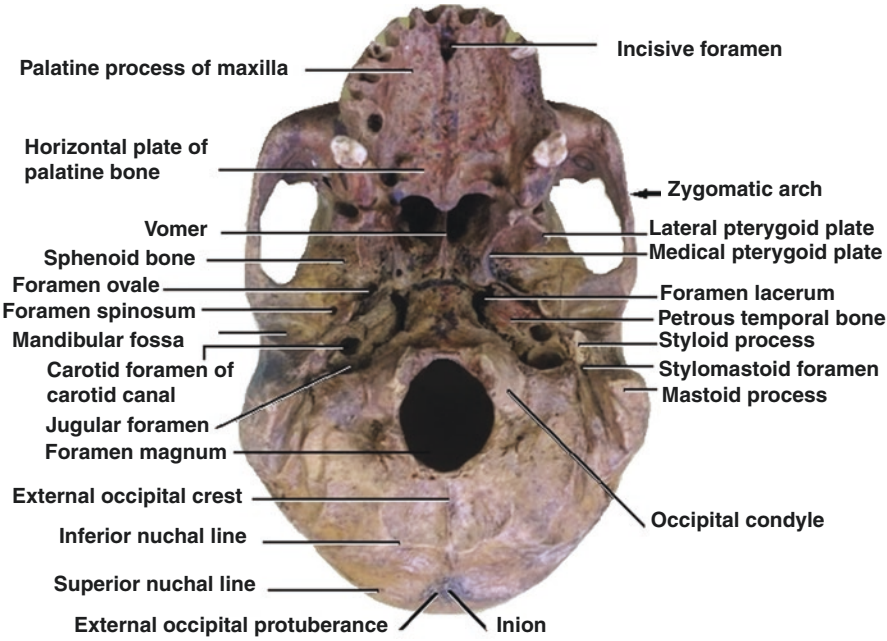

Fig. 10.11 Photograph of the external view of the base of the skull

10.4.6 External Occipital Protuberance

This lies at the middle of the squamous part of the occipital bone at the posterior aspect of the skull (Fig. 10.11). The protuberance gives attachment to the ligamentum nuchae, which runs in the neck between the muscles at its back. A line extending from it to the nasion roughly marks the underlying superior sagittal sinus and the attachment of the falx cerebri, extending into the longitudinal cerebral fissure between the two cerebral hemispheres [22].

10.4.7 Basion and Opisthion

These two craniometric points, important for both for anthropological and radiological purposes, are found at the foramen magnum of the occipital bone at the base of the skull. The basion is the middle point of the anterior margin of the foramen magnum; the opisthion is the corresponding point on the posterior margin of the foramen (Fig. 10.13) [45]. The antero-posterior diameter of the foramen magnum extending from the basion to the opisthion is about 34.38 ± 2.38 mm [46].

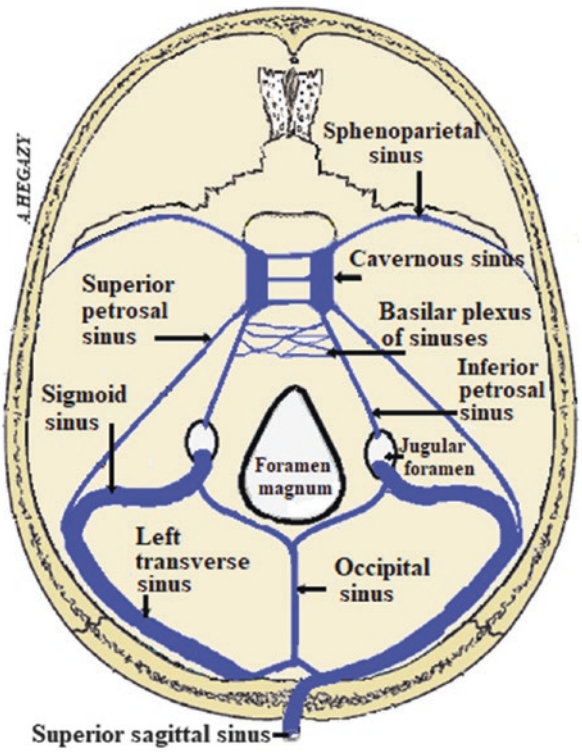

Fig. 10.12 Diagram showing the arrangement of intracranial venous sinuses at the base of the skull

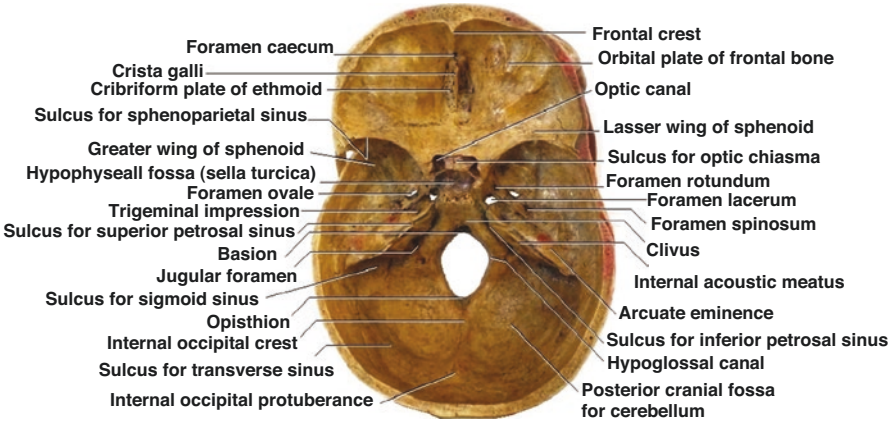

Fig. 10.13 Photograph of the internal view of the base of the skull

Knowlege of the normal occipitovertebral relationship aids in diagnosing its dislocation. The normal maximum limit for both the basion-dens and the basion-axis intervals is 12 mm in adults. Exceeding this range can suggest occipitovertebral dislocation. This method is not accurate for children under 13 years of age because ossification and fusion of the dens is variable [47]. Using multiple detector computed tomography (MDCT) scanning, it has been shown that the normal basion-dens interval is less than 8.5 mm, in contrast to the value of 12 mm detected on plain radiographs [48].

The anteroposterior distance of the foramen magnum is called the basion to opisthion diameter or the *McRae line*. This line is easily identified in CT or MRI. Any extension of the odontoid process beyond the McRae line is considered abnormal [49].

10.4.8 Obelion

This is the point where the sagittal suture intersects an imaginary line connecting the parietal or medial foramina to the single foramen. Ossification in the posterior third of the skull can be delayed in the region of the obelion, resulting in a V-shaped notch sometimes called the third fontanelle [50]. Parietal foramina are absent in about 10% of skulls. When present, the parietal foramen is located at the junction of the middle and posterior thirds of parietal bone region [51].

The obelion takes its name from the Greek word “obelos”, possibly because it resembles an obelos when surrounded by the dots of the parietal foramina. It corresponds to the commencement of the superior sagittal sinus occlusion [52].

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Chapter 11
A Brief Introduction to the Biomechanics of Craniofacial Sutures

Arsalan Marghoub, Mahbubeh Hejazi, Connor Cross, and Mehran Moazen

11.1 Introduction

Sutures are composites of mesenchymal cells that during development differentiate and deposit extracellular matrix, which consists primarily of collagens, various bone-related proteins and proteoglycans [1, 2]. Sutures are an integral part of the craniofacial system and together with the synchondroses they modulate the growth and development of that system [3, 4]. Their premature fusion leads a clinical condition called craniosynostosis [5, 6].

During development, sutures accommodate the radial expansion of the brain [7, 8]. By the time the brain has reached its maximum size, visible gaps at the sutures have diminished to micro/nanometer gaps where they have differentiated to bone [9]. A few sutures fuse, but many remain open during adulthood with different morphologies: abutted, overlapping, or to various degrees interdigitated [10–12]. During adulthood, they help to ensure uniform distribution of the mechanical loads applied to the craniofacial system and act as shock absorbers [13–15]. The mechanical loads that sutures experience arise from e.g. the growth of internal organs in the craniofacial system such as brain and eye; from daily activities such as biting; or from sudden impact by external objects [16].

A wide range of techniques such as tensile testing, nanoindentation, strain gauging and finite element methods have been used to elucidate the biomechanics of the sutures. These studies can be classified in three groups: to understand (1) the inherent mechanical properties of the sutures; (2) the role and function of the sutures (using in vivo and in silico techniques); and (3) how sutures respond to mechanical loads (using in vitro or in vivo experiments). There is a wealth of literature under each category.

A. Marghoub · M. Hejazi · C. Cross · M. Moazen (✉)
Department of Mechanical Engineering, University College London, London, UK
e-mail: m.moazen@ucl.ac.uk

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The aim of this chapter is to provide a short overview of the biomechanics of the craniofacial sutures under the aforementioned categories. The goal is not to offer a critical review of past studies or to summarize the entire literature. Rather, the objective is to inform the reader about key ongoing research areas, provide a brief overview of the methods used, and highlight the key studies to the best of our knowledge. Readers are referred to the studies cited here and other reviews on the mechanobiology of sutures [17–20].

11.2 Inherent Mechanical Properties of the Sutures

Tensile/compression testing, three/four-point bending and indentation are the most common techniques used to characterize the mechanical properties of sutures in a wide range of species (see the review of such studies on humans by Savoldi et al. [21]). In brief, these techniques characterize the load-displacement of the sutures under a specific loading rate, and on the basis of those data estimate parameters such as the elastic modulus, yield and ultimate stress. There are several key factors in such studies: biologically related factors such as species, anatomical region and age, and testing-related factors such as loading approach, loading rate, and indentation tip.

It is widely accepted that sutures are viscoelastic materials, the mechanical properties of which are nonlinear and are influenced by the rate and duration of loading [16, 22]. Nonetheless, a few studies have characterized the viscoelastic properties of sutures. Classical work by Tanaka et al. [22], Margulies and Thibault [23] and Popowics and Herring [24] reported the elastic moduli of sutures under different loading rates. At the same time, a good body of literature has quantified the elastic moduli using a specific set of parameters in comparative studies. Table 11.1 summarizes some of the key studies to the best of our knowledge. It is clear that there is considerable variation in the reported values of the elastic moduli, probably because of the aforementioned factors. Also, given that the sutures are undergoing tissue differentiation , at least during development, it can be expected that the elastic modulus will vary across a suture. Indentation is a powerful tool for characterizing such variation. Overall, it seems that the elastic moduli of the sutures are in the range 1–30 Mpa, which are quite low values (Table 11.1).

11.3 Role and Function of the Sutures

A range of techniques such as in vivo and ex vivo strain gauging and in silico computational methods have been used to quantify the level of loading across the craniofacial system and sutures. Given that sutures are mainly loaded during biting,

Table 11.1 Some key studies characterizing the elastic moduli (E) of sutures

Author	Animal	Age range	Clinical focus	Evolutionary focus	Developmental focus
Jaslow [25]	Goat	2–4 years	Internasal and coronal	10–35[a] & 120–240[a]	Three-point bending
Thibault et al. [26]	Human	3 months	Coronal	189[b]	Tension
Margulies and Thibault [23]	Pig	2–3 days	Coronal	194.2 ± 42.5	Three-point bending
McLaughlin et al. [27]	Rat	7 days	Sagittal, coronal & posterior frontal	13, 14 & 2.3	Tension
Tanaka et al. [22]	Rat	4 weeks	Sagittal	4.5 ± 1.8[c]	Tension
Radhakrishnan and Mao [28]	Rabbit	8 weeks	Pre-maxillomaxillar, nasofrontal & zygomaticotemporal	1.5 ± 0.2, 1.2 ± 0.2 & 1.2 ± 0.2	Atomic force microscopy
Henderson et al. [29]	Rat	2–60 days	Sagittal	4–80[d]	Three-point bending
Coats and Margulies [30]	Human	21 weeks gestation-12 month	Coronal	3.8–16.2	Tension
Grau et al. [31]	Human	9.1 ± 2.8 months	Synostosed metopic & synostosed sagittal	0.5 ± 0.1 & 0.7 ± 0.2	Nano-indentation
Popowics et al. [24]	Pig	3–6 weeks & 5–6 months	Nasofrontal	68 ± 32 (C); 43 ± 16 (T) & 115 ± 45 (C); 70 ± 33 (T)	Compression (C) & tension (T)
Davis et al. [32]	Human	6 years	NC	1100 ± 530	Four-point bending
Wang et al. [33]	Human	1.5 ± 0.5 years	Coronal & sagittal	354.8 ± 44.9 & 408.1 ± 59.1	Three-point bending
Rahmoun et al. [34]	Human	Average 88 years	Coronal	2038.4 ± 923.6	Three-point bending
Moazen et al. [35]	Mouse	10–20 days	Sagittal, coronal & posterior frontal	20 ± 12, 29 ± 23 & 34 ± 33	Nano-indentation

[a]Bending strength was reported in this study
[b]Mean stiffness was reported in N/mm
[c]Relaxed modulus was estimated following a series of loading-unloading detailed in the paper
[d]Average value of 22 MPa calculated based on suture thickness; "at a higher loading rate of 0.02 mm/s
Note: C: compression; T: tension; NC: not clear to us.

most of these studies have focused on biting and its associated muscles and soft tissues. Clearly, in vivo studies are the "gold standard" for quantifying the loading level across the sutures. Nonetheless, computational models are powerful tools for answering various "what if?" questions, and ex vivo studies are invaluable for validating in silico studies.

In vivo studies have mainly placed strain gauges across the skull and recorded strain across the bones and sutures during various biting scenarios. To the best of our knowledge, fewer studies have used this technique to measure strain specifically across the sutures, though several studies on e.g., fish [36], lizards [37, 38], rats [39], pigs [40–43] and macaques [44, 45] have measured in vivo strain across a range of sutures. These studies broadly highlight a correlation between the morphology of the sutures and the predominant loading they experience, highly interdigitated sutures being mainly loaded under compression, overlapping sutures under shear and abutted sutures under tension.

In silico studies have mainly used the finite element (FE) method (see following textbooks on this method [46, 47]). This computational technique enables us to carry out a structural analysis that can predict the deformation of the skull under a particular loading regime (see the reviews by Rayfield [48] and Prado et al. [49]). It is a powerful technique by which a variety of scenarios can be modeled and a wide range of questions can be asked and answered cost-effectively. This method requires various input parameters, i.e. the morphology of the skull, the inherent properties of its various constituents e.g., bones and sutures, and the loading applied to it.

FE models have been widely used over the past 30 years to elucidate the role and function of sutures in a range of species and to address a range of evolutionary, functional, developmental and clinical questions (see Table 11.2). Perhaps one of the earliest studies exploring evolutionary and functional questions and using FE to model sutures was by Rayfield et al. [50], a case study of a dinosaur. The same approach was then adopted by many others to study the roles of sutures in e.g., lizards [15, 51, 52], Sphenodon [53], macaques [54, 55], pigs [56], and recently amphibians [57]. Far fewer studies seem to have used the FE method to model the development of the craniofacial system (i.e., modeling the sutures). A few recent ones have used this technique to model the development of calvaria in mice [58–61] and humans [62–65]. A few others have used FE to inform clinical management of conditions associated with craniofacial sutures such as cleft lip/palate (e.g., [66–68]) and craniosynostosis (e.g., [69–73]; and see the review by Malde et al. [74]).

Regardless of the application of the FE method, validation of these models is crucial for building confidence in their outcomes. Hence, a wide range of validation studies have been carried out by comparing the FE results with in/ex vivo strain gauging, and recently with laser speckle interferometry. Perhaps some of the key studies in this respect are Kupczik et al. [75] and Wang et al., [45] on macaques; Bright and Groning [76] on pigs; and Cuff et al. [77] on ostriches. Overall, FE studies have demonstrated the importance of sutures in distributing strain across the skull more uniformly and have clearly shown the potential of this method to advance treatments of various clinical conditions.

Table 11.2 Short summary of key finite element studiesmodelling the cranial sutures

Author	Animal
Rayfield et al. [50]	Dinosaur
Kupczik et al. [75]	Macaque
Wang et al. [45, 54, 55]	Macaque
Moazen et al, [15, 51]	Lizard
Bright and Groning [76]	Pig
Bright [56]	Pig
Curtis et al. [53]	Sphenodon
Cuff et al. [77]	Ostrich
Jones et al. [52]	Lizard
Gruntmejer et al. [57]	Amphibian
Jin et al. [62]	Human
Lee et al. [58, 59][a]	Mouse
Burgos-Florez et al. [63]	Human
Libby et al. [64]	Human
Weickenmeier et al. [65]	Human
Marghoub et al. [60, 61]	Mouse
Pan et al. [66]	Human
Nagasao et al. [69, 70]	Human
Chen et al. [67, 68]	Human
Borghi et al. [71]	Human
Malde et al. [72]	Human
Bozkurt et al. [73]	Human

[a]A finite volume study

11.4 Response of Sutures to Mechanical Loads

In vivo and in vitro experimental loading setups have been developed and used to test the responses of sutures to controlled loading regimes. The loading has been either quasi-static (compressive or tensile) or dynamic (compressive or tensile). Perhaps the classical in vivo example of applying forces to sutures is cranial deformation. This has been practiced by various human groups among e.g. North and South American Indians, Pacific Islanders and various European stocks resulting in e.g. circumferentially or anteroposteriorly deformed crania [78, 79]. While the level of loading applied in these cases is unknown, the skull is clearly deformed; but interestingly, various sutural morphologies do not seem to be affected.

A large body of literature has described in vitro experiments in which sections of the skull including sutures have been placed and loaded in a dish. These controlled experiments have enabled us to study cellular and morphological changes in the sutures, their main limitations being their in vitro nature, i.e., lacking blood supply and surrounding anatomical structures, and alteration of the overall mechanics of the tissues. One early study that used such an approach was by Meikle et al. [80] on a rabbit model. This was followed by several other groups [81–85]. See the review

by Alaqeel et al. [86] for a detailed summary of studies of in vitro loading on sutures (and also in vivo studies). These authors summarized various changes in e.g. protein level, growth factor expression, and extracellular matrix due to the mechanical forces.

A relatively large body of literature has also described in vivo studies in which various sutures have been subjected to different loading regimes and durations. Table 11.3 summarizes some of the key in vivo experiments to the best of our knowledge. These studies, together with the in vitro studies, demonstrate that external tension across sutures up-regulates sutural cell proliferation, increasing the number of cells and their macroscopic width. A quasi-static tensile force seems to have a limited effect [87]; dynamic loading seems to have a larger and perhaps a longer-lasting effect. Kopher and Mao [88, 89] showed that both tensile and compressive cyclic loading can also enhance suture maintenance. Nonetheless, our understanding of the effects of various parameters in such studies (loading duration, frequency, etc.) is still limited and is largely based on the pioneering studies of Mao's team.

11.5 Discussion

The chapter has provided a short summary of the literature on the biomechanics of sutures. The wider literature is not covered here and readers are encouraged to research further. For example, a number of studies have focused on modeling and understanding sutural morphologies [105–107], and there is a wider literature on using FE to address various clinical conditions associated with the craniofacial system. Overall, we feel that this chapter is a good initial read for those beginning to explore the biomechanics of sutures, pointing them to the relevant literature.

Considering the topics covered here, the material testing experiments to date have significantly advanced our understanding of the inherent mechanical properties of sutures. Perhaps further studies can use this technique to quantify changes in the mechanical properties of sutures during development or in various craniofacial abnormalities. Similarly, computational and in vivo experiments can be further implemented to advance our understanding of various craniofacial conditions such as craniosynostosis. Indeed, combining geometric, morphometric, finite element, machine learning and experimental techniques can be a powerful approach to addressing various non-clinical questions (see e.g., [108]). External loading studies have so far mainly focused on normal sutures; applying same methods to various animal models of craniofacial conditions [109, 110] is another key avenue of research that requires further attention. This can potentially lead to the development of novel technologies for treating conditions such as craniosynostosis.

There is no doubt that the whole field of suture mechanobiology has shown immense progress during the past 30 years, advancing our fundamental understanding of this topic. We have already seen several examples that have found their way from basic scientific research to clinical practice. For example, spring-assisted

Table 11.3 A summary of key in vivo studies investigating the effect of external loads on the craniofacial sutures. See also studies of Wang and Mao (on rabbit cranial base – [90]) and Tang et al. (on rat cranial base – [91])

Author	Animal	Age	Suture	Level of loading	Duration	Q-static or dynamic
Cleall et al. [92]	Macaque	P90-120	Midpalatal	4 mm expansion achieved in 2 weeks then 2 mm at 4 weeks interval up to 12 weeks	Several intervals from 2 to 36 weeks	Q-static tension
Elder and Tuenge[93]	Macaque	NK	Several sutures	700 Gmat 40° angle to the occlusal plane was applied via a frame to the maxilla	57–72 days	Q-static tension
Ten Cate et al. [94]	Rat	NK - adults	Sagittal	2 mm deflection was induced in a wire frame that was placed across the sagittal suture	Various intervals from 2 h to 42 days	Q-static tension
Jackson et al. [95]	Macaque	P1200-P1440	Several sutures	300 Gm per side parallel to the occlusal plane was applied via a frame to the maxilla	63–114 days	Q-static tension
Southard and Forbes [96]	Rat	P53-58	Interpremaxillary	50–75 g , 150–175 g and 250–300 g was applied via a helical spring (made from stainless steel) across the maxillary incisors	12 h; 1, 2 and 4 days	Q-static tension
Anton et al. [78]	Human	unknown	Several sutures	Unknown – intentional head deformity	Unknown	Q-static
Losken et al. [97]	Rabbit	P10	Coronal	A total 3.97 mm distraction was applied to the coronal suture over 42 days	Twice per week for 6 weeks - P28-P70	Q-static
Bradley et al. [98]	Lamb	85–95 days gestation	Coronal	1 mm compression plate was placed across the mid portion of the coronal suture	28 and 56 days	Q-static compression
Tanaka et al. [99]	Rat	P28	Sagittal	65 g expansion was applied across the sagittal suture	For 15, 30 and 50 h	Q-static tension
Kopher and Mao [100] and Kopher et al., [88]	Rabbit	P42	Premaxillomaxillary, nasofrontal	5 N(compressive) applied to the maxillary incisors at 0 Hz & 1 Hz (sine & square wave)	10 min/day for 12 days	Q-static and dynamic

(continued)

Table 11.3 (continued)

Author	Animal	Age	Suture	Level of loading	Duration	Q-static or dynamic
Mao et al. [89]	Rabbit	P42	Premaxillomaxillary	2N (tensile) applied to the maxillary incisors 0 Hz, 0.2 Hz & 1 Hz	10 min/day for 12 days	Q-static and dynamic
Vij and Mao [101]	Rat	P17, P23, P32	Premaxillomaxillary, nasofrontal	0.3N (compressive) applied to the maxilla at 4Hz	20 min/day for 5 days	Dynamic
Peptan et al. [102]	Rabbit	P42	Premaxillomaxillary, nasofrontal	1N (tensile and compressive) applied to the maxillary incisors at 8 Hz & (sine wave)	20 min/day for 12 days	Dynamic
Han et al. [103]	Macaque	P960	Several sutures	3N was applied via cast class III magnetic twin-block appliance to the upper	For 45 and 90 days	Static
Takeshita et al. [87]	Mouse	P42	Sagittal	0.2N was applied to the sagittal suture by bending and placing a 0.3mm diameter nickel-titanium wire	For 28 days	Static
Soh et al. [104]	Pig	P90	Nasofrontal	800–1000 μm strain (tensile) was applied to the nasofrontal at 2–3 Hz	30 min/day for 5 days	Dynamic

NK: not known to us; Q-static: quasi-static

cranioplasty is becoming a popular treatment option for managing sagittal craniosynostosis (see e.g., [111]), early studies during the 1970s having applied the same concept to various animal models. Large bodies of ongoing research e.g. in the fields of tissue engineering and gene therapies (e.g., [112–114]) can potentially revolutionize the treatment of craniofacial conditions in years to come.

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Chapter 12
Radiological Evaluation of the Sutures of the Skull

Beom Sun Chung, Liz Hagan, and Markus Lammle

12.1 Introduction

12.1.1 Development of the Sutures

Cranial sutures are present in utero in the form of flexible membranes connecting the flat bones of the skull. At birth, the skull consists of those flat bones separated by the developing sutures, creating open spaces called fontanelles. During vaginal birth, these early sutures undergo some deformation, even to the extent of the flat bones overlapping, to allow the head to pass through the birth canal. Remodeling of the cranium continues during ossification as the flat bones grow together and the fontanelles close. Rapid growth occurs until the age of 6 or 7 years, but the sutures do not completely fuse until adulthood. To evaluate cranial pathology in pediatric patients, knowledge of age-specific normal anatomy, development of bones, fontanelles and cranial sutures is crucial [1].

B. S. Chung (✉)
Department of Neurosurgery, Tulane Center for Clinical Neurosciences, Tulane University School of Medicine, New Orleans, LA, USA
e-mail: bschung@ajou.ac.kr

L. Hagan
Tulane University School of Medicine, New Orleans, LA, USA

M. Lammle
Department of Radiology, Tulane University School of Medicine, New Orleans, LA, USA

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12.1.2 Gross Anatomy: Sectioned Images

For anatomical evaluation of the sutures in real color and high resolution, sectioned images of cadavers can be used. The diploic spaces appear in red because of the blood vessels, while the sutures appear white because of fibrous tissues (Fig. 12.1).

12.2 Imaging Modalities

12.2.1 Radiography

Radiography (X-ray) (Fig. 12.2) has traditionally been the most commonly-used imaging technique for assessing possible fractures in cases of head trauma. Now that CT scanners are available in most medical centers, this technique has been largely replaced by CT (Fig. 12.3), which have higher resolution and make fractures more conspicuous using a bone window algorithm.

Radiographs of the skull can make it difficult to distinguish skull fractures from the normal sutures, complicating diagnosis [2–4]. Radiography is prone to both false positive and false negative results owing to the superposition of different

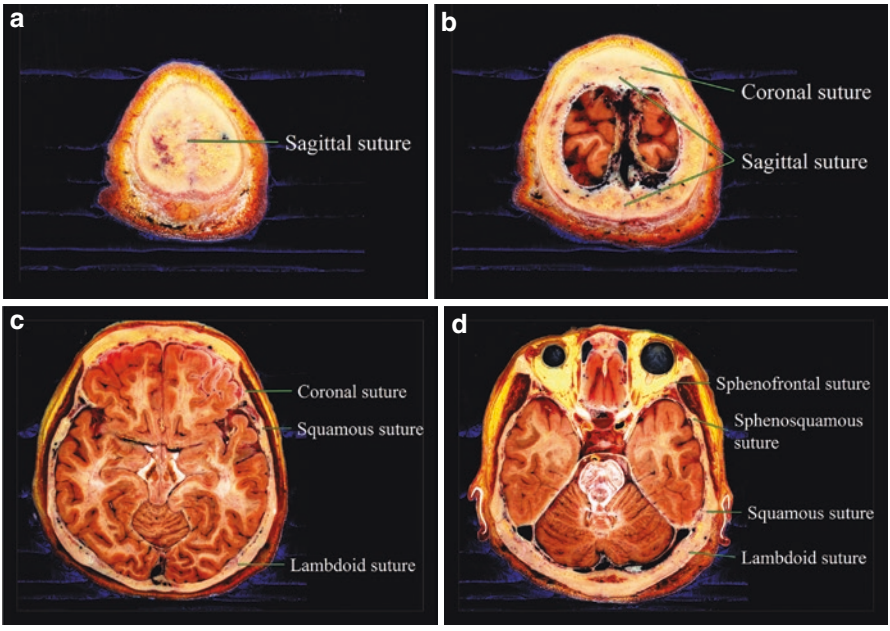

Fig. 12.1 Sectioned images (**a**–**d**) of cadaver head in the horizontal plane demonstrating the symmetric distribution of the cranial sutures

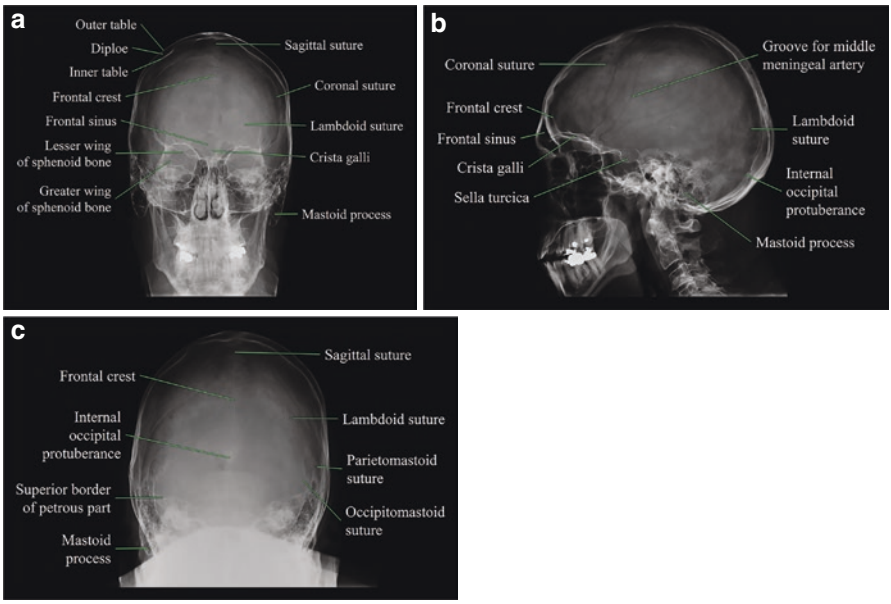

Fig. 12.2 Radiographs (**a**–**c**) of the adult skull

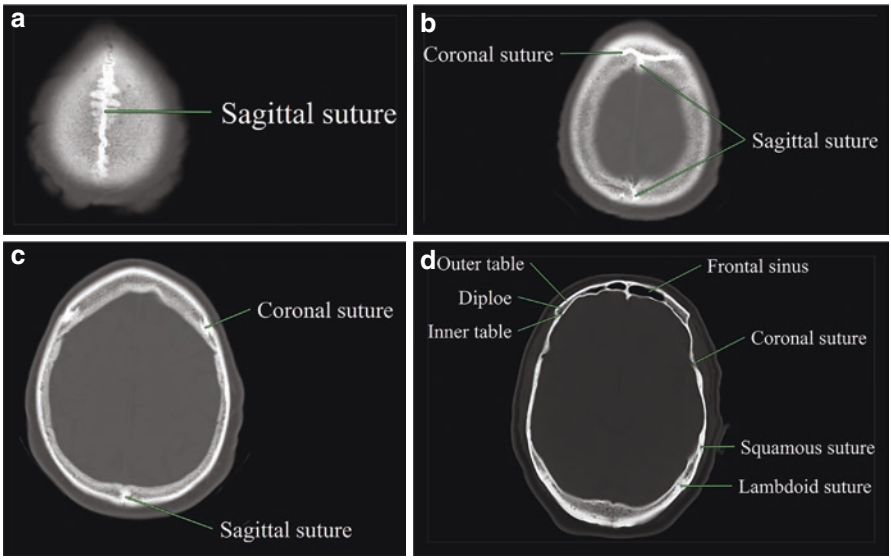

Fig. 12.3 CT scan of the normal head, axial bone filter images (**a**–**d**) of the calvaria demonstrating distinct visibility of the cranial sutures

anatomical structures potentially obscuring or falsely suggesting an underlying fracture. Standard skull radiographs are obtained in frontal and lateral projections. Additional projections are available to cone down on specific anatomical areas, e.g., Waters view and cranial base views. Soft tissue abnormalities such as scalp contusions or hematomas, which are commonly associated with fractures, are not often easily visualized on radiographic imaging.

12.2.2 Computed Tomography

Computed tomography (CT) (Figs. 12.4 and 12.5) is an imaging modality based on a computed image of X-ray beam attenuation, which varies among tissues. Solid tissues such as bone cause high attenuation and a lighter appearance on imaging, and soft tissues or air cause low attenuation and a darker appearance on imaging. This imaging modality is rapid in acquisition and less costly than magnetic resonance imaging. It offers higher image resolution, resulting in high diagnostic value for detection of fractures and acute intracranial hematomas [5]. Typically, computed tomographic images are reconstructed in slice thicknesses ranging from 0.5 to 5 mm. For each slice, spatial resolution is usually between 0.5 and 1.0 mm, which is superior to that of magnetic resonance images. Thin areas of the skull (e.g., frontal sinus and orbit) can be obtained for anatomy- or pathology-specific image protocols by using thinner slices and higher resolution [6]. Current CT technology uses helical acquisition, providing an image data set that can be used for reconstructions in orthogonal, oblique or curved planes, or in three-dimensional projections allowing for additional views that help in detecting fractures.

From the computed tomographs, three-dimensional reconstructions can be obtained providing accurate anatomical representation applicable to various technologies such as virtual reality and 3D printing with the option of bone segmentation [7].

Computed tomography delivers more ionizing radiation than radiography, however, which can cause DNA damage, and in particular a potentially increasing the risk for cancer. Frequently repeated use on reproductive organs and pregnant patients must be taken into account when choosing this imaging modality [8].

Post-processing of CT images using the bone filter algorithm and displaying in bone window settings optimize the visualization of anatomical details, including the outer and inner tables (compact bone) and diploic space (spongy bone) of the skull. Soft tissue settings are optimized for evaluating soft tissue lesions on CT.

Sutures in pediatric skulls have a different appearance from those in adult skulls. The proportionally larger cranial cavity gives the pediatric skull a different general shape. Imaging of the cranium depends on patient age, and expected developmental changes must be considered during evaluation [9]. The comparison between adults and children is evident in 3D surface reconstructions based on computed tomography data sets (Figs. 12.4 and 12.5).

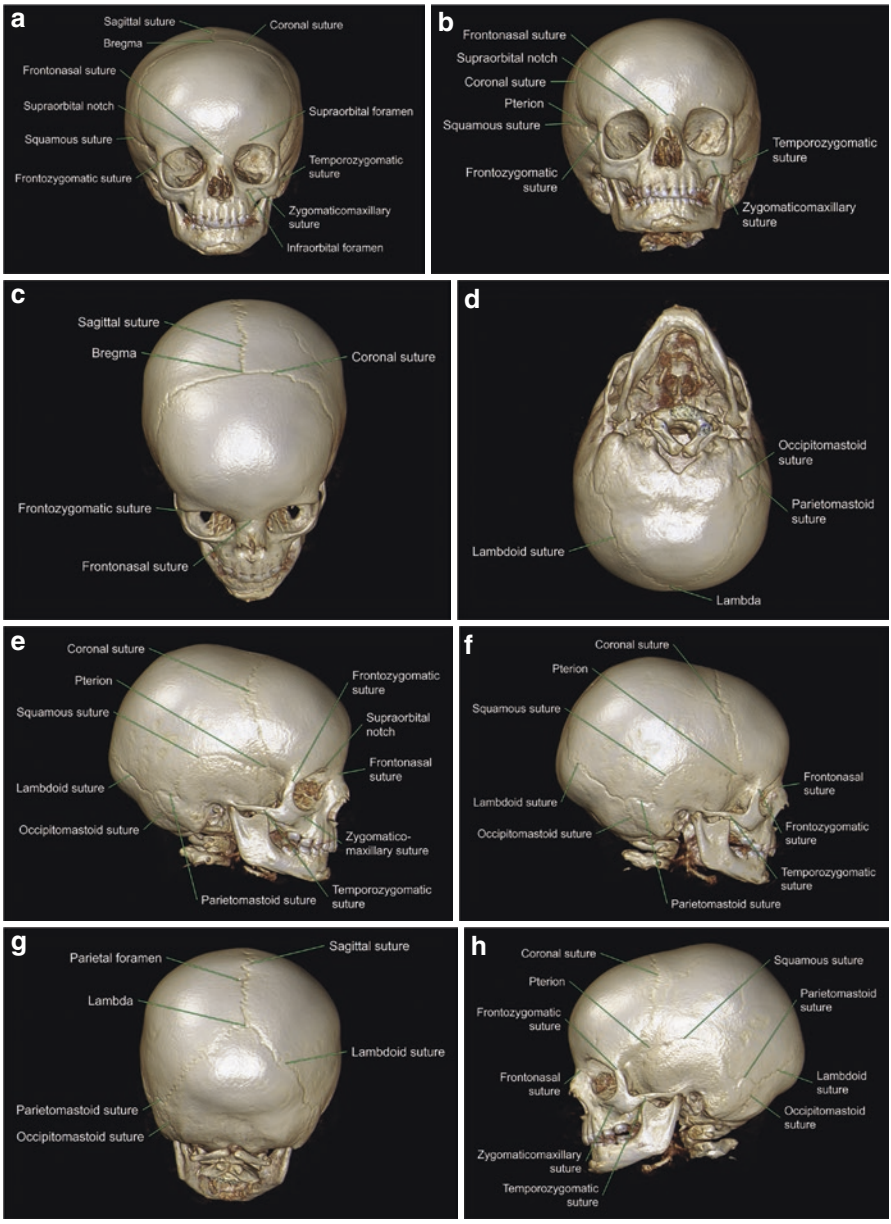

Fig. 12.4 Three-dimensional reconstructions (**a**–**h**) of a CT of a child's skull

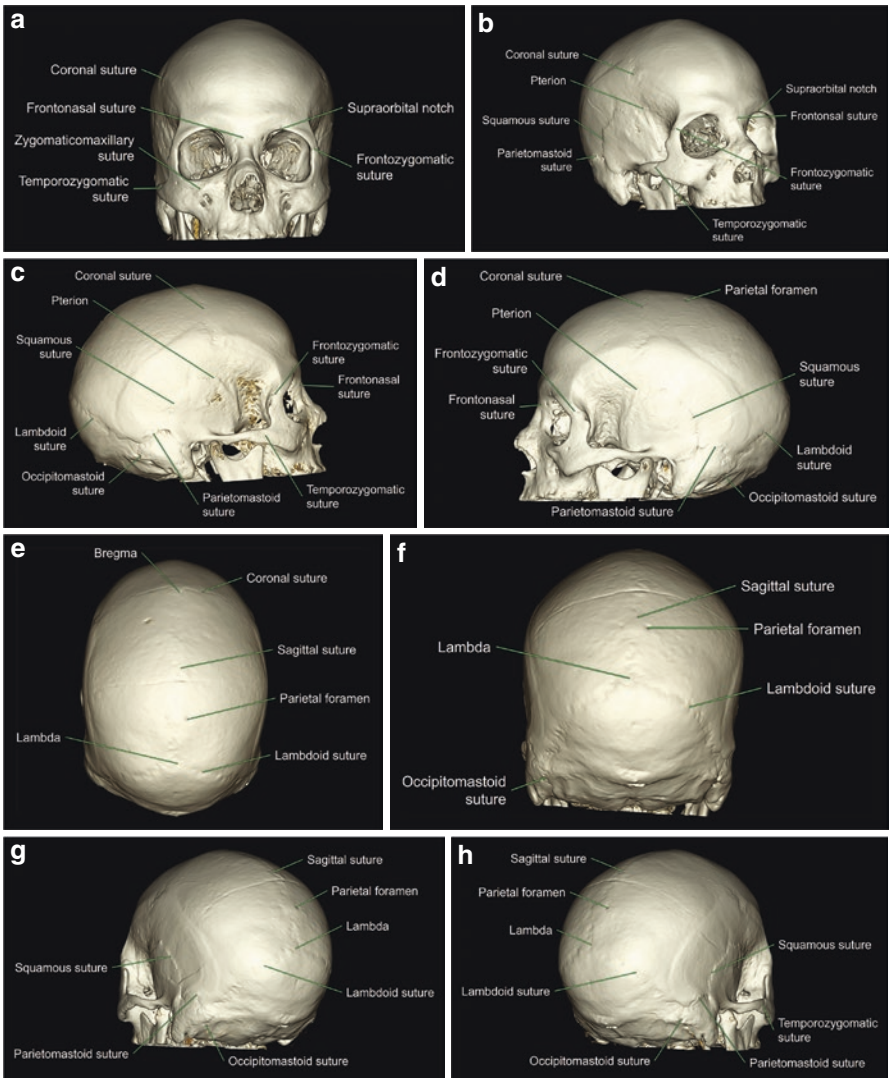

Fig. 12.5 Three-dimensional reconstructions (**a**–**h**) of a CT of an adult skull

12.2.3 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) (Fig. 12.6) is based on the magnetic properties of protons, which differ in precession frequencies and relaxation in a magnetic field depending on the way they bind to different atoms or molecules in different tissues. As magnetic resonance imaging does not involve ionizing radiation, in contrast to radiography or CT, it is a safer imaging modality especially for pediatric and

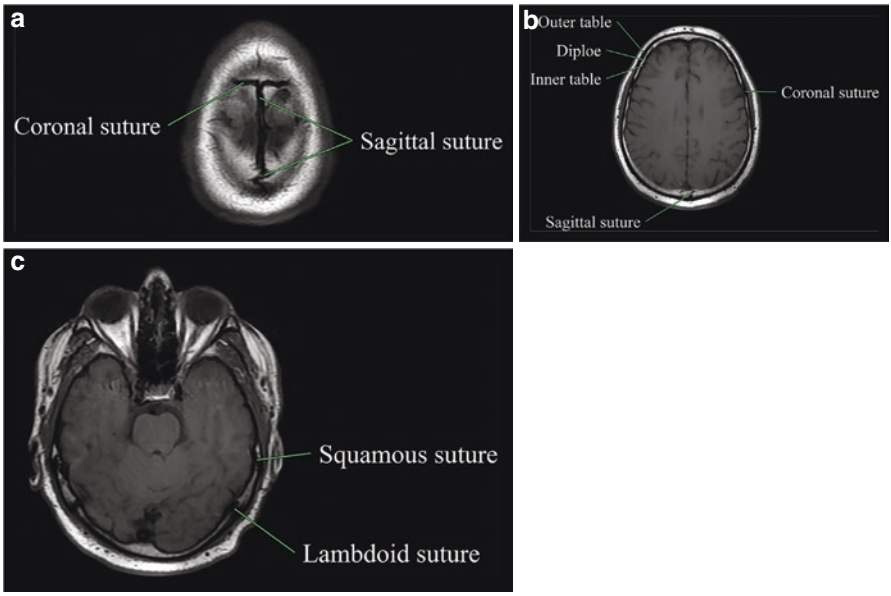

Fig. 12.6 MRI scan of the head, axial T1-weighted images (**a**–**c**)

pregnant patients. It is generally the preferred modality for imaging soft tissue lesions [10, 11]. However, it involves high cost and long acquisition time, and requires good patient cooperation. Sedation might be needed for pediatric or claustrophobic patients. Moreover, medical implants frequently cause image artifacts on MRI or patient safety concerns, precluding use of the technique on occasional patients [12].

While CT provides gives better image resolution of osseous structures than MRI, there is a potential role for MRI in trauma imaging given its ability to detect bone marrow edema in cases of non-displaced fractures, which are not always visible on CT.

Normal sutures can be identified on an MRI image. In T1-weighted images, the diploic space appears with high signal intensity because of the high lipid content of the bone marrow, while the sutures traversing the diploë have low signal intensity owing to their high calcium content.

12.2.4 Ultrasound

Ultrasound (US) shows the cranial cavity in real time, so it is mostly used for prenatal and neonatal patients [13, 14], using the open fontanelles as acoustic windows for viewing brain and cerebellum development and screening for intracranial pathologies. Transcranial ultrasound can only be used until the fontanelles close around the age of 9–12 months. Ultrasound provides high resolution images for

superficial soft tissues. For deep soft tissues, where lower frequency probes with lower image resolution are used, clarity is lower and visualization can be prone to acoustic shadowing artifacts from overlying structures. Ultrasound is fully absorbed or reflected by bone and so it is not used to examine osseous structures or cranial sutures.

12.3 Differential Diagnosis: Sutures and Fractures in Radiological Images

12.3.1 Radiography

On radiography, sutures appear radiolucent since fibrous connective tissues are less radiodense than cortical bones. The sutures have smooth zigzag patterns while fractures have sharp edges (Fig. 12.7).

12.3.2 Computed Tomography

CT is the imaging modality of choice for evaluating osseous structures and cranial sutures, and for detecting skull fractures (Fig. 12.8) or acute intracranial hematomas in trauma patients.

In terms of anatomy, the pterion is of particular interest because it is highly susceptible to fractures. The frontal, parietal, temporal, and sphenoid bones form multiple sutures that should be differentiated from fractures involving the sulcus of the middle meningeal artery, which frequently result in acute epidural hematomas [15].

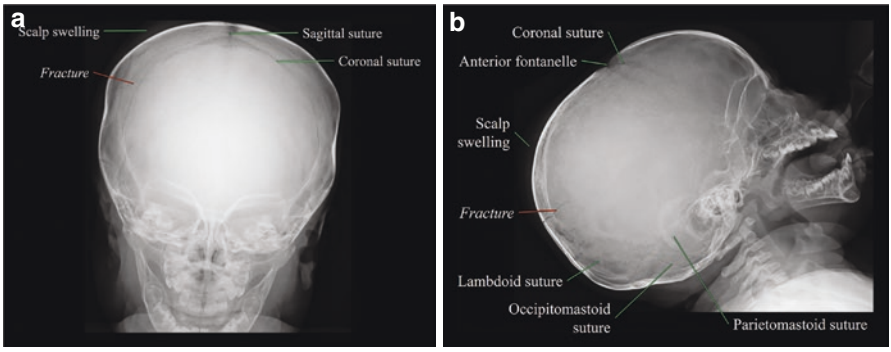

Fig. 12.7 Anteroposterior (**a**) and lateral (**b**) radiographs of a child with a skull fracture

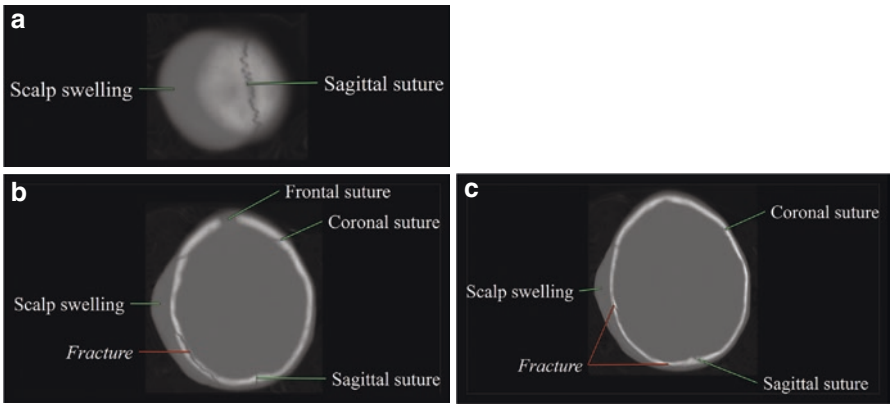

Fig. 12.8 CT scan of the head, axial bone filter images (**a**–**c**) of an 11-month-old boy status post trauma demonstrating a non-displaced fracture in the right parietal area

Table 12.1 Properties that differ between sutures and fractures

Sutures	Fractures
Sclerotic edge	Non-sclerotic edge
Consistent gap	Inconsistent gap
Zigzag pattern	Straight pattern
Possibly merge with other suture	Possibly intersect with other suture
Scalp swelling not associated	Scalp swelling associated

Several properties differentiate sutures from fractures. For instance, sutures have a jagged appearance while fractures are typically straight. These properties can help to distinguish fractures especially from accessory sutures [4] (Table 12.1).

The sutures can be landmarks for estimating the locations of planar images, since they are the borders between cranial bones. For instance, if a horizontal image shows a sagittal suture instead of a lambdoid suture, it can be confirmed that the bones in the posterior part are parietal rather than occipital. Comparing horizontal CT and MRI with three-dimensional reconstructions from a CT can help with stereoscopic understanding.

Clinicians should be aware of anatomical variations to avoid misdiagnosis. For instance, the metopic suture, which normally closes at 2 years of age, and is seldom present in adults, should be distinguished from a vertical fracture of the frontal bone [16].

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Chapter 13
The Biology of the Sutures of the Skull

W. Benton Swanson and Yuji Mishina

13.1 Introduction

The sutures of the skull provide critical growth sites in the skull which are dynamic throughout development. Coordinated cellular processes are responsible for maintenance of their patency (maintenance of an unfused suture), allowing growth, and subsequent fusion during maturation. Craniosynostosis is a debilitating condition where the cranial suture fuses prematurely, restricting cranial vault expansion and leading to severe comorbidities including mental retardation, increased intracranial pressure, blindness, and craniofacial dysmorphism. *The objective of suture biology*, broadly, is to understand normal and pathological development and morphogenesis. Critical aspects of suture biology include characterization of relevant cell populations and their interactions in healthy suture tissue, emphasized in this chapter. An understanding of suture physiology enables the design of innovative therapeutic strategies to prevent or alleviate disease.

Over the last 20 years, significant progress has been made to better understand suture biology, with particular emphasis on the cranial sutures. These advances include molecular profiling of human craniosynostosis patients to identify mutations and molecular etiologies involved in disease pathogenesis, identification of the skeletal stem cells in the suture mesenchyme potentially responsible for or involved in its coordinated processes, and *in vivo* and *in vitro* research models which allow for detailed studies of cranial suture physiology and pathology. Recent advances in cranial suture biology coincide with expanded recent findings in skeletal biology, particularly the identification of skeletal stem cell populations, and advancements in molecular biology techniques.

W. B. Swanson · Y. Mishina (✉)
Department of Biologic and Materials Science, University of Michigan, Ann Arbor, MI, USA
e-mail: wbentons@umich.edu; mishina@umich.edu

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This chapter is meant to provide a comprehensive overview of:

1. tissue components of the cranial suture,
2. a comparison of cranial suture tissue to bone,
3. a description of the cellular composition of the suture in the context of skeletal stem cell populations, with comparison to similar populations identified in long bone,
4. and interactions between neighboring tissues which regulate suture patency.

Emphasis in this chapter will be placed on the cranial suture. However, we will provide some comparison to facial sutures, where we hypothesize similar cellular mechanisms may be at play but are not yet well elucidated.

13.2 Components of the Cranial Suture

Although the skull appears to be one large bone, it is composed of five major bones (two frontal bones, two parietal bones, and one occipital bone) which are connected by fibrous joints known as the *cranial suture*. The major cranial sutures include the following: *metopic* (between frontal bones), *coronal* (between frontal and parietal bones), *sagittal* (between parietal bones) and *lambdoid* (between parietal and occipital bones). Each of these sutures fuses at different stages in development, in both humans and mouse models, as discussed in Chap. 7. Additionally, each are differently affected invarious clinical presentations of craniosynostosis [1]. Despite this, the tissue components of each suture are the same.

A comprehensive understanding of cranial suture biology requires an understanding of the complex microenvironment where the suture functions *in vivo*. A detailed presentation of suture anatomy is presented in Chap. 4. Here we will briefly review the major components of the suture in Fig. 13.1.

The *cranial suture mesenchyme* is a fibrous joint that sits between bones of the skull, holding them together. Flanking *calvarial bone* approximates the suture mesenchyme at *osteogenic fronts*—regions of bone formation that form an interface with the suture mesenchyme. Overlying *pericranium* is the calvarial periosteum enveloping the skull which lies between calvarial bone and the dermal epithelium. The underlying *dura mater* lines the endocranial surface of cranial vault bones and is the outermost membrane enveloping the brain. The cell populations in each tissue are critical to their unique properties. Interactions between these tissues contributes to changes in suture patency throughout growth and development.

13.3 Properties of the Cranial Suture, Compared to Bone

Throughout growth and development, the cranial sutures fuse to become calvarial bone. The mechanisms by which this process occurs will be discussed in detail later in the chapter. The process of bone development begins early in embryonic

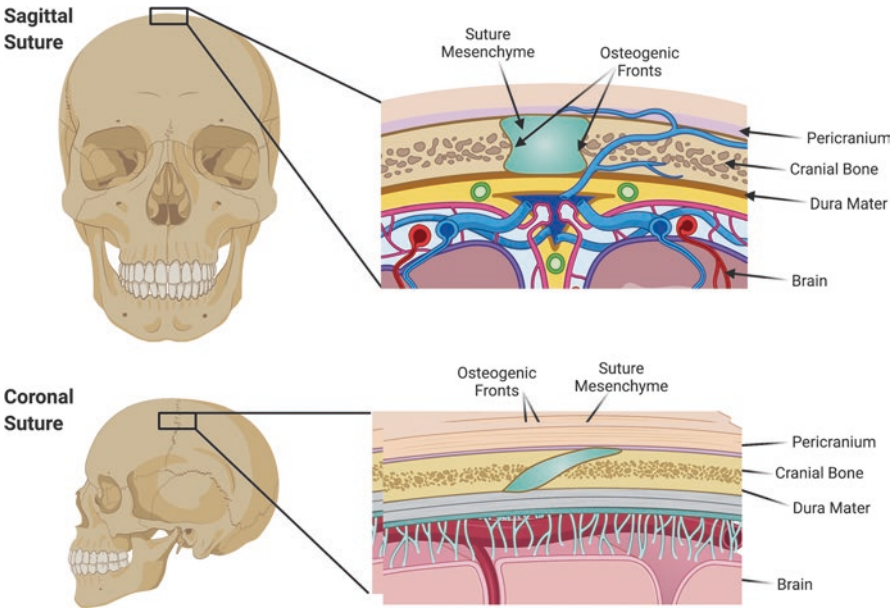

Fig. 13.1 Anatomy of the cranial suture. The cranial suture is a fibrous tissue connecting bony plates of the skull shown in the frontal plane (sagittal suture) and parasagittal plane (coronal suture). The cranial suture mesenchyme interfaces with adjacent cranial bone at osteogenic fronts, and borders adjacent pericranium (cranial periosteum) and dura mater tissues

development by *ossification*. Bone formation proceeds by two distinct osteogenic pathways—*intramembranous ossification* and *endochondral ossification*—both resulting in mineralized bone[2]. Flat bones, including most facial bones, are formed by *intramembranous ossification* where the undifferentiated mesenchyme condenses and differentiates directly along an osteogenic trajectory and becomes robustly vascularized. Differentiating mesenchymal stem cells (MSCs) secrete a mineralized matrix and differentiate directly to become osteoblasts. Long bones and the skull base, on the other hand, are formed by *endochondral ossification*, beginning from a cartilage template. MSCs must first condense and differentiate into chondrocytes. This cartilaginous template becomes vascularized and the perichondrium is transformed into periosteum. Primary ossification centers are formed at sites of initial vascularization and become mineralized. New vasculature provides a source for nutrients and osteoprogenitors, eventually forming bone. Cartilage remains proliferative, allowing the bones to increase in length.

Mature mineralized bone tissue is defined by its vascularization and extracellular matrix composition, two critical tissue-level properties. Matrix maturation and mineralization occurs early in development. Type I collagen accounts for approximately 90% of matrix protein content in bone [3]. Mature bone is composed of less than 5% collagen types III and V. The type I collagen genes are highly expressed in cells undergoing osteogenic differentiation. The Cbfa1 transcription factor regulating the

genes for the alpha1(I) and alpha2(I) sub-chains also modulates osteogenic differentiation [4]. Resulting collagen I matrix is mineralized by the excretion of membrane-bound matrix vesicles containing concentrated calcium and phosphate ions [5]. Osteoblasts readily populate the mineralized matrix to form bone [6].

Vascularization is another key event in both intramembranous and endochondral ossification and hallmark of bone tissue. Bone shows remarkable vascularity—small bore capillaries invade early bone tissue and mature to provide nutrients and osteoprogenitor cells. Close apposition between osteoblasts and large-bore capillaries is noted in developmental studies in chick embryos [6]. Recently Type H-vessels, which strongly express CD31 and Endomucin, have been implicated in bone formation in human subjects. These vessels have been demonstrated to localize osteoprogenitor cells. Reduced abundance of Type H-vessels is associated with aging and is an early event in bone deterioration [7]. Numerous studies corroborate that enhanced angiogenesis leads to significantly increased bone mass [8–10]. Blood vessels support a local microenvironment for osteoprogenitor cells in addition to nutrients and oxygen supply [11].

In contrast to bone, the cranial suture tissue shows markedly different tissue-level characteristics, as summarized in Table 13.1. Its tissue level properties correspond to its identity as a fibrous tissue, which accommodates mechanical stress in the growing skull. Modulated collagen synthesis, the major extracellular matrix component of connective tissues, is important for normal progression of processes like development and repair [12]. In newborn mice, the cranial suture is largely composed of type III collagen. Throughout maturation, there is a significant decrease in the abundance of type III collagen, compared to type I collagen which is present in bone, in the cranial sutures, which coincides with suture fusion [13]. Collagen III protein synthesis is also shown to increase rapidly under biomechanical stress, indicating that it plays a role in mediating mechanical forces experienced during cranial vault expansion [14]. The patent suturesare also absent from typical bone proteins like bone sialoprotein and osteopontin [15].

Angiogenesis, the maturation and growth of blood vessels in tissue, is tightly coordinated to bone formation in the case of both intramembranous and endochondral ossification. In mice, blood vessel ingrowth into the densely cellular suture mesenchyme precedes osteogenesis in the sagittal suture, where vessels are shown

Table 13.1 Tissue-level properties of calvarial bone and the cranial suture

	Vascularization	Extracellular matrix
Calvarial Bone	*Robust vascularization* results from intramembranous ossification. Vasculature, in particular Type H-vessels, is critical for supply of osteoprogenitors and nutrients.	The bone extracellular matrix is mostly composed of *mineralized Type I collagen*. Type I collagen comprises 90% of the protein content of bone, while Types III and V comprise less than 5%.
Cranial Suture	The suture is largely *avascular.* Increased vascularity of the suture is correlated to synostosis and aging.	The cranial suture is largely composed of *immature Type III collagen*. Throughout maturity, the relative abundance of Type III collagen decreases compared to Type I.

to increase in diameter as bone formation proceeds [16]. Vascularization in human patients likewise marks the process of synostosis associated with aging [17, 18]. Bone tissue relies on robust blood supply. Therefore, it is hypothesized that angiogenesis dysregulation may contribute to craniosynostosis and other craniofacial dysmorphology [18]. Physiologically, it is known that pre-chondrogenic and pre-osteogenic condensations of cells do not display vasculature from the time of their initial condensation until their ossification, or differentiation [19]. Avascular, low oxygen environments are known to maintain stem cells in their undifferentiated state and prolong their lifespan. Similarly hypoxia impedes osteogenic or adipogenic differentiation of mesenchymal stem cells [20]. These differences in tissue-level properties between bone and suture tissues support unique cellular microenvironments, specific to the cellular physiology of each tissue.

Craniosynostosis involves the premature fusion of the cranial suture, as discussed in detail in Chap. 15. Classically, suture fusion has been described as overgrowth of flanking calvarial bones through intramembranous ossification [21]. The alternative view is that instead *suture fusion is the result of changes in the suture mesenchyme*. The posterior frontal (PF) suture is the only cranial suture to fuse in mice, equivalent to the metopic suture in humans, which fuses early in human postnatal development [21]. The formation of cartilage in the PF suture has been observed in mice [22] and rats [23], and in the metopic suture in humans [24], prior to fusion. The presence of a cartilage tissue intermediate at the time of suture fusion indicates some kind of nascent tissue residing in the suture mesenchyme which changes its phenotype over time.

13.4 Unique Skeletal Stem Cell Populations are Responsible for Maintenance and Repair

Early efforts of isolating skeletal stem cells relied on their ability to adhere to plastic plates *in vitro* [25]. The bone marrow of long bones contains an osteogenic population of mesenchymal stem cells known as bone marrow mesenchymal stem cells (BMMSC), along with hematopoietic stem cells (HSCs) [26]. BMMSC are capable of maintenance, repair, and regeneration of skeletal tissues [27, 28]. Additionally, they are capable of differentiating towards osteoblastic, chondroblastic, and adipogenic trajectories, exhibiting *in vivo* and *in vitro* multipotency [29, 30]. According to the International Society for Stem Cell Research and International Society for Cellular Therapy, all mesenchymal stem cells should express CD90, CD73, CD105, CD146, and CD166, but lack expression of CD11b, CD14, CD45, and CD34 [31]. Specific markers of BMMSCs have not discretely been well-defined. This is because bone marrow aspirate is a heterogenous population containing a mixture of cells, likely from overlapping lineages. Whole genome transcriptome profiling indicates differential gene expression and differentiation potential within BMMSCs [32]. Additionally BMMSC subpopulation heterogeneity changes with time and passage,

in vitro [33]. Likely BMMSC isolates from bone marrow contain some skeletal stem cells along with osteoprogenitor and endothelial progenitor cells [34]. In contrast to BMMSCs, hematopoietic stem cells give rise to red blood cells, immune progenitors, and osteoclasts [35].

More recently, molecular markers have identified multiple unique niches of skeletal stem cells (SSCs); depending on their location, distinct SSC populations are reported. In order to qualify as stem cells, two critical criteria must be met: *in vivo* multipotency and self-renewal capacity [36]. Lineage tracing and clonal analysis in mice have helped to identify unique SSC populations. Table 13.2 and Fig. 13.2

Table 13.2 Summary of skeletal stem cell populations characterized to date

Location	Description of SSC Population	Key Publications
Resting Zone of Long Bone	*Pthrp*+ in the resting zone of the growth plate give rise to columnar chondrocytes in the proliferative zone, becoming osteoblasts in the primary spongiosa.	Mizuhashi, et al. *Nature*; 2018 [39]
Metaphysis of Long Bone	*Gremlin1*+ osteochondroreticular stem cells concentrated in the metaphysis of long bone. Gremlin1 is an antagonist of bone morphogenic protein (BMP-2/4/7), and agonist of VEGFR2.	Worthley, et al. *Cell*; 2015 [40]
	Gli1+ SSCs are a source of mouse osteoblasts throughout life. Gli1 augments Indian Hedgehog (Ihh) signaling that directs osteogenic function.	Shi, et al. *Nat Commun*; 2017 [41]
Trabecular Bone	*Hox11*+ cells give rise to all skeletal lineages and persist as MSCs, giving rise to previously described LepR+Osx+ MSCs.	Pineault et al. *Nat Commun*; 2019 [42]

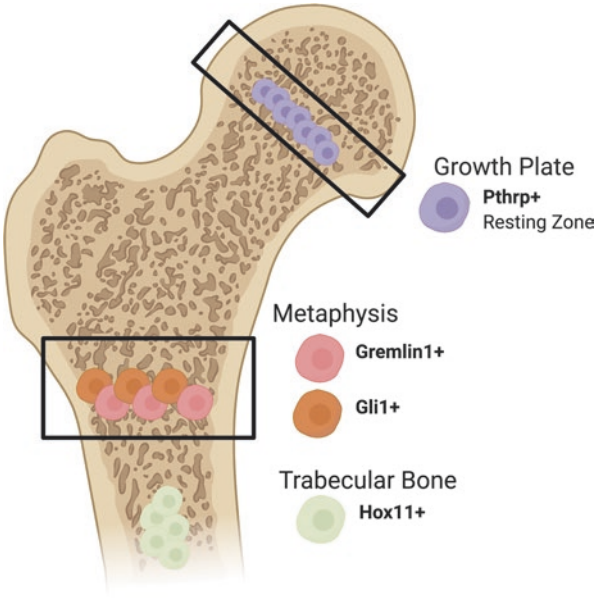

Fig. 13.2 Summary of skeletal stem cell populations in long bone characterized to date. Unique biomarkers mark SSC populations in distinct regions of long bone, summarized in Table 13.2

summarize key publications identifying long bone SSCs, which were reviewed in detail by Ambrosi et al. [37] and Matsushita et al. [38].

Cranial bones, formed by intramembranous ossification, are quite different from long bones, which are formed by endochondral ossification, as previously discussed. One major difference is the limited marrow space in calvarial bones. Another major difference is their embryonic origin. Long bones arise from the mesoderm, while the majority of cranial bones arise from the neural crest, with some exceptions originating from the paraxial and lateral mesoderm [43, 44]. These tissues arise from distinct embryonic origins, described in detail in Chap. 3. As a result, cranial bones likely have different resident skeletal stem cells. For example, homeobox (HOX) genes, are one molecular characteristic of the SSC population, in particular Hox11+ SSC as described by Pineault et al. [42]. During all stages of life, Hox11+ cells are present in long bones and behave as stem cells. The anterior expression boundary of Hox11 in the axial skeleton is the sacral region, responsible for a lumbar phenotype [45, 46]—distant from the craniofacial region. Hox1 is not expressed above the third pharyngeal arch, and responsible for development of the hindbrain segments along the anterior-posterior axis [47–49]. Therefore, it not likely for Hox genes to be involved in the craniofacial skeletal stem cell population. Different embryologic origins of craniofacial and trunk skeletal tissues may partly be responsible for unique SSC populations, as craniofacial patterning is distinctly different from the rest of the skeleton [50].

Compared to long bone, there are three unique growth sites in craniofacial skeletal tissue. These sites include the cranial base, cranial suture, and facial sutures. Much less is known about skeletal stem cell populations in these tissues. Table 13.3 and Fig. 13.3 summarize SSC cell populations identified to date.

Table 13.3 Skeletal stem cell populations identified in craniofacial skeletal tissue including the cranial base, cranial suture, and facial sutures. Much less is known about SSC populations in these tissues

Location	Description of Potential SSC Population	Key Publications
Cranial Base	*Col2a1*+ expressing progenitors of the skeletal lineage are involved in endochondral bone formation in the cranial base. These cells significantly contribute to craniofacial skeletal development No definitive SSC population has been described, to date.	Sakagami et al. *Orthod Craniofac Res;* 2017 [51]
Cranial Suture	*Gli1*+ identified as the main MSC population for craniofacial bones, residing throughout the suture mesenchyme, and behave as typical MSCs in vitro.	Zhao et al. *Nat Cell Bio*; 2015 [52]
	Axin2+ cells are restricted to the suture midline, and are slow-cycling in nature.	Maruyama et al., *Nat Commun*; 2016 [53]
	Prx1+ cells are identified in the calvaria and axial skeleton, but their ablation does not interfere with calvarial development.	Wilik et al., *Stem Cell Rep*; 2017 [54]
Facial Suture	No SSC populations described to date.	

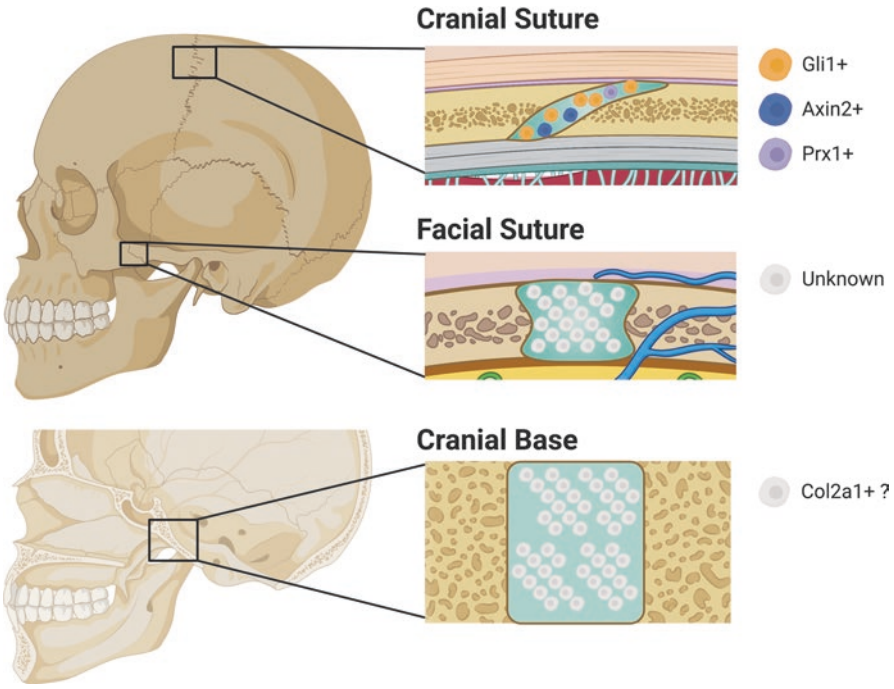

Fig. 13.3 Summary of skeletal stem cell populations in craniofacial tissues hypothesized and/or identified to date, summarized in Table 13.3

13.5 Cranial Suture Mesenchymal Stem Cellsare Responsible for Craniofacial Bone Growth and Repair

Due to their differences, it makes sense that unique cell populations are responsible for the maintenance, growth, and repair of craniofacial skeletal tissue in the same way that SSCs are the resident stem cell populations in long bone. Similar to the identification of long bone SSC populations, identification of SMSC populations has largely been propelled by the identification of specific markers expressed by these cells. However, with advanced in molecular biology, there is likely overlap between stem cell populations in the craniofacial and trunk skeleton based on the similarities between bone formation processes, yet to be elucidated. Recently **suture mesenchyme stem cell (SMSC)** populations have been described, suspected as the major skeletal stem cell of the calvaria. Three SMSC populations, described by characteristic molecular markers, to date are: *Gli1*+ [52], *Axin2*+[53], and *Prx1*+[54], summarized in Fig. 13.4.

Gli1 is a zinc-finger protein and transcription factor for Hedgehog signaling [55]. Zhao et al. hypothesized that Gli1 is a marker of craniofacial MSCs, as it is for the incisor mesenchyme [52, 56]. At birth, *Gli1* is expressed throughout the periosteum,

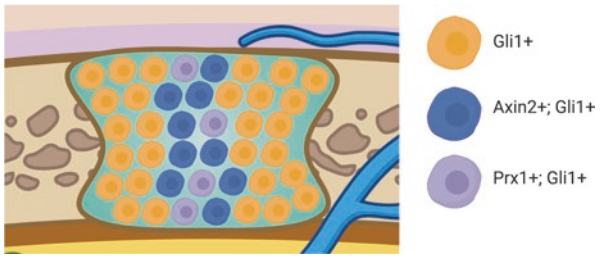

Fig. 13.4 Cranial suture mesenchymal stem cell populations have been identified, with three unique biomarker signatures. These populations are further described in Table 13.4

dura, and suture, and is eventually restricted to the suture mesenchyme by one month, absent from surrounding tissues. *Gli1*+ cells are present in all patent sutures (all sutures except the posterior frontal suture). Lineage tracing analysis demonstrates that *Gli1*+ SMSC are directly involved in bone growth, from the suture mesenchyme, based on their incorporation into calvarial bones. They are also incorporated into the dura and periosteum. In accordance with typical MSC character *in vivo*, *Gli1*+ SMSCs are not proliferative under homeostatic conditions, but readily repair calvarial bone injury by migrating from the suture mesenchyme and proliferating rapidly. *In vitro*, SMSC show typical MSC character by expressing CD44, CD90, Sca1, CD146, and CD73, but not CD34, clone forming ability, and capacity of osteogenic, chondrogenic, and adipogenic differentiation. Critical to the maintenance of the cranial suture, ablation of *Gli1*+ cells lead to skull growth arrest, osteoporosis, and compromised injury repair. A striking craniofacial phenotype in *Gli1-Cre*^{ERT2}*;R26*$^{DTAflox/flox}$ mice results from fusion of all sutures within two months of induction with tamoxifen, mimicking craniosynostosis. Finally, the authors confirmed the decrease of *Gli1*+ cells in a *Twist1+/-* mouse model of Saethre-Chotzen syndrome, the most common syndromic craniosynostosis, confirming their critical role in maintaining the suture [52].

Axin2 is a negative regulator of Wnt signaling, critical in regulating the signaling networks between Wnt, BMP, and FGF signaling [57]. Maruyama et al. identified *Axin2*+ cells in the cranial suture mesenchyme as a subset of naïve cells exhibiting stem cell-like behavior in craniofacial bone development, homeostasis, and repair [53]. *Axin2*+ SMSC are restricted to the midline of the cranial suture mesenchyme, in all sutures except the PF suture, thus like *Gli1*+ SMSC, *Axin2*+ SMSC are likely important in regulating suture patency. Likewise, both are slow-cycling, characteristic of quiescent stem cells. Unlike *Gli1*+ SMSC, *Axin2*+ SMSC are not found in the underlying dura or overlying periosteum. In a calvarial bone injury model with Axin2$^{Cre\text{-}Dox}$; R26RlacZ mice, significant *Axin2*+ SMSC from the suture migrated to the injury site and differentiated to mature bone, and are positive for *Osx* and *Sost*. Unique to their study, the authors characterized the regenerative ability of *Axin2*+ SMSC and demonstrated their ability to form ectopic bone in a kidney transplant model. A mixture of *Axin2* derivatives and non-*Axin2* derivatives were injected into the kidney capsule; on B-gal staining, the majority of regenerated bone was found to be derived from the *Axin2*+ transplanted cells. Interestingly, *Axin2*+ SMSC do

not express traditional SSC markers including CD146, Nestin, Leptin or Gremlin1. However, in line with traditional stem cell character, *Axin2*+ cells from the suture mesenchyme exhibit colony-forming potential, while *Axin2*+ cells from the femur and tibia of mice do not—indicating a unique role of *Axin2* in craniofacial tissue. *Axin2* expression has not been investigated in craniosynostosis models, to date. Global ablation studies have not been reported in *Axin2* models to date [53].

Prx1 is also a transcription factor, implicated in embryonic limb bud formation and craniofacial development [58]. *Prx1*+ cells in bone are known to play a role in fracture repair and homeostasis [59]. Wilk et al. report that *Prx1*+ cells reside exclusively in the suture and decrease in number with age, and differentiate to the osteoblast lineage *in vitro* and *in vivo* [54]. Similar to *Axin2*+ SMSC, *Prx1*+ SMSC are not found in the dura or periosteum during development. Unlike both *Axin2*+ and *Gli1*+ SMSC, *Prx1*+ SMSC are found in the fused PF suture up to 4 weeks; in all cases their abundance decreases with age. Deletion of *Prx1*+ cells in mice resulted in incomplete development of calvarial bones, absence of the cranial sutures, and impaired limb bud development. Similar to both *Gli1*+ SMSC and *Axin2*+ SMSC, *Prx1*+ SMSC likewise directly contribute to repair of calvarial defects in both a subcritical size defect without transplantation, and a critical sized defect with *Prx1*+ cell transplantation. Impaired regeneration of a subcritical defect was observed in mice with ablated *Prx1*+ cells, and in a suturectomy model which removes the cranial suture surgically, without disturbing the dura mater. Interestingly, ablation of *Prx1*+ SMSC in mice does not result in a significant craniofacial phenotype, in contrast to ablation of *Gli1*+SMSC. However complete ablation of *Prx1*+ cells has a significant long bone phenotype, demonstrating some developmental role [54].

Axin2+ cells highly express *Gli1*, while not all *Gli1*+ cells express *Axin2* [53]. *Axin2* marks a smaller cell population than *Gli1*; approximately 15% of the *Gli1*+ population is *Gli1*+*; Axin2*+, limited to the suture midline. Likewise *Prx1*+ cells overlap with *Gli1*+ cells in the cranial suture where *Prx1*+ are a subpopulation of the *Gli1*+ suture mesenchyme [54]. There is no specific overlap of *Axin2*+ and *Prx1*+ cells in the suture mesenchyme, indicating low expression of Axin2 in this specific *Prx1*+ SMSC cell population. To confirm this, *Prx1*+ cells were treated with rmWNT3a, which increased Axin2expression significantly, and at the same time caused*Prx1*+ SMSC osteogenic differentiation. The authors hypothesize that *Prx1*+ SMSC may be a subpopulation of *Axin2*+ SMSC based on the observations that *Prx1*+ ablation does not interfere with craniofacial development, and that *Axin2*+ cells globally co-express *Osx*, while *Prx1*+ SMSC differ from *Osx*+ cells in the suture [54]. A summary of properties of prospective SMSC populations is listed in Table 13.4.

Compelling evidence suggests a unique stem cell population in the cranial suture which modulates patency and fusion. Maintenance of the *Gli1*+ SMSC population is likely critical for maintaining the patent suture, as evidenced by ablation experiments. Premature loss of this cell population results in suture fusion and a significant craniosynostosis phenotype [52]. The *Gli1*+ SMSC population is widely distributed in the suture, whereas *Axin2*+ or *Prx1*+ SMSC seem to be subsets within the suture mesenchyme [53, 54]. The clinical ramifications of these cell

Table 13.4 Cranial suture mesenchymal stem cell populations are hypothesized to be responsible for maintaining the cranial suture mesenchyme and serve as a chief source of calvarial skeletal stem cells. To date, three populations of SMSCs have been identified

	Gli1+ [52]	*Axin2*+ [53]	*Prx1*+ [54]
Distribution in Cranial Mesenchyme	Patent suture, dura, pericranium	Midline of patent suture	Patent sutures
Self-Renewal Capacity	Not investigated	Yes	Not investigated
Bone-Forming Capability and Contribution to Repair *In Vivo*	Subcritical-sized defect healing	Subcritical-sized defect healing and ectopic bone formation in transplant model	Subcritical and critical-sized defect healing
MSC Behavior *In Vitro*	Yes	Yes	Yes
Effect of Cell Population Ablation	Significant craniofacial phenotype and premature suture fusion	Axin2-null mice exhibit premature suture fusion [60], but no ablation study was performed	No significant craniofacial phenotype
SMSC Marker Co-expression	Globally expressed in the cranial suture	*Axin2*+ cells also express *Gli1* and *OSX*	*Prx1*+ cells also express *Gli1*, but not *Axin2* or *OSX*

populations, with relevance to a human SMSC population and in the context of regenerative medicine potential, is unclear. Significant molecular and lineage tracing analyses are necessary to determine a common stem cell niche in the cranial suture. Only preliminary data exists to suggest a relationship or overlap within these populations identified.

13.6 Cellular Processes Involved in Suture Morphogenesis

Growth of the suture is described in detail in Chap. 7; here we will focus on the cellular processes involved in suture morphogenesis and fusion. Recently, *sufficient evidence exists to suggest that craniosynostosis is a stem cell disease*, rather than a bone disease, where premature suture fusion progresses through changes in the suture mesenchyme cell population. Detailed studies in mice indicate that the posterior frontal (PF) suture fuses by endochondral ossification, through a cartilaginous intermediate, as determined by characteristic gene expression and subsequent vascularization of the cartilage template [22, 61]. Similar support for chondrogenic differentiation and presence of ectopic cartilage in fusing sutures has been described in children with premature fusion of the lambdoid and posterior sagittal sutures, based on gene expression and histology [62]. Additional support for this alternative hypothesis stems from molecular analyses which indicate that survival, renewal, and differentiation of the suture mesenchyme are critical to maintaining a patent suture in many mouse models [63–67]. Further, at a genetic basis, craniosynostosis has been linked to mutations in several genes involved in

osteogenic differentiation and bone formation including: fibroblast growth factor receptors (FGFRs) [68, 69], homeobox protein MSX-2 (MSX2) [70, 71], Ephrin-B (EFNB) [72], Twist-related protein 1 (TWIST1) [73–75], and Runt-related transcription factor 2 (RUNX2) [76], and bone morphogenic proteins (BMPs) [77–79]. Details of the genetic basis of craniosynostosis are described at detail in Chap. 16.

Classically, suture fusion is thought to occur through bone growth, where craniosynostosis results from uncontrolled appositional bone growth into the suture mesenchyme [21, 80, 81]. Rudimentary early evidence in human patients suggested increased bone formation by 20–50% in children with fused sutures compared to normal sutures in the same patients, where these cells displayed an osteoblastic phenotype *in vitro* [80]. These early investigations, using rudimentary molecular biology techniques, led the field to believe that craniosynostosis was a bone growth disorder.

Zhao et al. demonstrated that ablation of the *Gli1*+ SMSC population lead to a significant craniosynostosis phenotype in mice, verifying the importance of SMSCs in suture maintenance and fusion [52]. This study, combined with other recent literature, supports the view that the suture population is unique from flanking calvarial bone, and craniosynostosis results from aberrant cell signaling and specification in the suture mesenchyme. With support of molecular biology evidence, two alternative hypotheses have emerged in cranial suture biology, both of which will be discussed with supporting evidence, summarized schematically in Fig. 13.5 and Table 13.5. The first alternative hypothesis is that suture fusion is the result of cell death of the SMSC stem cell/progenitor population in the suture mesenchyme; the depletion of these cells leads to cranial suture fusion. The second alternative hypothesis is aberrant cell fate specification of SMSC in the suture mesenchyme towards chondrocytes, creating an ectopic cartilage template for endochondral bone formation.

13.6.1 Cell Death in the Suture Mesenchyme Leads to Cranial Suture Fusion

Fibroblast growth factor (FGF) has been implicated in numerous syndromic forms of craniosynostosis, most notably Apert syndrome and Crouzon syndrome. Suture cells from transgenic mice with $FGFR2^{C342Y}$ mutation, Crouzon type craniosynostosis, demonstrate inhibition of preosteoblast differentiation and increased apoptosis *in vitro*. Exogenous FGF treatment restores proliferation in undifferentiated cells [82]. Another less severe form of $FGFR2^{C343Y}$ Crouzon syndrome (BALB/c mice background)likewise demonstrates abnormal osteoblast differentiation, increased apoptosis without changes in proliferation, and decreased bone formation and density [83]. The $FGFR2^{S250W}$ mutation resulting in Apert syndrome results in no changes to cell differentiation or proliferation, as determined by expression of typical osteogenic markers between wild type and mutant animals, but increased

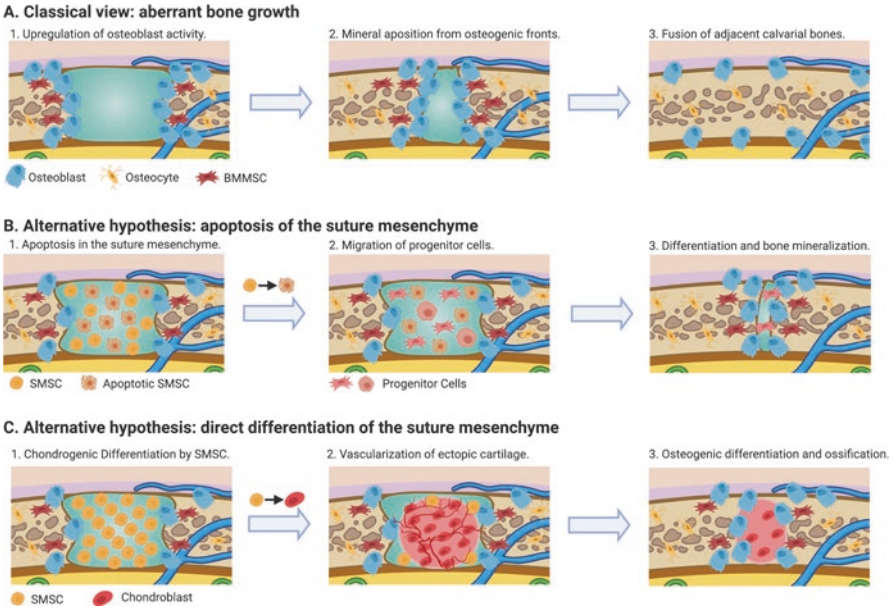

Fig. 13.5 Classical and alternative views of cranial suture fusion. The classical view of craniosynostosis and cranial suture fusion (**A**) is the result of upregulated osteoblast activity in flanking calvarial bone, leading to aberrant bone growth and fusion of adjacent bones. More recently two alternative hypotheses have been developed with robust supporting literature: apoptosis of the suture mesenchyme (**B**) and aberrant differentiation of the suture mesenchyme (**C**)

Table 13.5 Comparison of classical and alternative hypothesis of suture fusion

	Mechanism	Description	Key Supporting Literature
Classical Hypothesis	Aberrant bone growth	Upregulated osteoblast activity in flanking osteogenic fronts leads to uncontrolled appositional bone growth and fusion of calvarial bones.	Opperman et al., *Dev Dyn*; 2000 [21] De Pollack et al., *J Bone Miner Res*; 1996 [80]
Alternative Hypothesis	Apoptosis of the suture mesenchyme	SMSCs undergo apoptosis and are replaced by progenitor cells from surrounding tissues or from the vasculature. These newly emigrated progenitor cells differentiate towards an osteochondral phenotype in the former suture mesenchyme to form mineralized bone.	Hayano et al., *Development*; 2015 [63] Komatsu et al., *J Bone Miner Res*; 2013 [77] Holmes et al., *Dev Biol*; 2009 [65]
	Direct differentiation of the suture mesenchyme	SMSC in the suture mesenchyme directly undergo aberrant cell fate specification toward the chondrogenic fate. The resulting ectopic cartilage is vascularized, and bone formation results from endochondral ossification in the suture mesenchyme.	Coussens et al., *BMC Genomics*; 2015 [62] Zhao et al., *Nat Comm*; 2015 [52] Behr et al., *Front Physiol*; 2011 [66]

apoptosis is responsible for a decreased number of cells in the suture mesenchyme. Contrary to traditional speculation of craniosynostosis as a bone disease, $Fgfr2^{250/+}$ mice also exhibit decreased, rather than increased, bone formation, in addition to premature fusion of the coronal suture [84].

