Imaging in the Evaluation of Children with Suspected Craniosynostosis

Daniel N. Vinocur and L. Santiago Medina

I. What is the role of imaging in the diagnosis of craniosynostosis?
II. What is the cost and cost-effectiveness of imaging in children with suspected craniosynostosis?
III. Is imaging required when the clinical diagnosis has clearly been made?
IV. How often and what intracranial abnormalities are seen in craniosynostosis?
V. What is the role of imaging in the prenatal diagnosis of craniosynostosis?

Key Points

- Plain skull radiography demonstrates moderate to high sensitivity and specificity in craniosynostosis.
- Numerous publications support 3D-CT as the imaging modality with the best diagnostic performance, with reported sensitivities of 96–100%. CT also detects associated intracranial pathology.
- Higher diagnostic performance is obtained with plain films and CT if the studies are of good quality and interpreted by an experienced reviewer.
- Cranial sonography shows preliminary promise as a diagnostic test for craniosynostosis. The evidence is based on small cohorts; hence, larger series are needed before it is routinely used.
- Imaging strategies for children with suspected craniosynostosis should be based on their risk group. In healthy children with head deformity including posterior plagiocephaly, skull radiography is recommended. Syndromes such as Apert, Crouzon, and Pfeiffer nearly always have associated craniosynostosis and hence require 3D imaging for surgical planning.

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Imaging is not necessary for diagnosis or preoperative planning in isolated craniosynostosis with unequivocal clinical findings. However, in countries with high medicolegal issues, imaging may still be required.

Intracranial anomalies can be seen in some patients with craniosynostosis but the exact incidence is not well known.

Small retrospective US and MRI studies demonstrate the feasibility of prenatal diagnosis of craniosynostosis. However, large prospective studies are still required to understand the prenatal role of imaging in craniosynostosis and their effect on postnatal outcome.

Definition and Pathophysiology

Craniosynostosis is the premature fusion of the skull sutures. The resulting asymmetric calvarial growth causes characteristic cranial deformities. The clinical outcome varies between minor cosmetic deformity to severe head growth restriction with mental retardation and cranial palsies (1). Craniosynostosis cases can be classified as non-syndromic (isolated) and syndromic. The exact etiology of this disorder is unknown; however, in several syndromic cases, genetic disorders have been documented (2–4).

Epidemiology

The overall prevalence of craniosynostosis in the general population ranges from 34 to 48 per 100,000 live births (5, 6). Higher incidence has been reported in the state of Colorado, USA (7), but the reason for this difference is unclear. In the general population, syndromic cases of synostosis are less common than non-syndromic cases (8–11). Sagittal followed by coronal synostosis are the most frequent type, accounting for 56 and 22% of the cases, respectively (6). In children with syndromic craniosynostotic disorders, such as Crouzon, Apert, and Pfeiffer syndromes, synostosis is almost universally present (8–11).

Deformational plagiocephaly is defined as the asymmetric flattening of the head due to repeated pressure. Since 1992, there has been an exponential increase in the number of infants seen with deformational posterior plagiocephaly (positional molding) (12, 13). The most likely explanations are the 1992 American Academy of Pediatrics recommendation that infants sleep in the supine position to decrease the risk of sudden infant death syndrome (SIDS) and the increased awareness among pediatricians and other primary care providers of plagiocephaly (14–18). This specific entity usually presents some time after birth, progresses until 6 months of age, and remains stable thereafter (13). The skull deformity is generally considered to be only of cosmetic significance, and in the vast majority of cases it will respond to conservative measures such as changing sleep position or corrective helmets (3, 14).

Overall Cost to Society

We are not aware of studies documenting national costs of diagnosis or treatment of craniosynostosis or deformational plagiocephaly before or after the 1992 recommendations from the American Academy of Pediatrics. The cost of imaging studies and cost-effectiveness analysis are discussed in detail below.

