Research Article

Role of 99mTc-ECD SPECT in the Management of Children with Craniosynostosis

Mayadhar Barik,¹ Minu Bajpai,¹ Rashmi Ranajn Das,² Arun Malhotra,³ Shasanka Shekhar Panda,¹ Manas Kumar Sahoo,³ and Sadanand Dwivedi ⁴

¹ Department of Pediatric Surgery, All India Institute of Medical Sciences, New Delhi 110029, India
² Department of Pediatrics, All India Institute of Medical Sciences, Bhubaneswar 751019, India
³ Department of Nuclear Medicine, All India Institute of Medical Sciences, New Delhi 110029, India
⁴ Department of Biostatistics, All India Institute of Medical Sciences, New Delhi 110029, India

Correspondence should be addressed to Mayadhar Barik; barikmaya@gmail.com

Received 9 February 2014; Revised 31 March 2014; Accepted 31 March 2014; Published 16 April 2014

Academic Editor: Nader Pouratian

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Purpose of the Report. There is a paucity of data on correlation of various imaging modalities with clinical findings in craniosynostosis. Moreover, no study has specifically reported the role of 99mTc-ECD SPECT in a large number of subjects with craniosynostosis.

Materials and Methods. We prospectively analyzed a cohort of 85 patients with craniosynostosis from year 2007 to 2012. All patients underwent evaluation with 99mTc-ECD SPECT and the results were correlated with radiological and surgical findings.

Results. 99mTc-ECD SPECT revealed regional perfusion abnormalities in the cerebral hemisphere corresponding to the fused sutures preoperatively that disappeared postoperatively in all the cases. Corresponding to this, the mean mental performance quotient (MPQ) increased significantly \( P < 0.05 \) postoperatively only in those children with absent perfusion defect postoperatively.

Conclusions. Our study suggests that early surgery and release of craniosynostosis in patients with preoperative perfusion defects (absent on 99mTc-ECD SPECT study) are beneficial, as they lead to improved MPQ after surgery.

1. Introduction

Craniosynostosis is the premature closure of one or more of the calvarial sutures with a prevalence of 3 to 6 per 10,000 live births [1, 2]. It can be primary, where a developmental defect during embryogenesis is the cause, or secondary, where the causes can be mechanical including compression of the fetal skull against maternal pelvis; metabolic like rickets, hypophosphatasia, hypercalcemia, anemias, and hyperthyroidism; decreased intracranial pressure as a result of brain atrophy or after shunting procedure for hydrocephalus; and teratogens [1, 2]. Proteins encoded by genes like MSX2, FGFR1-3, TWIST1, and EFNB1 control the intramembranous ossification of the skull, and mutation of these genes may lead to premature sutureal and resultant craniosynostosis [3]. About 85% cases are nonsyndromic, occurring as isolated involvement of sutures without any associated extracranial anomaly, whereas remaining 15% occur as syndromic craniosynostosis [4].

Different imaging modalities have been used in the assessment of children with craniosynostosis [5]. Plain X-ray of skull is useful in diagnosis except during the first 3 months of life (due to low mineralization) and the features include periosteal sclerosis, absence of suture, localized breaking, and bony bridging. Computed tomography (CT) scan is a useful modality as it helps in assessing the brain (e.g., parenchyma problems, hydrocephalus, and congenital malformation) and the skull including the sutures simultaneously. MRI is helpful in the assessment of syndromic craniosynostosis as it delineates the soft-tissue structures including brain parenchyma more clearly. Though these imaging modalities are helpful in preoperative structural assessment of the affected subjects, they however are not much of help for assessment of perfusion abnormalities and functional problems (e.g., cognitive, visual) related to the craniosynostosis [6, 7]. Recognition of the latter problems improves surgical outcome and reduces treatment delay [8].
Single photon emission computed tomography (SPECT) using a number of neutral lipophilic radiotracers like $^{99m}$Tc-ethylene-cysteine-dimer ($^{99m}$Tc-ECD) and $^{99m}$Tc-hexamethylpropyleneamine-oxime ($^{99m}$Tc-HMPAO) has been shown to be very useful for the study of regional cerebral perfusion in a variety of disorders affecting the central nervous system [6, 9]. We have previously shown cerebral hypovascularity in craniosynostosis using $^{99m}$Tc-HMPAO in seven children [10]. In the present study, we analyzed a large number of children with craniosynostosis by using $^{99m}$Tc-ECD SPECT and compared it with other imaging modalities as well as clinical parameters.