Cells in the suture mesenchyme are responsible for maintaining the cranial suture as a fibrous joint. As the cells die, empty matrix is left, allowing for eventual physical contact of opposing calvarial bones, resulting in their fusion. Another potential scenario suggested by recent literature is that osteoprogenitor cells migrate to this empty mesenchyme matrix and begin the formation of a bone template. The $FGFR2^{S252W}$mutation, which also results in Apert syndrome, demonstrates *in vivo* that the loss of the basal suture mesenchyme leads to the contiguous skeletal membrane of flanking osteogenic fronts. Holmes et al. suggest that mutant cells are unable to respond to signals which would physiologically halt the recruitment or advancement of osteoprogenitor cells following suture mesenchyme apoptosis. Ectopic cartilage formation is identified which may be prerequisite to fusion by endochondral ossification [65].

Enhanced BMP signaling via BMP type 1 receptor BMPR1a results in a midline craniosynostosis phenotype in mice, representative of non-syndromic midline craniosynostosis [77, 85]. These *caBmpr1a;P0-Cre(+)* mice similarly show increased cell death in the anterior frontal suture. In this model BMP signaling is upregulated specifically in the cranial neural crest-derived cell populations, therefore upregulated in the suture, but not flanking bone. The same model shows increased p53 expression in the developing cranium at E12.5 and newborn stages, a transcription factor involved in cell growth arrest and apoptosis, without notable differences in cell proliferation [63]. Treatment with a p53 inhibitor, pifithrin-alpha, improved craniofacial morphology and prevented the premature fusion of anterior frontal, posterior nasal and *premaxilla* frontal sutures in these mutant animals by suppressing p53 nuclear translocation [63].

13.6.2 Aberrant Cell Fate Specification of the Suture Mesenchyme Leads to Cranial Suture Fusion

In the discussion of SMSC populations previously, each of *Gli1*+, *Axin2*+, and *Prx1*+ stem cells display typical MSC behavior *in vitro* [52–54]. In the case of *Gli1*+ SMSC, Zhao et al. demonstrated their capacity to differentiate along osteogenic, chondrogenic, and adipogenic trajectories. Compared to MSCs from the femur of mice, suture MSCs (SMSCs) were comparably able to differentiate to an osteogenic or chondrogenic fate, and less so to an adipogenic fate, indicating their commitment to an osteochondral lineage [52]. Aberrant growth factor signaling in progenitor populations has the potential to alter cell fate specification of multipotent progenitor cells towards osteochondral commitment within the suture mesenchyme.

As previously discussed, evidence of ectopic cartilage formation in fusing sutures suggests a potential for change in the stem cell behavior of SMSCs to participate in bone formation. The first fundamental step in bone formation is mesenchymal condensation of stem cells, for both endochondral and intramembranous ossification [86, 87]. This condensation is orchestrated by growth factor signaling which causes changes in cell-cell and cell-matrix interactions. In Apert syndrome patients, $FGF2^{S252W}$mutation leads to increased cell-cell aggregation and increased N- and E-cadherin expression, known to play a role in osteoblast differentiation [88].

Mesenchymal condensation gives way to cell differentiation and its functional determination. Differentiation of mesenchymal stem cells to bone tissue is a complex and highly coordinated process, summarized in Fig. 13.6. Wnt signaling is one key regulator of intramembranous versus endochondral ossification [89]. In the case of chondrogenic differentiation, the onset of differentiation is initiated by downregulation of condensation genes, B-catenin and Sox9 [90]. Sox9 is normally upregulated during PF suture fusion but not in the sagittal suture; haploinsufficiency in Sox9 in neural crest derived tissues has been shown to impair PF suture closure. Following cartilage formation, *Col1* and *Osteocalcien* expression increase, marking osteoblast differentiation as a bony bridge between osteogenic fronts forms in the suture [22].

The PF and sagittal suture are both neural crest-derived tissues; Behr et al, demonstrated that inhibition of Wnt signaling results in ectopic bone formation in the sagittal suture by endochondral ossification (normally remains patent throughout life), while exogenous Wnt administration results in suture patency as a result of inhibiting endochondral ossification. Physiologically, varied Wnt levels play some

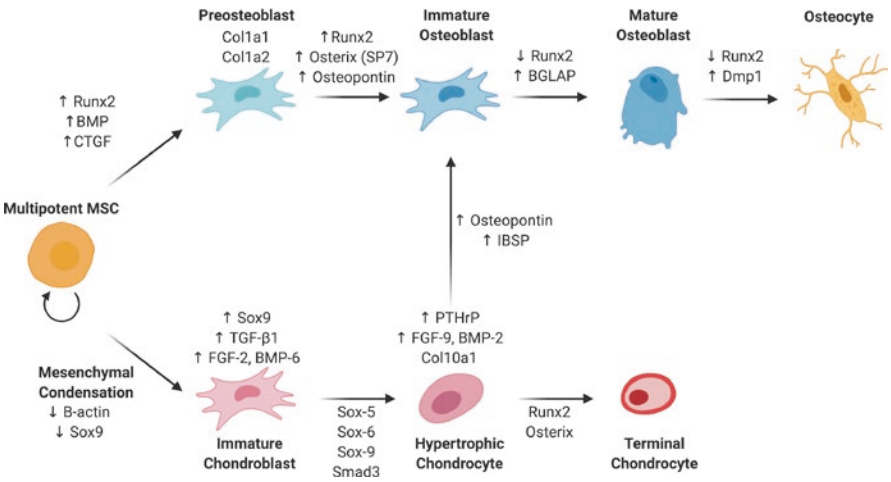

Fig. 13.6 Osteochondral specification of mesenchymal stem cells. Mesenchymal stem cells involved in bone formation proceed via two differentiation trajectories: osteogenic (top) and chondrogenic (bottom). Direct osteogenic differentiation is involved in intramembranous bone formation while chondrogenic differentiation is involved in endochondral ossification

role in regulating suture patency; inhibition of canonical Wnt signaling is necessary for timed chondrogenic differentiation of the suture mesenchyme [91]. Similar phenomena exist in a Saethre-Chotzen syndrome mouse model (Twist1$^{+/-}$) which exhibits premature fusion of the coronal suture by endochondral ossification; *Twist1* is a target of canonical Wnt-signaling and inhibitor of chondrogenesis. Gene expression in these tissues reveals a "clear chondrogenic pattern" initiated by downregulation of Sox9 and Col2 expression along with subsequent upregulation of ColX expression. As the ectopic cartilage matrix mineralizes to form bone, increased osteocalcien expression was observed [66].

Additional evidence for the differentiation of SMSCs leading to suture fusion comes from mechanosensory studies [92]. Persistent mechanical strain causes osteogenic differentiation of the suture. Cyclic loading results from blood vessel pulsation and mastication, while constant loading results from cranial vault expansion. Two weeks of stretching of a mouse sagittal suture causes upregulation of alkaline phosphatase and bone sialo protein (BSP), resulting in increased osteoid production*in vitro*, indicating the osteogenic potential of SMSC [93]. *In vivo* studies in rabbits increased osteoblastogenesis in the sagittal suture as a result of tension across the skull [94].

The clinical presentations of craniosynostosis, and their etiologies elucidated to date, are highly varied. Therefore, it is reasonable to infer that craniosynostosis and premature suture fusion cannot be accounted for by a single mechanism. As an example, FGFR mutants with different point mutations demonstrate different mechanisms of pathologic suture fusion. Contrary to former schools of thought where craniosynostosis was assumed to be a bone disease, two alternative hypotheses are supported by recent literature. The first alternative hypothesis, apoptosis, involves death of the suture mesenchyme and its replacement by osteoprogenitor cells. The second, aberrant differentiation, involves cell fate specification of the mesenchyme to a chondrogenic lineage as the result of aberrant growth factor signaling. In either case, substantial recent evidence points to craniosynostosis as a stem cell disease, rather than bone disease. Therefore, an intimate understanding of the cranial suture mesenchyme stem cell population is critical for designing future therapeutic or regenerative interventions.

13.7 Interactions Between Neighboring Tissues

The cranial suture-calvarial bone is in close proximity to two other tissues: the dura mater and pericranium, as shown in Fig. 13.1. Interactions between these tissues are important considerations in the regulation of suture patency and fusion, summarized in Fig. 13.7. The *pericranium*, also called calvarial periosteum, is a highly vascularized membrane that lines the surface of the calvaria [95]. As a result of its rich vasculature, it has been shown to be a rich source of osteochondral progenitor cells [96]. These cells are largely *Osterix*-expressing precursors, indicating some skeletal stem cell origin [97].

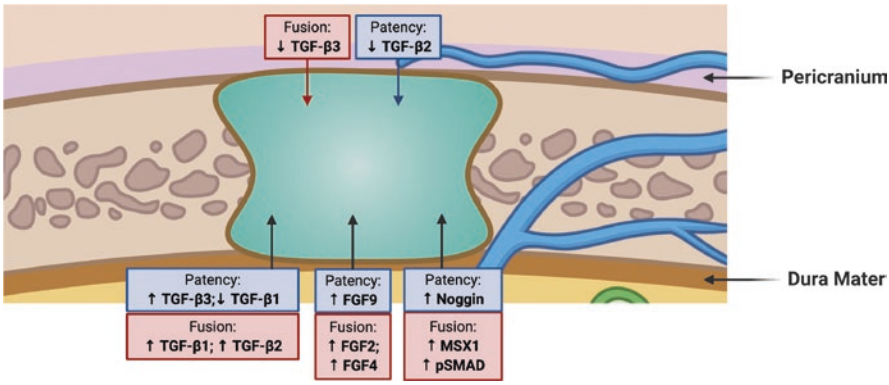

Fig. 13.7 Surrounding pericranium and dura mater tissue influences fusion and patency of the cranial suture through soluble factors and cell signaling pathways

In studies of long bone, the periosteum has been shown to be an important in the fabrication of bone grafts, predisposing a graft site to higher quality bone repair outcomes, in terms of vascularization and endochondral bone formation resulting in calcified tissue, compared to grafts placed against muscle facia [98]. Presence of the periosteum, or its conditioned media, increases osteoblast proliferation, indicating that both progenitor cells themselves and/or soluble factors may increase bone formation capacity [99]. In particular, transforming growth factor beta (TGF-β) is highly enriched in the periosteum [100]. Cells of the periosteum are also able to promote cartilage formation in a chondrogenic environment [101]. This is likely the result of growth factor signaling which induces progenitor cells, such as mesenchymal stem cells, within the periosteum membrane to differentiate, resulting in ectopic cartilage and new bone formation. Cells of the periosteum are also able to promote cartilage formation in a chondrotropic environment.

Specific to the cranial suture, Zhao et al. reported *Gli1*+ cells throughout the calvarial periosteum and dura mater at birth, indicating some similarities between the cranial suture mesenchyme and these adjacent tissues [52]. Removal of the sagittal suture impaired cranial bone repair, even with an intact calvarial periosteum and dura mater, indicating the suture population is critical to bone repair [52]. Opperman et al. demonstrated that the presence or absence of the periosteum is *not* a critical regulator of suture patency or osseous obliteration in a transplantation model, using the rat coronal suture [102]. In contrast, surgical removal of the periosteum resulted in consistent fusion of the frontonasal suture, and some fusions of the sagittal suture in rats [102]. But in agreement with Opperman, no fusion in the coronal sutures [103]. While TGF-β signaling in relation to the suture-pericranium interaction has not been explicitly studied, TGF-β isoforms have been shown to play a role in suture proliferation, differentiation, and apoptosis. Changes in TGF-β receptor expression have been described in actively fusing sutures compared to non-fusing sutures, so regulating receptor expression and therefore responsiveness to TGF-β signaling may regulate suture patency [104]. Antibody neutralization of

TGF-β3 resulted in premature suture obliteration, while the neutralization of TGF-β2 prevented obliteration [105]. The balance of TGF-β signaling from the pericranium likely regulates apoptosis and differentiation capacity of the suture mesenchyme. However, little is yet known about the direct signaling implications between thepericranium and suture mesenchyme. It is possible that various sutures respond differently to signals from thepericranium.

Interactions between the *dura mater*, the membrane below the suture and cranial bones, and the suture have been characterized in much greater detail. The dura mater is neural crest-derived, while the periosteum is mesoderm derived, which may explain their different roles in regulating the cranial suture [106]. For example, in rats, the dura mater is a critical regulator of the coronal suture. Its surgical excision causes premature fusion, while removal of the periosteum does not negatively affect its patency [102, 107].

The character of dural cells has been demonstrated to change dramatically between young and adult animals, which likely correlates to their ability to coordinate bone repair [108]. In addition to age-related differences, regional differences of dura osteoinduction have been described. Both chondrogenesis and osteogenesis can be coordinated by suture dura, while only osteogenesis can occur from calvarial bone dura, indicating some dural heterogeneity [109]. Finally, the dura shows temporal-related differences. In rats the PF suture fuses while the sagittal suture normally remains patent. When the dura underlying the PF and sagittal sutures was rotated by 180 degrees in infant animals, the sagittal suture fused while the PF suture remained patent, compared to sham treated rats [110]. In cases where the dura is removed completely, the suture has been shown to remain patent indefinitely [111], further ascribing a role of the dura mater in modulating the cranial suture mesenchyme fate, however they are likely able to maintain themselves in the absence of the dura.

Clearly the dura plays an important role in modulating suture patency and fusion, however it is unclear whether it is directly a cell source or a paracrine effector. In a rat calvarial defect model made with a trephine bur, Wang and colleagues isolated the edges of the bony defect from the dura with an impermeable cellulose acetate membrane, and demonstrated bone formation on the underside of the membrane, but not above, indicating that osteoprogenitor cells from the dura mater were responsible for bone formation [112]. In a separate study where the dura was isolated by a semipermeable expanded polytetrafluoroethylene (e-PTFE) membrane, animals treated with the membrane alone healed with bone and a suture-like tissue similar to the normal sagittal suture in the midportion [113]. The combination of these studies indicates that cellular, as well as soluble excreted factors from the dural tissue are critical drivers of skull development, maintenance, and repair. Opperman et al. characterized these soluble factors in a series of *in vitro* experiments to determine that heparin binding factors, members of the epidermal growth factor family (EGF), in dural conditioned media were found to maintain the sutures in their patent state, while non-heparin binding factors failed to prevent fusion [114]. A list of soluble growth and transcription factors implicated in paracrine interactions between the suture mesenchyme and dura is summarized in Table 13.6.

Table 13.6 Soluble growth and transcription factors implicated in paracrine interactions between the suture mesenchyme and dura mater

Family	Factors and Roles	Key Literature
Transforming Growth Factor Beta (TGF-β)	↑*TGF-β1* and ↑*TGF-β2* throughout suture fusion (PF); ↑*TGF-β3* expression and ↓TGF-β1 and ↓TGF-β2expression in patent sutures (coronal). The coronal suture fuses in the absence of the dura: ↑TGF-β1 + ↓ TGF-β3.	Opperman et al., *J Bone Miner Res*; 1997 [115] Most et al., *Plast Reconstr Surg*; 1998 [116] Slater et al., *Plast Reconstr Surg*; 2009 [117]
Fibroblast Growth Factor (FGF)	↑ *FGF2* is coexpressed with TGF-β1 in the time preceding and during PF suture fusion, and is associated with osteoblast differentiation. FGF2 downregulates Noggin expression and is a major regulator of suture-specific BMP activity. *FGF4* expression is not detected in patent sutures, but exogenous administration accelerates fusion. ↑ *FGF9* is expressed in patent sutures and the dura (sagittal).	Most et al., *Plast Reconstr Surg*; 1998 [116] Ogle et al., *Cells Tissues Organs*; 2004 [118] Warren et al., *Nature*; 2003 [119] Rice et al., *Development*; 2000 [120] Kim et al., *Development*; 1998 [121]
Bone Morphogenic Protein (BMP)	↑ *Noggin* in patent suture (sagittal and coronal). ↓ *Noggin*, an antagonist of BMP signaling and osteoblast differentiation, occurs during pathological suture fusion. FGF2 is thought to regulate BMP4-induced Noggin expression. ↑ *BMP4* and ↑ *BMP7* expression in the dura tissue underneath bone and the osteogenic fronts, but not suture mesenchyme. ↑ *BMP-SMAD signaling* (↑ SMAD phosphorylation, caBmpr1a) leads to premature fusion of the anterior frontal suture in mice.	Warren et al., *Nature*; 2003 [119] Jiang et al., *Int J Clin Exp Pathol*; 2015 [122] Lajeunie et al., *Childs Nerv Sys*; 1999 [123] Komatsu et al., *J Bone Miner Res*; 2013[77]; Pan et al., *Dev Biol*; 2017[124]; Kramer and Yang et al., *Genesis*; 2018 [79]
MSX Homeobox Transcription Factor	↑ *MSX1* and ↑ *MSX2* expression in the suture and dura; MSX2 expression decreases with age. MSX1 expression colocalizes with FGF4 expression.	Kim et al., *Development*; 1998 [121] Warren et al., *J Craniofac Surg*; 2003 [125]

Similar to the pericranium, TGF-β signaling plays a role in dural signaling in the suture microenvironment. These molecular interactions between the dura and cranial suture are well-characterized in *in vitro* and animal models, however little has been described in the clinical context. It is well known, however, that maintenance of an intact dura is critically important for human surgery [126]. Also, worthy to note, these signaling molecules and transcription factors are known to play a role in dural signaling are well-described mutations implicated with craniosynostosis. Likely the combination of signaling within the suture mesenchyme and between the suture mesenchyme and its adjacent tissues contribute to premature fusion in disease, as a result of cellular changes that take place amongst the SMSC population.

13.8 Comparison of Cranial Sutures to Facial Sutures

Like the cranial sutures, *facial sutures* are fibrous joints in the face and active sites of bone growth, consisting of the same major tissue components as cranial sutures: two adjacent bony units and fibrous layers above (periosteum) and below (vascularized). While some facial sutures fuse throughout development to form a union between facial bones, others may never completely close. Their anatomy is addressed in detail in Chap. 6. Changes in facial suture histology are parallel to changes in the appearance and growth of the face; similar to cranial sutures, cartilage has been found at the margins of the bones or in the suture tissue proper followed by intense phosphatase activity, suggesting fusion by endochondral ossification [127, 128]. Premature fusion of the facial sutures can potentially lead to facial asymmetry and dysmorphism [129]. To date, no stem cell populations have been identified in the facial suture. Unlike calvarial sutures, however, the sutures of the face are in a different physiological microenvironment, notably lacking contact from the dura mater. Likely similar adjacent tissues signaling mechanisms at least in part maintain the facial suture mesenchyme and coordinate its fusion. Facial sutures are required to grow in many different directions along with facial processes, whereas the cranial suture generally grows in one direction [130]. An understanding of facial suture biology, like cranial suture biology, is important in understanding the etiology of malocclusions and facial deformities. Compared to the cranial suture, much less is known about the facial suture.

In an early study of premature facial suture fusion, Alhopuro and colleagues transplanted free periosteal grafts overlying facial sutures and observed bone formation, in a rabbit model, sufficient to fuse the premaxilla-maxillary and frontonasal sutures. Fusion stopped growth and caused severe growth disturbance of the snout, resulting in deviation (so-called "twist") to the operated side and compensatory changes in other facial sutures to minimize the disturbance [128]. Faciostenosis describes the premature fusion of facial sutures, and is commonly observed in Crouzon syndrome patients [131]. As a result, these patients can exhibit a higher incidence of compromised facial growth and significant malocclusions, particularly with fused frontomaxillary, nasofrontal, and nasomaxillary sutures on the side of the synostosis [132]. Similarly, facial twist has been described in non-syndromic unilateral coronal craniosynostosis patients, where the midface deviates towards the synostotic side and lower face deviates away from the synostotic side, as a result of premature facial suture fusion [132]. In a rabbit model of coronal suture immobilization, significant craniofacial growth defects were observed where the facial sutures may compensate for premature cranial suture fusion [133].

In these cases where craniosynostosis and faciostenosis are comorbidities, it is unclear whether these occur independently, or if facial defects are secondary to cranial suture growth defects[134]. It is important to note that the premature facial suture fusion and premature cranial suture fusion are not mutually exclusive. A moue model for Muenke syndrome ($FGFR3^{P250R}$) exhibits premature fusion of facial sutures, but rarely the coronal suture as seen more commonly in humans. This model may be a useful tool for discovering previously unreported yet potentially

significant phenotypes of Muenke syndrome and elucidating the primary versus secondary phenotypes caused by specific mutations[135]. Other mouse models of Pfeiffer ($FGFR1^{P250R/+}$) and Apert ($FGFR2^{S252W/+}$) syndromes demonstrate premature fusion of the premaxillary-maxillary, nasal-frontal, and maxillary-palatine sutures of the face, resulting in midfacial hypoplasia, as primary synostoses. These models are useful for continued study in elucidating contributions of cranial suture synostosis, cranial base stenosis, and facial suture stenosis to development, and elucidating the cellular mechanisms underlying each.

13.9 Conclusions and Perspectives

Sutures of the skull are critical structures which allow for growth and expansion, as fibrous joints of the craniofacial skeletal complex. Over time, carefully timed cellular processes are responsible for their physiologic fusion. Premature fusion of sutures can result in significant and potentially morbid effects, as seen in craniosynostosis. Recent progress in cranial suture biology has identified stem cell populations unique to the suture mesenchyme that function in maintenance and repair of the skull. These populations, *Gli1*+, *Axin2*+, and *Prx1*+ SMSC are seemingly unique from recently identified skeletal stem cell populations in long bone. Identification and isolation of these tissues enables detailed *in vitro* and *in vivo* studies to better understand their behavior. In addition, surrounding tissues including the cranial periosteum and dura mater are critically important in regulating suture patency. Genome-wide association studies in humans [136] and a myriad of animal models of craniosynostosis [137, 138] have led to significantly increased understanding of physiologic and pathologic suture fusion. An intimate understanding of these processes is critically important in developing therapeutic and regenerative approaches to treating craniosynostosis. While appealingly similar in function and anatomy, significantly less is known about facial sutures compared to the cranial sutures.

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Chapter 14
Types of Craniosynostosis and their Etiology, Pathophysiology and Epidemiology

Fernando Chico Ponce de León and José Alfonso Franco-Jiménez

14.1 History

Craniosynostosis is a disease where or more cranial sutures presente abnormal closure, ossification and sclerosis producing brain compression and intracranial hypertension as well as intellectual and visual deterioration [1–3]. It can be present at skull base or at cranial vault and is frequently accompanied by cranial and facial dysmorphic features that require surgery.

Cranial surgery dates from prehistoric times with expressions found in the American and African-Eurasian continents. Evidence of the above are trepanned crania found in southern Europe as well as in South America (Peru). In Mexico, there are trepanned crania associated with Zapotec and Aztec cultures. Indian Sutra techniques are well known for rebuilding nasal features [4–12].

Galen made formal reference to craniosynostosis in his cranial anatomy treatises although they contain no illustrations [13, 14]. During the Renaissance, Vesalius in "*De humani corporis Fabrica"* as well as illustrations from Leonardo da Vinci, Durer and della Croce's editions show a number of craniosynostosis. Vesalius and della Croce drew malformed skulls, whereas da Vinci and Durer illustrated abnormal facies and heads [7, 12].

The first references to cranial sutures in American literature are found in works by Alonzo López de Hinojosos and Agustin Farfán (1578 and 1579, respectively) although there is no specific reference to craniofacial malformations [4, 5, 15, 16].

F. Chico Ponce de León (✉)
Pediatric Neurosurgery Department, Children's Hospital of México Federico Gómez, Mexico City, Mexico

J. A. Franco-Jiménez
Pediatric Neurosurgery Department, Children's Hospital of Toluca, Toluca, Estado de Mexico, Mexico

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The study of malformations in general was structured by the end of the 18th century, with special emphasis on malformations in internal organs, brain, thorax and abdominal cavities, genitalia and limbs. The 19th century was especially important in the study and classification of craniosynostosis. Becker and Virchow studied them and established laws where the cranium will develop in the same direction of the stenosed suture [17]. By 1890, surgery for these conditions began. In France, Marie Lannelonge published *"De la craniotomie dans la microcéphalie in L'Académie des Sciences"* [18]. At the same time, Lane published a private work describing surgery of a microcephalic cranium in the U.S. [9] This type of surgery was resumed in 1927 according to interventions carried out by Faber and Towne in "oxycephaly" cases, as craniosynostosis were called at the time, with better results than their preceding colleagues [18].

The development of new techniques from the French School led by Tessier, Marchac and Renier firmly settled the need to provide surgical treatment for craniosynostosis [18–28]. Specific techniques were refined to deal with a certain type of craniosynostosis such as Dhellemmes' technique used for trigonocephaly [29–31]. In Mexico, Fernando Ortiz Monasterio Garay and Antonio Fuente del Campo became international references on this type of surgery [32–37].

There are a few quality studies have been published (Esparza et al., Ferreira et al. and others), which are bibliographic reviews [17, 38–45].

14.2 Cranial and Facial Embryogenesis

The cranium develops from two embryogenic origins: (1) cranial vault, jaw and face develop from neural crest; (2) cranial base develops from mesoderm as well as vertebral column.

Formation of growth cartilages from cranial base bones starts at approximately the 5th gestational week with condensation of mesenchymatic cells in cartilaginous foci, which will take place at the occipital plate on each side of the notochord to form parachordal cartilage where the occipital scale will develop. The ethmoid bone will develop from trabecular cartilages, whereas nasal bone processes will form from nasal capsules. According to Testut, the sphenoid bone presents 18 ossification centers [46]. This description includes only six ossification centers with three centers at each side: a central part with sella turcica is formed by hypophyseal cartilage, one center for lesser wings of sphenoid from orbitosphenoidal cartilage and another center for greater wings of the sphenoid from alisphenoid cartilage. Towards the 6th and 7th gestational weeks, paired cartilages are already fused and will have contact with each other towards the 12th gestational week. At the same time, the temporal bone develops from otic capsule chondrification [47, 48].

Experiments carried out in animals have demonstrated cranial vault origins are linked to ectomesenchyme from neural crests. In human beings, this origin is yet to be demonstrated. Khonsari and Catala propose parietal bones and base bones as mesodermal derivates and consider that definitive arguments on their mesodermal

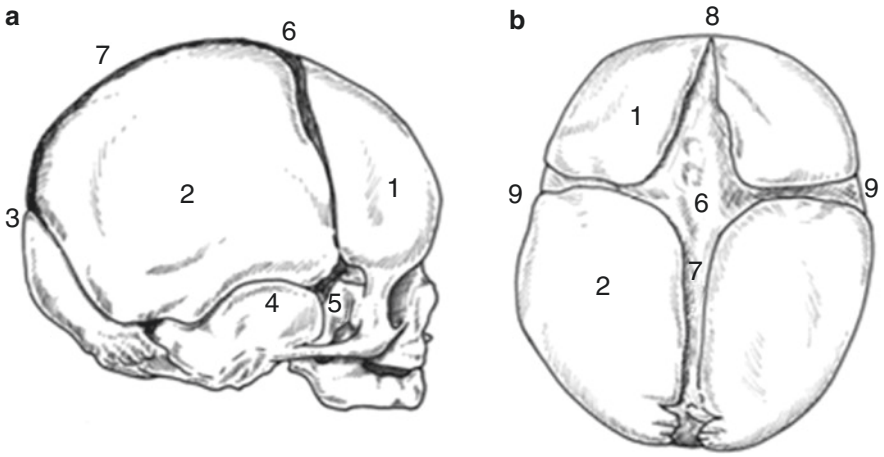


Fig. 14.1 (**a**) Lateral view of newborn skull. (**b**) Upper view of newborn skull: (1) frontal, (2) parietal, (3) interparietal occipital bone, (4) temporal scale, (5) pterion, (6) anterior fontanel, (7) sagittal suture, (8) metopic suture, (9) coronal suture

or ectomesenchymal origins are difficult to confirm for the time being. The occipital bone would be derived from neural crests as well as temporal, pterion and facial scales [49]. Ogle located frontal, parietal, occipital and temporal scale origins from ectomesenchyma of neural crests [48]. The authors agree that certain conditions must prevail so that sutures remain permeable and, when these conditions fail, craniosynostosis can take place (Fig. 14.1).

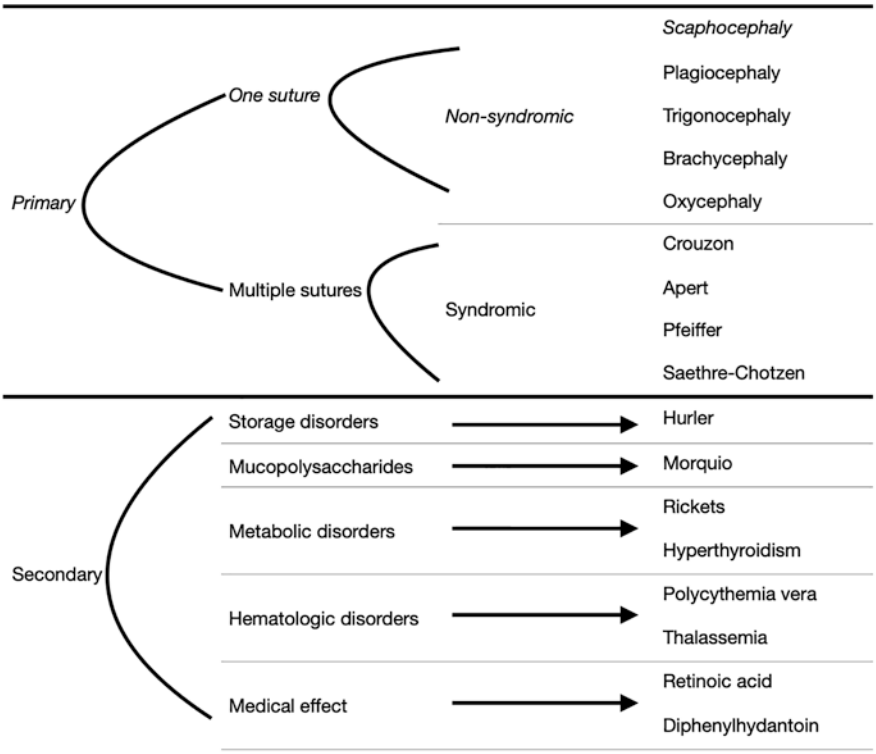
14.3 Epidemiology and Incidence

The non-syndromic primary craniosynostosis in one or more sutures presents in 1/2100 children. It has been estimated that this represents 10–16 cases/10,000 newborns. This pathological suture closure presents in 1/2000 children in France [25].

Secondary craniosynostosis include a number of syndromes ranging from 90 to 139 according to some authors. Metabolic, hematologic, storage dysfunctions and problems associated with medications can be associated with craniosynostosis [50]. Thompson and Hayward present a simple classification that summarizes these concepts (Table 14.1) [51].

Scaphocephaly is the most frequent craniosynostosis reported for most series (40–60%) [24, 39, 41, 42, 52, 53]. Next is coronal suture craniosynostosis (13.1–30%) [24, 39, 42, 54], which may be either unilateral, (plagiocephaly) or bilateral (brachycephaly). Metopic stenosis (trigonocephaly) presents in 6.6–20% of cases [24, 39, 42, 55, 56] although series from *Centre Hospitalier Universitaire des Enfants Malades Necker de Paris* (CHUNP) places it as the second most frequent craniosynostosis with 21.6% [24]. Cases where more than one suture is

Table 14.1 Thompson's craniosynostosis classification [51]



affected represent 4–% of cases. Esparza et al. report figures similar to the above for the Madrid population in 244 non-syndromic cases and 120 patients for Porto Alegre series [24, 39, 42, 50].

In our experience coronal plagiocephaly is the most frequent non-syndromic craniosynostosis (47%). It is possible that this frequency is associated with care provided by *Hospital Infantil de México Federico Gomez* (HIMFG) because it is a tertiary-care hospital where complex cases are concentrated. Next we have scaphocephaly (30%) and non-syndromic multiple craniosynostosis (4%). Syndromic craniosynostosis represent 17% of cases.

Syndromic craniosynostosis represents 11.30–27% of the total as observed from experiences at the HIMFG, CHUNP and Hospital October 12th in Madrid [23, 39]; at the HIMFG the presentation rate is 17%. The most frequent syndromic craniosynostosis are associated with Crouzon's disease ranging from 29.8% to 67% (34.37% for October 12th Hospital and 67% for HIMFG). Apert syndrome varies between 20% (HIMFG) to 34% (October 12th Hospital), whereas Pfeiffer syndrome ranges between 4.4% (HIMFG) and 21.8% (October 12th Hospital). Finally, Saethre-Chotzen syndrome occurs in from 2.2% (HIMFG) to 18.1% (CHUNP) of cases. The largest international series was presented by CHUNP with 3199

Table 14.2 Craniosynostosis at HIMFG and CHUNP

Non-syndromic craniosynostosis	*HIMFG (n = 138) (%)*	*CHUNP (n = 2710) (%)*
Coronal plagiocephaly	47	13.1
Scaphocephaly	30	48.6
Trigonocephaly	12	21.6
Brachycephaly	7	5.3
Others	4	11.4
Syndromic craniosynostosis	*HIMFG (n=28)*	*CHUNP (n=489)*
Crouzon	67	29
Apert	20	32
Pfeiffer	4.4	17
Saethre-Chotzen	2.2	18.1
Others	6.4	4.9

HIMFG: Hospital Infantil de Mexico Federico Gomez (n = 166). CHUNP: Centre Hospitalier Universitaire des Enfants Malades Necker de Paris (n = 3199)

cases, whereas the HIMFG series comprises 166 cases from 5 years' experience (Table 14.2) [24, 57].

14.4 Etiology

14.4.1 Genetic Factors

Some syndromic craniosynostosis are associated with Msx2 haploinsufficiency and mutations in fibroblast growth factors (FGFs) as well as four of their receptors located in chromosomes 4p, 51, 8p and 10q [58]. These are alterations in transforming growth factor-β (TGF-β) with errors in biochemical or biomechanical signal patterns. These factors are produced by the duramater and cells from sutures. An appropriate function of these substances prevents suture closure. All these mechanisms can also be applied to non-syndromic craniosynostosis [25, 48, 59].

Hereditary forms are predominant in syndromatic craniosynostosis. The distribution of hereditary cases is 39.2% for Crouzon's disease, 50.6% for Saethre-Chotzen syndrome, 24.5–30.2% for Pfeiffer syndrome and 33.3–35.7% in frontonasal dysplasia. On the other hand, non-syndromic craniosynostosis present a percentage ranging from 7.3% to 10.9%, except for brachycephaly where percentages increase to 29.6–32.6% [25].

Chromosomal alterations are frequent and have been detected in almost all genome chromosomes; however, there is a prevalence of alterations in chromosome 7p. Mutations of genes TWIST and GLI3 are responsible for certain craniosynostosis. Some examples are chromosome 10q, associated with Crouzon's disease, 8p with Pfeiffer syndrome and 7p with Saethre-Chotzen syndrome [60]. Syndromic craniosynostosis frequently represent an autosomal-dominant disorder [25, 61]. Clinical onsets vary when there are mutations in several genes or if a single gene presents several mutations [25, 38].

14.4.2 Metabolic Factors

Rachitic parents has been associated as a risk of factor for oxicephaly. Hypophosphatemia, hypothyroidism, mucopolysaccharoidosis and smoking have been mentioned as possible risk factors for craniosynostosis. Epileptic pregnant women who are treated with valproate sodium may deliver a child with trigonocephaly [25, 62].

14.4.3 Epidemiological Factors

It has been suggested that a possible factor for developing Apert and Crouzon's disease is paternal age >34 years. Oxycephaly has been associated with a similar mechanism because in northern Africa where there are very young mothers paired with older fathers there is a high prevalence of this condition. Other authors mention that maternal age may also be associated with these syndromes [25, 61].

14.4.4 Pathophysiology

Physiomechanical, chemical and genetic mechanisms have been associated with craniosynostosis [49, 63, 64]. These processes are found during the embryonic period in early stages such as formation of primary vesicles, specifically in prosencephalon [63]. Syndromic craniosynostosis are closely related with genetic alterations. Suture placement and its contact with duramater in a specific area participate in the abnormal closure of sutures and ossification mechanism. It has been observed in laboratory animals that if sutures are placed at a different site, ossification will take place faster in those placed near the duramater where sutures close rapidly and vice versa [65]. This finding has been associated with overexpression of TGF-β1, βFGF-mRNA, IGF-I and mRNA at the suture level.

Some mechanical factors have been suggested as responsible for trigonocephaly and scaphocephaly because a mechanical compression may increase TGF-β levels. Some authors report that breech births and twin pregnancies increase the frequency of craniosynostosis. Oligohydramnios may contribute to pathophysiological characteristics of these malformations [52, 55, 66–69].

14.4.5 Impact over Cranial Cavity

According to CHUNP series, most craniosynostosis, both syndromic and non-syndromic, present a decreased intracranial volume with the exception of most cases of Apert syndrome. A relationship between a smaller intracranial volume

and intracranial hypertension (ICH) has been established. However, several authors have reported different ICH figures for non-syndromic craniosynostosis. Renier reported figures >15 mmHg and found ICH in 66.6% of oxycephalies, 31.3% in brachycephalies, 15.2% in scaphocephalies, 12.7% in plagiocephalies and 7.9% in trigonocephalies. Lamboid craniosynostosis presented no ICH. A series with 41 cases with a high number of non-syndromic craniosynostosis reported 92.6% of cases presented ICH but there was no relationship between intracranial volume and ICH [20–23, 27, 70, 71].

Intracranial hypertension is more constant in syndromic craniosynostosis having a relationship with 68.8% of Crouzon's cases, 45% of Apert cases and 29% for other syndromes. ICH has been found in 44.4% of complex craniosynostosis [23, 24, 27, 72]. Recently, Tamburrini et al. found up to 24% of ICH cases associated with non-syndromic craniosynostosis and 52.8% associated with syndromic conditions [2, 3].

Cognitive capacities are also reduced [27, 72, 73]. Optic neuropathy produced by craniosynostosis with ICH and hydrocephaly with alteration of visual-evoked potentials (VEP) increases despite decompressing surgical treatment and only after correct cerebrospinal fluid diversion is it possible to revert alterations in VEP [68]. Other authors confirm this in 6–15% of patients. These alterations are attributed to ICH multifactorial origin, which includes brain venous congestion, obstruction of upper airways and hydrocephaly [3, 74, 75].

14.4.6 Ophthalmic Dysfunctions

Up to 67% of coronal plagiocephaly cases present vertical strabismus and possible development of amblyopia. All craniosynostosis can present a horizontal strabismus, which becomes more evident in upward gaze [76–78].

Ophthalmic dysfunctions are relatively frequent in syndromic craniosynostosis. It has been observed that 40% of cases present photophobic astigmatism and, therefore, amblyopia [65, 76, 78]. Cases from Crouzon's, Apert and Pffeifer syndromes present "V" pattern exotropia in upward gaze [76, 78].

Papilledema (PE) and papillary atrophy (PA) are major complications associated with nontreated craniosynostosis but less frequent than ICH, which is present in all craniosynostosis [79]. Between 0.3% and 0.8% of cases of scaphocephaly, trigonocephaly and plagiocephaly present PE, whereas only 0.1% scaphocephaly cases have reported PA. There are no reports of brachycephaly combined with PE or PA. Oxycephaly cases present 9.8% and 12.7% PE and PA, respectively. These are the highest figures for optic atrophies associated with these conditions.

Complex craniosynostosis present PE in 4.3% of cases and PA in 0.9% of cases: Apert syndrome shows PE in 3.2% of cases without PA evidence. Crouzon's disease is the most common PE-affected condition with 16.6% of cases and PA in 3.4% of cases [27].Sleep apnea and its associated hypoxia may worsen these conditions, producing a greater deficiency in visual sharpness [1]. Surgical correction of strabismus is suggested with special assessment depending on each case.

14.4.7 Impact over Intellectual Functions

CHUNP reported the largest series in the literature where analyzed craniosynostosis and intellectual quotient (IQ). It has been confirmed that delaying brain decompression 1 year has negative consequences for intellectual development. Assessment using scales such as *Brunet- Lezine, Nouvelle echelle metrique de l'intelligence* and *Wechsler Intelligence Scale for Children* revealed an IQ >90 in 93.8% of scaphocephaly cases before the first year of age and this percentage decreased to 78.1% of cases after the first year of age. As for brachycephaly, 89.2% of cases presented an IQ >90 before the first year or age and this percentage decreased to 52.2% of cases after the first year of age.

Non-syndromic craniosynostosis were associated with a higher deterioration of intellectual functions over time. Therefore, 86.4% of complex craniosynostosis presented an IQ >90 before the first year of age and this percentage dropped to 59.3% after the first year of age. Plagiocephaly cases presented a reduction from 90.4% before the first year of age to 80.7% after the first year of age. Oxycephalies are usually diagnosed after the first year of age and this is why it is difficult to find a comparative assessment, but only 40.8% of cases presented an IQ >90.

Apert syndrome was the most severe syndromic craniosynostosis where the proportion of cases with IQ >90 went from 45.5% before the first year of age to 7.4% after the first year of age. Crouzon's disease presented a proportion of 80% before the first year of age that dropped to 65.6% after the first year of age. During the same assessment, the remainder of the syndromic craniosynostosis dereased from 70% to 48.9% after the first year of age [53]. The French series, as well as most international literature reports, agrees that there is an intellectual impairment even in non-syndromic craniosynostosis [80–85].

14.4.8 Epidemiological Characteristics

There are reports in international literature where non-syndromic craniosynostosis show a higher prevalence in males than in females: 3:1 for trigonocephaly, 4:1 for scaphocephaly and 1:2 for plagiocephaly [24, 53, 70]. At the HIMFG, we have observed a female prevalence both for non-syndromic craniosynostosis (56%) as well as syndromic events (62%). In our series with 166 individuals, 57% of cases were female.

HIMFG patients were mostly newborns, infants and young children, representing 70% of cases, whereas 15% were older children and 15% were adolescents.

Craniosynostosis is essentially diagnosed clinically. However, imaging plays an important role in the precise classification of malformations even before birth [86].

14.4.9 Scaphocephaly

Definition and epidemiology. This condition occurs after isolated closure of sagittal sutures. It occurs in 1/1700 to 1/2100 newborns in the U.S. It is predominant among males with a 4:1 presentation rate and represents between 40% and 60% of craniosynostosis. However, it represents 24% for all craniosynostosis treated at HIMFG after coronal plagiocephaly [52, 53, 87].

Clinical characteristics. According to Virchow's law, malformations found in scaphocephaly include enlargement of fronto-occipital diameter and shortening of biparietal diameter (Fig. 14.2). There are variants regarding frontal shape, which can be bilateral and rectangular, normal or semi-spheric. When the frontal diameter is larger, the suture has been predominantly closed on the anterior axis; however, when the occipital diameter is larger, this is a sign of posterior suture closing. Occipital diameter is generally conical with apex towards the middle of the occipital scale. When both poles have deformed, the entire suture has presented an aggressive closure. In severe malformations, bone curve is inverted at parietal and temporal levels, presenting convexity towards the brain surface. There is also recession to different degrees at the pterional level, which accents frontal deformation and is associated with stenosis level on the sphenofrontal suture. Stenosed bone is thickened just like pterion. There are no other sutures involved in the development of the malformation [24, 53].

Imaging. Along with clinical diagnosis, this entity can be identified with a single cranial x-ray (CXR) with lateral incidence (L) that supports diagnosis: we will gen-

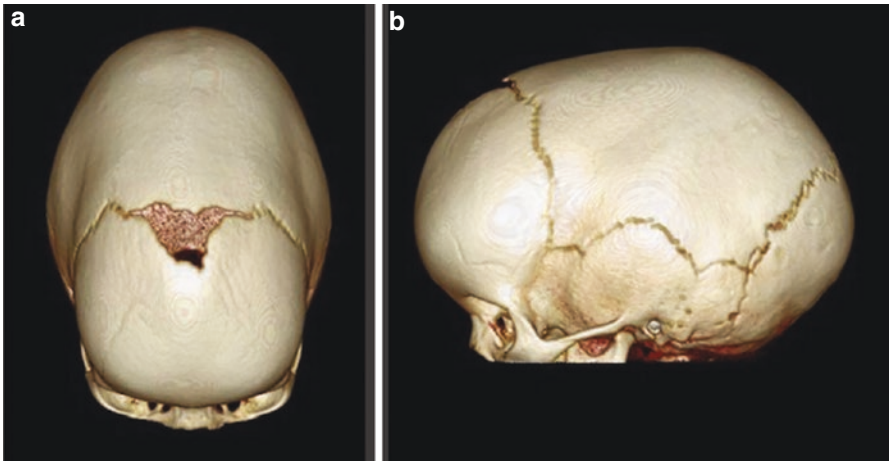


Fig. 14.2 Scaphocephaly. 3DCT images: (**a**) Frontal cranium view and from above. Absence of sagittal suture is appreciated with elevation where reduced interparietal diameter is shown. (**b**) Lateral projection where elongated cranial profile is observed with closed suture. Other sutures are distinguished clearly and correctly

erally find a lengthening of the anteroposterior (AP) diameter either with prevalence at frontal, occipital or both poles. This deformation resembles a zeppelin. It is frequent to find finger-like impressions at parietal levels and in a portion of the temporal and occipital bones. AP CXR shows absence of sagittal suture being replaced with dense bone in some cases. This entity shows a reduced biparietal diameter (Fig. 14.2). Cranial computed tomography scan (CT) confirms clinical and CXR findings, clearly revealing biparietal and occipital brain compression. Brain inside this skull is compressed, especially at biparietal and occipital areas, which are the narrowest. At frontal level, skull deformation favors open subarachnoid spaces of the brain folds, particularly at the prefrontal level. It has been documented that these spaces will disappear as the patient grows [24]. Sagittal suture closure can be identified through bone window X-ray and 3-dimensional computed tomography (3DCT). Coronal sections from bone window X-ray and 3DCT reveal a channel that contains the longitudinal sinus instead of the suture; this characteristic should be kept in mind at the time of surgery [24, 52, 53]. An electroencephalogram, developmental assessment and full ophthalmological examination are required with any type of craniosynostosis.

14.4.9.1 Coronal Plagiocephaly or Unilateral Coronal Craniosynostosis

Definition and epidemiology. This entity is the second most frequent condition documented in literature. At HIMFG it represents the most frequent craniosynostosis with 40% of cases, higher than scaphocephaly. This condition ranks third on CHUNP series and represents 13% of non-syndromic craniosynostosis. It presents a right side prevalence (61%) as well as a female prevalence (69%), which contrasts with scaphocephaly [22, 23, 53, 54, 88]. This malformation occurs after left or right coronal suture stenosis as well as involvement of sutures at the base level, especially frontosphenoidal and sphenotemporal through to the greater wing of the sphenoid (Figs. 14.3 and 14.4). Unilateral coronal closure partially explains ocular orbital deformation backwards with an edge that lacks definition as well as nasal scoliosis. Base deformation with temporal bone towards stenosed coronal side presents affected sutures at the base that involve half of the cranial coronal ring with a sphenofrontal, sphenosquamous and sphenopetrosal stenosis on the affected side [88, 89]. Strabismus favors amblyopia at the expense of the stenosed side [65, 77].

Clinical characteristics. As with other craniosynostosis, diagnosis is essentially clinical and accurate observation will allow a differential diagnosis regarding positional malformation, which is generally not subject to surgical treatment. At the frontal position, an orbitary dystopia will be observed on the affected site with orbit positioned upwards and backwards. Nasal scoliosis is common with scoliotic convexity located at the nose root towards the stenosed side. This sometimes conditions a divergent strabismus on affected side. On the sagittal plane there is lack of definition on the orbit edge, as well as flattening of the glabella on the affected site

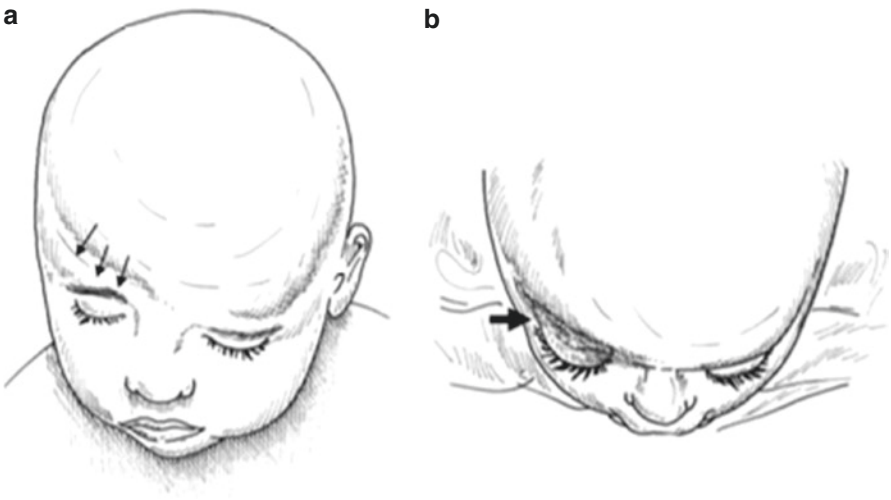


Fig. 14.3 Right coronal plagiocephaly. (**a**) Patient viewed from the front with a slight upward angle where orbit is pulled backwards and inwards (arrowheads). Orbital edge, almost absent externally, has a posterior and downwards tilt. Forehead is flattened and with caudal traction. (**b**) View from above clearly reveals exorbitism of eye from affected side (arrowhead)

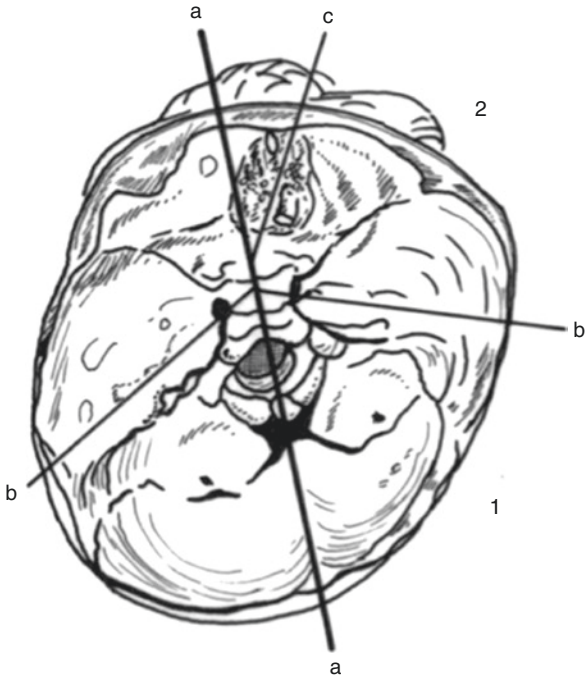


Fig. 14.4 skull base. Sagittal a-a line, petrosal b-b lines, ethmoid c line. Organic plagiocephaly shows an increased sagittopetrosal angle on affected side (*1*) as well as a reduced ethmoid-petrosal angle on the affected side (*2*). An ethmoid-sagittal angle opens that should normally not exist (*3*). The structure is drawn towards the base coronal ring, which is stenosed towards sphenofrontal and sphenotemporal sutures

with protrusion of the contralateral glabella and pterional and temporal regions. When observing the patient's head from above, we find a clear exorbitism on the affected side with protruding eyelid and absence of orbit edge as well as flattening of the corresponding glabella. The external ear is closer to the orbit at the affected site. At the axial plane, there is recession of frontoorbital region [54, 88, 89]. This particular cranial plicature with a torsion point at stenosed sutures both on vault and basal counterpart may produce a compensatory protrusion of the contralateral parietal bone. Some authors propose a complex cranial anthropometry with 59 indexes and distances to measure, which are [40, 89] regarded as difficult to implement for an appropriate plagiocephaly diagnosis and treatment [48]. Oblique oval skulls, functional deviation and flattening are antagonists. The external ear moves away from the fronto-orbital region, which is in a rear position, whereas the contralateral auricle that is more protruding is closer to the fronto-orbital region without exorbitism on the affected side [90].

Imaging. As with other craniosynostosis, imaging will confirm clinical diagnosis, which determined the type of presentation. Plagiocephaly shows typical images on CXR. PA reveals the lesser wing of the sphenoid raised on its external edge, which is a typical "harlequin" sign. In addition, it is asymmetric because the affected orbit is pulled outwards and upwards. Pterional and temporal protrusion can be observed on the affected side as well as nasal scoliosis. The lateral plate of the affected side reveals ossified stenosed suture without characteristic radiolucent lines. CT scan allows confirmation of the CXR images. We can observe the stenosed suture either in full or partially blurred. Three-dimensional reconstruction shows malformation as described and allows for careful surgical planning. Three-dimensional reconstructions of the skull base reveal that plagiocephaly from coronal stenosis presents specific characteristics. It is possible to distinguish deviation from temporal petrosa towards the stenosed side with an opening up to 71° of the petrosagittal angle where 50° is the normal opening angle. At the same time, ethmoid processes represented by the cribriform plate are deviated towards the stenosed side. Compression of the front pole at the craniosynostosis side is evident (Fig. 14.4) [24, 26, 54, 88, 89].

14.4.9.2 Deformational Posterior Plagiocephaly

Definition and epidemiology. This condition presents no pathological closure of any suture. Deformation of the entire skull including cranial base at times is harmonic and balanced. Angles at the base are not altered as in plagiocephaly associated with coronal suture closure and sclerosis [89].

Clinical characteristics. This malformation has been attributed to breech presentation during most of the pregnancy. In fact, during clinical examination we can observe that part of the face is set backwards. This position does not share characteristics with organic plagiocephaly. The external ear is set far from the orbit in functional plagiocephaly in contrast with organic plagiocephaly where, because of sphenopetrosal angle closure, the external ear is closer to the backward orbit. There

is evidence that patients sleep on the occipital flattened side and support their head when awake. Deformation usually improves when the child is able to sit up and stay in an erect position during most of the day [39].

Imaging. In this condition, both CRX and CT scan show all sutures open. There is no "harlequin" appearance and cranial base angles are normal.

14.4.9.3 Posterior Plagiocephaly (lamboid)

Definition and epidemiology. This entity presents closure and sclerosis of one or both lamboid sutures. This is not a common condition and ranks last among non-syndromic craniosynostosis in CHUNP series (0.77%). This figure is even lower when associated with syndromatic craniosynostosis. Posterior plagiocephaly may be associated with scaphocephaly [24, 26, 75].

Clinical characteristics. This condition is generally identified by flattening of the back of the skull on the stenosed suture side. This deformation is not very evident because of its position where it is generally covered by hair. When it is present in a female with long hair, it is even more difficult to identify. This may produce certain generally mild and discreet cranial obliqueness. Closure of both lamboid sutures is very rare and produces a particular deformation with severe flattening of the back of the skull. This is the only craniosynostosis, both syndromic and non-syndromic, that presents no ICH even though the number of cases is very small: six patients were reported by the CHUMP series [27].

Imaging. Diagnostic imaging is carried out using CXR and confirmed using 3DCT. Electroencephalogram is required because surgical intervention will be defined according to a possible cortical irritation on the stenosed side. There have been few surgeries of this craniosynostosis at HIMFG. According to some authors, surgery is always recommended [69, 91, 92].

14.4.9.4 Trigonocephaly

Definition and epidemiology. This entity ranks third according to the HIMFG series (10%) for non-syndromic craniosynostosis and second according to the CHUNP series (21.6%) after scaphocephaly [25, 52, 56].

C*linical characteristics*. This malformation is associated with closure and sclerosis of the metopic suture. In the axial plane, we observe a characteristic triangular forehead with apex pointing forward. The angle may present different closure degrees from acute to open. The frontal view reveals that orbits, both at sides and at the edge, show a backward position with medialization. At the same time, intercanthal internal and external distances decrease, reducing capacity of the anterior cranial fossa. We find hypotelorism with the vertical internal pillar and the external pillar is inclined inside with typical "raccoon eyes" presentation (Fig. 14.5) [24, 32]. The best angle to verify the aforementioned characteristics of this malformation is to view the patient's head from above.

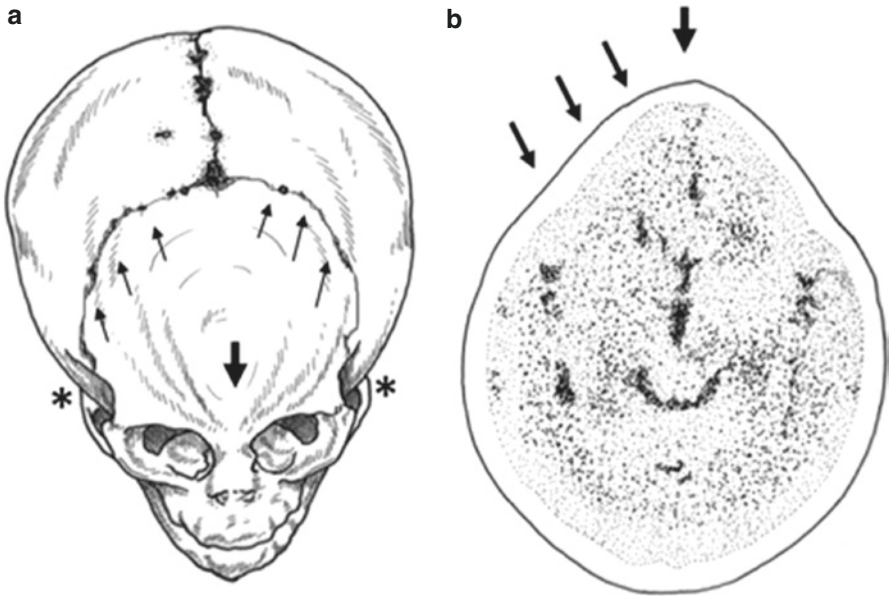


Fig. 14.5 Trigonocephaly. (**a**) 3DCT reconstruction: thin arrows mark coronal suture that limits the size of the frontal shell, which is small and has a pointed medial section. Constant hypotelorism; nasal bones advance with backward movement of bilateral orbit edge (thick arrow). Pterional regions are recessed, characteristic of this malformation (*). (**b**) CT scan with axial cuts: pointed forehead is shown with external extreme points towards inside (thick arrow). Thin arrows mark frontal bones pressing bilateral prefrontal regions

Imaging. CXR are always useful to verify thickening and increased bone density at the metopic level as well as hypotelorism and typical "raccoon eyes" presentation. Cranial CT scan shows, in frontal axial cuts, the characteristic deformation that names this craniosynostosis. It is possible to verify hypotelorism, thickening of the metopic suture and "pointy" forehead with several closure levels. We generally find a protrusion of the temporal fossa, which can be verified on plain x-rays and CT bone windows. Prefrontal regions are compressed by malformation. Reconstruction using 3DCT confirm clinical and CXR observations and allow the development of a surgical plan. 3DCT reconstruction of the base shows a narrow frontal fossa and narrowing at the pterional level (Fig. 14.5) [24, 26, 55].

14.4.9.5 Brachycephaly or Bilateral Coronal Craniosynostosis

Definition and epidemiology. Coronal sutures are stenosed in this malformation. This condition represents 7% of the HIMFG series for non-syndromic craniosynostosis and 6% of total cases. In the CHUNP series, it represents 5.3% of total non-syndromic events. There is a female prevalence (66%), which is similar to figures

found in coronal plagiocephaly. Esparza and Ferreira reported figures similar to the above [24, 39, 54, 56, 93]. This craniosynostosis is associated with the highest rate of chronic ICH (31.3%), although without papilla edema, possibly because of an early surgery.

Clinical characteristics. In accordance with Virchow's law, frontal view reveals biparietal protrusion with a clear increase of temporoparietal diameter and orbitary edges with diverse blurring levels and frank hypertelorism as well as flattened forehead. External ears are separated and concavity faces downwards giving the impression of being lower than normal (Fig. 14.6) [25, 27, 52, 88]. Lateral view reveals a decrease in AP cranial diameter. Forehead flattening is confirmed by a reduced orbitary edge and, in most cases, it is possible to observe exorbitism because the upper facial third is displaced backwards. In some cases, the skull is displaced upwards, giving a tower appearance, which justifies this entity to be also known as "turricephaly." Looking at the patient's head from above allows us to confirm the forehead backwards setting, orbitary edge blurring and exorbitism.

Imaging. PA CXR shows "harlequinization" of both orbits and, sometimes, finger-like impressions associated with chronic ICH. There is an increase of bitemporoparietal diameter and bone structure moves upwards resembling a tower. Lateral incidences lack coronal suture evidence and there are certain frontal flattening levels and orbitary edge blurring. Cranial CT and 3DCT reconstruction will confirm coronal suture closure and deformation that increase lateral diameter and shorten AP diameter. CT Bone windows will reveal coronal suture ossification and finger-like impression on internal table or even cranial perforations because of ICH (Fig. 14.6) [26, 93].

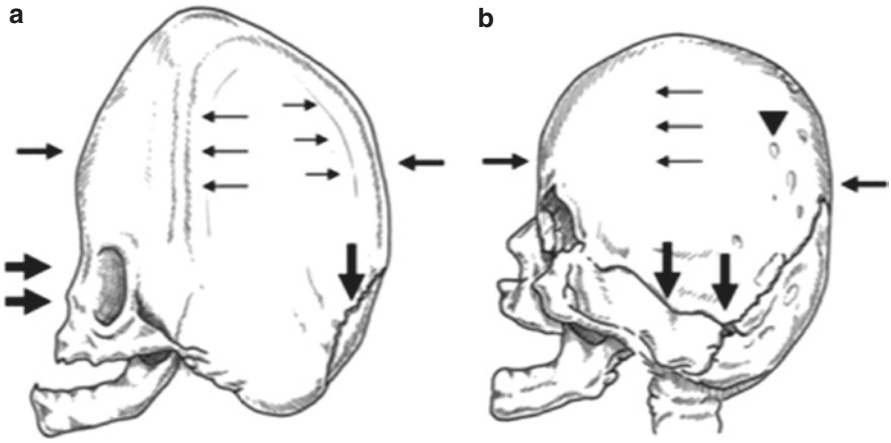


Fig. 14.6 Brachycephaly. 3DCT reconstruction. (**a**) Syndromic craniosynostosis with brachycephaly (lateral projection). (**a**) + (**b**) Note a reduced anteroposterior diameter (→□←). Stenosed suture is occasionally visible as a ridge (horizontal arrows). Other sutures are permeable (↓). (**b**) Nonsyndromic simple brachycephaly. Finger-like impressions are occasionally visible (▼)

14.4.9.6 Oxycephaly

Definition and epidemiology. This is a non-congenital and non-syndromic craniosynostosis that will occur between the second and third year of life even when children are born with all sutures permeable. This is a condition that prevails in northern Africa and is reported with relative frequency in French series because of the high immigration rate from those regions. Oxycephaly is a harmonious closure of all sutures in the cranial vault, resulting in a small and round skull with a special deformation that frequently presents severe ICH in most cases (61.6%), papillary edema (10%) and papillary atrophy (13%). Patients >1 year-old may present several blindness levels and >50% of cases report an IQ <90. The aggressiveness of this condition calls for surgical treatment at diagnosis [24].

Clinical characteristics. When oxycephaly is mild, we observe only a small harmonious head. Severe oxycephaly reveals a spheric skull with forehead, temporoparietal and occipital regions towards the inside of the skull, producing a backwards position of forehead and retraction of supraorbitary edge, moderate exorbitism because of orbitary edge backward setting that follows a generalized narrowing of the skull. Face and facial skeleton are usually normal. Mild cases do not report a faciocranial disproportion, which is observed in severe cases where the patient has a very small skull producing a facial skeleton that looks larger [24, 26].

Imaging. CXR reveals a typical well rounded skull, sometimes with a discreet bregma protrusion and mainly with severe finger-like impressions. Severe cases reveal forehead retraction with blurring or orbitary edge.

14.4.9.7 Syndromatic Craniosynostosis

Crouzon Syndrome

It was described by Octave Crouzon in 1912, associating a craniosynostosis, generally bicoronal and later on sagittal, with hypoplasia of the facial mass. This is the most frequent syndromic craniosynostosis [72, 94–96].

Clinical and imaging characteristics

Facial deformations at birth are already present, but they are slight and it is difficult to diagnose the disease at this time; This will be defined around 2 years old. In most cases, exophthalmos occurs due to recoil of the upper jaw and forehead. In severe cases of Crouzon, exophthalmos can be extreme, putting the eyeball at risk. Hypertelorism is rare, but there is often divergent strabismus due to defects in the insertion of the external ocular musculature. There is a type II anomaly dental occlusion, causing various degrees of prognathism. The nose is hooked (like “parakeet”) in most cases (Fig. 14.7). Sometimes these craniosynostosis resemble a scaphocephaly at birth (Fig. 14.8) [78, 97].

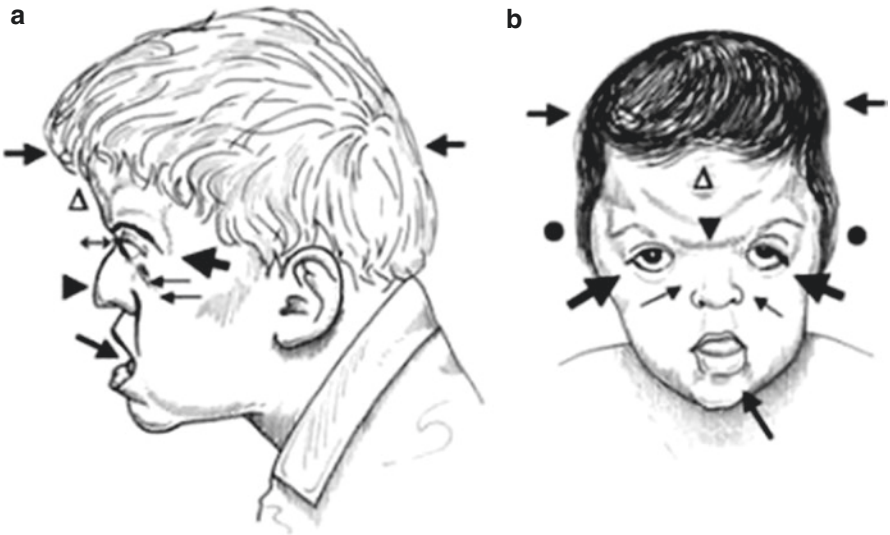


Fig. 14.7 Apert disease. (**a**) Profile view. (**b**) Front view. Most of the time there is brachycephaly with a tendency to turricephaly (→ ←), the forehead is bulging (Δ), various degrees of proptosis can be found (↔), the pterional and temporal regions are bulging (●), there is antimongoloid fold in the external commissure of the eyelids (↖), there is always a hypertelorism of various degrees (►), in addition to hypoplasia of the maxilla and malars ((), an open mouth and a reversal of the bite with the dental arch of the upper jaw, which is located behind the lower (↘)

The earliest forms from birth are the most serious: apart from the threat to the integrity of the eye, respiratory failure occurs due to the narrowing of the nostrils due to hypoplasia of the facial mass, especially of the upper and the choanas. This feature can lead to recurrent respiratory infections [23, 24, 96].

In 68.6% of cases presents intracranial hypertension, papilledema in 17% and optic atrophy in 3.4%. Hydrocephalus, occurs in 25% of cases. The brain must be decompressed before the first year of life to avoid a decrease in IQ since, from 80% with IQ> 90, it can decrease to 65.6%. It can be associated with cervical vertebral anomalies of the Klippel-Feil type and with acanthosis nigricans, due to a genetic mutation in the FGFR3 gene [24, 27, 51, 74, 98].

14.4.9.8 Apert Syndrome

It was described by Eugene Apert in 1906. It is a serious malformation that associates a facial-craniosynostosis with a syndactyly of the 4 extremities [99]. The stenosed sutures at the level of the vault are always the coronal ones, respecting the metopic and sagittal ones; There are reports of patent coronal sutures in the Apert [14]. As in Crouzon disease, there is hypoplasia of the upper jaw (Fig. 14.8); in the case of Apert, this is generally severest and anomalies of dental occlusion, a broad

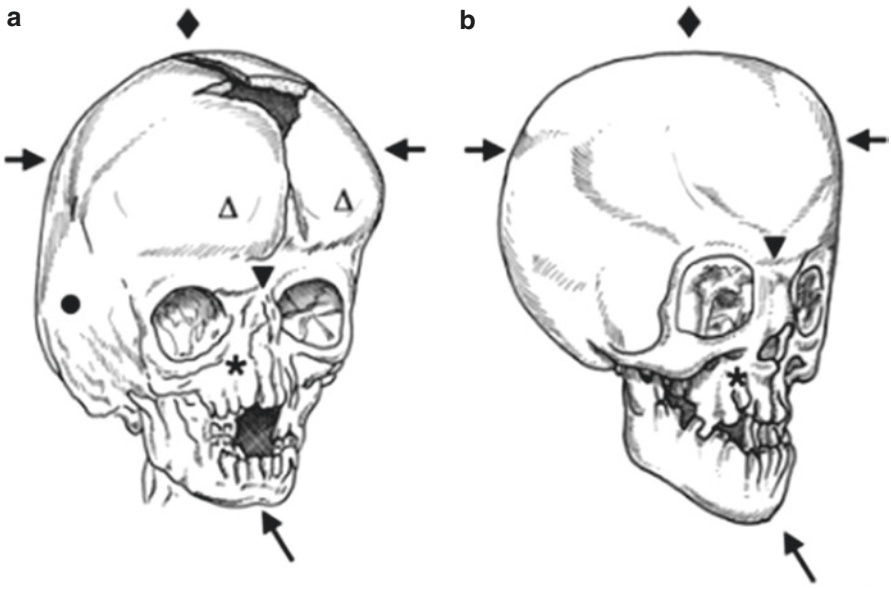


Fig. 14.8 Skull 3D CT scan. (**a**) Apert. (**b**) Crouzon. Hypertelorism is observed (▼), less marked in the Crouzon, hypoplasia of the upper jaw with various degrees of choanal atrophy (*), inversion of the dental joint due to recession of the upper jaw (↖). In (**a**), the persistence of the sagittal suture system (♦), the bulging of the pterional and parietal areas (●) and the bulging of the frontal (Δ) are observed, since they are generally brachycephalic skulls (→ ←). In (**b**) it is observed that both the coronal and sagittal sutures are generally closed (♦) and brachycephaly is less frequent (→ ←)

face, a hooked nose and constant hypertelorism with the external corners of the eyelids directed downwards and the antimongolic inclination of the outer corner of the eyelids (Fig. 14.7). 27% has a palatal fissure, the mouth remains open and has a choanal atresia. The skin is thick, oily and there is frequently acne [24, 26, 100, 101].

Clinical and imaging characteristics. Syndactylia are serious and disabling, since they are cutaneous and many times also bony. They generally affect the second, third and fourth fingers of the 4 extremities (type I) or, in the most frequent and severe forms, the little finger (type II) or the 5 joined fingers (type III) are also welded. There could be a worse prognostic factor the more fingers are welded. There is a single nail called a synanchia. There are various types of bone malformations, with abnormalities of the vertebrae and other bones [24, 100, 102–104].

Cerebral anomalies are frequent, with the presence of almost constant, non-progressive ventricular dilatation; cerebrospinal fluid bypass is rarely required. Various types of cortical dysplasias, neuronal migration, corpus callosum and septum disorders have been described [105, 106]. It seems that the presence of a cyst between the laminae of the septum marks a worse prognosis, as well as a poorly integrated family. Mental retardation is reported in most cases; 45.5% with IQ> 90 decreases to 7.4% when they are not decompressed before the first year of life.

There is a decrease in hearing in 56% and intracranial hypertension (ICH) in 45% of the series of the Center Hospitalier Universitaire des Enfants Malades Necker de Paris (CHUMP) [22, 24, 27, 51, 100].

14.4.9.9 Saethre-Chotzen Syndrome

Described by two German authors, Saethre in 1931 and Chotzen in 1932, it consists of a variable craniosynostosis that can affect any suture, although it predominates in the coronal ones.

Clinical and Imaging Characteristics

Both coronals are generally closed, resulting in a flat forehead and a straight nose, unlike the Crouzon which features a hooked nose. There is a single or bilateral palpebral ptosis, with hypertelorbitism of various magnitudes. The pinnae are small, round, with the presence of crux cimbae, that is, a helix that continues in a transverse fold that crosses the concavity of the shell. On the extremities, which are short, there can be a thick thumb, without pathological deviations. Frequently there is a membranous syndactylia between the index finger and the middle finger and between the second and third ear. A hallux valgus is present and there is a distal bone defect in the terminal phalanges. It is usually associated with cryptorchidism. IQ is also aggravated when there is no decompression before the first year of life [24, 26, 51, 107].

14.4.9.10 Pfeiffer Syndrome

It is a relatively recently described syndrome. R. Pfeiffer reported it in 1964 and it consists of a brachycephaly, with stenosis of the coronal and sagittal sutures, associated with membranous syndactyly in the hands and feet; as characteristic data, it presents thickened thumbs and toes, with a very clear deviation in varus. These abnormalities are due to the triangular shape of the first phalanx and the hypertrophy of the first metacarpal and metatarsal. All this is accompanied by brachydactyly and synostosis of the elbow.

Clinical and Imaging Characteristics

It presents the hypoplastic upper jaw, with hypertelorism, antimongolic inclination of the outer corner of the eyelids, exorbitism that can be severe, with the impossibility of closing the eyelids and strabismus due to exotropia, for the same causes as in Crouzon disease.

There are also various types of brain problems, such as hydrocephalus, a decrease in cerebellar tonsils, and venous return abnormalities due to the narrowness of the posterior torn holes.

The pinnae are low and there is hypoplasia of the upper jaw, sometimes with choanal atresia, calcification of the tracheal rings and vertebral, cervical and sacrococcygeal malformations.

A division of Pfeiffer syndrome into three types has been proposed: (1) type I, the classical, sporadic or autosomal dominant form; (2) type II, with cloverleaf skull, very frequently accompanied by brain malformations; and (3) type III, like type II but without a cloverleaf skull [24, 108].

14.4.9.11 Cloverleaf Skull

It is a severe craniosynostosis from birth, in which the majority of the vault sutures are stenosis, narrowing the temporoparietal and frontoparietal junction, bulging the temporal, parietal and occipital regions, thus giving the shape of a skull in clover (Fig. 14.9) [109].

Sometimes this type of craniosynostosis is accompanied by a reticular skull, with bone spicules that enter the brain grooves, always presenting a severe ICH.

A precise diagnosis is recommended, if possible antenatal, to think about the possible surgical treatments that should be as early as possible. knows that radical treatment from an early age reduces the consequences that this malformation condi-

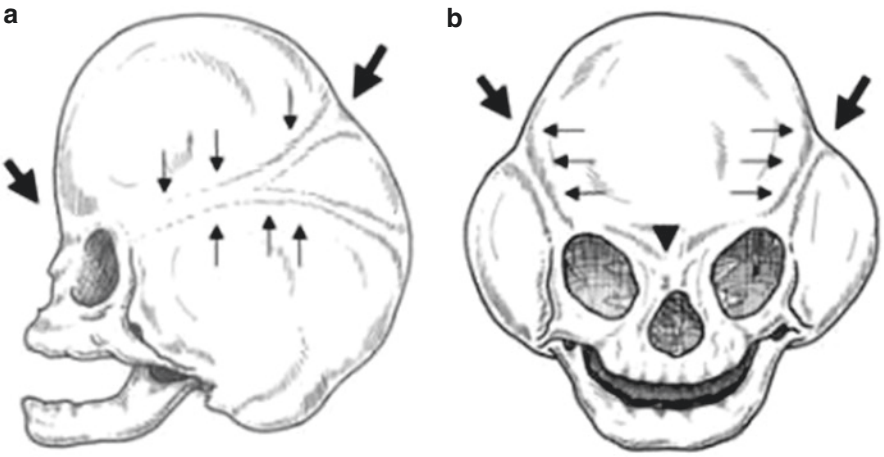


Fig. 14.9 Cloverleaf skull 3D Ct scan. (**a**) Side view. (**b**) Front view. The strictures that are formed at the level of the sutures are observed, giving the characteristic cloverleaf shape (↘↙); stenosed sutures are distinguishable at the level of constricted areas (↑↑↑). The cloverleaf skull is sometimes associated with hypertelorism (▼)

tions, when it is not treated early and effectively. It can be associated with Crouzon disease in its most serious forms, and also with the Saethre-Chotzen, Pfeiffer, Apert syndromes, and in thanatophoric dwarfism; the latter, as its name implies, is not compatible with life [75, 110, 111].

14.5 Treatment

The medical team in charge of treating these conditions must be multidisciplinary, consisting of neurosurgeons, plastic surgeons, anesthesiologists, pediatricians, geneticists, psychiatrists and psychologists, neurologists, neuroradiologists specialized in craniofacial malformations, in addition to the team specifically in charge of the face: ophthalmologists , maxillofacial surgeons, otorhinolaryngologists, orthodontists and dentists [18, 72, 112].

The team's imperatives will be: (a) to arrive at an accurate diagnosis, with the finest possible understanding of dysmorphia; (b) understand the functional alteration in the most complete way possible, for example, sometimes, some alterations may resemble others in their beginning, such as scaphocephaly to Crouzon disease; (c) detect associated malformations (when there is a brain malformation, pay special attention to it and classify it as well); (d) prepare the surgery, decompressive and corrective, (e) prevent the intellectual and visual deterioration that accompanies, to a greater or lesser degree, these conditions [18, 28, 80, 113] and (f) start early rehabilitation.

14.5.1 Surgical Treatment

The objective of surgical treatment is brain decompression that is necessary as a large part

The surgery can be limited only to the stenosed suture or performed as a complete remodeling surgery that, in the end, will give a better result of the brain-skull relationship and will immediately improve the physical appearance of the child.

Extensive surgery is recommended since it has been found that after surgical corrections of craniosynostosis due to the presence, to a greater or lesser degree, of chronic intracranial hypertension and, on occasions, papillary edema and atrophy, as well as developmental delay neurological, decreased IQ and mental disorders in some cases [20, 21, 26, 27]. The physical-aesthetic aspect is also important since, firstly, it will influence a good psychic development of the child and, secondly, the correction of the physical defect will allow a better insertion in society. Also, a correct cranial aspect will result in a good skull-brain relationship [37, 114].

14.5.1.1 Classic Surgical Treatment

Surgery, then, is the treatment of choice for most craniofacial malformations. The results will be better the better the condition to be treated is defined. In addition, it is necessary to obtain a clinical state as accurate as possible, evaluating the presence of ICH, mental state and ophthalmology. Analysis of affected organs is also required, mainly brain malformations, especially for non-syndromic craniosynostosis and those that are usually associated with this type of problem, such as trigonocephaly in simple suture. In syndromatic diseases, it is possible to find various types of brain affection.

14.5.1.2 Technical Details

The following objectives should be kept in mind:

- Cerebral decompression
- Allow the brain, with its growth, to assist bone molding in the first two to three years of life, during which the skull reaches more than 80% of adult volume [115].
- The need for restoration of an anatomy as close to normal.
- Provide the highest degree of aesthetics according to the ethnic characteristics of the patients.

The surgery can be limited only to the stenosed suture or performed as a complete remodeling surgery that, in the end, will give a better result of the brain-skull relationship and will immediately improve the physical appearance of the child. Extensive surgery is recommended as it has been proven that after surgical corrections of malformations with extensive remodeling techniques, there is a substantial increase in intracranial volume [28, 116].

In most cases, all craniosynostosis, whether syndromic or not, will require remodeling of the forehead and orbits. You must then have a special knowledge of the normal conformations of these structures, in order to mold them. Normal measurements, according to the ages and aesthetic characteristics of each ethnic group, must be rigorously observed. Currently, modern techniques in tissue engineering or promoted by distractors and the application of various materials, allow a more efficient remodeling [37, 117–119].

The fixation of the bone assembly can be carried out with a large number of elements: silk (little used for the reactions it causes), nylon and / or wire (which are more effective and better tolerated). Metal plates and screws have also been used. Bioabsorbable systems have been used lately, which have been useful [120, 121].

Bone distraction systems, for both simple and syndromic craniosinostoys, have taken their place within modern treatment techniques [117, 118].

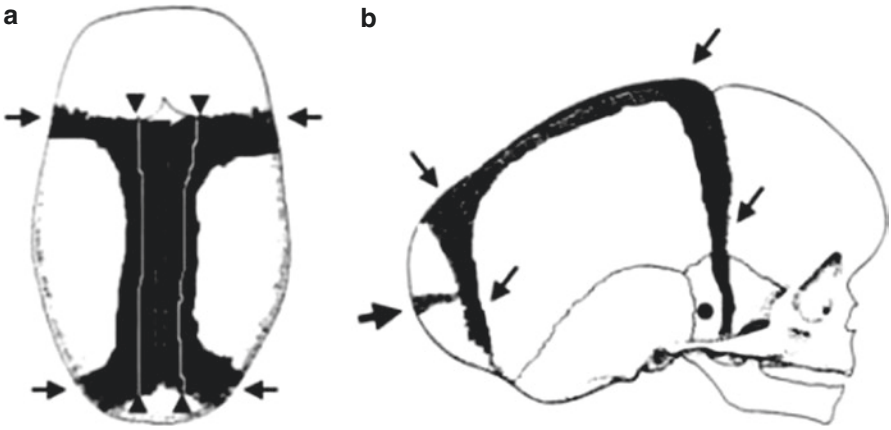


Fig. 14.10 Scaphocephaly, treatment with "bearskin" craniectomy and perisinusal devitalization. (**a**) Scaphocephalic skull seen from above, showing a "bearskin" osteotomy (→ ←) and formation of neosutures (▲). (**b**) Scaphocephalic skull seen in profile, where the osteotomy is observed in "bearskin" and the cut sites on the occiput, in cases where there is a significant protrusion (→), and in the temporal fossa, on the pterion (●)

14.5.1.3 Scaphocephaly. Surgical treatment

In the Federico Gómez Children's Hospital of Mexico (HIMFG), the stenosed sagittal suture ablation is generally performed with the "bear skin" technique, performing, at the same surgical time, a devitalization of the dura mater parallel to the sagittal sinus, with the purpose of forming neosutures (Fig. 14.10). In this technique, trenches should be made along the coronal and lambdoid sutures, to best normalize the conformation of the skull, which will result in a better skull-brain relationship. It is also necessary to advance to the floor of the temporal fossa, acting on the spheno-frontal suture at this level. When this area is opened well, a kind of sphenoid "bolt" is opened that allows a good postoperative evolution and better remodeling of the skull. At the back you reach the asterion.

There are other types of techniques that also give good results, with the prophylaxis of possible morbidity and a pleasant appearance. For some patients, some authors propose resection of the suture with 3 cm wide margins on the midline side and relaxation incisions in the parietals. In other cases, the simple linear craniectomy, a simple suturectomy is also used, as well as the calvariectomies [18, 52, 80, 113, 122].

14.5.1.4 Brachycephaly. Surgical Treatment

The anteroposterior diameter should be enlarged by means of a fronto-orbital advance. Both the forehead and the upper part of the orbits are separated from the face and repositioned, advancing what is considered necessary, generally 2 cm. The

pieces of this scaffolding are united as best as possible, so that the correction must be permanent and of good quality. It must be remembered that in this type of malformation, surgery is of some urgency because of the frequency of ICH and its repercussion on vision and intellectual level [20, 21, 93].

14.5.1.5 Trigonocephaly Surgical Treatment

It represents a special challenge for surgery; in fact, the movements to be printed on the facial flaps are due to the conformation of the malformation. The orbital rims are pulled backward, both in the sagittal and axial planes, causing the anterior pterional and temporal regions to internalize. This should then be corrected by making the outer ends of the orbital rims face forward, at the same time as they lean forward and downward; This must be accompanied by the section in the middle of the trigonocephalic part of the lower end of the frontal, which is between the orbits. In these, the hypotelorism and the "raccoon" orbits must be corrected, tilting the external part of these downwards. The prominence that the stenotic metopic suture prints should be removed from the frontal flap, leaving two flaps on the "coleopteran" wings, which will be placed again on the orbital mount [18, 30, 55].

14.5.1.6 Plagiocephaly. Surgical Treatment

The correction must take into account the characteristics of the deformation. It is necessary to reposition the orbit on the stenosed side taking into account that the orbital rim is poorly positioned in the three planes of space. Disarticulating both orbital ridges will allow the orbital mount to be adjusted in a good way and will also allow the brain to slowly correct the malformation. Discrete hypercorrection is desirable [123]. There is generally a tendency to reproduce the malformation postoperatively; This trend will be counteracted by the mentioned hypercorrection. When the results are partial and a certain degree of malformation is still found, a period of at least one to two years should be allowed before indicating a new surgery. The brain with its growth conditions, in a good part of the cases, a remodeling after the operation [18, 28, 90, 114].