Goals

The overall goal of neuroimaging for infants with suspected craniosynostosis is the early detection and characterization of this entity to enable appropriate treatment. Delayed diagnosis and treatment may lead to (1) cosmetic calvarial deformity which may be difficult to correct or may require more extensive cranioplasty and (2) potentially irreversible neurological impairment (18). Specific imaging goals include detailed characterization of the number of sutures, extent of suture involvement, and complexity of 3D calvarial deformity. Secondary goals include uncovering underlying brain anomalies associated with syndromic
synostotic disorders. More recently, there has been growing interest in the prenatal diagnosis of this disorder.

**Methodology**

Scientific article search was performed using the Medline/PubMed electronic database (National Library of Medicine, Bethesda, MD) and Ovid (Wolters Kluwer, New York, New York) for original research publications discussing the diagnostic performance and effectiveness of imaging strategies in craniosynostosis. The search for neuroimaging-related publications covered the period 1980–November 2007. The search strategy employed different combinations of the following terms: (1) Craniosynostosis, (2) Sensitivity, (3) Specificity, and (4) Diagnosis. This review was limited to human studies and the English language literature. The authors performed an initial review of the titles and abstracts of the identified articles followed by full text detailed review of relevant articles.

**Discussion of Issues**

I. What Is the Role of Imaging in the Diagnosis of Craniosynostosis?

**Summary of Evidence:** Plain skull radiography demonstrates moderate to high sensitivity and specificity in craniosynostosis (limited to moderate evidence). Numerous publications show 3D-CT as the test with the best diagnostic performance, with reported sensitivities of 96–100% (limited to moderate evidence). Additionally CT allows the detection of associated intracranial pathology. Higher diagnostic performance is obtained when radiographs and CT are of good quality and interpreted by experienced reviewers (limited to moderate evidence). An imaging diagnostic algorithm is summarized in Fig. 4.1. The diagnostic algorithm is based on the clinical differentiation between syndromic and isolated craniosynostosis. In isolated (non-syndromic) cases, we advocate starting with plain radiographs. If the radiographs are negative, clinical follow-up would be indicated. In equivocal cases, or when the radiographs are positive, further characterization with 3D-CT is recommended. Syndromic cases are best evaluated directly with 3D-CT, with surgical consultation indicated in positive cases.

Head sonography shows preliminary promise as a diagnostic test for craniosynostosis. The evidence is based on small cohorts; hence, larger series are needed before routine use in medical practice (limited evidence). Bone scintigraphy has fallen out of use, mainly due to its low accuracy, estimated at 66%. In addition, interpretation of images is complex and requires great expertise (limited evidence).

**Supporting Evidence**

**Skull Radiographs**

Plain radiographs are classically considered the first-line imaging modality in craniosynostosis (19, 20). The standard series includes an antero-posterior view, Towne projection, and both lateral views. The low cost per study, low radiation, and universal availability have made it an attractive diagnostic choice (21). However, large prospective studies addressing the diagnostic accuracy of plain radiographs for the detection of craniosynostosis are lacking. In a retrospective study by Cerovac and colleagues, the overall diagnostic accuracy of plain radiography was estimated to be 91% (20) (limited evidence). Vannier and colleagues (22) reported wide ranges of diagnostic accuracies depending on the suture evaluated, ranging from 56% for the metopic suture to 88% for the sagittal suture. Overall sensitivity and specificity were reported between 57 and 80% and 54 and 100%, respectively (limited to moderate evidence). Pilgram et al. showed poor quality radiographic studies had significant decrease in sensitivity and specificity estimated at 60 and 78%, respectively (23) (Table 4.1) (limited to moderate evidence). In an older study from 1985 with 36 patients (18), plain radiography was reported to have an accuracy rate of 89% when compared to surgical inspection and pathologic examination (limited evidence).

**Computed Tomography (CT)**

The introduction of computed tomography revolutionized the imaging of craniosynostosis. This modality not only depicts the
osseous pathology exquisitely but also allows for the detection of associated intracranial abnormalities, including hydrocephalus and brain developmental anomalies, such as agenesis of the corpus callosum (24). In addition, CT can identify alternative causes for asymmetric cranial morphology, such as brain hemiatrophy and chronic subdural collections (19).

