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REVIEW ARTICLE

Imaging in craniosynostosis: when and what?

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Abstract

Purpose Currently, the interest on craniosynostosis in the clinical practice is raised by their increased frequency and their genetic implications other than by the still existing search of less invasive surgical techniques. These reasons, together with the problem of legal issues, make the need of a definite diagnosis for a crucial problem, even in single-suture craniosynostosis (SSC). Although the diagnosis of craniosynostosis is primarily the result of physical examination, craniometrics measuring, and observation of the skull deformity, the radiological assessment currently plays an important role in the confirmation of the diagnosis, the surgical planning, and even the postoperative follow-up. On the other hand, in infants, the use of radiation or the need of sedation/anesthesia raises the problem to reduce them to minimum to preserve such a delicate category of patient from their adverse effects.

Methods, results and conclusions This review aims at summarizing the state of the art of the role of radiology in craniosynostosis, mainly focusing on indications and techniques, to provide an update not only to pediatric neurosurgeons or maxillofacial surgeons but also to all the other specialists involved in their management, like neonatologists, pediatricians, clinical geneticists, and pediatric neurologists.

Keywords Craniosynostosis · Radiological examinations · CT scan · MRI · Ultrasounds · Pediatric · Chiari

Introduction

Nowadays, the pediatric and neurosurgical interest on craniosynostosis keeps steadily increasing secondary to the growing frequency of the pathology [26, 66, 84, 101] and to the improved knowledge on the genetic implications [8, 11, 51]. In particular, in the last two decades, a significant increase in the diagnosis of craniosynostosis has been detected compared with the previous decades [26]. Such a phenomenon is considered the result of both a real increased incidence of the disease (especially the metopic synostosis) and an increased referral to tertiary centers for diagnosis and treatment. Furthermore, the still existing search of less invasive treatment techniques makes the craniosynostosis an always "current" topic in the clinical practice. Therefore, the importance of the diagnosis is crucial. On these grounds, the demand for "certain" diagnosis before surgery as well as the always more compelling problem of legal issues led to enhance the role of the radiological examinations, even in single suture craniosynostosis (SSC). Although the diagnosis of craniosynostosis is primarily the result of physical examination, craniometrics measuring, and observation of the skull deformity, the radiological assessment currently plays an important role in the confirmation of the diagnosis, the surgical planning, and even the postoperative follow-up. On the other hand, in infants, the use of radiation or the need of sedation/anesthesia raise the problem to reduce them to minimum to preserve such a delicate category of patient from their adverse effects.

This review aims at summarizing the state of the art of the role of radiology in craniosynostosis, mainly focusing on indications and techniques, to provide an update not only to pediatric neurosurgeons or maxillofacial surgeons but also to all the other specialists involved in their management, like neonatologists, pediatricians, clinical geneticists, and pediatric neurologists.

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When

Need to confirm the clinical diagnosis

In the preoperative workup, the role of radiological examinations resides in confirmation of the diagnosis, search for possible associated anomalies and investigation of their role (surgical plan and research), surgical planning, and finally formulation of the correct prognosis. Of course, this role may vary significantly in SSC compared with multisuture nonsyndromic craniosynostosis (MNSC) and, in particular, syndromic craniosynostosis (SC), due to the obvious differences among these three categories. In SSC, the diagnosis is primarily based on the clinical examination so that many authors stressed how there is no the need for radiological assessment in this setting of patients [27, 32, 82]. However, the use of radiological tools acquires importance in those (rare) doubtful cases in which the patency of the sutures is hard to be assessed and/or where the possible involvement of "minor" sutures deserves a better definition to make an accurate surgical plan [16]. The lambdoid craniosynostosis (posterior synostotic plagiocephaly) is a typical example of the first instance. The rarity of this condition, together with the more and more frequent occurrence of the posterior positional plagiocephaly, may make its diagnosis a challenge, especially in case of children with hairy head (Fig. 1). The differentiation between "true" and positional posterior plagiocephaly is based on well standardized clinical markers [24, 37, 38, 43, 76]. The suspicion of a synostotic form may deserve a radiological examination just because (1) the lambdoid synostosis could be one of the first cases seen by a not experienced clinician; (2) the lambdoid synostosis could be confused with a severe positional plagiocephaly; (3) the lambdoid craniosynostosis can be associated with anomalies of the skull and the cervical spine that should be assessed. As expected, this problem does not occur when dealing with other SSC where the deformation of the skull is more obvious, as it happens in metopic (trigonocephaly), sagittal (scaphocephaly), and anterior unicoronal craniosynostosis (anterior plagiocephaly). The latter condition, however, provides an example for the second instance. Indeed, unicoronal synostosis may be hard to differentiate form the pure frontosphenoidal synostosis or from a combined form (unicoronal plus frontosphenoidal synostosis) (Fig. 2). The differentiation between synostotic and positional anterior plagiocephaly could be a further argument in favor of the use of radiology although the latter condition is often poorly evident and quickly self-remitting [27, 55].

The need of a radiological assessment to obtain a "certain" diagnosis is often raised by the risk of legal issues connected with misdiagnosis or surgical complications. This problem is frequently debated but the radiological diagnosis currently seems to be mandatory in most of the centers dedicated to the management of craniosynostosis. According to the recommendations provided in 2015 by the Working Group on Craniosynostosis; X-rays of the skull; or, alternatively, ultrasounds, can be used whenever a craniosynostosis is suspected [58]. The examination should be repeated after 1–2 months if unclear (e.g., because of very young age of the patient). Three-dimensional CT scan is used if X-rays confirm or do not exclude a craniosynostosis, or as first line examination if a craniosynostosis is strongly suspected. Therefore, to reduce as much as possible the use of ionizing radiation, specific protocols have been designed, which are based on ultrasounds and X-rays as first-line diagnostic tools [83]. In this context, MNSC are a particular setting because they might represent a pitfall in diagnosis. In fact, children thought to have a SSC might harbor a multisutural one as seen, for example, in children affected by the so-called Mercedes craniosynostosis (sagittal plus bilambdoid synostosis) who may appear like scaphocephalic patients until the execution of preoperative exams (Fig. 3). Furthermore, associated anomalies to be considered for surgical planning, prognosis, and follow-up, such as Chiari malformation, are more frequent in this kind of patients [20].

Things are different in SC where the diagnosis is achieved by the physical examination and confirmed by the genetic tests. In this subset of patients, however, the radiological examinations may be useful to assess the timing/pattern of premature closure of the sutures, since all or most of them progressively close but with different patterns according to the different syndromes [22]. Of course, children with SC need a scheduled radiological assessment for the associated anomalies other than for the surgical planning. Indeed, this subset of patient is often burdened by a worsening evolution of the disease, mainly (but not only) depending on the progression of the suture fusion, leading to a clinical and/or a radiological worsening which, therefore, deserves a clinical and radiological follow-up. An example is represented by the Chiari I malformation secondary to Crouzon or Pfeiffer syndrome, which can deteriorate over the time, thus requiring a late (new) occipital expansion.