The deformed forehead may be treated with a rotation of the bone flap or with the number of cuts required, also allowing the brain to act, which in the future will condition better remodeling. Marchac and collaborators [18] and Goodrich [114] recommend the taking of a skull fragment that contains the appropriate shape for the reconstruction of the forehead, using for this the Marchac compass.

The dura will be acted on as described in the scaphocephaly, performing a devitalization of the external leaf of the dura with a soft coagulation in the place of the stenosed suture.

Techniques that obey these same guidelines have been reported with the unpinning of the external edge of the diseased orbit and its advancement, after a frontal craniotomy. Jiménez and Barone recommend endoscopic surgery [124–126].

14.5.2 Syndromic Craniosynostosis: Crouzon and Apert Syndromes. Surgical Treatment

The special challenge that this type of malformation created was first taken by Paul Tessier in France and later continued in Mexico by Ortiz Monasterio and Fuente del Campo [127]. While Tessier divided his advances into two parts, Ortiz Monasterio and collaborators proposed a monoblock advance that revolutionized the approach to these malformations. Monobloc bone cutting and advancement with distractors are currently being used, thus avoiding the reproduction of the malformation due to the receding of the middle third of the face after surgery [10, 33, 35–37, 117, 127].

14.5.2.1 Endoscopic Surgery

Endoscopic approaches have been used for the treatment of non-syndromic craniosynostosis, especially scaphocephaly. The published reports, from the end of the 90's to date, make these techniques a safe alternative and with good quality results [51, 107]. However, more serious publications are expected with everything that is required to affirm the primacy of these techniques. Regardless of whether it is presumed not to transfuse and a short stay in the hospital, there is still no follow-up and the degree of recurrence, which will indicate with greater certainty the effectiveness or not of these techniques [124–126].

14.5.2.2 Helmets as an Adjacent Treatment

The use of helmets to mold the deformed skull has been another of the proposed treatments for these diseases; Although they can be used as primary treatment, they are basically applied after surgery [90].

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Chapter 15
Genetic Features of Craniosynostosis

Alican Tahta, Mehmet Turgut, and Walter A. Hall

15.1 Introduction

Craniosynostosis is usually observed as a malformation of the cranial vault and/or premature closure of the fontanelles, which is caused by premature ossification and fusion of the sutures of the skull [1]. It occurs in 1:2000 live births so it can be classed as a common malformation. Fusion of the sutures defines the shape of the cranial vault, which is compensated by growing in a direction not restricted by those sutures. Premature fusion leads to growth in a plane parallel to the closed suture, whereas physiological growth [1] follows a plane perpendicular to the suture. The most common prematurely-fused suture is the sagittal suture, resulting in a scaphocephalic phenotype, which can be defined as growth in the antero-posterior direction [2, 3]. The second most common is the coronal suture; bilateral involvement of the coronal suture causes brachycephaly, and unilateral involvement causes anterior plagiocephaly. The metopic and lambdoid sutures are prematurely fused in only 15–20% of clinical cases [4].

Craniosynostosis is a genetically heterogeneous disorder associated with more than 180 syndromes [5]. Accurate diagnosis can be difficult because these clinically heterogeneous syndromes often have overlapping features [6]. Syndromic

A. Tahta
Department of Neurosurgery, Istanbul Medipol University School of Medicine, Istanbul, Turkey

M. Turgut (✉)
Department of Neurosurgery, Aydin Adnan Menderes University School of Medicine, Efeler, Aydin, Turkey

Department of Histology and Embryology, Aydin Adnan Menderes University Health Sciences Institute, Efeler, Aydin, Turkey

W. A. Hall
Department of Neurosurgery, State University of New York (SUNY). Upstate Medical University, Syracuse, NY, USA

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craniosynostosis accounts for 15% of patients with craniosynostosis, who are more severely affected than those with non-syndromic craniosynostosis [7].

The most common craniosynostosis syndromes are Muenke, Crouzon, Pfeiffer and Saethre-Chotzen syndromes [8]. In an affected patient, the possibility of such a syndrome should be considered in terms of its related anomalies or if there is a developmental delay. Syndromic craniosynostosis can occur with either multiple suture fusion (e.g., Apert, Pfeiffer, Crouzon, and Antley-Bixler syndromes) or single suture fusion (e.g., Saethre-Chotzen and Muenke syndromes) [2, 9, 10]. The molecular and clinical features of craniosynostosis are becoming significantly clearer. The most common and best-characterized syndromes are caused by mutations in the FGFR1, FGFR2, FGFR3, TWIST1, and MSX2 genes. Today, many types of syndromic craniosynostosis for which the molecular basis is known can be accurately diagnosed using diagnostic testing strategies. In many cases, management is not directly influenced by the genetic diagnosis; however, it is beneficial to obtain a prenatal diagnosis and to provide genetic counseling [6]. Nevertheless, more than 85% of craniosynostosis cases are non-syndromic [4].

15.2 Development and Growth of the Normal Cranial Vault

When the cranial vault develops normally, intramembranous ossification stimulates undifferentiated mesenchymal cells towards condensation and then they surround the sutures [11, 12]. After condensation, these cells begin to proliferate from the osteogenic fronts [13]. Chondrocyte and perichondral cell proliferation is stimulated by mesenchymal cell condensation [14, 15]. At approximately the 13th week of gestation, the membrane derived from the paraxial mesoderm causes the cranial vault to mineralize, proceeding outward from several ossification centers [16]. When the mineralizing bone fronts meet, during the 18th week of gestation, sutures form along the lines of their juxtaposition. Afterwards, with the deposition of permineralized bone matrix (osteoid), the skull grows in an overlapping manner at the suture [6]. Certain transcription factors are significant in the ossification process: in osteoblast development, RUNX2 and OSX [13]; in inhibition of chondrocyte proliferation, transforming growth factor beta (TGF-β); and in inhibition of calvarial osteoblast differentiation, MSX2 [12]. This differentiation is managed primarily by the fibroblast growth factor (FGF) signaling pathway. During the process, excess bone deposition or a premature arrest of brain development results in the premature fusion of sutures, which can cause functional, physiological and morphological malformations such as craniosynostosis [10].

15.3 Signaling Mechanisms Underlying the Pathophysiology of Craniosynostosis

Migration of the progenitor cells from mesoderm or neural crest and their differentiation while the cranial sutures form (e.g., genes encoding transcription factors such as TWIST1, MSX2, EN1, and ZIC1), and osteogenic proliferation, differentiation

and homeostasis (e.g., FGFR1, FGFR2, RUNX2, and POR), involve proteins encoded by genes that are crucial in the pathogenesis of the craniosynostosis [17]. The function of the protein encoded by a mutated gene determines the form of craniosynostosis likely to develop by altering different signaling pathways [17]. The most common FGFR mutation involves the RAS/MAPK signaling pathway [18], which is involved in the differentiation of mesenchymal cells to osteoblasts and chondroblasts. FGFR gene mutations cause increased receptor activity or decreased receptor specificity, which leads to activation of the downstream RAS/MAPK pathway [17]. Craniosynostosis develops in some patients with RASopathies, which are disorders caused by germline mutations in genes encoding RAS/MAPK pathway components, verifying the role of this pathway in suture fusion and skull formation. The FGF family has 23 members, which bind to five different receptors (FGFR1-4 and FGFRL) in order to initiate a cellular response [19]. FGFR1 controls osteogenic differentiation while FGFR2 manages stem cell proliferation [20]. Mutations in FGFR2 are more common than in the other receptors in cases of syndromic craniosynostosis [17]. Another mutation responsible for the premature closure of single or multiple sutures is in the ERF gene, which encodes an effector protein of the RAS/MAPK signaling pathway [21–23].

The effects of TGF-β2 and TGF-β3 on sutures have been studied: TGF-β2 enhances the process of obliteration (loss of suture patency) while TGF-β3 has the opposite effect [24]. The study by Opperman et al. indicated that TGF-β2 stimulates cell proliferation, causing premature fusion of sutures [25]. The absence of TGF-β2 inhibits cell differentiation but does not affect proliferation.

Komatsu et al. in 2013 demonstrated that BMP signaling via the BMP type 1 receptor pathway in cranial neural crest cells results in premature suture closure in mouse models [26]. BMPs belong to the TGF-β family and are responsible for bone and cartilage formation. Transcriptions of MSX2 and RUNX2 are controlled by the SMAD-dependent BMP pathway during cranial development [27]. During a study on mice, Komatsu et al. demonstrated a correlation between SMAD-dependent BMP pathway activity and syndromic craniosynostosis [26]. They concluded that BMP has a strategic role in the early development of craniofacial syndromes [26]. In addition, Maruyama et al. recently showed for the first time that Axin2, which is highly expressed in a stem cell population, is also strategically important in midline sutures (sagittal, metopic) [28].

To date, two pathways have been proposed that explain why Twist1 mutations result in coronal synostosis [29]. Connerney et al. proposed that Twist1 has two alternative functions, either to interact with E protein and form heterodimers (T/E) or to generate homodimers (T/T) [30]. The homodimers could potentially facilitate osteogenic cell differentiation on the osteogenic fronts by stimulating FGFR2 expression [30]. The other pathway proposed for Twist1 pathophysiology is the Eph/Ephrin signaling pathway [31]. According to this hypothesis, Twist1 and Msx2 interact with the Eph/Ephrin pathway to cause disruption of the mesoderm-neural crest lineage boundary [31]. The Eph/Ephrin pathway sends downstream signals to Twist1 and Msx2 [32]. According to some studies, coronal suture synostosis is the result of Ephrin downregulation, which causes the invasion of neural crest cells into

mesenchymal cells of the coronal suture [31]. Ephrin downregulation could be a consequence of Twist1 haploinsufficiency, which causes increased Msx2 expression leading to increased expression of EphrinA2 and A4 [31].

15.4 Genetics of Craniosynostosis

The form of craniosynostosis is identified not only by its phenotypic variations but also by the specific identity of the closed suture, e.g., coronal or lambdoid, and whether the fusion is unilateral or bilateral. Craniosynostosis syndromes are classified into two types, primary and secondary, the latter being more common. Mucopolysaccharidosis malformations, metabolic disorders and fetal exposure to environmental factors can cause secondary craniosynostosis [33, 34].

15.4.1 Genetics of Syndromic Craniosynostosis

Although most cases of craniosynostosis are nonsyndromic, 15–25% of cranisynostosis cases are syndromic [35]. Syndromic craniosynostosis, usually an autosomal dominant disorder, involves certain body malformations and deformities of the genitourinary, cardiac and musculoskeletal systems [34]. There are more than 180 syndromes associated with craniosynostosis. The main ones are Apert, Crouzon, Pfeiffer, Saethre-Chotzen, Jackson-Weiss, Beare-Stevenson, and Antley-Bixler syndromes [36, 37].

Most common forms of syndromic craniosynostosis have an autosomal dominant inheritance, but there are also examples of incomplete penetrance, recessive inheritance and variable expressivity [5, 38, 39]. There is also another cause of craniosynostosis: mosaicism. A mutation in the FGFR2 gene is considered significant for identifying a mosaic individual [40], and the level of mosaicism has been predicted at 19% for an EFNB1 gene mutation. Therefore, further examination is needed for patients with unsolved molecular diagnoses [2, 41]. Mutations in certain genes such as FGFR1, FGFR2, FGFR3, TWIST1 and MSX2 are associated with syndromic craniosynostosis.

Pfeiffer, Crouzon, Apert, Muenke, Jackson-Weiss, and Beare-Stevenson syndromes are associated with FGFR1-3 gain-of-function mutations [42]. These syndromes are indicated by bicoronal craniosynostosis or cloverleaf skull, craniofacial abnormalities, and hand and foot anomalies [43]. Some FGFR2 mutations, e.g. G298P, C342T, and C278F, have also been detected in patients with Crouzon, Pfeiffer, and Jackson-Weiss syndromes [43]. These syndromes probably represent a clinical spectrum with genetic modifiers [44].

Mutations in different genes can cause the same clinical phenotype, e.g. FGFR1 and FGFR2 mutations in Pfeiffer syndrome [43]. This finding suggests functional redundancy among the FGFR genes. There are distinct similarities between

craniofacial anomalies resulting from linker area mutations in FGFR1 (P252R) (Type I Pfeiffer), FGFR2 (P253R), (S252W) (Apert), and FGFR3 (P250R) (Muenke). The coronal suture is involved in all these craniofacial anomalies, and if there is bilateral involvement, a similar calvarial phenotype (turribrachycephaly) results that differs from the calvarial phenotype of Crouzon syndrome [45].

TWIST1 is another gene involved in the development of syndromic craniosynostosis, especially Saethre-Chotzen syndrome (SCS) [46]. Loss-of-function mutations in the transcription factor TWIST1 are found in most patients with SCS [47, 48]. This transcription factor negatively regulates FGFR1, 2 and 3, and the osteogenic transcription factor Runx2. The Twist-box domain of TWIST1 binds to the DNA-binding domain of Runx2 and inhibits its function in osteoblast development reversibly [49]. Runx2 also interacts with the vitamin D receptor and increases osteocalcin expression [50]. The pathogenesis of SCS is associated with the derepression of Runx2 when there is a TWIST1 mutation [50].

A gain-of-function mutation in MSX2 (muscle segment homebox 2) has been demonstrated in a single family with variable anomalies that extend from metopic ridging to cloverleaf skull and hand abnormalities, described as Boston-type craniosynostosis [51]. MSX2 is expressed in osteoblasts close to the calvarial sutures. Skull ossification defects are detected in humans with loss-of-function mutations in this gene, suggesting that MSX2 is involved in bone formation [52].

Previous studies have shown that cytogenetic abnormalities, deletions and duplications appear in all chromosomes related to craniosynostosis except chromosomes 16 and 19. Midline synostosis is associated with most of these chromosomal abnormalities [53], which are also found in 16% of patients with syndromic craniosynostosis [54].

15.4.2 Genetics of Non-Syndromic Craniosynostosis

Non-syndromic craniosynostosis (NSC) (isolated craniosynostosis) is the most common kind of primary craniosynostosis [33, 55–57]. Only 8% of NSC cases are familial [58]. NSC is a complex trait and Mendelian patterns are uncommon, so polygenic effects and epigenetic factors are implicated in its pathogenesis [58, 59]. This is the main difference between NSC and syndromic craniosynostosis [60]. Because the pheonotype is genetically heterogenenous, very large patient groups are needed to determine genetic risk factors in complex traits [60]. To date, small numbers of patients have been diagnosed with rare mutations in FGFR2, TWIST1, FREM1, and RUNX2 genes [61].

The incidence of coronal NSC in first degree relatives of probands is <1% [35]. However, the FGFR3 P250R mutation has been detected in a significant number of families [62]. One major causative gene for coronal NSC is TCF12, which encodes a partner protein of TWIST1 [63].

The first genome-wide study of sagittal NSC was organized by the International Craniosynostosis Consortium in 2011 [61]. They investigated 130 European

families (patients and parents) to locate regions of the genome in NSC patients that were received from the parents [61]. They identified two genomic regions associated with sagittal NSC, one within an intron of BBS9 (a gene for cilia formation), the other being BMP2 (osteoinductive for BMP receptors) [61]. In 2016, Timberlake et al. sequenced genomes from 132 families and an additional 59 patients (total 191 cases) with sagittal and/or metopic NSC [64]. They found that both de novo and protein-damaging mutations in SMAD6 were involved in sporadic disease [64]. In 2017, they augmented their cohort and found a highly significant excess of protein-damaging de novo mutations in negative regulators of BMP, Wnt, and Ras/ERK signaling [65].

The rarest type of NSC is lambdoid craniosynostosis, which affects 3–5% of NSC patients [35]. To date, there has been no large study analyzing the genetics of lambdoid NSC.

15.5 Genetic Counselling

According to Johnson and Wilkie (2011), the penetrance risk to offspring is ~5% in sagittal, metopic or unilateral coronal craniosynostosis patients with no prior family history and no genetic or cytogenetic alterations. However, this risk increases to 30–50% in patients with bicoronal or multiple suture craniosynostosis [2]. The risk of recurrence is still <1% even in negative parental mutation testing because of potential gonadal mosaicism [1].

Chorionic villus sampling at 10–14 weeks of gestation or amniocentesis at 16–18 weeks are prenatal tests for craniosynostosis [6]. There is another alternative for patients who want to avoid terminating a pregnancy in the event of a positive prenatal diagnosis [1]. If the patient wishes to ensure that his/her children will not be affected by craniosynostosis, preimplantation genetic diagnosis is a potential option. Genetic tests allow genetically normal embryos to be selected for in vitro fertilization.

15.6 Conclusion

Craniosynostosis is a malformation of the cranial vault that results from early fusion of one or more cranial sutures. The shape of the skull depends on which sutures are fused and on the compensatory growth that occurs in the direction not restricted by the sutures. Craniosynostosis occurs in 1:2000 live births and is a genetically heterogeneous disorder associated with more than 180 syndromes. There are two distinct groups: nonsyndromic and syndromic. Nonsyndromic craniosynostosis (85% of cases) is characterized by one or more sutures that have fused prematurely. Syndromic craniosynostosis, which affects 15–25% of patients, is associated with developmental delays and dysmorphic abnormalities of the face, skeletal system,

and central nervous system. Muenke, Crouzon, Pfeiffer and Saethre-Chotzen syndromes are the most common craniosynostosis syndromes. There is single suture involvement in Saethre-Chotzen and Muenke syndromes, whereas multiple sutures are fused in Apert, Crouzon, Pfeiffer, and Antley-Bixler syndromes. The most common genetic mutations in craniosynostosis involve the genes for FGFR1, FGFR2, FGFR3, TWIST1, RUNX2, and MSX2. Syndromic craniosynostosis cases where the molecular basis is known can be diagnosed accurately using an appropriate diagnostic testing strategy. Determination of the genetic abnormality does not necessarily influence patient management, but an accurate prenatal diagnosis can help in parental genetic counseling.

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Chapter 16
Imaging Modalities for Craniosynostosis

Ersen Ertekin, Tuna Sahin, and Ahmet T. Turgut

16.1 Introduction

Craniosynostosis is premature fusion of one or more of the cranial sutures. Its incidence is one in 2500 births or one in 10,000 live births. As a result of stopping perpendicular growth of the fused suture, skull deformities specific to the affected suture(s) occur. Familiarity with the associated deformities is essential in diagnosis and treatment [1].

Craniosynostoses are classified as single and multi-sutural according to the number of affected sutures or as 'syndromic and non-syndromic' depending on whether they are a part of a syndrome. In syndromic craniosynostosis, more than one suture is usually affected, along with anomalies of the face, trunk and/or limbs. In non-syndromic craniosynostosis, there is usually a single suture fusion in order of frequency, sagittal, coronal, metopic and lambdoid sutures, respectively [2].

The vast majority of craniosynostoses are non-syndromic. Although the exact cause is not known, factors such as isolated spontaneous mutation of a syndromic gene, intrauterine fetal restriction (multiple pregnancies, etc.), low birth weight, preterm delivery, maternal valproate use and shunted hydrocephalus may all play a role [1]. Syndromic Craniosynostosis accounts for about 8–9% of cases [1, 2]. Although heredity is generally autosomal dominant, the clinical presentation spectrum due to penetration differences is variable [1]. The coronal sutures are most frequently affected and are accompanied by mid-face hypoplasia and/or syndactyly.

E. Ertekin (✉) · T. Sahin
Department of Radiology, Aydın Adnan Menderes University Faculty of Medicine, Efeler, Aydın, Turkey

A. T. Turgut
Department of Radiology, Yüksek İhtisas University Faculty of Medicine, Balgat, Ankara, Turkey

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Although there are numerous gene mutations associated with Syndromic Craniosynostosis, the most frequently affected route is the fibroblast growth factor receptor pathway [3, 4].

Radiological evaluation plays an important role in the diagnosis, detection of additional pathologies, treatment planning and postoperative follow-up. A multidisciplinary approach is recommended for the evaluation of the patient with craniosynostosis. This team includes craniofacial surgeons, neurosurgeons, pediatricians/neurologists, ophthalmologists, otolaryngologists, radiologists and geneticists [5, 6].

The purpose of this chapter is to provide a framework for understanding the role of radiology in evaluating craniosynostosis, and how best to use these imaging methods.

16.2 Radiological Approach

16.2.1 Preoperative Evaluation

In the preoperative evaluation, the task of radiological examination is to confirm the diagnosis of craniosynostosis, to determine any accompanying anomalies, to contribute to treatment planning and to make a prognostic prediction.

16.2.1.1 Confirmation of the Diagnosis

Diagnosis in craniosynostosis is based on clinical examination. Especially, the diagnosis of single suture craniosynostosis can easily be made by clinical examination. For this reason, many authors believe that radiological imaging is not required at this stage [7]. However, it may be necessary to use radiological imaging in cases where the patency of the sutures is difficult to assess (such as a lack of clinical experience or the presence of an excessively hairy scalp) and/or if there is a suspicion that small sutures are affected (that may alter surgery planning). An example of this situation is lambdoid suture craniosynostosis, which is sometimes difficult to differentiate from positional plagiocephaly, which is increasing in frequency. In addition, lambdoid suture craniosynostosis may need to be evaluated radiologically because it may be accompanied by cervical spinal anomalies. Similarly, radiological imaging may be required to differentiate metopic suture craniosynostosis from a simple metopic ridge (Fig. 16.1), which may occur due to the physiological fusion of the metopic suture [8].

Another issue related to the use of radiology for diagnostic purposes is legal regulations. The use of radiology is gradually increasing due to legal problems caused by mis/delayed diagnosis, delayed treatments, and complications that may occur due to these [7].

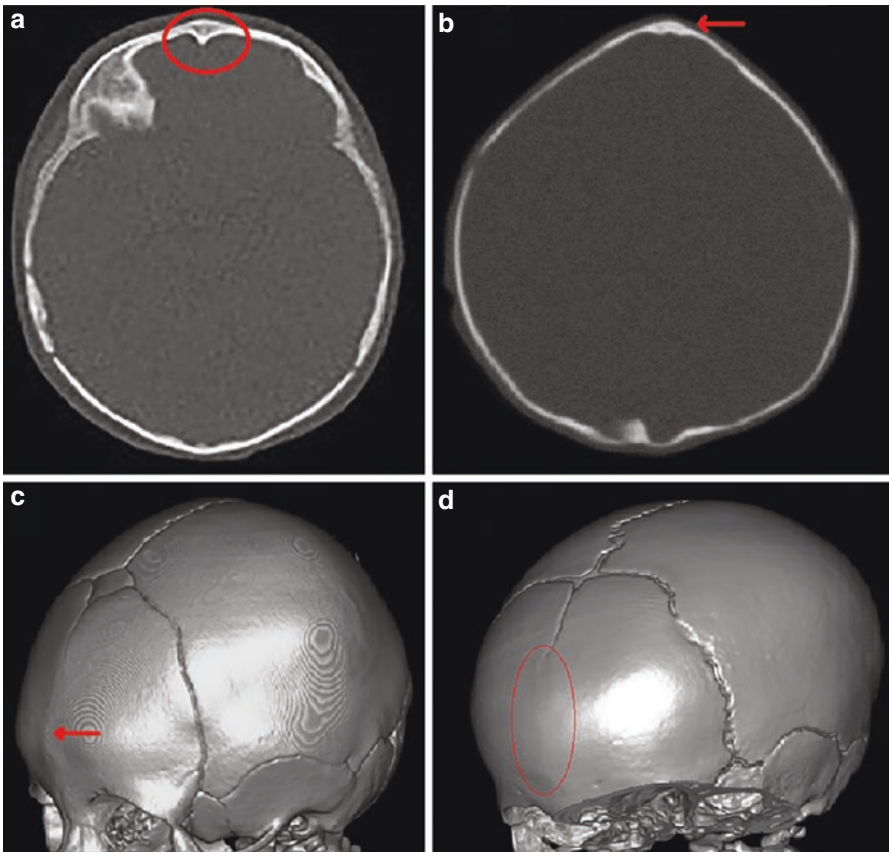

Fig. 16.1 A sample of physiological (**a** and **c**) and premature (**b** and **d**) fused metopic sutures can be seen. (**a**) Axial CT image shows a metopic ridge secondary to physiological fusion of the suture, but the head shape is normal. (**b**) Metopic suture is not observed due to the premature fusion causing trigonocephaly. (**c**) and d: 3-dimensional postprocess images of these cases (**c** physiological fusion of metopic suture, **d** metopic craniosynostosis)

16.2.1.2 Detection of Concomitant Anomalies

The situation is somewhat different in syndromic craniosynostosis. Although physical examination and genetic tests are sufficient in diagnosis, radiological evaluation may be useful in evaluating the closing patterns and times of sutures that differ in different syndromes. However, more importantly, radiological imaging is essential for the detection of anomalies with increasing frequency in syndromic craniosynostosis. Radiological evaluation provides useful information in the detection of extracranial facial and body anomalies, especially intracranial anomalies (Chiari type 1, venous sinus anomalies, callosal hypoplasia or dysgenesis, brain malformations, increased intracranial pressure, hydrocephalus, etc.) [7] (Fig. 16.2).

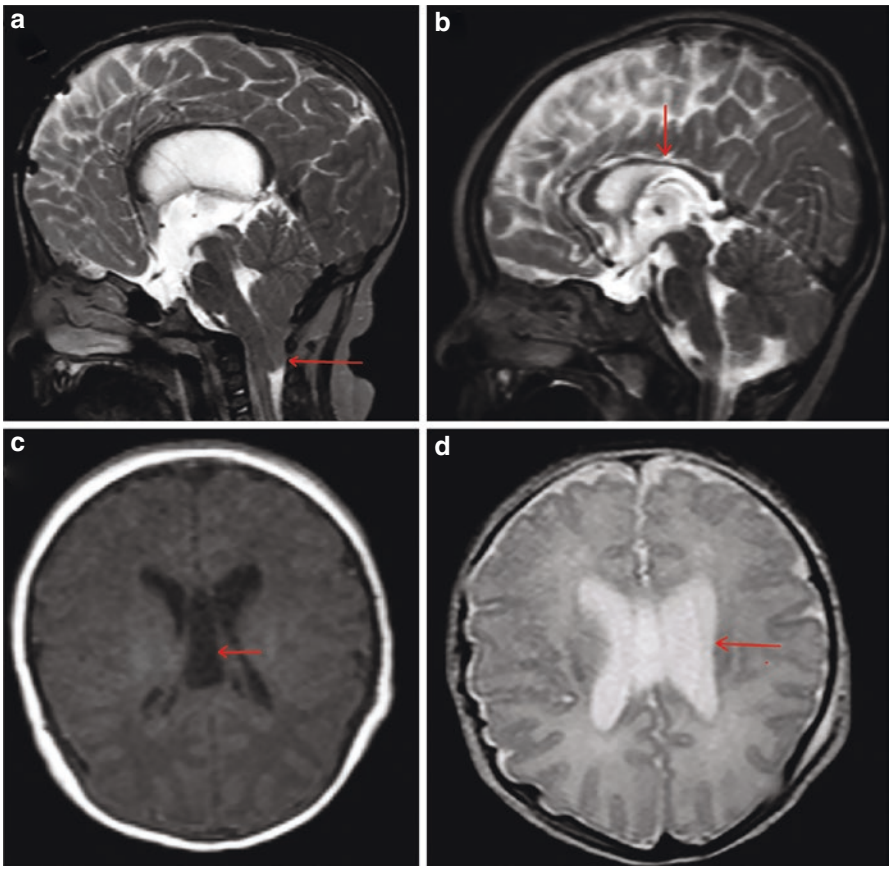

Fig. 16.2 MRI images of accompanying brain anomalies are observed in case samples with craniosynostosis. (**a**) On the sagittal plane T2 weighted MRI, the cerebellar tonsils extend from the foramen magnum to the spinal canal (cerebellar herniation). (**b**) On the sagittal plane T2 weighted MR image, the thinning of the corpus and splenium of corpus callosum (callosal hypoplasia) are observed. (**c**) The cavum septum pellucidum variation is seen in axial T1-weighted MRI. (**d**) On the axial T2 weight MR image, the lateral ventricles are enlarged (hydrocephaly)

These anomalies can also be detected in some non-syndromic sporadic craniosynostosis cases. For example, it is known that the incidence of hydrocephaly increases with scaphocephaly, and Chiari type 1 malformation increases with lambdoid and sagittal suture craniosynostosis. Nevertheless, non-syndromic multiple suture craniosynostoses cases require radiological imaging because Chiari malformation is more common [9, 10].

In addition, the increased diagnostic capability in the prenatal period makes the role of radiology more important, especially in the diagnosis of syndromic craniosynostosis cases and in the detection of associated anomalies. While single suture craniosynostosis cases are mostly encountered in the postnatal diagnosis,

prenatal radiological examinations reveal significantly increasing diagnosis rates in syndromic craniosynostoses cases, thanks to the detection of concomitant anomalies [11].

While more single suture craniosynostoses are encountered in the postpartum diagnosis, significant increase in diagnosis rates are observed in syndromic craniosynostosis cases thanks to the detection of anomalies accompanying with prenatal radiological examinations. The prenatal diagnosis of craniosynostosis also provides the parents with adequate information before birth (on these issues), as well as early planning of surgical intervention and prognosis prediction [7, 11].

16.2.1.3 Treatment Planning

It is important to keep in mind that surgical treatment is recommended in craniosynostosis because of the possibility of developing problems such as restriction of cranial growth, hydrocephalus and increased intracranial pressure in untreated cases, and psychosocial problems. As the treatment options are a separate chapter, only the role of radiology will be emphasized here.

Preoperative radiological evaluation is required to reveal intrinsic problems that may cause problems during surgery in patients. In unilateral coronal and lambdoid suture craniosynostosis midline structures are not in their normal position. Also, with sagittal craniosynostosis, the superior sagittal sinus may be pinched or displaced, or surrounded by a bone tunnel. Knowing all these and similar conditions is very important for accurate surgical planning in mini-invasive/endoscopic surgical approaches [1].

In addition, preoperative radiological imaging is required to prevent postoperative complications. Increased intracranial pressure, large venous drainages, the presence of bone recesses (beaten copper cranium) in the area of the bone defect minimizes the risk of operation-related bleeding, brain damage and the development of a CSF fistula [7]. Preoperative radiological evaluation is required to reveal intrinsic problems that may cause problems during surgery in patients who are planned for surgery. With unilateral coronal and lambdoid craniosynostosis midline structures are not in their normal localization. Also, with sagittal suture craniosynostosis, the superior sagittal sinus may be pinched or displaced, or surrounded by a bony tunnel. Knowing all these and similar conditions is very important for accurate surgical planning in mini-invasive/endoscopic surgical approaches [1].

16.2.1.4 Prognosis Estimation

The prognosis in craniosynostosis is complemented by radiological evaluation of possible related anomalies. The suture closure and small sutures can also affect the prognosis. Di Rocco et al. [12] evaluated the skull bones in patients with unicoronal suture craniosynostosis. According to this, the classification is determined as

follows. Type I: unilateral flattening of the frontal bone and elevation of the supraorbital ridge; Type 2A: contralateral deviation of the nasal pyramid, homolateral anterior displacement of the petrous bone and the presence of frontal and orbital anomalies; Type 2B: the anterior displacement of the petrous part of the temporal bone is more pronounced, with accompanying vomer shift; Type III: in addition to the above, severe sphenobasilar deviation and the presence of secondary craniovertebral junction asymmetry. These different clinical presentations refer to the fusion occurring at different times in the frontoparietal suture and are causally related to the prognosis due to changing surgical procedures or reoperation requirements [12].

16.2.2 Postoperative Evaluation

The main indication in postoperative radiological evaluation is the detection of complications. Since the operations are mostly for the calvaria only, the rate of major complications such as bleeding, CSF flow (dynamic) disorders, bone reabsorption, shifting of the metallic fixators/materials used on the mid-face are low (1.2%). It is common to see minor complications clinically. Of these, radiology is more valuable in the evaluation of osseous lacunae, and may assist in planning a possible second operation for neurological protection and/or cosmesis. Another indication for radiological follow-up is the evaluation of associated anomalies in SC [13] (Fig. 16.3).

Radiological examinations are not indicated, since the main factor in single suture craniosynostosis follow-up is improvement in head shape, confirmation of decompression, and especially cosmetic purposes. Tracking can be performed using 3D laser, morphometric evaluation or smartphone-based photogrammetry. Radiological imaging should be used if new symptoms or late complications occur [7].

16.3 Radiological Imaging Modalities

16.3.1 Plain X-rays

Skull X-rays have been used as the initial imaging method in children with abnormal head shapes in the past. However, due to their low sensitivity, it has been replaced by other modalities. Today, it continues to be used in some centers and for limited cases [7].

A normal suture is seen on radiographs as radiolucencies in a non-linear course with serrated surface. In craniosynostosis, the premature fused suture is seen as complete loss of radiolucency or bony bridges accompanied by perisutural sclerosis with a linearity (Fig. 16.4). In addition, the appearance of ‘beaten copper cranium’

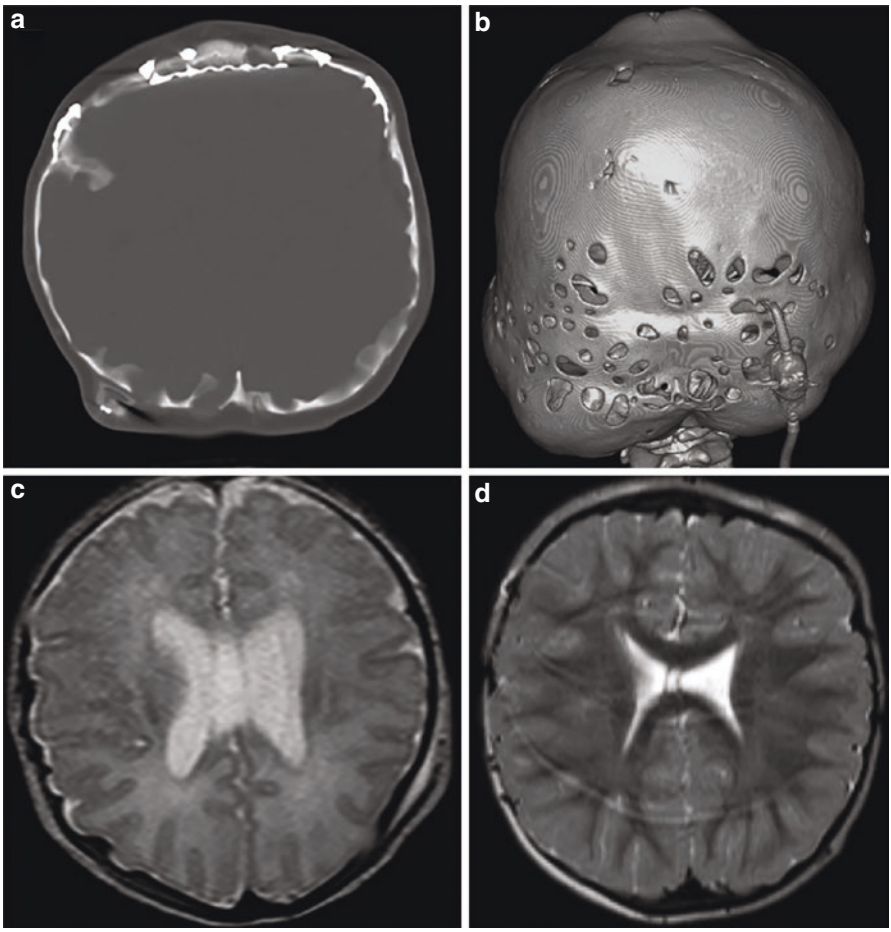

Fig. 16.3 In the postoperative period, follow-up CT images of a patient with Apert syndrome are seen. Metallic suture materials and lacunas are seen in bone structures in axial CT image (**a**) and 3D volume rendered image (**b**). In the same case, hydrocephalus was seen on axial T2 weighted image (**c**). It is observed that the hydrocephalus regressed by shunt application in the control MRI (**d**) taken 2 years later (**d**)

due to high intracranial pressure, calvarial deformities, early closure of fontanelles and mid-face anomalies can be detected as secondary findings [7].

Although plain X-rays have very high specificity in detecting single and major suture synostosis, they are poorly sensitive in detecting complex and minor sutural synostoses. In addition, due to lack of bone mineralization in newborns, it is not a reliable method for detecting craniosynostosis in the first months of life. There is also no possibility to evaluate the increased intracranial pressure and soft tissue and brain anomalies that can accompany such malformations. In addition, false negative and false positive results can occur due to radiographs that cannot be performed at

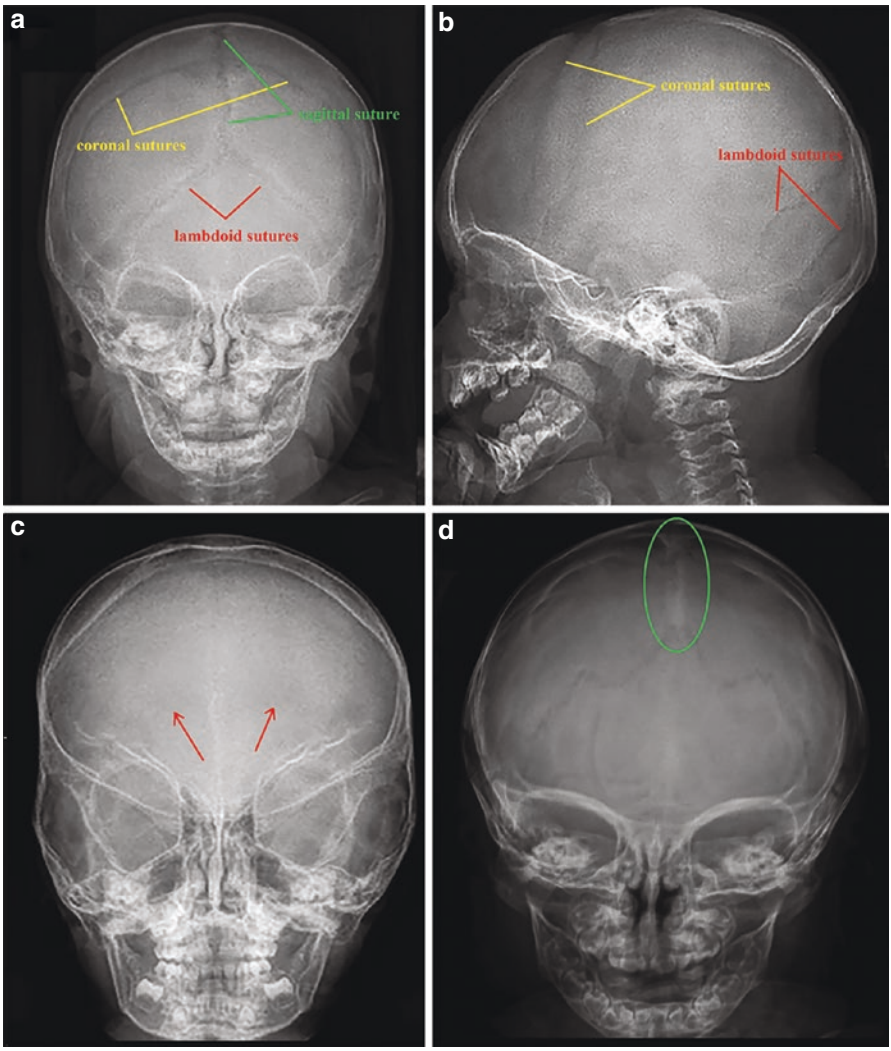

Fig. 16.4 Plain x-rays of normal (**a** and **b**) and fused (**c** and **d**) sutures are seen. Normal sutures are seen as radiolucencies on the AP (**a**) and lateral (**b**) head radiographs. Yellow lines indicate coronal sutures, red lines indicate lambdoid sutures, and green lines shows sagittal suture. In **c**, Anteroposterior head plain X-rays of craniosynostosis samples are seen in **c** and **d**. Complete loss of radiolucency is observed in coronal craniosynostosis (**c**), and bony bridges with linear perisutural sclerosis is demonstrated in sagittal suture craniosynostosis (**d**) on anterior-posterior head radiographs

an appropriate dose and angle. For an optimal evaluation, X-rays must reach perpendicular to the relevant suture. Although technically anteroposterior and lateral radiographs are sufficient, Towne and tangential radiographs may be required in some cases [7]. The findings of craniosynostosis on radiography are summarized in Table 16.1.

Table 16.1 Plain X-Ray findings in Craniosynostosis

Craniosynostosis	Plain X-Ray findings
Sagittal	*Scaphocephalic skull appearance;* *Abnormally high bregma, anterior shift of the vertex*
Metopic	*Oval shaped and upward angled orbits with hypotelorism;* *Anterior displacement of coronal sutures*
Unicoronal	*Narrowed anterior cranial fossa;* *Harlequin appearance of the orbit: lateral displacement of the anterior fontanelle to the side of the patent coronal suture*
Bicoronal	*Brachycephalic and Turricephalic appearance;* *Wide forehead with oval and oblique orbital edges*
Unilateral lambdoid	*Narrowed posterior cranial fossa;* *Contralateral shift of the posterior fontanelle and sagittal suture;* *Downward displacement of ipsilateral petrous bone and ear*
Bilateral lambdoid	*Turricephalic appearance with narrowed posterior cranial fossa;* *Downward displacement of bilaterally petrous bones and ears*

16.3.2 Computed Tomography

The gold standard radiological imaging method for the diagnosis of craniosynostosis is computed tomography (CT). High resolution images with 3 dimensional (D) surface-rendered image reconstruction are very useful in evaluating all suture synostoses, including minor sutures and skull-base hypoplasia [7, 14]. CT is a useful tool for the diagnosis of craniosynostosis, as well as for the screening of parenchymal-related anomalies, treatment planning, monitoring postoperative complications and patient follow-up [7, 8].

Raw data obtained in the axial plan with multislice CT are processed in the bone algorithm with multi-plane reconstructions and 3D volume rendering techniques. 3D reconstructions must be created at lowest possible threshold level to eliminate all soft tissue structures on the surface of the bone. A slight increase in this threshold value can increase suture width, or, more importantly, cause closed sutures to be considered as patents. A threshold value of 120-150 Hounsfield unit (HU), increasing from young to old, is usually ideal for the evaluation of the sutures. Due to these misconceptions that may occur with the change of threshold value, suture patency must also be evaluated with 2D reformatted images. 2D reformatted images should be reconstructed using a 1–2 mm thickness bone algorithm. Thin (2–3 mm) and thick (5–50 mm) images reconstructed with bone algorithm with maximum density projection are also useful in suture evaluation. In addition, evaluation of intracranial structures with 5 mm thickness images reconstructed with a brain parenchyma window at least in one plan (axial); and a global assessment of the skull over 3D volume rendering images reconstructed with the soft tissue algorithm are necessary [7, 8].

On CT, the fused suture is generally seen as a bony prominence with perisutural sclerosis and ridging, may be accompanied by focal bone thickening and erosions. Since growth perpendicular to the suture is limited, compensatory over-

growth is observed along the synostosis line, and as a result, deformity in the skull occurs (Fig. 16.5). Some specific appearances may occur due to the affected suture (Fig. 16.6). CT findings of synostosis are summarized in Table 16.2.

Although CT provides very important information in craniosynostosis, its pediatric use should be careful due to ionizing radiation [15]. It is reported that children who take 50–60 mGy (about 2–3 head CT scans) have three times the risk of developing leukemia or a brain tumor than children who are not exposed to radiation [7]. Many articles today focus on providing different radiation schemes that try to

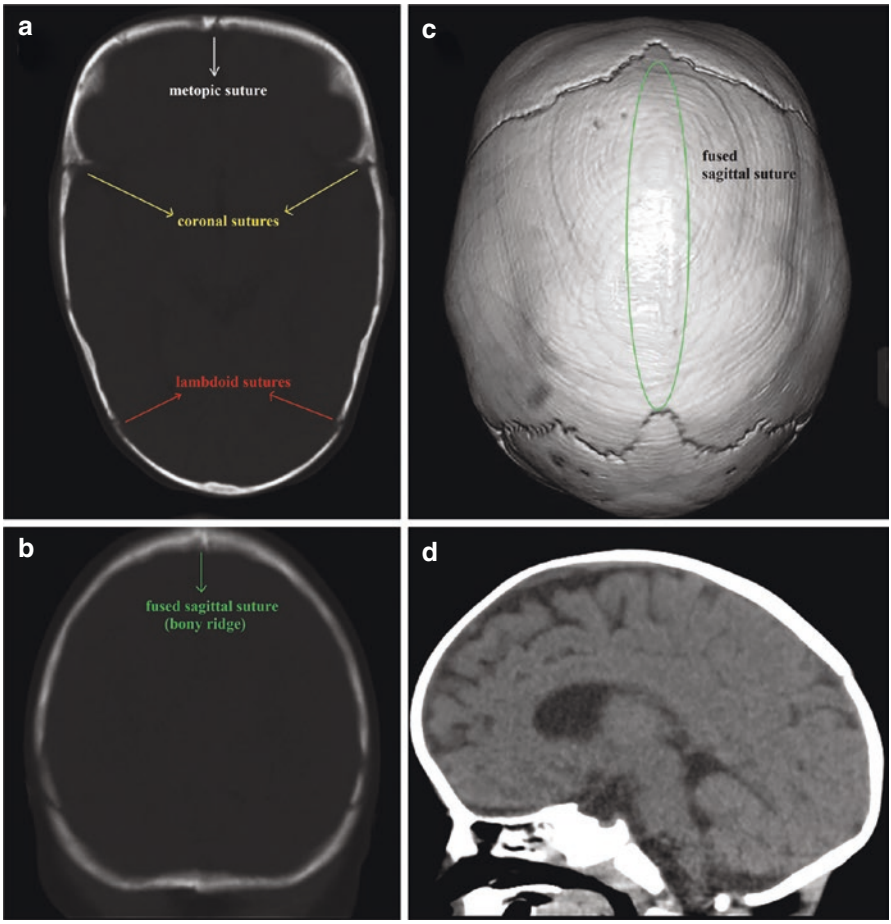

Fig. 16.5 Computed tomography (CT) plays an important role in the diagnosis of craniosynostosis. While '**a**' shows normal appearance of sutures, '**b**, **c**, and **d**' shows a case with sagittal suture synostosis. Bony ridging and perisutural sclerosis in the sagittal suture are observed on the coronal plane reformat CT image with bone algorithm (**b**). 3-dimensional surface rendered image (**c**) shows a fused sagittal suture and related scaphocephaly appearance. Scaphocephaly skull view is observed in in the sagittal plane reformat CT image with parenchymal algorithm (**d**), and it can be evaluated whether there is an additional parenchymal anomaly

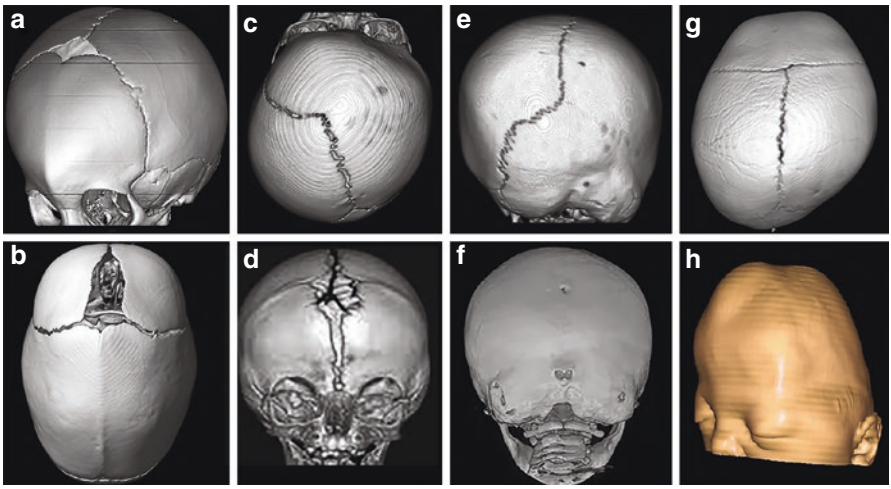

Fig. 16.6 Some specific cranium appearances are seen on 3-dimentional volume rendered CT (VRT) images. Trigonocephaly (**a**), due to premature fusion of metopic suture, and as a result sagittal suture fusion, scaphocephaly (**b**) are seen on VRT images. Ipsilateral frontal flattening and contra-lateral frontal bump are shown in unilateral coronal synostosis (**c**), and bilateral frontal flattening in bilateral coronal synostosis (**d**). Uni/bilateral occipital flattening and uni/bilateral mastoid prominence are observed due to unilateral (**e**) or bilateral (**f**) lambdoid suture fusion. In '**g**', a sample of posterior plagiocephaly is seen with patent lambdoid sutures called positional plagiocephaly. In '**h**', VRT image with soft tissue algorithm is seen in a patient with Apert syndrome. In addition to suture evaluation, soft tissue VRT images allow for global assessment of skull and especially facial anomalies (Courtesy of Dr. Saim Kazan)

reduce the dose administered while maintaining good anatomical details. The protocols used to reduce the dose are usually carried out using iterative reconstruction techniques that improve image quality by reducing noise and/or changing exposure parameters such as tube current, rotation time, and tube voltage [14, 16]. Despite the reduction in radiation dose, especially in follow-up imaging, it is important to consider the cumulative radiation risk and keep in mind other modalities that do not contain ionized radiation.

16.3.3 Ultrasonography

Although the importance of radiology in craniosynostosis is an undeniable fact, curiosity is increasing in alternative diagnostic methods due to exposure to ionizing radiation in X-ray and CT. For this purpose, the use of ultrasonography (US) is becoming more important [7]. US is a very useful technique because it is easily accessible, inexpensive, fast, does not contain ionizing radiation, and does not require sedation [11]. However, there are disadvantages such as a limited period of usage due to hair growth, presence of thin sutures, and the inability to show sutures

Table 16.2 Computed Tomography findings in Craniosynostosis

Suture Involved	
Sagittal	• *Scaphocephalic appearance with occipital protuberance and frontal bossing;* • *Decreased interorbital distance (hypotelorism)*
Metopic	• *Triangular pointed forehead; Narrowed anterior cranial fossa; Parietooccipital bossing;* • *Bilateral narrowing of the frontal bones in the pterion region; Lateral orbital hypoplasia, Insufficient supraorbital ridges; superomedially curved orbital roof (quizzical appearance)* • *Hypoplastic ethmoid sinuses;*
Unicoronal	• *Flattening of the ipsilateral frontal bone; Compensatory frontal bossing;* • *Partial or complete fusion of ipsilateral anterior fontanelle;* • *Harlequin orbit deformity (ipsilateral elevated orbital roof with hypoplasic orbit, and supraorbital ridge)*
Bicoronal	• *Brachy- and turricephalic appereance (shortened and enlarged head);* • *Occipital flattening and anterior displacement of vertex;* • *Bilateral Harlequin orbit deformity; Wide forehead; Hypertelorism;* • *Craniofacial deformities; mid-face hypoplasias*
Unilateral lambdoid	• *Ipsilateral occipitoparietal flattening; contralateral occipitoparietal and frontal bossing (trapezoidal shape);* • *Contralateral shift of posterior fontanelle and sagittal suture;* • *Posterior skull base swings to abnormal suture*
Bilateral lambdoid	• *Hypoplasic posterior cranial fossa (Turricephaly);* • *Compensatory growth of bregma;* • *Bilateral occipitoparietal flattening*
Minor sutures	• *Frontoethmoid; Frontosphenoid; Occipitomastoid; Sphenosquamous and sphenoparietal; Parietosquamous and parietomastoid synostoses* • *Anterior or posterior plagiocephaly variants according to the fused suture*

located at the base of the skull. According to many authors, although US can be performed in patients up to 3–8 months, there are some who have used it in up to 18 months [17–19].

For a reliable sonographic evaluation, the US probe should be placed perpendicular to the long axis of the suture being imaged. In this way, a coronal image of the relevant suture and adjacent bone is obtained. The hypoechogenic observation of the suture between the hyperechoic bone surfaces adjacent to the suture (end-to-end appearance) indicates that the suture is a patent. On the contrary, loss of hypoechogenicity between the hyperechogenic bone end plates is considered synostosis. In order not to overlook partial synostosis cases, coronal, sagittal, lambdoid and metopic sutures should be scanned throughout their length [19]. In the literature, the sensitivity and specificity values of US for detection of craniosynostosis range from 71% to 100% and 89% to 100%, respectively [11, 17–19].

In the postnatal period, US can be a useful both for monitoring suture patency, and for evaluating brain development and ventricular sizes with the trans-fontanelle approach [7]. Trans-fontanelle US cannot be used in screening for general anomalies because it can only evaluate a limited part of the brain parenchyma to the extent

allowed by the open fontanelle. Therefore, studies with postnatal cranial US have generally focused on the evaluation of sutures. However, we believe that the transfontanelle approach may be useful in the follow-up of intracranial pressure increase or hydrocephaly in craniosynostosis, especially syndromic cases. In the presence of hydrocephalus, shunt timing or regression in hydrocephalus in shunted cases can be followed sonographically.

Another usage area of US is the possibility of recognizing craniosynostosis in intrauterine period (especially in the third trimester). Prenatal diagnosis can be made by detecting cranial and / or facial morphologic deformities such as abnormal cephalic index, rather than direct visualization of fused sutures [11]. Cephalic index, which is the ratio of the biparietal diameter to the occipitofrontal diameter, is normal between 75–85%. While this rate is below 75% in scaphocephaly, it is observed over 85% in brachiocephaly. Abnormal head shape can be unilateral flattening, asymmetrical appearances or some specific shapes such as scaphocephaly and etc. (Fig. 16.7). However, since the most important issue in prenatal evaluation is the distinction between isolated and syndromic craniosynostosis, evaluation in terms of craniofacial anomalies is required. For this purpose, brain parenchyma, ventricular system, orbital sizes and distances between orbitals (hyper/hypotelorism) can be a sign of craniosynostosis. The sutures and facial anomalies can be detected with 3D US earlier than 2D US [20]. In addition, a complete fetal examination is mandatory for other organ and limb anomalies that may accompany in cases of syndromic craniosynostosis. Fetal hands and feet, long bones, and heart should be evaluated in detail [11, 20].

16.3.4 Magnetic Resonance Imaging

With increased concern for ionizing radiation due to CT examinations, interest in magnetic resonance imaging (MRI) is increasing in clinical practice as an alternative method of radiological evaluation. Although MRI eliminates the risk of ionizing radiation, it brings with it the need for general anesthesia or sedation, especially in infants, due to the need for immobility during the long examination period. The need for anesthesia during MRI procedure raises new concerns due to intubation, anesthesia care, and vascular line risks [7].

Previously, MRI was used to assess associated cerebral and craniofacial soft tissue anomalies rather than the diagnosis of craniosynostosis [7]. In a by Cotton et al. [21], which was the first study to analyze the sutures with MRI, it was stated that the sutures, appearing as signal void, were better visualized in sequences of 5 mm thickness. In 2015, Eley et al. [22] stated that sutures were best evaluated on T2A images, but they also added concerns that signal void areas were also observed in blood vessels. They designed the “Black Bone” MRI sequence, which uses gradient echo parameters to provide suture visualization and 3D evaluation [22]. This sequence uses a short TE, TR and low flip angle used to obtain 3D volume, and min-

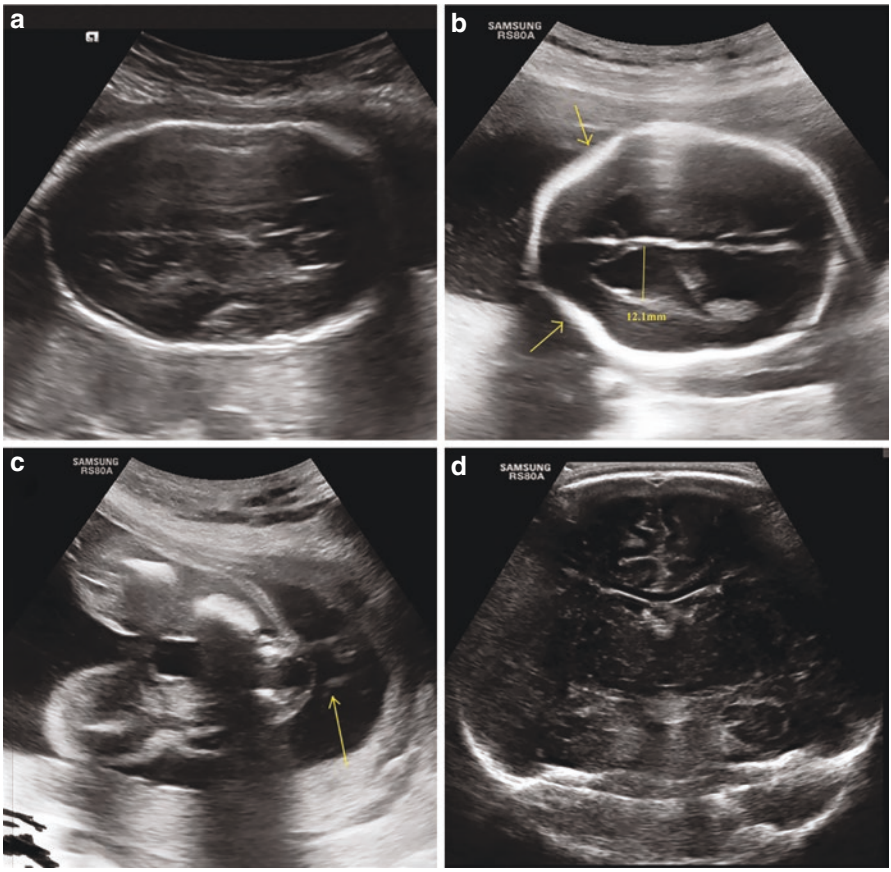

Fig. 16.7 In prenatal ultrasonography (US), scaphocephaly appearance (**a**) due to sagittal suture synostosis (**a**) and lemon sign (**b**) due to bilateral coronal suture synostosis are observed. Hydrocephaly (**b**) and sacral meningomyelocele (**c**) anomalies accompanying coronal synostosis have been shown prenatally. In a case with sagittal craniosynostosis (**d**), normal brain parenchyma and ventricles are observed in the imaging performed from the anterior fontanel in the postnatal period

imize soft tissue contrast to optimize bone-soft tissue separation. The average time of the sequence is four minutes. Imaging is performed in the axial plane, including all the bones of the skull and face, and images are obtained by post-processing in the coronal and sagittal planes. The imaging should be acquired so as to cover the whole head, including the mandibles, in order to detect associated facial anomalies. The cranial sutures appear as areas with increased signal intensity in the "Black Bone" MRI, where bones are seen as signal void areas. On the other hand, synostotic sutures remain as signal voids in the suture localization. This technique can also be used for surgical planning, as well as detection of synostosis. Although a good technique, it has structural difficulties in assessing areas with air-bone interfaces such as the mastoid region and paranasal sinuses [22].

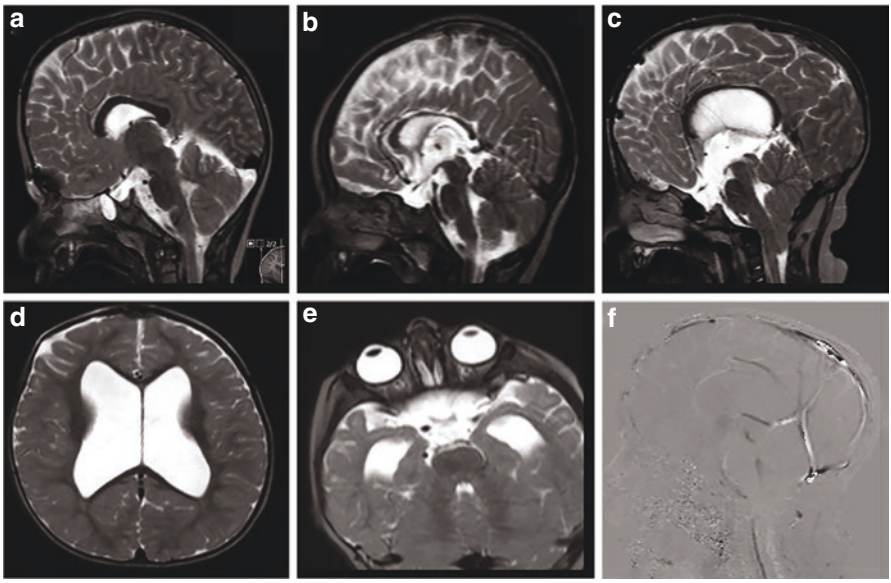

Fig. 16.8 Cranial Magnetic Resonance Imaging (MRI) images show head deformities and accompanying cranial anomalies due to craniosynostosis. In a patient with Apert syndrome (**a**), narrowed and prolonged head appearance (turricephaly), flattened frontal and occipital bones, narrowed posterior fossa are observed on T2-weighted sagittal MRI. A case with bilateral lambdoid craniosynostosis (**b**) shows flattened occipital bone and accompanying thinning of the corpus callosum. Patient with bi-coronal craniosynostosis (**c**) has narrowed posterior fossa, cerebellar herniation and enlargement in the third ventricle. In the axial T2-weighted MR images of the same patient, enlargement of the lateral ventricles (**d**) and hypo-telorism (**e**) are observed. In the cerebrospinal fluid (CSF) flow imaging (**f**), stenosis of the flow at the aqueduct of sylvius is seen

Apart from imaging the sutures, the main indication for MRI is the detection of cranial anomalies. Although intracranial anomalies are more frequently associated with syndromic craniosynostosis, the possibility of the possibility of anomalies in single suture craniosynostosis (e.g., incidence of Chiari 1 malformation 5.6%) reveals the need for MR. MRI is superior to CT in identifying associated intracranial anomalies and complications such as hydrocephalus and cerebellar tonsillar ectopia due to its excellent soft tissue contrast resolution [23] (Fig. 16.8).

Moreover, functional information can be obtained with advanced MRI techniques in addition to anatomical information. In a study with functional MRI (fMRI), it is revealed that emotional response disorders can be observed in craniosynostosis cases at school age, although the patient is operated [24]. In another study, patients with sagittal and metopic suture synostosis and isolated sagittal suture synostosis were compared using fMRI and diffusion tensor imaging (DTI), and they found that sagittal and metopic craniosynostosis showed connectivity changes in the posterior cingulate cortex (PCC) similar to attention deficit hyperactivity disorder [25]. These and similar newer studies may provide us with additional information in terms of approach to the patient and prognostic expectation in craniosynostoses.

16.3.5 Digital Angiography

The role of angiography, which is accepted as the gold standard in the diagnosis of vascular abnormalities, is very limited in craniosynostosis. Angiography may be useful in imaging venous abnormalities accompanying craniosynostosis, but these anomalies can be displayed very successfully today with CT or MR angiographies. Therefore, angiography can be used to reduce bleeding before surgery or in cases where endovascular treatment can be performed rather than detection of concomitant anomalies [7].

As a result, radiological imaging methods play an important role in craniosynostosis today. Although CT is the gold standard in diagnosis, ultrasonography and new MRI techniques are becoming increasingly important for protection from ionizing radiation. Although none of these techniques are yet at the CT level, especially progress in MRI is promising. Further studies that focus on new techniques will be useful.

16.4 Conclusion

Although clinical evaluation is often sufficient for diagnosis in craniosynostosis, radiological imaging methods should be used especially for the syndromic ones and for the detection of minor suture synostoses. In addition to diagnosis, radiology plays an important and critical role in treatment planning, detection of concomitant anomalies and post-surgery follow-up. As well as the most reliable radiological method is computed tomography, searches for alternative methods are still ongoing since it contains ionizing radiation. The timing of imaging is as important as which radiological method to choose. Therefore, a multidisciplinary approach is required in craniosynostosis, involving the surgeon, clinician and radiologist.

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Chapter 17
Syndromic Craniosynostosis

Priyadarshi Dikshit, Arun Srivastava, Kamlesh Singh Bhaisora, Ved Prakash Maurya, Kaushik Mandal, and Sanjay Behari

17.1 Introduction

'Syndromic craniosynostosis' (SC) refers to compound, multi-sutural synostosis along with extracranial manifestations such as limb anomalies, lower respiratory tract (tracheal) malformations, and cardiac anomalies. Central nervous system (CNS) anomalies often underlie the craniofacial malformations.

SC accounts for about one-fifth of all craniosynostoses, and to date up to 180 different craniosynostosis-associated syndromes have been identified. The distinction between SC and the nonsyndromic craniosynostoses is important owing to the multiple associated anomalies, especially in the former group, some of which can be life-threatening. SC requires a dedicated multidisciplinary team approach to deal with the cranial deformity, underlying CNS anomalies, nasopharyngeal and upper airway abnormalities, visual loss, need for correction of limb anomalies, need for speech therapy, and dietary modifications.

Cranial sutures are areas of dense connective tissue between membranous bones. They contain osteoprogenitor cells that mature into osteoblasts and lead to membranous bone formation. This explains the maximum growth of the calvarial bone at its borders. Fibroblast growth factors (*FGFs*) are a group of 22 known signal molecules that regulate the proliferation, migration, and differentiation of osteoblasts. Mutations of the *FGF* receptor subtype genes (*FGFRs*) are implicated in various SCs. *FGFR 2* mutations have diverse clinical manifestations ranging from isolated coronal synostosis to multisutural synostoses with myriad extracranial anomalies.

P. Dikshit · A. Srivastava · K. S. Bhaisora · V. P. Maurya · S. Behari (✉)
Department of Neurosurgery, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

K. Mandal
Department of Genetics, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India

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In addition to *FGFR 2*, several other genes including *TWIST*, *MSX 2*, and *EFNB1* have been implicated in the causation of these craniosynostosis syndromes, with up to 60 different mutations reported in them [1].

The common SCs include Apert, Crouzon, Pfeiffer, Antley-Bixler, Muenke, Saethre-Chotzen, and cranio-fronto-nasal (CFNS) syndromes. The first four of these are associated with multisutural synostoses, while the last three are associated with isolated coronal synostosis [2, 3].

17.2 Clinical Features

The characteristic skull shape in SCs is explained by growth of the skull in planes parallel to the prematurely closed sutures but not perpendicular to them (Virchow's law); for example, coronal synostosis leads to brachycephaly or turricephaly. Kleeblattschadel (cloverleaf skull) is a consequence of combined coronal, metopic, sagittal, and lambdoid sutural synostoses, with the brain protruding through the anterior and parietal fontanelles. Kleeblattschadel is a descriptive term depicting the result of severe grade combined multiple craniosynostoses, and is not a distinct entity [1–3].

Facial dysmorphisms, especially upper and mid face dysmorphisms are commonly associated with unilateral and especially with bilateral coronal synostosis, and skull base synostosis. To evaluate the craniosynostosis associated calvarial and facial dysmorphism in a more objective manner, various indices have been used (Figs. 17.1 and 17.2). Normal cephalic index (CI) ranges from 76 to 81; and, a CI of more than 81 is considered brachycephalic, while a CI of less than 76 is considered dolichocephalic. Decreased mid-facial depth with mid-lower third facial depth index (mid-facial depth × 100/ lower facial depth, <86) is seen in mid-facial hypoplasia [4]. Upper facial index (upper face height × 100/ upper face width) is also reduced (<45) in mid-facial hypoplasia. In the case of turricephaly, the head-face height index (head height × 100/ face height) is increased (>130) with reduced head length and width [5]. The specific clinical features associated with different craniosynostosis syndromes are described as follows:

17.2.1 Apert Syndrome

Apert syndrome is characterized by multisutural craniosynostosis with involvement of all the coronal sutures. It is associated with hand and foot anomalies, specifically syndactyly of the fingers and toes. Complex soft tissue and skeletal fusion can lead to a characteristic "mitten" deformity in both hands and feet.

The cranial manifestations take the form of oxycephaly, with a flat, steep forehead. The facial manifestations include midfacial hypoplasia (retraction), proptosis, hypertelorism, external strabismus, trapezoid mouth, mandibular prognathism,

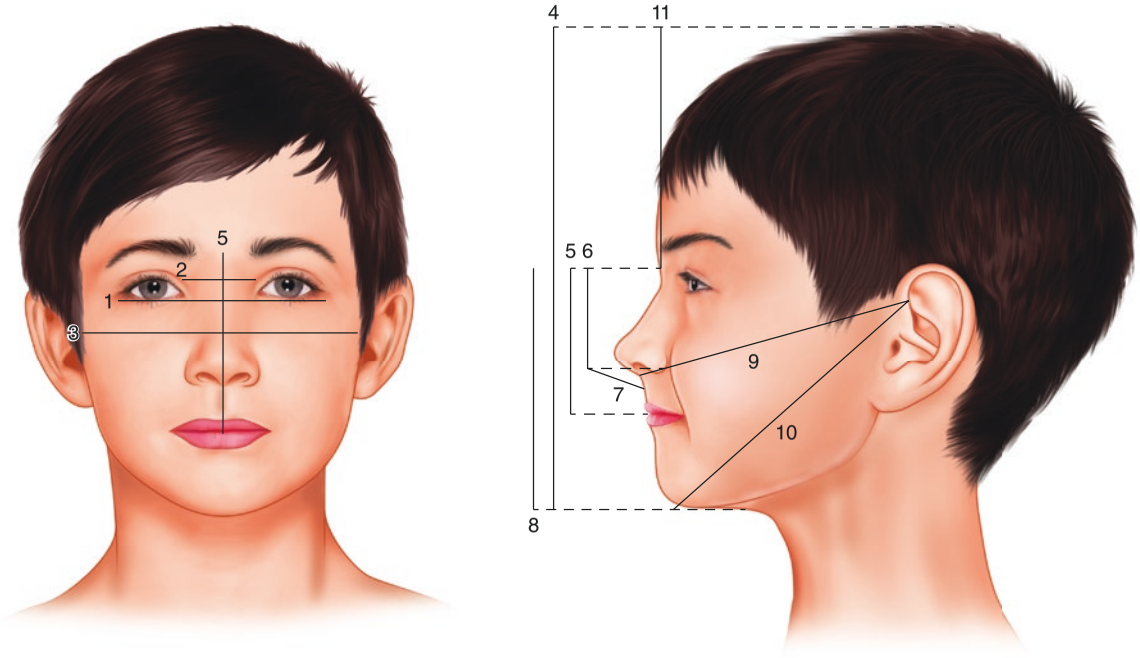

Fig. 17.1 Sketch representing the front and side views of face of a normal child. Various lines for facial proportions are described as follows: *1*: Bi-ocular width: Between the landmarks at the right and left exocanthi; *2*: Inter-canthal width (endocanthion-endocanthion): Between the landmark at the inner comissure (en) of the right and left palpebral fissures; *3*: Upper face width (bi-zygomatic diameter): Between the most lateral points of the zygomatic arches; *4*: Cranio-facial height: Between the vertex and the gnathion *5*: Upper face height: Between the nasion and the stomion in the middle of the labial fissure in gently closed lips; *6*: Nose length (height): Between the nasion and the midpoint at the base of the columella; *7*: Nasal tip protrusion; *8*: Face height: Between the nasion and the chin point (gnathion). *9*: Middle facial depth (maxillary depth): Between the tragion point just above tragus, and the sub-nasal landmark, the midpoint at the base of the columella; *10*: Lower facial depth: From the tragion to the gnathion; *11*: Head height: Between the vertex and nasion

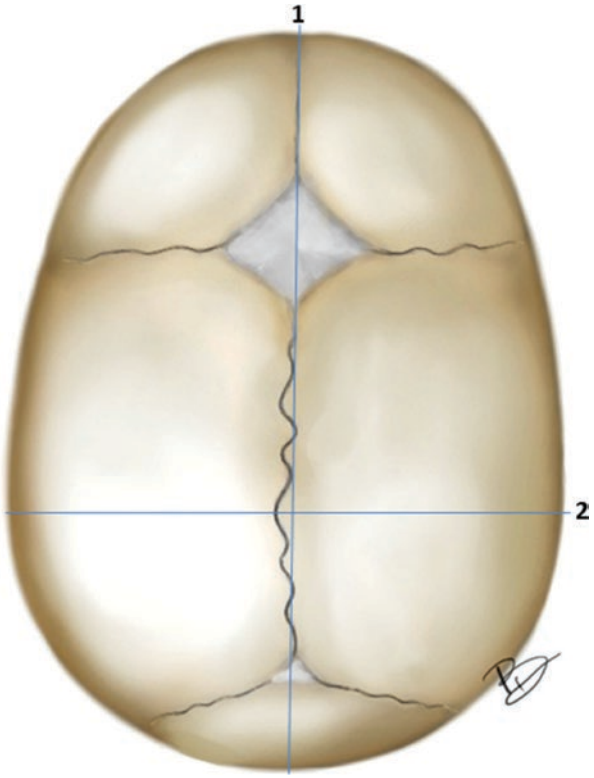

Fig. 17.2 Head width (HW): Between the most lateral points of the skull (euryon); Head length (HL): Between the glabella and the most posterior point of the cranium. Cephalic index: HW X 100/ HL

beak-shaped nose, and low-set ears (Figs. 17.1, 17.2, and 17.3). Mid-facial retraction and narrow airways lead to upper airway obstruction and obstructive sleep apnea (OSA). Other manifestations include poor joint mobility, middle ear ossicular ankyloses leading to conductive hearing loss, cleft palate, and malocclusion of teeth (Figs. 17.4, 17.5, 17.6, 17.7, and 17.8).

Most cases of Apert syndrome are sporadic in origin, but others could involve autosomal dominant inheritance of the *FGFR 2(10q26)* mutation. Other possible influencing factors include viral embryopathy, maternal infection, and perhaps environmental factors in a genetically predisposed child.

17.2.2 Crouzon Syndrome

Crouzon syndrome is a cranio-facial dysostosis syndrome characterized by a tall and flat forehead, proptosis, and midfacial hypoplasia. The facial anomaly in Crouzon syndrome is relatively mild and cleft palate is rare. Proptosis is prominent,

Fig. 17.3 Apert syndrome: Cranial manifestations are in the form of oxycephaly, with a flat, steep forehead. The facial manifestations include mid-facial hypoplasia (retraction), proptosis, hypertelorism, external strabismus, trapezoid mouth, mandibular prognathism, beak shaped nose, and low set ears

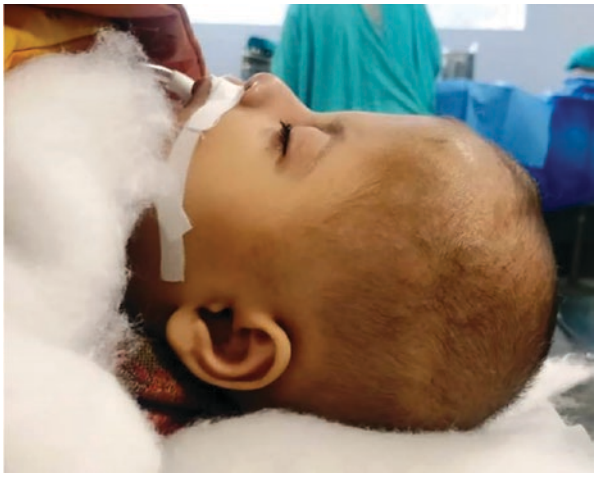

Fig. 17.4 Apert syndrome: Cranial manifestations are in the form of oxycephaly, with a flat, steep forehead. The facial manifestations include mid-facial hypoplasia (retraction), proptosis, hypertelorism, external strabismus, trapezoid mouth, mandibular prognathism, beak shaped nose, and low set ears

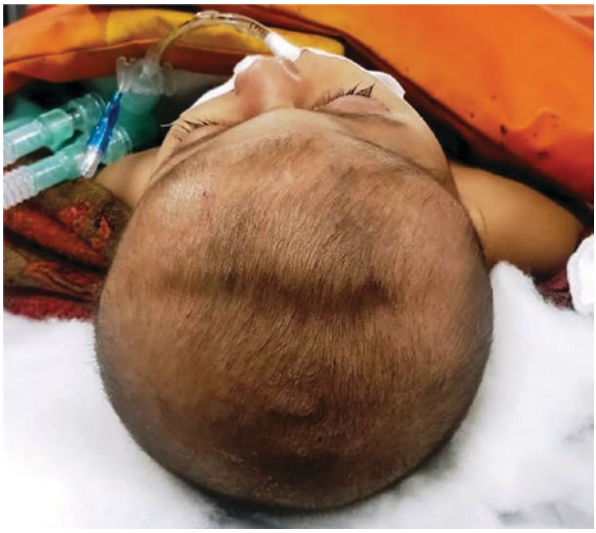

Fig. 17.5 Apert syndrome: Cranial manifestations are in the form of oxycephaly, with a flat, steep forehead. The facial manifestations include mid-facial hypoplasia (retraction), proptosis, hypertelorism, external strabismus, trapezoid mouth, mandibular prognathism, beak shaped nose, and low set ears

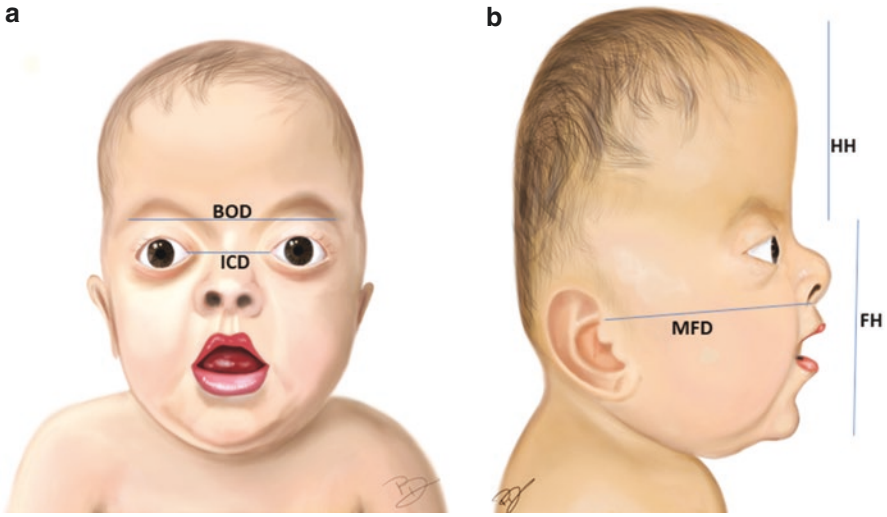

Fig. 17.6 Artist's impression of Apert syndrome. (**a**) Proptosis with hypertelorism is noticed with increased intercanthal distance (ICD) and bi-ocular distance (BOD); (**b**) There is midfacial hypoplasia, with reduced midfacial depth (MFD), and turricephaly (increases head height: face height ratio). There are low set ears, with downward displaced zygomatic arch

along with hypertelorism and maxillary hypoplasia. Associated frontal bossing is common (Figs. 17.9, 17.10, and 17.11). In florid cases, there is turribrachycephaly, midfacial retraction, proptosis with an inferior scleral show and a small beak-shaped nose. In contrast to other craniosynostosis syndromes (such as Apert or Pfeiffer syndrome), patients with Crouzon syndrome have normal intelligence and usually

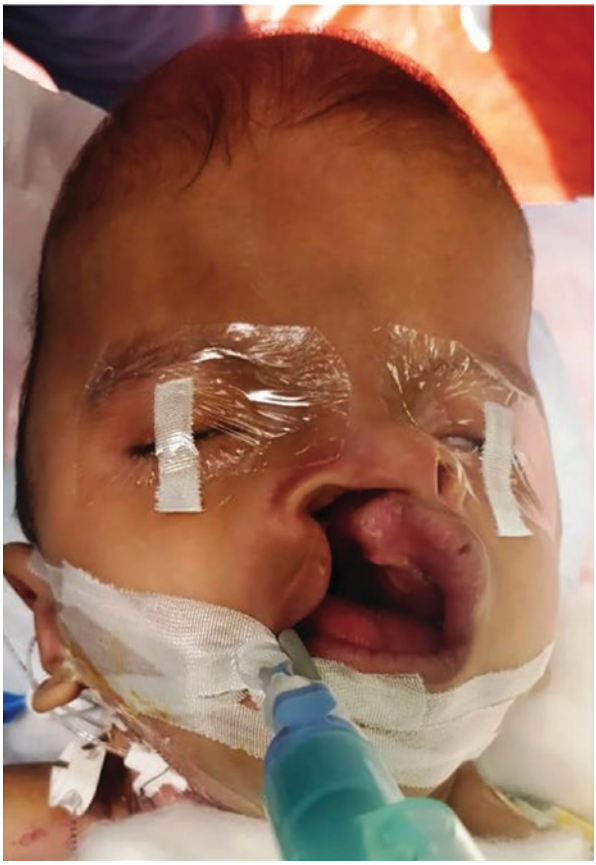

Fig. 17.7 Apert syndrome: Mid-facial retraction and narrow airways lead to upper airway obstruction and obstructive sleep apnoea (OSA). Other associations include poor joint mobility, middle-ear ossicular ankyloses, leading to conductive hearing loss, cleft palate, and malocclusion of teeth

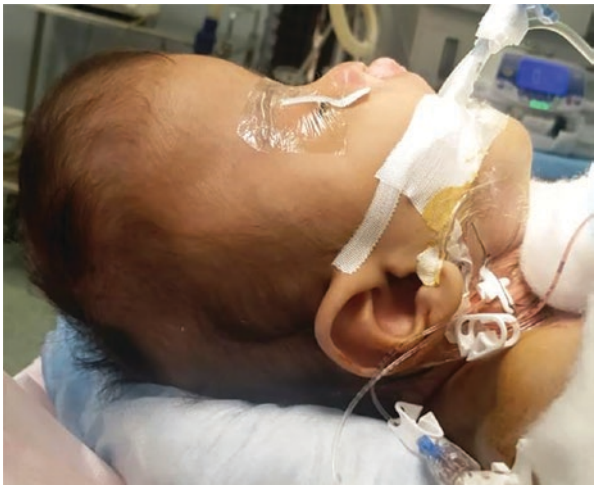

Fig. 17.8 Apert syndrome: Mid-facial retraction and narrow airways lead to upper airway obstruction and obstructive sleep apnoea (OSA). Other associations include poor joint mobility, middle-ear ossicular ankyloses, leading to conductive hearing loss, cleft palate, and malocclusion of teeth

Fig. 17.9 Crouzon syndrome: It is characterized by a tall and flat forehead, proptosis, and mid–facial hypoplasia. Proptosis is prominent, along with hypertelorism, and maxillary hypoplasia. Often, there is associated frontal bossing. Figure 17.9 shows features of hypertelorism with increased BOD and ICD, along with proptosis, mid-facial retrusion with reduced mid-facial: lower facial depth ratio (MFD; LFD), along with a beaked nose having reduced nose tip protrusion (NTP)

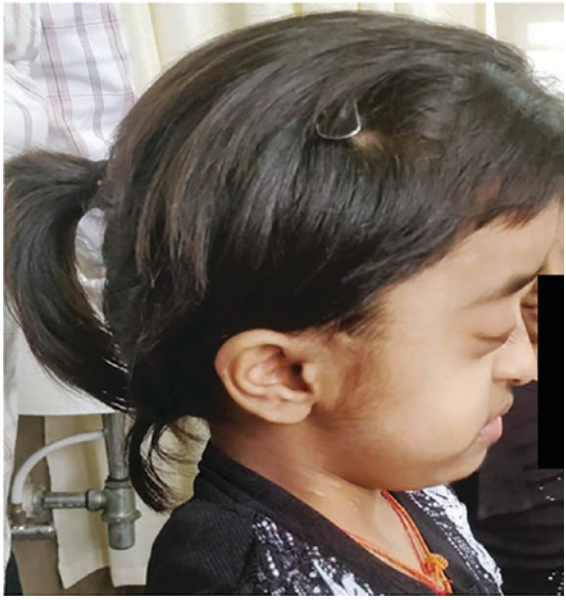

Fig. 17.10 Crouzon syndrome: It is characterized by a tall and flat forehead, proptosis, and mid–facial hypoplasia. Proptosis is prominent, along with hypertelorism, and maxillary hypoplasia. Often, there is associated frontal bossing. Figure 17.10 shows features of hypertelorism with increased BOD and ICD, along with proptosis, mid-facial retrusion with reduced mid-facial: lower facial depth ratio (MFD; LFD), along with a beaked nose having reduced nose tip protrusion (NTP)

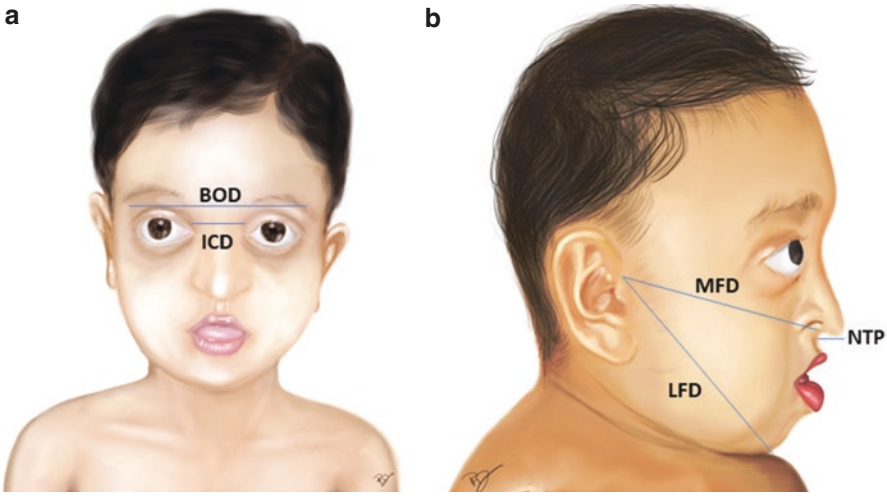

Fig. 17.11 Crouzon syndrome: It is characterized by a tall and flat forehead, proptosis, and mid–facial hypoplasia. Proptosis is prominent, along with hypertelorism, and maxillary hypoplasia. Often, there is associated frontal bossing. Figure 17.11 (**a**) Frontal; and, (**b**) Lateral view shows features of hypertelorism with increased BOD and ICD, along with proptosis, mid-facial retrusion with reduced mid-facial: lower facial depth ratio (MFD; LFD), along with a beaked nose having reduced nose tip protrusion (NTP)

have no limb anomalies. One-third of cases are sporadic, while the rest show autosomal dominant inheritance, the commonly-implicated genes being *FGFR 2* (common) and *FGFR 3*.