Numerous studies have been published in the literature demonstrating the high diagnostic performance of CT (Table 4.1). Agrawal et al. (25) reported an overall sensitivity of 100% for CT diagnosis of synostosis in 12 infants (limited evidence). A blinded study performed on a relatively small cohort (25 infants) reported that the sensitivity of CT with 3D surface-rendered reconstructions to be in the range of 96–100% (limited evidence) (26). An older study from 1985 using thicker axial slices and no 3D reconstructions (18) reported an overall accuracy for CT diagnosis of 94%. CT reviewer experience and image quality play an important role in the achieved diagnostic performance. Vannier et al. demonstrated sensitivity and specificity of 96.4 and 100%, respectively, for experienced CT reviewers (limited to moderate evidence) (27). They also revealed that less experienced CT reviewers had a significant drop in specificity of the test to 83% (limited to moderate evidence) (Table 4.1) (27). Pilgram et al. demonstrated that poor quality CT studies had a significant decrease in sensitivity and specificity estimated at 73 and 78%, respectively (limited to moderate evidence) (23).

The use and risks of sedation or general anesthesia to perform CT examinations in children have been considered by several authors (20, 21). The overall risk of death from sedation is very low and has been estimated at 1 in one million (28–30). Furthermore, with the advent of spiral and multidetector CT, imaging time has been reduced drastically; hence, most children no longer need sedation for routine head CT.

Imaging post-processing also has an impact on the diagnostic performance of CT. Vannier et al. (22) compared and concluded that 3D shaded rendering of the skull was superior to the combined information from 2D-CT and plain radiography (limited to moderate evidence). In a technical note, Medina (31) reported from a small group of 10 patients the advantages of 3D maximum intensity projections (MIP) in the comprehensive assessment of craniosynostosis (limited evidence).

**Ultrasound (US)**

Lately growing interest has been placed on ultrasonographic examination for craniosynostosis given its lack of ionizing radiation and need for sedation. However, sonography is operator dependent, requires special technologist training, and is not feasible in infants older than 13 months (32). Technically the examination consists in scanning the sutures with high-frequency transducers (typically 7.5 MHz), utilizing gel as contact medium.

In 2006, Jan Regelsberger and colleagues from Hamburg, Germany, published a small series of 26 patients in which the diagnosis of craniosynostosis was established by ultrasound and confirmed later with CT. The study reported US sensitivity of 100% relative to CT (limited evidence) (32).

Plagiocephaly is a common problem with an estimated prevalence of 20% at 8 months of age (33). There was a sharp increase in posterior plagiocephaly over the last 25 years (13), after the widespread adoption of the AAP infant positioning recommendations to decrease the incidence of SIDS (34). A few articles addressed the use of ultrasound for this specific clinical concern (i.e., unilateral occipital craniosynostosis versus deformational molding) (32, 35). Sze and colleagues (35) published a prospective study of 41 subjects (including controls) to understand the role of US in characterizing posterior plagiocephaly (limited to moderate evidence). Their study correlated ultrasonographic findings with CT results. The overall sensitivity for US diagnosis was 100% and the specificity was 89% (limited to moderate evidence).

**Bone Scintigraphy**

Older literature emphasized the role of Tc99m-based bone scintigraphy for the diagnosis of craniosynostosis. The literature estimates the overall accuracy of scintigraphy to be approximately 66% (18), which renders it essentially valueless for current practice use. In addition, interpretation of this modality requires expert knowledge regarding the different normal phases of activity along calvarial bone maturation (36).
II. What Is the Cost and Cost-Effectiveness of Imaging in Children with Suspected Craniosynostosis?