Another aspect is represented by the increasing capability in antenatal diagnosis. Usually, in the postnatal setting, SSC are much more commonly diagnosed than SC (90% vs 10%), simply because they are more frequent, while in the antenatal period, such a ratio is inverted, because the skull, facial, and brain anomalies of SC are much more evident than in SSC. Most of the antennal diagnosis is made during the third trimester, even though sometimes it is possible to make the diagnosis even in the first and second one [61]. After the screening with ultrasounds, the feasibility of in utero MRI can reinforce the diagnostic suspect, possibly driving the need of invasive procedure (like amniocentesis) to confirm it. The prenatal diagnosis offers also the advantage to foresee the need of an early surgical intervention and/or to give the parents correct information on the prognosis and the therapeutic plans before the birth. The continuous progresses in the

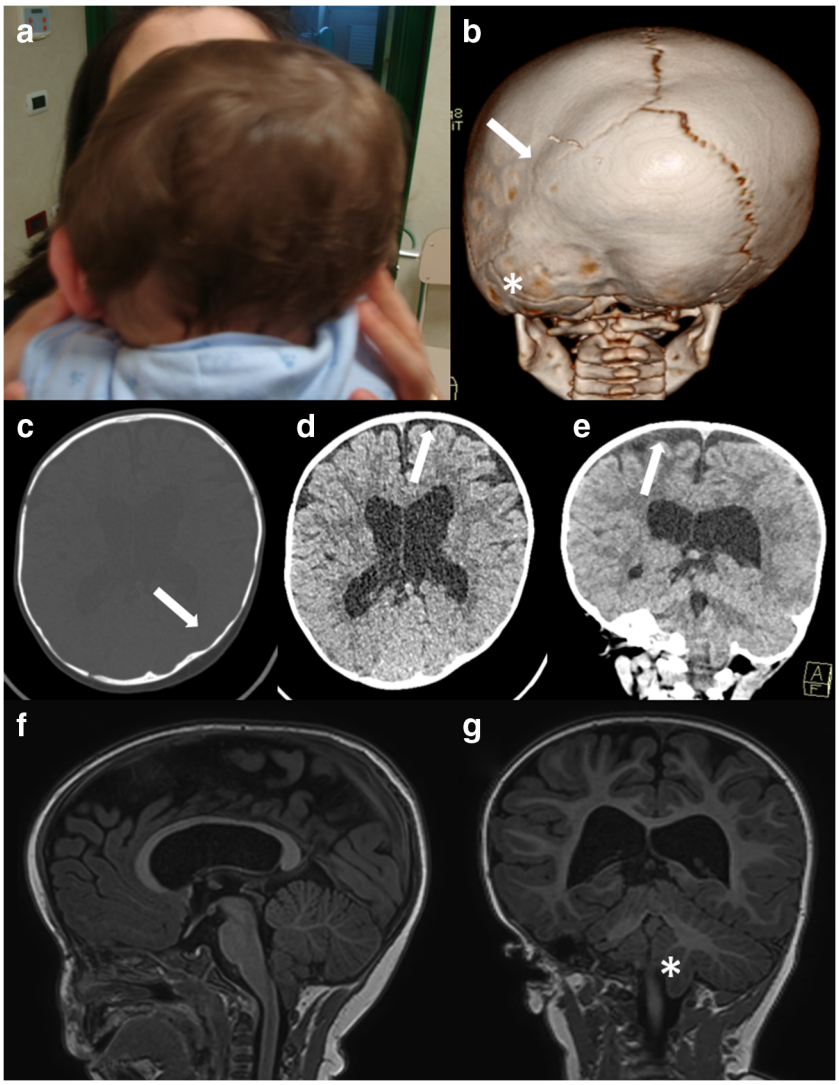

Fig. 1 **a** Clinical appearance of an 8-month-old boy with hairy head and left lambdoid synostosis. The downward dislocation of the left ear and the mastoid bossing can be roughly appreciated. **b** On the 3D reconstruction of the CT scan, the mastoid bossing (asterisk) and the premature fusion of the left lambdoid suture (arrow), which can be also appreciated on the axial bony reconstruction **c**, are clearly demonstrated. **d**, **e** Brain axial CT scan reconstruction showing the left occipital flattening and associated ventriculomegaly, enlarged convexity spaces (arrows), and caudal herniation of the left cerebellar tonsil (asterisk). **f**, **g** These intracranial details are well showed by sagittal and coronal T1 MRI

diagnostic techniques and the increasing attention payed by obstetrical gynecologists to this problem significantly enhanced also the prenatal diagnosis of SSC (up to 61% of detection rate) [40, 41, 98].

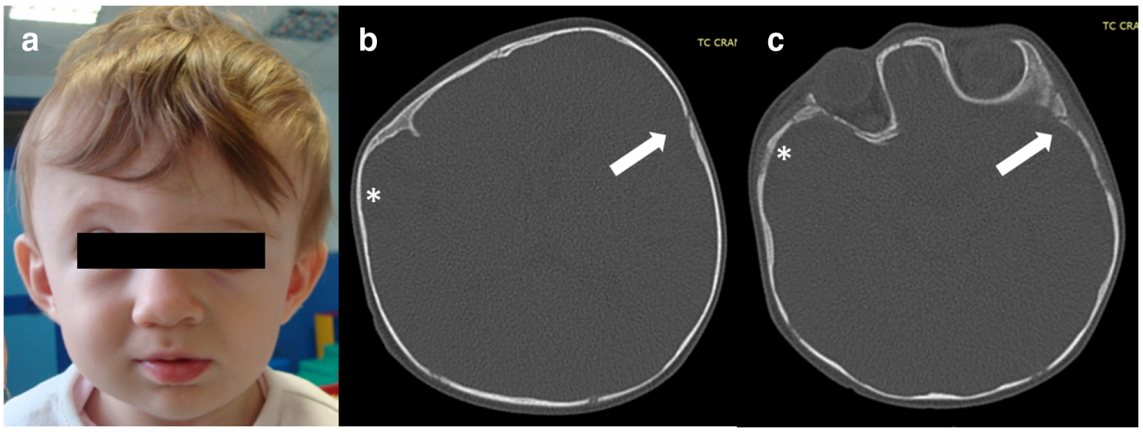

Fig. 2 A 7-month-old boy with right coronal synostosis + fusion of the frontosphenoidal suture. **a** The clinical characteristics overlap those of the unicoronal synostosis (fronto-orbital flattening, advancement of the ipsilateral ear, deviation of the nasal pyramid; **b**, **c**). On bone CT scan, the frontal flattening is evident as well as the deformation of the right orbit. The left hemicoronal and frontosphenoidal sutures are patent (arrows) while the right ones are not recognizable (asterisks)