17.2.3 Pfeiffer Syndrome

The distinctive features of Pfeiffer syndrome include broad, radially deviated thumbs and great toes along with craniosynostosis, and there can be partial syndactyly. Other manifestations include hydrocephalus, proptosis, ankylosed elbow, visceral anomalies, and neuropsychological developmental delay. The severity of craniofacial malformation is variable, and Pfeiffer syndrome is subclassified into three types:

Type 1 is characterized by brachycephaly, midface hypoplasia, occasional hydrocephalus, and finger and toe anomalies (medially deviated thumb and great toe, and brachydactyly). These patients have normal intelligence, and in general have a good outcome.

Type 2 patients have more severe craniofacial deformity with turricephaly, and often have classic clover leaf skull and proptosis with hypertelorism (Figs. 17.12, 17.13, and 17.14). The patient can have difficulty in closing the eyes, leading to the risk of exposure keratitis. Patients also have extracranial manifestations such as thumb and great toe deviations and brachydactyly.

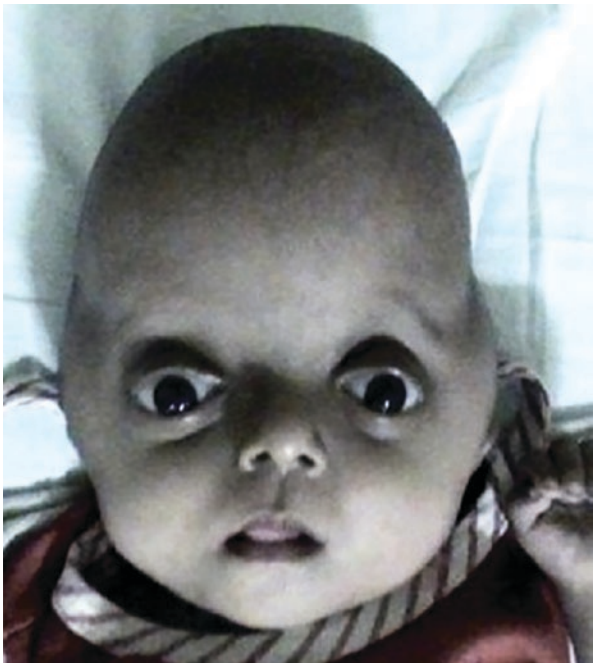

Fig. 17.12 Pfeiffer syndrome: Type 2 patients have severe cranio-facial deformity with turricephaly, and often have classic clover leaf skull and proptosis with hypertelorism. These patients also have extra-cranial manifestations in the form of thumb and great toe deviations and brachydactyly. Figure 17.14 shows significant proptosis with increased ocular protuberance (OP) measured from the lateral orbital wall, with hypertelorism, and turricephaly. A groove can be appreciated just above the temporal swelling (solid star), causing the characteristic "clover-leaf" deformity. The zygomatic arch is inferiorly displaced (asterisk) with low set ears

Type 3 is the most severe form, associated with extreme proptosis and occasionally globe prolapse, external strabismus, coexisting limb deformities in the form of elbow ankyloses, brachydactyly, and developmental delay with neurological complications. Mutations in *FGFR 1 and 2* are implicated in Pfeiffer syndrome, the *FGFR 2* mutations overlapping with those in Crouzon syndrome.

Types 2 and 3 can be associated with choanal stenosis/atresia, laryngotracheal abnormalities, hydrocephalus, seizures, sacro-coccygeal eversion, and the risk of early death. Hand and foot anomalies differentiate Crouzon syndrome from Pfeiffer syndrome.

17.2.4 Antley-Bixler Syndrome

This is a rare form of syndromic craniosynostosis characterized by multiple craniosynostosis with radiohumeral or radioulnar synostosis. The facial features include midfacial hypoplasia with upper airway narrowing and obstruction. Some patients

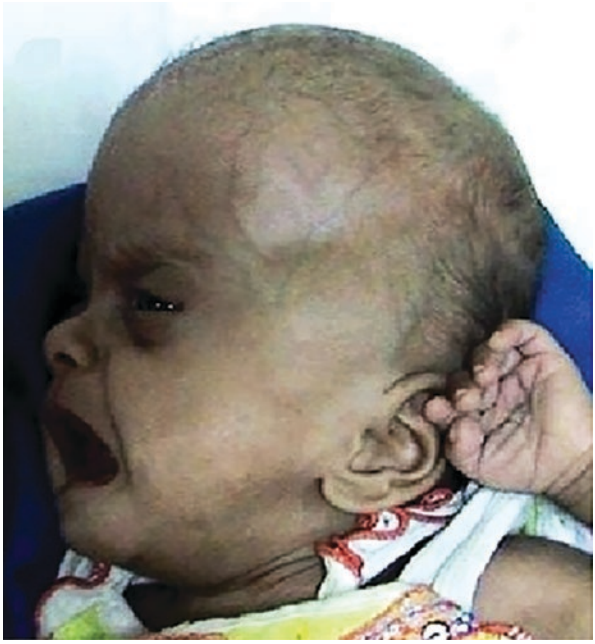

Fig. 17.13 Pfeiffer syndrome: Type 2 patients have severe cranio-facial deformity with turricephaly, and often have classic clover leaf skull and proptosis with hypertelorism. These patients also have extra-cranial manifestations in the form of thumb and great toe deviations and brachydactyly. Figure 17.14 shows significant proptosis with increased ocular protuberance (OP) measured from the lateral orbital wall, with hypertelorism, and turricephaly. A groove can be appreciated just above the temporal swelling (solid star), causing the characteristic "clover-leaf" deformity. The zygomatic arch is inferiorly displaced (asterisk) with low set ears

have congenital cardiac and renal anomalies along with congenital adrenal hypoplasia. The underlying mutations include *FGFR2* and *P450 oxido-reductase (POR)* mutations, the former having an autosomal dominant inheritance and the latter having an autosomal recessive inheritance.

The *POR*-deficient patients are characterized by impaired sexual development (ambiguous genitalia), impaired steroidogenesis (associated with congenital adrenal hyperplasia), and skeletal malformations. In comparison, *FGFR 2*-mutated patients manifest severe skeletal manifestations without endocrinopathy or genital anomalies.

17.2.5 Muenke Syndrome

Muenke syndrome is characterized by mild unilateral or bilateral coronal synostosis along with variable extracranial skeletal manifestations. It has an autosomal dominant inheritance with mutation in *FGFR 3*.

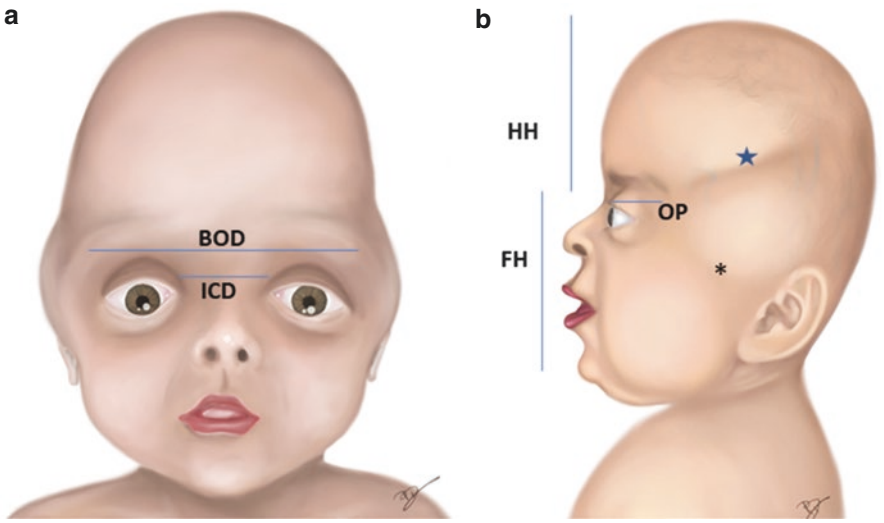

Fig. 17.14 Pfeiffer syndrome: Type 2 patients have severe cranio-facial deformity with turricephaly, and often have classic clover leaf skull and proptosis with hypertelorism. These patients also have extra-cranial manifestations in the form of thumb and great toe deviations and brachydactyly. Figure 17.14 (**a**) Frontal view; and, (**b**) Lateral view show significant proptosis with increased ocular protuberance (OP) measured from the lateral orbital wall, with hypertelorism, and turricephaly. A groove can be appreciated just above the temporal swelling (solid star), causing the characteristic "clover-leaf" deformity. The zygomatic arch is inferiorly displaced (asterisk) with low set ears

The craniofacial features include proptosis, down-slanting palpebral fissures, and hearing loss. There can be developmental delay and specific bone anomalies in the hands and feet. There is often an overlap of features between Muenke syndrome and Saethre–Chotzen syndrome.

17.2.6 Saethre–Chotzen Syndrome

This is characterized by unilateral or bilateral coronal synostosis and mild limb anomalies. Severe cases involve multisutural synostosis. The underlying defect is a loss-of-function mutation in *TWIST*, which has significant role in calvarial osteoblast proliferation and differentiation, and the syndrome has an autosomal dominant inheritance. Other features include facial asymmetry, ptosis of the eyelids, low-set ears, hearing loss, shortened fingers, soft tissue syndactyly of the second and third fingers (partial syndactyly), and clinodactyly (Fig. 17.15).

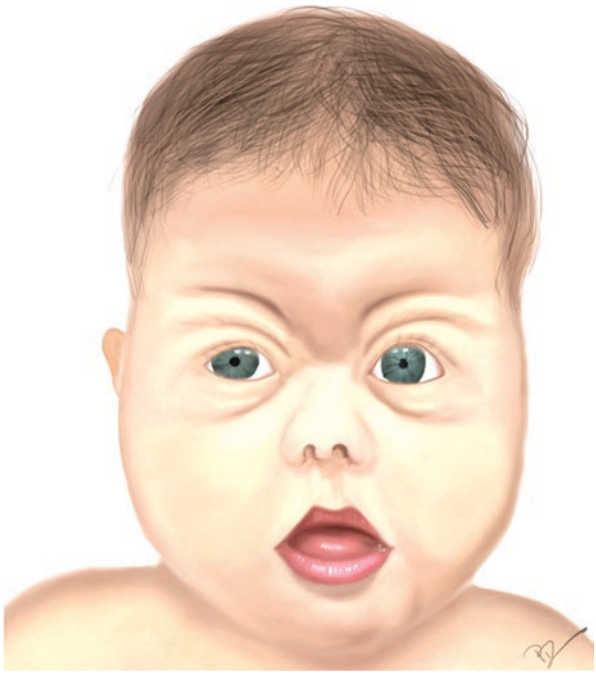

Fig. 17.15 Saethre-Chotzen syndrome: It is characterized by supra-orbital retrusion with shallow orbits, small beak shaped nose, facial asymmetry and ptosis. There is turri-brachycephaly with a high forehead and a low hair line

17.2.7 Cranio-Frontonasal Syndrome

This is a rare craniosynostosis having an X-linked dominant inheritance. It includes bilateral coronal synostosis, and has unique facial dysmorphism in the form of hypertelorism along with frontal bossing, bifid nasal tip, cleft lip, and a high arched or cleft palate. Other manifestations include syndactyly, grooved nails, clinodactyly, broad thumbs, wiry hair, and dental anomalies. The implicated gene is *EFNB 1* (chromosome Xq12); however, in contrast to most X-linked disorders, female patients are paradoxically more severely affected.

Apart from the specific clinical features of these syndromes, there can be vision loss, possibly resulting from exposure keratitis secondary to incomplete closure of the palpebral fissure due to globe prolapse. Visual loss can also result from long-standing raised intracranial pressure (ICP), leading to secondary optic atrophy.

The ICP could be raised by impaired venous drainage, possibly secondary to jugular foraminal stenosis, and the emissary veins can be enlarged, leading to prominent scalp veins. The ICP can also be raised by hydrocephalus or hypercarbia caused by impaired ventilation, and can also be associated with secondary Chiari malformation.

These patients commonly have obstructive sleep apnea (OSA), varying in severity and requiring sleep studies. The disorder often necessitates nocturnal monitoring

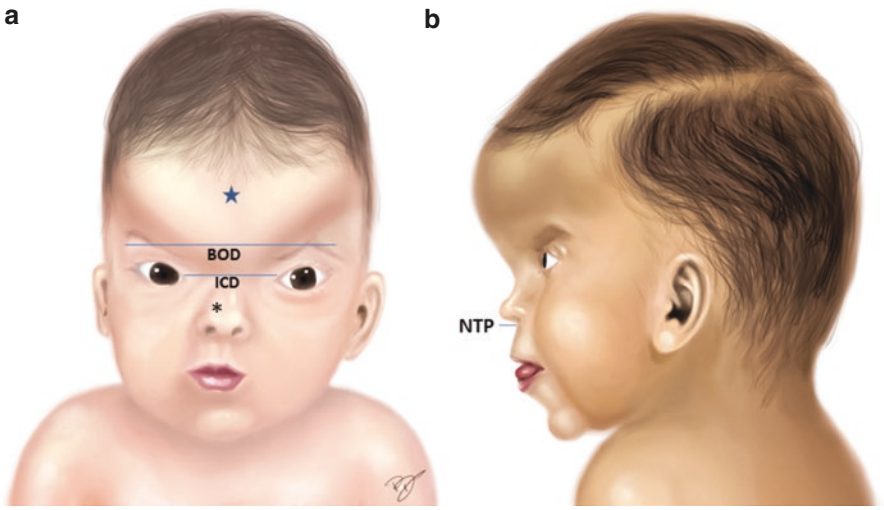

Fig. 17.16 Cranio-fronto nasal syndrome: Figure 17.16 (**a**) Frontal view; and, (**b**) Lateral view show that there is significant midline frontal bossing (solid star) with marked hypertelorism, facial asymmetry, short nose and broad (often bifid) nasal tip (asterisk)

of oxygen saturation. Chronic hypoxia along with raised ICP can lead to impaired neurological and intellectual development. The underdevelopment of the midfacial region leads to respiratory complaints and the maxillofacial maldevelopment results in anomalous dental growth and malocclusion. The associated choanal stenosis and adenoid hyperplasia in such children can lead to persistent mouth breathing, further worsening the malocclusion.

These children also have feeding difficulty secondary to the structural abnormalities (such as midfacial hypoplasia), which also lead to respiratory difficulty. The abnormal palatal shape along with the feeding difficulty often mandates the use of a nasogastric tube, or a gastrostomy in severe cases (Fig. 17.16).

17.3 Radiology

The aim of radiological assessment is to assess the severity and extent of craniosynostosis and the status of the underlying brain parenchyma and the ventricles, to rule out any associated Chiari malformation, and to evaluate the systemic abnormalities for surgical planning and follow-up. Dedicated imaging to assess cervical vertebral fusion anomalies and limb anomalies are also required.

Craniosynostosis can be diagnosed prenatally with ultrasonography during the second or third trimester of gestation. Typically, ultrasonography shows hyperechoic bridging of the sutures with or without ridge formation, which is characteristic of craniosynostosis. A normal suture has a hypoechoic appearance between the hyperechoic bone plates.

17.3.1 Plain Roentgenogram

Plain radiographs are valuable for the initial evaluation. They also serve to delineate the skull abnormalities and serve as a reference for follow-up postoperative radiographs. A skull radiograph is typically conducted after the child is 3 months old and includes anteroposterior (AP), Towne's, and lateral views.

Perisutural sclerosis, localized bony bridging with loss of visualization of sutures, indicates synostosis. Secondary signs include a beaten copper appearance of the cranial vault owing to raised ICP along with the abnormal skull shape. Elevation of the sphenoid wings suggests basal craniosynostosis.

17.3.2 Multidetector Computed Tomography (MDCT) with Three-dimensional (3D) Volume Rendering

A thin 0.625 mm cut MDCT is preferred for the evaluation of bone in craniosynostosis, with 3-dimensional (3D) volume rendering and surface shaded display (SSD) for proper surgical planning (Figs. 17.17 and 17.18). Metopic synostosis appears as

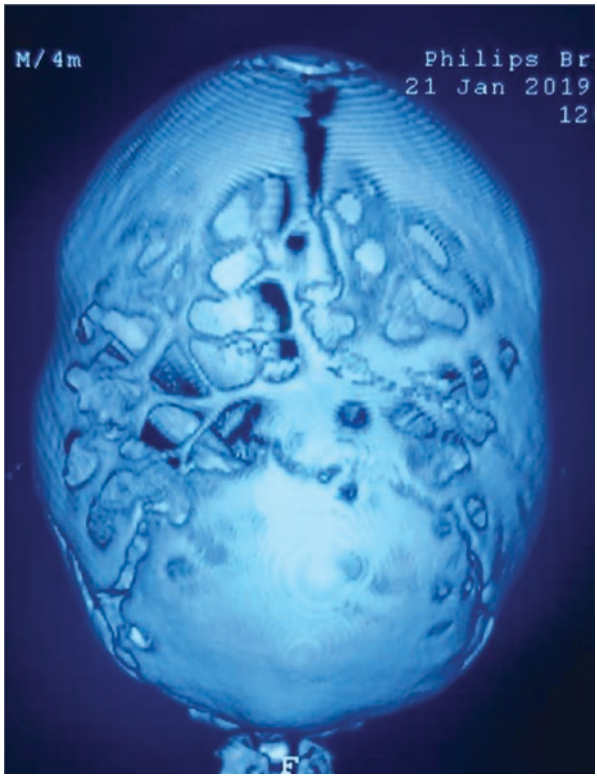

Fig. 17.17 A thin cut CT evaluates bone in craniosynostosis, with three- dimensional (3D) volume rendering and surface shaded display (SSD) for proper surgical planning. Metopic synostosis appears as focal bone thickening and sclerosis in the midline in the frontal bone. Sagittal and lambdoid synostosis are seen as perisutural sclerosis with thickened bony ridges

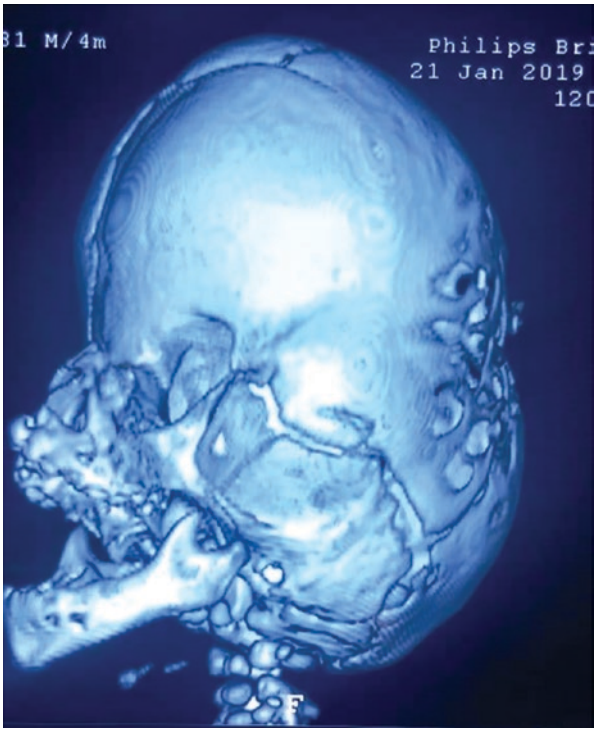

Fig. 17.18 A thin cut CT evaluates bone in craniosynostosis, with three- dimensional (3D) volume rendering and surface shaded display (SSD) for proper surgical planning. Metopic synostosis appears as focal bone thickening and sclerosis in the midline in the frontal bone. Sagittal and lambdoid synostosis are seen as perisutural sclerosis with thickened bony ridges

focal bone thickening and sclerosis in the midline in the frontal bone. Sagittal and lambdoid synostoses are seen as perisutural sclerosis with thickened bony ridges.

There can be jugular foramen stenosis, or atresia, with collateral venous circulation via enlarged emissary veins. The CT scan images should also include facial sections because they help to detect the degrees of midfacial hypoplasia and basal craniosynostosis. Failure of the maxilla to grow antero-inferiorly leading to airway obstruction and nasopharyngeal constriction can be clearly demonstrated on sagittal and coronal reconstructions.

Multiple cranial synostoses involving the major and minor sutures associated with other craniofacial anomalies can be studied effectively with volume-rendered images. Premature fusion of minor sutures of the skull base leads to significant changes in the craniofacial axis of the child. These minor sutures include the squamous sutures, synchondroses of the mid and posterior skull base, paired sphenooccipital sutures, and anterior and posterior intraoccipital, petro-occipital, and occipitomastoid sutures. Shallow orbits with a short orbital roof, and maxillary hypoplasia leading to proptosis, need to be evaluated preoperatively to aid in the surgical planning of orbital advancement.

17.4 MRI

MRI plain sequences help in assessing the underlying brain parenchyma, ventriculomegaly, any associated periventricular lucency, hippocampal hypoplasia, white matter aberrations, and septum pellucidum agenesis. MR venography helps in assessing the associated venous anomalies, and arterial spin-labelling MRI sequences can be used in place of single photon emission computed tomography (SPECT) for identifying areas of hypoperfusion of the brain parenchyma.

17.4.1 Follow-up Imaging

CT scans should be carried out immediately in the postoperative period to look for scalp/extradural collections secondary to dural tears. Follow-up with sequential radiographs at intervals of 1 year can be used to assess bony remodeling by comparison with the preoperative radiograph.

17.5 Management

Attenuation of raised ICP, amelioration of cephalocranial disproportion and treatment of respiratory dysfunction is the triad that needs to be addressed in managing SC.

The goals of surgical treatment for SC are:

1. To address the ICP change resulting from altered CSF dynamics and venous circulation.
2. To re-establish the spatial associations between the calvarium and the vascular and cerebral structures within it.
3. To realign the calvarial vectors responsible for cranial growth.
4. To rectify the cosmetic and functional anomalies, which follows once the above goals are achieved.

The timing of surgery in craniosynostosis has been a longstanding topic of debate. The choice of the surgical procedure and the timing of surgery depend on the structural and functional anomalies. The variable clinical course and unpredictable patient-related factors make surgery necessarily an individualized, staged, tailored, growth- and age-related procedure.

For an optimal perioperative and anesthetic management, a thorough medical evaluation is mandatory for each individual case. If there is syndromic craniosynostosis, additional anesthetic challenges arise in the form of associated airway and

cardiac anomalies. Up to 50% of cases of syndromic craniosynostosis are associated with airway abnormalities with multilevel airway obstructions. The anesthesiologist checks for pre-existing cardiac abnormalities such as velo-cardio-facial syndrome, Williams's syndrome and van der Woude's syndrome. A congenital atrial septal defect (ASD) can warrant preventive operative closure before patients are subjected to cranial surgery. Any associated bleeding diathesis or any altered metabolic status needs to be addressed preoperatively [6–8].

Intraoperative anesthetic challenges should be dealt with meticulously. These can take the form of tube dislodging, hypotension and hypothermia. Metabolic changes can also arise from fluid and electrolyte imbalance (the incidence of hyponatremia can be up to 30% in the peri-operative period) [7–13].

The various surgical procedures include:

- Posterior expansion
- Anterior advancement
  - Fronto-orbital advancement
  - Craniofacial advancement
  - Maxillo-mandibular advancement
- CSF diversion for hydrocephalus.

17.5.1 Posterior Expansion

17.5.1.1 Indication and Timing

This is the first step in cranial vault remodeling, which is performed at 2–3 months of age in order to decrease the intracranial pressure (ICP). The effect of calvarial expansion on ICP is confirmed by invasive monitoring before and after the procedure. Cranial vault reconstruction can be delayed by up to 6–8 months if the ICP is not raised. This delay in the surgical procedure makes the operative outcome more stable. A thorough radiological evaluation using thin-section CT and MR images with venous angiogram defines the extent of constriction. The surgical procedure needs to be tailored according to the severity of the SC. This procedure is more relevant in Crouzon syndrome and severe Pfeiffer syndrome, which are accompanied by elevated ICP.

When the calvarial bone is thicker than 1 mm, associated with dural venous sinus compression along with constriction of the posterior fossa structures, standard expansion of the posterior cranial vault is recommended [14–17].

17.5.1.2 Procedure

A standard bicoronal scalp incision is placed, followed by blunt dissection of the skin flap away from the periosteal layer. Leaving the periosteum in place reduces the risk of bleeding from transosseous vascular channels. A high-speed drill and a

craniotome are used conventionally to carry out the craniotomy, followed by careful separation of the bone from the underlying dura mater. The parieto-occipital bone is reshaped, the parietal eminence is reconstructed and the high-speed drill is used to remove any bony spur or ridge present on the internal aspect of the bone flap. The tongue-and-groove technique is employed for fronto-orbital advancement, the bone being fixed to the desired place with absorbable sutures. Midline suboccipital decompression is an additional procedure if a Chiari malformation or a thickened bony ridge in the midline is noticed, compressing the brainstem.

When the calvarial bone thickness is less than 1 mm, or there are lattice bone defects or any severe venous sinus compressions, the preferred procedure is a free-floating parieto-occipital flap. In this technique, the bone pieces are not separated from the underlying dura mater. This helps to prevent the risk of bleeding, dural tear, and most importantly, helps to shorten the surgical procedure.

17.5.2 Anterior Advancement

Anterior advancement is significant in several ways for syndromic craniosynostosis, in addition to the conventional procedures that are carried out for all craniosynostosis cases. A few important ones are:

- Fronto-orbital advancement
- Fronto-facial single stage advancement
- Facial advancement as a second stage procedure
- Mandibular advancement

17.5.3 Fronto-orbital Advancement

17.5.3.1 Indication and Timing

Fronto-orbital advancement (FOA) is an integral part of any form of SC correction, sometimes but not always accompanied by forehead advancement. In this procedure, the supra-orbital bar is mobilized and given a new shape, while a new upper forehead with the desired curvature is generated simultaneously. This surgical procedure is preferably performed before the first birthday of the child. Most surgeons prefer a bilateral advancement for obvious symmetry to be maintained, although both unilateral and bilateral advancements have proven to be equally effective [15, 17].

17.5.3.2 Procedure

A bicoronal wavy scalp incision is given, the subgaleal flap is elevated and the temporalis muscle is detached down to the temporal fossa. A periosteal flap based anteriorly is raised, which exposes the supraorbital rim, the upper part of lateral wall of orbit and the base of the nasal bone (Fig. 17.19). The fronto-orbital bandeau (FOB)

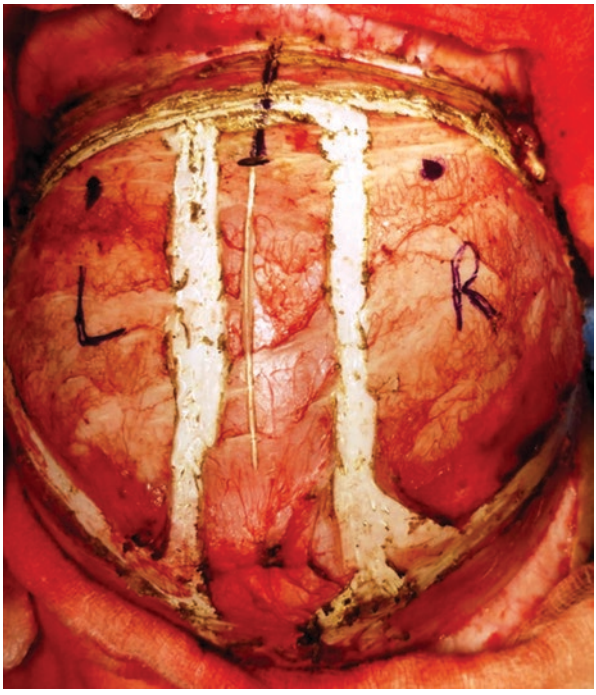

Fig. 17.19 Fronto- orbital advancement: A bi-coronal wavy scalp incision is given, the subgaleal flap is elevated and the temporalis muscle is detached down to the temporal fossa. A periosteal flap which is based anteriorly is raised, which exposes the supraorbital rim, upper part of lateral wall of orbit and base of the nasal bone

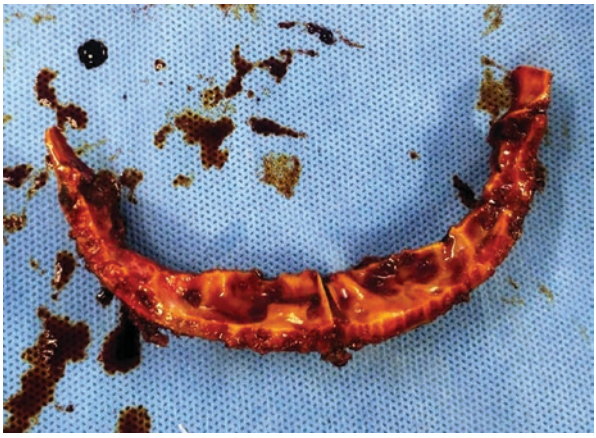

Fig. 17.20 The fronto-orbital bandeau is carried out using a tongue-in-groove fashioned osteotomy at the temporal squama. The width of the FOB needs to be around 2.5 cm. The pre-requisite curvature is obtained by the gentle drilling of the inner table and performing green-stick fractures

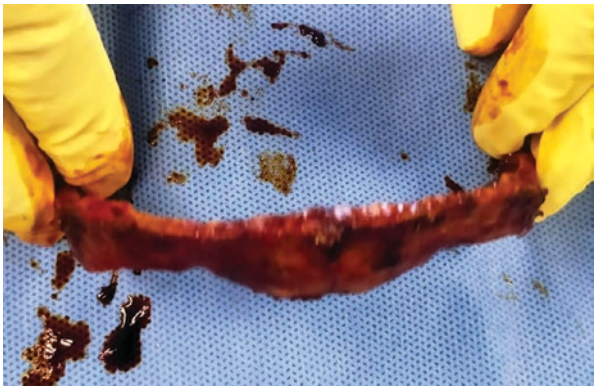

Fig. 17.21 The fronto-orbital bandeau is carried out using a tongue-in-groove fashioned osteotomy at the temporal squama. The width of the FOB needs to be around 2.5 cm. The pre-requisite curvature is obtained by the gentle drilling of the inner table and performing green-stick fractures

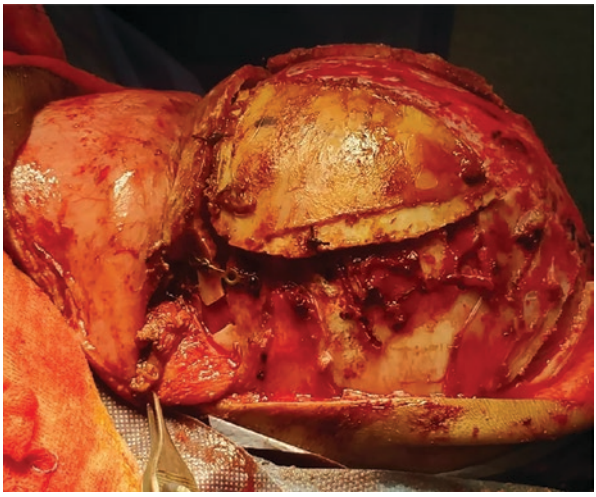

Fig. 17.22 The usual placement of the fronto-orbital bandeau is nearly 12 to 13 mm anterior to the cornea and on the affected side. A bandeau advancement of 8 to 15 mms is considered prudent

is outlined, employing a tongue-in-groove fashioned osteotomy at the temporal squama, and the required craniotomies are performed using a pneumatic oscillating saw along with a craniotome. The width of the FOB needs to be around 2.5 cm. This is followed by epidural dissection (Figs. 17.20 and 17.21). The prerequisite curvature is obtained by gentle drilling of the inner table and inducing greenstick fractures. The usual placement of the FOB is nearly 12–13 mm anterior to the cornea and on the affected side. A bandeau advancement of 8–15 mm is considered prudent (Fig. 17.22). Then the forehead is split at the midline and the resulting bone pieces are placed appropriately.

17.5.4 Fronto-facial Advancement

This procedure is mostly performed at the age of 5–6 years with the intention of achieving a stable result. The anterior advancement includes either a fronto-facial or an isolated frontal advancement in order to address ocular, respiratory and cosmetic issues.

A Le Fort IV osteotomy, i.e., a fronto-facial osteotomy in a single block, is performed followed by the placement of internal distractors. The harvested bifrontal bone is then reshaped as required. The midface is then mobilized using the Le Fort III osteotomy. If hypertelorism is noticed, it can be managed at this stage. A pair of internal distractors is placed anteriorly at the maxilla and fixed posteriorly at the temporal bone. The frontal bone flap is then secured to the orbital bandeau with silk sutures and remains floating over the midfacial complex. This complex is gradually advanced, keeping the lower face and the posterior portion of skull as a fixed structure. With the ongoing physiological growth pattern, a corrected antero-caudal position for the midfacial structures is obtained.

The fronto-facial distraction has significant functional and esthetic advantages, but these are associated with significant morbidity in 10–60% of cases, the most common being CSF leak.

17.5.5 Complementary Procedures

17.5.5.1 Barrel Staving

The intention of this procedure is to improve the chances of bone remodeling during the postoperative period. Multiple radial cuts are placed in the parietal and temporal bones without complete removal of those bones. This enlarges the cranial capacity, which is often required in cases of multisutural synostosis.

17.5.5.2 Suturectomy

This was first started and is most commonly performed for sagittal synostosis. A wavy bicoronal scalp incision is placed followed by dissection of the scalp flap and excision of a strip of suture nearly 2 cm wide by placing burr holes on either side of the superior sagittal sinus. Other sutures involved are dealt with, either alone or in combination, by removing the fused suture line.

17.5.5.3 Free Floating Bones

This is performed if the child has raised ICP with very thin calvarial bones that cannot hold calvarial screws and plates. The bone pieces are left in situ and multiple thin strips are placed both parallel and perpendicular to the suture line involved. It reduces the potential risk of bleeding and injury to the underlying structures.

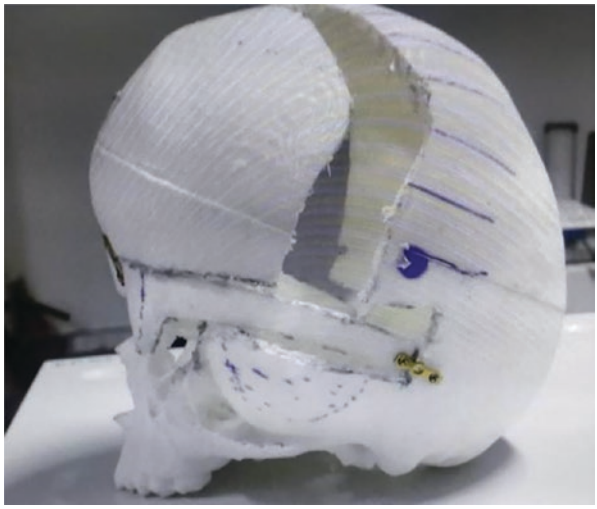

Fig. 17.23 Three-dimensional models enable the trainee surgeon to deal with simulated scenarios that exactly resemble the real-time surgical situations

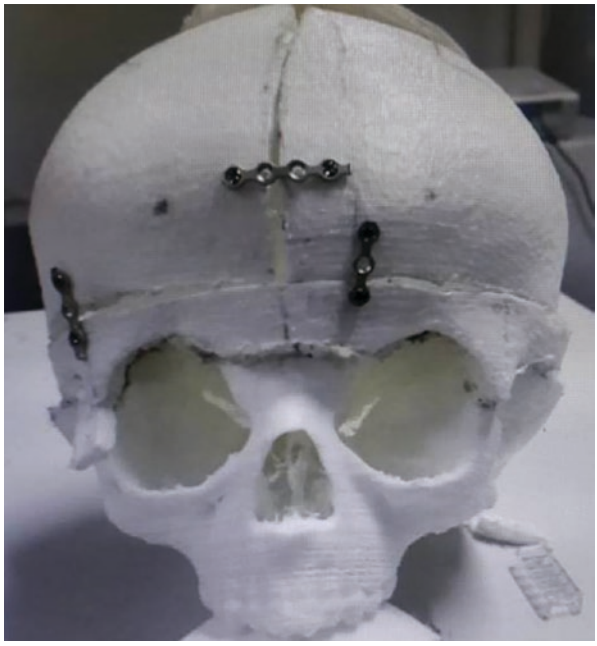

Fig. 17.24 Three-dimensional models also enable the young trainees to try out various techniques and get an idea of the final cosmetic outcome prior to the performance of the actual surgical procedure

Three-dimensional Printing, an Important Adjunct
In addition to very high quality CT and MRI scans, the virtual three-dimensional (3D) reconstruction and remodeling of skull is of paramount importance and has become a part of standard care. It includes a 3D software and model preparation using a 3D printer. This facilitates the preoperative planning and defines the methods for angulating the bone flaps, which are intended to be removed during surgery. This technique of additive manufacture of a 3D structure from a computer-based design is called Computer Aided Design (CAD). Simulators have been developed using thermoplastic material, which mimic tissues of different textures from the scalp to the skull. These models enable the trainee surgeon to deal with intraoperative complications such as bleeding in simulated scenarios that exactly resemble real-time surgical situations (Figs. 17.23 and 17.24).

17.5.6 Teamwork

Management of syndromic craniosynostosis is a prime example of teamwork, requiring neonatal counseling of the parents by both the pediatrician and the operating team. A thorough genetic analysis is provided by the Department of Human Genetics, the possibility of recurrence in a future pregnancy being factored in. A dedicated team of pediatric neuroanesthetists, who are devoted to caring in the postoperative intensive care unit along with the neurosurgeon, completes the joint SC management team. The plastic surgeon helps in flap rotation and helps to salvage the situation when there is a shortage of galea aponeurotica during the generous barrel stripping. The maxillofacial surgeon has an important role in the midfacial correction and the cosmetic aspects involved during the second and later stages of surgery.

17.5.7 Complications

1. Postoperative infection in the form of CSF leakage and bone flap osteomyelitis occurs in approximately 2% of cases. If there is a deep-seated infection, the bone flap needs to be removed and a full course of intravenous antibiotics must be administered based on culture-sensitivity of the infective organism [18].
2. Regrowth of sutures in the form of redevelopment of the bony ridge is common following craniosynostosis surgery (approximately 8% of cases). This can require a second surgery for drilling and smoothening of the ridge to bring that part of the bone into a plane similar to the rest of the surface of the skull [18, 19].
3. Injury to a vascular anomaly (for instance a sinus pericranii or a venous aneurysm), which is inconsistently associated with syndromic craniosynostosis, carries a high mortality risk. Thus, vascular variations need to be analyzed thoroughly before the surgical intervention is planned [19–21].

4. The hydrocephalus associated with syndromic craniosynostosis need not to be overcorrected because ICP is the principal driving force for the requirement of calvarial expansion in a growing skull [22].

17.5.8 Tips and Rules

1. A team effort, with adequate counseling of the parents right from the outpatient department, forms the cornerstone of management to achieve a realistic and favorable outcome.
2. The procedures must be prioritized and tailored to the individual case depending upon the clinical presentation, as these children often have multi-system anomalies.
3. A dedicated pediatric neuroanesthesia team must evaluate intraoperative concerns. If the upper airway is difficult, a submental intubation should be considered to provide a wide and safe operative field.
4. Thorough water infiltration is often required to prepare an adequate plane between the galea aponeurotica and the pericranial fascia. Xylocaine infiltration along the incision line is also required.
5. The operative procedure must be staged in close consultation with the anesthesia team in order to minimize blood loss and other intraoperative insults such as third space loss, hypothermia, electrolyte imbalance and seizure (due to severe hyponatremia).

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Chapter 18
Surgery for Craniosynostosis

Robert Shumkovski, Ivica Kocevski, and Mikjun Mikjunovikj

18.1 Introduction

Dawn of life. New life. Starts with fertilization, then intrauterine development. New life emerges with an extraordinary quantitative transformation of material, brain matter into soul. The supreme pinnacle of evolution, the human brain, the result of 4 billion years of evolution, is created within a supportive and protective structure, a hermetically sealed helmet ensuring its mechanical, thermal, and biological protection: the skull. Perfectly configured, the skull provides the optimum architecture for the human brain and all of its supporting structures.

The development of the skull still seems miraculous. It emerges as bone elements, initially separate (providing for easy transfer through the birth canal), given by birth, genetically defined. During early childhood these skull and facial bones develop and fuse at sutures with various time delays, providing time and space for brain development. Didactically, these junctura cartilaginea and junctura ossea, systematized as sutures of the face, skull base and calvaria, including fontanelles, represent the unique symbiosis of skull creation.

Anatomical understanding of the architecture of the skull and its sutures, presented as "look through X-ray-type knowledge", is essential in several ways. It provides landmarks that define positions for orientation during surgery and craniotomy, provide correlative orientation in respect of intracranial pathology, and enable traumatic skull fractures to be identified.

R. Shumkovski (✉) · I. Kocevski (✉)
Univ. Clinic for Neurosurgery, School of Medicine, Univ. St. Cyril & Methodius, Skopje, Republic of North Macedonia

M. Mikjunovikj
Specialized Hospital for Orthopedic Surgery and Traumatology, St. Erazmo, Ohrid, Republic of North Macedonia

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Anatomically, by PNA (Parisian nomenclature), the normal cranial sutures (paired and single) are: frontonasal, frontomaxillary, frontolacrimal, frontoethmoidal, frontozygomatic, temporozygomatic, metopic, coronal, sphenofrontal, sphenoparietal, sphenosquamosal, temporoparietal-squamosal, parietomastoid, occipitomastoid, sagittal, lambdoid, sutures of the skull base, and facial sutures. During genetically controlled development, the sutures of the face, skull base and cranium can present numerous variations. The evolutionarily determined, genetically coded, development of the skull serves primarily to provide compatible, normal evolution-development of the brain and its structures.

Developmental disorders of the skull bones and structures can provoke delayed or early suture closure. Early suture union constitutes cranial pathology, systematized as craniosynosthosis. Numerous cranial sutures, symmetric and midline single can be subjects of early union of the bones, consecutively creating anatomical, developmental and physiological disturbances, often with dramatic consequences.

The causes of craniosynostoses are generally unknown; there are many possibilities and hypotheses: the teratogenic effects of valproic acid, aminopterin, hydantoin, retinoic acid, oxymetazoline, diseases such as hyperthyroidism, rickettsiosis, thalassemia, sickle cell anemia, thyroid diseases in pregnant woman, shunt induced after treatment for hydrocephalus, amniotic bands, mucopolysaccharidoses, and genetic mutations especially of FGFR1–3, NELL1, MSX2, TWIST and GLI3 [1–4].

The principle of formation of craniosynostoses has been modified in response to the thoughts and observations of authorities. Virchow (1851) suspected that craniosynostosis is a primary malformation, while the deformity of the cranial base is secondary; Moss (1959) concluded that malformation of the cranial base is essential for the appearance of premature fusion of the cranial sutures on the calvaria; and Park and Powers (1920) proposed the much more plausible conjecture that the primary defect is located in the mesenchymal blast tissue that leads to anomalies in the cranial vault and the cranial base [3, 4].

The general classification of craniosynostoses includes nonsyndromic craniosynostosis (primary, simple—involving one or two premature suture closures) and syndromic craniosynostosis (craniofacial misdevelopments associated with other anatomical and organ dysfunctions). Most often, systematized nonsyndromic craniosynostosis presents according the anatomical location and the suture involved, and can be sagittal synostosis, metopic synostosis, unilateral parietal synostosis, bilateral parietal synostosis, lambdoid synostosis or oxycephaly (closure of all sutures of the calvaria).

The craniofacial syndromes are a heterogeneous group of rare conditions in which premature suture closure (craniosynostosis) occurs alongside other manifestations of disordered craniofacial development [5], and additional skeletal abnormalities that include, in particular, those of the hands and feet [6, 7].

18.2 Indications for Surgery

The two main indications for the surgical treatment of craniosynostosis are: to correct the skull shape for esthetic and psychosocial considerations, and to make certain that there is adequate space for normal brain growth. From an esthetic perspective, the deformities associated with craniosynostosis are generally progressive during the first year of life, and their social and psychological impact on affected children is sufficiently concerning to justify treatment [8]. The effects of craniosynostosis on brain development can include focal brain hypoperfusion, mechanical deformation of neuroanatomical structures and global intracranial hypertension. The last-named can be explained by venous hypertension, respiratory obstruction, cranio-cerebral disproportion, hydrocephalus, or a mixture of all four. Hydrocephalus requires a CSF-diversion procedure, either an endoscopic third ventriculostomy or a ventriculoperitoneal shunt. Venous hypertension is effectively treated by a vault-expanding operation that can be posterior (parieto-occipital), bilateral (biparietal) or anterior (a fronto-orbital advance) [9]. Although the risk varies depending on the specific diagnosis, a small but significant percentage (4–14%) of patients with single-suture synostosis develop intracranial hypertension, and the incidence is as high as 47–67% in patients with multiple involved sutures [10, 11]. There are data suggesting that early surgical treatment is beneficial; however, recent genetic studies have suggested that some genes implicated in craniosynostosis are also essential for brain growth [12, 13], and it remains unclear if skull morphology is simply associated with or is an influential factor in abnormal brain development. A multicenter study demonstrated mean neurodevelopmental scores consistently lower than controls in 3-year-old children who had been treated for single-suture craniosynostosis [14], suggesting that these children are at risk for developing cognitive and behavioral disabilities in their school years regardless of surgical correction. Several studies have shown that craniosynostosis can lead to global intracranial hypertension [8–12], focal brain hypoperfusion [15–17], and mechanical deformation of neuroanatomical structures [18–22]. Studies attempting to demonstrate a relationship between intellectual and behavioral disabilities and craniosynostosis have given various and sometimes contradictory results [21–42].

In 1989, Renier et al. at the Hôpital des Enfants Malades in Paris [11], demonstrated elevated ICP (>15 mmHg) in 6% of infants with metopic craniosynostosis (8% of patients with sagittal synostosis, 12% of those with unilateral coronal synostosis.) Infants with multiple fused synostosis or those presenting after 1 year of age had higher rates of elevated ICP.

18.3 General Surgical Considerations

After precise clinical examination of the child, radiographic explorations, consulting pediatric expertise, and determination of nonsyndromic or syndromic craniosynosis, surgical correction must be perfectly timed. Operative reconstruction

should be performed between the 3rd and 7th months of life, allowing the child time to acquire his own immunological responses and to establish his eating habits and diurnal pattern. This also precludes permanent deformity of the brain and skull. Operations performed before three months of age entail a higher risk of recurrence of the deformity [43]. This recommendation applies to children with single or double suture nonsyndromic craniosynostosis, because the more complex syndromic craniosynostoses usually need more than one surgical intervention and all must be finished before 4 years of age when the sense of physical image generally develops [44].

The pattern of positioning during surgery can depend on the surgical plan for reconstruction: the child supine on a padded horseshoe headrest; prone on a "padded" horseshoe headrest for better access to posterior part of calvaria; or in modified prone position with chin support in a padded beanbag to allow simultaneous access to the front and back of the skull.

The skin should be incised in or near the area with either curvilinear or "zig-zag" incisions using a scalpel or Colorado Microdissection Needle diathermy to cover and minimize skin cicatrix [45].

All operative interventions (open or endoscopic) follow same basic principle: craniectomy of the prematurely fused suture, or suturectomy, which must be enough wide to prevent early closure after the intervention. This destructive procedure usually needs to be completed with proper craniotomies to enlarge the cranial space and reshape the cranial vault to be as nearly normal as possible for further symmetrical skull development. There are many types of craniotomy: barrel-stave, radial, or curvilinear osteotomies of the free bone flaps; the one preferred depends on the experience of pediatric surgeon in achieving the goal of reshaping and enlarging the cranial vault.

During craniotomies/craniectomies in infants, blood loss is to be expected, so perioperative blood transfusions need to be planned, including postoperative measurments of red blood cell count, hemoglobin and hematocrit. The amount of bleeding can correlate significantly with the duration of surgery, but not with the patient's age. The mean blood loss during surgery can range from 80 to 400 mL [46].

Craniotomies/craniectomies in infants entail a risk of injuring the underlying dura, and all perioperative lesions of the dura must be recognized and meticulously repaired with watertight suturing to prevent CSF leakage, postoperative infection or creation of postoperative leptomeningeal cysts (growing skull fracture).

There are insufficient data about the efficiency of subgaleal drainage in open skull remodeling, and this must be considered before planning the galea and skin closure. There is wide variability among surgeons regarding drain use, and this seems to depend on belief and tradition. The few studies so far conducted have demonstrated no definite benefit of drain use [20]. However,, subgaleal drain placement has a clinical benefit for earlier resolution of postoperative facial edema and a significantly shortened length of hospital stay [47].

The role of the pediatric neurosurgeon, collaborating with pediatricians, radiologists, and anesthesiologists, is essential for prevention, early recognition, analysis, information, diagnosis, planning and tailoring intervention, and resolving the problem.

The procedure comprises several phases:

1. Inspection, assessment, estimation, evaluation
2. Precise diagnosis, defining the problem
3. Analysis, team decision-making
4. Planning, tailoring the procedure individually on the basis of the "double individual concept" (morpho-anatomical specifics of the patient considered together with the personal and professional profile of the surgeon), following "lege artis" standards
5. Resolution: mostly surgery, endoscopic or open surgery, helmet therapy
6. Follow-up

The essential surgical therapy for craniosynosthois basically comprises:

1. Initial destructive phase – craniotomy and/or craniectomy,
2. Division, desuturing (punch, rongeur, drill)
3. Fracture (greenstick fracture) with pseudoarthrosis where needed
4. Reconstruction – reposition, rotation, remodeling, remote fixation

18.4 Surgery for Nonsyndromic Craniosynotosis

18.4.1 Metopic Synostosis (Trigonocephaly as Phenotypic Presentation)

Premature fusion of the metopic suture is referred to as trigonocephaly. The term trigonocephaly was coined by Welcker in 1862 [48] to describe the triangular shape of the forehead when viewed from above. The main event in metopic suture craniosynostosis is premature fusion of the metopic suture, followed by growth arrest at that site. This type of craniosynostosis presents morphologically as metopic suture ridging, bilateral lateral retrusion of the frontal bones, anterior displacement of the coronal sutures, lateral flaring of the posterior parietal regions and flattening of the supraorbital ridges, often accompanied by orbital hypotelorbitism, ethmoidal hypoplasia and severe bitemporal narrowing. Compensatory posterior growth at the coronal and lambdoid sutures and lateral growth at the sagittal suture together lead to widening of the parietal regions, accentuating the overall triangular or pear shape of the skull.

The metopic suture usually closes by the end of the first year of age, but sometimes not until the end of the second year [49], although physiological closure can occur as early as three months of age without leading to trigonocephaly.

Trigonocephaly varies in severity. Milder forms can be managed conservatively and usually do not require surgical treatment. The severe forms, containing the stigmata previously mentioned, do require surgery. As metopic synostosis is a problem of the suture (the metopic suture in this case), a closed fontanelle is not indicative of metopic craniosynostosis.

Metopic synostosis has been associated with neurodevelopmental delay, and it has also been suggested that trigonocephaly has the highest rate of associated cognitive impairment among the single suture synostoses. It has been estimated that as many as 10% of the children with isolated, nonsyndromic trigonocephaly have neurodevelopmental delay [50–54]. The cognitive impairment could result from the increased intracranial pressure on the frontal lobes or from associated underlying midline brain anomalies (such as holoprosencephaly or corpus callosum agenesis).

Usually, trigonocephaly is an isolated anomaly, but it can also be encountered as part of syndromes involving prosencephalic or holoprosencephalic (rhinencephalic) structures, such as Opitz syndrome [55–58], Say–Meyer syndrome or Frydman syndrome [59]

On the basis of clinical and radiological findings, Di Rocco et al. proposed two subgroups [60]. Group I presents with bilateral frontal bone hypoplasia associated with extreme retrusion of the supraorbital margins, where hypotelorism is associated with an abnormally deep position of the lamina cribriformis, giving the ethmoidal region a hollow appearance. In this group of patients the nasion-pterional angle is severely restricted and the nasion-clinoidal distance significantly increased (Figs. 18.1 and 18.2a, b).

Group II also shows bilateral frontal hypoplasia with hypotelorism, supraorbital retrusion, and reduced nasopterional angle. However, the nasion–clinoidal distance is almost normal, and pterional evidence is scarcely noticeable [60]. Moreover, patients in group II showed less compensatory temporal expansion. The authors propose that in some patients a compensatory elongation of the nasion–clinoidal distance and incomplete synostosis of the frontoethmoidal sutures allow partial

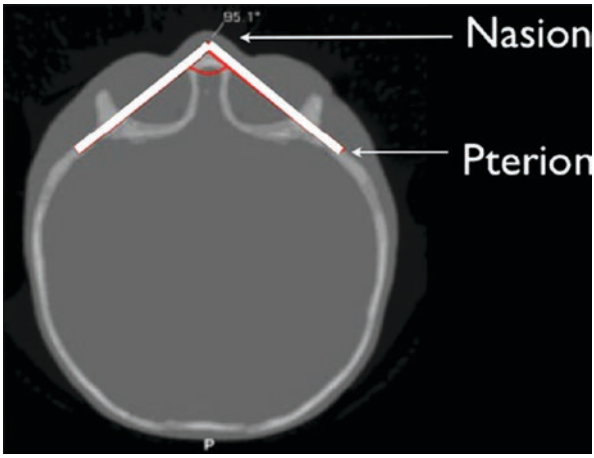


Fig. 18.1 Frontal angle as described by Oi in 1986 (van der Meulen, J. Metopic synostosis. *Childs Nerv Syst* 28, 1359–1367 (2012). https://doi.org/10.1007/s00381-012-1803-z)

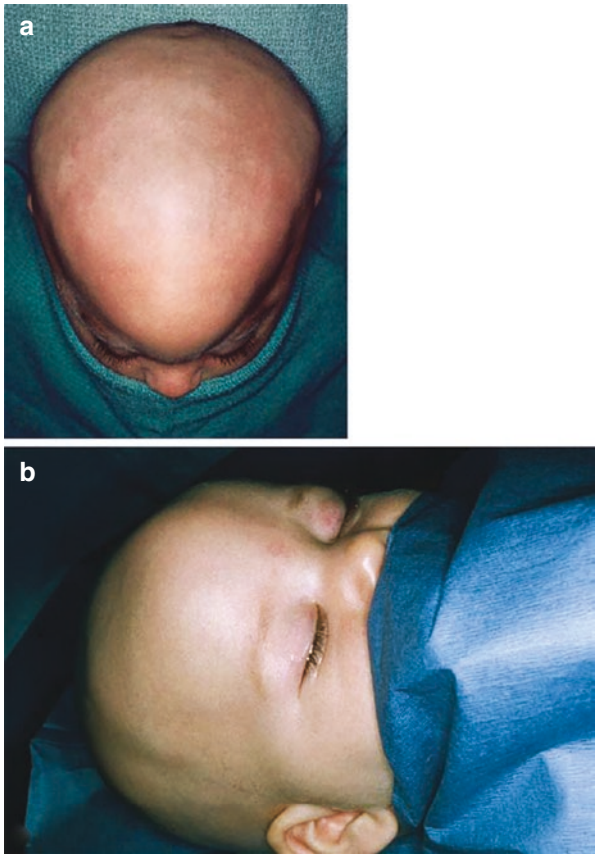


Fig. 18.2 Typical craniofacial appearance of a child with metopic craniosynostosis. Photos taken just prior to surgery. (Aryan, H.E., Jandial, R., Ozgur, B.M. et al. Surgical correction of metopic synostosis. *Childs Nerv Syst* 21, 392–398 (2005). https://doi.org/10.1007/s00381-004-1108-y)

lateral expansion of the anterior cranial fossa, which could diminish the need for posterior calvarial expansion. On the other hand, children with more severe involvement of the nasoethmoidal sutures, resulting in diminished lateral expansion of the anterior fossa, need compensatory changes in the temporal and parietal regions. Patients in group II showed good correction of the associated hypotelorism, whereas patients in group I did not reach normal interorbital values after undergoing the same surgical procedure, which did not include specific treatment for hypotelorism. Other authors have addressed the importance of this and the degree of involvement of pathological changes in the anterior chondrocranial structures. Milder forms of trigonocephaly affect only the upper metopic suture, whereas more severe forms include involvement of presphenoid, mesoethmoid, and ectoethmoid structures.

In addition, Tubbs and coworkers found a 30% incidence of type I Chiari malformations when they evaluated patients with simple metopic ridges and inferred that these children were at greater risk secondary to the diminished anterior cranial volume [61]. At the other end of the spectrum, severe cases of metopic synostosis have been associated with underlying frontal brain dysmorphology and other congenital anomalies [62].

18.4.1.1 Diagnosis, and Indications for and Timing of Operative Treatment

The diagnosis of metopic craniosynostosis is based on medical history and physical examination. Additionally, a head CT scan can be used to assess the extent of the abnormalities. Further, these infants should be evaluated by an ophtalmologist for fundoscopic examination and a pediatrician for potential neurodevelopmental delay. However, definitive diagnosis requires a 3D CT scan, which is expected to offer adequate bone definition and also the possibility of brain parenchyma evaluation. If additional abnormalities are suspected, an MRI scan should be performed (Figs. 18.3 and 18.4).

The indications for surgical correction of metopic craniosynostosis can be divided into two main categories: primary and secondary. The primary indications

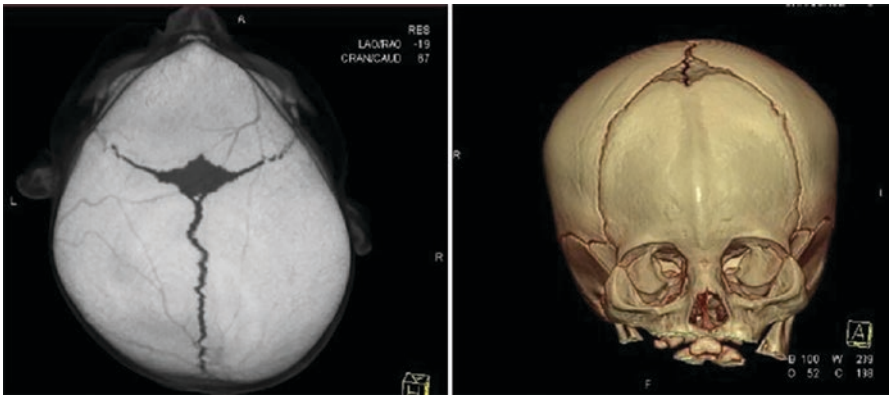


Fig. 18.3 3D reconstructed CT scan. Note the metopic suture synostosis, seen as a mid-forehead ridge, hypotelorism, flattening of the frontal bones, anterior displacement of the coronal sutures, compensatory bulging of the parieto-occipital region and temporal narrowing (Shumkovski R, Kocevski I, Micunovic M. Trigonocephaly: Case Report, Review of Literature and a Technical Note. Open Access Maced J Med Sci. 2019 Jan 15; 7(1):117–120. https://doi.org/10.3889/oamjms.2019.031)

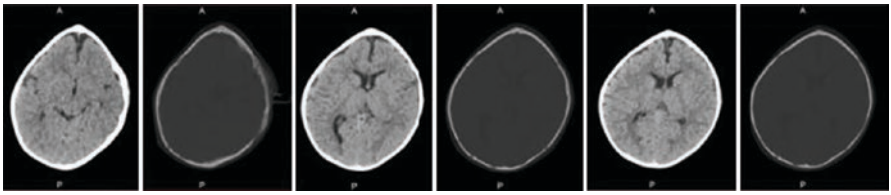


Fig. 18.4 *Axial cross section head CT scan: note the triangular forehead, prominent midline sagittal ridge and shortening of the anterior cranial fossa, with compensatory bulging of the parieto-occipital region and temporal narrowing* (Shumkovski R, Kocevski I, Micunovic M. Trigonocephaly: Case Report, Review of Literature and a Technical Note. Open Access Maced J Med Sci. 2019 Jan 15; 7(1):117–120. https://doi.org/10.3889/oamjms.2019.031)

are related to potential neurocognitive impairment. As several studies have shown, craniosynostosis can lead to global intracranial hypertension [63–67], focal brain hypoperfusion [15–17], and mechanical deformation of neuroanatomical structures [18–22]. In a 1989 report from the Hôpital des Enfants Malades in Paris [11], elevated ICP (>15 mmHg) was demonstrated in 6% in infants with metopic craniosynostosis (8% of patients with sagittal synostosis, 12% of those with unilateral coronal synostosis). Infants with multiple fused synostosis or those presenting after 1 year of age had higher rates of elevated ICP. Increased ICP is considered as absolute indication for operative treatment.

The secondary indications are related to the esthetic and psychosocial aspects of metopic synostosis, often referred to as deformity correction surgery. Since the deformities associated with craniosynostosis are generally progressive during the first year of life, their potential social and psychological impact on the affected child is in itself considered sufficient to justify operative treatment [68].

The age of the patient undergoing corrective surgery is another highly controversial subject. Most surgeons would agree that surgery is best performed before the child reaches the age of 1 year, while some would argue as early as two months of age. The author's preferred age for surgery is six months (or 5–6 months, depending on the weight and general health of the child) [69, 70].

18.4.1.2 Preoperative Planing, Surgical Objectives and Special Equipment

Besides a head CT scan, the preoperative preparation for surgery should include routine blood tests, including complete blood count, electrolyte panel, and partial thromboplastin time and prothrombin time. A blood type should be obtained since there is a potential for significant blood loss. İf the patients' parents are prepared to donate, they should be given the option to do so. The child along with its mother is admitted to the ward on the day of surgery or the day before, and should be kept fasting for at least 4–6 h before the planned surgery.

The objectives of the surgical correction should be to achieve the best possible and durable correction of deformity with a single operation at the lowest possible risk to the patient.

Equipment needed during these operations includes a Mayfield headring or horseshoe head holder, although Mayfield headring usage is preferred to the horseshoe head holder because it provides much better head stability intraoperatively and a lower chance of postoperative infection. Basic pediatric neurosurgical operative instruments are needed, and a high-speed drill or handheld Hudson brace with pediatric burrs. Different kinds of sutures should be available, but monofilament polypropylene sutures are recommended. Resorbable plates and screws are mostly used to stabilize bony fragments. Use of local anesthetic is encouraged (bupivacaine or lidocaine with epinephrine) for local analgesia, reducing the need for additional dosing with intravenous analgesics and providing better control over intraoperative bleeding.

18.4.1.3 Anesthetic Considerations

At least two large bore intravenous lines (≥20 gauge) are required owing to potential blood loss during surgery. A urinary catheter is useful for recording urinary output. A thermistor is needed to record body temperature, and intraoperative body warmers are advised. Arterial and central venous lines will enable total body intravascular volume to be monitored and ensure postoperative fluid management.

Endotracheal intubation should be performed in standard manner, securing the tube according to local practice. Some authors advise use of circummandibular or circumdental wire to avoid the need for taping and to ensure full accesss during surgery. Temporary tarsorrhaphy sutures are rarely used in our practice, but some authors advise them for corneal protection. İn our practice, the use of oily eye drops (Vit A and Vit D) with hydrophobic tape over the child's eyes have been sufficient for corneal protection.

Preoperative antibiotics are given before the skin incision (cefazoline 10–20 mg/kg as loading dose, 8mg/kg intravenosly every 8 h for 48 h) as per local practice.

The author's preference is total removal of hair by hair clippers. Total hair clipping is expected to facilitate skin closure and postoperative wound care.

18.4.1.4 Operative Procedure

Positioning

For anterior skull exposure, as needed for metopic suture reconstruction, the patient is placed in a supine position with the head in slight extension. The head is secured in a Mayfield headring, according to the author's preference. Additionally, cotton pads are used on different body parts to ensure a comfortable position during the lengthy operation.

Sterile Scrub, Draping and Local Anesthetic

The skin is prepared with povidone-iodine or other skin antiseptic as per local practice. Betadine Ophthalmic (5% povidone-iodine) can be used when prepping near or around the eyes. Alternatively, 70% ethanol followed by a prescrub with scrub brush and then a two-step Betadine preparation, first with Betadind soap, then by a Betadine scrub. Single use drapes are preferred and advised. For local analgesia and to minimize intraoperative bleeding, the following combinations can be used: 0.5% lidocaine and 1:400.000 parts epinephrine or 0.25% bupivacaine and 1:200.000 epinephrine.

Skin Incision

A standard bicoronal incision is used, extending from just above (or behind) one ear across to the opposite side. Alternatively, a zigzag variation of the bicoronal incision can be used, referred to as the stealth incision or sinusoid-type incision, to minimize the chance of incisional scalp alopecia (Fig. 18.5). Another variation of the bicoronal scalp incision is posterior inclination in the parieto-occipital scalp providing excellent camouflage of the scar line, especially in balding adults. It is necessary to preserve the ascending branch of the superficial temporal arteries for adequate blood supply [71]. Bleeding is controlled by bipolar coagulation, but Raney clips can also be used. Further dissection of the skin flap proceeds in a subperiosteal or supraperiosteal fashion. The advantage of the supraperiosteal dissection is reduced bleeding; the periosteum is incised approximately 1–2 cm above the supraorbital rim and the dissection is further advanced subperiosteally, ensuring bilateral exposure of the supraorbital rim and avoiding injury to the branches of the facial nerve. The temporalis muscles are dissected off their attachments to the temporal bone and should be split and advanced after the lateral orbital rims are advanced to avoid postoperative temporal hollowing (Figs. 18.6 and 18.7).

Temporal hollowing is thought to be caused primarily by bone growth inhibition along the anterior bandeau [72, 73] or temporal muscle thinning, caused by anterior retropositioning concomitant with the fronto-orbital advancement [73]. One way to prevent temporal hollowing is elevation of the temporalis muscles off their insertions and leaving them attached to the undersurface of the scalp flap, at the same time allowing access to the infratemporal hollow.

The scalp flap is elevated down to the level of the supraorbital rim. The supraorbital neurovascular bundle should be preserved and should be left attached to the scalp flap. The dissection should then be extended down to the level of the lateral orbital rim, detaching the lateral canthi to the junction with the inferiororbital rim,

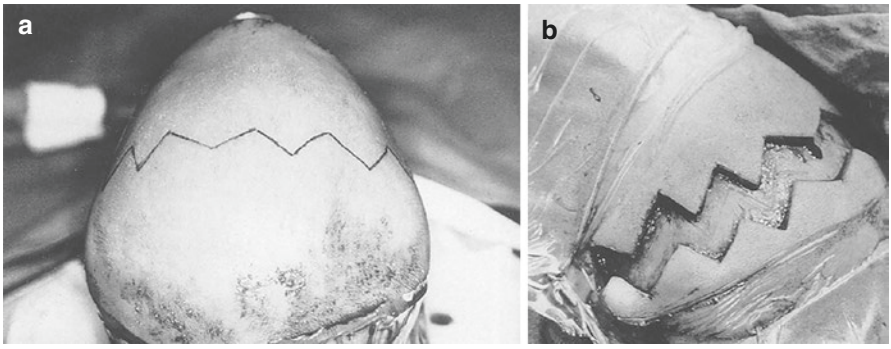


Fig. 18.5 The bicoronal skin flap is designed in a zig-zag fashion (**a**) and using a monopolar friquency needle (**b**) to minimize blood loss and the need for skin clamps (Di Rocco, C., Velardi, F., Ferrario, A. et al. Metopic synostosis: in favor of a "simplified" surgical treatment. *Child's Nerv Syst* 12, 654–663 (1996). https://doi.org/10.1007/BF00366147)

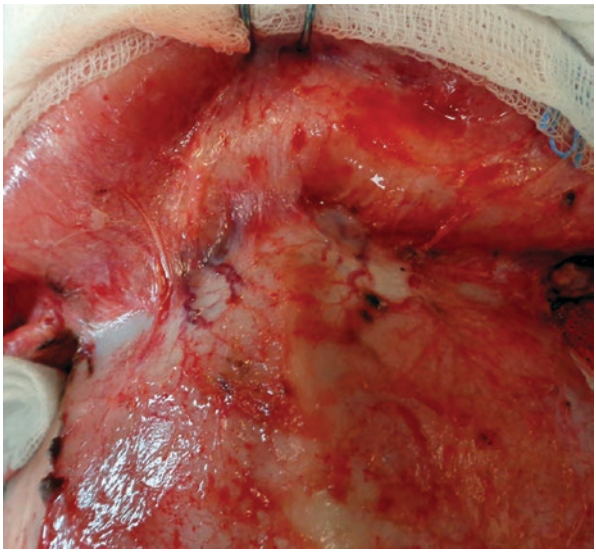


Fig. 18.6 Intraoperative image showing the typical emissary veins in the area of the periosteum in trigonocephaly (di Rocco, F., Gleizal, A., Lohkamp, L. et al. Control of metopic emissary veins in trigonocephaly surgery. Technical note. *Childs Nerv Syst* 34, 2481–2484 (2018). https://doi.org/10.1007/s00381-018-3928-1)

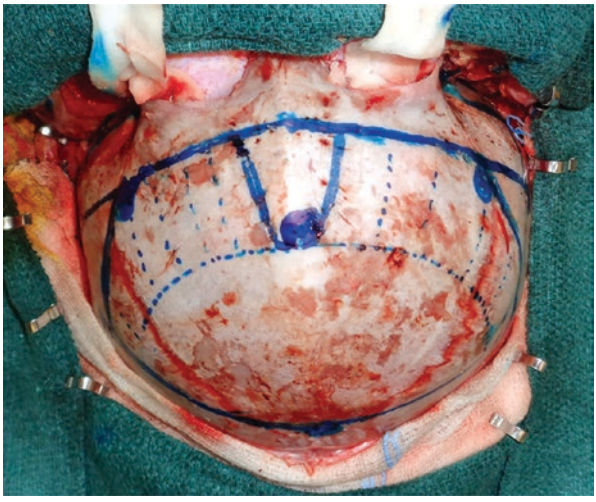


Fig. 18.7 Intraoperative image showing the outline of the craniotomies (di Rocco, F., Gleizal, A., Lohkamp, L. et al. Control of metopic emissary veins in trigonocephaly surgery. Technical note. *Childs Nerv Syst* 34, 2481–2484 (2018). https://doi.org/10.1007/s00381-018-3928-1)

and medially up to, but not detaching, the insertion of the medial canthal tendons. The nasolacrimal apparati are also carefully preserved. The nasion is exposed during this part of the dissection as well. Inferolaterally, the anterior aspect of the maxilla, the malar eminence, and the anterior aspect of the zygomatic arch are also exposed. The temporal and sphenoid bones are exposed from the lateral orbital rim close to the junction where the zygomatic arch meets the posterior temporal bone. This area will allow for the formation of a tenon extension on the temporal bone, once the orbital osteotomies have been performed.

Using a narrow periosteal elevator or dissector, the periorbita is dissected off the supraorbital rim and about 1 cm off the orbital roof bilaterally. The skin flap is than secured in place using scalp hooks (Fish hooks with Songer cables**,** Songer hooks).

In summary, the limits of the exposure should include the coronal suture, anterior fontanel, the nasion, the supraorbital rims, and bilaterally, the fronto-zygomatic suture (Figs. 18.7 and 18.8).

Initial Deconstructive Phase

The standard surgical approach for trigonocephaly consists of bifrontal craniotomy, fronto-orbital advancement with recontouring, and flap remodeling. Often, barrel-stave-like osteotomies in the parietal and squamous portions of the temporal bone are performed as an additonal step.

Creation of the bifrontal flap should include the entire length of the metopic suture, from nasion to vertex (metopic and both coronal sutures), and the bregmatic fontanelle (the anterior part of the anterior fontalelle). Burr holes should be placed behind the coronal suture, superior to the pterion; and below, about 1cm above the supraorbital rim in the midline. Care should be taken not to injure the underlying dura, and efforts should be made to detach the dura carefully from the inner table whenever possible. The metopic notch presents the invagination of the dura into the metopic suture, and its anterior limit is the nasion [74]. About 1cm of the frontal bone is left attached to the supraorbital bar. After removal of the bifrontal bone flap,

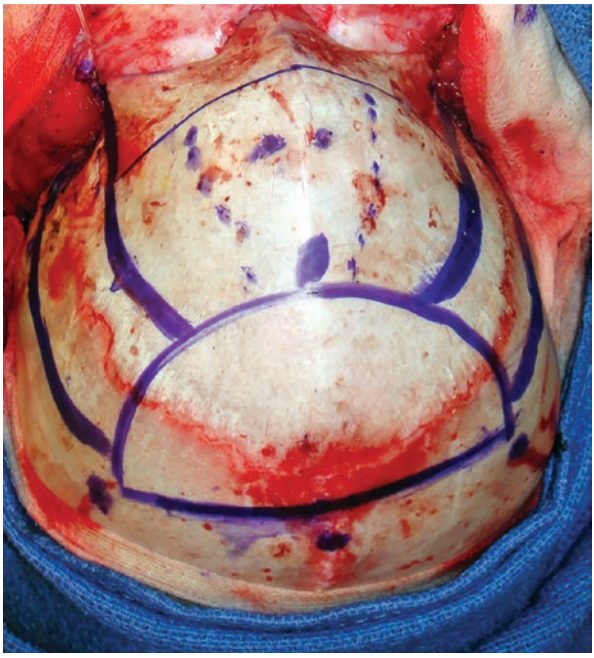


Fig. 18.8 Intraoperative image showing the outline of the craniotomies with a different design (di rocco, F., Gleizal, A., Lohkamp, L. et al. Control of metopic emissary veins in trigonocephaly surgery. Technical note. *Childs Nerv Syst* 34, 2481–2484 (2018). https://doi.org/10.1007/s00381-018-3928-1)

the underlying dura and anterior cranial fossa are exposed. Additionally, the anterior cranial fossa is exposed extradurally along with the anterior two thirds of the orbital roof. An important step is the removal of the lateral portions of the sphenoid wings to ensure adequate brain expansion and to provide sufficient access to the middle cranial fossa during the orbital osteotomies.

The next steps are the supraorbital osteotomies, extending across the orbital roof, lateral orbital wall, lateral aspect of the orbital floor into the inferior orbital fissure, and the superior aspect of the medial orbital wall. During this phase, it is important to remain anterior to each olfactory bulb and the foramen cecum. The cuts begin at the junction of the inferior orbital rim with the zygoma, approximately 1cm behind the rims, extending superiorly until the sphenoid bone is reached. Depending on the desired advancement, the cut is extended laterally into the sphenoid and temporal bones in the form of tenon extension, usually about 15 mm in width, with variable length. This way, tenon extensions are created, extending laterally into the sphenoid and temporal bones. The next cut connects the supraorbital cut edge with the anterior cut edge of the bifrontal craniotomy. The following cuts are done on the orbital surface. Usually the cut is taken from the lateral junction of the greater sphenoid wing and the lateral orbital rim, across the orbital roof, up to the superior orbital fissure across the midline, staying anterior to the clinoid process, cribriform plate, and foramen cecum, meeting the opposite cut in the middle (Figs. 18.9 and 18.10).

The last cut is made across the nasion, just above the naso-frontal suture. A single piece supraorbital unit is created and reshaped accordingly. The underside of the fused suture usually has a thick bone crest, which could need reshaping. Using bone benders, bends can be made in the tenon extensions in the temporal bone. This lateral advancement is expected to correct the temporal narrowing,

Fig. 18.9 Front view and anterior skull base view showing the outline of osteotomies. (Dhellemmes, P., Pellerin, P., Lejeune, J.P. et al. Surgical treatment of trigonocephaly. *Child's Nerv Syst* 2, 228–232 (1986). https://doi.org/10.1007/BF00272491)

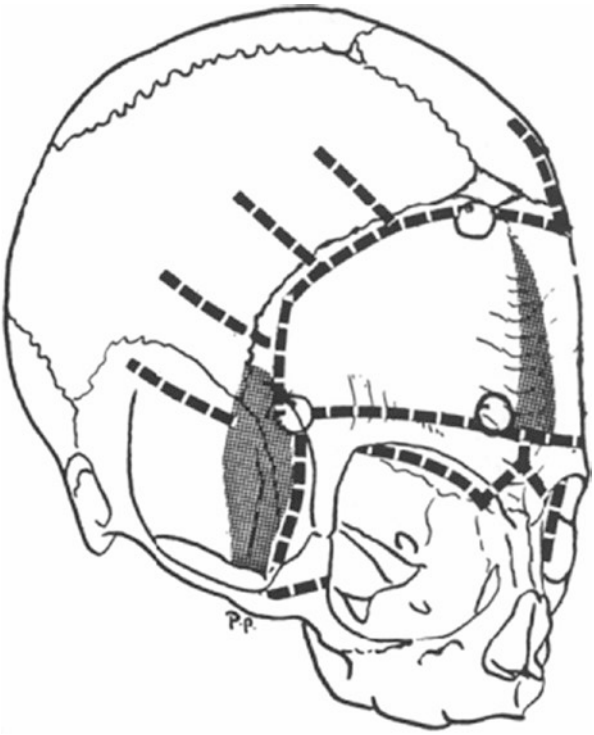


Fig. 18.10 Lateral view showing osteotomies and ostectomies (Dhellemmes, P., Pellerin, P., Lejeune, J.P. et al. Surgical treatment of trigonocephaly. *Child's Nerv Syst* 2, 228–232 (1986). https://doi.org/10.1007/BF00272491)

Fig. 18.11 The craniotomy is outlined; the abnormal forehead is elevated. The emissary veins are spared. Then the triangular bone above the initial segment of the superior sagittal sinus is removed to continue the surgical operation in a standard way (removal of the orbital rims and lateral pieces of bone) (di Rocco, F., Gleizal, A., Lohkamp, L. et al. Control of metopic emissary veins in trigonocephaly surgery. Technical note. *Childs Nerv Syst* 34, 2481–2484 (2018). https://doi.org/10.1007/s00381-018-3928-1)

often seen in trigonocephaly. İn general, the reshaping of the supraorbital bar is expected to assume a more convex configuration, especially along the supralateral and lateral orbital rims (Figs. 18.11, 18.12 and 18.13). İn mild forms of hypotelorism, no attempt to correct should normally be made since it is not considerred a significant deformity. İn such cases, the supraorbital bar can be left attached to the midline with no further reconstruction. İnstead, if the lateral orbital rims do not require advancement, a transposition of the anterior portion of

Fig. 18.12 The triangle of bone is preserved during the osteotomy including the entire forehead After removal of the forehead and control of the emissary veins, the metopic bony triangle and the fronto-orbital bandeau and temporal tongues are successively removed. The forehead will be tilted at 180°, reshaped, and replaced together with the fronto-orbital bone (di Rocco, F., Gleizal, A., Lohkamp, L. et al. Control of metopic emissary veins in trigonocephaly surgery. Technical note. *Childs Nerv Syst* 34, 2481–2484 (2018). https://doi.org/10.1007/s00381-018-3928-1)

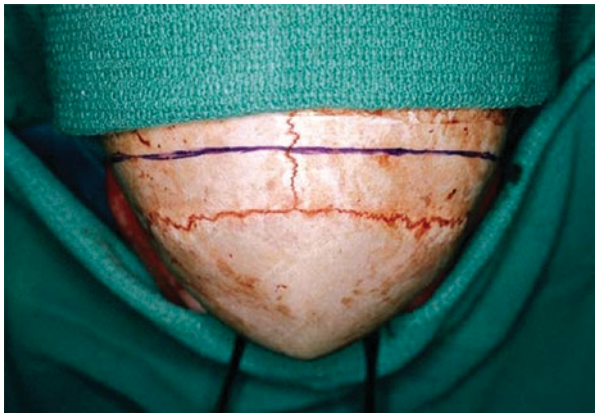


Fig. 18.13 Intraoperative photograph showing metopic abnormality and marking for craniotomy. (Aryan, H.E., Jandial, R., Ozgur, B.M. et al. Surgical correction of metopic synostosis. *Childs Nerv Syst* 21, 392–398 (2005). https://doi.org/10.1007/s00381-004-1108-y)

the temporalis muscle can be sufficient to correct the deformity. However, in the more severe forms of hypotelorism, there are different methods for reconstruction, such as interposing a bone graft harvested from the frontal bone after a medial osteotomy of the supraorbital bar. İn the more severe cases of facial deformity an additional horizontal cut can be made in the nasal bones, about 15–20 mm below the fronto-nasal suture. A bone graft can be interposed into the superior part of the osteotomy for additional correction of the facial deformity, though other authors [75, 76] believe that internasal grafting will not increase interorbital width (Figs. 18.14, 18.15, and 18.16).

At the end of the deconstructive phase, a bifrontal craniotomy flap and a supraorbital bone bar are created. Bending, drilling or burring of bone and other osseous elements is also performed during this phase. Before the begining of the reconstruction, barrel-stave-like (radial) osteotomies and outfractures in the parietal and squamous portions of the temporal bone are performed to provide further recontouring. İn simpler cases, with no significant hypotelorism, a less radical procedure is needed [77] such as simple burring of the prominent metopic suture. It is still up for debate whether these cases should be considered as forms of trigonocephaly.

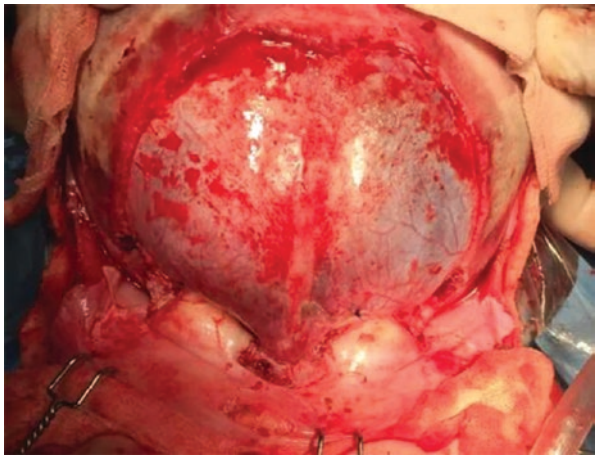


Fig 18.14 *Intraoperative look just after frontal bone craniotomy, supraorbital arch osteotomy. Exposure of the dura underneath and the orbital tissues* (Shumkovski R, Kocevski I, Micunovic M. Trigonocephaly: Case Report, Review of Literature and a Technical Note. Open Access Maced J Med Sci. 2019 Jan 15; 7(1):117–120. https://doi.org/10.3889/oamjms.2019.031)

Fig. 18.15 Fronto-supraorbital advancement (Author's method) (van der Meulen, J. Metopic synostosis. *Childs Nerv Syst* 28, 1359–1367 (2012). https://doi.org/10.1007/s00381-012-1803-z)

Subsequent Reconstructive Phase

The barrel-stave-like (radial) osteotomies and outfractures in the parietal and squamous portions of the temporal bone are expected to correct the temporal narrowing often seen in trigonocephaly.