2. Materials and Methods

This was a prospective study conducted on 85 children attending to outpatient department of pediatric surgical unit and clinically diagnosed with craniosynostosis between February 2007 and April 2012 (Table 1). All the affected children had undergone a detailed clinical evaluation including assessment of vision, fundoscopy, and plain X-rays of the skull obtained in four views (AP, lateral, basal, and Towne’s) followed by noncontrast computed tomography (NCCT) scan (SOMATOM, Siemens Healthcare, USA) of the head to evaluate the extent of sutural involvement, associated ventriculomegaly, and parenchymal changes. MRI of the brain (MAGNETOM Avanto, Siemens Healthcare, USA) was carried out only in children with syndromic craniosynostosis. Subsequently, $^{99m}$Tc-ECD Brain SPECT (Symbia T6, Siemens Healthcare, USA) studies were carried out preoperatively in all the children. Psychological assessment was done using the Vineland Social Maturity Scale (VSMS), to assess the social maturity of the child and to assess self-help skills. The AIIMS developmental schedule was prepared to assess the mental performance in terms of quotient (MPQ) of children from 0 to 5 years of age and to calculate the motor, adaptive, mental performance in terms of quotient (MPQ) of children having experience in handling the SPECT images, and the final interpretation was based on a consensus. An abnormal study included asymmetry on two sides greater than 10% (qualitatively), defect size of more than one slice (1 pixel) in thickness, and extent of the lesion in more than one plane. Institutional ethics committee approval was obtained for the study.

All the children underwent surgery. The surgical procedure involved a linear craniectomy of coronal and metopic suture and parasagittal craniectomy extending to bilateral lambdoid craniotomies when indicated. The frontoorbital segment was detached from the calvarium by dissection at the anterior cranial fossa base, nibbling of the frontosphenoid sutures, and division of the frontonasal and frontozygomatic sutures. This detached segment was advanced 1-1.5 cm according to the requirements of the individual case by the modified tongue in groove technique. Again, $^{99m}$Tc-ECD Brain SPECT studies were carried out postoperatively in all the children. All children had uneventful postoperative recovery and were well at follow-up (ranging from 3 months to 15 years). All the descriptive data were entered into Excel sheet. Paired $t$-test was used to compare the MPQ scores before and after surgery. A $P$ value of <0.05 was considered significant.

3. Results

A total of 85 patient children were studied. There were 55 boys and 30 girls with age range being 1 to 38 months prior to corrective surgery. The observed detection rates of craniosynostosis were 72% (61/85), 94% (80/85), and 26% (4/15) by using X-ray, NCCT, and MRI, respectively.

Table 1: Clinical profile of children studied.

| Variables                      | Number | Percentage |
|--------------------------------|--------|------------|
| Age (months, mean ± SD)        | 15.6 ± 10.6 | —          |
| Male                           | 55     | 64.7%      |
| Syndromic type                 | 15     | 17.6%      |
| Nonsyndromic type              |        |            |
| Brachycephaly                  | 36     | 51.4%      |
| Scaphocephaly                  | 18     | 25.7%      |
| Trigonocephaly                 | 10     | 14.3%      |
| Plagiocephaly                  | 04     | 5.7%       |
| Oxymcephaly                    | 02     | 2.8%       |
| Sutures involved               |        |            |
| Coronal                        | 36     | 42.4%      |
| Sagittal                       | 18     | 21.2%      |
| Metopic                        | 10     | 11.7%      |
| Lambdoid                       | 02     | 2.3%       |
| Multiple                       | 19     | 22.3%      |
| Fundoscopy (papilledema)       | 44     | 51.7%      |
| Hydrocephalus or raised intracranial pressure | 21 | 24.7% |
| Microcephaly                   | 16     | 18.8%      |
| Asymptomatic                   | 59     | 69.4%      |
Table 2: Results of preoperative and postoperative investigations.