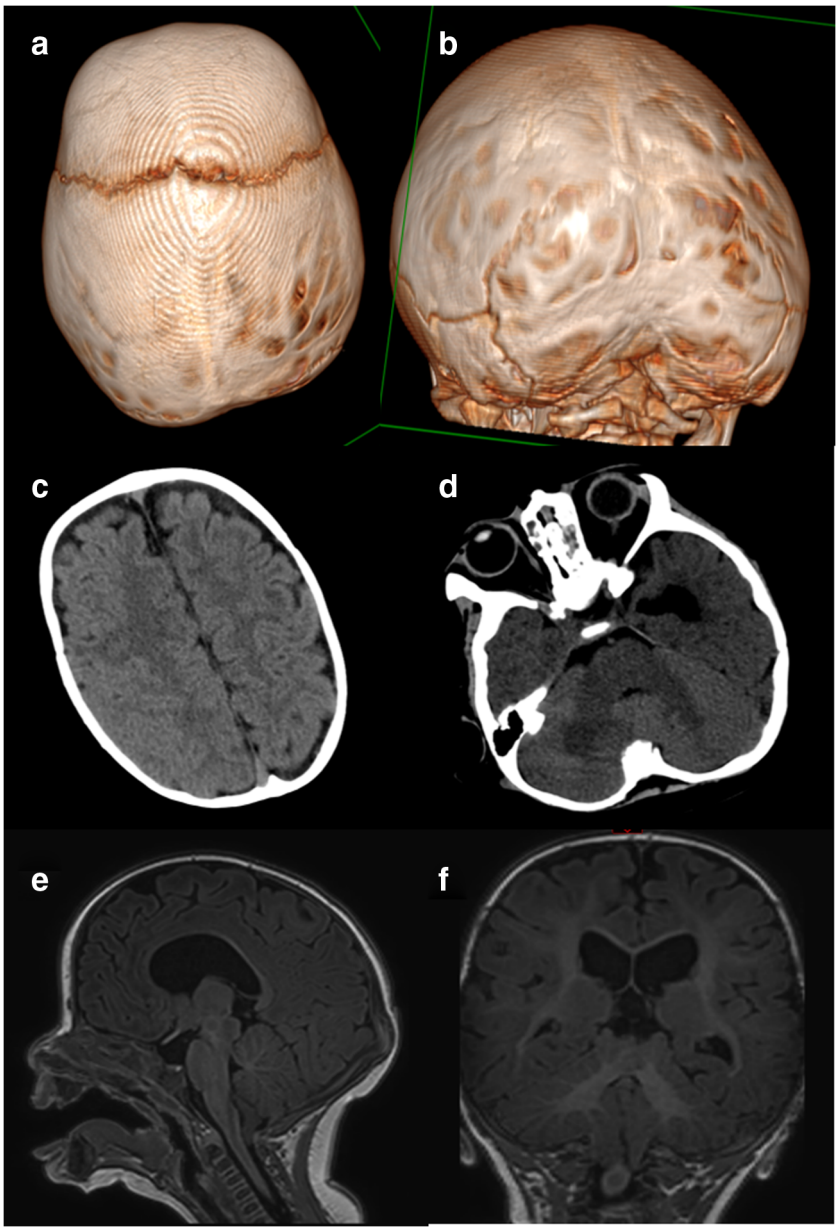

Fig. 3 A 5-month-old girl with Mercedes syndrome. The scaphocephalic shape of the skull is evident on the superior (3D reconstruction, (**a**)) and axial 2D view (**c**) of the CT scan. However, other than the fusion of the sagittal suture, also, the bi-lambdoid synostosis is evident as well as the midline occipital indentation (**b**, **d**). The sagittal and coronal T1 MR images clearly show the secondary Chiari I malformation with reduced volume of the posterior fossa (**e**, **f**)

Associated anomalies

As mentioned, in SC, the radiological assessment is mandatory due to the high incidence of associated anomalies. The most common of those concerning the intracranial space are Chiari I malformation (70–100% of cases), anomalies of the venous sinuses, callosum hypoplasia or dysgenesis, brain malformations, signs of severely raised intracranial pressure, and hydrocephalus (40–70% of the cases) [21, 79, 80, 85]. In these cases, a careful assessment is needed to define the best timing and modality for surgical correction, to underline possible criticism during the procedure, and to define the optimal follow-up. Furthermore, radiology is useful or necessary to assess some of the anomalies composing the clinical phenotype, which can be complicated by a wide spectrum of extracranial (midface retrusion, high-arched palate or cleft lip and palate, widely spaced eyes, ptosis, proptosis etc.) or body anomalies (vertebral fusion, ankylosis, syndactyly, polydactyly, heart malformation etc.) [1, 3, 18, 65, 92, 100].

On the other hand, these anomalies are sporadically diagnosed in SSC, as it may happen, for example, for scaphocephaly and hydrocephalus [85] (Fig. 4). An exception is represented by Chiari I malformation, which can occur in up to 60% of lambdoid craniosynostosis [33] (Fig. 1) and about 5% of sagittal craniosynostosis [52], thus producing an argument in favor of the radiological assessment of these types of craniosynostosis. Surprisingly, Chiari I malformation can be encountered in children with unicoronal synostosis