The reconstructive phase begins with addressing the supraorbital bar, with reshaping and recontouring of the superior and lateral part of the orbits. Although

Fig. 18.16 Fronto-supraorbital remodelling (Author's method) (van der Meulen, J. Metopic synostosis. *Childs Nerv Syst* 28, 1359–1367 (2012). https://doi.org/10.1007/s00381-012-1803-z)

many authors have emphasized the importance of hypotelorism correction [78, 79] there is still no consensus on this matter. Some authors [78, 79] propose adding a nasofrontal osteotomy with bone graft interposition to the supraorbital bar and nasoethomoidal area in order to correct hypotelorism with lateral orbital wall expansion [80, 81] or three quarter orbital wall osteotomies. Other authors [75, 76] believe that internasal grafting will not increase interorbital width. However, it has been demonstrated that undercorrection of hypotelorism and persistence of abnormally low intraorbital distance are common when orbital widening is not addressed [79, 81] (Figs. 18.16 and 18.17).

However controversial, as previously mentioned, there are several ways to reconstruct the supraorbital bar. In the mild forms of hypotelorism, no attempt to correct should usually be made, since it is not considered a significant deformity. In such cases, the supraorbital bar can be left attached to the midline with no further reconstruction. Instead, if the lateral orbital rims do not require advancement, a transposition of the anterior portion of the temporalis muscle can be sufficient to correct the deformity.

In general, the reshaping of the supraorbital bar is expected to assume a more convex configuration, especially along the supralateral and lateral orbital rims. In the author's experience, in certain cases, medial or two paramedial osteotomies can be sufficient to correct the orbital deformity without interposition of an osseous graft. If only a medial supraorbital osteotomy is performed the supraorbital bar is split in the middle, and in the case of two paramedial osteotomies the cuts are just lateral to the frontonasal junction.

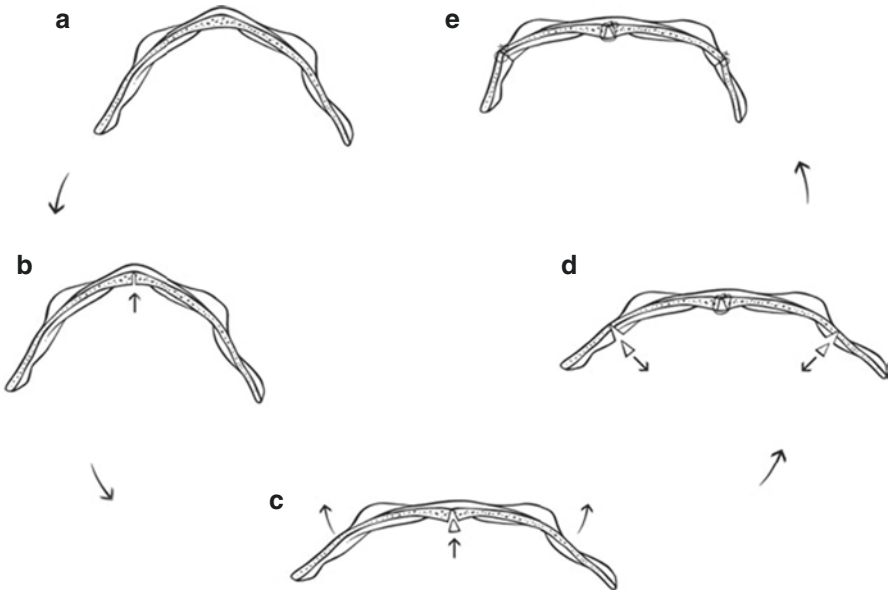


Fig. 18.17 Remodelling of supraorbital bar (Author's method) (van der Meulen, J. Metopic synostosIs. *Childs Nerv Syst* 28, 1359–1367 (2012). https://doi.org/10.1007/s00381-012-1803-z)

In the more severe forms of hypotelorism, requiring remodeling of the supraorbital bar and increasing the intercantal distance, it is considered an adequate option to interpose a bone graft harvested from the frontal bone after a medial osteotomy of the supraorbital bar (Figs. 18.18 and 18.19).

The inner table of the supraorbital bar usually has a thick bone crest, which can need reshaping by burring. After reshaping, the supraorbital bar is positioned in place. There are several different methods of fixing. Sutures, wires or resorbable (micro)plates and screws are most commonly used. İn general, the supraorbital bar is advanced anteriorly by about 1cm and is secured at the lateral orbital rims with intraosseous wires just below the level of the zygomatico-frontal suture to the inferior orbital rim, and also at the tenon extensions using resorbable plate and screw fixation. İn the author's experience, the reconstructed supraorbital bar does not always need rigid fixing, and the reconstructed position of the orbits can often be maintained even without it [77].

There are also several different ways to address the frontal bone. İn cases with less prominent midline crests, burring can be used to reduce the prominence. Another method for frontal bone reconstruction, preferred by some authors, is reshaping using a combination of Tessier bone benders and burring of the inner table, and of the protuberant outer table at the site of the fused metopic suture. İn other cases, the frontal bone can be reconstructed by radial, barrel-stave-like osteotomies. Another way is the author's preference, as described above: multiple longitudinal cuts on the bifrontal bone flap, creating a few separate "bone plates". The

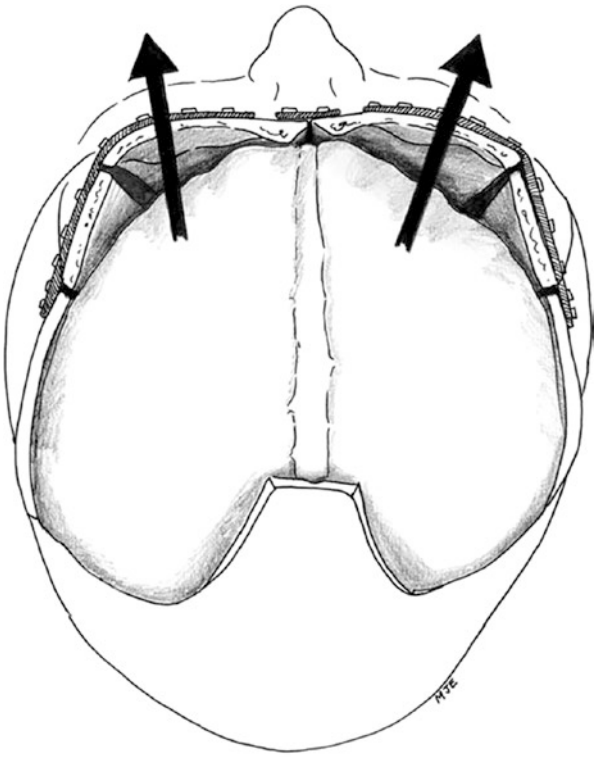


Fig. 18.18 Axial drawing showing fronto-orbital advancement (Kelleher, M.O., Murray, D.J., McGillivary, A. et al. Non-syndromic trigonocephaly: surgical decision making and long-term cosmetic results. *Childs Nerv Syst* 23, 1285–1289 (2007). https://doi.org/10.1007/s00381-007-0386-6)

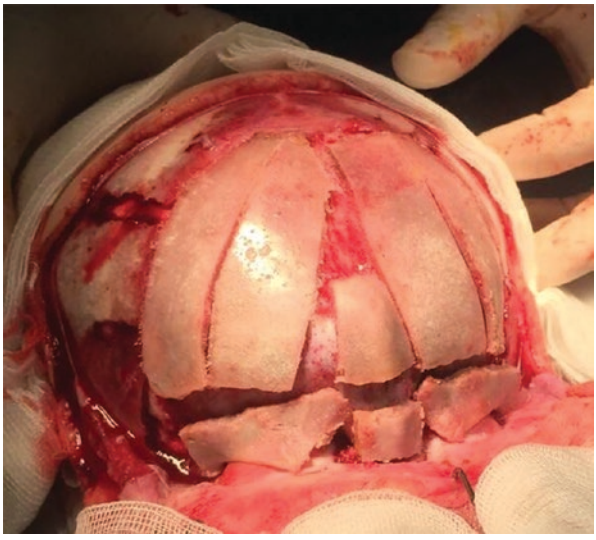


Fig. 18.19 *Arrangement of the bone flaps. The bone fragments were left loose, as no fixing plates or other fixing techniques were used* (Shumkovski R, Kocevski I, Micunovic M. Trigonocephaly: Case Report, Review of Literature and a Technical Note. Open Access Maced J Med Sci. 2019 Jan 15; 7(1):117–120. https://doi.org/10.3889/oamjms.2019.031)

first longitudinal cut is usually made in the middle down through the fused metopic suture, thus creating two pieces. Typically, both of these pieces are again cut down the middle, longitudinally, and arranged as preferred by the surgeon, but they are usually arranged in the same manner and position as before the craniotomy. Another variant of frontal bone reconstruction is rotation of the bone flap by 180°. This would result in a broader forehead from an esthetic point of view. The frontal bone can be fixed with a combination of absorbable plates and screws and also resorbable sutures (Figs. 18.23 and 18.24). Resorbable sutures are preferred for frontal bone fixation (Fig. 18.20). İn the author's opinion, the frontal bone flap does not always need fixing [77], although resorbable sutures are fairly often used. Note: permanent hardware has been associated with transcranial migration, causing dural involvement, which can be a disadvantage in this age group if a secondary procedure is needed. This further emphasizes the need to use resorbable materials.

Whatever the chosen method, the goal of frontal bone reshaping is to distribute the prominence lateral to superior, achieving a less acutely angled midline shape and finally providing additional cranial volume. The lower edge of the frontal bone should (even if only approximately) mirror the contours of the upper edge of the supraorbital bar, so that adequate compatibility can be achieved, which also affects the estethic outcome (Figs. 18.19, 18.20, 18.21, and 18.22).

İt is a good practice to reflect the scalp flap back intermittently over the bony reconstruction in order to ensure a good cosmetic outcome.

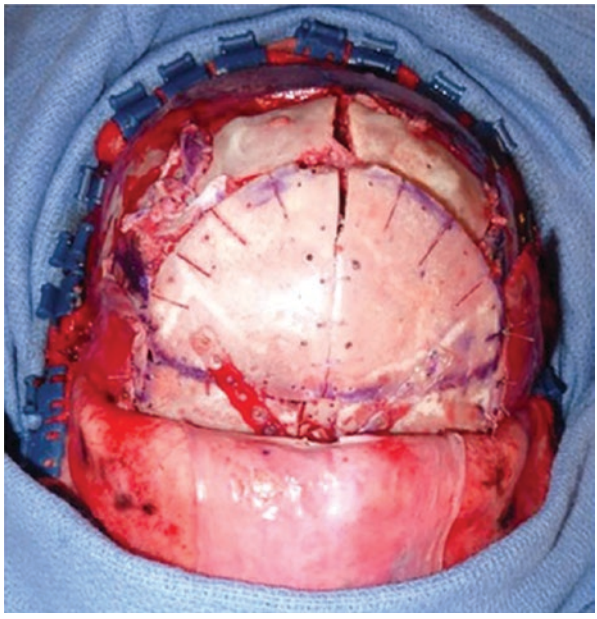


Fig. 18.20 Fixation of the forehead with resorbable plates and anterior transposition of the temporal muscles (Di Rocco, F., Arnaud, E., Marchac, D. et al. Anterior fronto-orbital remodeling for trigonocephay. *Childs Nerv Syst* 28, 1369–1373 (2012). https://doi.org/10.1007/s00381-012-1841-6)

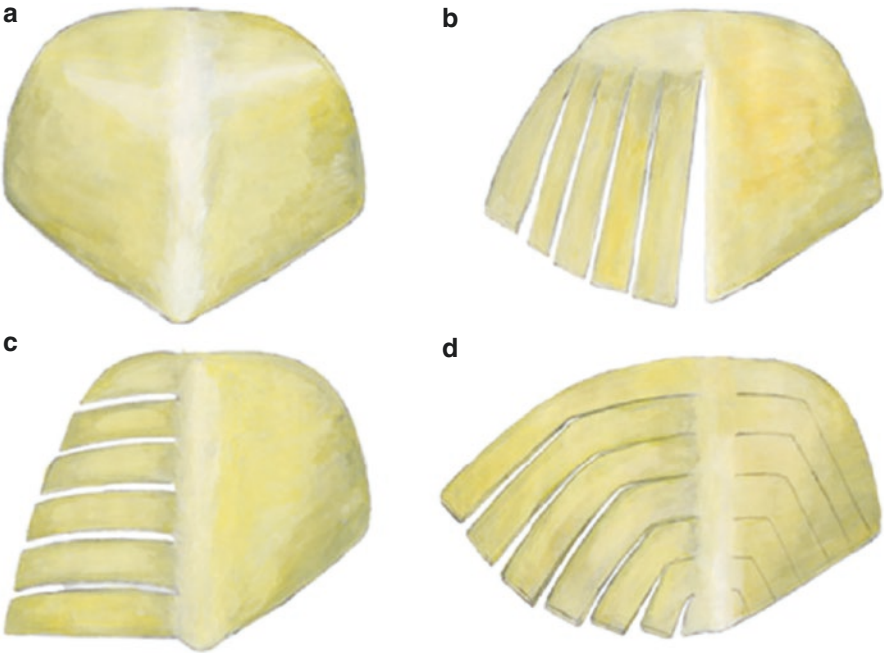


Fig. 18.21 Drawings showing the advantage of the angulated slat cuts technique over single-plane parallel osteotomies. (**a**) Trigonocephalic forehead. (**b**) Parallel sagittal osteotomies allowing for a single-plane anterior expansion of the frontal flap. (**c**) Parallel coronal osteotomies also allowing for a single-plane lateral expansion of the frontal flap. (**d**) Parallel angulated slat cuts with outward greenstick fractures at the parasagittal hinge line permit simultaneous forward and sideways expansion of the forehead with wider, fuller, and rounder contour. Angulated lines are drawn on the left, uncut, side (Pang, D., Zovickian, J., Wong, S. et al. Parallel angulated frontal bone slat cuts for treatment of metopic synostosis and other frontal skull deformities: the "cathedral dome procedure". *Childs Nerv Syst* 29, 2171–2182 (2013). https://doi.org/10.1007/s00381-013-2242-1)

Closure

Before the beginning of the closure it is important once again to check the position of the bone fragments, to make sure they are in proper position. The operative field should be clear of debris such as bone parts or fragments, or bone dust. Irrigation with warm saline often removes invisible debris. The bifrontal skin flap is closed in a standard fashion. The galea aponeurotica is approximated/closed using buried absorbable sutures, and the skin is closed according to surgeons' preferences: non-resorbable sutures can be used, or absorbable sutures such as 4-0 monocryl or 5-0 fast absorbing plain gut. A subgaleal drain is seldom used, to avoid the risk of siphoning cerebrospinal fluid from potential microabrasions of the underlying dura during craniotomies. In the author's experience, subgaleal drains can occasionally be used, although they are not advised on regular basis. In cases where a subgaleal

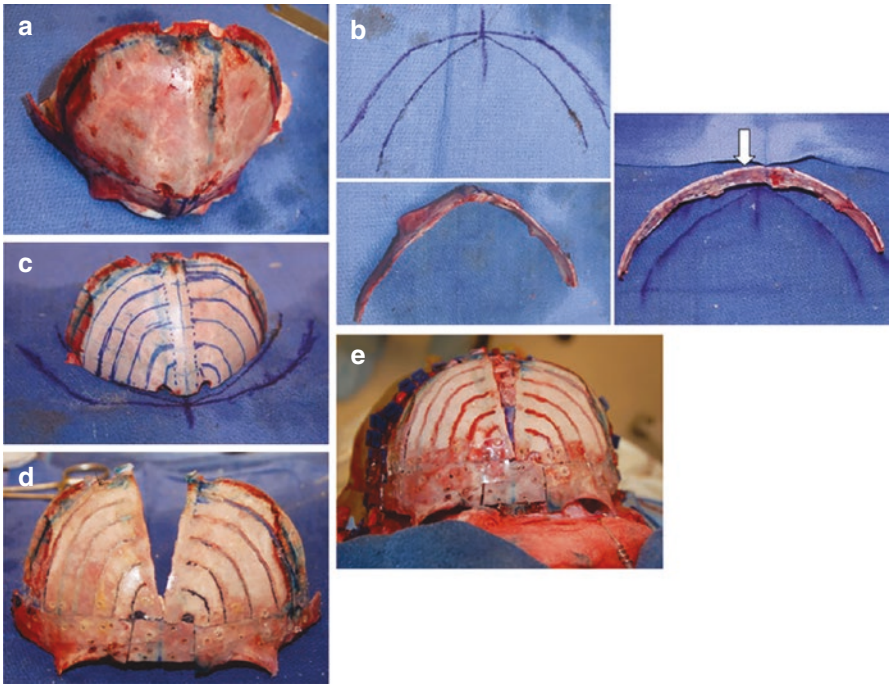


Fig. 18.22 Fronto-orbital reconstruction for trigonocephaly (case 1). (**a**) Bilateral frontal bones removed in one piece. The triangular bandeau is also removed and is beneath the frontal flap. (**b**) Remodelling of bandeau. The lower left shows the uncorrected bandeau, which traces an acute angle outline on the towel (left upper rear tracing). The tracing in front of the triangular outline represents an idealized bandeau shape, widened in the middle, and the sides rounded and swung forwards. The right side shows a remodelled bandeau with an interpositional bone graft (block arrow) and new rounded contour splinted and fixed by inside absorbable strips. The remodelled bandeau now conforms to the idealized tracing. (**c**) The frontal flap marked for the parallel angled slat cuts proceeding from the anterior edges upwards. The medial base of each slat ends on the medial edge of the flap along a parasagittal hinge line 5 or 6 mm from the midline, where the greenstick fractures are to be oriented outwards after the cuts. (**d**) Assemblage of the cut flaps and the remodelled bandeau. The remodelled bandeau shows the interpositional graft and the fixed reshaping. Note the posterior lateral flanges on the sides. The angulated slat cuts had been made and the outward greenstick fractures imposed. The slats had been made to flare or spread forwards and sideways to eliminate the lateral retrusion and temporal hollowing. The free ends of the slats are fixed to the top of the bandeau by absorbable plates and strips from the inside. (**e**) The assembled frontal–orbital complex had been replaced on to the skull base. Note the two 28-gauge wires joining the bandeau to the nasal bones. The two lateral flanges are fixed on to their respective grooves by absorbable plates. The V-shaped gap in the midline had been reduced by in-bending the lateral flanges. Bone chips fill the V gap (Pang, D., Zovickian, J., Wong, S. et al. Parallel angulated frontal bone slat cuts for treatment of metopic synostosis and other frontal skull deformities: the "cathedral dome procedure". *Childs Nerv Syst* 29, 2171–2182 (2013). https://doi.org/10.1007/s00381-013-2242-1)

drain is not used, it is necessary to have the head and the upper part of the body elevated. Periorbital and facial swelling is quite common on the first or second postoperative day, but usually resolves spontaneously by the third or fourth postoperative day without additional complications. The final step of the intervention is sterile dressing of the wound: the wound is covered using sterile towels or gauze, the surrounding skin is cleaned with wet and dry towel, and an elastic tubular net bandage is placed over the head. Alternatively, a regular bandage can be used to create a Hippocratic cap.

Specific Instrumentation

High-speed drill and saw systems are very important parts of these reconstructive operations, making the operative procedure technically much easier at the same time. Kerrison roungers are often used during these operations. Other basic pediatric neurosurgical operative instruments are also needed. Resorbable plates and and screws are used to stabilize bony fragments. Previously used metallic (permanent) fixation hardware is no longer is use because of possible transcranial migration. The absorbable plate and screw systems consist of polymers of polylactic acid and are designed to be totally absorbed within 9–15 months following implantation. Studies have shown that they have tensile strength comparable to the previously used permanent hardware at the time of their use (Figs. 18.23 and 18.24).

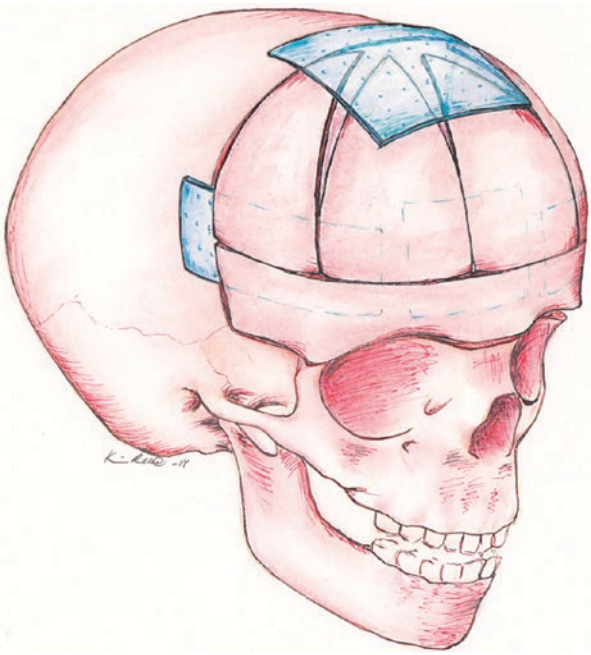


Fig. 18.23 Drawing illustrating the endocranial and extracranial location of the plates. Specifically, the plates are endocranial in the frontal areas where the overlying skin is the thinnest (Salokorpi, N., Sinikumpu, J., Iber, T. et al. Frontal cranial modeling using endocranial resorbable plate fixation in 27 consecutive plagiocephaly and trigonocephaly patients. *Childs Nerv Syst* 31, 1121–1128 (2015). https://doi.org/10.1007/s00381-015-2657-y)

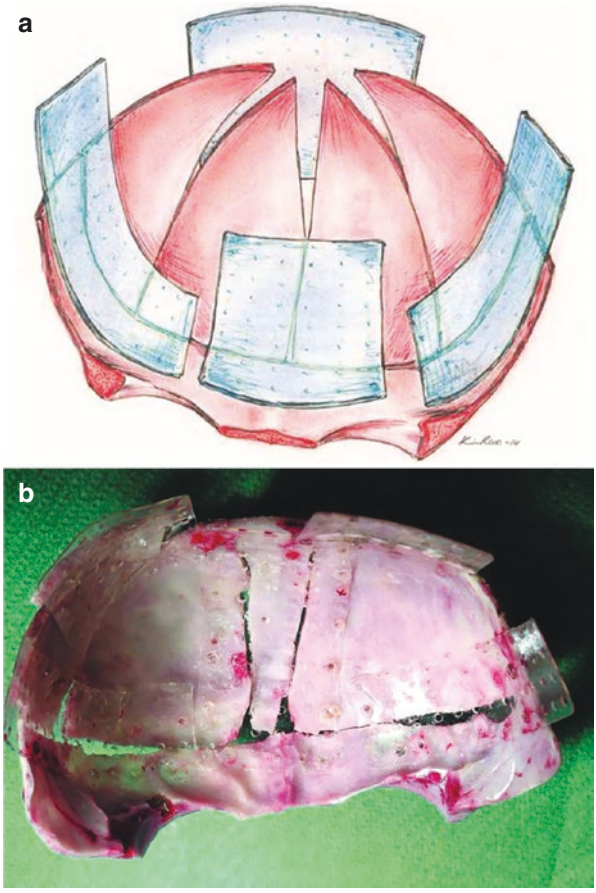


Fig. 18.24 Resorbable PLGA plates fixed on the inner surface of the frontal bones. (**a**) Drawing illustrating the position of the plates. (**b**) Intraoperative photograph (Salokorpi, N., Sinikumpu, J., Iber, T. et al. Frontal cranial modeling using endocranial resorbable plate fixation in 27 consecutive plagiocephaly and trigonocephaly patients. *Childs Nerv Syst* 31, 1121–1128 (2015). https://doi.org/10.1007/s00381-015-2657-y)

18.4.1.5 Postoerative Management

Postoperatively, the child is transferred to the intensive care unit, preferably the pediatric ICU if possible. İf problems are not expected, the patient can be awakened and extubated immediately postoperatively. The child is positioned in bed on its back, with the head and torso elevated by about 30° to prevent postoperative periorbital and facial swelling. Periorbital swelling usually develops on the first or second day postop and resolves on itself by postop day 3–4. Vital signs are monitored and laboratory values are obtained about 4–6 h postoperatively. Blood transfusions are often needed, especially if hemoglobin is below 8 g/L. Analgesia is essential for keeping the child calm and comfortable. One of the most common issues encountered postoperatively is fever, but this is usually self-limiting [82]. After about 24 h, if no additional problems are encountered, the child is transferred to the ward. The child is considered stable for discharge when a regular diet has been established and

the facial swelling has started to resolve sufficiently for the eyes to open. A follow-up visit is arranged no longer than 1 week after discharge.

Since absorbable plate and screw systems wre first used, there have been reports of painless scalp swelling occurring after about 9–15 months postoperatively. This is thought to be associated with the period of plate resorption and can occur in up to 25% of cases when absorbable plate and screw systems are used [83]. The parents should be advised not to be alarmed by this occurrence.

18.4.1.6 Complications

Many of the operative and postoperative complications for metopic synostosis are the same as those for other types of craniosynostosis. İn general, the complications can be divided into two main categories: intraoperative and postoperative. The latter can further be divided into subcategories of early and late postoperative complications.

In the category of intraoperative complications, one of the most important is intraoperative blood loss followed by inadequate blood transfusion. Care must always be taken to achieve perfect and meticulous hemostasis. Some studies have reported blood loss ranging from 19% to 58% of the estimated blood volume, and blood transfusion volumes of approximately 34% of estimated blood volume [84–87]. The superior sagittal sinus can be torn during the craniotomy or various intraoperative manipulations, and the resulting bleeding can often have dramatic consequences, emphasizing the importance of repairing the tear, which should always be prompt. Another threatening complication of a sagittal sinus tear is air embolism. Doppler ultrasound and end-tidal volume spectrometry can detect air embolism if it occurs. Immediate action should be taken, including placing the patient in a Trendelenburg position and flooding the field with saline to prevent further intake of air into the circulation. Sealing the defect is, of course, a priority.

A further intraoperative problem is dural tear. İf noticed, or recognized, most such tears can be easily repaired by monofilament nonabsorbable sutures (4-0 prolene). However, unrecognized tears can cause persistent CSF leaks. Injury to the brain is also a possibility, although rare. Injury to the periorbita or deeper tissues of the periorbita rarely occurs with experienced cranio-facial teams.

The postoperative complications, as mentioned previously, can further be divided into early and late subcategories, although a strict distinction cannot always be made. One of the most important early postoperative complications is unrecognized blood loss. It is a very preventable complication with potentially devastating consequences, as infants are especially sensitive to blood loss and the resulting hypoxia. Simple blood work will reveal the problem, easily corrected by transfusion. Another possible early postoperative complication is the previously-discussed fever, occurring at about day 3 or 4 postoperatively; rarely a cause for alarm, as it is reactive and it should be expected. Facial and periorbital sweling is self-limiting and no cause for alarm, resolving spontaneosly in about 3–4 days. Early postoperative infection can

have devastating consequences if not addressed in time, requiring prolonged use of antibiotics and significantly extended hospital stay. Rarely, infection can lead to osteomyelitis, carrying a high risk of loss of the bone flap.

Late postoperative complications are centered around poor cosmetic outcome due to restenosis. Although uncommon, about 8% of the children in one series had recurrence (regrowth) of the bony ridge in the metopic suture, requiring a second operation [88]. Temporal hollowing has also been an indication for re-operation in up to 15% of patients [89–94].

18.4.1.7 Outcome, Prognosis and Follow-up

The outcome of metopic suture reconstruction is considered to be exellent in more than 90% of patients presenting with metopic suture synostosis [89, 95–103]. The rates of recurrence requiring re-operation has been reported to be 7% by Pearson et al., and a 2.5% revision rate in infants was reported by Fearon et al. [96, 97]. Additional surgery can be required but the rates are low [103, 104]. In general, the outcome and prognosis are favorable and satisfactory (Figs. 18.25, 18.26, 18.27, and 18.28)

18.4.2 Unilateral and Bilateral Coronal Synostosis (Anterior or Frontal Unilateral and Bilateral Plagiocephaly, as Phenotypic Presentation)

18.4.2.1 Unilateral Coronal Synosthosis (Anterior or Frontal Unilateral Plagiocephaly, as Phenotypic Presentation)

The premature fusion of a unilateral coronal suture is referred to as anterior (or frontal) plagiocephaly. Unilateral coronal synostosis is often a cause of severe cranial and facial dysmorphia. If there is bilateral involvement (bilateral coronal synostosis) the resulting defect will be brachycephaly. For reasons not yet known, anterior plagiocephaly shows a right-sided predilection with a ratio of approximately 3:2 [105]. In general, unicoronal suture synostosis is recognized easily and diagnosed early owing to the significant asymmetry. Anterior plagiocephaly should be differentiated from deformational plagiocephaly, as etiology and treatment differ. Most cases are sporadic, but there is a familial association in up to 8% of cases [106, 107]. Although anterior plagiocephaly is associated with unilateral coronal synostosis, it is known to occur in association with synostosis of other parts of the coronal ring, such as fronto-sphenoidal or fronto-ethmoidal synostosis [108, 109].

Several explanations for unilateral coronal suture synostosis have been proposed, mainly revolving around the underlying dura and the underlying brain. Some studies have suggested that abnormal morphology of the cortical sulci and gyri can be accompanied by overlying abnormal dura and suture.

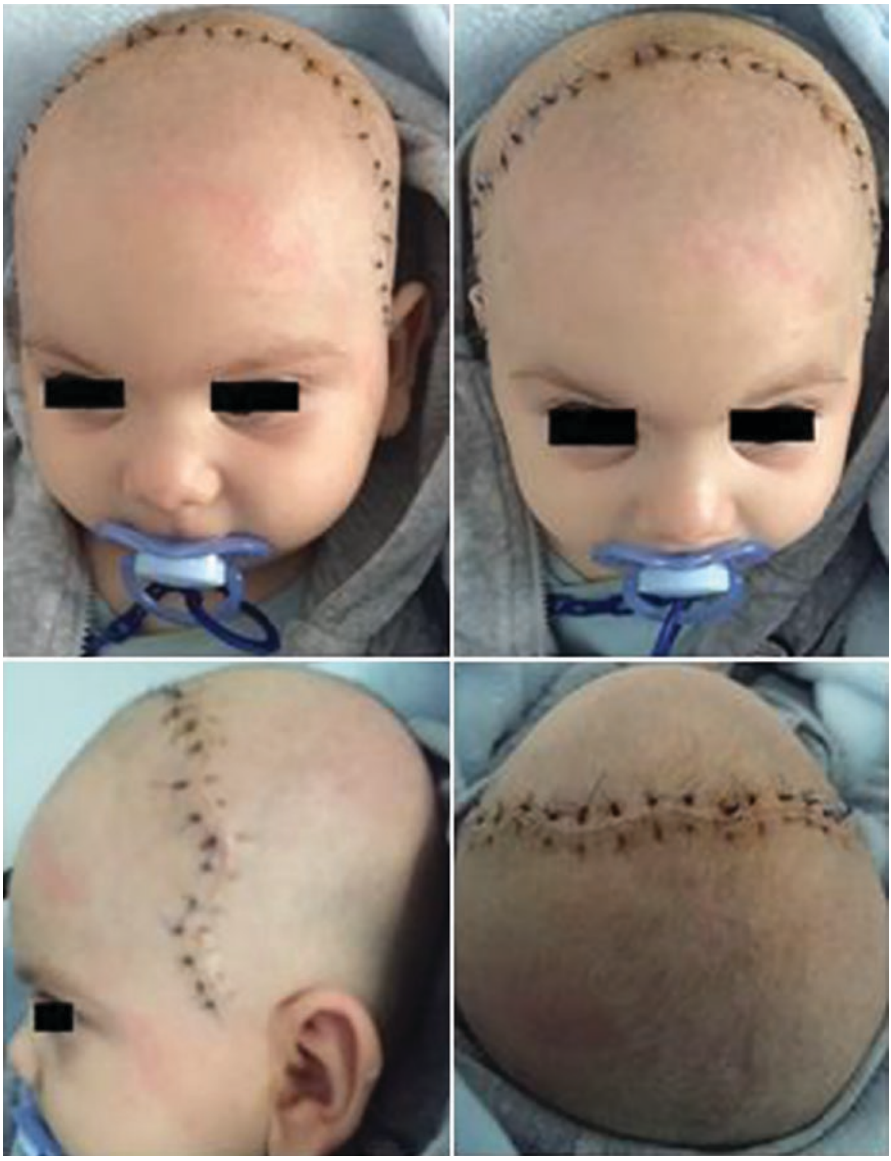


Fig. 18.25 *Follow-up at 10 days postop, just before suture removal* (Shumkovski R, Kocevski I, Micunovic M. Trigonocephaly: Case Report, Review of Literature and a Technical Note. Open Access Maced J Med Sci. 2019 Jan 15; 7(1):117–120. https://doi.org/10.3889/oamjms.2019.031)

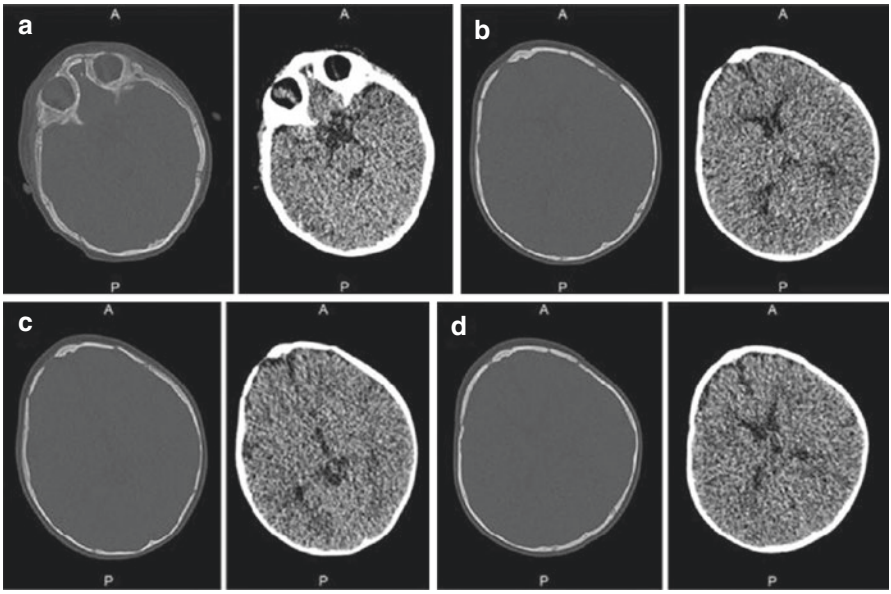


Fig. 18.26 *Postoperative head CT scan at 3 months follow-up. Note the anterior cranial base decompression* (Shumkovski R, Kocevski I, Micunovic M. Trigonocephaly: Case Report, Review of Literature and a Technical Note. Open Access Maced J Med Sci. 2019 Jan 15; 7(1):117–120. https://doi.org/10.3889/oamjms.2019.031)

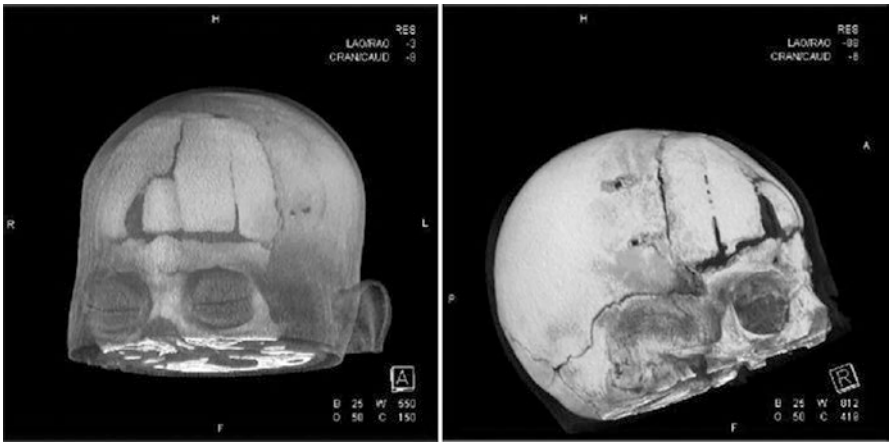
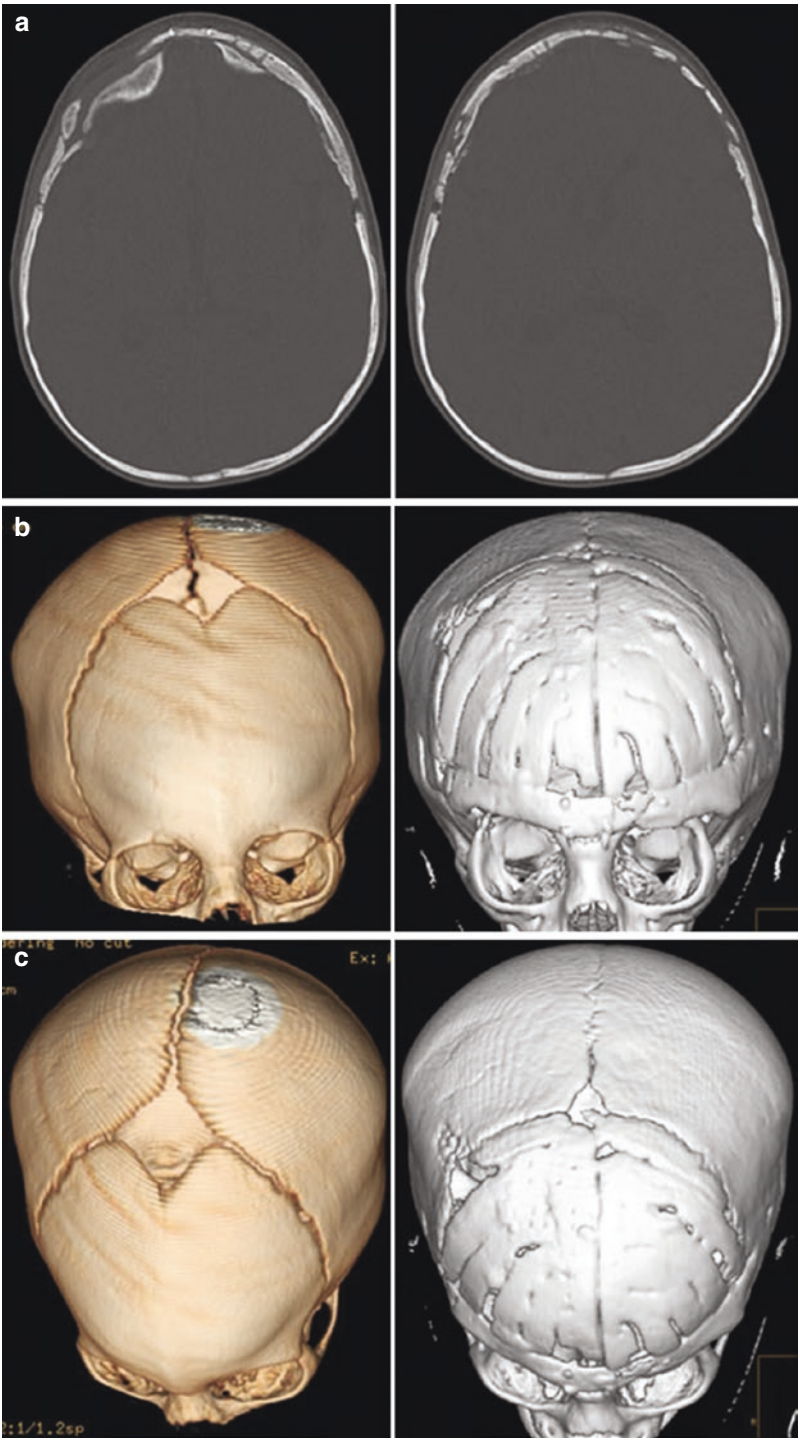


Fig. 18.27 *Post-operative 3D reconstructed head CT at 3 months follow-up visit decompression* (Shumkovski R, Kocevski I, Micunovic M. Trigonocephaly: Case Report, Review of Literature and a Technical Note. Open Access Maced J Med Sci. 2019 Jan 15; 7(1):117–120. https://doi.org/10.3889/oamjms.2019.031)


a
b
c

The phenotypic presentation of unilateral coronal suture synostosis is by calvarial growth restriction on the ipsilateral side of the prematurely fused unicoronal suture, accompanied by compensatory growth on the contralateral side. The resulting defect will manifest as ridging of the prematurely fused unicoronal suture, flattening of the ipsilateral frontal and parietal bones, bulging of the ipsilateral squamous portion of the temporal bone due to malposition in anterior and asymmetric descending fashion, and bulging of the contralateral frontal and parietal bones. The orbit on the affected side will also not be spared, presenting as retrusion of the supraorbital rim (postero-lateral displacement) due to the distorted sphenoid wing. The deformity of the ipsilateral orbit as seen on plain X-ray or CT scan is referred to as Harlequin deformity and is attributable to the superiorly displaced ispilateral greater wing of the sphenoid bone, making the ipsilateral globe and eyebrow higher and the palpebral fissure wider than on the nonsynostotic side. This characteristic deformity of the orbit is also accompanied by shortening of the medial-to-lateral diameter of the orbit. In contrast, the contralateral side will have anterior advancement of the lateral orbital wall. The nasal radix is deviated to the side of the fused suture, making the nasal axis oblique, with the tip of the nose pointing to the nonsynostotic side. The ear on the same side as the fused suture is displaced anteriorly in comparison to the other side. A head CT, which is routinely performed, is expected to demonstrate shortening of the anterior cranial fossa and narrowing of the ipsilateral spheno-petrosal angle. The zygoma and the maxilla on the affected side appear hypoplastic. Another common finding with its own burden is strabismus, seen in about 50–60% of patients with anterior plagiocephaly [110, 111]. It is thought to occur because the anterior cranial fossa is shortened, resulting in posterior deplacement of the orbital roof and trochlea, leading to superior oblique muscle dysfunction [111] (Figs. 18.29 and 18.30). Although the operative treatment is expected to improve the strabismus to some degree, an ophthalmologist should be consulted for definitive correction. Another interesting observation is the finding of left-handedness, three times more common in patients with anterior plagiocephaly than in control subjects, and four times more likely with left-sided fusion.

Unicoronal synostosis is often sporadic (nonsyndromic), but it can be associated with other craniofacial syndromes or extracranial manifestations involving the cardiovascular, genitourinary and skeletal systems. It is rarely associated with hypertelorism.

If the natural course of unilateral coronal synostosis is not surgically corrected, a severe deformity of the forehead, face, orbit and the nose will develop over time as

Fig. 18.28 Improvement after 3 months of the cathedral dome procedure. (**a**) Axial CTs of the bandeau (left) and frontal flaps 3 months after repair (right), showing dramatic correction of frontal retrusion and hypotelorism. (**b**) Frontal view comparison using preoperative 3D-CT (left) and scans at 3 months after surgery (right), showing elimination of the frontal lateral retrusion, temporal hollowing, and hypotelorism. There is no midfrontal gap or large skull defect. (**c**) Top view comparison, as above, highlights the improvement in the frontal contour (Pang, D., Zovickian, J., Wong, S. et al. Parallel angulated frontal bone slat cuts for treatment of metopic synostosis and other frontal skull deformities: the "cathedral dome procedure". *Childs Nerv Syst* 29, 2171–2182 (2013). https://doi.org/10.1007/s00381-013-2242-1)

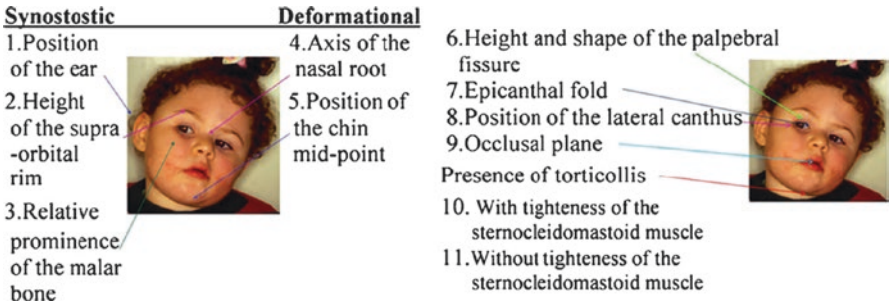


Fig. 18.29 Physical findings useful for the differential diagnosis between synostotic and deformational anterior plagiocephaly (Di Rocco, C., Paternoster, G., Caldarelli, M. et al. Anterior plagiocephaly: epidemiology, clinical findings, diagnosis, and classification. A review. *Childs Nerv Syst* 28, 1413–1422 (2012). https://doi.org/10.1007/s00381-012-1845-2)

the head grows. It has been demonstrated that failure to correct unilateral coronal synostosis within the first year of life results in progressive deformity of the cranial base, leading to abnormal facial growth and asymmetry of the maxilla and the mandible.

Diagnosis, Indications, and Timing for Operative Treatment

One of the most important parts of the evaluation of patients with unilateral coronal synostosis, as in any other craniosynostosis, is the physical examination. A careful physical examination is expected to determine the diagnosis. Children with craniosynostosis are often referred to pediatricians or pediatric neurologists, who can be very helpful in defining the child's neurodevelopmental and neurocognitive status; studies have revealed a significantly higher incidence of minor learning disorders in children with nonsyndromic suture synostosis.

One of the most important diagnostic tools, establishing the diagnosis immediately, is the high resolution CT scan, especially with 3D reconstruction, which is expected to reveal bone and suture definition and also to make evaluation of the brain parenchyma possible. If additional abnormalities are suspected, an MRI scan should be performed (Figs. 18.31, 18.32, and 18.33).

In unilateral coronal synostosis, the main indication for sugery is considered to be reshaping of the skull and correction of the cranial and orbital deformities. Correction of the associated skull deformities is expected to result in release of the fused sutures, allowing the brain to grow and develop normally, precluding issues associated with increased ICP. Correction of the orbit is potentially needed to correct the strabismus, and also to prevent anomalies in binocular vision or even amblyopia. The psychosocial impact of this condition should not be underestimated; in certain cases the psychosocial factor alone can be, and should be, an indication for operative treatment.

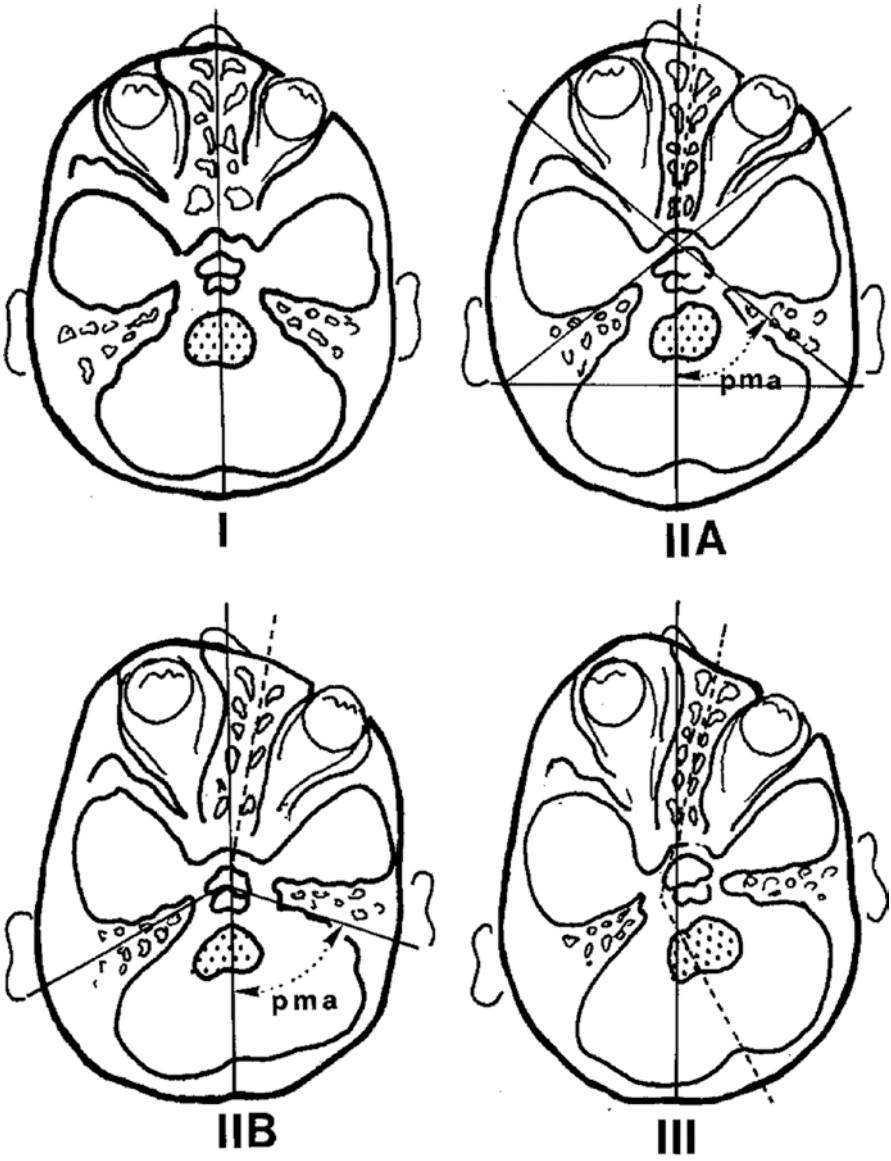


Fig. 18.30 Classification of plagiocephaly: Di Rocco C, Velardi F (1988) Nosographic identification and classification of plagiocephaly. Childs Nerv Syst 4(1):9–15

The best timing for surgical correction of unilateral coronal synostosis is still up for debate, although most authors agree that the surgery is best performed during early infancy (<1 year). There are two opinions about the best time for surgery, the first advocating early surgery up until six months of age, and the other advocating later treatment between nine and ten months of age. Whitaker et al. proposed an age

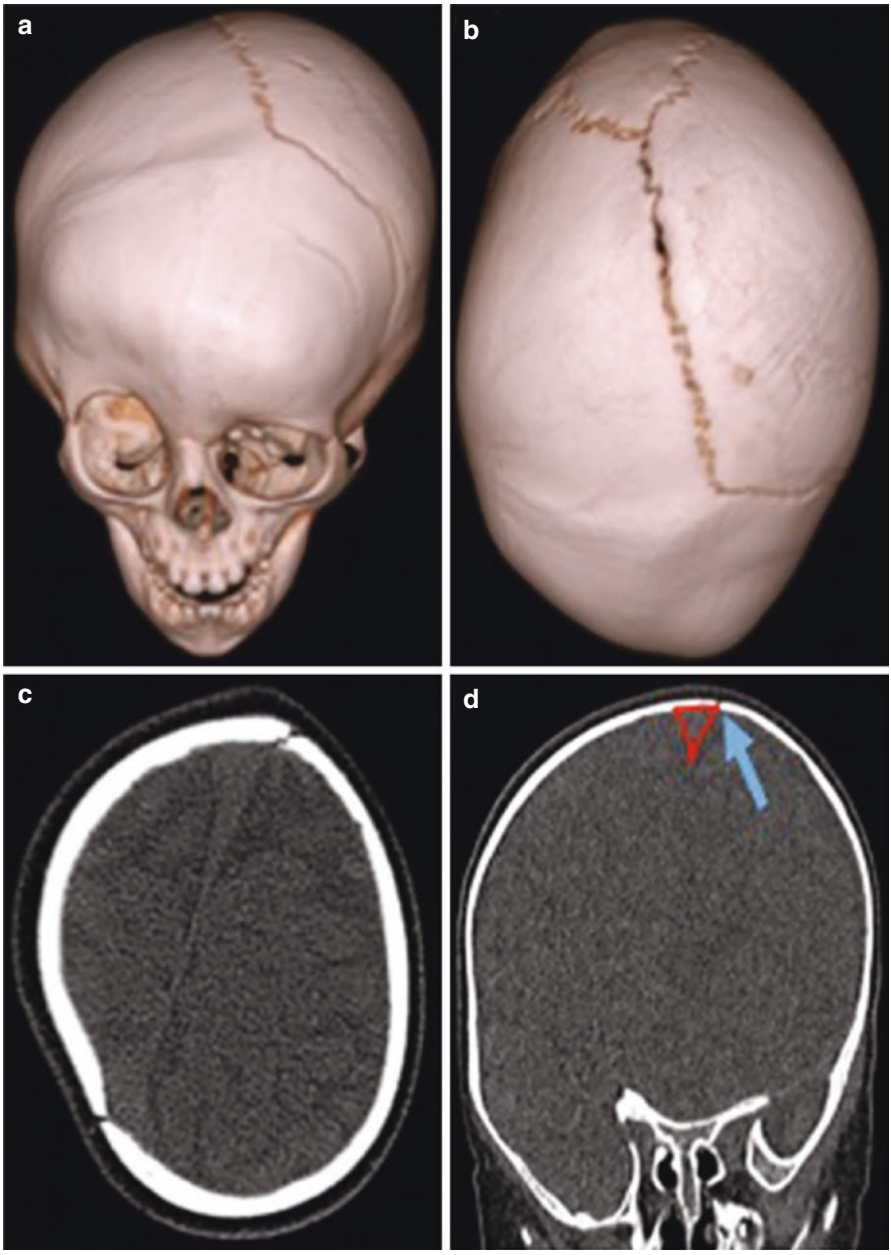


Fig. 18.31 Right unicoronal craniosynostosis. (**a**, **b**) Three dimensional CT reconstructions of an 8-month-old patient with right unicoronal craniosynostosis, with an oblique path of the sagittal suture. **c**, **d** CT imaging allows the SSS (red) to be visualized; it is deviated towards the fused coronal suture in relation to the sagittal suture (arrow) (Iyer, R.R., Wu, A., Macmillan, A. et al. Use of computer-assisted design and manufacturing to localize dural venous sinuses during reconstructive surgery for craniosynostosis. *Childs Nerv Syst* 34, 137–142 (2018). https://doi.org/10.1007/s00381-017-3601-0)

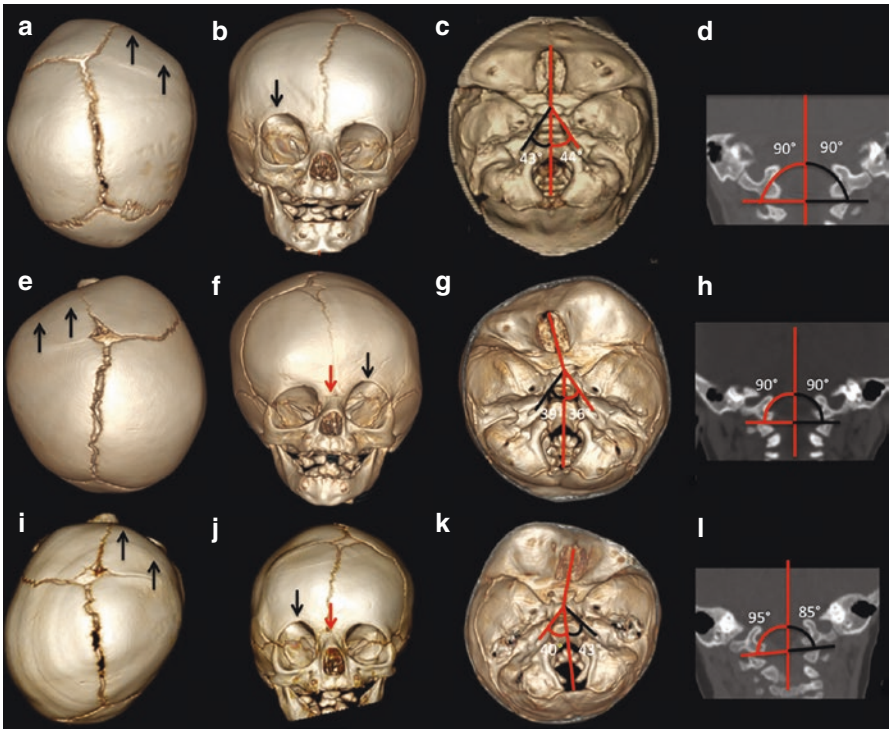


Fig. 18.32 Classification scheme of anterior synostotic plagiocephaly based on cranio-facial dysmorphology. 3D-CT ((**a**, **b**, **c**, **e**, **f**, **g**, **i**, **j**, **k**) and coronal 2D-CT (**d**, **h**, **l**). Vertex (**a**, **e**, **i**) and endocranial (**c**, **g**, **k**) 3D views have been rotated. Angles and lines on the synostotic side are shown in red while angles and lines on the unaffected side are shown in black. Group IIA (**a**–**d**); Note frontal bone flattening ipsilaterally to the affected suture (arrows, a), and elevation of the orbital roof (arrow, **b**), normal positioning of the vomer, mild or absent anterior displacement of the petrous bone on the affected side (**c**), and symmetry of the craniovertebral junction (**d**). Group IIB (**e**–**h**); Note frontal bone flattening ipsilaterally to the affected suture (arrows, **e**) and elevation of the orbital roof (black arrow, **f**), contralateral deviation of the nasal pyramid (red arrow, **f**), moderate degree of vomer deviation, anterior displacement of the petrous bone (**g**), and symmetry of the craniovertebral junction (**h**). Group III (**i**–**l**); Note frontal bone flattening ipsilaterally to the affected suture (arrows, **i**) and elevation of the orbital roof (black arrow, j), contralateral nasal deviation (red arrow, **j**), ipsilateral deviation of the vomer, anterior displacement of the petrous bone (**k**), and asymmetry of the craniovertebral junction (**l**) (Calandrelli, R., Pilato, F., Massimi, L. et al. Quantitative analysis of cranial-orbital changes in infants with anterior synostotic plagiocephaly. *Childs Nerv Syst* 34, 1725–1733 (2018). https://doi.org/10.1007/s00381-018-3824-8)

of 4–12 months on the basis of experience with 164 patients. The same group led by Whitaker later updated their recommendation, proposing that reconstructive operations for unilateral coronal synostosis should be delayed until the age of at least 6 months in order to avoid relapse or restenosis [110, 111]. Marchac et al. recommend the age of 6–9 months for cranial vault reconstruction for unilateral coronal synostosis [112]; McCarthy et al. propose the age of six months [113]. Posnik recommends 10–12 months for operative treatment for unicoronal synostosis for anterior plagiocephaly [114].

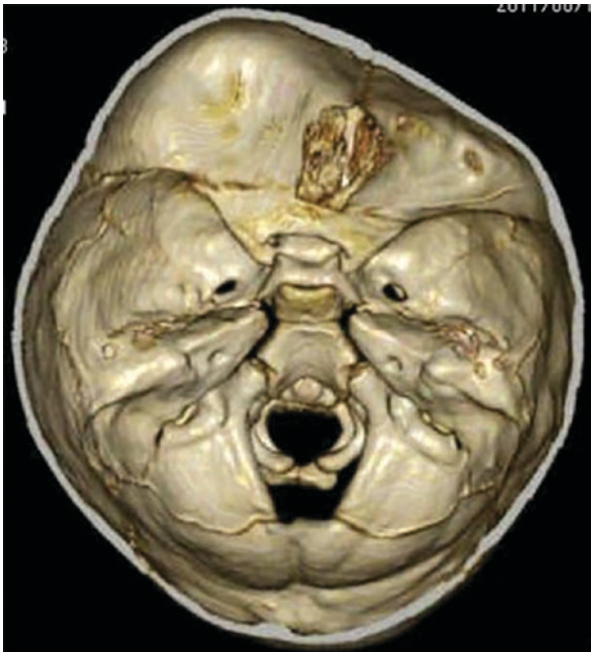


Fig. 18.33 The basal cranial angles by 3D-reconstructed CT image. Red line: the sagittal line passing through the middle point on the line connecting the tips of the two anterior clinoid processes and the middle point on the line linking the tips of the two posterior clinoid processes. (**a**) EA, deviation of the ethmoidal axis from the sagittal line; (**b**) n-APSA, anterior-petrosal-sagittal angle (APSA, in degree) on the normal side; (C) a-APSA, APSA on the affected side (Oyoshi, T., Fujio, S., Bohara, M. et al. The assessment of relationship between the skull base development and the severity of frontal plagiocephaly after bilateral fronto-orbital advancement in the early life. *Childs Nerv Syst* 30, 155–159 (2014). https://doi.org/10.1007/s00381-013-2182-9)

In the author's opinion, this type of surgery is best performed at an age of about 4–8 months, depending on the weight and general health of the child. Other authors agree that by this age the child will have sufficiently developed calvarial bones, thick enough to support fixation and to provide structural stability. Also, the bone is malleable enough to make remodeling easier and facilitate the healing of bone defects, and the rapid brain growth is expected to promote bone remodeling.

Preoperative Planning, Surgical Objectives and Special Equipment

Besides obtaining a head CT scan, the preoperative preparations for surgery should include routine blood tests including complete blood count, electrolyte panel, and partial thromboplastin time and prothrombin time. A blood type should be obtained since there is a potential for significant blood loss. İf the patient's parents are prepared to donate they should be given the option to do so. The child should be kept fasting for at least 4–6 h before the planned surgery.

The objectives of the surgical correction should be to achieve the best possible and most durable correction of deformity with a single operation at the lowest possible risk to the patient. Several reconstructive procedures have been described. However, for anterior plagiocephaly, bilateral fronto-orbital advancement for expansion of the affected forehead and orbit is now recommended, with concomitant recession of the contralateral orbit. Bilateral fronto-orbital advancement was first proposed in 1979 by Marchac and Renier in the form of the "floating forehead" procedure [115], also employed in bilateral fronto-orbital advancement for bicoronal stenosis. It is expected to provide bilateral frontal as well as orbital correction (Figs. 18.34 and 18.35).

Equipment needed during these operations includes a Mayfield headring or horseshoe head holder, although the Mayfield headring usage is advised in preference to the horseshoe head holder because it provides much better head stability intraoperatively and a lower risk of postoperative infections. Basic pediatric neurosurgical operative instruments are needed, and a high-speed drill or handheld Hudson brace with pediatric burrs. Resorbable plates and and screws are used to stabilize bony fragments, although they are not always deployed. Local anesthetic

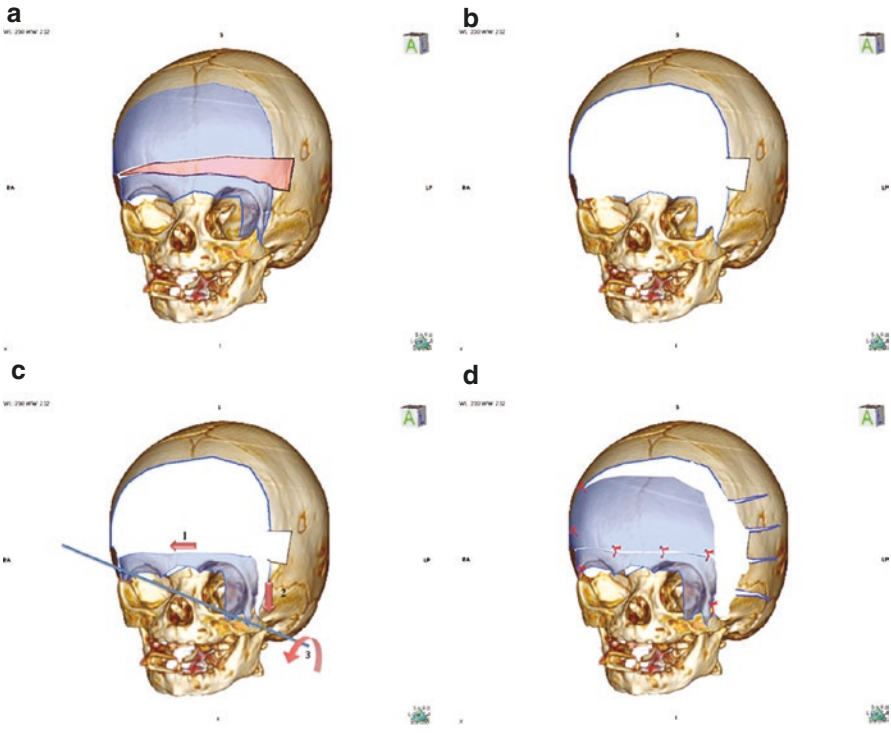


Fig. 18.34 Drawing of the osteotomies on the patient's 3D C.T. scan reconstruction (Pellerin, P., Calibre, C., Vinchon, M. et al. Unicoronal synostotic plagiocephaly: surgical correction: Lille's technique. *Childs Nerv Syst* 28, 1433–1438 (2012). https://doi.org/10.1007/s00381-012-1793-x)

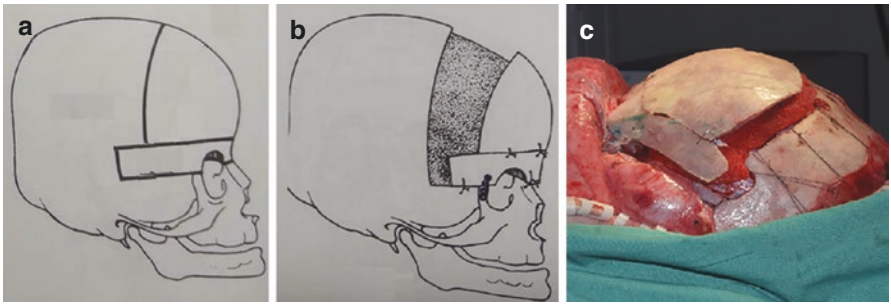


Fig. 18.35 Schematic drawings of modified fronto-orbital advancement used for patients with anterior plagiocephaly (**a** and **b**). The intraoperative photograph presented shows the result of a free-floating forehead and temporal region (**c**) (Yang, B., Ni, J. & Li, B. 3D morphological change of skull base and fronto-temporal soft-tissue in the patients with unicoronal craniosynostosis after fronto-orbital advancement. *Childs Nerv Syst* 34, 947–955 (2018). https://doi.org/10.1007/s00381-018-3721-1)

is encouraged (bupivacaine or lidocaine with epinephrine) for local analgesia, reducing the need for additional dosing with intravenous analgesics and better control over intraoperative bleeding.

According to current understanding, unilateral coronal synostosis presents with bilateral dysmorphic changes, and bilateral correction is now believed to be the optimal approach [114, 116–118].

Anesthetic Considerations

At least two large bore intravenous lines (≥20 gauge) are required because of potential blood loss during surgery. A urinary catheter is useful for recording urinary output. A thermistor is needed to record body temperature, and intraoperative body warmers are of course advised. Arterial and central venous lines will allow total body intravascular volume to be monitored and postoperative fluid management to be achieved.

Endotracheal intubation should be performed in the standard manner, securing the tube according to local practice. Some authors advise circummandibular or circumdental wire to avoid the need for taping and ensure full accesss during surgery. Temporary tarsorrhaphy sutures are rarely used in our practice, but some authors recommend them for corneal protection. İn our practice, oily eye drops (Vit A and Vit D) with hydrophobic tape over the child's eyes suffice for corneal protection.

Preoperative antibiotics are given before the skin incision (cefazoline 10–20 mg/kg as loading dose 8mg/kg intravenously every 8 h for 48 h) as per local practice.

The author's preference is total removal of hair by hair clippers. Total hair clipping is also expected to facilitate skin closure and postoperative wound care.

Operative Procedure

Positioning

At the beginning of the reconstructive procedure for anterior plagiocephaly, the patient is placed in a supine position on the operating table with the head in slight extension. The head is secured in a Mayfield headring according to the author's preference. Alternatively, a horseshoe headrest can be used. Cotton pads are applied to different body parts to ensure a comfortable position during the lengthy operation.

Sterile Scrub, Draping and Local Anesthetic

The skin is prepped with povidone-iodine or other skin antiseptic as per local practice. Some authors prefer a solution of 2% chlorhexidine and 70% isopropyl alcohol. Betadine Ophtalmic (5% povidone-iodine) can be used when prepping near or around the eyes. Usually, we use 70% ethanol followed by a prescrub with a scrub brush followed by a two-step Betadine preparation, first with Betadine soap, and then by a Betadine scrub. Single use drapes are preferred and advised. For local analgesia and to minimize intraoperative bleeding, the following combinations can be used: 0.5% lidocaine and 1:400.000 parts epinephrine or 0.25% bupivacaine and 1:200.000 epinephrine.

Prior to incision an antibiotic is administered according to local practice and regulations on antibiotic usage.

Skin Incision

Using a No. 15 scalpel, a bicoronal incision is made at the level of the mid-vertex extending well behind the hairline, from just above (or behind) one ear across to the opposite side. Alternatively, a zigzag variation of the bicoronal incision can be used, referred to as the stealth incision, or a sinusoid-type incision to minimize the visibility of incisional scalp alopecia. Another variation of the bicoronal scalp incision is posterior inclination in the parieto-occipital scalp, providing excellent camouflage of the scar line, especially in balding adults. It is necessary to preserve the ascending branches of the superficial temporal arteries for adequate blood supply [71]. Bleeding from the skin flap is controlled by bipolar coagulation, but Raney clips can also be used. Further dissection of the skin flap proceeds in a subperiosteal or supraperiosteal fashion. The advantage of supraperiosteal dissection is reduced bleeding: the periostium is incised approximately 1–2 cm above the supraorbital rim and the dissection is further advanced subperiosteally, ensuring bilateral exposure of the supraorbital rim and also avoiding injury to the branches of the facial nerve. The temporalis fascia and muscles are split and dissected off their attachments to the temporal and sphenoid bone but left attached to the skin flap.

The scalp flap is elevated down to the level of the supraorbital rim. The supraorbital neurovascular bundle should be preserved and left attached to the scalp flap; if necessary, an osteotome can be used to release it. The dissection should then be extended down to the level of the lateral orbital rim, exposing the fronto-zygomatic suture. Medially, the nasion is also exposed during this part of the dissection, thus revealing the orbital roof. The temporal and sphenoid bones are exposed laterally from the lateral orbital rim. This area will allow a tenon extension to be formed on the temporal bone, after the orbital osteotomies (Fig. 18.36).

Using a narrow periosteal elevator or dissector, the periorbita is dissected off the supraorbital rim and about 1cm off the orbital roof bilaterally. The skin flap is than secured in place using scalp hooks (fish hooks with Songer cables**,** Songer hooks). If needed, the posterior scalp flap can be deflected backwards to expose the midparietal region.

In summary, the limits of the exposure should include the coronal suture, anterior fontanel, the nasion, the supraorbital rims, and bilaterally, the fronto-zygomatic suture (Fig. 18.37).

Initial Deconstructive Phase

The deconstuctive phase begins with planning and performing the bifrontal craniotomy. The anterior extent of the bifrontal cranitomy should reach about 10–15 mm above the supraorbital bar; the posterior extent should encompass both coronal sutures (fused and nonfused), about 20–25 mm dorsal to them; laterally, the osteotomy should reach the pterion; and the inferior and ventral extent is expected to reach the lateral orbital wall near the fronto-zygomatic suture. First, a burr hole is made at the site of the proposed osteotomy. Using a dissector, the dura is dissected off the inner table of the bone as preparation for the bony cuts. The bifrontal craniotomy is performed using a high speed osteotome. When the bony cuts of the bifrontal flap

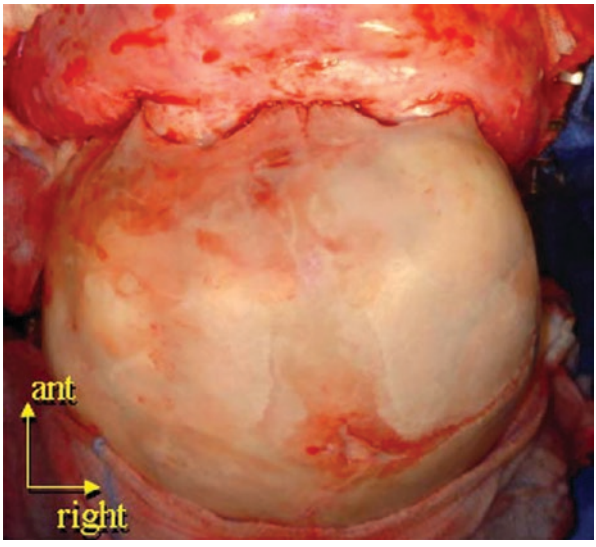


Fig. 18.36 Operative superior view. The calvaria is exposed subperiosteally down to the floor of the orbits, with exposure of the nasal and zygomatic bones (Vinchon, M., Pellerin, P., Pertuzon, B. et al. Vestibular orientation for craniofacial surgery: application to the management of unicoronal synostosis. *Childs Nerv Syst* 23, 1403–1409 (2007). https://doi.org/10.1007/s00381-007-0471-x)

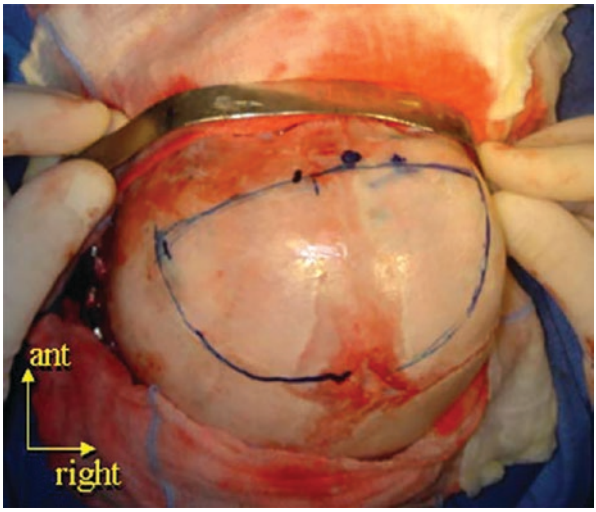


Fig. 18.37 Operative superior view. The future forehead is harvested from an aptly shaped area of the calvaria (in the frontal or parietal region) according to a template shaped according to the future orbital rim (Vinchon, M., Pellerin, P., Pertuzon, B. et al. Vestibular orientation for craniofacial surgery: application to the management of unicoronal synostosis. *Childs Nerv Syst* 23, 1403–1409 (2007). https://doi.org/10.1007/s00381-007-0471-x)

are completed, respecting the boundaries, as described earlier, the dura should be carefully stripped from the inner table of the frontal bone. Any dural laceration should be immediately repaired. Care must be taken while performing the osteotomy across the sphenoid wing on the affected side, as its superior deplacement could cause difficulty when the bifrontal flap is removed and sometimes lead to unwanted dural laceration or injury to the middle meningeal artery. After the bifrontal bone flap is removed, the dura is exposed. To prepare for the rest of the bony cuts, the dura should be carefully stripped from the inner table of the supraorbital bar, and from the anterior cranial fossa to the level of the crista gali in the middle. Finally the dura is stripped from the inner table of the temporal fossa and the greater wing of the sphenoid bone, or as some authors would prefer, from pterion to pterion (Fig. 18.38).

When the dural disection is finished, the supraorbital osteotomy can be performed. The boundaries of the supraorbital osteotomies are as follows: medially, just anterior to the cribriform plate and laterally to the pterion. During supraorbital osteotomy the dura and the periorbita should be protected by malleable retractors. In the anterior cranial fossa, the osteotomy should reach the crista gali in the medial part, advancing laterally behind the supraorbital bar to the level of the pterion. At the level of the pterion the cut is connected to the cut at the level of the fronto-zygomatic suture. The osteotomy then continues to the orbital roof, protecting the orbit using malleable retractors. On the level of the medial aspect of the orbital roof, the osteotomy proceeds from the anterior lacrimal crest to the contralateral anterior lacrimal crest across the nasofrontal suture. A narrow osteotome and a mallet can be used to complete the osteotomy and to separate the supraorbital bar as a single unit. When available, a reciprocating saw can be used. A technical note: on the affected side, at the level of the fronto-zygomatic suture, the osteotomy is carried back to join the osteotomy at the level of the pterion, whereas on the contralateral ("unaffected") side, it is performed vertically at the level of the lateral orbital rim. Any aberrant bone can be resected and/or reshaped using a combination of roungers and bone benders.

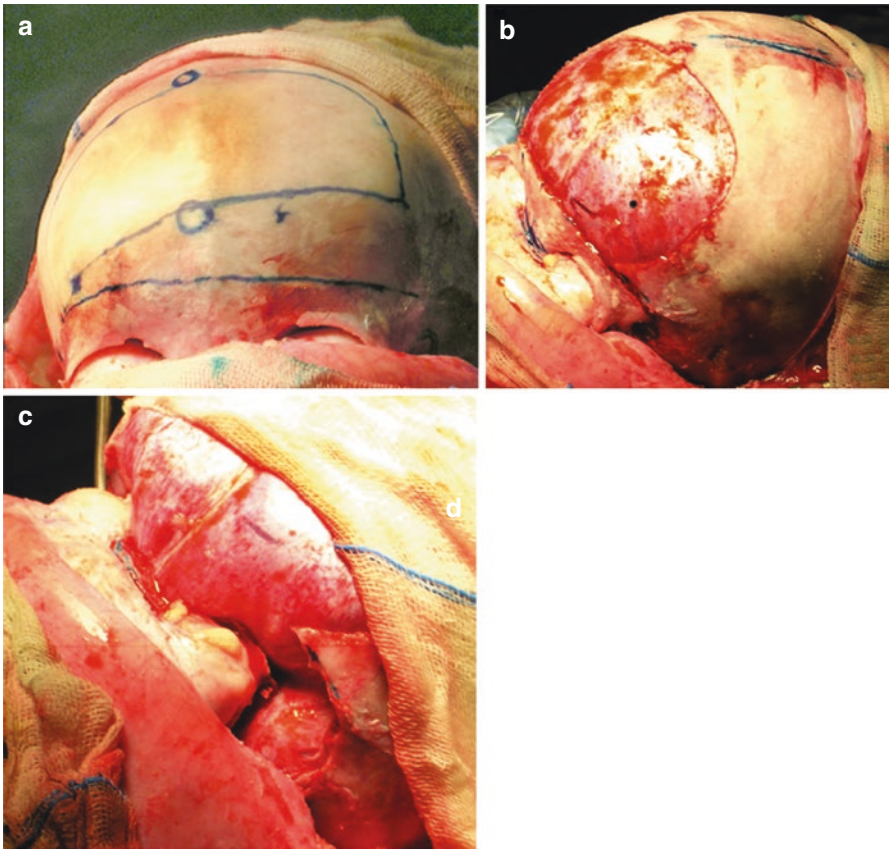


Fig. 18.38 Dissection. (Pellerin, P., Calibre, C., Vinchon, M. et al. Unicoronal synostotic plagiocephaly: surgical correction: Lille's technique. *Childs Nerv Syst* 28, 1433–1438 (2012). https://doi.org/10.1007/s00381-012-1793-x)

During the deconstructive phase, bleeding from bone should be addressed by generous use of bone wax, and any dural laceration should be repaired using nonabsorbable sutures (4-0).

Subsequent Reconstructive Phase

The reconstruction and reshaping of the supraorbital unit is considered a key step in surgery for unicoronal synostosis, specifically the overcorrection of it. To achieve this, a few steps are undertaken. First, the supraorbital bar is divided at the midline. Each of the two separate supraorbital bars is then once again split in the middle at the level of the highest point. Next, each supraorbital bar is widened or narrowed according to the desired reconstruction, as planned preoperatively on the basis of the CT scan. During this stage, the ipsilateral orbital unit is advanced and the contralateral unit is recessed, combined with a forwards tilt of the entire unit. In other

words, the affected supraorbital bar is advanced into an overcorrected position and the temporal tenon extension on the affected side is infolded and a resorbable plate is used to fix it to the adjoining part of the temporal bone. The contralateral portion of the supraorbital bar is then recessed, if necessary, and inserted into position. If the desired position is not achieved, a full-thickness bone graft can be inserted into the superior margin of the affected orbit. Burring can be used to accommodate the shape and size, and resorbable plates and screws are used for fixing (Fig. 18.40). The desired advancement of the entire supraorbital bar should be 7–15 mm, depending on the preoperative measurements and the degree of correction desired.

In summary, the goal of the reconstruction of the supraorbital unit is to advance the ipsilateral orbital rim to an overcorrected position, advance the retruded supraorbital rim in relation to the infraorbital rim to create a new shape of the anterior orbit to match the opposite side, and recess the contralateral lateral orbital rim.

The bone along the fused coronal suture should be removed. The rest of the frontal bone is addressed by making a series of barrel–stave-radial osteotomies, and Tessier bone benders are used to adjust the shape of the frontal bone, increasing or decreasing its convexity. The end result should be a symmetrical frontal bone. Absorbable rigid fixation is used after placing the frontal bone over the supraorbital bar. Alternatively, the bone from the unaffected side can be rotated and placed over the advanced supraorbital bar, and the affected frontal bone, after the affected coronal suture is removed, is placed on the other, unaffected side. The previously-removed bone can be used to fill defects. The bone flaps are secured in place using rigid absorbable fixation (Figs. 18.39, 18.40, 18.41, and 18.42).

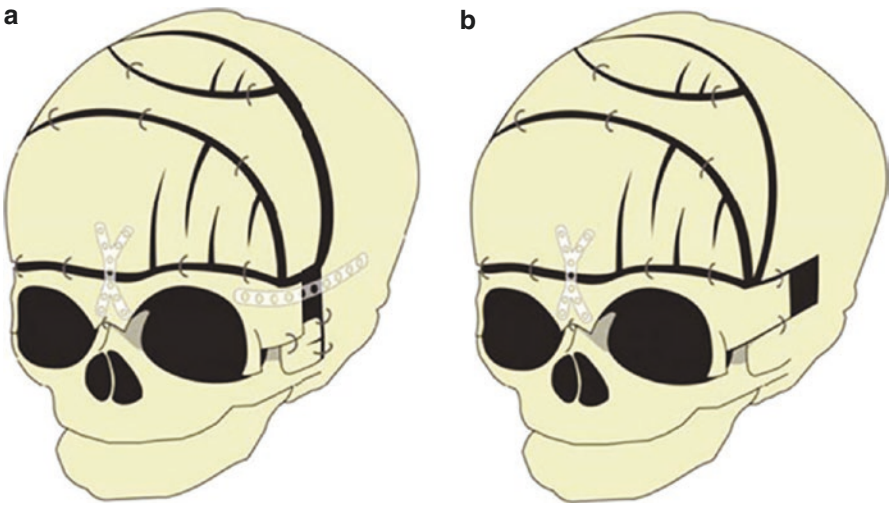


Fig. 18.39 Drawing of left coronal synostosis corrected by FOA. (**a**) Final construct with stabilization of the frontal–orbital bar with plate and remodeling of the temporal bossing. (**b**) Final construct with "tongue-in-groove" technique (Matushita, H., Alonso, N., Cardeal, D.D. et al. Frontal–orbital advancement for the management of anterior plagiocephaly. *Childs Nerv Syst* 28, 1423–1427 (2012). https://doi.org/10.1007/s00381-012-1765-1)

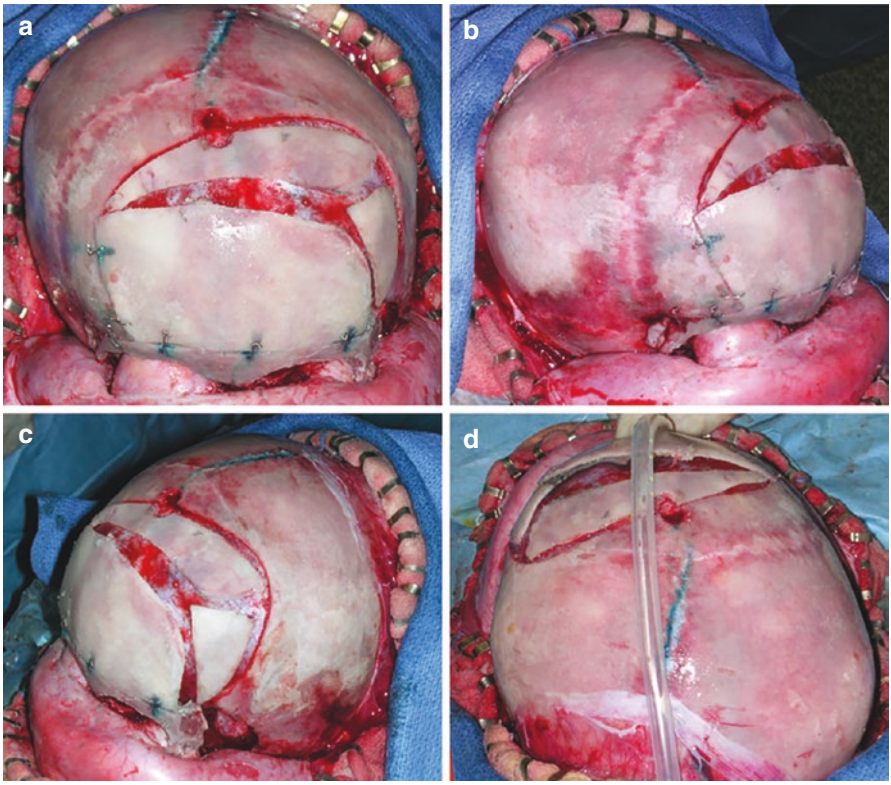


Fig. 18.40 Reconstruction: intra-operative views (Pellerin, P., Calibre, C., Vinchon, M. et al. Unicoronal synostotic plagiocephaly: surgical correction: Lille's technique. *Childs Nerv Syst* 28, 1433–1438 (2012). https://doi.org/10.1007/s00381-012-1793-x)

The nasal radix is usually not addressed because it is expected to correct on itself with subsequent growth in most patients [116]. Nasal osteotomy has been shown to improve the short-term results [119] (Fig. 18.43).