| Conventional imaging findings (number of patients) | Preoperative 99mTc-ECD SPECT | Dural vascularity at surgery | Mean (±SD) mental performance quotients (MPQ) Pre-op | Post-op | Postoperative 99mTc-ECD SPECT |
|--------------------------------------------------|------------------------------|------------------------------|-----------------------------------------------------|---------|-----------------------------|
| Fusion of bilateral coronal, lambdoid, and sagittal sutures (N = 19) | Absent | Scanty | 85.1 (17.9) | 92.6 (16.6)* | Normal |
| Fusion of left coronal and sagittal suture (N = 18) | Absent | Scanty | 86.2 (15.2) | 94.2 (13.4)* | Normal |
| Fusion of bilateral coronal sutures (N = 11) | Absent | Scanty | 87.2 (14.1) | 93.8 (15.7)* | Normal to increased |
| Fusion of bilateral coronal sutures (N = 07) | Normal | Scanty | 89.8 (14.6) | 93.1 (14.8) | Normal to increased |
| Fusion of left coronal suture (N = 04) | Normal | Normal | 92.7 (15.3) | 94.5 (13.7) | Normal |
| Fusion of right coronal suture (N = 14) | Normal | Normal | 93.6 (14.9) | 95.1 (13.6) | Normal |
| Fusion of metopic suture (N = 10) | Normal | Scanty | 92.5 (12.7) | 94.3 (16.4) | Normal |
| Fusion of right lambdoid suture (N = 02) | Normal | Normal | 94.9 (13.1) | 95.3 (15.5) | Normal |

*P value < 0.05.
The lower detection rate with MRI is due to the fact that cortical bone is not well imaged by MRI due to low proton content; rather it detects any associated intracranial malformation/parenchymal abnormality, hydrocephalus, and raised intracranial tension. The images obtained in all children after injection of $^{99m}$Tc-ECD demonstrated three patterns of sutureal (underlying cerebral cortical activity) activity: normal, absent, and increased. When correlated with surgical findings, “absent” indicated fused sutures and “increased” indicated fusing hyperactive sutures or sutures reacting to fusion elsewhere. So, a $^{99m}$Tc-ECD SPECT/CT hybrid imaging might prove to be superior over other imaging modalities as it can detect bony and underlying perfusion defects simultaneously. Most of the children showed evidence of hypoperfusion corresponding to the abnormally fused sutures on $^{99m}$Tc-ECD SPECT (Figures 1, 2, 3(b), and 4(b)), and few showed evidence of normal perfusion. For providing further information about the correlation of imaging modality, both pre- and postoperative noncontrast CT images of the skull of one case have been provided (Figure 3(a)). The corresponding $^{99m}$Tc-ECD SPECT scan image has been shown in Figure 3(b). The preoperative clinical photograph of twins with craniosynostoses have been provided (Figure 3(c)) with one of the twins having the radiological images as in Figures 1 and 2.
Figure 3: (a) Preoperative axial noncontrast CT (NCCT) skull images showing affected sulcal spaces of left frontoparietal lobe at the convexity and ventriculomegaly (A). Postoperative images showing decreased ventricular size and (B). (b) $^{99m}$Tc-ECD brain SPECT preoperatively showing absent radiotracer uptake involving left frontoparietal lobe suggestive of hypoperfusion, upper panel images axial (A), sagittal (B), and coronal (C), and postoperatively showing increased radiotracer uptake involving left frontoparietal lobe suggestive of hyperperfusion, lower panel images axial (A), sagittal (B), and coronal (C). (c) The preoperative clinical image of twin patients. Note the enlarged skull secondary to craniosynostoses and hydrocephalus in the patient on right arm of the mother.