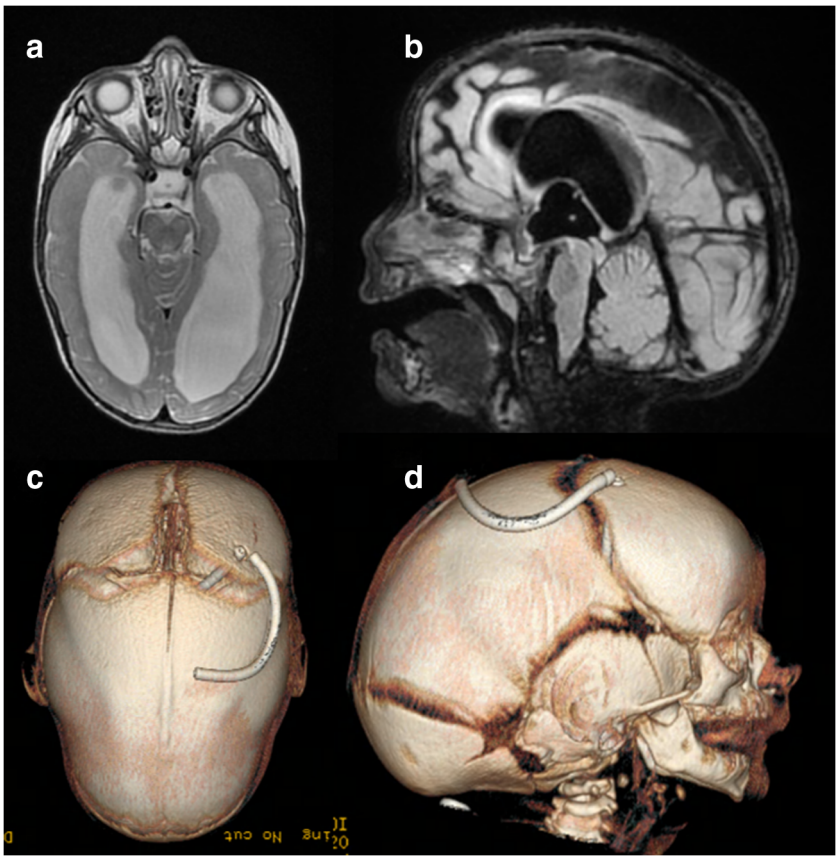

Fig. 4 A 1-month-old preterm young girl (born at 36 weeks of gestation) with a prenatal US diagnosis of hydrocephalus and clinical diagnosis of sagittal craniosynostosis at birth. **a**, **b** Axial T2 and sagittal FLAIR MRI confirming the triventricular hydrocephalus resulting from aqueductal stenosis. **c**, **d** The 3D CT scan, performed after the placement of a subgaleal shunt (realized to gain time for a reliable endoscopic third ventriculostomy) to rule out possible bone anomalies (suspected syndrome), shows the stenosis of the sagittal suture (severe narrowing of the anterior third and complete fusion of the posterior two thirds) with resulting scaphocephaly only

(sometimes more frequently than in sagittal synostosis) [52, 93], possibly because of the secondary anterior attraction of a hemi-posterior cranial fossa. Obviously, a radiological investigation is required in symptomatic children with not corrected craniosynostosis (namely, the sagittal one), who may present with raised intracranial pressure, secondary Chiari I malformation, and even syringomyelia [71, 91]. As expected, finally, Chiari I malformation is relatively common in MNSC (35%), with a peak in Mercedes craniosynostosis (about 60%) (Fig. 3) and oxycephaly (80–100%) [20, 46, 93], reinforcing the indication to radiological examinations in this subset of patients.

Surgical planning

First, preoperative imaging may be required for a correct surgical planning because of some craniosynostosis-specific intrinsic problems. In the unicoronal synostosis, for example, the anterior fontanel and the superior sagittal sinus are dislocated contralaterally to the affected side, so that they do not run along the midline. Moreover, in the sagittal stenosis, namely when a significant sellar deformation of the vertex is present, the sagittal sinus can be significantly compressed and/or duplicated and/or (exceptionally) surrounded by a bony tunnel. The information on the location and appearance of the sagittal sinus is of paramount importance for a correct surgical planning, especially when mini-invasive/endoscopic approaches are realized.

The radiological assessment for the surgical planning is necessary mainly in SC, where it is important to know and to simulate in advance the extent of the needed remodeling in order to limit as much as possible the risk of recurrence as well as to accommodate the altered bone growth during the patients' life [43, 73]. This can be obtained through a model of the skull of the patients obtained by a 3D printer [68] or through a frame-based template where to remodel the skull intraoperatively [42]. Such a technology is currently used also in SSC.

Furthermore, preoperative examinations can be utilized to plan surgery in order to avoid complications. Examples for this hint are the presence of indentations of the bone secondary to elevated ICP (beaten copper cranium) or large venous drainages or area of bone defect [14]. To detect in advance, such anomalies, indeed, can reduce the risk of CSF fistula, hemorrhage, or brain damage.

Postoperative evaluation

Passing from the presurgical assessment to the postsurgical one, the first and most obvious indication for it is to detect complications such as bleeding, CSF dynamics problems, bone displacement or reabsorption, and dislocation of springs

or distractors used for midface advancement. Fortunately, this is not a routine indication for radiological examinations because the occurrence of severe surgical complications is rare in craniosynostosis (1.2%) [62]. However, some minor complications are quite likely to occur as, for example, postoperative bony lacunae. In this instance, the radiological assessment of the areas of bone resorption/lacuna is more precise than the mere clinical evaluation and can help in the planning of a possible second surgery for increasing the neuroprotection and/or limiting the cosmetic impact.

As mentioned, the need to monitor the associated anomalies in SC is the main indication for a neuroradiological follow-up that, obviously, must be driven by a scheduled, multidisciplinary clinical follow-up according to the genetic phenotype.

As far as the follow-up of SSC is concerned, it is mainly focused on verifying the improvement of the shape of the head over the time, to verify the brain decompression and, in particular, for cosmetic purposes. Apart from the appearance of (new) symptoms (e.g., papilledema) or the occurrence of a late complication (e.g., bone resorption needing a cranioplasty or recurrence requiring a new correction) (Fig. 5), radiological investigations are not indicated in the follow-up of SSC. Actually, it can be carried out by replacing radiological examinations with several grading scales, such as the Sloan classification [88], that can be used as a first step to monitor the cosmetic evolution, leaving radiology as a way to investigate doubtful situations. Currently, moreover, several non-radiological tools are also available for this purpose, like the 3D laser, morphometric assessment, or smartphone-based photogrammetry. Three-dimensional laser measurement can be acquired using dedicated software taking care in covering the patient's head in a tight cap in order to minimize contouring errors. Then, images are acquired by four lasers projected into wide beams to form a line of light around the cranial surface which are recorded by cameras in order to recreate the 3D surface of the patient's head. Cranial measurements, namely head circumference, oblique diameter, cephalic ratio, vault asymmetry index, and volume measurement, are then calculated from planar cross sections of the reconstructed head [5]. According to Martini et al., on the other hand, a morphometric assessment of cranial parameters can be obtained by using a 3D light optical scan [56]. Referral point are defined in each 3D cephalometric surface scan according to the anthropometric standards as a way to analyze the specific morphological features of the cranium. To complete the morphometric assessment, at least three reference planes (horizontal, sagittal, and vertical) are needed to grant the possibility to derive cranial measures. Other authors proposed even the smartphone-based photogrammetry for the diagnosis of diagnosis [9]. To surpass the lack of compliance of active children during medical examination and the need for adequate illumination of the shooting stage, the use of videos and, specifically, slow-motion videos was found to be a good alternative to obtain high-resolution, well-focused images. Furthermore, a setup of multiple synchronized cameras that take images at the same exact moment, each one from a different location around the head can temper the movement error. It is important to remember how to obtain accurate measurements, and the 3D model of a large number of images is needed in order to obtain images with the help of the software. All those tools are currently gaining appeal due to the ever-growing need in making a diagnosis without the need for radiological investigation, thus emerging as modern imaging technology in the diagnosis of craniosynostosis. Such a modern technology is particularly useful in the diagnosis of positional deformities. Indeed, according to the Evidence-Based Guidelines for the management of patients with positional plagiocephaly provided by the Joint Guidelines Committee of the American Association of Neurological Surgeons and Congress of Neurological