It is essential to prevent an hour-glass deformity of the clavaria from forming. For this purpose, the temporalis muscle should be advanced and then reattached using absorbable sutures.

Symmetry and satisfactory reconstruction are checked and confirmed as the scalp flap is reflected backwards. Before closure, extensive irrigation should be used to wash off debris such as bone parts or bone dust.

Closure

The bicoronal skin flap is closed in a standard fashion. The galea aponeurotica is approximated/closed using buried absorbable sutures, and the skin is closed according to surgeons' preferences: nonresorbable sutures can be used, or

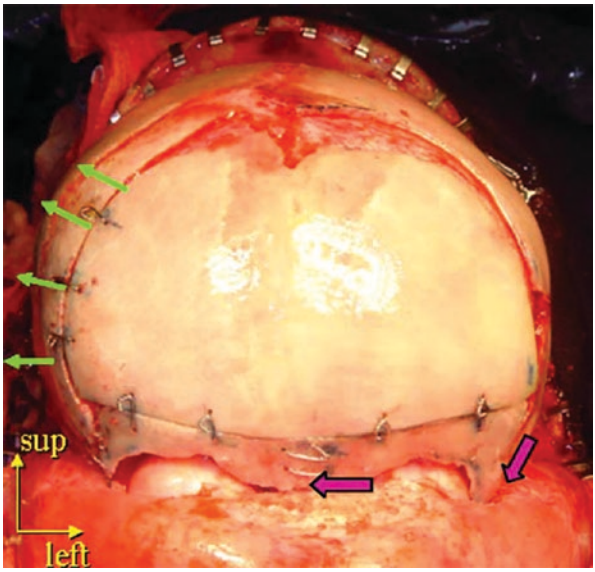


Fig. 18.41 Operative antero-posterior view. The orbital ridge is advanced and translated as measured on the preoperative 3D model. It is repositioned in a semirigid construct fixed on the nonsynostotic side and to the nasal bones with wires. The forehead is then fixed in position with wires that exert a dynamic strain, reshaping the orbital bar. The fixations on the nonsynostotic side are the hinge of this asymmetrical floating forehead (Vinchon, M., Pellerin, P., Pertuzon, B. et al. Vestibular orientation for craniofacial surgery: application to the management of unicoronal synostosis. *Childs Nerv Syst* 23, 1403–1409 (2007). https://doi.org/10.1007/s00381-007-0471-x)

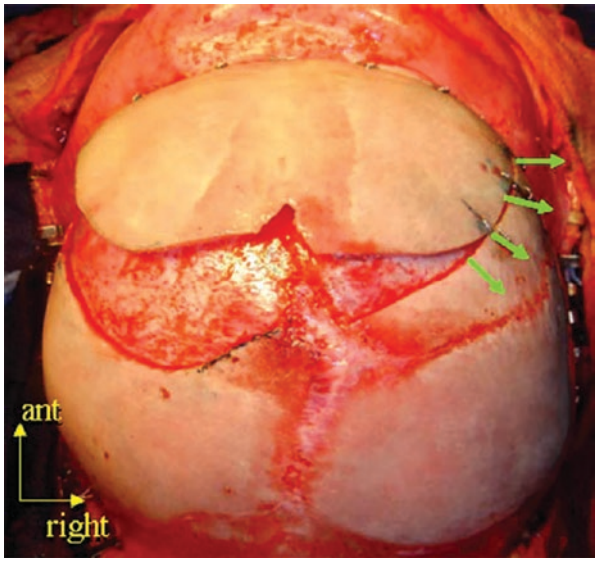


Fig. 18.42 Operative superior view showing the advancement of the forehead and orbital ridge. Note that the new forehead is perpendicular to the sagittal suture. The gaps in the skull vault are to be filled with bone chips (Vinchon, M., Pellerin, P., Pertuzon, B. et al. Vestibular orientation for craniofacial surgery: application to the management of unicoronal synostosis. *Childs Nerv Syst* 23, 1403–1409 (2007). https://doi.org/10.1007/s00381-007-0471-x)

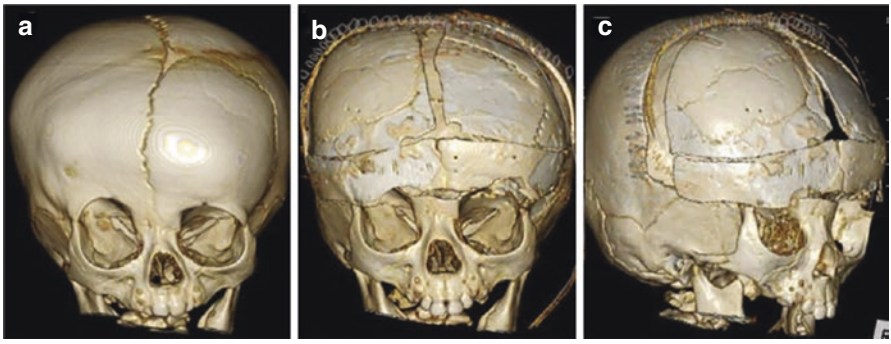


Fig. 18.43 Procedures of fronto-orbital advancement. (**a**) Preoperative 3D CT image showing early synostosis of the right coronal suture and compensatory growth of the contralateral forehead. (**b**, **c**) Postoperative 3D CT images showing the fronto-orbital bar, which is removed as a single piece and symmetrically reshaped by the remodeling using an absorbable plate and screw. The asymmetrical frontal bone flap is separated on the midline to exchange the flattened bone for the bossing bone, and each flap is rotated 120° and fixed to the fronto-orbital bar using absorbable devices (Oyoshi, T., Fujio, S., Bohara, M. et al. The assessment of relationship between the skull base development and the severity of frontal plagiocephaly after bilateral fronto-orbital advancement in the early life. *Childs Nerv Syst* 30, 155–159 (2014). https://doi.org/10.1007/s00381-013-2182-9)

absorbable sutures such as 4-0 monocryl or 5-0 fast absorbing plain gut. Use of a subgaleal drain is often avoided in order to preclude siphoning of CSF from potential microabrasions on the underlying dura during craniotomies. In the author's experience, subgaleal drains can occasionally be used, but they are not advised on a regular basis. In cases where no subgaleal drain is used, it is necessary to keep the head and the upper part of the body elevated. Periorbital and facial swelling is quite common on the first or second postoperative day, but it usually resolves spontaneously by the third or fourth postoperative day without additional complications. The final step of the intervention is sterile dressing of the wound. The wound is covered using sterile towels or gauze, the surrounding skin is cleaned with wet and dry towels, and an elastic tubular net bandage is placed over the head. Alternatively, a regular bandage can be used to create a nonconstricting Hippocratic cap.

Specific Instrumentation

Absorbable plates and screw systems are used for fixing, providing a rigid support for 3–6 months. Reabsorption time is estimated to be 9–15 months. Historically, titanium plates were used to ensure rigid fixing. Since permanent fixation hardware was shown to be subject to transcranial migration over time, it is no longer used in this patient population.

18.4.2.2 Postoperative Management

Postoperatively, the child is transferred to the intensive care unit, or the pediatric ICU if possible. If no problems are expected, the patient can be awakened and extubated immediately postoperatively. The child is positioned in bed on their back, with the head and torso elevated about 30° to prevent postoperative periorbital and facial swelling. Periorbital swelling usually develops on the first or second day postoperatively and resolves on itself by postoperative day 3–4. Vital signs are monitored and lab values are obtained about 4–6 h postoperatively. Blood transfusions are often needed, especially if hemoglobin is below 8 g/L. Hematocrit is maintained above 20. Analgesia is essential for keeping the child calm and comfortable. One of the most common issues encountered postoperatively is fever, but this is usually self-limiting [82]. After about 24 h, if no additional problems are encountered, the patient is transferred to the ward. The child is considered stable for discharge when a regular diet is established and the facial swelling has started to resolve enough for the child to open its eyes. A follow-up visit is arranged no longer than 1 week after discharge. It is a good practice to perform a postoperative CT scan before discharging the patient. The scan is used to document the reconstruction and to confirm the advancement and symmetry.

Since absorbable plate and screw systems were first used there have been reports of painless scalp swelling about 9–15 months postoperatively. This is thought to be associated with the period of plate resorption and can occur in up to 25% of cases when absorbable plate and screw systems are used [83]. The parents should be advised not to be alarmed by this occurrence.

18.4.2.3 Complications

One of the most common complications of a unicoronal synostosis reconstructive operation is failure of the first operation [96, 97, 110, 111, 116, 120, 121]. The reported re-operation rates for this condition are 3.1–29% [96, 97, 110, 111, 116, 122]. Sleber et al. concluded that patients with unicoronal synostosis treated at an age of 6–12 months had a rate of secondary surgery of about 7%, statistically significantly less than for patients operated on when younger than six months or older than 12 months.

Most of the other perioperative complications related to unicoronal synostosis are the same as the complications for other types of craniosynostosis. In general, they can be divided into two main categories: intraoperative and postoperative. The postoperative complications can be further divided into early and late subcategories.

In the category of intraoperative complications, one of the most important is intraoperative blood loss followed by inadequate blood transfusion. Care must always be taken to achieve perfect and meticulous hemostasis. The superior sagittal

sinus can often be torn during the craniotomy or various intraoperative manipulations, and the resulting bleeding can have dramatic consequences, emphasizing the importance of repairing the tear, which should always be prompt. Another threatening complication of a sagittal sinus tear is air embolism. Doppler ultrasound and end-tidal volume spectrometry can detect an air embolism if it occurs. Immediate action should be taken, including placing the patient in Trendelenburg position and flooding the field with saline to prevent further intake of air into the circulation. Sealing the defect is, of course, a priority. Another intraoperative problem is dural tearing. If noticed or recognized, most such tears can be easily repaired by monofilament nonabsorbable sutures (4-0 prolene). However, unrecognized tears can cause persistent CSF leaks. Injury to the brain is also possible, although rare. Injury to the periorbita or tissues deeper to the periorbita is rare with experienced craniofacial teams.

As mentioned previously, the postoperative complications can be further divided into early and late subcategories, although a strict distinction cannot always be made. One of the most important early postoperative complications is unrecognized blood loss. It is a very preventable complication but has potentially devastating consequences, as infants are especially sensitive to blood loss and the resulting hypoxia. Simple blood work will reveal the problem, easily corrected by transfusion. Another early postoperative complication is the previously-discussed fever, which can occur at about day 3 or 4 postoperatively; it is rarely a cause for alarm because it is reactive and it should be expected. Facial and periorbital swelling is self-limiting and no cause for alarm, resolving spontaneously in about 3–4 days. Early postoperative infection can have devastating consequences if not addressed promptly, requiring prolonged use of antibiotics and significantly extended hospital stay. Infection rarely leads to ostheomyelitis, but this entails a high risk of loss of the bone flap.

Late postoperative complications are centered around poor cosmetic outcome, as discussed above, sometimes requiring re-operation. Other late postoperative complications include persisting cranial bone defects and hardware-related complications. Defects greater than 2cm will often persist and eventually require grafting. Hydroxyapatite paste can be used to fill defects larger than 1cm. In rare cases, abscesses form at the sites of hardware placement, which sometimes require exploration.

Outcome, Prognosis and Follow-up

Postoperative mortality rates are near 0% for unicoronal synostosis [96, 111, 122, 123]. In fact, most patients undergoing bilateral fronto-orbital advancement for unilateral coronal synostosis are expected to have significant improvement and excellent long-term outcome [124–126].

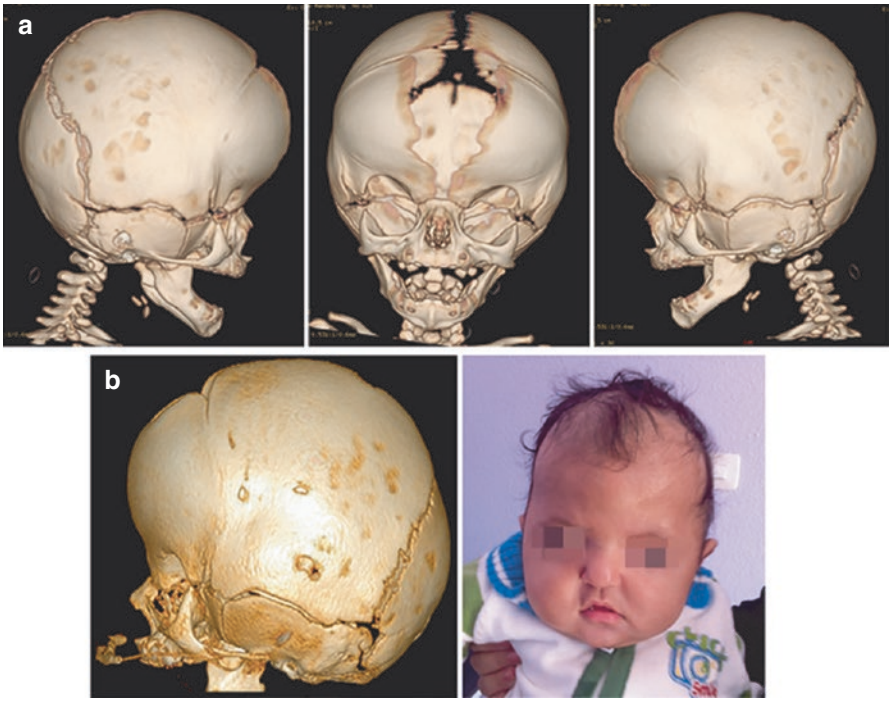
18.4.2.4 Bilateral Coronal Synostosis (Brachycephaly as Phenotypic Presentation)

General Considerationds (Diagnosis, Surgery)

The diagnosis, indications and timing for operative treatment of bilateral coronal synostosis are basically identical to those for unilateral synostosis of the coronal suture. Furthermore, the preoperative planing, surgical objectives, specific equipment and anesthetic considerations are entirely compatible with those for the unilateral form. The assumptions, principles and standards are common to both unilateral and bilateral synostoses of the coronal suture. Care must be taken in advance to consider a possibly greater blood loss and longer time for surgery in bilateral than unilateral craniosynostosis.

In general, surgery for bilateral synostosis of the coronal suture, emerging as the phenotypical presentation termed brachicephaly, by can be didactically classed into three groups depending on the age of the child undergoing the procedure.

Group I, children younger than 1 year of age
Group II, children older than 3 years of age
Group III, children between 1 and 3 years of age



Brachycephaly in a patient with Pfeiffer syndrome; (b) brachycephaly with coronal suture involvement in a patient with Apert syndrome (Hinojosa J. (2018) Syndromic Craniosynostosis. In: Di Rocco C., Pang D., Rutka J. (eds) Textbook of Pediatric Neurosurgery. Springer, Cham)

Children younger than 1 year. Surgical treatment for bilateral coronal synostosis reconstruction can be quite challenging because the resulting changes are distributed in the posterior and the anterior skull. The surgical approach in bicoronal synostosis reconstruction can be a single or a two-stage operation. The two-stage approach should be selected in supine and thereafter in prone position if the patient has an associated Arnold-Chiari malformation and instability of the cervical spine. The problem with the bilateral deformity as seen in bilateral coronal synostosis seems to arise from the configuration of the brachycephaly, but also the height of the skull and the malposition of the superior and lateral orbital rims. The objectives of the reconstruction are based on advancement of the supraorbital bar and expansion of the cranial base region, ensuring a reduced skull height (Fig. above). The patient is placed in the sphinx position, a modified prone position. Adequate padding should be ensured. The modified prone position has been proved optimal for better simultaneous exposure of anterior and posterior parts of the skull, but only after craniovertebral abnormalities are excluded. The skin incision follows the coronal pathway, usually in front of both tragi, and anterior and posterior supraperiosteal dissection follows. The anterior limit is the lateral portion of the orbital rims at the level of the fronto-zygomatic suture bilaterally, and the posterior limit goes to the foramen magnum. After a supraperiosteal elevation of the skin flap, the calvaria should be properly exposed (Fig. 18.44).

The deconstructive phase begins with creation of the bone flaps. In bicoronal synostosis reconstruction, two bone flaps are created, frontal and parieto-occipital. Additionally, a smaller, biparietal bone flap can be created containing the anterior fontanelle and, posteriorly, a strip of the paramedial part of the parietal bone. The creation of the biparietal bone flap is expected to ensure protection of the superior sagittal sinus and safety during the craniotomies. First, several burr holes are strategically created to facilitate creation of the flaps. The first is usually placed on the pterion, bilaterally; also parasagitally in the parietal bone on both sides of the calvarial projection of the superior sagittal sinus, just posterior to the coronal suture. Additional burr holes are created adjacent to the projection of the sagittal and transverse sinuses in order to outline the planned creation of the bone flaps. Using a footplate, the parieto-occipital bone flap is created and then the frontal one. The two bone flaps are elevated, leaving the bone over the vertex of the skull and two lateral struts of bone extending from the vertex to the base of the skull. Since the bone flaps are elevated, epidural dissection can be performed below the level of the transverse sinus to ensure a safe outfracture of the occipital bone. Barrel-stave osteotomies are performed in the occipital region, individual bone segments being fractured posteriorly to increase the potential space in the posterior skull. Also, these radial osteotomies are longer than those placed laterally to promote elongation of the skull along the antero-posterior axis. This new expansion of the cranial space is expected to allow the brain to accomodate to the new space distribution owing to gravity. The superior orbital rims are elevated bilaterally to the level of the fronto-zygomatic suture, contoured and fixed in the advanced position. The squamous portion of the temporal bone is elevated with the overlying temporal muscle and advanced and attached to the superior orbital rims (Figs. 18.45 and 18.46).

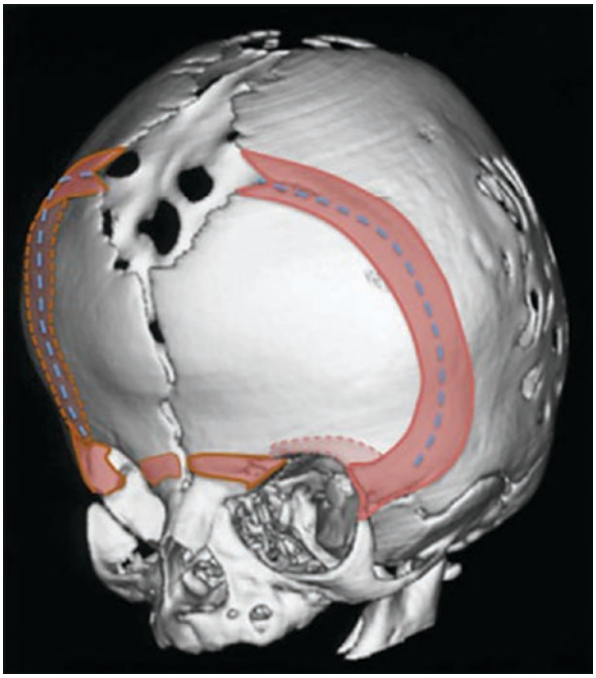


Fig. 18.44 Perifrontal craniectomy. This technique is used in newborns requiring emergency decompression. The craniectomy (brown shading) removes the coronal suture down to the fronto-malar suture, the roof of the orbit behind the orbital rim, and extends to the fronto-nasal suture. The frontal bone is thus set free and allows the growing brain to remodel the skull. In addition, coagulation is applied to the dura mater along the site of the coronal suture (blue dotted line) in order to prevent early reossification (Vinchon, M., Pellerin, P., Baroncini, M. et al. Non-syndromic oxycephaly and brachycephaly: a review. *Childs Nerv Syst* 28, 1439–1446 (2012). https://doi.org/10.1007/s00381-012-1800-2)

On the other hand, by leaving the temporal bone in place, the overall lateral stability of the skull is increased. The abnormally elevated and thick greater wing of the sphenoid bone is removed and remodeled using a rounger. An ICP monitor should be placed in the right parietal bone, off the midline. The struts extending from the vertex of the skull in the parietal region to the basal temporal region are divided, shifted posteriorly and reduced in height (usually 1–1.5 cm) to change the position of the vertex of the skull, flatten the frontal contour and reduce skull height. Height reduction corrects the abnormal turret shape of the skull and encourages the brain and dura to shift to fill the space created in the occiput. This technique elongates the anterioposterior axis of the skull. The height is reduced slowly by monitoring the ICP under normotension and normocapnia. The ICP should only be increased for brief periods, followed by rapid reduction to normal tension as the skull height is reduced. The bifrontal bone graft undergoes radial osteotomies, reshaping as desired and attached to the superior orbital rim but not the anterior parietal region. A neocoronal suture bone defect approximately 1cm wide is created at the site of

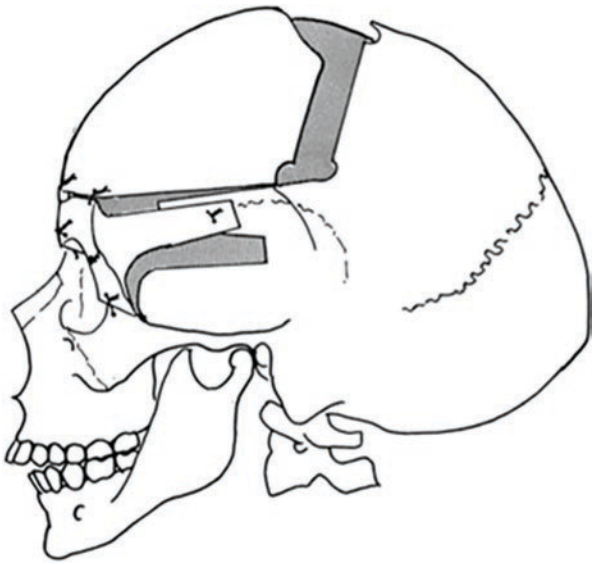


Fig. 18.45 Fronto-orbital advancement and remodeling with kyphosis of the bandeau. Sketch of the standard construct for fronto-orbital advancement in our craniofacial unit (art by P Pellerin). The bandeau is cut along a two-tongue osteotomy in the temporal region then advanced and kyphosed, with overlap of the tongues, secured by wire sutures. This allows a precise advancement and a stable construct to be achieved, able to withstand the pressure of the soft tissues during closure (Vinchon, M., Pellerin, P., Baroncini, M. et al. Non-syndromic oxycephaly and brachycephaly: a review. *Childs Nerv Syst* 28, 1439–1446 (2012). https://doi.org/10.1007/s00381-012-1800-2)

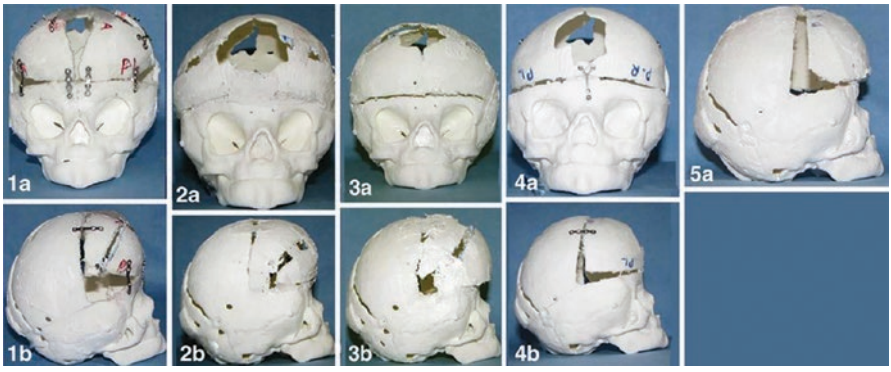


Fig. 18.46 **1a**, **b**: Multiple osteotomy technique in brachycephaly in anteroposterior (**a**) and sagittal view (**b**); **2a, b**: fronto-orbital advancement technique with 180° rotation of fronto-parietal flap with horizontal osteotomy and angling in anteroposterior (**a**) and sagittal (**b**) view; **3**: fronto-orbital advancement technique with only horizontal osteotomy and angling in anteroposterior (**a**) and sagittal (**b**) view; **4**: only rotation technique in anteroposterior (**a**) and sagittal view (**b**); **5a**: only advancement technique (Emmez, H., Küçüködük, İ., Börcek, A.Ö. et al. Effectiveness of skull models and surgical simulation: comparison of outcome between different surgical techniques in patients with isolated brachycephaly. *Childs Nerv Syst* 25, 1605 (2009). https://doi.org/10.1007/s00381-009-0939-y)

the normal coronal suture. The posterior occipital bone is reshaped to achieve greater convexity. A defect of approximately 1cm is created between the reshaped bone graft and the surrounding bone to allow the parieto-occipital region to expand preferentially.

Once the remodeling is complete, the bone fragments are placed in the desired position and fixed to the advanced supraorbital unit, and also to the radially cut temporal bone laterally and the outfractured occipital bone posteriorly. If they are removed separately, the vertex of the infant is loosly reattached to the top of the skull using resorbable sutures to the adjoining bone fragments.

Children older than 3 years. As in the previous technique, a zigzag coronal incision and supraperiosteal dissection of the flap are performed, elevating the bifrontal and parietal occipital bone craniotomies; barrel-stave osteotomies are performed in the occipital region. The orbital rims are elevated and advanced as a unit extending into the frontal process of the zygoma. The squamous temporal bone and temporalis muscle are elevated as a composite and advanced to attach to the posterior border of the advanced orbital rim. Skull height is again reduced and ICP should be monitored as well. However, patients older than 3 years can need much longer periods of accommodation than the younger child, and ordinarily, less reduction is achieved. Correction of more than 1cm is unusual in a child older than three, whereas 1.0–1.5 cm correction is quite common in a child younger than one. The bifrontal and parietal occipital bone grafts are then remodeled by dividing the bone segments into vertical slats weakened on the endocranial surface by kerfs (channels) and then reshaped with bone-molding instruments and microfractures. Individual bone slats are reapproximated frontally to the superior orbital rim and proceed posteriorly to the occiput (Fig. 18.47 and 18.48).

The weak moment, a disadvantage of bicoronal synostosis reconstruction, leaves the defect created superolaterally of the supraorbital rim, elongating posteriorly through the lateral wall of the orbit towards the major wing of the sphenoid and inferiolateraly to the skull base. In addition, the temporalis muscle can atrophy, contributing to a resulting "hourglass" configuration of the skull postoperatively.

Authors with different preferences respond to this moment with different techniques and strategies. As mentioned earlier, this problem can be addressed by elevating the temporal squama with the temporalis muscle as a composite, transposed and fixed to the superolateral portion/margin of the advanced supraorbital bar.

In contrast, some authors prefer not to compromise the stability of the skull by elevating the temporal squama, but to detach and split the anterior portion of the temporalis muscle and reattach it at the superolaterally advanced orbital rim.

In our opinion, this technique, although sufficient in general, can still create a certain bone defect bilaterally, which together with possible long-term atrophy of the temporal muscle can lead to an hourglass skull shape. This can necessitate additional reconstructive surgery, most likely involving autologous bone implants.

Children between one and 3 years of age. Just as the previously explained procedures are similar, so are the principles for cranial vault reconstructions in bilateral coronal synostosis. The difference must be stressed: the maturity of the bones of the skull requires careful choices of techniques for bone cutting, molding and reshaping (Figs. 18.49 and 18.50).

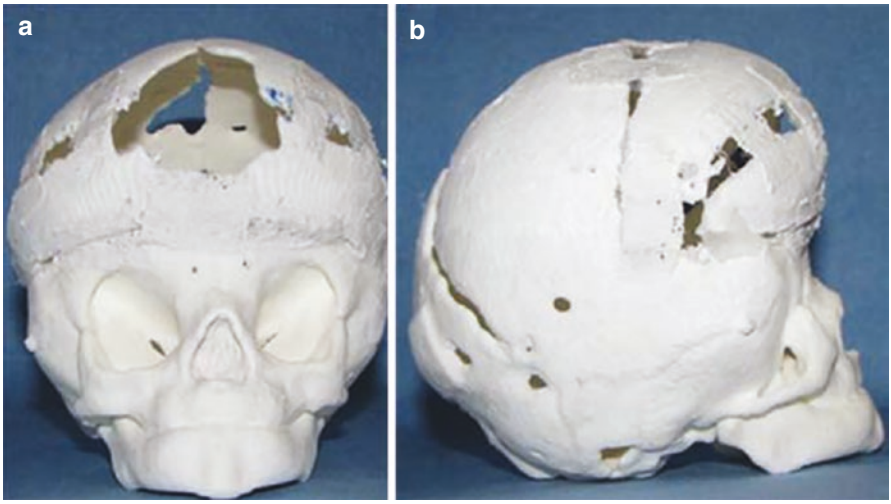


Fig. 18.47 (**a**, **b**) Fronto-orbital advancement model with 180° rotation of fronto-parietal flap with horizontal osteotomy and angling (Emmez, H., Küçüködük, İ., Börcek, A.Ö. et al. Effectiveness of skull models and surgical simulation: comparison of outcome between different surgical techniques in patients with isolated brachycephaly. *Childs Nerv Syst* 25, 1605 (2009). https://doi.org/10.1007/s00381-009-0939-y)

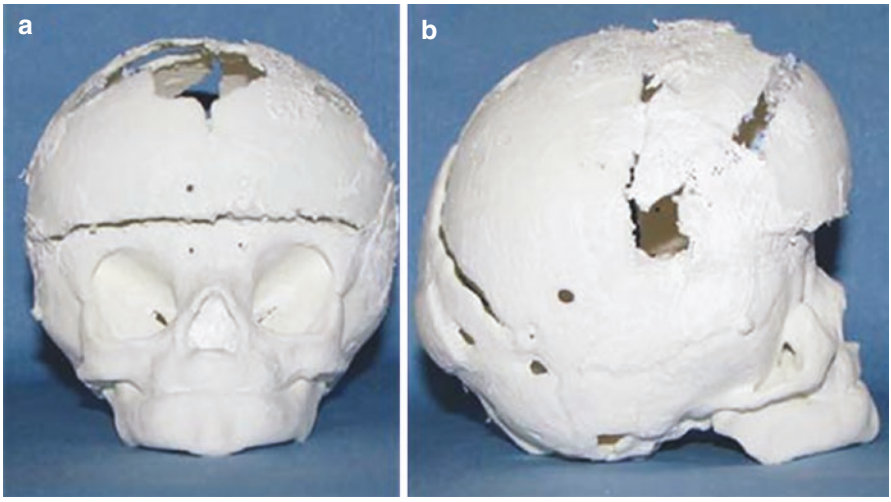


Fig. 18.48 (**a**, **b**) Fronto-orbital advancement model with only horizontal osteotomy and angling (Emmez, H., Küçüködük, İ., Börcek, A.Ö. et al. Effectiveness of skull models and surgical simulation: comparison of outcome between different surgical techniques in patients with isolated brachycephaly. *Childs Nerv Syst* 25, 1605 (2009). https://doi.org/10.1007/s00381-009-0939-y)

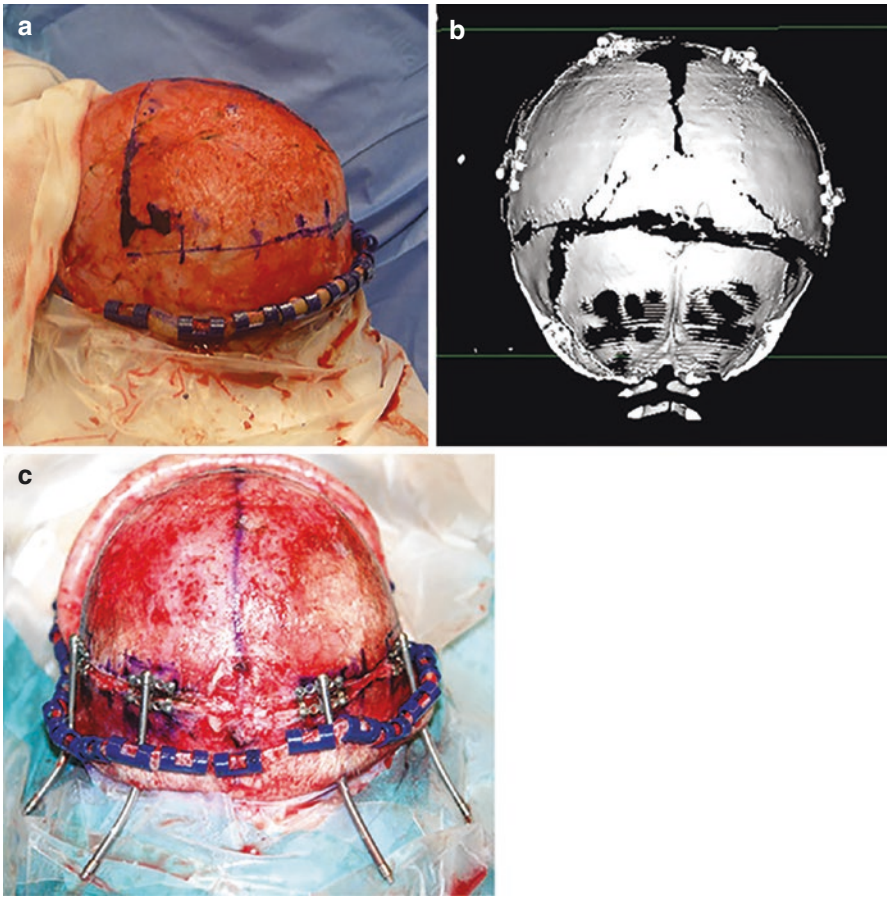


Fig. 18.49 Posterior cranial vault expansion with two pairs of distractors. **a** Vertical craniotomy from vertex and horizontal craniotomy above the torcula; **b** 3D CT inside posterior calvaria depicting horizontal craniotomy just above the confluence of sinuses; **c** two pairs of distracters placed with horizontal and parallel vectors (Saiepour, D., Nilsson, P., Leikola, J. et al. Posterior cranial distraction in the treatment of craniosynostosis—effects on intracranial volume. *Eur J Plast Surg* 36, 679–684 (2013). https://doi.org/10.1007/s00238-013-0874-8)

Distraction Osteogenesis in Bicoronal Synostosis

Closure

The bicoronal skin flap is closed in a standard fashion. The galea aponeurotica is approximated/closed using buried absorbable sutures, and the skin is closed according to surgeons' preferences; nonresorbable sutures can be used, or absorbable sutures such as 4-0 monocryl or 5-0 fast absorbing plain gut. Use of a subgaleal

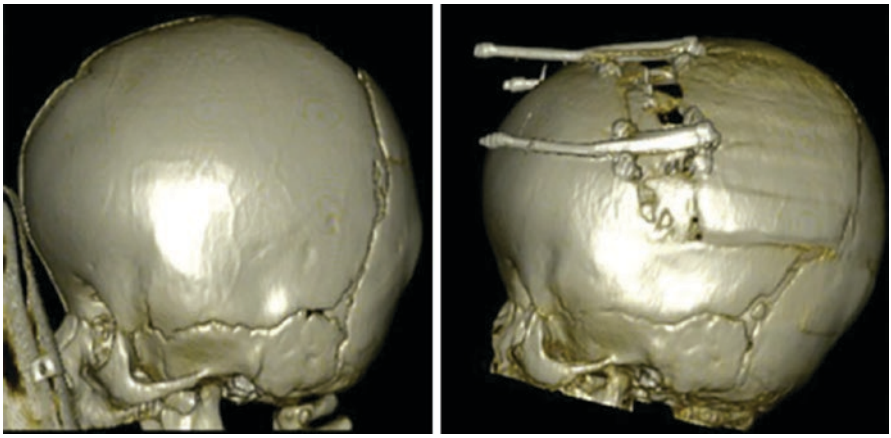


Fig. 18.50 Pre- and post-op 3D CT in sagittal view NSBC (nonsyndromic bicoronal craniosynostosis) (Saiepour, D., Nilsson, P., Leikola, J. et al. Posterior cranial distraction in the treatment of craniosynostosis—effects on intracranial volume. *Eur J Plast Surg* 36, 679–684 (2013). https://doi.org/10.1007/s00238-013-0874-8)

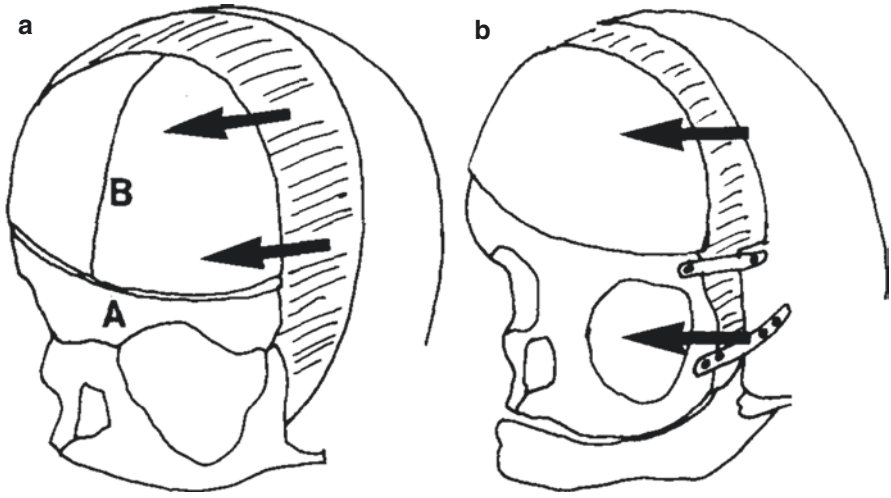


Fig. 18.51 Diagramatic representation of floating face procedure and monoblock advancement: (**a**) Floating forehead, A-supraorbital bar, B-frontal bone, (**b**) infant monoblock frontofacial advancement (Cremin, B.J., Zeeman, B.J. Three dimensional reconstruction in coronal synostosis: pre and post operative appearances. *Pediatr Radiol* **19,** 313–315 (1989). https://doi.org/10.1007/BF02467301)

drain is often avoided so that CSF is not siphoned from potential microabrasions in the underlying dura during craniotomies. In the author's experience, subgaleal drains can occasionally be used, although they are not advised on regular basis.

When no subgaleal drain is used, it is necessary to elevate the head and the upper part of the body. Periorbital and facial swelling is quite common on the first or second postoperative day, but usually resolves spontaneously by the third or fourth postoperative day without additional complications. The final step of the intervention is sterile dressing of the wound. The wound is covered using sterile towels or gauze, the surrounding skin is cleaned with wet and dry towels, and an elastic tubular net bandage is placed over the head. Alternatively, a regular bandage can be used to create a nonconstricting Hippocratic cap.

Specific Instrumentation

Absorbable plates and screw systems are used to provide a rigid support for 3–6 months. The reabsorption time is estimated to be 9–15 months. Historically, titanium plates were used, but since such permanent fixation hardware was shown to be subject to transcranial migration over time, it is no longer used in this patient population.

Postoperative Management

Postoperatively, the child is transferred to the intensive care unit, or the pediatric ICU if possible. If no problems are expected, the patient can be awakened and extubated immediately postop. The child is positioned in bed on their back with the head and torso elevated about 30° to prevent postoperative periorbital and facial swelling. Periorbital swelling usually develops on the first or second day postop and resolves by postop day 3–4. Vital signs are monitored and lab values are obtained about 4–6 h postop. Blood transfusions are often needed, especially if hemoglobin is below 8 g/L. Hematocrit is maintained above 20. Analgesia is essential for keeping the child calm and comfortable. One of the most common issues encountered postoperatively is fever, which is usually self-limiting [82]. After about 24 h, if no additional problems are encountered, the child is transferred to the ward. The child is considered stable for discharge when a regular diet has been established and the facial swelling is sufficiently resolved for the child to be able to open its eyes. A follow-up visit is arranged no longer than 1 week after discharge. It is good practice to perform a postoperative CT scan before discharging the patient. The scan is used to document the reconstruction and to confirm the advancement and symmetry.

Since absorbable plate and screw systems were first used, there have been reports of painless scalp swelling about 9–15 months postoperatively. This is thought to be associated with the period of plate resorption and can occur in up to 25% of cases when absorbable plate and screw systems are used [83]. The parents should be advised not to be alarmed by this occurrence.

Complications

The reported complication rate for bicoronal synostosis ranges from 20% to 50% [116, 120–123].

The perioperative complications of bicoronal synostosis are the same as those for other types of craniosynostosis. In general, the complications can be divided into two main categories: intraoperative and postoperative. The postoperative complications can further be divided into early and late subcategories.

In the intraoperative complications category, one of the most important is intraoperative blood loss followed by inadequate blood transfusion. Care must always be taken to achieve perfect and meticulous hemostasis. Superior sagittal sinus tears often happen during the craniotomy or various intraoperative manipulations, and the resulting bleeding can have dramatic consequences, emphasizing the importance of repairing the tear, which should always be prompt. Another threatening complication of sagittal sinus tears is air embolism. Doppler ultrasound and end-tidal volume spectrometery can detect an air embolism if it occurs. Immediate action should be taken, including placing the patient in a Trendelenburg position and flooding the field with saline to prevent further intake of air into the circulation. Sealing the defect is, of course, a priority. Another intraoperative problem is dural tearing. If noticed, or recognized, most such tears can easily be repaired using monofilament nonabsorbable suture (4-0 prolene). On the other hand, unrecognized tears can cause persistent CSF leaks. Injury to the brain is also possible, although rare. Injury to the periorbita, or tissues deeper to the periorbita, is rare with experienced craniofacial teams.

The postoperative complications, as mentioned previously, can be further divided into early and late subcategories, although a strict distinction cannot always be made. One of the most important early postoperative complications is unrecognized blood loss. It is an easily preventable complication but has potentially devastating consequences, as infants are especially sensitive to blood loss and the resulting hypoxia. Simple blood work reveals the problem, easily corrected by transfusion. Another possible early postoperative complication is the previously-discussed fever, occurring at about day 3–4 postop. It is rarely a cause for alarm, being reactive, and it should be expected. Facial and periorbital swelling is self-limiting and no cause for alarm, resolving spontaneously in about 3–4 days. Early postoperative infection can have devastating consequences if not addressed in time, requiring prolonged use of antibiotics and significantly extended hospital stay. Rarely, infection can lead to ostiomyelitis, which entails a high risk of loss of the bone flap.

Late postoperative complications are centered around poor cosmetic outcome, as discussed above, sometimes requiring re-operation. Other late postoperative complications include infection, sometimes endangering the bone flaps.

Outcome, Prognosis and Follow-up

The outcome of open reconstruction of bicoronal synostosis has been evaluated in numerous studies [96, 97, 110, 111, 116, 120, 121]. Reported re-operation rates for bicoronal synostosis range from 20% to 50% (p. 165, Principles of Neurological Surgery 4e, refs. 115, 116, 118, 127, 128). Postoperative mortality rates for bicoronal synostosis range from zero to 10% [97, 116, 120, 122, 123]. Despite initial improvement after the reconstruction, re-operations are often needed, probably because of frequent syndromic association [129–131]. Because ICP can be raised, these patients should be closely monitored (Fig. 18.52).

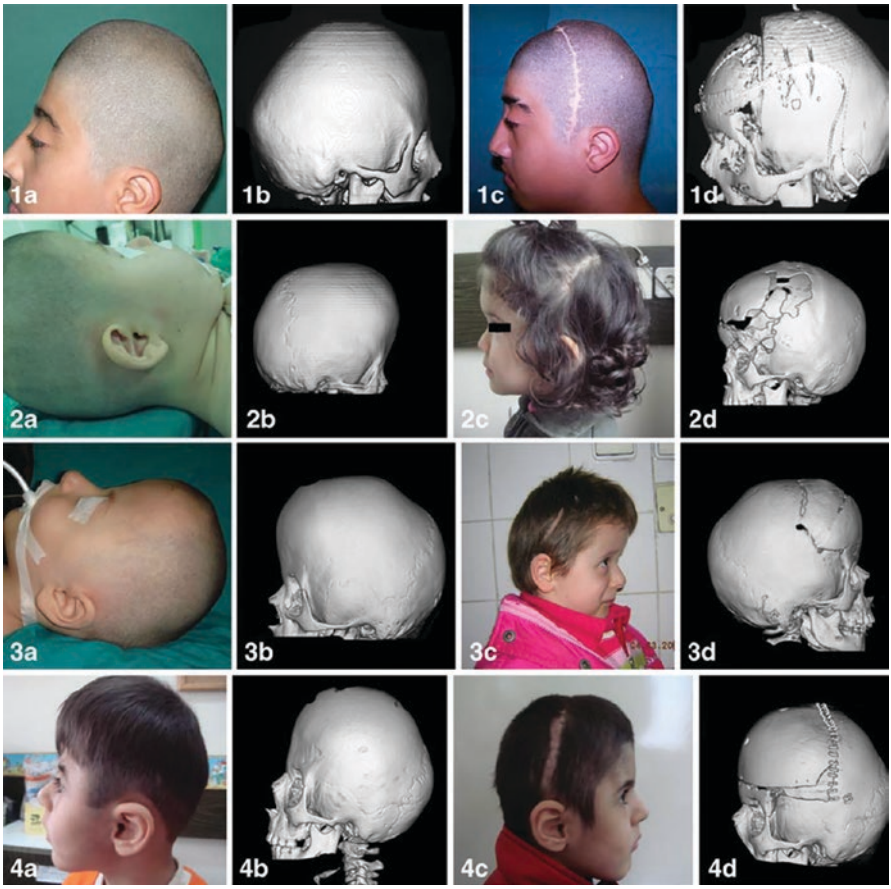


Fig. 18.52 Photograph showing four patients and their 3D CT preoperatively and postoperatively (1**a**–1**d**, 2**a**–2**d**, 3**a**–3**d**, 4**a**–4**d**) (Emmez, H., Küçüködük, İ., Börcek, A.Ö. et al. Effectiveness of skull models and surgical simulation: comparison of outcome between different surgical techniques in patients with isolated brachycephaly. *Childs Nerv Syst* 25, 1605 (2009). https://doi.org/10.1007/s00381-009-0939-y)

18.4.3 Sagittal Synostosis (Dolichocephaly, Scaphocephaly as Phenotypic Presentation)

Premature fusion of the sagittal suture is referred to as dolichocephaly or scaphocephaly. It is considered one of the most common types of craniosynostosis, accounting for 50–60% of all nonsyndromic craniosynostoses, and is found in about one in 2000 births. About 80% of sagittal synostoses are sporadic, and the male to female ratio is estimated at 3:1–4:1 [132].

The shape of the skull in sagittal synostosis is characterized by ridging of the fused sagittal suture, bitemporal narrowing, and frontal and/or occipital bossing, sometimes associated with premature or delayed closure of the anterior fontanel. The deformity can differ depending on the location of the involvement along the sagittal suture and also the timing of closure. There is frontal bossing if the sagittal suture closes anteriorly, and posterior bossing will prevail if the fusion is posterior. In general, there are three types of sagittal synostosis: anterior compensation, posterior compensation, and bathyrocephalic deformity. In most cases the orbits and the midface are spared. If both fontanels are closed, the posterior part of the sagittal suture is predominantly affected, resulting in occipital bossing. This condition is usually accompanied by a thin forehead with severe pterional indentation, referred to as leptoscaphocephaly. The most severe form of this scaphocephaly is named bathrocephaly, where the head adopts a saddle shape (Figs. 18.53, 18.54, and 18.55).

It is considered that most patients with sagittal synostosis do not have elevated ICP. The incidence of elevated ICP is reported to be 13.8–25%. It is noteworthy that the degree of deformity seems unrelated to the risk for increased ICP. Sagittal synostosis is associated with language and learning difficulties, more so in children older than 1 year at the time of the operation than in those undergoing surgery when

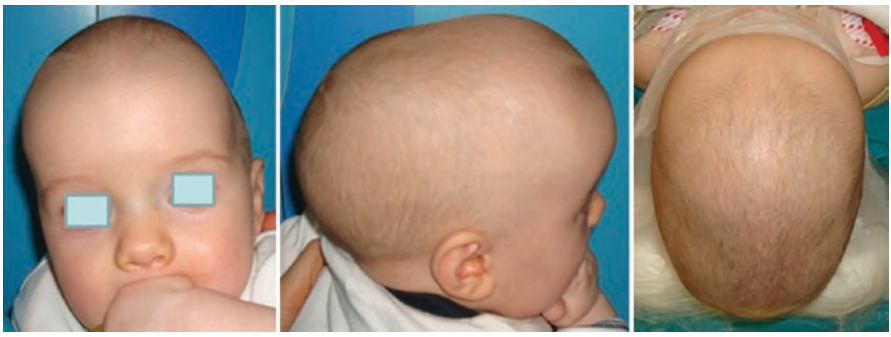


Fig. 18.53 Anterior scaphocephaly: frontal bossing and retrocoronal band are evident in spite of a grossly normal occipital region. The scalp veins are clearly visible (Massimi, L., Caldarelli, M., Tamburrini, G. et al. Isolated sagittal craniosynostosis: definition, classification, and surgical indications. *Childs Nerv Syst* 28, 1311–1317 (2012). https://doi.org/10.1007/s00381-012-1834-5)

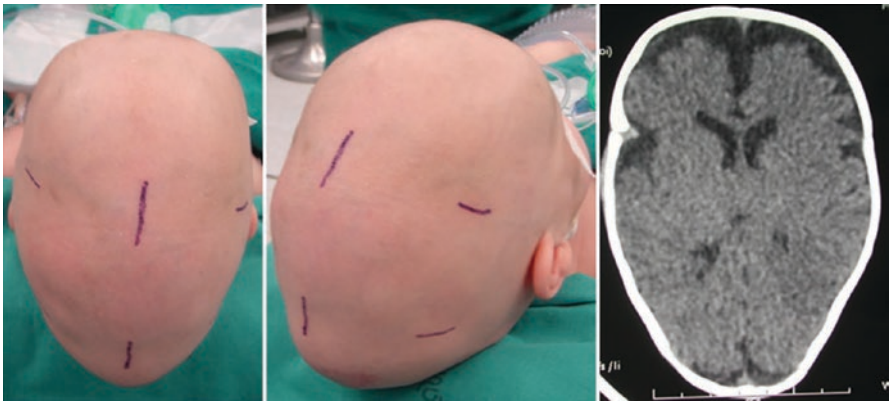


Fig. 18.54 Posterior scaphocephaly: prominent stenosis of the posterior third of the sagittal suture with occipital narrowing, confirmed by CT scan (note the compensatory frontal subarachnoid spaces) (Massimi, L., Caldarelli, M., Tamburrini, G. et al. Isolated sagittal craniosynostosis: definition, classification, and surgical indications. *Childs Nerv Syst* 28, 1311–1317 (2012). https://doi.org/10.1007/s00381-012-1834-5)

younger than 1 year. Becker et al. reported a 39% rate of speech, cognitive, and behavioral abnormalities in patients with sagittal synostosis, which appeared to be the lowest rate of neuropsychological morbidity for single-suture synostoses [23].

18.4.3.1 Diagnosis, Indications and Timing for Operative Treatment

The diagnosis of scaphocephaly is primarly based on physical examination. A plain X-ray or a CT scan can be obtained to confirm the diagnosis. High quality X-rays can reveal fusion and/or ridging of the fused sutures and the coronal or lambdoid suture could be fused. The finding of digital markings on plain X-rays is a sign of elevated ICP. A more sensitive finding than digital markings is considered to be suture diastasis and sellar erosion. İn the author's experience, obtaining a head CT scan is strongly advisable, preferably high resolution with 3D reconstruction, especially if an operation is planned. The advantage of the head CT is that both the brain and the bony calvaria can be evaluated (Fig. 18.56). İn about 5% of patients with sagittal suture synostosis, unanticipated intracranial pathology is seen [133, 134], including hydrocephalus, corpus callosum agenesis, or focal cortical dysplasia. Obliterated basal cisterns and a pulsatile enlarged sella are diagnostic of elevated ICP. An MRI of the brain can be obtained if coexisting pathology is suspected.

As discussed previously for other types of craniosynostosis, the indications for surgical treatment of sagittal suture synostosis are similar. The main indication for operative reconstruction of sagittal synostosis is elevated ICP. Improving the overall appearance of the skull is also an important indication for treatment and should not be underestimated, since the shape of the skull correlates with brain development.

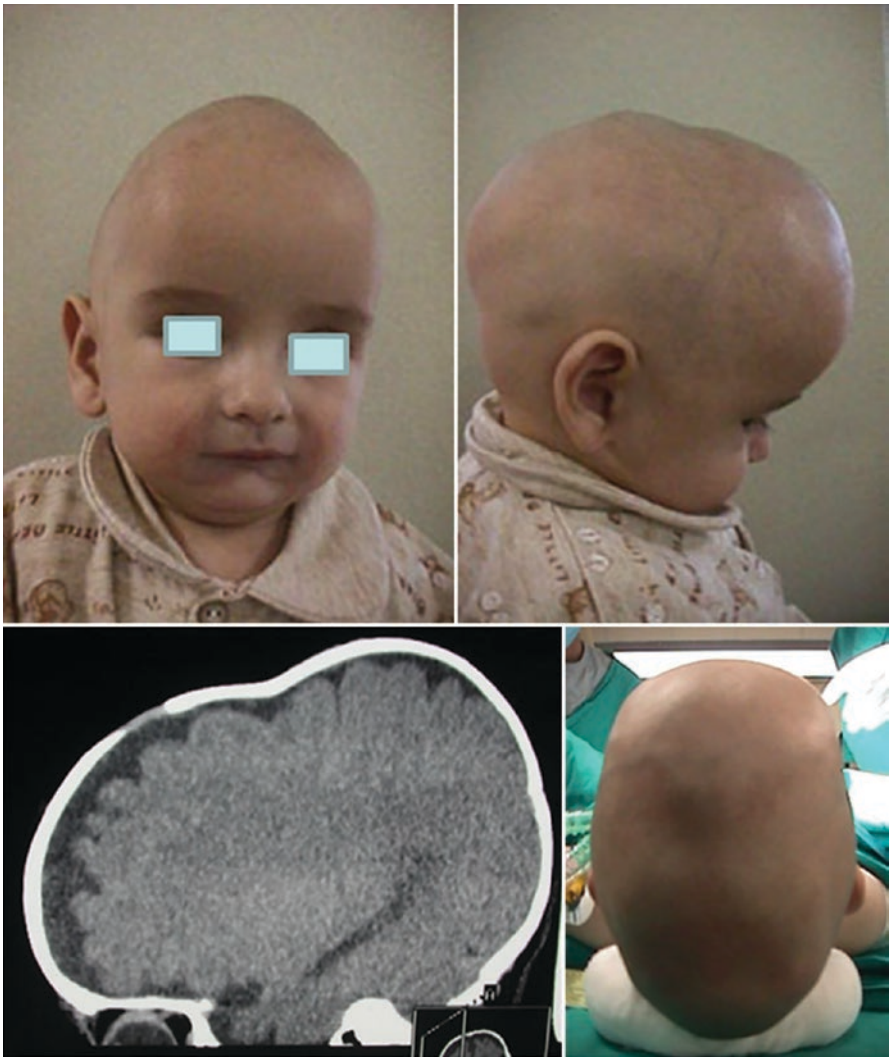


Fig. 18.55 Complete scaphocephaly: both frontal bossing and occipital narrowing are present, and there is as sellar deformation of the vertex owing to hyperostosis of the anterior and posterior thirds of the sagittal ridge. The sellar deformation can also be appreciated on CT scan (Massimi, L., Caldarelli, M., Tamburrini, G. et al. Isolated sagittal craniosynostosis: definition, classification, and surgical indications. *Childs Nerv Syst* 28, 1311–1317 (2012). https://doi.org/10.1007/s00381-012-1834-5)

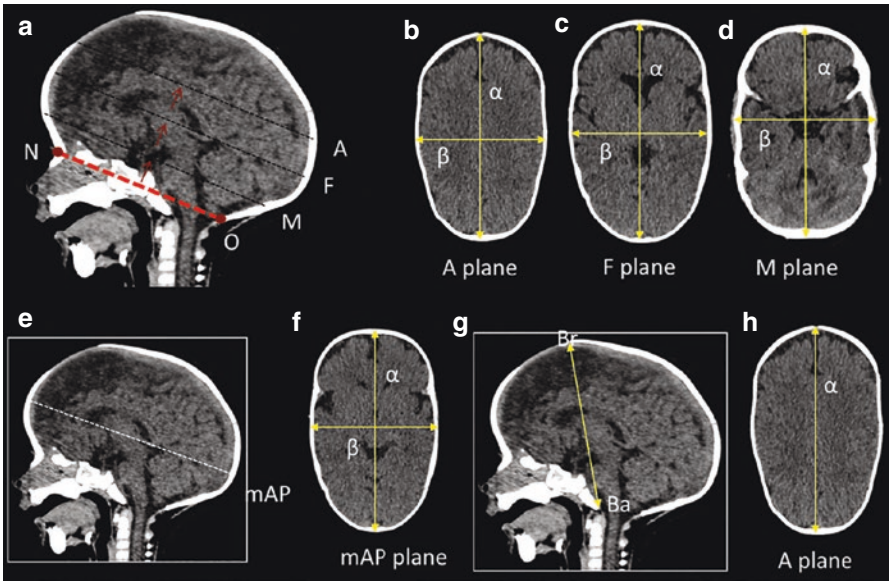


Fig. 18.56 Quantificatin of skull shape severity using traditional cephalic index (CI) and scaphocephaly severity indices (SSIs), in the A, F, and M planes, and vertico-longitudinal index (VLI). SSIs in the A, F, and M planes (**a**–**d**). With a lateral view of a 3D reformation of the skull, a skull base plane was determined using the frontal nasal suture anteriorly and the opisthion posteriorly (dotted red line in a). This plane was shifted superiorly until positioned (1) just above the top of the lateral ventricles (A plane in **a**), (2) at the foramina of Monroe (F plane in a), and (3) at the level of the maximum dimension of the fourth ventricle (M plane in a). Three ratios (cranial width/cranial length × 100) define SSI-A (**b**), SSI-F (**c**), and SSIM (**d**), respectively. Traditional CI (**e**, **f**) represents the ratio of maximum cranial width to maximum cranial length × 100. VLI in plane A (**g**, **h**) represents the ratio of cranial length to cranial height × 100. The cranial height represents the distance between the basion (Ba) and the bregma (Br) (Calandrelli, R., Pilato, F., Massimi, L. et al. The unseen third dimension: a novel approach for assessing head shape severity in infants with isolated sagittal synostosis. *Childs Nerv Syst* 35, 1351–1356 (2019). https://doi.org/10.1007/s00381019-04246-5)

Although still a subject of debate, the timing of surgery depends on the general health of the child and the presence of elevated ICP. Six months is considered a reasonable age for open cranial vault reconstruction in sagittal suture synostosis, since the child should have gained enough weight and be better able to tolerate blood loss, but also because the bones of the skull are malleable enough to make the reconstruction easy to perform. An important factor is that brain volume almost triples during the first year of life, so the growth and volume of the brain can be used to maintain skull shape following reconstruction.

In infants who appear to have an elevated ICP, surgical correction is performed as soon as possible.

18.4.3.2 Preoperative Planning, Surgical Objectives and Special Equipment

The preoperative preparations should involve routine blood tests including complete blood count, electrolyte panel, and partial thromboplastin time and prothrombin time. A blood type should be obtained since there is potential for significant blood loss. If the patient's parents are prepared to donate, they should be given the option to do so. The child along with its mother is admitted to the ward on the day of the surgery or the day before, and should be kept fasting for at least 4–6 h before the planned surgery.

The objectives of the surgical correction should be to achieve the best possible and most durable correction of deformity with a single operation, at the lowest possible risk for the patient. In this case, this means normalization of the skull shape by enlarging the biparietal diameters relative to the long axis of the head and ensuring normal cranial volume.

Equipment needed during these operations includes a Mayfield headring or horseshoe head holder, although the horseshoe could be more practical because of the specific position required for the body. Basic pediatric neurosurgical operative instruments are needed, and a high-speed drill or handheld Hudson brace with pediatric burrs. Different kinds of sutures should be available, but monofilament polypropylene sutures are recommended. Resorbable plates and screws can be used to stabilize bony fragments, though they are not always needed. Local anesthetic is encouraged (bupivacaine or lidocaine with epinephrine) for analgesia, reducing the need for additional dosing with intravenous analgesics and providing better control over intraoperative bleeding.

18.4.3.3 Anesthetic Considerations

One or two large bore intravenous lines ($\geq$20 gauge) are required in view of the potential blood loss during surgery. A urinary catheter is useful for recording urinary output. A thermistor is needed to record body temperature, and intraoperative body warmers are of course advised. Arterial and central venous lines allow for total body intravascular volume monitoring and postoperative fluid management.

Endotracheal intubation should be performed in standard manner, securing the tube according to local practice. Some authors advise circummandibular or circumdental fixing. In our practice, oily eye drops (Vit A and Vit D) and hydrophobic tape over the child's eyes suffices to protect the cornea.

Preoperative antibiotics are given before the skin incision (cefazoline 10–20 mg/kg as loading dose, 8mg/kg intravenosly every 8 h for 48 h) as per local practice.

The author's preference is total removal of hair using hair clippers. Total hair clipping is also expected to facilitate skin closure and postoperative wound care.

18.4.3.4 Operative Procedure

Positioning

Positioning should be as simple as possible. The prone position is most often used (Fig. 18.57), or a modification thereof called the "sphinx" position. The supine or lateral position can be used depending on the specific deformity. Those positions are more desirable from an anesthetic point of view because they are simple. The sphinx position is used in cases with significant occipital but also frontal bossing. It provides good exposure of the frontal bones down to the supraorbital rims, and of the occipital bones. Padding on pressure points is crucial in the prone position.

The supine position is used for predominant frontal bossing without significant occipital bossing.

Sterile Scrub, Draping and Local Anesthetic

The skin is prepped with povidone-iodine or other skin antiseptic as per local practice. Alternatively, 2% chlorhexidine gluconate can be used. Single-use drapes are preferred and advised. Any excess liquid is absorbed using sterile towels.

For local analgesia and to minimize intraoperative bleeding, the following combinations can be used: 0.5% lidocaine and 1:400.000 parts epinephrine, or 0.25% bupivacaine and 1:200.000 epinephrine, or 0.25% xylocaine and 1:400.000 adrenaline.

Skin Incision

Using a No. 15 scalpel, a wavy bicoronal incision is made well behind the hairline from behind one ear across to the opposite side, crossing the midline at the anterior third of the sagittal sinus. The scalp flap is elevated supraperiosteally anteriorly to

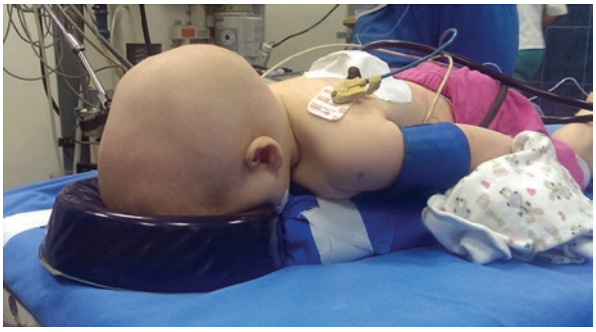


Fig. 18.57 The patient is set in prone position with slightly elevated and retroflexed head placed on a silicone headrest (Micovic, M., Zivkovic, B., Bascarevic, V. et al. Triple square extended osteotomies for treatment of scaphocephaly (Renier's "H" technique modification). *Neurosurg Rev* 39, 115–122 (2016). https://doi.org/10.1007/s10143-015-0661-z)

the level of the supraorbital rims, but it is not necessary to expose these. The posterior flap is deflected backwards supraperiosteally to expose the lambdoid suture. Bleeding from the skin flap is controlled by bipolar coagulation, but Raney clips can also be used. The temporalis fascia and muscles are dissected off their attachments during the subperiosteal dissection but are left attached to the scalp flap.

In open cranial vault reconstruction for sagittal synostosis it is important to expose the fused sagittal suture, coronal suture, lambdoid suture, and laterally the squamosal suture (Fig. 18.58).

Initial Deconstructive Phase

Many treatment options and surgical variants have been described for open cranial vault reconstruction for sagittal synostosis, but a step common to all of them is removal of the fused sagittal suture. In this chapter we will present a method of reconstruction that is optimal for most cases, along with variants considered by the author.

After the skin incision and elevation of the scalp flaps reveals the bony structure of the cranium, the bones and sutures are identified, and so is the anterior fontanel if still present. If the anterior fontanel remains open, the dura can be detached from the tabula interna using a dissector. If it is closed, burr holes can be made on either side of the sagittal suture, posterior to the bregma and anterior to the lambda. Subsequently, a biparietal bone flap with variable width is created containing the fused sagital suture. Using a craniotome, or different roungers, the coronal and lambdoid sutures are addressed. Parallel cuts are made at the level of those sutures and both are removed on both sides at a width of approximately 1–2 cm, depending

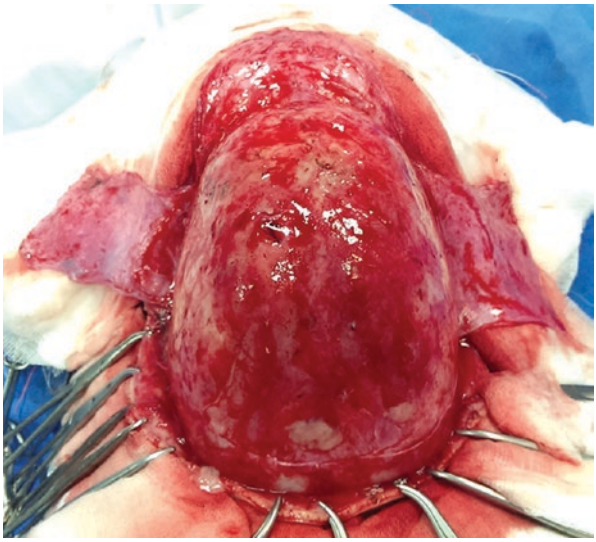


Fig. 18.58 The periosteal flap is stretched outside the operative field (Micovic, M., Zivkovic, B., Bascarevic, V. et al. Triple square extended osteotomies for treatment of scaphocephaly (Renier's "H" technique modification). *Neurosurg Rev* 39, 115–122 (2016). https://doi.org/10.1007/s10143-015-0661-z)

on the desired reduction in the antero-posterior direction. After the sagittal suturectomy (biparietal craniotomy) and the bilateral coronal and lambdoid suturectomy, the remaining two lateral temporo-parietal bone segments are reshaped using a series of barrel-stave-radial osteotomies and Tessier bone benders to adjust their position. The temporo-parietal bone segments are left attached inferiorly, but an outfracture should be performed to achieve the desired lateral widening. The previously-removed biparietal flap can be adjusted and tailored to act as a strut for maintaining the temporo-parietal bone segments at the level of the convexity, above the superior sagittal sinus.

If a dominant type of deformity persists, the procedure is tailored to address it. As previously mentioned, there are three types of sagittal synostosis (depending on the part of the sagittal suture that primarily fuses): anterior compensation, posterior compensation, and the bathyrocephalic deformity. In cases of anterior compensation there is bilateral frontal bossing. In milder cases, surgical removal of the fused suture followed by application of distraction devices can give a satisfactory result [135]. In more severe cases, more aggressive reshaping can be needed, such as removal of the frontal bone; radial barrel-stave osteotomies are performed, flattening the bone using bone benders, adjusting the position and fixing the bone to the adjoining bone (Figs. 18.59 and 18.60).

The posterior compensation type can be surgically addressed with a posteriorly-oriented modified π procedure consisting of occipital craniotomy, parietal craniotomies and removal of the lambdoid suture in order to allow forwards movement of the occiput (Fig. 18.61).

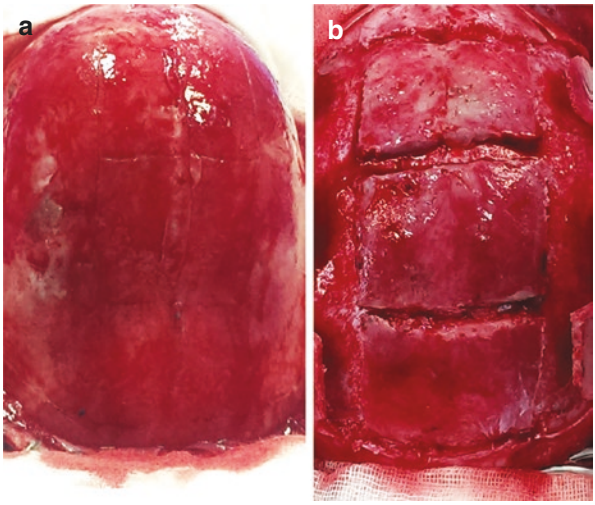


Fig. 18.59 Planning osteotomies using monopolar diathermy as a drawing tool (**a**). Modeling three bone squares in the midline over the sagittal suture without detaching the bone from the underlying dura (**b**). (Micovic, M., Zivkovic, B., Bascarevic, V. et al. Triple square extended osteotomies for treatment of scaphocephaly (Renier's "H" technique modification). *Neurosurg Rev* 39, 115–122 (2016). https://doi.org/10.1007/s10143-015-0661-z)

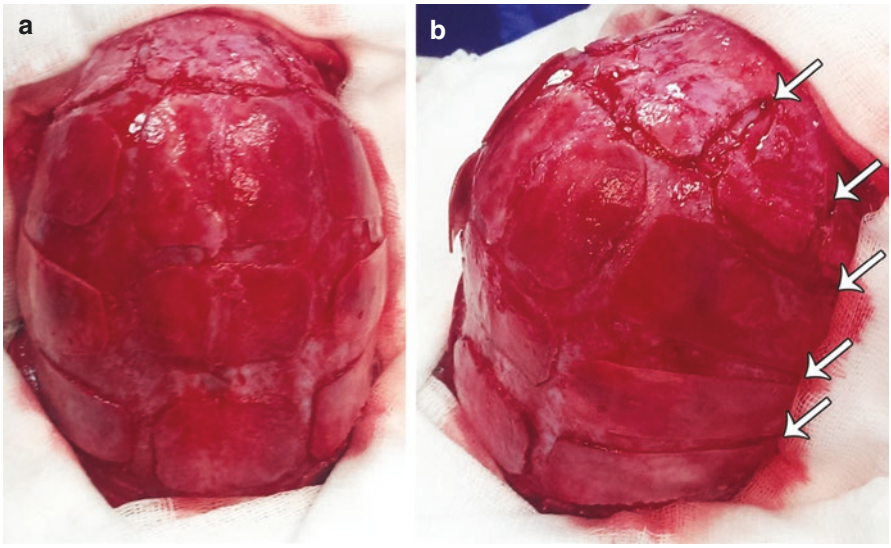


Fig. 18.60 Parallel supplementary extended V-shaped osteotomies from both sides of the midline extending towards the occiput (**a**). Osteotomized parietal bone and V-shaped (tongue-like) extended osteotomies after rounding of bone edges using heavy bone scissors (**b**) (Micovic, M., Zivkovic, B., Bascarevic, V. et al. Triple square extended osteotomies for treatment of scaphocephaly (Renier's "H" technique modification). *Neurosurg Rev* 39, 115–122 (2016). https://doi.org/10.1007/s10143-015-0661-z)

Patients with significant deformities in the frontal and occipital regions benefit from bifrontal and bioccipital craniotomies. The occipital craniotomy should be extended inferiorly to the occipital knob. Great care must be taken to protect the torcula and the transverse sinus during removal of this bone. If a bioccipital flap has been removed, the occipital knob is reshaped by a series of radially oriented barrel-stave osteotomies. Once reshaped, the bone is gently squeezed towards the temporoparietal segments to shorten the skull and simultaneously cause a bulging of the dura and brain laterally to reinforce the outfractured segments. This squeezing is maintained by rigidly fixing the bones in place using absorbable plates and screws. If forehead correction is also necessary (as it is in most cases), the bifrontal craniotomy is reshaped in a fashion similar to that used for the occipital knob. The skull is further shortened by bringing the frontal bone in proximity to the attached temporoparietal segments and fixing the flap using absorbable miniplates. The frontal bone is reattached to the supraorbital rims using either absorbable sutures or miniplates. The remaining bone segments from the removed coronal, lambdoid, and sagittal sutures are then loosely attached to adjoining skull segments and any gaps filled with absorbable Vicryl sutures. Rigid fixing is used only in areas under stress to maintain the anteroposterior squeezing and transverse widening.

The skull can be shortened anteroposteriorly by gentle compression of the bone fragments, fixed in position by resorbable plates and screws. This maneuver can only be performed if the width of the skull has been increased previously so that very little global pressure is applied to the brain and the venous circulation.

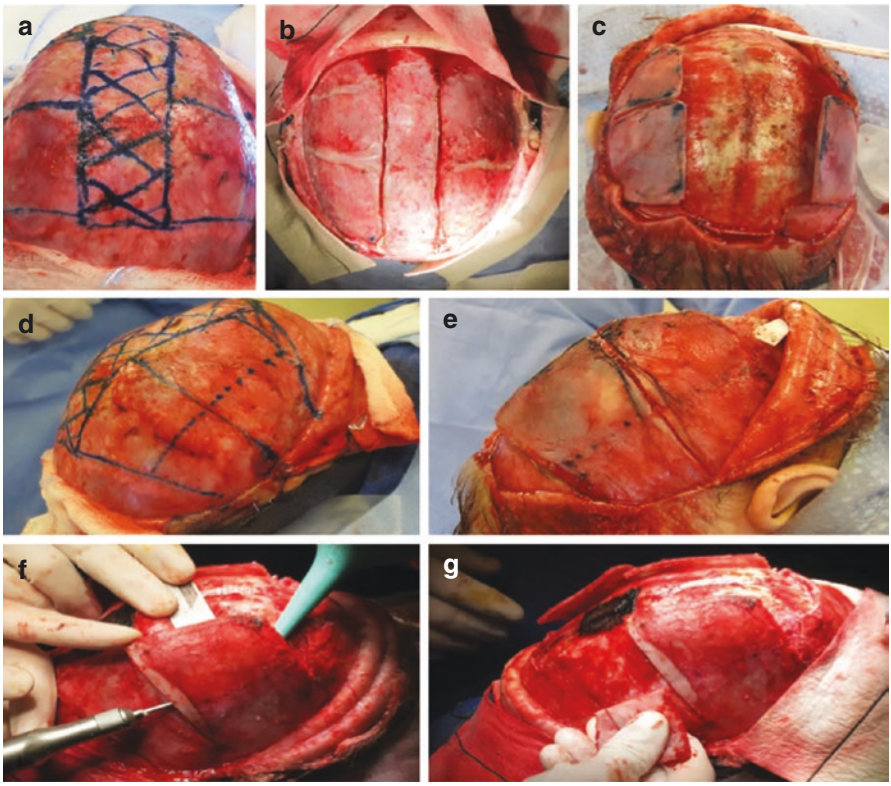


Fig. 18.61 (**a**) Anterior view, 3cm strip of bone to be excised over the sagittal suture. (**b**) Strip of bone cut, lambdoid suture osteotomies visible at the top. (**c**) Cranial vault immediately before closure; parietal bones are fractured and loose allowing for lateral expansion with drain visible posteriorly. (**d**) Anterolateral view showing planned parietal bone osteotomies and lambdoid wedge. (**e**) Lateral view after osteotomies. F Greenstick osteotomy made in the parietal bone. g Greenstick fracture in parietal bone (Escher, P.J., Tu, A., Kearney, S. et al. Minimizing transfusion in sagittal craniosynostosis surgery: the Children's Hospital of Minnesota Protocol. *Childs Nerv Syst* 35, 1357–1362 (2019). https://doi.org/10.1007/s00381-019-04157-5)

If there is a bathyrocephalic deformity, the occiput must be removed and reshaped using barrel-stave osteotomies and flattening of the abnormal curvature using bone benders. The posterior midline strut is shortened and the parieto-occipital bone flaps are reshaped and fixed to the central strut, thus recreating the posterior skull.

Closure

Irrigation of the operative field with warm saline is vital for removing debris and nonviable tissue, which could serve as a nidus for future infection. Since the temporalis muscle is not detached from the scalp flap there is no need for reattachment, as is will assume its position spontaneously. The skin flap is closed in a standard fashion.

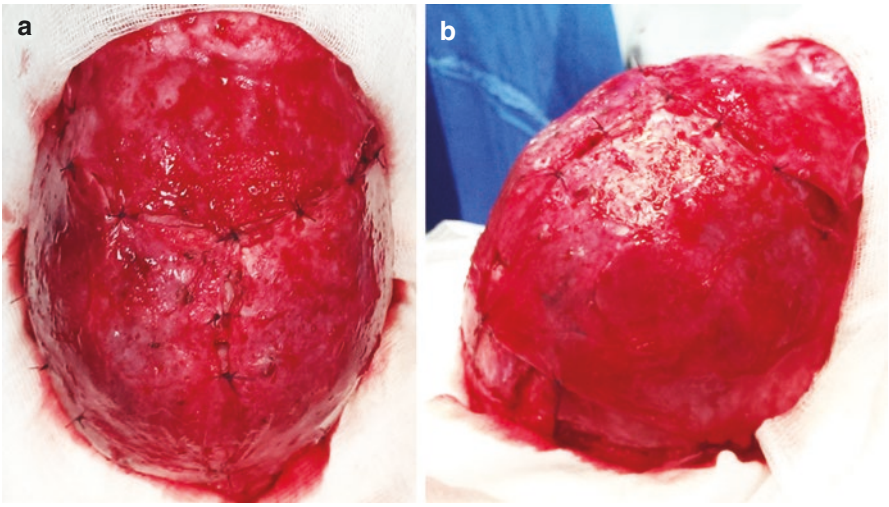


Fig. 18.62 The pericranium is stretched over the remodeled bones serving as a fixation device (Micovic, M., Zivkovic, B., Bascarevic, V. et al. Triple square extended osteotomies for treatment of scaphocephaly (Renier's "H" technique modification). *Neurosurg Rev* 39, 115–122 (2016). https://doi.org/10.1007/s10143-015-0661-z)

The galea aponeurotica is approximated/closed using buried absorbable sutures (Fig. 18.62), and the skin is closed according to surgeons' preferences. Nonresorbable sutures can be used, or subcuticular absorbable sutures such as Vicryl rapide 4-0 or 4-0 monocryl or external running 5-0 fast absorbing plain gut. Use of a subgaleal drain is often avoided so that CSF is not syphoned from potential microabrasions in the underlying dura during craniotomies. In the author's experience, subgaleal drains can be occasionally used, though they are not recommended on a regular basis. If no subgaleal drain is used, the head and the upper part of the body must be elevated. Periorbital and facial swelling is quite common on the first or second postoperative day, but usually resolves spontaneously by the third or fourth postoperative day without additional complications. The final step of the intervention is sterile dressing of the wound. The wound is covered using sterile towels or gauze, the surrounding skin is cleaned with wet and dry towels, and an elastic tubular net bandage is placed over the head. Alternatively, a regular bandage can be used to create a nonconstricting Hippocratic cap.

Specific Instrumentation

Absorbable plates and screw systems are used to provide rigid support for 3–6 months. Reabsorption time is estimated to be 9–15 months. Historically, titanium plates were used, but since it was shown that permanent fixation hardware is subject to transcranial migration over time, it is no longer in use in this patient population.

18.4.3.5 Postoperative Management

Many authors recommend postoperative helmet therapy for additional reshaping and maintenance of the skull shape. According to their recommendations, the helmet is ideally worn for 23 h/day over six months. Regular visits to the orthotist are recomended for follow-up and helmet adjustment.

Postoperatively, the child is transferred to the intensive care unit, or the pediatric ICU if possible. If no problems are expected, the patient can be awakened and extubated immediately postop. The child is positioned in bed on their back, with the head and torso elevated about 30° to prevent postoperative periorbital and facial sweling. Periorbital swelling usually develops on the first or second day postop and resolves on itself by postop day 3–4. Vital signs are monitored and lab values are obtained about 4–6 h postop. Blood transfusions are often needed, especially if hemoglobin is below 8 g/L. Hematocrit is maintained above 20. Analgesia is essential for keeping the child calm and comfortable; paracetamol, acetaminophen, and ibuprofen are most often used. One of the most common issues encountered postoperatively is fever, but it is usually self-limiting [82]. After about 24 h, if no additional problems are encountered, the patient is transferred to the ward. The child is considered stable for discharge when a regular diet has been established and the facial swelling has resolved sufficiently for the eyes to open. A follow-up visit is arranged no longer than 1 week after discharge. It is a good practice to perform a postoperative CT scan before discharging the patient. The scan is used to document the reconstruction and to confirm the advancement and symmetry.

Since absorbable plate and screw systems were first used, there have been reports of painless scalp swelling about 9–15 months postoperatively. This is thought to be associated with the period of plate resorption and can occur in up to 25% of cases when absorbable plate and screw systems are used [83]. The parents should be advised not to be alarmed by this occurrence.

18.4.3.6 Complications

The perioperative complications associated with sagittal synostosis are the same as those for other types of craniosynostosis. In general, they can be divided into two main categories: intraoperative and postoperative. The postoperative complications can be further divided into early and late subcategories.

In the category of intraoperative complications, one of the most important is intraoperative blood loss followed by inadequate blood transfusion. Care must always be taken to achieve perfect and meticulous hemostasis. The superior sagittal sinus can often be torn during the craniotomy or various intraoperative manipulations, and the resulting bleeding can have dramatic consequences, emphasizing the importance of repairing the tear, which should always be prompt. Another threatening complication of a sagittal sinus tear is air embolism. Doppler ultrasound and end-tidal volume spectrometry can detect an air embolism if it occurs. Immediate action should be taken, including placing the patient in Trendelenburg position and

flooding the field with saline to prevent further intake of air into the circulation. Sealing the defect is, of course, a priority. Another intraoperative problem is dural tearing. If noticed or recognized, most such tears can be easily repaired by monofilament nonabsorbable sutures (4-0 prolene). However, unrecognized tears can cause persistent CSF leaks. Injury to the brain is also possible, although rare. Injury to the periorbita or tissues deeper to the periorbita is rare with experienced craniofacial teams.

As mentioned previously, the postoperative complications can be further divided into early and late subcategories, although a strict distinction cannot always be made. One of the most important early postoperative complications is unrecognized blood loss. It is a very preventable complication but has potentially devastating consequences, as infants are especially sensitive to blood loss and the resulting hypoxia. Simple blood work will reveal the problem, easily corrected by transfusion. Another early postoperative complication is the previously-discussed fever, which can occur at about day 3 or 4 postoperatively; it is rarely a cause for alarm because it is reactive and it should be expected. Facial and periorbital swelling is self-limiting and no cause for alarm, resolving spontaneously in about 3–4 days. Early postoperative infection can have devastating consequences if not addressed promptly, requiring prolonged use of antibiotics and significantly extended hospital stay. Infection rarely leads to ostheomyelitis, but this entails a high risk of loss of the bone flap.

Late postoperative complications are centered around poor cosmetic outcome, as discussed above, sometimes requiring re-operation. Other late postoperative complications include persisting cranial bone defects and hardware-related complications. Defects greater than 2cm will often persist and eventually require grafting. Hydroxyapatite paste can be used to fill defects larger than 1cm. In rare cases, abscesses form at the sites of hardware placement, which sometimes require exploration.

18.4.3.7 Outcome, Prognosis and Follow-up

Despite the variety of surgical techniques in use, almost all of them report satisfactory outcomes. However, few prospective or long term comparative data about these techniques are available [116, 136–139], though some studies have demonstrated that the more extensive reconstructions yield better results [140–143]. (Figs. 18.63 and 18.64) Maugans and coworkers found the cosmetic outcomes of total calvarial reconstruction to be superior to strip craniectomy; 79% in the calvarial remodeling group were rated excellent in contrast to 41% in the strip craniectomy group. These authors also noted that two patients required a second operation for poor cosmetic results after strip craniectomy [144]. Greensmith and coworkers found a 3.3% rate of major complications (one air embolus) and a 10% rate of minor complications (one hematoma and two prominent wires) following total cranial vault remodeling [145].