Figure 4: (a) CT volumetric rendering technique (VRT) images showing fusion of left fronto-parieto-temporo-occipital lobe sutures preoperatively (A) and release of all these sutures postoperatively (B). (b) $^{99m}$Tc-ECD brain SPECT preoperatively showing absent radiotracer uptake involving left fronto-parieto-temporo-occipital lobe suggestive of hypoperfusion, upper panel images axial (A), sagittal (B), and coronal (C), and postoperatively showing increased radiotracer uptake involving left fronto-parieto-temporo-occipital lobe suggestive of improved perfusion, lower panel images axial (A), sagittal (B), and coronal (C).
3(a) and 3(b). For providing further information about the correlation of imaging modality, both pre- and postoperative CT volumetric rendering technique (VRT) images of the skull of one case have been provided (Figure 4(a)). The corresponding $^{99m}$Tc-ECD SPECT scan image has been shown in Figure 4(b). Postoperative follow-up imaging studies done at 3 months demonstrated a significant improvement of the perfusion defects and normalization of brain perfusion following surgical decompression (Table 2). Corresponding to this, the mean mental performance quotient (MPQ) increased significantly ($P < 0.05$) postoperatively only in those children (48/85) with absent perfusion defect preoperatively, when measured at 12 months during follow-up (Table 2).

### 4. Discussion

Craniosynostosis is one of the most common craniofacial anomalies with incidence of 1 in 2,500 live births. It can be “isolated” or “nonsyndromic” or may be “syndromic”. The former implies a sporadic occurring problem that usually affects a single suture causing a characteristic pattern of skull deformity, whereas the latter usually involves multiple sutures along with other associated malformations that include that of digital, skeletal, cardiac, or other organs. Though the syndromic variety can be diagnosed clinically, nonsyndromic variety requires imaging studies to confirm the diagnosis. Though plain X-ray of skull demonstrates a moderate to high sensitivity and specificity in diagnosing craniosynostosis, recent data support three-dimensional CT scan (3D-CT) as the best imaging modality with sensitivities ranging from 96 to 100% [11]. CT also detects associated intracranial abnormalities in brain of the children with craniosynostosis, whatever the etiological factors, there exists abnormality in perfusion and functional abnormalities in brain of the children with craniosynostosis [10, 15]. Previously, we have shown this by using $^{99m}$Tc-HMPAO SPECT [10].

In the present study, we used another isotope $^{99m}$Tc-ECD for SPECT imaging and found the preoperative studies in 56.5% (48/85) cases being abnormal in form of regional hypoperfusion in the underlying cerebral hemisphere, corresponding to the fused sutures (Figures 1–4). Every preoperative $^{99m}$Tc-ECD SPECT study was repeated at 3 months after surgery and demonstrated a significant postoperative improvement of the perfusion defects and normalization of brain perfusion following surgical decompression (Figures 1–4). Corresponding to this, the mean mental performance quotient (MPQ) significantly increased postoperatively only in those children (48/85) with absent perfusion defect preoperatively ($P < 0.05$), when measured at 1 year during follow-up. Also during follow-up at 1 year, the head circumference (measured by the cephalometric score) increased significantly (from mean of 59.4 in case of scaphocephaly and 77.1 in case of brachycephaly preoperatively to 65.2 in case of scaphocephaly and 83.6 in case of brachycephaly postoperatively) ($P < 0.05$). These findings strongly suggest that in craniosynostosis there is cerebral hypoperfusion at the microvascular tissue level, and the postoperative positive clinical and radiological impact can be attributed to the better function of the brain both by release of the stenosis and probably due to excellent collateral supply from the opposite side. Though the current indication of surgery for craniosynostosis is mainly for cosmetic reasons in most of the cases of an isolated craniosynostosis till now, present study shows, $^{99m}$Tc-ECD SPECT can prospectively identify patients benefiting from surgery.

### 5. Conclusions

Our study suggests that early surgery and release of craniosynostosis in patients with preoperative perfusion defects (absent on $^{99m}$Tc-ECD SPECT study) are beneficial as they lead to improved MPQ after surgery.

### Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

### Acknowledgments

The authors are thankful to Dr. Jyotish chandra samantaray, Dr. Sambhunath das, Dr. Madhavi tripathy, Dr. Satyanand das, Dr. Anjan trikha, Dr. Sunil kumar, and Dr. Snehalata for helping in the study and providing suggestions on improvement of the paper. Indian Council of Medical Research (ICMR) provided fund to conduct this study. The funder has no role in study design, data collection and analysis, decision to publish, or preparation of the paper.
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