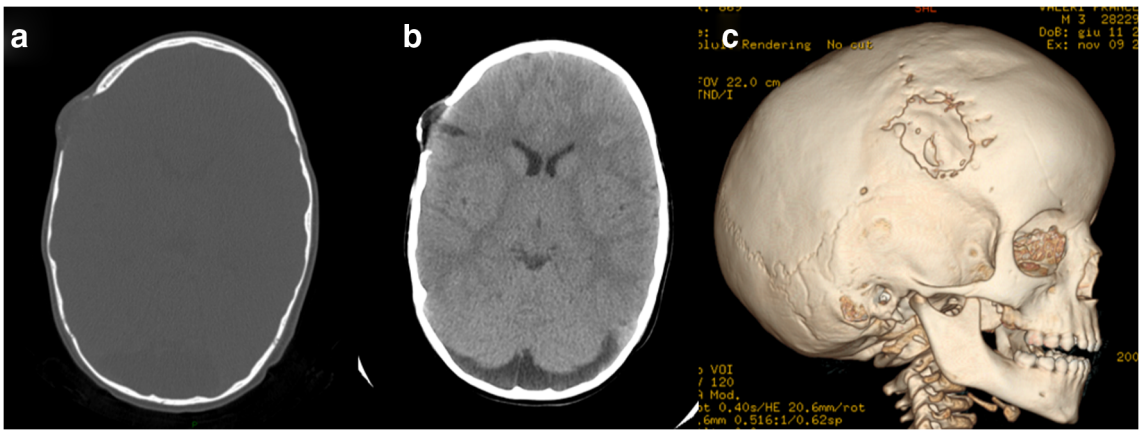

Fig. 5 Postoperative axial 2D bone (**a**) and brain (**b**) and 3D CT scan (**c**) of a 1.5-year-old young boy operated on for scaphocephaly showing a growing fracture at level of the craniectomy along the lower arm of the right hemi-coronal suture (about 8 months after surgery). This complication resulted from a dural tear. Since no brain herniation was evident, MRI was not performed as CT scan was considered enough to plan the cranioplasty

Surgeons, the diagnosis should be clinical and dimensional surface imaging or stereophotogrammetry should be used for the assessment of this subset of patients, unless a strong suspicion of craniosynostosis is present [35].

Definition of the prognosis

The prognosis of a craniosynostosis depends on the clinical and the genetic phenotype. The prognostic picture is completed by the radiological assessment of the possibly associated anomalies. In some specific instances, however, the pattern of closure of the sutures and the so-called minor sutures can affect the severity of the synostotic form and, therefore, the prognosis. For example, in 1988, Di Rocco et al. proposed a radiological classification of unilateral coronal craniosynostosis into three types of increasing severity, taking into account also skull base involvement [25]. According to the deformation of the skull base, anterior plagiocephaly was then divided into type I: unilateral flattening of the frontal bone and elevation of the superior orbital ridge without deviation of the nasal pyramid and the petrous bone; type IIA: frontal and orbital anomalies accompanied by contralateral deviation of the nasal pyramid and homolateral anterior displacement of the petrous bone; type IIB: anterior displacement of the petrous bone is more evident and a vomer bone deviation is present compared with type IIA; and type III: besides the above-described anomalies, occurrence of severe deviation of the sphenobasilar bone, with secondary asymmetry of the craniovertebral junction. This subdivision is not only diagnostic but reflects on the prognosis, because the cosmetic and functional results of the surgical correction and the subsequent risk of reoperation vary according to the type (high risk of second surgery in types IIB and III). Such a connection is linked to the severity of skull base involvement (as well as the asymmetry of the facial complex) resulting from the different timing of closure of the frontoparietal suture [55]. The usefulness of the previously described classification in defining the prognosis is also underlined by the analysis of the late outcome of adults treated for unicoronal synostosis [69]. Late CT scan controls revealed a strict relationship between the cosmetic outcomes and the different degrees of the initial involvement of the skull base sutures.

Research

Lastly, radiology may have a role in the research in some fields such as the postoperative morphovolumetric brain modifications, the role of the sutural pattern in defining the severity of the disease, or the perfusion/tractography assessment. Regarding the morphometric changes of the brain, for example, some authors surprisingly did not find significant changes after surgery, thus suggesting that the brain shows a growth pattern in part independent from the skull [2]. Based on these evidences, other authors also proposed the craniosynostosis as a model to study how the skull/brain ratio changed in the evolution [77]. With the ongoing studies on craniosynostosis, the interest in the role of sutures and their importance in defining the severity of the pathology keeps growing. In fact, while the role of the major suture has already been described in modifying the spectrum of presentation [25], novel studies underlined the importance of the minor suture and the extent of their involvement in changing the severity of the craniosynostosis and of its related anomalies [17]. Finally, tractography studies suggests that in SC fractional anisotropy is similar to the controls while mean diffusivity, axial diffusivity, and radial diffusivity (RD) are significantly higher. These differences might indicate abnormalities in tissue microstructural properties, such as myelin deficiency and axonal loss, but it is not possible to exclude confounding contributions of partial volume effects secondary to cranial malformation, bony prominences, and CSF space enlargement [78].

What

Plain X-rays

Skull X-rays historically had the role of a starting imaging modality in children with abnormal head shape. Today, such a role still persists in several centers due to its favorable cost-effectiveness ratio in infants with low risk of craniosynostosis [60]. Moreover, X-rays are a fast and low-radiation diagnostic tool with a reported specificity of 95% [97]. A normal unfused suture is usually lucent, serrated, and nonlinear, while a prematurely fused one shows perisutural sclerosis, linearity, bony bridging or complete non-visualization, heaping up of the bone, straightening or narrowing of the suture, and loss of suture clarity [6, 7, 10, 48, 64]. In addition to these primary signs, further consideration is deserved by the secondary ones, which result from raised intracranial pressure, such as a copper-beaten appearance (visible in severe cases), altered calvarial shape, changes in shape and timing of closure of fontanels, and facial anomalies [10, 96].

Even though radiography can detect craniosynostosis with a quite high specificity [60, 83], its sensibility is not adequate. In fact, plain X-rays have poor sensitivity in detecting complex and minor sutural synostoses; its findings are often unreliable in the first 3 months of life due to the low mineralization of the neonatal cranium [48, 64], and the evaluation of associated soft tissue and brain anomalies as well as raised intracranial pressure is suboptimal [7]. Moreover, skull X-rays need to be performed correctly because poorly performed exams may result in misdiagnosis. X-rays, indeed, can give false positive or false negative results, in particular because of an inappropriate inclination of the radiant beam

(the X-ray beam must result tangentially to the surface of the skull, pointed along the line of the affected suture) or an inadequate radiation exposure (which may result in loss of visualization of the suture). On the other hand, when a fibrous union affects the pathological suture or in case of partial suture fusion, no primary radiological changes may be noted.

Technically speaking, anteroposterior and lateral scans are usually sufficient for a complete examination although some authors suggest the addition of Towne's view and tangential view [34].

Coming to the radiographic representation of the prematurely fused suture, they can be divided accordingly to the craniosynostosis type [83]. The main findings are summarized in Table 1.