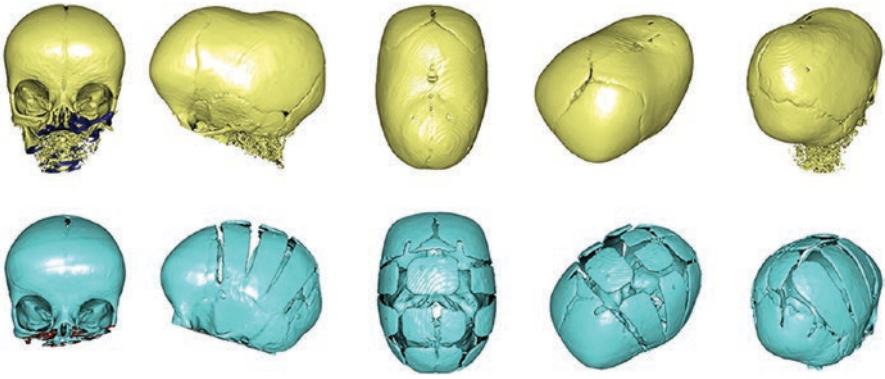


Fig. 18.63 3D reconstructions by InVesalius software: comparison of the preoperative (upper row) and postoperative (lower row) calvarial configuration of patient number 1. Immediate shortening of the cranial length and widening of the cranial breadth are obvious (Micovic, M., Zivkovic, B., Bascarevic, V. et al. Triple square extended osteotomies for treatment of scaphocephaly (Renier's "H" technique modification). *Neurosurg Rev* 39, 115–122 (2016). https://doi.org/10.1007/s10143-015-0661-z)

The more extensive procedures necessitate a longer hospital stay and entail a higher percentage blood loss and therefore require more blood transfusions [145–149]. The average length of stay for total cranial vault remodeling was five days [146].

18.4.3.8 Lambdoid Synostosis (Posterior Plagiocephaly as Phenotypic Presentation)

Premature fusion of the lambdoid suture is referred to as posterior plagiocephaly. It is considered the least common of all the single suture nonsyndromic craniosynostoses. True lambdoidal craniosynostosis should not be confused with deformational plagiocephaly, which is usually due to positional sleeping patterns or torticolis resulting in a parallelogram shape. In true (unilateral) lambdoidal synostosis, the shape of the cranium is trapezoidal when viewed from above. The appearance of the cranium in unilateral lambdoid suture synostosis is characterized by ipsilateral ridging over the fused suture, ipsilateral flattening of the occiput, inferior displacement of the temporal-mastoid region, posterior displacement (pulled backwards) of the ipsilateral ear, contralateral occipital bossing, skull base changes leading to cranial scoliosis, or a tight sternocleidomastoid muscle [105] (Fig. 18.65 and 18.66). In bilateral lambdoid synostosis, the flattening of the occiput is symmetrical. Mild forms of bilateral lambdoid synostosis with late onset seldom require reconstruction since the deformities are subtle. In the more severe cases with early bilateral fusion of the lambdoid suture there are skull deformities in the frontal region, including elevation of the vertex.

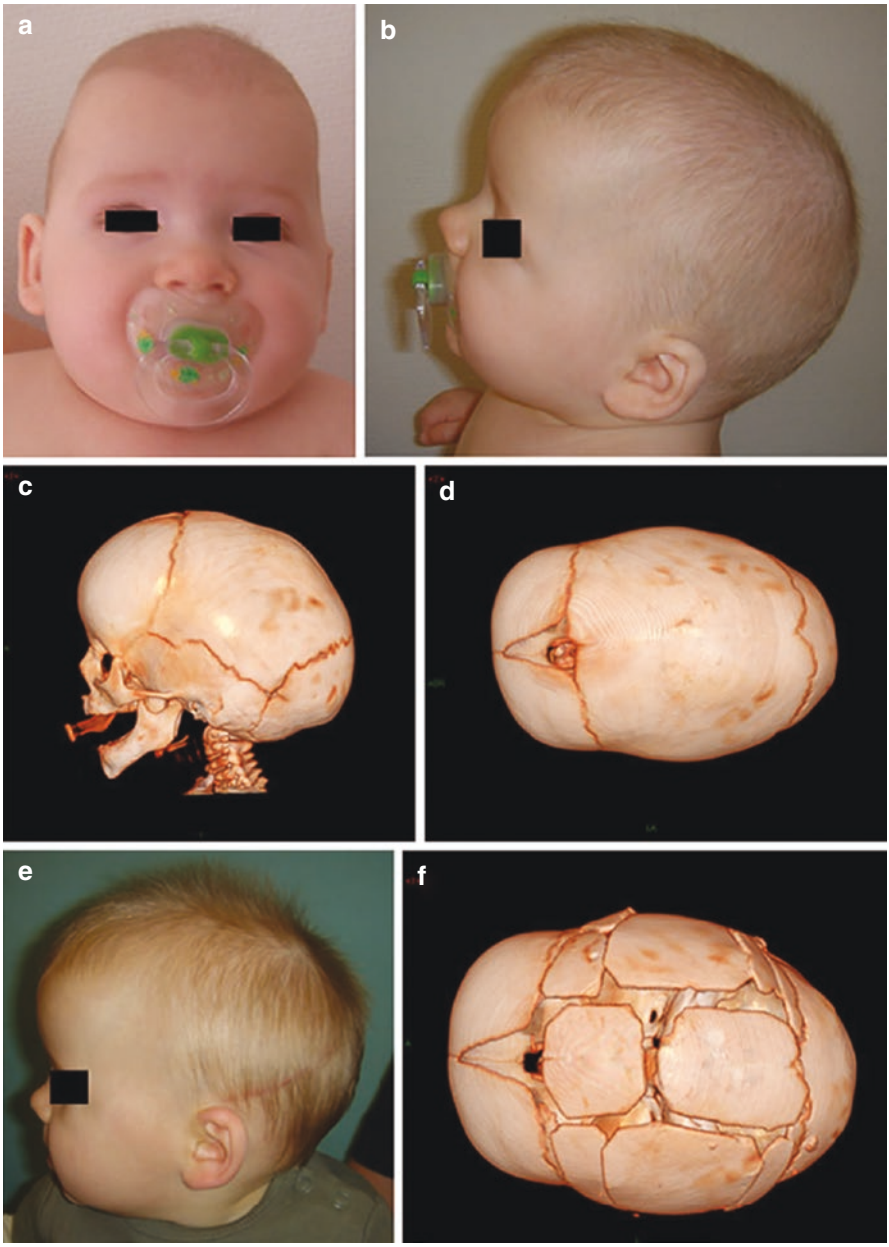


Fig. 18.64 A 5-month-old boy with a sagittal synostosis (**a**, **b** clinical aspect; **c**, **d** perioperative 3D CT scan reconstruction). The same childt 3 months (**e**, **f**), 1 year (**g**, **h**), and 2 years after surgery (**i**, **j**) (Di Rocco, F., Knoll, B.I., Arnaud, E. et al. Scaphocephaly correction with retrocoronal and prelambdoid craniotomies (Renier's "H" technique). *Childs Nerv Syst* 28, 1327–1332 (2012). https://doi.org/10.1007/s00381-012-1811-z)

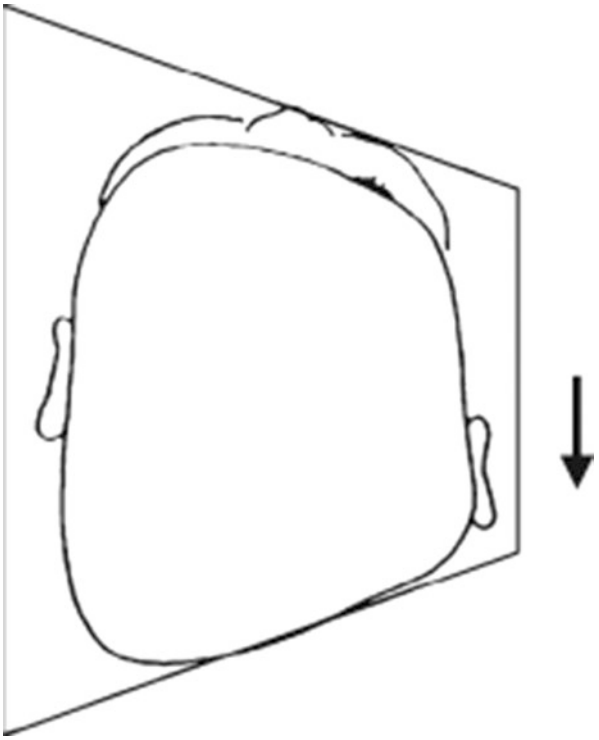


Fig. 18.65 Lambdoid synostosis with trapezoid vertex view (Kalra, R., Walker, M.L. Posterior plagiocephaly. *Childs Nerv Syst* 28, 1389–1393 (2012). https://doi.org/10.1007/s00381-012-1784-y)

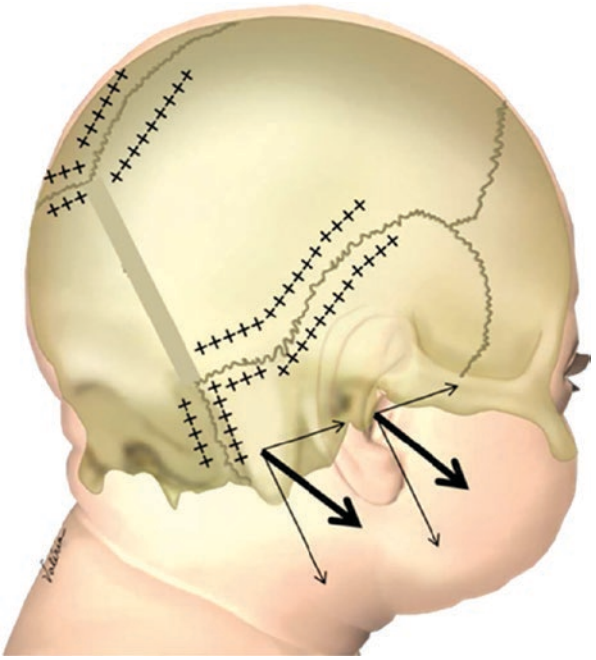


Fig. 18.66 Illustration of the hyperactivity of the sagittal and contralateral lambdoid sutures and of the occipitomastoid and parietomastoid sutures. Large arrow indicates the resulting vector of dislocation of the external auditory meatus and mastoid (Matushita, H., Alonso, N., Cardeal, D.D. et al. Major clinical features of synostotic occipital plagiocephaly: mechanisms of cranial deformations. *Childs Nerv Syst* 30, 1217–1224 (2014). https://doi.org/10.1007/s00381-014-2414-7)

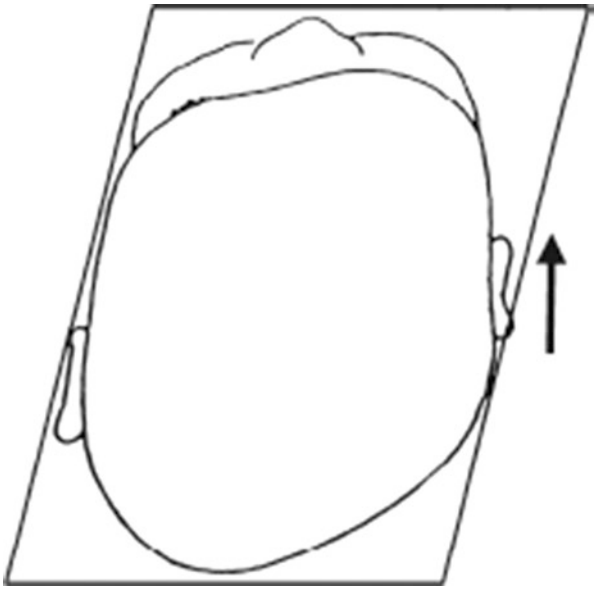


Fig. 18.67 Positional molding with parallelogram vertex view (Kalra, R., Walker, M.L. Posterior plagiocephaly. *Childs Nerv Syst* 28, 1389–1393 (2012). https://doi.org/10.1007/s00381-012-1784-y)

In contrast, posterior deformational plagiocephaly, despite the parallelogram shape of the head, is characterized by absence of palpable ridging over the lambdoid suture, ipsilateral frontal bossing, and anterior displacement of the ipsilateral ear (Fig. 18.67).

18.4.3.9 Diagnosis, Indications for Operative Treatment and Timing

The diagnosis of lambdoid suture synostosis, and its differentiation from deformational plagiocephaly, is primarily based on physical examination. A plain X-ray or a CT scan can be obtained to confirm the diagnosis (Figs. 18.68 and 18.69). An MRI of the brain can be obtained if a coexisting pathology is suspected.

As far as the indications go, open reconstruction of the lambdoid synostosis is generally performed in cases of severe cosmetic deformity.

The timing of the surgery depends on the general health of the child, but the ideal age for open reconstruction is considered to be 4–8 months, since the child should have gained enough weight and would be able to tolerate blood loss better, and also because the bones of the skull would be malleable enough for the reconstruction to be easy [150].

18.4.3.10 Preoperative Planning, Surgical Objectives and Special Equipment

The preoperative preparations should involve routine blood tests including complete blood count, electrolyte panel, and partial thromboplastin time and prothrombin time. A blood type should be obtained since there is potential for significant

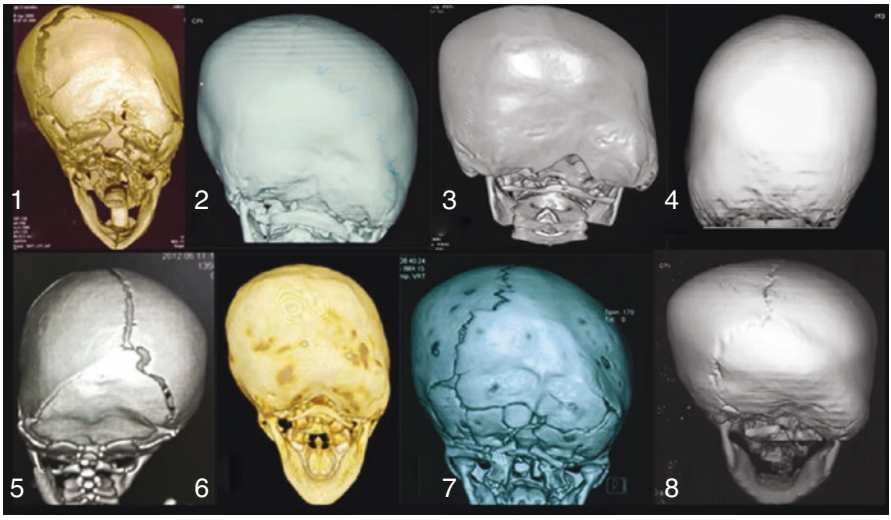


Fig. 18.68 Three-dimensional CT scans of the patients (Matushita, H., Alonso, N., Cardeal, D.D. et al. Major clinical features of synostotic occipital plagiocephaly: mechanisms of cranial deformations. *Childs Nerv Syst* 30, 1217–1224 (2014). https://doi.org/10.1007/s00381-014-2414-7)

blood loss. If the patient's parents are prepared to donate, they should be given the option to do so. The child along with its mother is admitted to the ward on the day of the surgery or the day before, and should be kept fasting for at least 4–6 h before the planned surgery.

The objectives of the surgical correction should be to achieve the best possible and most durable correction of deformity with a single operation, at the lowest possible risk for the patient. In this case, this means normalization of the skull shape by enlarging the biparietal diameters relative to the long axis of the head and ensuring normal cranial volume.

Equipment needed during these operations includes a Mayfield headring or horseshoe head holder, although the horseshoe could be more practical because of the specific position required for the body. Basic pediatric neurosurgical operative instruments are needed, and a high-speed drill or handheld Hudson brace with pediatric burrs. Different kinds of sutures should be available, but monofilament polypropylene sutures are recommended. Resorbable plates and screws can be used to stabilize bony fragments, though they are not always needed. Local anesthetic is encouraged (bupivacaine or lidocaine with epinephrine) for analgesia, reducing the need for additional dosing with intravenous analgesics and providing better control over intraoperative bleeding.

18.4.3.11 Anesthetic Considerations

One or two large bore intravenous lines (≥20 gauge) are required in view of the potential blood loss during surgery. A urinary catheter is useful for recording urinary output. A thermistor is needed to record body temperature, and intraoperative

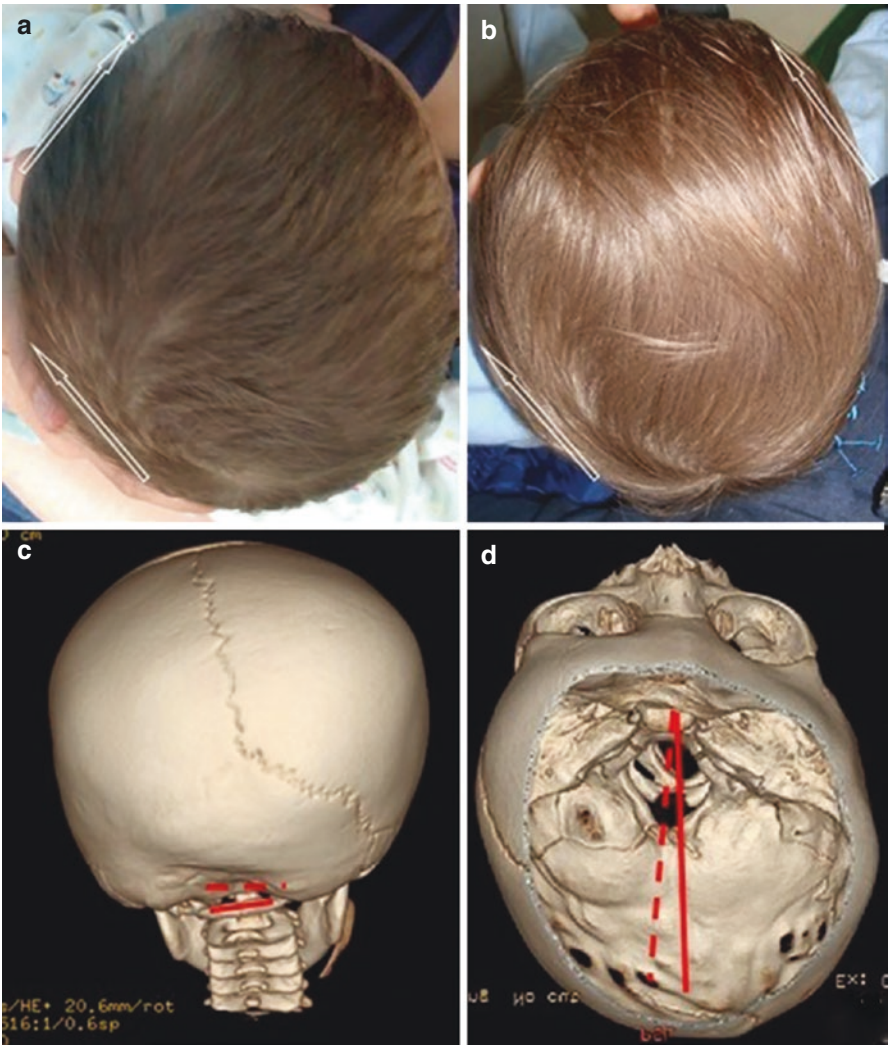


Fig. 18.69 (**a** and **b**) Top view of the head of a child with positional plagiocephaly (a) and lambdoid synostosis (**b**). The child with positional plagiocephaly (**a**) shows an anterior displacement of the homolateral frontal region, in the direction of the positional molding. On the contrary the child with lambdoid synostosis (**b**) shows an attraction to the closed suture of the homolateral frontal region with relative prominence of the contralateral anterior part of the skull. (**c** and **d**) 3D CT reconstruction of a child with lambdoid synostosis. It is evident the prominence of the homolateral mastoid and the downwards deviation of the C0-C1 axis (**c**). The internal view of the skull shows a deviation of the midline to the synostotic side (**d**) (Tamburrini G., Mohsen Amen M., Di Rocco C. (2018) Lambdoid Synostoses. In: Di Rocco C., Pang D., Rutka J. (eds) Textbook of Pediatric Neurosurgery. Springer, Cham)

body warmers are of course advised. Arterial and central venous lines allow for total body intravascular volume monitoring and postoperative fluid management.

Endotracheal intubation should be performed in standard manner, securing the tube according to local practice. Some authors advise circummandibular or circumdental fixing. In our practice, oily eye drops (Vit A and Vit D) and hydrophobic tape over the child's eyes suffice to protect the cornea.

Preoperative antibiotics are given before the skin incision (cefazoline 10–20 mg/kg as loading dose, 8mg/kg intravenosly every 8 h for 48 h) as per local practice.

The author's preference is total removal of hair using hair clippers. Total hair clipping is also expected to facilitate skin closure and postoperative wound care. Occasionally, the area of the planned skin incision is shaved.

18.4.3.12 Operative Procedure

Positioning

For adequate exposure of the occiput the patient must be placed in a prone position, with the head resting on a horseshoe. Care must be taken to pad pressure points adequately, and no pressure should be applied to the eyes while the face rests on the horseshoe. The head should be at the level of the heart (Fig. 18.70).

Sterile Scrub, Draping and Local Anesthetic

The skin is prepared with povidone-iodine or other skin antiseptic as per local practice. Betadine Ophthalmic (5% povidone-iodine) can be used when prepping near or around the eyes. Alternatively, 70% ethanol followed by a prescrub with scrub brush and then a two-step Betadine preparation, first with Betadind soap, then by a Betadine scrub. Single use drapes are preferred and advised. For local analgesia and to minimize intraoperative bleeding, the following combinations can be used: 0.5% lidocaine and 1:400.000 parts epinephrine, or 0.25% bupivacaine and 1:200.000 epinephrine.

Skin Incision

A standard bicoronal incision is used, extending from just above (or behind) one ear across to the opposite side. Alternatively, a zigzag variation of the bicoronal incision can be used, referred to as the stealth incision or sinusoid-type incision, to minimize the chance of incisional scalp alopecia. Another variation of the bicoronal scalp incision is posterior inclination in the parieto-occipital scalp providing excellent camouflage of the scar line, especially in balding adults. It is necessary to preserve the ascending branch of the superficial temporal arteries for adequate blood supply [71]. Bleeding is controlled by bipolar coagulation, but Raney clips can also be

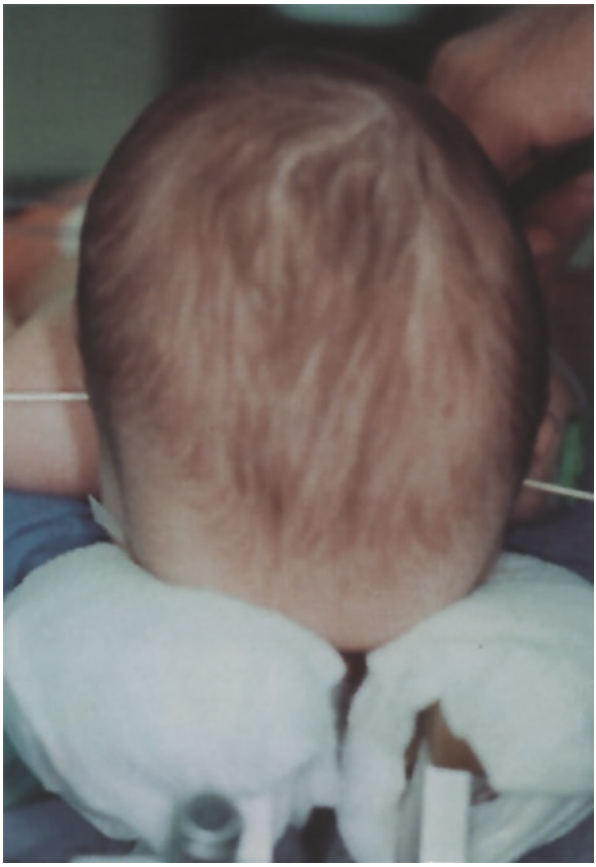


Fig. 18.70 Preoperative positioning. Cotton tip applicators placed in the extarnal ear canals make it easy to appreciate early malrotation of the skull base. The left lambdoid is affected and, as a result, the left ear is pushed forwards and downwards relative to the right. The left forehead is pushed outwards and forwards in a compensatory pattern to allow for adequate brain growth. (Goodrich, J.T., Argamaso, R. Lambdoid stenosis (posterior plagiocephaly) and craniofacial asymmetry: long-term outcomes. *Child's Nerv Syst* 12, 720–726 (1996). https://doi.org/10.1007/BF00366157)

used. Further dissection of the skin flap proceeds in a subperiosteal or supraperiosteal fashion. The advantage of the supraperiosteal dissection is reduced bleeding; the periosteum is incised approximately 1–2 cm above the supraorbital rim and the dissection is further advanced subperiosteally, ensuring bilateral exposure of the supraorbital rim and avoiding injury to the branches of the facial nerve. The temporalis muscles are dissected off their attachments to the temporal bone and should be split and advanced after the lateral orbital rims are advanced to avoid postoperative temporal hollowing.

Using a No. 15 scalpel, the incision is made on one side of the scalp well behind the hairline, from just behind one ear and across to the opposite side behind the other ear. It is often said that the incision should have a posterior inclination for adequate exposure of the parieto-occipital region. The scalp flap is elevated in a subgaleal/supraperiosteal manner posteriorly, exposing the entire occiput and the lambdoid sutures. Bleeding from the skin flap is controlled by bipolar coagulation, but Raney clips can also be used. The periosteum can be elevated as a separate layer along with the nuchal musculature (Fig. 18.71).

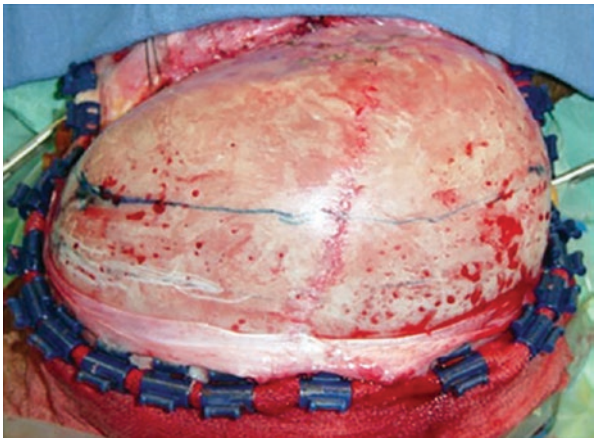


Fig. 18.71 Intraoperative picture showing severe positional deformation (Di Rocco, F., Marchac, A., Duracher, C. et al. Posterior remodeling flap for posterior plagiocephaly. *Childs Nerv Syst* 28, 1395–1397 (2012). https://doi.org/10.1007/s00381-012-1842-5)

The limits of the exposure should include the fused and nonfused lambdoid suture, the inion and as far as possible under the inion, the asterion, to just behind the anterior fontanelle.

Initial Deconstructive Phase

Depending on the severity of the deformity and the desired degree of reconstruction, several different techniques can be used for lambdoid synostosis reconstruction. Here we present a method considered best by the author.

One of the simplest approaches to lambdoid synostosis reconstruction, whether the synostosis is unilatereal or bilateral, is to create a biparietal-bioccipital bone flap. The first part of this reconstruction begins with making several burr holes, preferably using small drill bits, on strategic and carrefully planned spots on the parietal and occipital bones.

The first burr holes are placed about 2cm apart on the highest spots on the convexity, paramedially, on both sides of the projection of the superior sagittal sinus. The next burr holes are placed just above and behind the asterion. Burr holes can be placed at the level of or just lateral to the inion, about 2cm apart (Fig. 18.72). During the creation of burr holes and the craniotomy, great care must be taken to avoid injury to the venous sinuses.

Before the craniotomy, it is advisable to strip the dura off the inner table. As soon as the craniotomy is completed, the bone flap is elevated in one piece as a biparietal-bioccipital flap (Fig. 18.73).

Radial barrel-stave osteotomies are created on the bone flap. For unilateral lambdoid suture synostosis, the affected side is outfractured to increase the occipital projection, and the bulging side is fractured inwardly to reduce bossing on the contralateral side. The convex side is made flatter and the flatter side is made more convex using greenstick fractures. For bilateral lambdoid suture synostosis, despite the radial osteotomies, additional contouring can be needed to achieve adequate

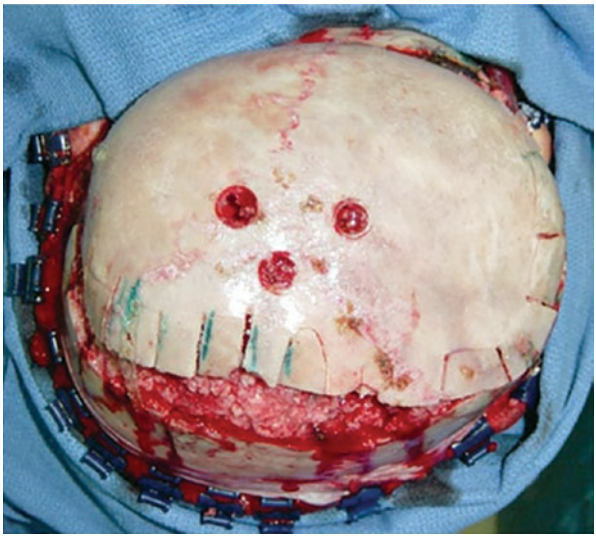


Fig. 18.72 Intraoperative picture showing the position of the rotated flap secured with resorbable plates. Note the three burr holes around the lambda and the presence of both lambdoid sutures (Di Rocco, F., Marchac, A., Duracher, C. et al. Posterior remodeling flap for posterior plagiocephaly. *Childs Nerv Syst* 28, 1395–1397 (2012). https://doi.org/10.1007/s00381-012-1842-5)

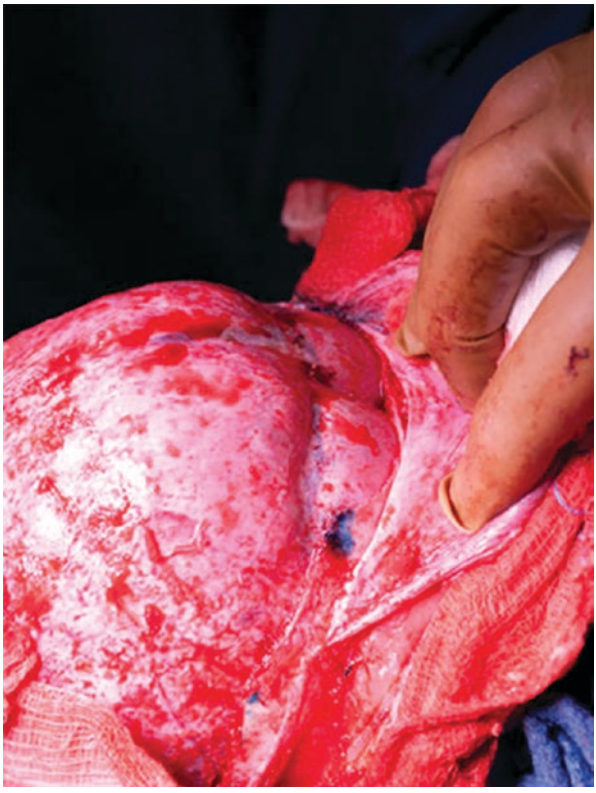


Fig. 18.73 This figure shows the lambdoid region after the entire calvarial unit is removed. The surgeon is holding down the pericranial flap. The transverse sinuses can be seen just above the fingers, and the outline caused by the overlying skull can be seen. The prominent "knobby" inion is appreciated just above the transverse sinuses. With only the removal of the bone, this shape changes dramatically (Goodrich, J.T., Tepper, O. & Staffenberg, D.A. Craniosynostosis: posterior two-third cranial vault reconstruction using bioresorbable plates and a PDS suture lattice in sagittal and lambdoid synostosis. *Childs Nerv Syst* 28, 1399–1406 (2012). https://doi.org/10.1007/s00381-012-1767-z)

convexity. The portion of the bone below the inion, or below the limits of the craniotomy, is also addressed with radial barrel-stave osteotomies. The reconfigured bone flap is fixed using absorbable rigid fixation.

More substantial reconstruction can be required in severe cases. For this, a few bony cuts are needed to create a bandeau, a new backhead and an occipital unit. The first step in this reconstruction is to create a burr hole with a diameter of about 5mm on either side, placed just behind the asterion, using a high speed drill with a round bit. Once the dura is detached on the level of the burr hole, the footplate attachment is used to complete a strip craniotomy from the asterion to the midline on one side and from the contralateral asterion to the level of the previous osteotomy. The footplate is then again returned to the burr hole at the level of the asterion in order to create a horizontal cut, oriented frontally over a length of about 15–20 mm; then the footplate is turned upwards towards the convexity to a level just behind the anterior fontanelle, thus creating a bandeau that will serve as a foundation for the following reconstruction. After the bandeau is created, another osteotomy is performed from the lower level of that bandeau, at the level of the asterion. First, the dura is detached from the tabula interna. Next, using a footplate, the backhead is created, starting from the level of the asterion to the midline. The basis of the backhead should match the middle third of the bandeau as they will later be fixed. The convex edge of the backhead is recreated to represent the posterior convexity adequately. A final cut is performed to mobilize the remaining occipital unit. This cut should start at the level of the asterion on one side, oriented backwards as far as possible, under the inion, pointing to the base of the skull and around to the contralateral asterion, thus creating the remaining occipital unit or parieto-occipital bone flap (see below).

The third remaining piece, or the occipital unit, can be addressed in several ways. It can be cut into several pieces of bone and replaced in a mosaic fashion. It can also be cut into strips, which can then be placed radially to give a “sunrise” appearance to the new occipital complex (Fig. 18.74).

Additional Reconstructive Phase

In the first technique described, applicable in mild-to-severe cases, the bone flap is reconstructed using radial barrel-stave osteotomies on the parieto-occipital bone flap. Additional adjustment of this flap is ensured using greenstick fractures.The radial barrel-stave osteotomies on the portion of the bone below the inion, or below the limits of the craniotomy, are also an important part of the reconstruction. The reconfigured bone flap is fixed using absorbable rigid fixation (Fig. 18.75).

The reconstruction in the second technique described, applicable to more severe cases, begins with the creation of the “tiara” adjoining the backhead to the upper edge of the bandeau using three absorbable miniplates. This construction serves as a foundation on which the reconstruction is based. Before being created, the bandeau had a vertical orientation from the asterion to the midlevel. During reconstruction, the newly-formed tiara is placed horizontally in a tongue-and-groove fashion into the asterion region, forming the newly-formed occiput, with the backhead fixed above the the bandeau. The rest of the pieces from the remaining occipital unit are

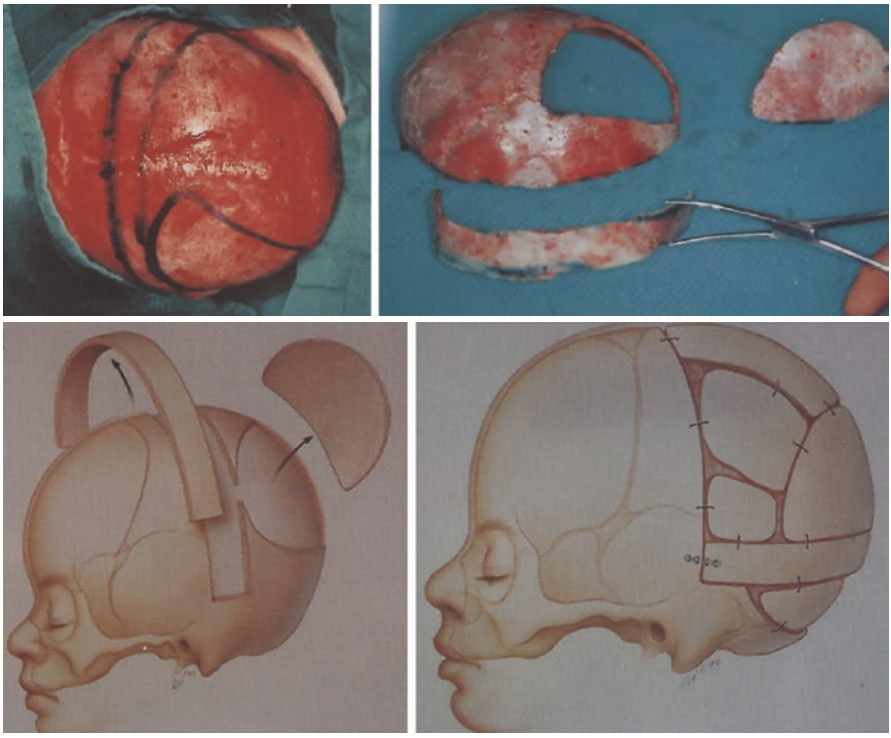


Fig. 18.74 (Upper left) Intraoperative view of the parietaland occipital region, with• the sagittal suture clearly seen in the midline. Methylene blue has been used to mark out the new bandeau. The new "backhead" unit is marked with a Marchac template over the left parieto-occipital region. (Middle fig.). Artist's reconstruction showing the operative area despicted in Fig. 10 but only from a more lateral view, detailing where the backhead and bandeau are harvested. (Reproduced with permission from [4]) (Upper right) Intraoperative illustration of the parieto-occipital unit, which has been harvested as a single piece. The bandeau is held with a clamp. At the upper right the new backhead unit is seen. (Lower fig) Artist's reconstruction showing fixing of the bandeau and backhead to the asterion by the tongue-and-groove technique. A strut is placed from just behind the anterior fontanel to the top of the backhead unit. This piece is extremely important for stability. The remaining bone pieces are replaced in a mosaic fashion to fill in the remaining defects. The split calvarial bone can also be used in the reconstruction so that no defects larger than 2 cm remain. Larger defects can sometimes not be filled in, even in a child under 1 year of age. (Reproduced with permission from [4]). (Goodrich, J.T., Argamaso, R. Lambdoid stenosis (posterior plagiocephaly) and craniofacial asymmetry: long-term outcomes. *Child's Nerv Syst* 12, 720–726 (1996). https://doi.org/10.1007/BF00366157)

used to reconstruct the rest of the calvaria, maintaining symmetry at the same time. The strut piece is considered important; it is placed from the region of the fontanelle to the most superior point of the tiara.

As mentioned, the occipital unit can be addressed in several ways. It can be cut into several pieces of bone and replaced in a mosaic fashion, or it can also be cut into strips, which can than be placed radially to give a "sunrise" appearance to the new occipital complex.

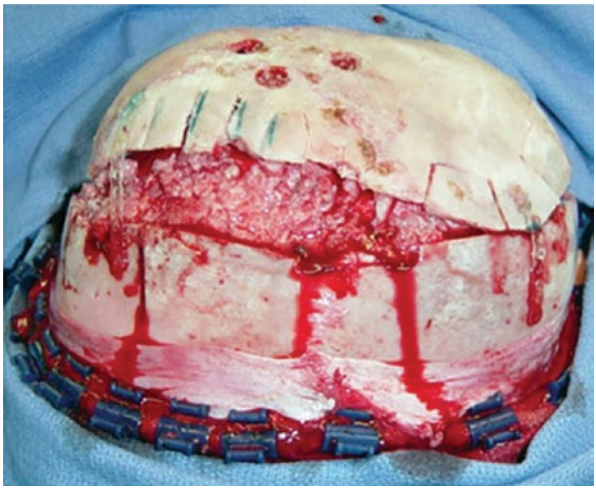


Fig. 18.75 Intraoperative picture showing the immediate correction of the posterior deformation sutures (Di Rocco, F., Marchac, A., Duracher, C. et al. Posterior remodeling flap for posterior plagiocephaly. *Childs Nerv Syst* 28, 1395–1397 (2012). https://doi.org/10.1007/s00381-012-1842-5)

The bone pieces are then fixed in place using absorbable plate and screws, but resorbable sutures can also be used, as preferred or as available. The pericranial flap is reflected over the cranium and secured in place using absorbable sutures (Figs. 18.76 and 18.77).

Closure

Irrigation of the operative field with warm saline is vital for removing debris and nonviable tissue, which could serve as a nidus for future infection. Since the temporalis muscle is not detached from the scalp flap there is no need for reattachment, as is will assume its position spontaneously. The skin flap is closed in a standard fashion.

The galea aponeurotica is approximated/closed using buried absorbable sutures, and the skin is closed according to surgeons' preferences. Nonresorbable sutures can be used, or subcuticular absorbable sutures such as Vicryl rapide 4-0 or 4-0 monocryl or external running 5-0 fast absorbing plain gut. Use of a subgaleal drain is often avoided so that CSF is not syphoned from potential microabrasions in the underlying dura during craniotomies. In the author's experience, subgaleal drains can be occasionally used, though they are not recommended on a regular basis. If no subgaleal drain is used, the head and the upper part of the body must be elevated. Periorbital and facial swelling is quite common on the first or second postoperative day, but usually resolves spontaneously by the third or fourth postoperative day without additional complications. The final step of the intervention is sterile dressing of the wound. The wound is covered using sterile towels or gauze, the surrounding skin is cleaned with wet and dry towels, and an elastic tubular net bandage is placed over the head. Alternatively, a regular bandage can be used to create a nonconstricting Hippocratic cap.

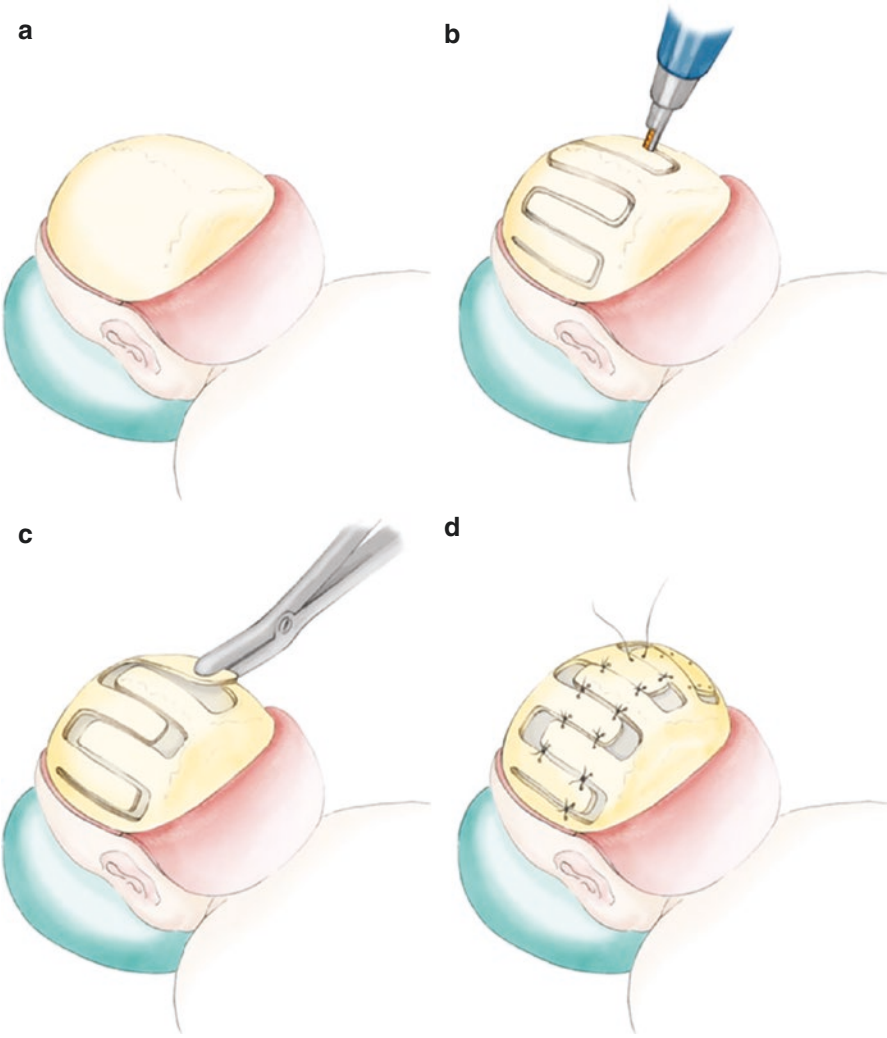


Fig. 18.76 The meander technique. **a–d** Schematic drawings depicting the different steps of the surgical procedure as described in the text (Wagner, W., Schwandt, E., Huthmann, A. et al. Posterior calvarial augmentation in premature craniosynostosis: a technique avoiding foreign implants or free bone flaps. *Childs Nerv Syst* 26, 1549–1553 (2010). https://doi.org/10.1007/s00381-010-1158-2)

Specific Instrumentation

Absorbable plates and screw systems are used to provide a rigid support for 3–6 months. Reabsorption time is estimated to be 9–15 months. Historically, titanium plates were used to obtain rigid fixation. Since it was shown that permanent fixation hardware is subject to transcranial migration over time, it is no longer used in this patient population.

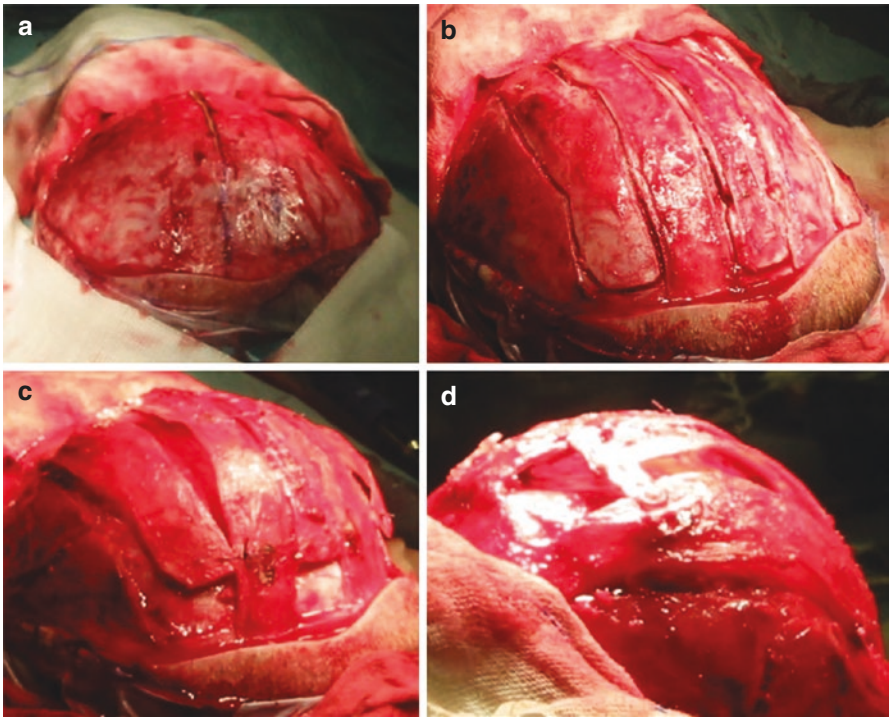


Fig. 18.77 The meander technique. (**a**–**d**) Intraoperative photographs displaying the main steps of the surgical procedure (case RU). The patient is in the prone position. The posterior calvaria is prepared (**a**, vertical view). With the craniotome, bone strips are formed that stay alternately attached to the cranial base or apex (**b**, oblique vertical view). These bone tongues are elevated, optionally held in place by underlying gel foam and fixed to each other with resorbable 2.0 sutures, and also with absobable plates and screws if necessary (**c**, oblique vertical view). A lateral view of the fixed bone tongues shows the remarkable distance between dura and calvaria after the posterior advancement (**d**, lateral view) (Wagner, W., Schwandt, E., Huthmann, A. et al. Posterior calvarial augmentation in premature craniosynostosis: a technique avoiding foreign implants or free bone flaps. *Childs Nerv Syst* 26, 1549–1553 (2010). https://doi.org/10.1007/s00381-010-1158-2)

18.4.3.13 Postoperative Management

Postoperatively, the child is transferred to the intensive care unit, preferably the pediatric ICU if possible. İf problems are not expected, the patient can be awakened and extubated immediately postoperatively. The child is positioned in bed on its back, with the head and torso elevated by about 30° to prevent postoperative periorbital and facial swelling. Periorbital swelling usually develops on the first or second day postop and resolves on itself by postop day 3–4. Vital signs are monitored and laboratory values are obtained about 4–6 h postoperatively. Blood transfusions are often needed, especially if hemoglobin is below 8 g/L. Analgesia is essential for keeping the child calm and comfortable. One of the most common issues encountered postoperatively is fever, but this is usually self-limiting [82]. After about 24 h,

if no additional problems are encountered, the child is transferred to the ward. The child is considered stable for discharge when a regular diet has been established and the facial swelling has started to resolve sufficiently for the eyes to open. A follow-up visit is arranged no longer than 1 week after discharge.

Since absorbable plate and screw systems wre first used, there have been reports of painless scalp swelling occurring after about 9–15 months postoperatively. This is thought to be associated with the period of plate resorption and can occur in up to 25% of cases when absorbable plate and screw systems are used [83]. The parents should be advised not to be alarmed by this occurrence.

18.4.3.14 Complications

One of the most serious complications in the lambdoid synostosis reconstruction surgery is the injury to the venous sinuses during elevation of the bone flaps. In most cases, direct pressure on the injured sinus and use of cottonoids, Gelfoam, Avitene or Surgiflo will help to control the bleeding. If feasible, the tear should be directly sutured.

In general, the complications can be divided into two main categories: intraoperative and postoperative. The postoperative complications can further be divided into early and late subcategories.

In the intraoperative complications category, one of the most important is intraoperative blood loss followed by inadequate blood transfusion. Care must always be taken to achieve perfect and meticulous hemostasis. Superior sagittal sinus tears often happen during the craniotomy or various intraoperative manipulations, and the resulting bleeding can have dramatic consequences, emphasizing the importance of repairing the tear, which should always be prompt. Another threatening complication of sagittal sinus tears is air embolism. Doppler ultrasound and end-tidal volume spectrometery can detect an air embolism if it occurs. Immediate action should be taken, including placing the patient in a Trendelenburg position and flooding the field with saline to prevent further intake of air into the circulation. Sealing the defect is, of course, a priority. Another intraoperative problem is dural tearing. If noticed, or recognized, most such tears can easily be repaired using monofilament nonabsorbable suture (4-0 prolene). On the other hand, unrecognized tears can cause persistent CSF leaks. Injury to the brain is also possible, although rare. Injury to the periorbita, or tissues deeper to the periorbita, is rare with experienced cranio-facial teams.

The postoperative complications, as mentioned previously, can be further divided into early and late subcategories, although a strict distinction cannot always be made. One of the most important early postoperative complications is unrecognized blood loss. It is an easily preventable complication but has potentially devastating consequences, as infants are especially sensitive to blood loss and the resulting hypoxia. Simple blood work reveals the problem, easily corrected by transfusion. Another possible early postoperative complication is the previously-discussed fever, occurring at about day 3–4 postop. It is rarely a cause for alarm, being reactive, and

it should be expected. Facial and periorbital swelling is self-limiting and no cause for alarm, resolving spontaneously in about 3–4 days. Early postoperative infection can have devastating consequences if not addressed in time, requiring prolonged use of antibiotics and significantly extended hospital stay. Rarely, infection can lead to ostiomyelitis, which entails a high risk of loss of the bone flap.

Late postoperative complications are centered around poor cosmetic outcome, as discussed above, sometimes requiring re-operation. Other late postoperative complications include persisting cranial defects and hardware-related complications.

18.4.3.15 Outcome, Prognosis and Follow-up

Only a handful of studies have generated reliable data on the outcome of unilateral and bilateral lambdoid synostoses [96, 97, 122, 151–153]. Re-operation rates range from zero to 10% and complication rates from 5.4% to 13.6%. In addition to reconstruction of the posterior cranial vault, studies have noted correction of most of the facial asymmetries with surgeries performed at less than 1 year of age [151, 153]. However, satisfactory results with normalization of the posterior cranial vault are seen in most infants [151–153] (Fig. 18.78a–f).

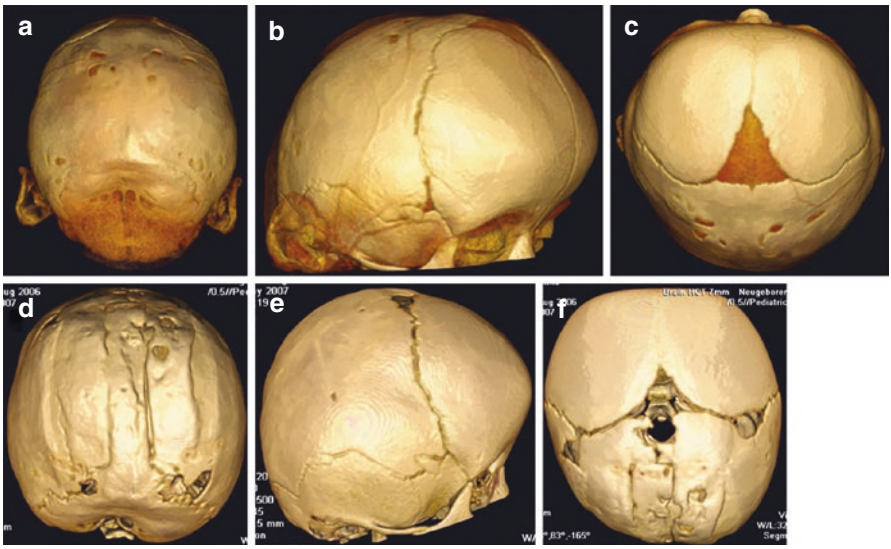


Fig. 18.78 (**a**–**f**)Lateral photographs and mid-sagittal MR of a baby with Mercedes Benz syndrome and strong flattening of the posterior calvaria (case DD). Photos before surgery at the age of 6 weeks (**a**), 4 weeks (**b**), 19 months (**c**) and 1.5 years (**d**) after posterior advancement. MR before surgery at the age of 3.5 months (**e**) and 2 years after surgery (**f**) (Wagner, W., Schwandt, E., Huthmann, A. et al. Posterior calvarial augmentation in premature craniosynostosis: a technique avoiding foreign implants or free bone flaps. *Childs Nerv Syst* 26, 1549–1553 (2010). https://doi.org/10.1007/s00381-010-1158-2)

Regular follow-up visits should be scheduled at one month, three months, six months, and a year postop.

18.5 Surgery for Syndromic Craniosynosthosis

Nonsyndromic craniosynostosis is more common, with a reported frequency of 0.4–1.0 per 1000 live births [154]. In contrast, the frequencies of syndromic craniofacial anomalies associated with craniosynostosis are one per 25.000 births for Crouzon's syndrome and one per 160.000 for Apert's syndrome [155], while others such as Pfeiffer's, Saethre-Chotzen and Carpenter's syndromes are even more sporadic and unusual. Although the phenotypic manifestations of these conditions vary, almost all have associated craniosynostosis, faciostenosis (deformities), and various patterns of limb abnormalities. The patients need a complex multidisciplinary approach involving geneticists, neurosurgeons, plastic surgeons, pediatric anesthesiologists, ophthalmologists, otolaryngologists, orthodontists, speech and physical therapists and psychologists. Care of these patients is complicated and extended. It includes long-range planning over the entire period of childhood and adolescence into adulthood.

Surgical treatment of craniosynostosis began with Lane (1892) and Lannelongue (1890) [155, 156]. They both performed strip craniectomies for fused sutures in young infants. Such procedures enjoyed temporary popularity but did not gain widespread interest because operations were conducted on misdiagnosed children. The investigations of facial fractures by Rene Le Fort, published in 1901 in the *Revue de Chirurgi*, were of considerable significance. They elucidated the "three great lines of weakness" of the facial skeleton, lines along which the facial bones routinely break after trauma (Le Fort I, II and III) [157]. The first midfacial osteotomy to correct the facial deformities associated with syndromic craniosynostosis was reported by Gillies in 1950 [158]. The published photographs and operative diagrams detail a subcranial Le Fort III osteotomy and midfacial advancement for probable Crouzon's syndrome. In 1964, Paul Tessier and Gerard Dyuit [159], familar with Gillies's and Le Fort's work, performed the first transcranial hypertelorism correction. This was the start of the modern era of craniofacial surgery. Tessier's recommendations include using wide exposure, the intracranial approach for correcting some forms of facial deformity, liberal and exclusive use of autogenous bone grafting, and reliance on rigid bony fixation. Subsequent developments have included three-dimensional radiographic visualization and precise computed-guided modeling. Improved pediatric anesthesia, critical care and monitoring have contributed to an overall decrease in morbidity and mortality. Rigid microfixation and development of resorbable plates and screws and bone substitutes have also greatly improved the efficacy of the surgical armamentarium. Techniques of dictated osteogenesis applied to the cranial vault and the facial skeleton have radically altered and expanded the surgical options for correcting these deformities [44].

The aim of surgical treatment of craniofacial syndromes is to correct the remarkable exorbitism and the malocclusion secondary to retrusion of the maxilla, to decompress the compressed and obliterated nasal pharynx, and to correct the recession of the frontal bone, which is a manifestation of coronal synostosis [160].

The fundamental elements of Tessier's technique[164] for correction of craniofacial syndromes are:

1. Total correction of the orbital and maxillary anomalies;
2. A monoblock osteotomy, extending to the pterygoid processes of the facial mass;
3. Infrabasal and orbital rim osteotomies with sagittal splitting of the lateral walls of the orbits;
4. Frontonasal and frontomalar triple osteosynostosis for fixing;
5. Bone graft wedges to fix the intercranial and facial separations and correct inframaxillism, facial shortness and vertical atresia of the orbit;
6. Correction of hypertelorism, if present;
7. Advancement of the inferior portion of the frontal bone via the cranial route if the frontal cranial deformity needs correction.

The complexity of the syndromes requires that many surgical techniques applied to different parts of the skull and face depend of the maturity and growth of the specified bones. Therefore, more than one procedure is required for functional and cosmetic improvement in these patients. The earliest times that surgery can be considered in the various regions of the craniofacial skeleton are when that region has completed its full growth potential, and this is approximately as follows: Cranium: one year (six months for sagittal); Orbits: 5 years and above; Upper maxilla: 9−12 years; Lower maxilla: 17 years and above; Mandible: 17 years and above. The reasoning behind this careful timing is to minimize the risk of relapse of the deformity and the need for repeat surgeries. It means that the final stage of facial correction can effectively be undertaken at the age of 17−18 years, whereas the unisutural, purely cranial, deformities can be corrected between six and 24 months of life [161].

18.5.1 Craniofacial Syndromes

18.5.1.1 Crouzon Syndrome (Acrocephalosyndactyly Type II)

Crouzon syndrome is characterized by premature fusion of the calvarial sutures, midface hypoplasia, shallow orbits, and ocular proptosis. The clinical features were first described by Crouzon, a French neurologist, in 1912. It is one of the more common craniosynostostic syndromes [162] and is transmitted as an autosomal dominant condition (similar to Apert syndrome, where increased paternal age seems significant) [163]. Premature fusion of both coronal sutures, resulting in brachycephaly, is the most common calvarial deformity, but scaphocephaly, trigonocephaly and cloverleaf skull deformity have been observed as well (Fig. 18.80). The craniosynostosisis is often complete by 2–3 years of age, but occasionally the

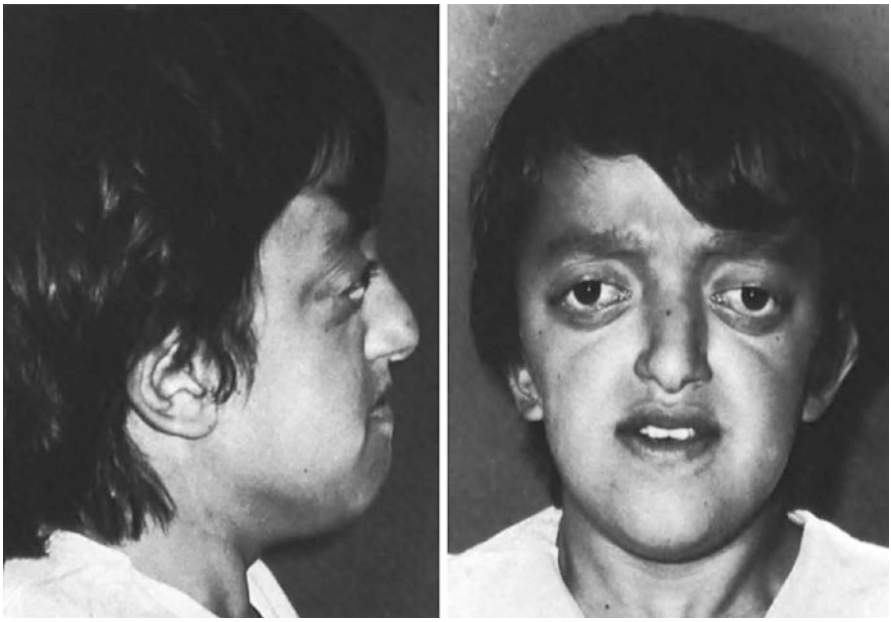


Fig. 18.79 Twelve-year-old boy with Crouzon syndrome. Surgical management in The Craniosynostoses_ Causes, Natural History, and Management-Springer David John David FRCS, FRACS, David Ernest Poswillo DDS, DSc, FDSRCS, FRCPath, Donald Allen Simpson AM, MS, FRCS, FRACS (auth.)

sutures are fused at birth. The cranial base sutures are frequently involved, resulting in maxillary or midface hypoplasia. Maxillary hypoplasia is evidenced by a narrower dental arch and a constricted high palatal arch. Normal mandibular growth leads to a class III malocclusion (mandibular prognathism). The midface hypoplasia is reflected in the shallow orbits with exorbitism, a consistent finding, and can result in exposure conjunctivitis or keratitis. The exorbitism can be so severe that the globe can be herniated through the eyelids, requiring immediate reduction (Fig. 18.79). A trap for the unwary is that the sutures are not always fused at birth; fusions can appear during the first 2 years of life [164], with a high risk for development of raised ICP [165]. A conductive hearing deficit is not uncommon. There are no commonly-reported anomalies of the digits in this patient population.

Apert Syndrome (acrocephalosyndactyly type I)

In 1906, Apert described a syndrome characterized by craniosynostosis, exorbitism, midface hypoplasia, and symmetric syndactyly of both hands and feet [166]. Most cases are sporadic, although several with autosomal dominant transmission have been reported. In an affected child the head is “tall” but shortened from front to back (turribrachycephaly) and there is midfacial (maxillary) retrusion, proptosis, a downwards cant(us) of the palpebral fissures, and hypertelorism [13] (Fig. 18.81).

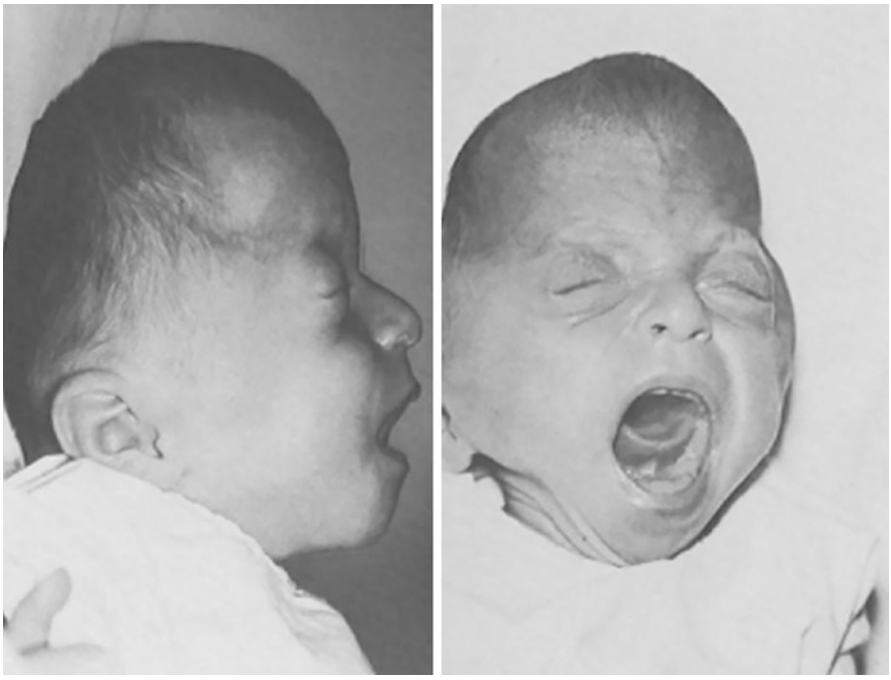


Fig. 18.80 Crouzon syndrome in a 3-week-old infant. Right: There is widespread calvarial synostosis and severe craniostenosis; the middle cranial fossae have expanded disproportionately giving a cloverleaf deformity in A-P projection (triphyllocephaly). Left: The same child: the temporal bulges were even more striking than these photographs suggest. Craniofacial Syndromes in The Craniosynostoses_ Causes, Natural History, and Management-Springer David John David FRCS, FRACS, David Ernest Poswillo DDS, DSc, FDSRCS, FRCPath, Donald Allen Simpson AM, MS, FRCS, FRACS (auth.)

However, the essential clinical feature is complex fusion (syndactyly) of the fingers and toes [167–169], which can require frequent surgical procedures before functional effectiveness is achieved [170].

Visceral [171] and cutaneous [172] abnormalities can also occur. At birth, perhaps only the coronal sutures will be fused in the child with Apert syndrome, the sagittal and (in particular) the metopic sutures remaining wide open. However, all the sutures fuse progressively and the process is usually complete before the age of 2 years. When the thumb is free, it is broad and deviates radially. In the feet, the syndactyly usually involves the second, third, and fourth toes. The hand anomalies are so severe and functionally deabilitating that referral to a hand surgeon with special expertise in this area is essential (Fig. 18.82). An extensive review of central nervous system (CNS) problems in patients with Apert syndrome shows a higher than normal incidence of delayed mental development, but many of them develop normal intelligence.

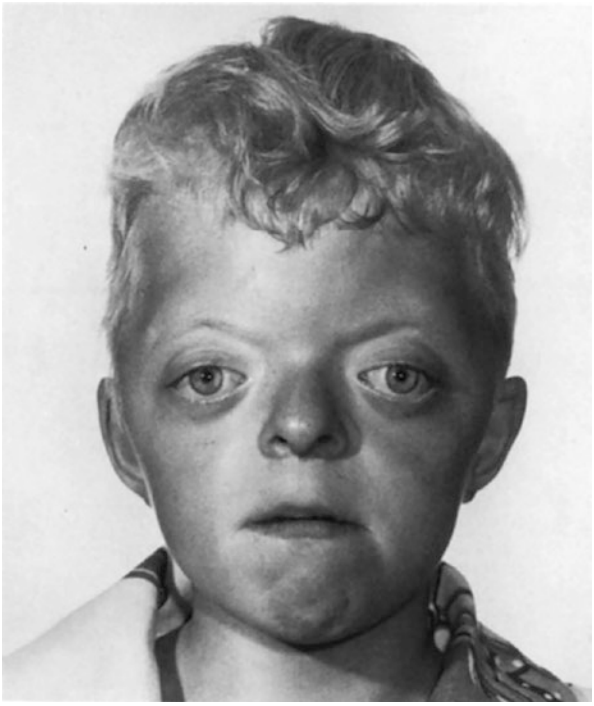


Fig. 18.81 Eight-year-old boy with Apert's syndrome. Apert's and Crouzon's Syndromes Contrasted: Qualitative Craniofacial X-Ray Findings, Kreiborg, Sven (et al.) in Craniofacial Surgery, Springer, 1987

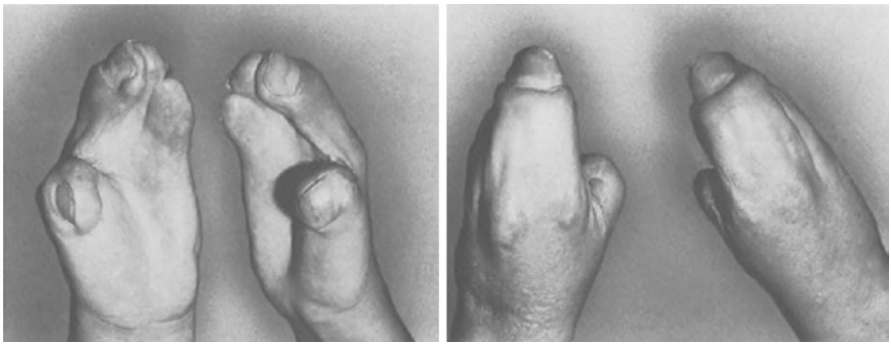


Fig. 18.82 The hands in Apert syndrome. Craniofacial Syndromes, in The Craniosynostoses_ Causes, Natural History, and Management-Springer David John David FRCS, FRACS, David Ernest Poswillo DDS, DSc, FDSRCS, FRCPath, Donald Allen Simpson AM, MS, FRCS, FRACS (auth.)

Pfeiffer Syndrome (acrocephalosyndactyly type V)

This syndrome was described by Pfeiffer in 1964. It includes an autosomal-dominant craniosynostosis-associated syndrome characterized by suture fusions that range from bicoronal synostosis alone to pan-synostosis (with or without the cloverleaf skull deformity) [173]. Those affected have digital abnormalities such as curved and shortened thumbs and great toes [174], and digital fusions.

Cohen [175] divided Pfeiffer syndrome into three types on the basis of clinical severity. In children with type 1, those least affected, there is often little more than bicoronal synostosis and midface retrusion. Their neurocognitive development can be normal, particularly if early complications have been aggressively treated [176]. In types 2 and 3 Pfeiffer syndrome, the degree of midface and frontal retrusion is severe enough to obstruct the upper airway and cause ocular protrusion sufficient to threaten the corneas (Fig. 18.83). The shortening of the skull base and crowding of the posterior fossa due to the bilateral lambdoid component of the pan-synostosis produces an increased risk for hydrocephalus. Ankylosis (bony and soft tissue) of the elbows [46] and knees is common, as are fusions of the cervical vertebrae [177]. The broad thumbs and great toes are the hallmark of the syndrome, but the findings are frequently subtle.

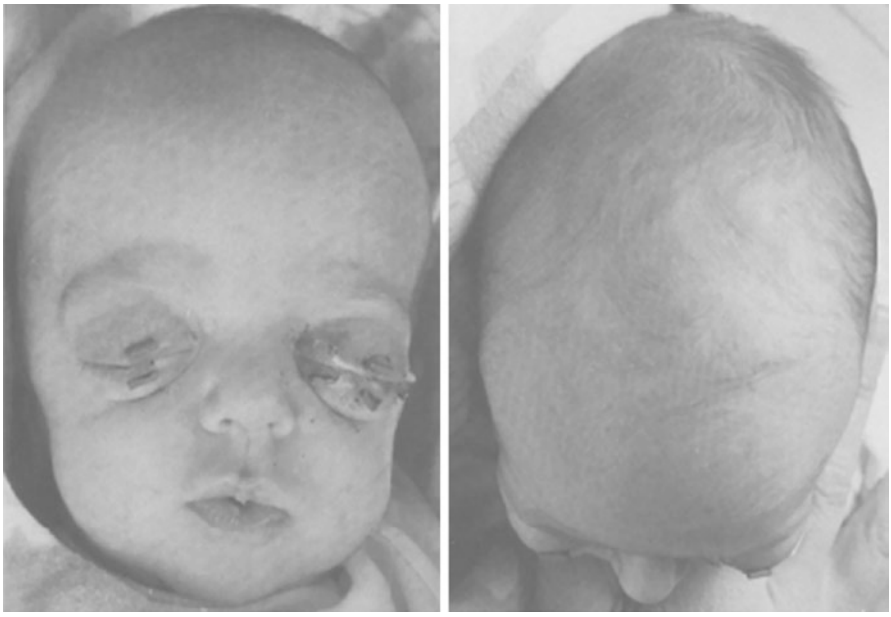


Fig. 18.83 A Pfeiffer syndrome is associated with ocular proptosis and hypertelorism. Temporary tarsorrhaphies serve to maintain the ocular globes within their shallow orbits. Note the turricephaly. B Viewed from above, the ocular proptosis is striking. There are ridges at the sites of the prematurely fused coronal sutures. Craniosynostoses, p. 33-61, in Craniofacial Deformities, Atlas of Three-Dimensional Reconstruction from Computed Tomography, Springer-Verlag New York, 1990

18.5.2 Saethre-Chotzen Syndrome (acrocephalosyndactyly type III)

This syndrome was first described by Saethre in 1931 and by Chotzen in 1932. It is autosomal-dominant but very variable in presentation [178], generally a brachycephalic skull, a low-set frontal hairline, and facial asymmetry with ptosis of the eyelids. The low-set hairline is a constant feature. Complications such as exorbitism and airway obstruction are uncommon, raised ICP is rarely of functional significance [179], and the neurocognitive outcome is often no more than modestly affected, if at all [178] (Fig. 18.84).

18.5.3 Carpenter Syndrome

This rare syndrome [180] was first described by Carpenter in 1901, but not recognized as a significant clinical syndrome until 1966, when it was reported by Temtamy. The mode of transmission is autosomal recessive, the only craniofacial syndrome with this type of inheritance. It is also known as acrocephalopolysyndactyly because

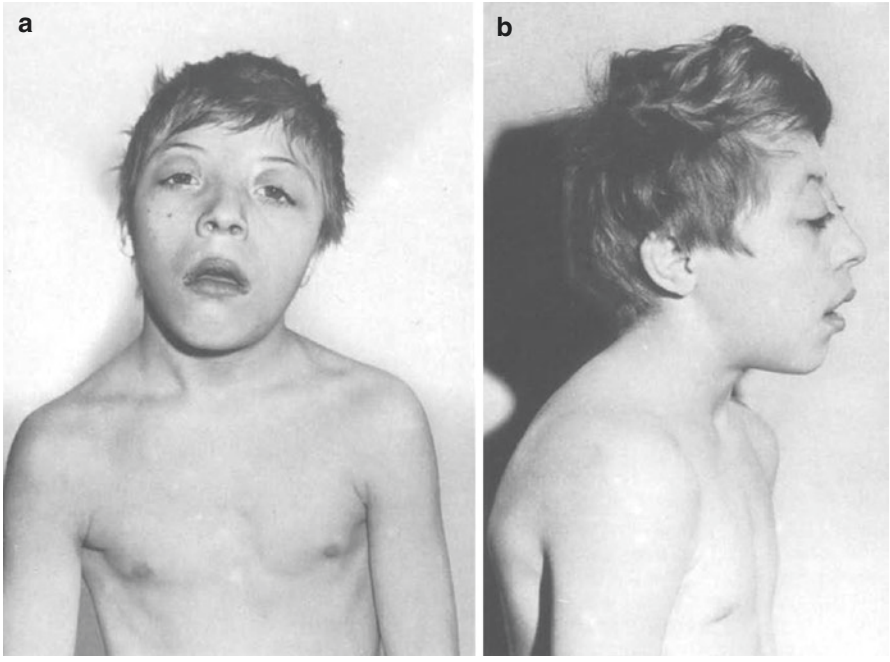


Fig. 18.84 Nine-year-old patient with Saethre-Chotzen Syndrome. Kopyść, Z., Stańska, M., Ryżko, J. et al. The Saethre-Chotzen syndrome with partial bifid of the distal phalanges of the great toes. *Hum Genet* 56, 195–204 (1980). https://doi.org/10.1007/BF00295694

of the extra digits that form part of the clinical presentation. The cranial deformity is due to various combinations of craniosynostosis [181, 182]. Low-set ears and lateral displacement of the inner canthi are also prominent features. Mental deficiency has been reported, and congenital heart defects have been reported in as many as 33% of cases (Fig. 18.85).

18.5.4 Muenke Syndrome

This condition, one of the less severe craniofacial syndromes, was "discovered" during the explosion of knowledge of genetics during the 1990s [127]. Muenke syndrome has many manifestations [128], but the synostosis typically affects either one or both coronal sutures [183]. Those with bicoronal synostosis typically have a broad and shallow supraorbital region with a protruding upper forehead (Fig. 18.86). Complications such as raised ICP and airway obstruction are rare; however, although a child with Muenke syndrome can develop normally, a degree of learning difficulty is not uncommon [127].

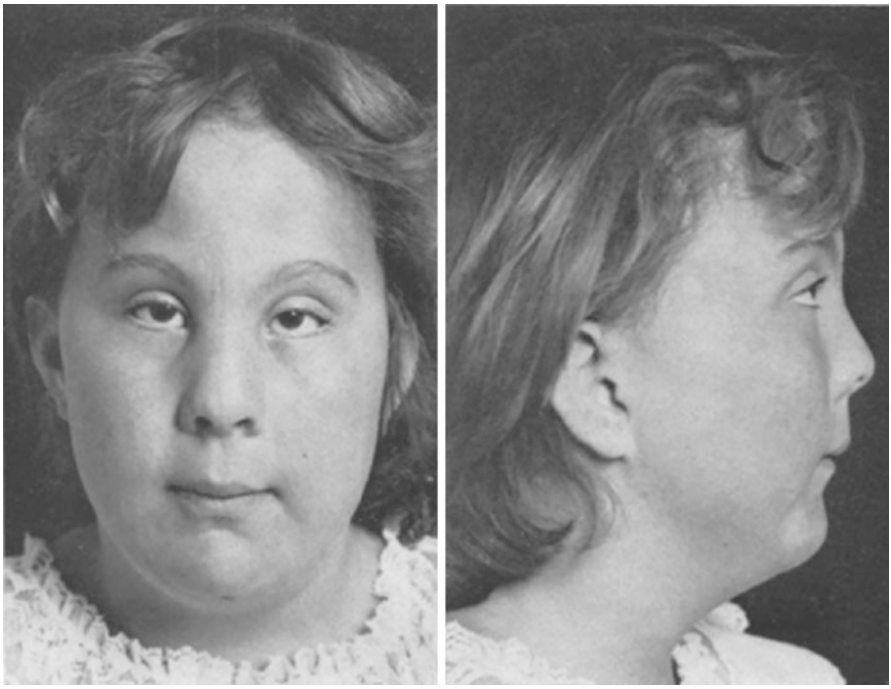


Fig. 18.85 Carpenter syndrome; patient age is 8 years. (White, J., Boldt, D.B., David, D.J. et al. Carpenter syndrome with normal intelligence and precocious growth. *Acta neurochir* 57, 43–49 (1981). https://doi.org/10.1007/BF01665112)

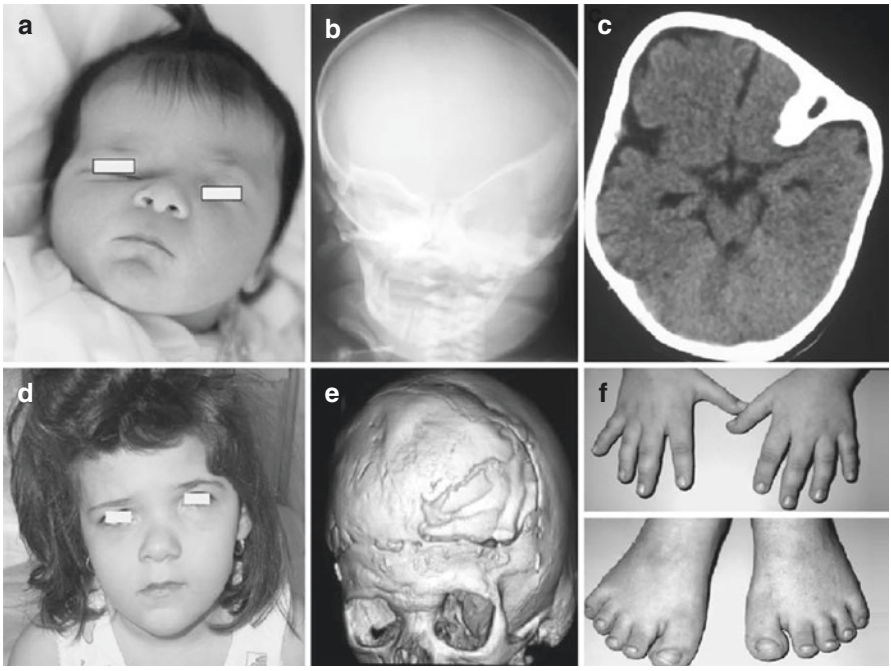


Fig. 18.86 (**a**) Patient at birth. Note the left frontal and facial hypoplasia, the abnormal appearance of the left orbit and the contralateral deviation of the nose. (**b**) The plain X-ray of the skull shows the typical harlequin orbit. (**c**) The skull CT scan demonstrates the unilateral flattening of the left frontal bone and the typical monolateral deviation of the midline. (**d**) The patient at 6 years of age presenting with residual left anterior plagiocephaly, which was also evident in (**e**), a 3D CT scan of the skull. (**f**) The thumbs are minimally proximally placed and **g**, the toes are slightly broad, Sabatino, G., Di Rocco, F., Zampino, G. et al. Muenke syndrome. *Childs Nerv Syst* 20, 297–301 (2004). https://doi.org/10.1007/s00381-003-0906-y

18.5.5 Cloverleaf Skull (Kleeblattschädel) Deformity

Cloverleaf skull is a descriptive term given to a particularly severe form of synostosis-associated cranial deformity [184], one that poses a particular challenge for the craniofacial surgeon [185, 186]. Although it usually occurs in association with Pfeiffer syndrome (of which it forms type 2), it can occasionally complicate Apert and Crouzon syndromes. Cloverleaf skull is produced by a particular combination of suture fusions and raised ICP due to hydrocephalus. The sagittal and squamoparietal sutures are open, but the complexity comes from a bony constriction band that runs posteriorly from the pterions to the lambdoids. When hydrocephalus is added to this bony pattern, the infant's skull expands upwards (above) and laterally (below) the constriction band to produce a characteristic trefoil (cloverleaf) shape [175, 187–189] (Fig. 18.87a, b).

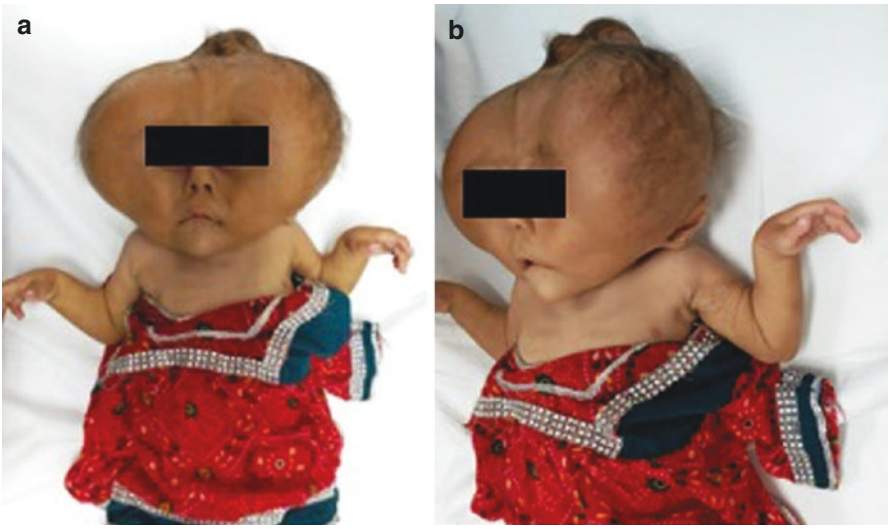


Fig. 18.87 Patient with trilobar skull. b A side angle of the trilobar skull (Sajid, M.I., Malik, N., Balouch, S.S. et al. Kleeblattschädel skull presenting in concert with Pfeiffer syndrome. *Egypt J Neurosurg* 34, 41 (2019). https://doi.org/10.1186/s41984-019-0068-1)

18.5.6 Surgical Approaches and Treatments for Craniosynostosis

There are various treatments for children with syndromic craniosynostosis. Some conditions need urgent interventions, such as tarrsorhaphy for exposure keratopathy and corneal ulceration, ventricular shunting or urgent surgical decompression for patients with multiple suture closure and papilledema, and even tracheostomy for airway management. The most common type of craniosynostosis is bilateral coronal synostosis, but this can have different patterns. Cervical abnormalities must be encountered for modification of operative positioning, ventriculoperitoneal shunting and skull height reduction. Most interventions preclude a modified prone position for whole-vault cranioplasty; sometimes a two-stage procedure is required.

18.5.6.1 Bilateral Coronal Synostosis

Bilateral coronal synostosis is usually described with flattened occiput, flattening of the caudal portion of the frontal bones and supraorbital ridges, and bulging of the cephalad portion of the frontal bones. The squamous portion of the temporal bones is unusually prominent. The techniques differ according to the patient's age.