**Summary of Evidence:** Selection of children with suspected craniosynostosis based on their risk group and use of the most appropriate evaluation strategy could maximize clinical and economic outcomes for these patients. A comprehensive cost-effectiveness analysis comparing different imaging strategies in the diagnosis of craniosynostosis was performed by Medina et al. (21) (moderate to strong evidence). In healthy children with head deformity, including posterior plagiocephaly, the skull radiographic strategy had the most reasonable cost per quality-adjusted life year (QALY) gained. Three-dimensional CT was more effective but had a high cost per QALY gained. In children with syndromic craniofacial disorders (high risk), 3D-CT was the most effective strategy and had a reasonable cost per QALY gained. Figure 4.1 summarizes the best imaging approach in suspected craniosynostosis.

**Supporting Evidence:** Medina et al. (21) performed formal cost-effectiveness analysis (CEA) on diagnostic strategies in children with suspected craniosynostosis (moderate to strong evidence). Three risk groups were analyzed on the basis of the prevalence (pretest probability) of disease: low (completely healthy children; prevalence, 34/100,000), intermediate (healthy children with head deformity; prevalence, 1/115), and high risk (children with syndromic craniofacial disorders (i.e., Crouzon’s syndrome or Apert’s syndrome); prevalence, 9–10/10). The analysis was based on cost (not charge) expressed in 1999 U.S. dollars. Cost data for the study are shown in Table 4.2.

In the low-risk group, the radiographic plus 3D-CT strategies resulted in a cost per quality-adjusted life year (QALY) gained of more than $560,000. In the intermediate risk group, the radiographic strategy resulted in a cost per QALY gained of $54,600. Three-dimensional CT was more effective than the two other strategies but at a higher cost, with a cost per QALY gained of $374,200. In the high-risk group, 3D-CT (without initial radiographs) was the most effective strategy with a cost per QALY gained of $33,800. Less experienced radiologists and poor-quality studies increased the evaluation cost per QALY gained for all of the risk groups because of decreased effectiveness.

The authors concluded that radiologic screening of completely healthy children (low risk for synostosis) is not warranted because of the high cost per QALY gained for any imaging. In healthy children with head deformity (intermediate risk), the initial workup with radiographs is the most cost-effective choice. Three-dimensional CT is more effective but more expensive. In children with syndromic craniofacial disorders (high risk), 3D-CT was the most cost-effective imaging approach.

III. Is Imaging Required When the Clinical Diagnosis Has Clearly Been Made?

**Summary of Evidence:** Isolated craniosynostosis with unequivocal clinical findings probably does not warrant preoperative imaging for diagnostic correlation and preoperative planning (moderate evidence), though imaging may be important for medicolegal considerations.

**Supporting Evidence:** In the setting of growing concern regarding radiation exposure (37), Agrawal et al. (25) studied the usefulness of preoperative imaging of clinically diagnosed isolated sagittal craniosynostosis. In their retrospective study of 114 cases, they correlated clinical diagnosis and pre-surgical imaging (plain radiography and CT) with surgical and pathologic findings and found a correlation of 100% for clinical diagnosis (moderate evidence). Both imaging studies also had a 100% correlation with surgical pathology results. In this preliminary work, they concluded that clinically typical isolated sagittal craniosynostosis does not warrant imaging.

Similarly, Cerovac and colleagues from the Great Ormond Street Hospital for Children in UK (20) published a retrospective series of 109 clinically diagnosed cases of isolated craniosynostosis (non-syndromic) and correlated them with pre-surgical imaging (CT and radiography) and surgical findings. They also demonstrated 100% confirmation of clinical and CT diagnosis (moderate evidence). Furthermore,
they reported no additional treatment benefit from CT in screening for intracranial abnormalities or change in surgical planning.

IV. How Often and What Intracranial Abnormalities Are Seen in Craniosynostosis?

Summary of Evidence: There are few studies addressing this question and those published have been small and without well-defined cohorts. Therefore, intracranial anomalies can be seen in some patients with craniosynostosis but the exact incidence is not well known.

Supporting Evidence: The exact incidence of associated intracranial anomalies in craniosynostosis is not well known. In a study from 1982, Goldstein and Kidd (38) reported on a heterogeneous group of patients with a variety of syndromic and isolated craniosynostosis (limited evidence). In this group, 5 out of 13 patients (38%) demonstrated an associated intracranial abnormality, most commonly hydrocephalus. However, only 1 of the 5 patients with an intracranial abnormality led to change in therapy (insertion of a shunt for hydrocephalus).