Table 1 Main findings of craniosynostoses on plain X-Rays

Craniosynostosis	Lateral view	Frontal view
Sagittal	Scaphocephalic skull shape, abnormal high bregma anterior shifting of the vertex; Fused suture: very straight course, reduced serration, or sclerosis along the margins	No particular features
Metopic	Anterior cranial fossa with the coronal suture displaced anteriorly	Hypotelorism with ovoid-shaped and angled upward orbits. Fused suture: narrowed or not visible; if visible, a very straight course with sclerosis along its margins is visible
Unicoronal	Narrowed anterior cranial fossa; Fused suture: narrowed or not visible	So-called harlequin appearance, lateral displacement of the anterior fontanelle towards the side of the patent coronal suture
Bicoronal	Brachy- and turricephalic aspects; Fused suture: narrowed or not visible	Wide forehead with orbital margins oval and oblique
Unilateral lambdoid	Small posterior cranial fossa	Deviation of the posterior fontanelle and its adjacent sagittal suture to the not-affected side; skull base tilted to the fused side, shifting the ipsilateral ear, including the petrous bone, downwards; Fused suture: narrowed or not visible
Bilateral lambdoid	Small posterior cranial fossa with turricephalic appearance	Downward displacement of both petrous bones and ears

Ultrasounds

Because of the increasing attention payed to the exposure to radiation in children [70] and the frequent need of a "radiological" tool to support the clinical and differential diagnosis in craniosynostosis (e.g., to differentiate between posterior positional plagiocephaly and lambdoid craniosynostosis), the use of ultrasounds is gaining more and more popularity in the clinical practice [54].

Ultrasounds appear to be a useful technique thanks to several advantages, such as the fastness of the execution, the absence of ionizing rays, and the possibility to proceed with the examination without sedation. On the other hand, there are some limitations with it, the most relevant being the "operator-dependency" of the technique [74, 75]. Furthermore, ultrasounds can be easily used only in the first months of life due to the hair growth, the skull growth, the presence of thinner sutures (especially the coronal ones), and due to natural closure of some of the suture, like the metopic one. Children can be monitored with ultrasounds until 8 months of life according to some authors [72], while other authors reported on cases in which such analysis could be done until 13 [39, 70, 74, 75] or even 18 months [95].

The technique consists in the use of an ultrasound probe that has to be held perpendicular to the plane of the long axis of the suture to obtain a coronal view of the suture and the adjacent bone, precise enough for a reliable assessment [70, 87]. Sutures are considered normal (patent suture) if a hypoechoic gap is identified between two hyperechoic bony plates, with end-to-end appearance or beveled or overlapped appearance [7, 70, 81, 89]. Instead, sutures are considered closed (synostosed suture) if there is a loss of hypoechoic fibrous gap between bony plates [7, 70, 81, 90].

In order to validate the diagnostic role of ultrasounds, many authors compared its results with CT scan and plain radiography. A specificity of 100%, a sensitivity of 100%, positive and negative predictive values of 100%, and 100% are reported by many authors [70, 72, 74, 75, 81, 87], while others showed a 100% sensitivity and an 89% specificity in differentiation positional molding from a fused lambdoid suture [95]. Alizadeh et al. reported a sensitivity, specificity, and positive and negative predictive values of 96.9%, 100%, 100%, and 92.3%, respectively [4], and Krimmel et al. demonstrated a sensitivity of 71.4% (95% confidence interval, 35.5%, 100%), a specificity of 95.7% (89.9%, 100%), a positive predictive value of 71.4% (35.5%, 100%), and a negative predictive value of 95.7% (89.9%, 100%) [49].

A further use of ultrasounds concerns the prenatal evaluation and the possibility to recognize SSC during the third trimester [40, 61]. Prenatal ultrasound diagnosis can be made by visualizing indirect signs, such as abnormal cephalic index, cranial shape and/or face morphology. However, the most important consideration in prenatal assessment is the

distinction between isolated and syndromic craniosynostosis. Therefore, a whole fetal examination is mandatory and the use of the 3D ultrasound can address fetal hands and feet, long bone growth, and central nervous system and heart [40, 41].

Finally, ultrasounds can represent a useful tool not only to follow-up suture patency but also the brain development and the ventricular size trough transfontanellar approach.

CT scan

The high-resolution CT scan with 3D surface-rendered image reconstruction is considered the gold standard in the radiological diagnosis of craniosynostosis [13]. Moreover, intracranial 3D images are a useful tool in evaluating skull base hypoplasia and minor suture synostoses [7, 16]. Technically speaking, beginning from the native axial images, the data are processed using multiplanar reconstructions with bone algorithms with a thickness of 0.65 mm and 3D volume rendering reconstructions (3D VR). Using complementary 2D multiplanar images with bony algorithm and the 3D VR, all the sutures (minor and major) and the synchondroses of the four sutural arches can be identified. Three-dimensional reformatted images can be easily obtained using a surface rendering software. 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. The width of a suture on 3D reconstruction may be considerably altered when different thresholds are selected. An increase in threshold value can "open" the sutures and enlarge the pseudoforamina. Generally, threshold values ranging from 120 HU for younger patients to 150 HU for older patients are adequate. Because of the "artifact" related to the threshold, the classic 2D images should be always considered for an appropriate evaluation of the suture patency.

The optimal visualization of images should include evaluation of intracranial structures with 5-mm thickness images reconstructed with a soft tissue algorithm, at least in the axial plane and brain window; evaluation of bones and sutures with 1- to 2-mm thickness images reconstructed with a bone algorithm, maximum intensity projection evaluation of thin (2–3 mm) and thick (5–50 mm) bone algorithm reconstructed images; and, finally, global evaluation of the skull (bones and sutures) in 3D volume rendering of soft tissue algorithm-reconstructed images [99].

CT scan can be then used to monitor patency or absence of the sutures, to plan therapy, to check for parenchymal associated anomalies as well as being a useful tool in monitoring postoperative complications and in follow-up [7, 27, 31, 99].

The morphologic findings in patients with craniosynostosis are well documented by CT, thus providing objective data on the bone structures. Thickened bony ridges predominate at the sagittal suture, focal bone thickening, and erosions are more likely to be found at the metopic suture, and perisutural sclerosis is the prevalent finding on one side of the lambdoid suture [34, 47, 48, 97].