18.5.7 Children Younger than 1 Year

The modified prone position has been proved optimal for better simultaneous exposure of the anterior and posterior parts of the skull, but only after craniovertebral abnormalities are excluded. A two-stage approach should be elected in supine and subsequently in prone position if the patient has associated Arnold-Chiari malformation and instability of the cervical spine. The skin incision follows the coronal pathway, usually in front of both tragi, and subperiosteal dissection is done anterior and posterior. The anterior limit is the lateral portion of the orbital rims at the level of the fronto-zygomatic suture bilaterally and the posterior limit is the foramen magnum. Frontal and parieto-occipital bone flaps are elevated, leaving the bone over the vertex of the skull and two lateral struts extending from the vertex to the skull base. Barrel-stave osteotomies are performed in the occipital region, individual bone segments being fractured posteriorly to increase the potential space in the posterior skull. The superior orbital rims are elevated bilaterally to the level of the fronto-zygomatic suture, contoured and fixed in the advanced position. The squamous portion of the temporal bone is elevated with the overlying temporal muscle and advanced and attached to the superior orbital rims. An ICP monitor should be placed in the right parietal bone, off the midline. The struts extending from the vertex of the skull in the parietal region to the basal temporal region are divided, shifted posteriorly and lowered (usually 1–1.5 cm) to change the position of the vertex of the skull, flatten the frontal contour and reduce the skull height. Height reduction corrects the abnormal turret shape of the skull and encourages shifting of the brain and dura to fill the space created in the occiput. This technique elongates the anterioposterior axis of the skull. The height is reduced slowly by monitoring ICP under normotension and normocapnia. The ICP should only be increased for brief periods, followed by rapid reduction to normal tension as the skull height is reduced. The bifrontal bone graft undergoes radial osteotomies, reshaping as desired, and attached to the superior orbital rim but not to the anterior parietal region. A neocoronal suture bone defect approximately 1cm wide is created at the site of the normal coronal suture. The posterior occipital bone is reshaped to achieve greater convexity. A defect of approximately 1cm is created between the reshaped bone graft and surrounding bone to allow the parieto-occipital region to expand preferentially (Fig. 18.88).

18.5.8 Children Older than 3 Years

As in the previous technique, a zigzag coronal incision and supraperiosteal dissection is used to elevate the bifrontal and parietal occipital bone craniotomies. Barrel-stave osteotomies are performed in the occipital region. The orbital rims are elevated and advanced as a unit extending into the frontal process of the zygoma. The squamous temporal bone and temporalis muscle are elevated as a composite and

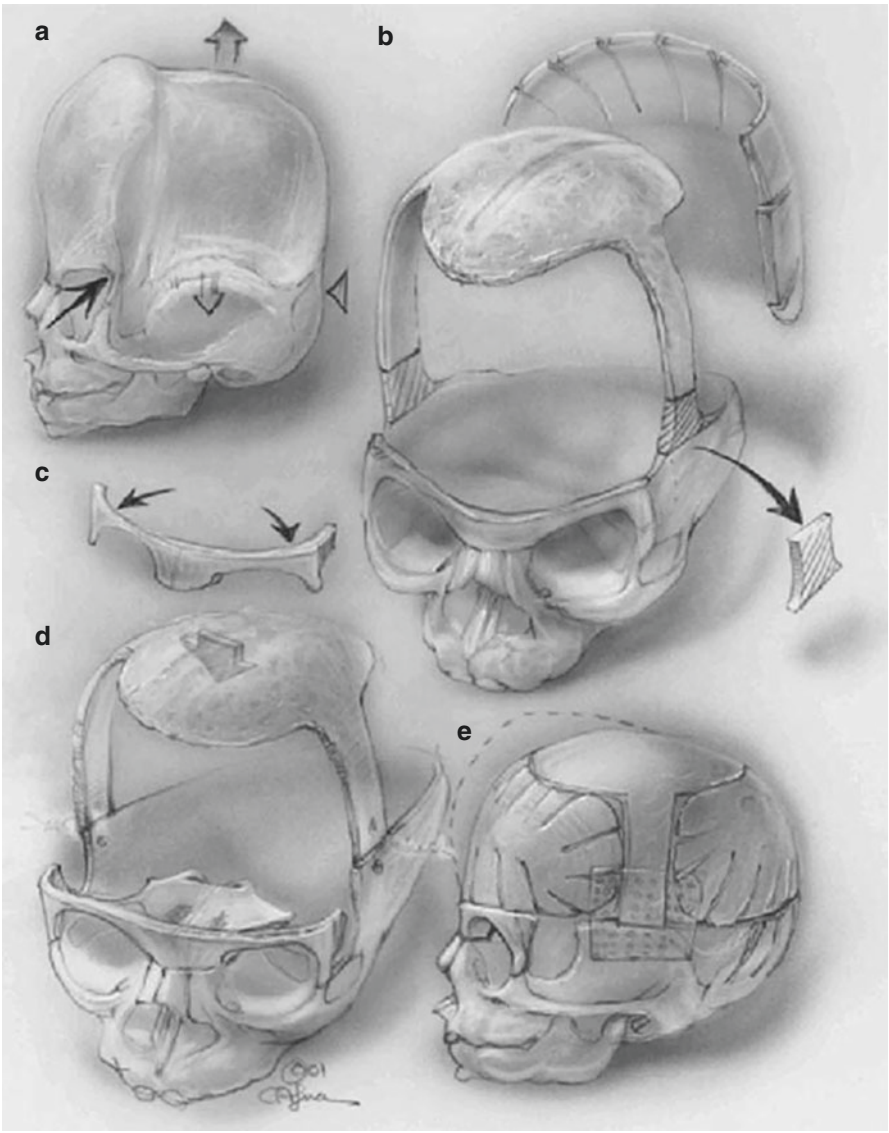


Fig. 18.88 Bilateral coronal synostosis. (**a**) Primary pathology and compensatory changes. (**b**) Bi-fronto–parietal and parieto–occipital craniotomies. (**c**) Orbital rim reconstruction. (**d**) Vault reconstruction. (**e**) Reconstruction of vault. (Jane J.A., Dumont A.S., Lin K.Y.K., Jane J.A. (2005) Craniosynostosis. In: Moore A.J., Newell D.W. (eds) Neurosurgery. Springer Specialist Surgery Series. Springer, London)

advanced to attach to the posterior border of the advanced orbital rim. The skull height is again reduced and ICP should be monitored as well. However, patients older than 3 years can require a much longer period of accommodation than the

younger child and the reduction is ordinarily less complete. Correction of more than 1cm is unusual in a child older than 3 years, whereas a 1.0–1.5 cm correction is quite common in a child younger than one. The bifrontal and parietal occipital bone grafts are then remodeled by dividing the bone segments into vertical slats weakened on the endocranial surface by kerfs (channels) and then reshaped with bone-molding instruments and microfractures. Individual bone slats are reapproximated frontally to the superior orbital rim and proceed posteriorly to the occiput.

18.5.9 Children Between 1 and 3 Years of Age

The principles of cranial vault reconstruction in bilateral coronal synostosis are the same as in the previously-explained procedures. The maturity of the bone of the skull must be considered carefully so that the appropriate techniques for bone cutting, molding and reshaping are chosen.

18.5.9.1 Posterior Vault Distraction

The advantages of distraction osteogenesis have been highlighted by its application to the cranial vault, midface, and mandible, including maintenance of bone vascularity, production of vascularized bone, limiting production of dead space, and gradual expansion of the soft tissue envelope that allows for greater advances in the jaws to be achieved and maintained [190–194]. The disadvantages of distraction include the need for a second procedure for device removal, potential for device-related complications, and prolonged treatment time. Distraction has been used for over a decade to address the frontoorbital region in craniosynostosis; however, its application to the posterior vault (PVD) in syndromic craniosynostosis has been described only recently [190, 195, 196]. It is particularly advantageous for patients with severe turricephaly and occipital flattening because posterior expansion allows for a significant expansion of the intracranial space and improvement of head shape. Initial reports indicate potential improvement in the appearance of even the anterior vault, which was untouched, although no supporting quantitative data have been presented [195]. Another interesting benefit of distracting the posterior vault is the remarkable improvement in the cerebellar anatomy of patients with syndromic craniosynostosis and its frequent accompaniment, Chiari malformation [195, 197, 198]. PVD in these patients appears to affect the cerebellum as significantly as a traditional decompression procedure; however, no side-by-side comparison of the two techniques has been published to date. Perhaps the most significant advantage of distracting the posterior over the anterior vault is the simplicity of the anatomy. The posterior vault is more forgiving, with a large surface area for distribution of tension, and irregularities easily hidden by hair. The posterior vault has fewer esthetically critical bony features, whereas the anterior vault has to account for the orbital volumes, cornea to orbital rim relationships, and facial proportions and harmony.

Thus, PVD allows for greater movement, certainly more than distraction in the anterior vault and supraorbital region. Advancements of over 30mm and volumetric gains of over twice those of a single-stage FOA are routine (Derderian et al, unpublished data, 2012) [190]. The long-term durability of these procedures and the ability of the distracted calvaria to grow are not yet known. However, it will be interesting to see how maintenance of the bone flap vascularity affects growth and retention of the overcorrection in the long term. Certainly the stability added to the rigid fixation by the distraction devices during the distraction and consolidation phases withstands the propensity for relapse created by the weight of the head while in the supine position. PVD could provide such protection to the growing brain that FOA can be delayed until an older age, perhaps even making a monobloc the first frontoorbital procedure; however, long-term data on growth and function are not yet available. The procedure is performed with the patient in a prone position. A bicoronal incision is used for access, the scalp is reflected, and limited dural dissection is performed to allow a posterior craniotomy and barrel-staving at the base of the occiput that prevents a step-off deformity. Two collinear 1.5mm mandibular distraction devices are applied along a posterior or posteroinferior vector, depending on skull morphology, and the scalp is closed. Activation starts at the end of a 5–7-day latency period and proceeds at 1mm/day to reach advancements of 20–30 mm. After a consolidation period of 6–8 weeks, a limited procedure is required for device removal (Fig. 18.89).

18.5.9.2 Spring-assisted Cranioplasty

Spring-assisted cranioplasty (SAC) uses continuous force generated by a spring across either an osteotomy or a patent suture to achieve a change in head shape and expand the intracranial volume. It is most commonly used in sagittal suture synostosis; however, Lauritzen and others advocate its use in any of the symmetrical patterns of craniosynostosis including syndromic craniosynostoses [199, 200]. It is optimally employed at younger ages when the cranial bones and scalp are most pliable. The morbidity associated with the spring-assisted technique is less than that with open procedures, with shorter operative times; however, it does require a second procedure for device removal [201]. Even though a constant force is applied across the osteotomy or suture with this technique, the surgeon has no control over the distance or rate of advancement at which the bones separate from one another. The expansion is limited only by the equilibrium of forces between the spring and the opposing bones and scalp, which is reached rapidly; thus, this is not a form of distraction osteogenesis. Nevertheless, this is purely a technical note as infants younger than six months can have large bony defects closed with good-quality bone. Despite several reports of favorable outcomes from the use of spring-assisted techniques, SAC remains somewhat controversial. In particular, one must consider the control and stability of expansion when planning SAC in the posterior vault to account for the additional opposing force from the weight of the infant skull (Figs. 18.90 and 18.91).

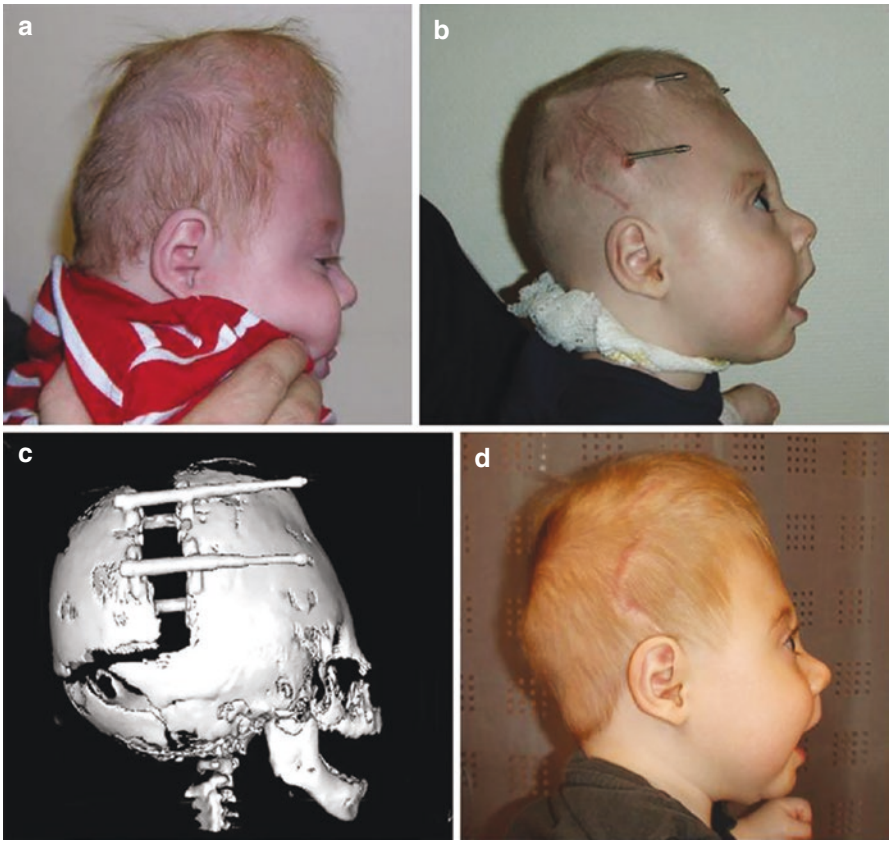


Fig. 18.89 (**a**) Preoperative photograph at corrected age of 4 months. (**b**) Photograph at the end of consolidation. (**c**) Three-dimensional CT at the end of consolidation. (**d**) Photograph at 6 months follow-up, prior to frontoorbital advancement (Nowinski, D., Saiepour, D., Leikola, J. et al. Posterior cranial vault expansion performed with rapid distraction and time-reduced consolidation in infants with syndromic craniosynostosis. *Childs Nerv Syst* 27, 1999 (2011). https://doi.org/10.1007/s00381-011-1563-1)

18.5.9.3 Fronto-orbital Advancement

The surgical goals of frontal-orbital advancement are threefold: (1) to release the synostosed suture and to decompress the cranial vault; (2) to reshape the cranial vault and advance the frontal bone; and (3) to advance the retruded supraorbital bar, providing improved globe protection and an improved esthetic appearance. The procedure is performed through a coronal incision. With the assistance of a neurosurgical team, a frontal craniotomy is performed to release the synostotic suture and elevate the frontal bone. Once the frontal bone is removed, the brain is gently retracted to expose the underlying retruded supraorbital bar, which is advanced in a

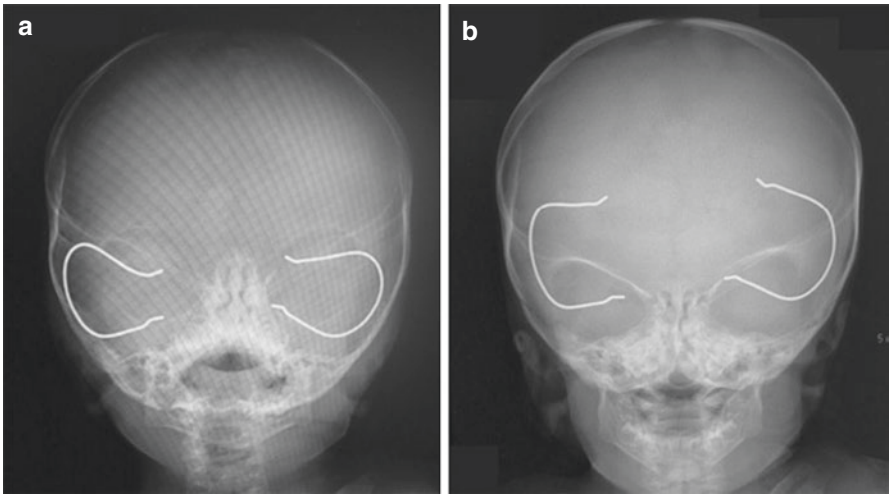


Fig. 18.90 Orientation of the springs in a vector along the line of the sagittal suture, rather than perpendicular to the suture, to prevent exacerbation of brachycephaly. (**a**) At the time of spring insertion, (**b**) 7 weeks after spring insertion (Davis, C., MacFarlane, M.R. & Wickremesekera, A. Occipital expansion without osteotomies in Apert syndrome. *Childs Nerv Syst* 26, 1543–1548 (2010). https://doi.org/10.1007/s00381-010-1144-8)

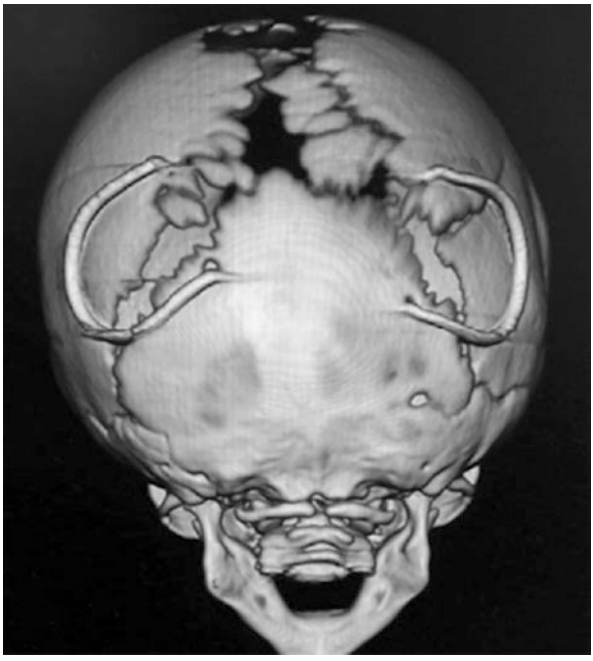


Fig. 18.91 The quality of the adjacent bone as is shown in this case could prevent orientation of the springs directly along the line of the sagittal suture (Davis, C., MacFarlane, M.R. & Wickremesekera, A. Occipital expansion without osteotomies in Apert syndrome. *Childs Nerv Syst* 26, 1543–1548 (2010). https://doi.org/10.1007/s00381-010-1144-8)

tongue-in-groove manner and secured with wires, miniplates, or sutures. Cranial vault remodeling depends on the preoperative head shape. For severe turricephaly, a total cranial vault reshaping is performed. This procedure allows for a significant reduction in the vertical height of the skull. For the child with mild turricephaly, only the anterior two-thirds of the vault are remodeled. The supraorbital bar and forehead are advanced into an overcorrected position to allow for increased growth of the cranial vault. Following this initial frontal-orbital advancement and cranial vault remodeling procedure, the child is seen on a 6–12-month basis by the craniofacial team. Continued growth of the cranial vault and midface are monitored closely by three-dimensional CT scans and clinical observation. Although frontal-orbital advancement provides excellent decompression of the craniosynostosis and moderate improvement in the shape of the cranial vault in the early postoperative period, continued growth restriction in both the cranial vault and the midface region often produces poor long-term esthetic results (David and Sheen, 1990) (Posnick et al., 1993) (Whitaker et al., 1985). If signs of increased ICP, severe exorbitism, or an abnormally shaped cranial vault develop or persist, further surgery for cranial vault remodeling is indicated [202]. Craniotomies are planned and executed to preserve the bone pieces needed for forehead remodeling. First, the placement of drill holes is planned and executed and the dura is carefully and bluntly dissected from the cranial surface of the bone around the drill hole and under the planned osteotomy lines. Then a craniotome is used for the necessary osteotomies in the cranial bone. When the bone piece is circumferentially osteotomized, it is carefully lifted up and the sites of dural attachment are freed under direct vision. The bone piece is secured with a bone-holding forceps during this maneuver. The bone pieces are temporarily removed and kept in swabs soaked in saline. The dura mater is carefully released from the posterior or cranial surface of the supraorbital bar, which is removed after the osteotomies have been done with small cutting osteotomes. The intraorbital content is carefully protected with a brain spatula of medium width. Care must be taken not to exert any traction or pressure on the orbital septum and its contents. The tip of the osteotome must be visible in the orbit at all times during the osteotomy. The supraorbital bar is then removed and reshaped to improve the esthetic appearance of this area. The curving can be adjusted or the slight hypo- or hyper-telorism can be corrected. The forehead is remodeled using the previously-removed bone pieces. After the shape is improved, osteosynthesis is done with resorbable 3-0 Vicryl sutures in a figure-eight type suture to fix the new forehead rigidly in its desired three-dimensional shape. The new forehead is then put back on to the supraorbital bar and advanced ‘en bloc’ anteriorly to enlarge the volume of the anterior cranial fossae and to deepen the superior aspect of the orbits. With an advancement of 10–25 mm it is necessary in most cases to use stainless steel or titanium miniplates for rigid fixation, to prevent the forehead from falling back postoperatively. The miniplates are fixed with screws to the lateral surface of the supraorbital bars as well as to the parietal bone or bone overlying the temporal fossa. All plates and screws are routinely removed after 6–8 weeks (Fig. 18.92).

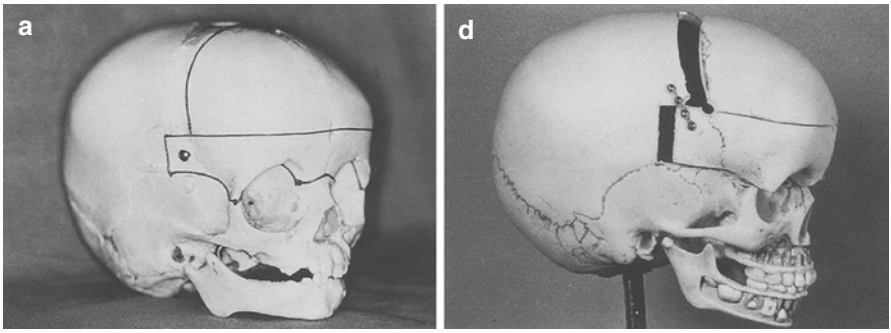


Fig. 18.92 Scheme of procedure for bilateral fronto-orbital advancement. (Reinhart, E., Mühling, J., Michel, C. et al. Craniofacial growth characteristics after bilateral fronto-orbital advancement in children with premature craniosynostosis. *Child's Nerv Syst* 12, 690–694 (1996). https://doi.org/10.1007/BF00366152)

18.5.10 Surgical Approaches and Treatments for Midface Hypoplasia

The first attempt to correct the midface deformity in a syndromic craniosynostosis patient was by Sir Harold Gillies, who performed a Le Fort III procedure. This procedure, initially abandoned by Gillies, was later popularized by Tessier. The Le Fort III can be performed alone or, if all permanent teeth have erupted, in conjunction with a Le Fort I advancement. The monobloc frontofacial advancement procedure, which involves advancement of the LeFort III fragment in coordination with the frontal bar, was developed by Ortiz-Monasterio. It offers the advantage of simultaneously correcting the supraorbital and midface deformities, but is associated with greater blood loss and a higher infection rate, probably as result of the direct communication between the cranial and nasal cavities. This increased risk makes the monobloc procedure contraindicated during the neonatal period. Currently, Le Fort III via a subcranial approach is probably the procedure of choice for correcting the midface deformity, although good results with the monobloc have been reported, especially via distraction. The exact timing of midface correction remains controversial among craniofacial surgeons [203]. Some craniofacial centers advocate early surgical correction between the ages of 4 and 7 years; others prefer to wait until skeletal maturity is reached at around puberty, unless airway obstruction or severe exorbitism dictates immediate early surgery. Advocates of delayed surgical correction cite evidence of a high incidence of recurrent class III malocclusion in patients who undergo surgery earlier (4–9 years), often requiring a secondary Le Fort III procedure during teenage years. Advocates of early correction of the midface deformity believe the overall esthetic improvement will have a significant positive psychological effect and improve self-esteem in these children, and they accept a secondary Le Fort III or monobloc osteotomy as a standard step in treatment [203].

18.5.10.1 Le Fort III Osteotomy

The Le Fort III procedure increases the projection of the midface medially at the nose, laterally at the inferior orbit, and inferiorly at the level of the occlusal arch in the maxilla. It effectively enlarges the orbit by advancing the orbital rim, decreasing globe prominence and proptosis. The timing of repair varies, but generally a Le Fort III osteotomy is performed on patients 4–5 years of age because of its positive psychological benefit. It might need to be performed later in life because the advanced midface does not always grow commensurately during the postoperative period. The procedure could be required before this time, especially if exorbitism (particularly in patients with Crouzon's syndrome) results in corneal exposure or keratopathy. The Le Fort III procedure can be performed through subcranial or intracranial routes. Determination of the optimal route is based on the position of the cribriform plate, previous surgical procedures and the need to advance the superolateral orbital rim to correct the frontal abnormalities.

If the subcranial route is elected, the patient is placed supine and intubated nasotracheally if possible. Tracheostomy or, if occlusion is less critical, oral intubation can be performed. Arch bars are applied to the teeth. An occlusal wafer constructed from preoperative dental models is sometimes required postoperatively to fix the advanced maxilla securely.

A coronal incision is made, and the subperiosteal dissection is carried out after the orbital rim dissection. Periorbital dissection is performed posterior to the lacrimal system and the medial canthus is left intact. If inferior osteotomies cannot be made from above, a transconjunctival inferior lid incision can be used to expose the orbital floor. Osteotomies are performed transversely through the nasal bone, caudal to the frontonasal suture, posterior to the lacrimal crest and inferior to the inferior fissure. Lateral osteotomies are made through the zygoma at the level of the frontozygomatic suture or more superiorly along the orbital rim. The lateral orbital osteotomy is extended through the pterygomaxillary fissure with a curved osteotome. A finger is placed intraorally to gauge the depth and direction of the osteotome. The midline osteotomy is directed inferiorly and posteriorly through the perpendicular plate of the ethmoid. Care must be taken to avoid sectioning the endotracheal tube. A separate intraoral incision and sectioning of the pterygomaxillary fissure can be needed to complete the osteotomy from above (Fig. 18.93).

Rowe disimpaction forceps are used to down-fracture the maxilla (Fig. 18.94). Hemorrhage can be brisk at this time but can be controlled by reimpaction of the maxilla. Branches of the internal maxillary artery often bleed heavily but they rarely require direct control. Once the maxilla is completely mobile, anterior and inferior displacement is performed. Bone grafts harvested from the ilium, cranium, or rib are then interposed in the gaps between the cranium and maxilla. An acrylic wafer is placed and intermaxillary fixation of the mandibule is performed, unless the child is young enough for occlusion not to be critical. Miniplate fixation stabilizes the bone grafts and the maxilla at the nasomaxillary, zygomaticomaxillary, nasofrontal and frontozygomatic buttresses and junctions. The zygomatic arc is also plated or wired. The nasal bone can require onlay grafting using a costochondral graft, and

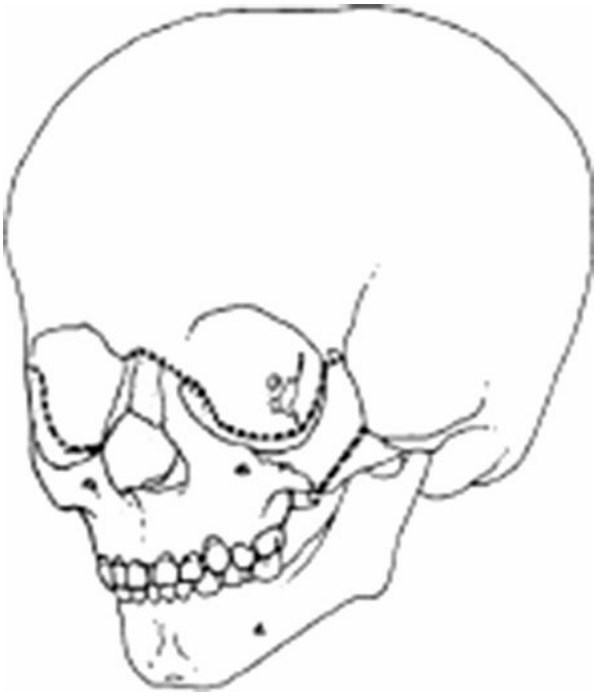


Fig. 18.93 Le Fort III corresponds to a craniofacial disjunction and permits the whole midface to be advanced. (Marchac, D., Arnaud, E. Midface surgery from Tessier to distraction. *Child's Nerv Syst* 15, 681–694 (1999). https://doi.org/10.1007/s003810050458)

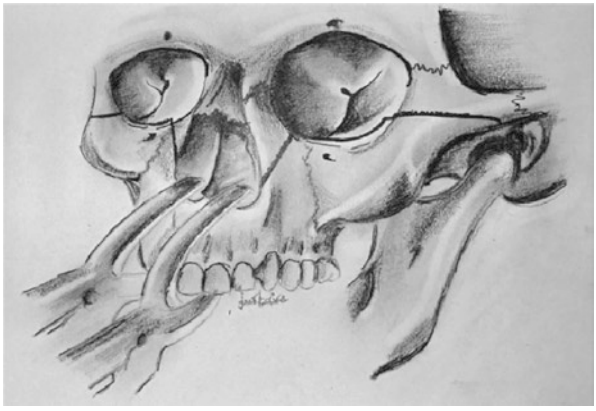


Fig. 18.94 Rowe forceps are placed with a palatal protector. (García y Sánchez, J.M., Romero Flores, J., Gómez Rodríguez, C.L. et al. "Modified Oblique Le Fort III Osteotomy" New Concepts. *J. Maxillofac. Oral Surg.* 16, 22–42 (2017). https://doi.org/10.1007/s12663-016-0893-7)

the orbital floor usually requires additional bone grafts to reconstruct the new floor. Postoperatively, miniplate fixation is typically left in for 4–6 weeks, but if the fixation is rigid and secure, the intermaxillary fixation device can be removed considerably earlier.

The intracranial approach to Le Fort III is essentially the same as for the subcranial Le Fort III, except that a frontal craniotomy is performed to retract the frontal lobes and dura before the midline and lateral periorbital osteotomies are performed.

This approach provides greater safety for patients who have a low-lying cribriform plate; however, this risk is balanced by the inherent risk of a frontal craniotomy in a patient who has probably had previous surgery in this area.

18.5.10.2 Monobloc Advancement

The monobloc procedure was developed by Ortiz Monasterio and colleagues [204] and represents an effort to correct the fronto-orbital and anterior cranial base hypoplasia and simultaneously to address the midface and maxillary retrusion in one operation. The procedure assumes that the length of the nasal profile is correct or will not be changed at surgery (Fig. 18.95).

The patient is placed supine and a lumbar drain might be required. A bifrontal craniotomy is performed, and a bifrontal bone graft with parietal "tongues" to secure the bifrontal segment is taken as a unit. A 5mm segment of frontal bone is left above the apex of the superior orbital rim, which transverses the forehead. An orbital roof osteotomy is performed posterior to the midpoint of the globe, extending medially to the midline, but with the anteriormost osteotomy line in front of the cribriform plate (Fig. 18.96). The rest of the procedure is identical to Le Fort III. The frontal bone can be reshaped if necessary using vertically oriented slats to achieve a normal forehead contour. Elements of the bony fixation are similar, except that the anterior cranial base is covered by a large pericranial flap secured to the surrounding

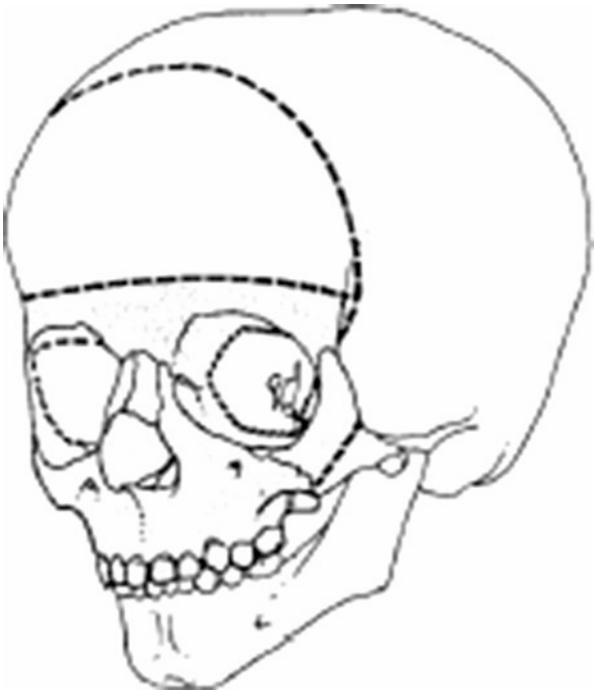


Fig. 18.95 Frontofacial monobloc: the total orbit is advanced with the midface, and the forehead is advanced above, as necessary (Marchac, D., Arnaud, E. Midface surgery from Tessier to distraction. *Child's Nerv Syst* 15, 681–694 (1999). https://doi.org/10.1007/s003810050458)

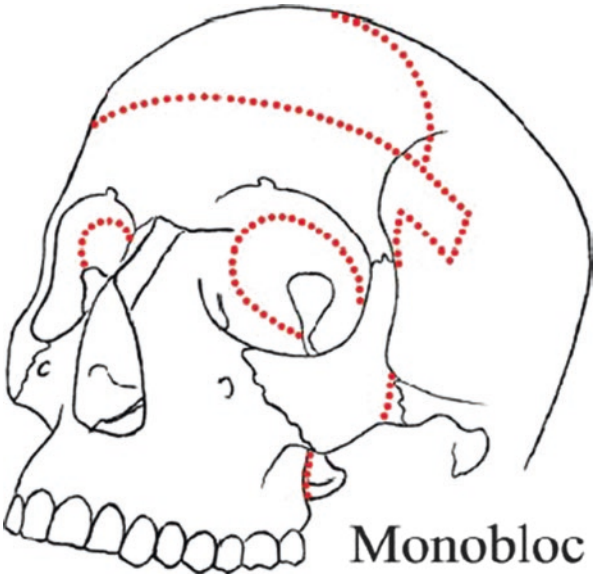


Fig. 18.96 Illustration of a "monobloc" osteotomy, with bone cut depicted across the forehead and circumferentially around the orbital walls and across the zygomatic arch. In addition, the bone cut traverses the anterior cranial base in front of the cribriform bone. The skull base and the maxilla are separated at the pterygo-maxillary fissure. Illustration courtesy of Min Li, M.D. (Havlik R.J. (2008) Distraction Osteogenesis of the Facial Skeleton. In: Pietrzak W.S. (eds) Musculoskeletal Tissue Regeneration. Orthopedic Biology and Medicine. Humana Press)

cranial base dura. This tissue separates the nasal cavity from the dura and provides support for interpositional calvarial bone grafts, which are used for the cranial base between the cribriform plate and the posterior fronto-orbital segment.

This procedure is most beneficial in the young child with a growing brain. Retrofrontal dead space can be minimized by active brain growth. When used in the older child or adult, it can be fraught with significant complications (e.g. infection) because retrofrontal dead space can persist and become infected.

18.5.10.3 Distraction Osteogenesis of the Midface

Technical advances in craniofacial surgery have included application of the techniques of distraction osteogenesis to the craniofacial skeleton. In 1992, following the work of Ilizarov [205], MacCarthy initiated distraction of the craniofacial skeleton by performing the first mandibular distraction procedure with an external distraction device [206]. Since then, technical innovations have appeared in rapid succession, leading to distraction of the maxilla and the mandible. As demonstrated by Persing [207], distraction of the cranial base as an adjunct to surgery for craniosynostosis syndrome is being developed. The techniques of distraction osteogenesis as applied to the craniofacial skeleton have shown several benefits. Gradual

distraction of bone at a rate of 1mm/day appears to create sufficient quantity and quality of bone without the need for bone grafting and associated donor morbidity. The distraction process as applied to bone also effects expansion of the soft tissue envelope, thereby reducing the constrictive component of the soft tissues. This could ameliorate the relapse seen when bone grafting is used despite the use of rigid fixation. Maxillary distraction can be carried out in multiple planes and can be external or internal. The monobloc procedure and Le Fort I and Le Fort III maxillary advancements can be performed. Advantages of distraction include (a) less blood loss and shorter operative time at the initial procedure; (b) greater advancement (up to 20mm or more) than with standard advancement techniques (6–10mm maximum); (c) no need for bone grafts as new bone forms at the osteotomy sites (hence the term *distraction osteogenesis*); (d) less risk of infection with the monobloc procedures; and (e) less relapse. Disadvantages include (a) prolonged time needed for distraction and consolidation; (b) need for a second procedure to remove the buried devices; and (c) need to wear an external device for a prolonged period. Overall, distraction osteogenesis has improved the results obtainable for midface advancement while minimizing the complications (Fig. 18.97).

Fig. 18.97 Distraction halo and splint in place in mid-distraction (Havlik R.J. (2008) Distraction Osteogenesis of the Facial Skeleton. In: Pietrzak W.S. (eds) Musculoskeletal Tissue Regeneration. Orthopedic Biology and Medicine. Humana Press)

18.5.11 Surgical Approaches and Treatments for Hypertelorism

Hypertelorism is an abnormally increased distance between two organs or body parts, usually between the orbits (eyes), or orbital hypertelorism. In this condition the distances between the inner eye corners and between the pupils are greater than normal. Hypertelorism should not be confused with telecanthus, in which the distance between the inner eye corners is increased but the distances between the outer eye corners and the pupils remain unchanged. More specifically, the distance is increased between the two dacrya, the junction of the lacrimal bone, the frontal process of the maxilla, and the frontal bone [208, 209]. The normal distance is approximately 28mm in an adult female and 32 mm in an adult male [209, 210]. Tessier [209, 210] classified orbital hypertelorism into three categories; grade I (30–34 mm), grade II (35–39mm), and grade III (>40mm). A grade III deformity involves gross facial disfigurement and requires surgical intervention. The corrective surgeries depend on the degree of deficiency and the underlying cause. A set of five diagnostic criteria has been proposed for the diagnosis of hypertelorism: frontonasal malformations, craniofrontonasal dysplasia, craniofacial clefts, encephaloceles, and a miscellaneous group that includes syndromic or chromosomal disorders [211]. The origin of the deformity guides the selection of surgical treatment. Orbital medialization depends on the axis of the orbits. If the bony orbits are widely displaced, then the corrective procedure will involve a box osteotomy; however, when the intercanthal distance is increased, a medial osteotomy is sufficient. If there are occlusal alterations, the treatment will be facial bipartition with rotation of the hemifaces. The most common surgical approach is intracranial, though a subcranial approach is an option if the deformity is less severe. The timing of the surgery should take anatomical and functional aspects into consideration, along with the more important psychological benefits for a growing child with an increased awareness of and exposure to the outside world. The operative correction is usually performed between 5 and 6 years of age. Before age five, the craniofacial bones are thin and fragile, making surgical correction difficult. Surgery to the orbit during infancy can impair midface growth. Therefore, the orbit is not subjected to operative manipulation until the child is between 5 and 6 years of age, unless there are other circumstances such as a large frontoethmoid encephalocele or dermoid tumor. Even under those circumstances a two-stage procedure is often planned: the associated lesion is reduced during infancy, and the orbitoplasty is delayed until the age of 5 or 6 years to achieve correction that will benefit the child psychologically during early schoolage years.

18.5.11.1 Box Orbitotomy and Medial Orbit Translocation

The beginning of the operation is planned with the previous insertion of a lumbar drain for perioperative brain relaxation to decrease the pressure under the dura for better manipulation, especially around the frontal lobes. Sometimes, hypertonic

agents (e.g. mannitol) or diuretics (e.g. furosemid) are given to relax the brain further. The patient is positioned in supine position with the head over a horseshoe-shaped headrest or a clamp. A coronal skin incision is followed by subperiosteal dissection of the anterior frontal scalp flap. Burr holes are drilled in the frontolateral regions bilaterally above the superior temporal line, and one parasagittal one posterior to the coronal suture. A bifrontal craniotomy is performed excluding the temporalis muscles. Osteotomies of the supraorbital bar are made 1cm wide at the level of the orbital rim apex. The supraorbital bar is then bisected transversely, except at the nasal midline, before orbital translocation. After measures to decrease the intradural pressure, the frontal lobes are gently retracted to allow an osteotomy to be performed in the orbital roof that extends posterior to the midpoint of the globe's anteriopoterior axis. In a similar fashion, the anterior tip of the temporal lobe is carefully retracted, allowing a lateral orbital wall osteotomy to be conducted posterior to the midpoint of the anteroposterior axis of the globe. The lateral cribriform plate is the medial limit of the roof osteotomy to avoid injury to the olfactory nerves. The cribriform plate is characteristically widened and typically obstructs medial translocation of the orbital rim. The anterior olfactory fibers are usually divided, followed by oversewing of the proximal segments of the nerve fibers and the surrounding dura. This step is performed to prevent postoperative CSF rhinorrhea. The latter portions of the ethmoid air cells are removed using a rongeur to provide room for further medial translocation of the orbit. A medial orbit osteotomy is performed using a sagittal or oscillating saw to avoid uncontrolled fracture of the nasal and lacrimal bones. If the nasal profile is acceptable, a 3mm segment of midline bone can be left as the nasal bridge. Paramedian resection of excess bone responsible for the excess "medial width" is then resected (Fig. 18.98a–c). If the nasal profile is unacceptable, two approaches have been devised to address this defect. In the first, the midline bone is resected, and after translocation the medial orbital walls form a new nasal profile. In the second, more common, case, a 2–3 mm midline segment of nasal

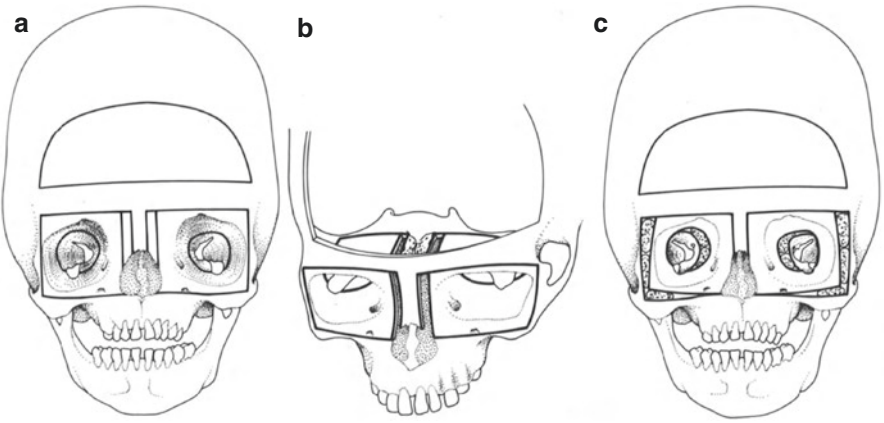


Fig. 18.98 (David D.J., Poswillo D.E., Simpson D.A. (1982) Surgical Management. In: The Craniosynostoses. Springer, London)

bone is preserved as scaffolding for onlay bone graft augmentation of the nasal dorsum. Infraorbital dissection and osteotomy follow after the previous stages. A lateral canthotomy, transconjunctival, or Caldwall-Luc incision can be needed to ensure adequate exposure. For the transconjunctival and lateral canthotomy approaches, preseptal dissection is performed to expose the inferior orbital rim. Horizontally-oriented osteotomies are placed on the anterior maxillary wall at the level of the infraorbital foramen; the more cephalad osteotomy is performed to avoid injury to the developing tooth buds. After the osteotomies are completed, the bony orbits are mobilized medially. The greatest resistance to movement is usually encountered in the deep nasomaxillary region. An osteotome is carefully used to "pry" the rim free from bony and soft tissue attachments. Great care must be taken during these maneuvers to avoid injury to the nasolacrimal duct. With medial translocation of the orbits, the nasal septal and upper lateral cartilages and the nasal mucosa are usually infolded. This requires trimming of the excess tissue and subsequent closure of the mucosal openings to prevent air and bacterial contamination entering the epidural space postoperatively. The medial orbital walls of the nasal bone are trimmed with the air-drill shaping burr such that the resulting distance between the bilateral dacryons is approximately 10mm at most. The nasal process of the maxilla at its medial inferior portion is aggressively contoured to avoid occlusion of the nasal airway during medial mobilization of the orbit. The orbital rims are placed in position but not secured at this point. The medial canthi are assessed, and if they are positioned reasonably, the surgeon should dissect around the canthi, avoiding detachment from the dacryon to preserve optimal positioning and fixation postoperatively. The medial canthi sometimes require repositioning. A transnasal medial canthopexy is performed before the bones are stabilized because the mobile and easily separable bone fragments allow greater exposure. An air-drill is used to create an opening into the posterior superior lacrimal bone. The lacrimal wall, along with the rest of the medial orbital wall, is quite thin and prone to fracture with operative manipulation. If this occurs, a split calvarial bone graft from the parietal region is used to buttress the medial orbital wall. This effectively stabilizes the medial canthopexy and helps to prevent anterior and lateral migration of the canthus postoperatively. After this step is completed, the orbits are translocated medially and secured to each other and to the frontal supraorbital bar superiorly (Fig. 18.99).

In patients with orbital hypertelorism, the lateral canthi usually require repositioning. They are typically positioned at a level approximately 2mm above the medial canthi. After translocation and fixation of the orbits, the lateral canthi are frequently attached to a point on the "internal" aspect of the zygomatic process of the frontal bone. If severe proptosis coexists, the lateral canthi are anchored to a point on the exterior surface of the eyelid. After lateral canthopexy, the temporal fossa is assessed. If the translocation has created a large gap between the lateral orbit and temporal region (as often occurs), a composite muscle (temporalis) and squamous temporal myo-osseous flap is designed to reduce the likelihood of postoperative hourglass deformity in the temporal fossa. Filling in this area with bone chips and advancing the temporalis muscle alone have been ineffective in precluding the deformity. The midline nasal profile is again evaluated. If the profile remains

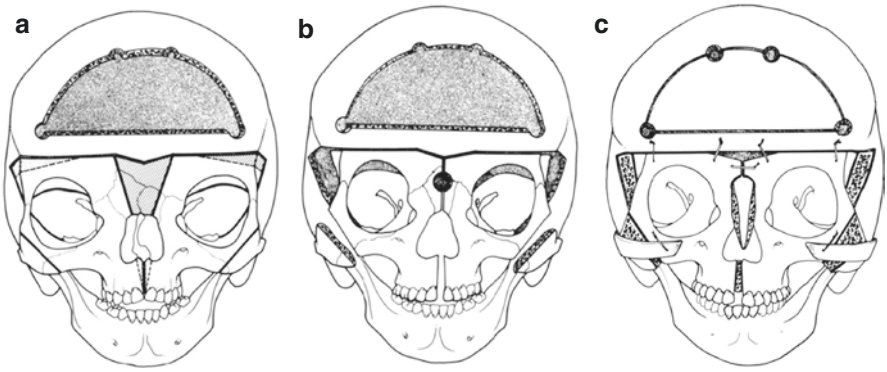


Fig. 18.99 The *facial bipartition procedure when there is no alveolar defect.* In such cases, the facial bipartition is generally made through the mid part of the alveolus of a no. O-14 cleft. (**a**) Outlining the osteotomies and resection. (**b**) The interorbital resection. c Bringing together the upper parts of both hemifacial segments. Bone grafts in the orbital defects; bone graft of the nasal bridge; small bone graft in the alveolar gap to maintain the width of the maxilla (Tessier, P. (1987). Facial Bipartition: A Concept More Than a Procedure. Craniofacial Surgery, 217–245. https://doi.org/10.1007/978-3-642-82875-1_44)

unacceptable after orbital medial translocation, a cantilever costochondral bone graft can be harvested to augment it. In contrast to cortical membranous bone, a costochondral rib is the ideal graft material because the cartilaginous tip resists resorption quite well. Before closure, a pericranial or galeal flap is elevated from the anterior scalp flap and tacked over the ethmoid air cells on the anterior cranial base to decrease the potential for postoperative epidural infections [212].

18.5.11.2 Facial Bipartition

In certain cases of congenital hypertelorism, facial bipartition can be used for correction. A single frontoorbitomaxillary segment is created that is divided in the midline and mobilized medially and caudally. With medial rotation, the interorbital space is narrowed and the "vertical" dimension of the paramedian maxilla effectively lengthened. The procedure potentially corrects orbital hypertelorism while elongating the vertical midline and providing an opportunity for anterior advancement of the maxilla. Van der Meulen [213] proposed facial bipartition. The operation starts with mobilization of the frontofacial segment, as in a monobloc, but then a V-shaped piece of bone is cut from the frontonasal region, the apex of the V being at the level of the (often high-arched) hard palate. A vertical cut below this turns the V into a Y. Closure of the V brings the orbits closer together [214] and expands the maxilla [215]. This corrects any downwards slant of the eyes and also bends the face convex and forwards in the horizontal plane, which makes the procedure particularly effective for a child with Apert syndrome, whose facial deformity includes hypertelorism combined with midface recession in both the horizontal and vertical planes [216]. As with the monobloc advancement, the bipartioned segment can, if required, be moved forwards with distraction [217] (Fig. 18.100).

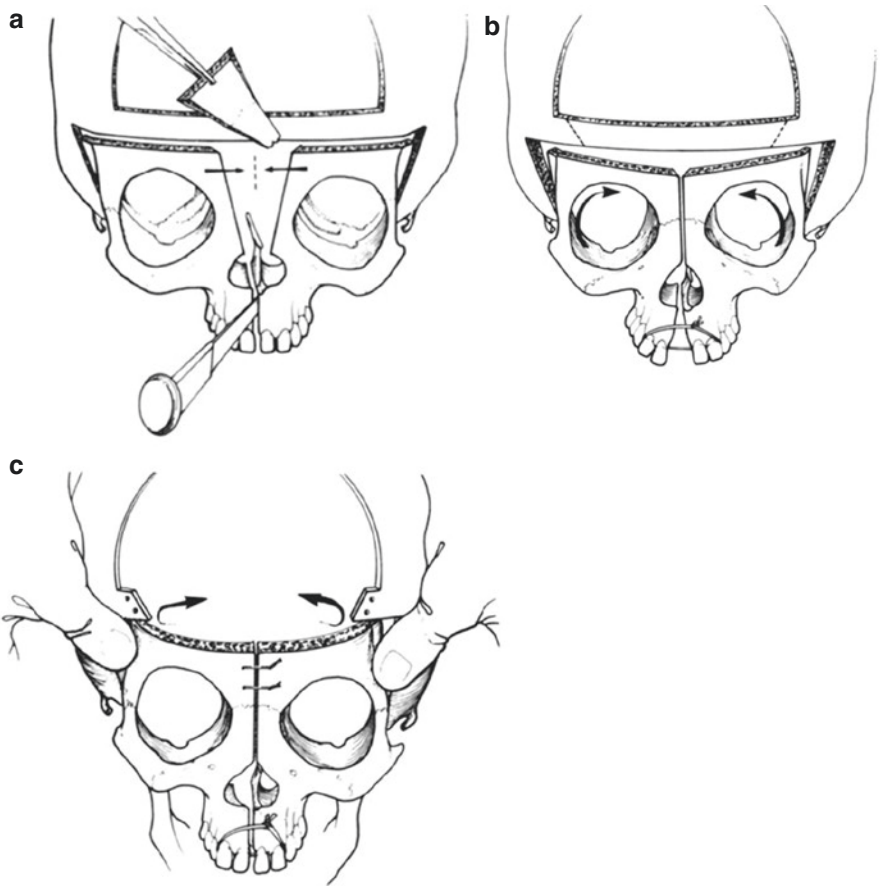


Fig. 18.100 *The facial bipartition procedure made within a frontofacial single-block segment.* When used for Apert syndrome, the maxilla must be enlarged and telorbitism and orbital extorsions reduced (Tessier VIII procedure). (**a**) Nasoglabellar resection and splitting of the palate. (**b**) Bending the orbitofrontal complex backwards to narrow the face further. (**c**) Closing up the orbital complexes completed together. Wiring between the incisors to limit maxillary expansion. (Tessier, P. (1987). Facial Bipartition: A Concept More Than a Procedure. Craniofacial Surgery, 217–245. https://doi.org/10.1007/978-3-642-82875-1_44)

18.5.12 Complications in Surgery for Syndromic Craniosynostosis

Operative procedures for patients who undergo cranial vault expansion, correction of midface hypoplasia and hypertelorism entail a high risk of numerous complications regarding the complexity of the interventions.

Cerebrospinal fluid leaks: Inadvertent dural tears can go unnoticed during surgery. Various authors have reported incidences of 5-60% [218–221]. This can result in CSF leaks into the drain or wound. These tend to settle down with conservative management by lumbar drainage and discontinuing negative suction drainage to the

wound. Dural tears are likely to occur during craniofacial operations when there has been previous surgery (particularly if metallic plates and screws have had time to migrate inwards [222]) and when the skull base is very constricted. Osteotomy cuts through the anterior skull base make the frontal extradural compartment communicate with the (bacterially contaminated) nose, allowing CSF leakage to present as rhinorrhea. The patient is then at risk for meningitis, and contamination of the extradural space can lead to infection of the often-devascularized surrounding bone. Measures to reduce the risk for CSF leakage complicating monobloc and similar procedures include (in addition to previous experience [192]) the following: prophylactic placement of a lumbar drain at the start or end of the operation; placement of the skull base osteotomy no further posteriorly than the foramen cecum; careful attention to closure of any dural tears; covering the gap in the anterior skull base before the frontal bone is replaced with a vascularized pericranial flap; and finally, the use of tissue adhesive to seal the area. Fortunately, most CSF leaks cease spontaneously. Those that show no sign of settling over a day or so should be treated by inserting a lumbar drain. Leaks that persist (or recur) despite this can require a formal skull base repair, either transcranially or transnasally.

Infection and dead space: Infections can present as fever, meningitis or sometimes as osteomyelitis. If the bone becomes infected it needs to be debrided. Infection is the commonest and most dreaded complication of craniofacial surgery and the reported incidence is about 6% in transcranial cases [223]. Risk factors that predispose to infection are opening of the nasal or sinus mucosa at the time of surgery. It has been observed that completely repairing the mucosal breach and separation of the nasal/sinus mucosa using vascularized frontogaleal flaps can reduce the chance of infection in such cases [224]. Salyer [225] and Murray et al. [226] have concluded that the chances of infection in infants and younger children are less than in adults because the brain expands rapidly to obliterate any extradural dead space that develops in transcranial surgeries. The monobloc procedure, by definition, places the frontal extradural space and the nasal cavity in communication, which does not happen when the surgical components are separated into fronto-orbital and Le Fort III advances. However, any operation that increases the ICV carries the risk of leaving an air, blood, and serous fluid–filled dead space [227], which together with the often-devascularized bone surrounding it provides an excellent substrate for bacterial growth.

Bone defects: Cranial vault expansion often leaves areas of bone defect that in a child older than 1–2 [228] years of age are unlikely to be filled spontaneously. A "salami" of milled bone fragments mixed with tissue adhesive is "rolled out" in a thin strip to provide permanent bone cover for such defects [229]. For the elective closure of bone defects in the older child, split calvarial bone can be used [230].

Fixation: The tendency of metallic plates and screws to migrate inwards [222] has led us to avoid using them when possible, particularly in young children in whom absorbable sutures usually provide sufficiently rigid fixing. Metal plates and screws complicate subsequent operations when they become buried in bone; they sometimes eventually penetrate the dura, making tears that are difficult to repair inevitable during subsequent operations.

Difficult airway: Patients with craniofacial anomalies can have difficult airways, but an experienced anesthetist can intubate almost every patient and there is seldom any need for tracheostomy. However, in patients with skull base tumors for which access is planned using maxillary swing osteotomy, we have found submental intubation to be very helpful without adding any major morbidity [231, 232]. Most patients can be extubated safely after the end of the surgery. We routinely give a single induction dose of steroids to avoid postoperative edema of the respiratory tract following a prolonged surgery. The justification for this is anecdotal, but some studies have indicated a beneficial effect in reducing postoperative facial edema [233, 234]. Some units secure the endotracheal tube with a wire to the teeth. During the postoperative period, one must watch out for any respiratory distress that develops because of unrecognized bleeding in the respiratory tract. When in doubt, the extubation can be delayed for 24 h or so.

Blood loss: Craniofacial surgeries involve major soft tissue and bony reconstructions so they can result in major blood loss, which can be significant enough in smaller children to qualify for almost whole body transfusion. Nearly all craniofacial surgery patients require blood transfusion [235–237]. The blood loss can be minimized by tumescent infiltration of the incision sites and keeping the head end up. The neck should not be flexed as this can lead to venous engorgement. Use of bone wax, gelatin sponge, and surgicel is quite helpful in reducing the blood loss. Sometimes, if the blood loss is extensive, the procedure has to be abandoned [237]. Some authorities recommend hypotensive anesthesia, but others do not favor this approach as it can lead to neurological sequelae of reduced cerebral blood flow [237]. The units in England use cell saver technology (autologous blood transfusion), especially relevant in Jehovah's Witness patients [238].

Hyponatremia and electrolyte imbalance: It has been suggested that short-term hyponatremia can result from inappropriate secretion of antidiuretic hormone caused by frontal lobe retraction [219, 235, 239]. However, others feel it could also result from cerebral salt wasting syndrome [240]. The treatment would differ between these two conditions.

Venous air embolism: The position of the head in most craniofacial cases is above the heart, so there is a risk of sucking air into the venous channels through open emissary/diploic veins or sinuses during craniotomy, especially in small children. Meyer et al. [236] reported an incidence of about 2.6% in patients undergoing craniosynostosis surgery. Insertion of a central venous pressure line and monitoring of end-tidal carbon dioxide helps diagnose an air embolism. Management includes cessation of surgery, lowering of the head end, 100% oxygen inhalation and even open cardiac massage [241].

Occulocardiac reflex: There can be hypotension and bradycardia because of globe manipulation during transcranial surgery [219]. Jones et al. [235] reported two cases of severe occulocardiac reflex during periorbital dissection, necessitating adrenalin administration.

Death: The earlier series reported mortality ranging from 1.6% to 4.3% [242–244]. However, with better equipment, safer anesthesia and cumulative experience, this figure has decreased steadily to about 0.1% in large craniofacial

centres in the USA. Most of these were in syndromic children and happened because of excessive bleeding either on the table or during the immediate post-operative period.

18.6 Conclusion

Fused cranial sutures lead to abnormal growth of the cranial vault. Virchow's law states that skull growth is inhibited in the plane perpendicular to the affected suture, while compensatory growth is enhanced in a plane parallel to it. Multiple techniques are available for surgical treatment of craniosynostoses depending on the patient's age, severity of the deformity, and preference of the family and surgical team. However, skull deformities are significant, and surgical correction to reshape the skull to normal contours is indicated.

In the past, children with craniosynostosis syndromes were stigmatized as mentally challenged because of their craniofacial features when, in fact, they were often of normal intelligence. The advent of craniofacial surgery techniques, although far from perfect, offers these children a chance to acquire a more normal facial appearance and to grow, develop, and integrate socially with their peers. The craniosynostosis-associated syndromes are dynamic as opposed to static phenomena. The incidence of complications such as raised ICP is strongly correlated with particular syndromes (e.g., high in Pfeffer syndrome, low in Muenke syndrome) and their severity. The more severe the phenotype, the more likely it is that anomalies corrected by early reconstructive surgery will revert to their preoperative status.

Management of these patients can be complicated, and referral to centers of excellence should be considered, such as "quaternary" centers especially for complex management of syndromic craniosynostosis. The complication rate is usually low with an experienced team and a state-of-the-art facility.

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Chapter 19
Experimental Animal Models in Cranial Suture Biology: Molecular and Pharmacological Treatment Strategies

Martin Rachwalski

19.1 Introduction

The growth and development of the craniofacial skeleton includes precise processes of differentiation, proliferation, and patterning, where cranial sutures have an important role. If these molecular and cellular interactions are disrupted it can result in craniosynostosis - the premature fusion of cranial sutures. Craniosynostosis is a heterogeneous malformation affecting 3.1–7.2 per 10.000 live births, where, most cases (79%) are non-syndromic (isolated) and involve a single suture fusion [1, 2]. Premature suture fusion results in restriction of brain expansion and skull growth at right angles to the affected suture, causing a dysmorphic skull shape and potentially resulting in functional CNS abnormalities, developmental delay, and learning disabilities. Craniosynostosis occurs in approximately 21% of cases as a syndromic feature. More than 180 syndromes have been described, which frequently present as overlapping phenotypes. Some such syndromes, e.g., Apert, Pfeiffer, Saethre-Chotzen, often display limb malformation, multi-suture synostosis and overlapping phenotypes [3].

Because of the frequent multi-suture synostosis, functional and morphological consequences often have greater severity in comparison to non-syndromic patients, including but not limited to: increased intracranial pressure, chronic cerebellar tonsillar herniation and cognitive impairment, exorbitism, hypertelorism, visual disturbances, midface hypoplasia and sleep apnea [3–5]. A multi-stage interdisciplinary treatment is required because of the clinical complexities of these symptoms. The treatment for craniosynostosis is surgical and includes skull vault osteotomies with anterior and/or posterior expansion. Even though operative (e.g., distraction osteogenesis) and anesthesia techniques have improved gradually, these procedures

M. Rachwalski (✉)
Department of Plastic Surgery and Maxillofacial Surgery, Hôpital Universitaire Henri-Mondor, Créteil, France

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remain linked to infant morbidities, e.g., infection risk, bleeding, venous air emboli, and brain damage [3, 6].

Although it may be possible to develop future non-surgical methods for treating or preventing craniosynostosis, its exact etiology is still to be deciphered. Whilst the causes of non-syndromic craniosynostosis are usually multifactorial and involve environmental and genetic aspects, delineation of the molecular causes of syndromic types of this condition have been more successful [4, 5, 7]. A new research area was heralded on cranial suture biology and stemmed from the identification of the gain-of-function mutation (p.P148H) in genes which code for the transcription factor MSX2 as a genetic cause in larger families with Boston-type craniosynostosis [8].

In the last two decades, a number of gain-of-function mutations were identified in genes which code for fibroblast-growth-factor-receptors (*FGFR1-3*) and the transcription factor TWIST1, which are a cause of syndromic craniosynostosis and sporadic cases of non-syndromic coronal synostosis [3, 9, 10–15].

Wilkie and colleagues found that around 1/5 (21%) of children had a detectable craniosynostosis genetic cause, including gain-of function mutations in *FGFR2* (32%) and *FGFR3* (25%) and loss-of-function mutations in *TWIST1* (19%). The single-gene mutations can be identified in more than three quarters of monogenic diagnoses, amongst which Crouzon, Pfeiffer, Apert, Muenke and Saerthre-Chotzen syndromes are the most common [16]. Implementing next generation sequencing (NGS) technologies has hastened the gene discovery process. There are currently 52 genes which are known to be linked to craniosynostosis [17–20]. Treating non-syndromic and mutation-negative patients usually requires only a single corrective operation. However, this is not so for mutation-positive patients, who due to their functional abnormalities and genetically determined pathological growth inhibition will undergo several surgical procedures during their development [3].

Mutation-positive (*FGFR2-3* and *TWIST1*) patients have a much greater re-operation rate for complications, i.e., for recurring intracranial hypertension or sleep apnea, as confirmed in various studies [3, 16, 21, 22]. To reduce the morbidity or to prevent invasive surgical procedures in the growing child, researchers have begun to develop alternative biological and pharmacological treatments strategies using animal models, for example mice, rats, and rabbits. Specifically, models of mice for *FGFR2*-realted syndromes such as Crouzon syndrome (with the C342Y substitution, the most-used animal model for such conditions) are valuable for dissecting this gene's role in the regulation of the proliferation, apoptosis and differentiation of cells in cranial sutures [3, 23]. In this chapter, we present these alternative pharmacological and molecular targets for treating craniosynostosis, which have been researched in a number of animal models and critically discuss if they can be potentially used in humans [3, 24].

19.2 FGF/FGFR Signaling

There are four highly conserved fibroblast growth factor receptors (FGFRs) and 22 ligands and fibroblast growth factors (FGFs) which have been detailed in humans and that have a vital role in the mediation of molecular processes, e.g. development in the embryo and oncogenesis in the adult organism. Up until now, only *FGFR1-3* are known to be implicated in craniosynostosis and osteogenesis. Usually, FGFR molecules contain an extracellular ligand-binding domain with three immunoglobulin-like domains (IgI, IgII and IgIII), a single-pass transmembrane (TM) domain and a split intracellular tyrosine kinase (TK) domain. Heparan sulfate (HS) glycosaminoglycans is required to bind FGF to FGFR, to induce dimerization and overactivation of the intrinsic tyrosine kinase domain and autophosphorylation of multiple tyrosine residues on the receptor [3, 7, 25, 26]. This also yields cascades of intracellular signaling via a number of downstream pathways such as MAPK/ERK, PLCg and P38, the interaction with craniosynostosis relevant downstream targets such as TGFβ, BMP, TWIST1 and MSX2 and finally gene transcription in the nucleus [3, 7, 25, 26].

Regarding craniosynostosis, gain-of-function mutations are usually to be found in the ligand-binding (IgI, IgII and IgIII) and intracellular tyrosine kinase domains of FGFR2, FGFR3 and FGFR1. Hot-spot mutations in these three genes are responsible for over half of all craniosynostosis syndromic forms, e.g.: Apert (FGFR2, IgII-IgIII (p.S252W; p.P253R)), Crouzon (FGFR2, IgII-IgIII), Pfeiffer (FGFR2, FGFR1 IgII-IgIII-; IgIIIa-IgIII), Muenke (FGFR3, IgII-IgIII (p.P250R) and also in sporadic cases of non-syndromic coronal synostosis (FGFR2) [3–5, 7].

With better knowledge underlying overactive FGF/FGFR signaling and the genetic etiology of craniosynostosis, multiple research groups are now developing molecular and pharmacological therapies focusing on directly interfering at the ligand-binding site or downregulating the FGF/FGFR downstream signaling cascade. In their research on a murine calvaria culture system, Greenwald et al. modulated protein levels with the use of a truncated FGFR1 molecule, which does not have a cytoplasmic domain. Using their strategy, the FGF2-ligand induced signal was prevented and the downstream MAP kinase activation was impaired [27]. They demonstrated that when the dominant-negative FGFR construct was transfected into the PF sutures in utero, the postnatal fusion of posterior part of the frontal (PF) suture in fetal rats was avoided [3, 27].

Glycosaminoglycans (GAGs) such as heparan sulfate (HS) are crucial for regulating FGF-FGFR signaling, FGF ligand binding and differentiating osteoblasts. Through the dose-dependent manipulation of HS and FGF concentration levels, the group around McDowell et al., antagonized the over-activated FGFR signaling in cells transfected with the Apert syndrome-specific *FGFR2b* (S252W) mutation [3, 28, 29]. Another method used by Eswarakumar et al., was to insert two additional

mutations (L424A and R426A) in the juxta membrane domain of an activated Fgfr2c of a Crouzon mouse model (C342Y). This knock-in-gene-targeting method of substituting the two amino acids inhibits the recruitment and tyrosine phosphorylation of Frs2a (FGF receptor substrate 2), the primary FGFR2 docking protein, leading to a normal craniofacial phenotype in the mice by the prevention of the premature fusion of the coronal sutures [3, 30]. More recently, on calvaria tissue cultures of Apert mice, nanogels were impregnated with a purified soluble form of FGFR2 carrying the S252W mutation (sFGFR2^{S252W}). Delivering nanogels which contain sFGFR2^{S252W} led to suture patency through the inhibition of FGF2-regulated proliferation and phosphorylation of intracellular signaling molecules, and the mineralization of FGFR2^{S252W}-overexpressing osteoblasts, whereas when nanogels devoid of sFGFR2^{S252W} were administered coronal synostosis was observed [3, 31]. There is still difficulty in interpreting the results of these culture model studies, since they have been obtained in relatively non- physiological conditions. Only by translating them into in vivo studies may prove the efficiency of these molecular treatment strategies. Using an in vitro approach, Shukla et al., completely rescued the normal phenotype in a mouse model of Apert syndrome, by the direct targeting of the mutant Fgfr2 (S252W) transcripts by a small hairpin RNA (shRNA). Normal FGFR2 signaling was re-established by manipulating extracellular signal-regulated kinases 1 and 2 (ERK1/2), modulating the genes downstream of ERK and phenotype expressivity [3, 32]. Table 19.1 summarizes an overview of current molecular and pharmacological in vitro and in vivo treatment approaches [3].

FGF/FGFR signaling is important for craniofacial development and has also been implicated in tumor development and progression. Various cancer tissues harbor somatic *FGFR* point mutations such as: Gastric adenocarcinoma (*FGFR1*), melanoma (*FGFR1*, *FGFR2*), uterine (endometrial carcinoma) (*FGFR2*), cervical cancer (FGFR2) and high-grade bladder cancer (*FGFR3*) [3, 33].

A genetic screen on endometrial carcinoma tissues identified identical mutations as the activating germline mutations which are found in Apert, Beare-Stevenson and other skeletal dysplasia syndromes (hypochondroplasia, achondroplasia and SADDAN) [3, 34]. The effects of activating *FGFR* mutations depends on the developmental stage, the cell and tissue type where they are expressed currently exhibits no evidence that FGFR-mutation positive craniosynostosis patients have an increased cancer risk [35–37]. Initially used only for oncological applications, small-molecule FGF receptor (FGFR) kinase inhibitors are increasingly being researched as a possible treatment modality in craniosynostosis [3].

Their efficiency was firstly proven by Perlyn and colleagues, where the FGFR tyrosine kinase inhibitor PD173074 prevented bilateral coronal suture fusion in calvaria cultures from a Crouzon mouse model (*Fgfr2*^{C342Y}) [3, 23]. Similar results were found when Crouzon (*Fgfr2c*$^{C342Y/+}$) mouse calvaria were co-cultured with a small-molecule inhibitor of FGFR (PLX052) [3, 30]. Whereas only partly alleviating premature coronal synostosis was achieved when the Erk1/2 inhibitor (PD98059) was applied in murine calvaria cultures of Apert syndrome (*Fgfr*^{P253R}) [38]. Shukla et al. performed the first in vivo study and injected the MEK1/2 inhibitor U0126 into pregnant mice which carried the Apert syndrome mutation (*Fgfr2*$^{+/S252W}$).

Table 19.1 Molecular and pharmacological treatment strategies (From Rachwalski et al. [3])

Model	Condition	Target	Treatment	Effects	References
• In vitro- • Cells: calvaria • Animal: WT CD1 mice and rats	Wildtype	Fgfr1	Dominant negative Fgfr1	Prevented fusion of the posterior frontal suture	Greenwald et al. (2001) [27]
• In vitro- • Cells: calvaria • Animal Fgfr2 $^{C342Y/þ}$mouse	Crouzon syndrome	Fgfr2	FGFR tyrosine kinase inhibitor (PLX052)	Prevented premature fusion of the coronal suture	Eswarakumar et al. (2006) [30]
• In vitro- • cells: calvaria • Animal: Fgfr2 $^{C342Y/þ}$ mouse	Crouzon syndrome	Fgfr2	FGFR tyrosine kinase inhibitor (PD173074)	Prevented premature fusion of the coronal suture	Perlyn et al. (2006) [23]
• In vitro- • Cells: calvaria • Animal: Fgfr2$^{P253R/þ}$ mouse	Apert syndrome	ERK1/2	MEK1 inhibitor (PD98059)	Partially prevented premature fusion of the coronal suture	Yin et al. (2008) [38]
• In vitro- • Cells: calvaria • Animal: Fgfr2^{S252W} mouse	Apert syndrome	Fgfr2	Purified soluble form of ^{FGFR2}(sFGFR2 ^{S252W}) on nanogel vehicle	Prevented premature fusion of the coronal suture	Yokota et al. (2014) [31]
• In vivo- • Animal: Mouse model with Crouzon syndrome (Fgfr2 $^{C342Y/þ}$)and additional juxtamembrane mutations	Crouzon syndrome	Frs2a docking protein-dependent Fgfr2c	Insertion of additional L424A and R426A mutations in mouse model with Crouzon syndrome $^{C342Y/þ}$) prevents recruitment and tyrosine phosphorylation of Frs2a	Prevented premature fusion of the coronal suture	Eswarakumar et al. (2006) [30]

(continued)

Table 19.1 (continued)

Model	Condition	Target	Treatment	Effects	References
• In vivo- • Animal: Mouse model with Apert syndrome ($Fgfr2^{S252W/þ}$)	Apert	ERK1/2	Intraperitoneal injection of MEK1/2 inhibitor (U0126)	Prevented premature fusion of the coronal suture and partially rescued phenotype in Apert mouse	Shukla et al. (2007) [32]
• In vivo- • Animal: Mouse model with Apert syndrome ($Fgfr2^{S252W/þ}$)	Apert syndrome	Fgfr2	Heterozygous U6-Fgfr2 ^{S252W} shRNA transgenic mouse mated with Apert syndrome mouse	Prevented premature fusion of the coronal suture and total rescue of phenotype in Apert mouse	Shukla et al. (2007) [32]
• In vivo- • Animal: Mouse model with Beare-Stevenson cutis gyrata syndrome ($Fgfr2^{+/Y394C}$)	Beare-Stevenson cutis gyrate syndrome	p38	Intraperitoneal injection of p38 inhibitor (SB203580)	Amelioration of skin abnormalities, no effect on craniofacial phenotype	Wang et al. (2012) [39]
• In vivo- • Animal: Rabbit model with bilateral coronal suture craniosynostosis	Bi-coronal craniosynostosis	TGFβ2	Neutralizing TGFβ2 antibody after suturectomy	Prevented postoperative resynostosis of the coronal suture and improved intracranial volume and cranial vault growth	Mooney et al. (2007a, b) [61, 62] and Frazier et al. (2008) [63]
• In vivo- • Animal: Chimeric human/nude (athymic) rat xenotransplant model of craniosynostosis containing Crouzon and Apert FGFR2 mutant human osteoblasts	Apert syndrome Crouzon syndrome	Noggin	rh Noggin	Prevented premature fusion of the coronal suture	Shen et al. (2009) [55]
• In vivo- • Animal: Mouse model with postoperative resynostosis treated with suturectomy	Bi-coronal craniosynostosis	Noggin	Cells expressing Noggin	Inhibited bone formation	Cooper et al. (2009) [56]

Although the majority of the offspring appeared at birth to be phenotypically normal, there was a gender specific difference observed. To obtain a complete rescue of the male phenotype, early drug delivery (post-natal day 5) was required, while female pubs showed unstable phenotypic expression including mortality after birth independently of injection time points of U0126 [3, 32].

In another study, on Fgfr2+/Y394C mice with Beare-Stevenson cutis gyrata syndrome (BSS), the p38 kinase inhibitor (SB203580) was injected in utero for the treatment of syndrome specific epidermal hyperplasia and craniosynostosis. Although the skin anomalies were able to be improved, no changes in craniofacial phenotype was observed [3, 39].

19.3 TGFβ/BMP Signaling

The TGFβ superfamily is formed of over two dozen structurally related signaling molecules mediating several stages in normal growth and development. According to functional and structural criteria, TGFβ fall into two main classes: (1) TGFβs/activins and (2) bone morphogenetic proteins (BMPs) [3, 40–42].

Immunohistochemical research on samples of fused human sutures reveals that TGFβ1, TGFβ2 and TGFβ3 were expressed differentially in the dura and in the osteoblasts, which line the skull vault bones periosteal surfaces during and after suture morphogenesis [3, 43]. Moreover, differential expression patterns of TGFβ isoforms have been researched in obliterated as well as open sutures [3, 43, 44]. During the usual processes of posterior frontal suture closure in rats, increased TGFβ1 and TGFβ2 expressions with a reduced level of TGFβ3 were found, whereas in patent sutures an increase in immunoreactivity of TGFβ3 and downregulation of TGFβ1 and TGFβ2 could be seen [3, 44].

The effects of alternating TGFβ levels have been researched in both in vitro and in vivo models [3, 43–47]. A number of studies in fetal rat calvaria cultures has shown that increased cell proliferation and suture fusion could be induced with the addition of TGFβ2 protein neutralizing anti-TGFβ3 antibodies. Contrastingly, coronal sutures remained patent, when TGFβ3 or neutralizing TGFβ2 antibodies were introduced using a collagen vehicle [48, 49]. Two other studies also showed that subperiosteal application of TGFβ3 in a New Zealand white rabbit model of familial craniosynostosis prevented coronal suture fusion, whilst locally applying anti-TGFβ2 antibodies into suturectomy sites stopped postoperative re-synostosis [3, 47, 50].

Cell proliferation in the suture and the surrounding bone fronts appear to be under the direct control of TGFβ isomers, therefore any imbalances between the growth factors will affect apoptosis and proliferation, which will determine suture fate [3, 42]. In addition, extra-cellular signal-related kinases (Erk1/2) are potent downstream modulators of TGFβ2. In another study, embryonic mouse calvaria with TGFβ2 were co-cultured with the Erk1/2 inhibitor PD98059, resulting in

downregulating Erk1/2 expression and phosphorylation, but which also disrupted TGFβ2-related suture fusion [3, 51].

Following another methodology, mouse dura cells were transfected with a selective siRNA pool to knockdown TGFβ1 mRNA transcripts which cause a significant reduction of mRNA levels of TGFβ, FGF2, FGFR1 and TGFR2. However, Gosain and colleagues (2009) indicated that applying TGFβ1 siRNA might alter murine dura signaling, which has responsibility for suture fusion in vitro, they also found that suppressing FGF2 and FGFR1 mRNA only occurred briefly. It appears there may be cross-talk between TGFβ1 and FGF2 signaling, requiring additional research [3, 52].

Bone morphogenetic proteins (BMPs) belong are part of the TGFβ family of growth factors and have a crucial role in skeletal development as well as in suture formation [3]. Using in situ hybridization, BMP2, BMP4 and BMP7 in osteogenic bone fronts, and BMP4 and BMP7 in the suture mesenchyme and underlying dura mater were found [3, 53]. BMP4 expression levels, and subsequently BMP2, declined when the sutures were formed [3, 53]. Irrespective of these findings, Warren and colleagues theorized that BMPs and their antagonist Noggin must feature in suture morphogenesis. They discovered that Noggin was expressed in unfused coronal, sagittal and posterior frontal sutures, while downregulation occurred in the fusion process. Although BMP4 will induce Noggin expression, Noggin translation is blocked by FGF signaling in a dose-dependent manner, either by directly applying FGF2 or by osteoblast transfection with *FGFR2* gain-of-function mutations [3, 54].

Additionally, overexpressing Noggin using an adenovirus in postnatal mice at day three resulted in abnormal maintaining of the posterior frontal suture. Therefore, it was concluded that overactive FGF/FGFR signaling (as observed in *FGFR2* gain-of-function mutations) decreases sutural expressions of the BMP antagonist Noggin, causing an increase in suture osteogenesis and then suture fusion [3, 54]. In another experiment using a chimeric rat model it was shown that coronal sutures stayed open when xenotransplantation with mutant FGFR2 osteoblasts was carried out with the application of recombinant human (rh) Noggin [55]. For testing the long-term effect of Noggin exposure on cranial sutures of a mouse model, a gel-foam scaffold impregnated with Noggin and GFP-expressing cells was inserted into the suturectomy site [3, 56]. Although, Noggin treatment effects were brief and restricted to the initial bone healing phase; inhibition was not significant in comparison to untreated controls 12 weeks post-operatively. The authors conclude that either "(1) long-term Noggin exposure was never achieved (e.g., through the death of implanted cells or the loss of Noggin expression in implanted cells); or (2) Noggin treatment, regardless of the duration, only has effects in the initial phases of bone healing" [3, 56]. It therefore appears that further investigation is required for understanding Noggin gene therapy effects to prevent re-synostosis in the long term.

19.4 Future Directions

Currently, the standard treatment procedure for infants with craniosynostosis remains intracranial surgery at an early age. In the last decade, there have been a number of attempts to identify less invasive treatment alternatives, by testing molecular and pharmacological agents through in vitro and in vivo assays. However, before these therapeutic modalities may be implemented in humans there are a number of issues which must be resolved. Since only a few familial forms have been found, craniosynostosis is not usually anticipated at birth [3].

In regard to syndromic forms of craniosynostosis, at least half of them are caused by de novo mutations in FGFR1-3, while in most craniosynostosis cases, which are non-syndromic, point mutations are usually unidentified [3]. Although two significantly associated loci were identified in a GWAS of sagittal synostosis, one locus downstream of BMP2 (encoding a ligand in BMP signaling) and the other in a BBS9 intron, the etiology of non-syndromic craniosynostosis is still unknown [3, 57]. There is also the implication that there are currently not any direct molecular targets which could be modified either pharmacologically or genetically. Advanced paternal age increases the risk for FGFR2 point mutations which cause conditions like Apert syndrome at an average rate of 10^5 per male gamete [58]. Analyses of different murine models of Apert syndrome have shown that coronal synostosis occurs at an early stage, at embryonic days 13.5–15.5, a gestational period in mice corresponding to weeks 10–12 in humans [3, 29, 59].

Up until now, detecting de novo mutations has not been possible as a routine prenatal screening method. Furthermore, there is no need to make the assumption that the fetus has a rare craniosynostosis syndrome and therefore the probability of early diagnosis and in utero remains a challenge [3, 29]. Currently, tyrosine kinase inhibitors appear to the best treatment option for tackling aberrant FGFR signaling. These agents, initially developed for oncological use, are more frequently being tested variously in vitro and in vivo assays in craniosynostosis (Table 19.1) [3, 33]. An interesting study was conducted by Shukla et al., whereby the in utero treatment by injecting the tyrosine kinase inhibitor (U0126) intraperitoneally into pregnant mice with Apert syndrome who were carrying pups [3, 32]. However, rescuing the craniofacial phenotype could not be performed in every heterozygous mutant pub and necessitated early and continuous delivery of (U0126) if it is to be successful. Even then, there was still instability in the phenotypic expressivity in females [3, 32]. Likewise, Wang and colleagues were only partly successful in reversing the phenotype in mice with Beare-Stevenson syndrome by injection of a p38 MAP kinase inhibitor in utero. In this study, the skin anomalies could be improved, however the craniofacial phenotype was not changed [39]. This shows that in spite of a tractable molecular target, several variables have an influence on the success of the treatment, such as the specificity and the exact duration and timing of the drug delivery. It is not likely that applying a single agent will entirely inhibit the cross-talk

between activated downstream FGFR signaling pathways and therefore sufficiently rescue all syndrome-associated features. Moreover, pharmacological agents such as tyrosine kinase inhibitor could have harmful and unpredictable consequences for the developing fetus [3].

Although the majority of craniosynostoses occur prenatally, some patients present with late-onset Crouzon syndrome and then develop craniosynostosis during childhood [23]. These patients may benefit from the postnatal application of a tyrosine kinase inhibitor (TKI) for the prevention of additional suture fusion of the vault, cranial base, and midface. Children with progressive cranial suture fusion (e.g., pansynostosis) or skull base synchondrosis undergo repeated surgical procedures for correcting intracranial hypertension, exorbitism and maxillary hypoplasia [3].

It is possible that postnatal application of TKIs as an adjuvant therapy to surgery, could help with limiting the progression of genetically determined growth disturbances and lead to a reduction in the amount of invasive surgical interventions [23]. Undoubtedly, a safe drug dose and delivery in utero has an increased risk for postnatal applications, however the long-term toxicity of TKIs is still not known. Shukla et al. demonstrated that to maintain postnatal phenotypic stability in Apert mice, continual application of tyrosine kinase inhibitor (U0126) was required, leading to the demise of some pubs [3, 32]. It remains unclear if mortality was caused by $Fgfr^{P253R}$ mutation-associated developmental defects or drug toxicity.

Many reports have found negative side effects caused by systemically delivering tyrosine kinase inhibitors in adult oncologic patients, meaning that drug safety is one of the main concerns and limitations of their use in developing children. As there is a high cost to drug development, efficacy testing and safety monitoring, it is not likely that agents, unable to be used in oncology, will be designed specifically for the therapy of rare craniosynostosis syndromes [60]. Thus, searching for a safe drug delivery technique, ideal dose and application timing are the main challenges [3].

19.5 Summary

Although there has been much progress in previous decades, increased knowledge of the molecular mechanism which underlies craniosynostosis is still required. The underlying causes of non-syndromic craniosynostosis still need to be elucidated, implying there are no direct molecular targets which can be pharmacologically or genetically tackled. Conversely, animal models of FGFR2-related syndromes have been found to be of use in vitro and in vivo studies of syndromic craniosynostoses. It seems that direct manipulation at the ligand-binding site or downregulating the FGF/FGFR downstream signaling cascade using tyrosine kinase inhibitors are the best methods for developing molecular and pharmacological therapies.

Currently, applying these therapies in humans however appears unfeasible, as craniosynostosis usually occurs prenatal and there are procedures for identifying de

novo mutations in utero as a routine method. Postnatal systemic long-time drug application with tyrosine kinase inhibitors may be of benefit for the craniofacial phenotype. Yet, this is limited by the random and toxic effects in the developing infant. Additional research is required for improving pre-natal detection methods and drug safety prior to pharmacological and biological therapies which have feasibility for treating children with craniofacial conditions and potentially abrogate future surgical needs [3].

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