On the other hand, Hayward et al. (39) published a selective study of 30 patients with severe craniosynostosis and complex clinical syndromes who had MR imaging. The authors found more associated pathologies with the following prevalence: hindbrain herniation 19/30; syringomyelia 1/30; hydrocephalus 12/30; and non-specified anomalies of cerebral white matter 4/30.

The association of intracranial anomalies with syndromic craniosynostosis has been well established. Crouzon syndrome is associated with chronic tonsillar herniation (Chiari I malformation) in approximately 70% of cases and syringomyelia in 20% of cases. Other associations include hydrocephalus and absent corpus callosum (40).

Apert syndrome has been associated with megalencephaly and stable ventriculomegaly. Interestingly, progressive hydrocephalus appears to be relatively uncommon (20%) (41). Additional associations include agenesis of the corpus callosum/septum pellucidum, encephalocele (42), limbic and gyral malformations, and heterotopic gray matter among others (24, 41).

Finally, Pfeiffer syndrome demonstrates considerable heterogeneity, with subgroups of patients with mild phenotypes without mental retardation (43) to more severe phenotypes associated with mental retardation, hydrocephalus, and Arnold Chiari II malformation (40).

V. What Is the Role of Imaging in the Prenatal Diagnosis of Craniosynostosis?

Summary of Evidence: Small retrospective US and MRI studies in the prenatal diagnosis of craniosynostosis have been published (limited evidence). However, large prospective studies are still required to understand the prenatal role of imaging in craniosynostosis and their effect on parental counseling, surgical planning, and postnatal outcome of these fetuses.

Supporting Evidence: Recently, there has been increasing interest in the antenatal diagnosis of craniosynostosis. Early detection could potentially allow for different interventions, including elective termination of pregnancy in severe syndromic synostosis, elective cesarean section, early postnatal surgery, and perhaps fetal surgery (44).

Ultrasound (US)
In the largest series found in the literature, Delahaye and colleagues (4) performed a retrospective study in 40 fetuses with high risk of craniosynostosis. The inclusion criteria included (1) patients with positive family history of craniosynostosis and (2) those with an abnormal screening obstetrical ultrasound. Abnormal screening ultrasounds were based on altered head measurements and indices. Reported sensitivity and specificity was 100 and 97%, respectively, for this retrospective study (4) (limited evidence).

Miller and colleagues used screening ultrasound (non-targeted) in the second and third trimesters to compile a heterogeneous retrospective cohort of 21 fetuses with craniosynostosis. In this study, the authors correlated postnatal diagnosis with indirect signs of craniosynostosis on screening ultrasound
examinations (cranial geometry and indices). Their study demonstrated poor correlation between routine parameters of a non-dedicated prenatal ultrasound in the proper identification of synostosis (limited evidence). Using cranial geometry and indices, only 15 of the 26 (estimated sensitivity 58%) cases were diagnostic of postnatally documented craniosynostosis (limited evidence) (44).

**MRI**

Fjortoft and colleagues reviewed the imaging in a small group of 15 fetuses that demonstrated abnormal screening US during the second and third trimesters and were subsequently referred to fetal MRI imaging with the specific suspicion of craniosynostosis. In this cohort, MRI demonstrated 100% sensitivity and specificity when correlated to follow-up postnatal medical records (limited evidence) (45). No prospective MR imaging studies were found.

**Take Home Figures and Tables**

Figure 4.1 is an algorithm with a suggested diagnostic approach for suspected craniosynostosis.

Tables 4.1 and 4.2 discuss the performance of imaging tests for suspected craniosynostosis and the costs of imaging tests, respectively.

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**Figure 4.1.** Suggested diagnostic approach algorithm. Summary of the best imaging approach according to suspected syndromic versus non-syndromic skull deformity.