Since CT scan is the gold standard in craniosynostosis assessment, a brief analysis of the principle suture involved is reported below. *Sagittal suture synostosis*: the fused suture appears as a bony prominence with ridging and heaping of it; the premature fusion of the sagittal suture results then in a restricted growth perpendicular and a compensatory overgrowth along the synostosis. The cranium has a narrow, elongated shape with prominent occipital protuberance and frontal bossing. In 3D reconstruction, due to the aforementioned features, a decrease in anterior interorbital distance (hypotelorism) can be seen [7, 10, 48, 64]. *Metopic suture synostosis*: in 3D reconstruction, metopic synostosis shows a fused metopic suture with a triangular pointed forehead, an ectocranial ridge with parietooccipital bossing, hypotelorism, and a narrow anterior cranial fossa. Characteristic of the condition is the presence of lateral orbital hypoplasia with bilateral constriction of the frontal bones in the region of pterion. Other features include hypoplastic ethmoid sinuses, deficient supraorbital ridges, and a quizzical appearance to the orbits where the orbital roof is slanted upward medially [7, 10, 48, 64]. *Unicoronal suture synostosis*: this synostosis is characterized by the premature fusion of unilateral coronal suture with ipsilateral flattening of the frontal bone. The contralateral one undergoes unimpeded growth with compensatory frontal bossing and the metopic suture, if not fused, is deviated to the affected side. The ipsilateral half of the anterior fontanel might be partly or completely fused. Even the ipsilateral orbit appears hypoplastic with a supraorbital ridge, an elevated roof resulting in the classic "harlequin eye deformity" [7, 10, 48, 59, 64]. Secondary to the wide spectrum of possible presentation in this peculiar craniosynostosis, many authors tried subdivide it in categories [25]. *Bicoronal synostosis*: in this instance, both the hemi-coronal sutures are fused as well as the anterior fontanel. The cranium appears shortened and widened with a bony prominence along the affected suture. A frontal prominence with occipital flattening and anterior displacement of the vertex is typically seen, and bilateral orbital harlequin eye deformity is evident with increased interorbital distance (hypertelorism). Often associated to these features are upper and midface hypoplasias with other craniofacial deformities [7, 10, 48, 64]. *Lambdoid suture synostosis*: premature fusion of the lambdoid suture results in a bony prominence along the suture, an ipsilateral occipitoparietal flattening and contralateral occipitoparietal and frontal bossing. The shape of the skull gains a trapezoidal shape with the posterior skull base tilted downward on the side of the synostosis. Secondary to the impossibility to grow in the affected site, the posterior skull-base axis swings towards the abnormal suture [7, 10, 48, 64]. *Bilateral lambdoid synostosis*: being closed both the lambdoid sutures, in this kind of synostosis, there is a bilateral occipitoparietal flattening with

underdevelopment of the posterior fossa. Unimpeded compensatory growth at the bregma results in a tall cranium leading to a turricephalic deformity [7, 10, 48, 64]. *Minor suture synostosis*: this definition encloses those synostoses of minor suture such as the ethmoido-frontal, the frontosphenoidal, the sphenosquamous and sphenoparietal, the occipitopetrosal, the parietosquamous, and the parietomastoid sutures. According to the fused suture, a variant of anterior or posterior plagiocephaly can be seen [16].

The radiation risk

As mentioned, CT scan represent the gold standard in craniosynostosis diagnostics. Even though radiations offer a multitude of information, their use in the pediatric population has to be carefully evaluated secondary to the possible ionizing effect, as reported by several authors [12, 15, 19, 28, 44, 57, 67]. Those papers report how, in the USA, as much as 70 million CT scan per year are performed, the diagnostic in pediatric disorders being one of the highest responsible for such a number. It is estimated that almost one million head CT scan in children are made each year [12, 53]. This steadily increase in the use of radiological ionizing exams and the long-life expectancy in pediatric patients lead the scientific community to study the matter. There are reports in the literature that enlighten how children receiving 50- 60 mGy (approximately, 2-3 head Ct scan at normal settings) have a risk three times higher than non-exposed children to develop leukemia or brain tumors [67]. Nevertheless, the authors concluded that, since these cancers are relatively rare, the cumulative absolute risks are small (one excess case of leukemia and one excess case of brain tumor per 10,000 head CTs, 10 years after the first scan, in children younger than 10 years). Indeed, Chen et al. calculated an estimated risk of 1 excess brain malignancy after 4000 CT scans, confirming 1 extra brain tumor per 10,000 children exposed to 10 mGy at < 10 years of age 10 years after the exposure [51]. Therefore, the radiological risk associated to CT scan in craniosynostosis is not particularly elevated, although it could account for 100 extra brain tumors in the USA in the next 10 years (the estimate of new brain cancer in children (birth to 14 years) in the USA during 2018 was about 2750 new cases) [86]).

Anyway, efforts are constantly made to try to balance the need for radiological assessment and the risk for the young patients. Many papers are nowadays centered on proposing different radiation schemes trying to reduce administrated dosage keeping good anatomical details [16, 82]. Other authors, like Ernst et al., proposed an iterative reconstruction technique to develop optimized low-dose CT protocol reducing image noise, thus improving image quality [31]. A similar approach was also suggested by Kaasalainen et al. and Zarella et al. [45, 102], while Morton et al. tried to reduce the dose-decreasing tube current intensity [63]. Even though no direct connection has ever been demonstrated linking CT scan and tumor development [12], it is of the utmost importance to know the potential risk and to keep it in mind while performing follow-up in pediatric patient preferring whenever possible other modalities free from ionizing rays.

MRI scan

Due to the ever-growing concern about the impact of repeated CT examination in young patients with benign conditions [12, 15, 19, 28, 44, 57, 67], the interest towards MRI as an alternative for radiological evaluation is increasing more and more in the clinical practice. However, while MRI eliminates the risks of ionizing radiation, the need for stillness of the baby in a long exam generally requires general anesthesia or sedation, both with their inherent risks within the MRI environment [30]. The need of anesthesia may represent a major concern when dealing with MRI in young babies due to the related risks (intubation, anesthesia maintenance, vascular lines and so on).

Historically, MRI was considered a complementary technique used to evaluate cerebral and craniofacial soft tissue anomalies associated with craniosynostosis, especially SC. Furthermore, MR venography and cerebrospinal fluid studies might reveal chronic venous hypertension, tonsillar herniation, and cerebrospinal fluid obstruction as well as other anomalies such as cranial neuropathies, vascular malformations, orbital abnormalities, and optic nerve atrophy [7, 48, 64].

Cotton et al. provided one of the first papers in the literature about MRI and suture analysis, in which the appearance of cranial sutures and craniometric points was studied in 150 patients aged between 20 and 49 years [52]. The imaging protocol consisted of 5-mm sagittal spin echo T1-weighted images, axial transverse 5-mm spin echo T2-weighted images and gradient echo T2*-weighted images, and gadolinium enhanced 3D T1-weighted images with a 1-mm isotropic voxel size. Sutures appeared as areas of signal void and were more easily identified using a 5-mm slice thickness rather than 1-mm. Mean suture widths were 1.2 (SD, 0.4), 1.4 (SD, 0.4), and 1.3 (SD, 0.3) mm for the coronal, sagittal, and lambdoid sutures, respectively [23]. On the other hand, Eley et al. had some concerns about the use of MRI use in infants as a mean to study suture patency [53]. Indeed, in their study, where axial T1, axial T2, coronal fluid–attenuated inversion recovery (FLAIR), axial short tau inversion recovery (STIR), and sagittal T1 were tested, the most promising sequence was the axial T2 in which a void signal can be found in correspondence of the patent suture. The most relevant concern is that the axial T2 void signal is peculiar of many other structures, such as blood vessels [29]. Based on this analysis, the need for a short acquisition time MRI sequence to provide both diagnostic information and 3D-reconstructed bone anatomy is necessary. Accordingly, the same authors devised the so-called