**Table 4.1.** Diagnostic performance of imaging tests

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Sensitivity (%)</th>
<th>Range</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiographs (good quality)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>80</td>
<td>57–80</td>
<td>(22)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>95</td>
<td>54–100</td>
<td>(22)</td>
</tr>
<tr>
<td><strong>Radiographs (poor quality)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>60</td>
<td>40–80</td>
<td>(23)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>78</td>
<td>56–100</td>
<td>(23)</td>
</tr>
<tr>
<td><strong>CT&lt;sup&gt;a,b&lt;/sup&gt; (experienced reviewer)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>96</td>
<td>93–96</td>
<td>(26)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>100</td>
<td>95–100</td>
<td>(26)</td>
</tr>
<tr>
<td><strong>CT&lt;sup&gt;a,b&lt;/sup&gt; (less experienced reviewers)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>96</td>
<td>89–100</td>
<td>(26)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>83</td>
<td>43–100</td>
<td>(26)</td>
</tr>
<tr>
<td><strong>CT (poor quality)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>73</td>
<td>52–83</td>
<td>(23)</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>78</td>
<td>30–81</td>
<td>(23)</td>
</tr>
</tbody>
</table>

<sup>a</sup>CT with 3D reconstructions.

<sup>b</sup>Good quality.

Modified with permission of the ARRS from Medina et al. (21)
Table 4.2. Cost of imaging tests

<table>
<thead>
<tr>
<th>Variable</th>
<th>Direct cost ($)</th>
<th>Total cost$ ($)</th>
<th>Medicaidb ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skull radiography</td>
<td>44</td>
<td>76</td>
<td>38</td>
</tr>
<tr>
<td>3D-CT</td>
<td>80</td>
<td>191</td>
<td>261</td>
</tr>
<tr>
<td>Sedation</td>
<td>70</td>
<td>121</td>
<td>0c</td>
</tr>
<tr>
<td>CT plus sedation</td>
<td>150</td>
<td>312</td>
<td>261</td>
</tr>
</tbody>
</table>

$Medical center cost estimates include direct (fixed and variable) and indirect (overhead) costs.

bMedicaid reimbursement (Ohio). This cost was used for the case-based study.

cSedation by nonanesthesiologist is not reimbursed by Medicaid.

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Imaging Case Studies

Figures 4.2, 4.3, and 4.4 illustrate representative cases of non-syndromic and syndromic craniosynostosis. In addition, a case of the commonly seen non-synostotic plagiocephaly is presented.

Figure 4.2. Case 1. Another case of isolated sagittal craniosynostosis. Superior view from a 3D-CT reconstruction demonstrating fusion of the sagittal suture (star) with associated dolichocephaly.
Figure 4.3. Case 2. Non-synostotic occipital plagiocephaly (positional molding or deformational plagiocephaly). A: Superior projection from a 3D-CT reconstruction demonstrating the skull deformity. B: Posterior projection from a 3D-CT reconstruction demonstrating patent lamboid sutures (stars).

Figure 4.4. Case 3. Apert syndrome. Anterior oblique projection from a 3D-CT reconstruction demonstrating coronal (star) and squamosal (†) sutures synostosis. Also note the facial hypoplasia.

Suggested Imaging Protocol for Craniosynostosis

Plain Radiographs

Excellent quality plain films including anteroposterior, Towne, and both lateral radiographs.

CT

Spiral or MDCT with surface rendering and maximum intensity projections.

Axial acquisition with the following suggested parameters.

- 120 kVp
- 200 mA
- Thickness 2.5 mm
- Parenchymal reconstruction: 5 mm with soft tissue algorithm

3D Images: 0.625 mm high-resolution bone reconstruction using 3D volume rendering and high-definition maximum intensity projection.

Future Research

- Large studies are needed to evaluate the role of ultrasound in the diagnosis of craniosynostosis, particularly in the differentiation between this entity and deformational plagiocephaly.
- Further research is required to establish the role of MRI and US in the antenatal diagnosis of craniosynostosis.
- Better-defined cohorts should be studied to determine the incidence of intracranial abnormalities based on the type of synostotic disorder.
References

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