"Black Bone" MRI which utilizes novel gradient echo parameters optimized to minimize soft tissue contrast to enhance the bone-soft tissue boundary [30]. Such a sequence is achieved by using 3D volume acquisition, a short TE, TR, and low flip angle. As a result, imaging times are short, the average time to acquire "Black Bone" images of the craniofacial skeleton being 4 min. Imaging is acquired in the axial plane from above the skull vertex to below the mandible, with post-processing in the coronal and sagittal planes. Then, a 3D reconstruction is made to create the "Black Bone" images, setting a threshold mask in order to have the bone contained within the upper and lower threshold limits. However, as this setting also includes the surrounding, the mask is edited using a combination of multiple-slice edit and 3D edit functions. On "Black Bone" MRI, the cranial sutures appear as areas of increased signal intensity, making them distinct from the surrounding signal void of the bone. In children with craniosynostosis, the patent sutures are seen as areas of increased signal intensity, with these features being absent at the site of synostosis [30]. Other authors emphasized how "Black Bone" MRI can be also used in virtual surgical planning [94] and as a way to make differential diagnosis between posterior synostotic plagiocephaly and positional plagiocephaly [50]. Though appearing as a wonderful technique, "Black Bone" MRI has intrinsic difficulties in evaluating areas with air-bone interface such as the mastoid region and paranasal sinuses due to the difficulty in the 3D editing being the pixel values not discernible between bone and air [30].

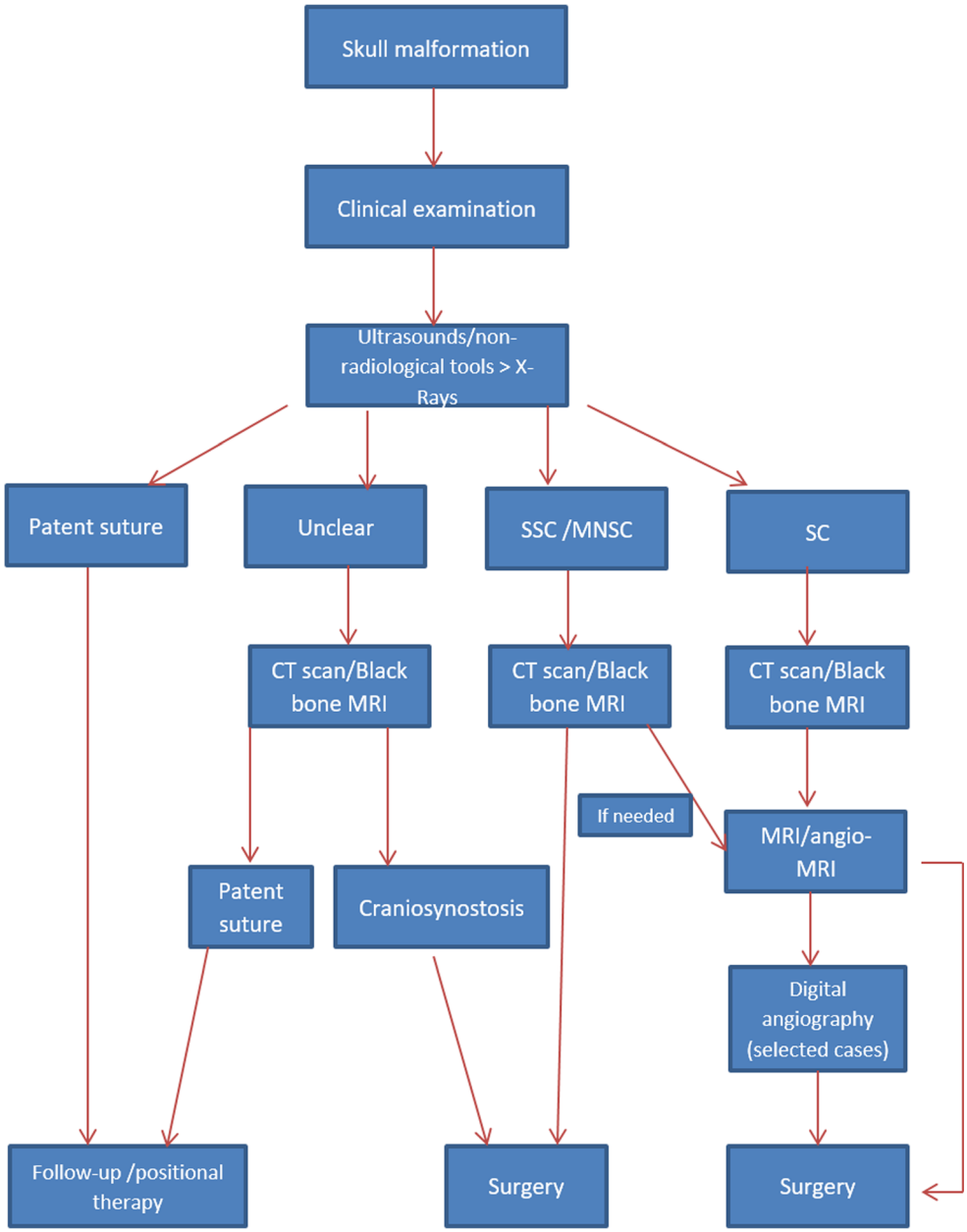

Fig. 6 Flowchart showing the summary of the main indications resulting from the present review of the literature, including the use of modern emerging techniques (non-radiological tools)

Digital angiography

Still today, digital angiography represents the gold standard in the diagnosis of vascular abnormalities. However, its role in craniosynostosis is very limited. Nonetheless, it can be useful in those conditions in which important venous abnormalities are suspected or already visualized through other exams, like angio-CT or angio-MRI scans. Actually, the use of MR venograms (with phase contrast and contrast enhancement techniques) and angio-CT helps to demonstrate anomalies of venous drainage with development of superficial/extracranial veins resulting from encroachment of basal foramina. Digital angiography, therefore, can be used not only to clearly visualize the abnormality but, rather, to plan an endovascular treatment prior to surgery in order to reduce the expected bleeding. This scenario is however more likely to be seen in SC as reported by Frassanito et al. who described a huge subcutaneous collector functioning as venous drainage for the intracranial venous system [36].

Conclusion

Nowadays, radiological diagnosis assumes a central role in the craniosynostosis workout. Even though CT scan remains the gold standard in diagnosis, several "new-old" techniques are increasingly taking spots in order to overcome the ionizing limit of the leading technique. None of the new techniques is yet at the level of CT for completeness of information, rapidity of execution, and goodness of the visualization but still lots of progress are visible in particular in ultrasounds and MRI scan. A personal flowchart is here reported to summarize the main indications resulting from the present review of the literature, including the use of modern emerging techniques (non-radiological tools) (Fig. 6). Further studies focused on the new techniques will be useful to overcome their current limits.

Compliance with ethical standards

Conflict of interest No conflict of interest to disclose.

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