Technetium-99m-HMPAO SPECT Cerebral Blood Flow Study in Children with Craniosynostosis

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Premature closure of cranial sutures (primary craniosynostosis) in children leads to characteristic skull deformities and prevents the constricted brain from growing normally. Although the cause remains unknown, several etiological factors have been cited. Recently, hypovascularity has been reported as a possible cause of craniosynostosis. **Methods:** In a prospective study regional cerebral blood flow studies were carried out with ^{99m}Tc-HMPAO SPECT in seven children with craniosynostoses. Five preoperative and six postoperative studies were conducted and the results correlated with radiological and surgical findings. **Results:** Preoperative studies revealed regional hypovascularity in the underlying cerebral hemisphere, corresponding to the fused sutures. Postoperative studies revealed disappearance of these perfusion defects in most cases, indicating normalization of perfusion following surgical decompression. **Conclusion:** This study establishes the presence of cerebral hypovascularity in craniosynostoses and suggests that early surgery and release of craniostenosis is essential to achieve optimum perfusion and brain development.

Key Words: technetium-99m-HMPAO; brain SPECT; regional cerebral blood flow; craniosynostosis

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Premature closure of cranial sutures (primary craniosynostosis) in children leads to characteristic skull deformities depending upon the suture(s) involved. This developmental abnormality, which may be present at birth, prevents the brain from growing normally. Early detection and treatment is imperative if permanent brain damage is to be prevented and optimal cosmetic repair achieved. Despite the many advances in medical science craniosynostosis (which may occur as an isolated anomaly or as a part of a syndrome) still remains an etiological enigma. Factors such as genetic mutation, metabolic disorders, intrauterine constraints and biochemical abnormalities have been identified as possible causes of this disease (*1–12*). However, none of these has consistently explained the cause of sutural fusion in craniosynostosis. Hypo- or hypervascularity of the cranium has been reported as one possible cause of craniosynostosis. Recent reports of hypoperfusion in the cerebral hemisphere corresponding to the fused sutures by ^{123}I-IMP SPECT studies (*13*) support the hypothesis that hypervascularity may cause craniosynostosis. Experimental demonstration of a high incidence of ipsilateral coronal sutural fusion following ligation of unilateral common carotid artery in rats also supports the above idea (*14*). With our experience in children with plagiocephaly where paucity of dural vasculature and compressed brain tissue on the affected side were observed. Those findings serve as pointers to possible underlying vascular malformation as an etiological factor. That result has led us to undertake this study in order to ascertain the perfusion status of cerebral cortex of children with craniosynostoses and to monitor the changes following corrective surgery.

MATERIALS AND METHODS

Seven children with craniosynostosis were evaluated between November 1992 and August 1993. A 3-mo-old male and a 1-yr-old male both suffering from obstructive renal disease were also included in the study as control subjects (Table 1). Both children showed no evidence of central nervous system (CNS) abnormalities. All the affected children underwent a detailed clinical evaluation including assessment of vision, fundoscopy and mental performance quotient (MPQ). All of the children had plain x-rays of the skull obtained in four views (AP, lateral, basal and towen's). This was followed by a CT scan of the head to evaluate the extent of sutural involvement associated ventriculomegaly and parenchymal changes (Table 2).

Subsequently, ^{99m}Tc-HMPAO SPECT studies were carried out preoperatively in five of seven children. Each patient received oral sedation with vellargan forte and an intravenous canula was inserted about 10 min before the isotope injection. The children were kept in a semi-dark, quiet room and intravenously administered 350 MBq–550 MBq of ^{99m}Tc-HMPAO. Immediately preceding the study, each child was given pethidine intravenously (0.5 mg/kg of body weight). Patients 6 and 7 did not undergo any preoperative HMPAO studies but were included in the study and evaluated postoperatively.

SPECT studies were performed between 15 and 30 min of intravenous administration of ^{99m}Tc-HMPAO on an Elscint SP-4,

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TABLE 1
Clinical Details of Children Studied

Patient no.	Age (mo)	Sex	Diagnosis	Sutures involved	Associated abnormalities
1	05	F	Left plagiocephaly	Left coronal and anterior sagittal	—
2	54	F	Multiple suture synostoses	Bilateral coronal, sagittal and bilateral lambdoid	—
3	02	F	Brachycephaly	Bilateral coronal	—
4	05	F	Brachycephaly	Bilateral coronal	Alpert's syndrome
5	30	M	Left plagiocephaly	Left coronal	Hydrocephalous
6	24	F	Right plagiocephaly	Right coronal	—
7	05	F	Left plagiocephaly	Left coronal	—
8	03	M	Control		
9	12	M	Control		

32-bit SPECT system with a truncated single head. SPECT images at 360° were acquired with 6° intervals in the step and shoot mode, in a circular orbit. The raw data was normalised for uniformity, center of rotation and gantry motion correction. Transaxial slices were generated with convoluted backprojection reconstruction, using a ramp and Hanning filter. A factor of 0.125 was applied for attenuation correction. Single pixel slices in the coronal, sagittal and oblique planes were obtained. All the slices were viewed on a color monitor by three observers. An abnormal study included:

1. Asymmetry on two sides greater than 10%.
2. Defect size of more than one slice (1 pixel) in thickness.
3. Extent of the lesion in more than one plane.

Six of seven children had surgery. The surgical procedure involved a linear craniectomy of both coronal sutures, metopic suture and parasagittal craniectomy extending to bilateral lambdoid craniectomies when indicated. The fronto-orbital 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 1–2 cm according to the requirements of the individual case by the modified tongue in groove technique (*3*).

All children had uneventful postoperative recovery and were well at follow-up (ranging from 3 to 16 mo). A postoperative clinical evaluation together with ^{99m}Tc-HMPAO SPECT studies were carried out in all cases.

RESULTS

The results in the control subjects revealed uniform distribution of radiotracer with no evidence of perfusion defects (Fig. 1). All five children who had preoperative HMPAO scans showed evidence of hypoperfusion corresponding to the abnormally fused sutures (Table 2, Figs. 2 and 3). Mental performance quotients (MPQ), determined in five children preoperatively (Table 2), were normal in three, dull normal in one and retarded in one.

The surgical findings are listed in Table 2. Scanty and

TABLE 2
Results of Preoperative and Postoperative Investigations

Patient no.	X-ray and CT	Preoperative ^{99m}Tc-HMPAO SPECT	Dural vascularity at surgery	MPO Preop/Postop	Postop HMPAO-SPECT
1	Fusion of lt. coronal and ant. half of sagittal suture	Solitary left fronto-parietal defect	Scanty	93/95	Normal
2	Fusion of bilateral coronal, lambdoid and sagittal sutures	Bilateral multiple perfusion defects	Normal	52/50	Normal
3	Fusion of bilateral coronal sutures	Bilateral fronto-parietal defects	Normal	–/95	Normal
4	-do-	Bilateral frontal defects	Scanty	76/78	Normal
5	Fusion of left coronal suture	Left fronto-parietal defect ventriculomegaly	No surgery	–/–	—
6	Fusion of right coronal suture	n/a	Scanty	102/100	Normal
7	Fusion of left coronal suture	n/a	Scanty	94/98	Normal

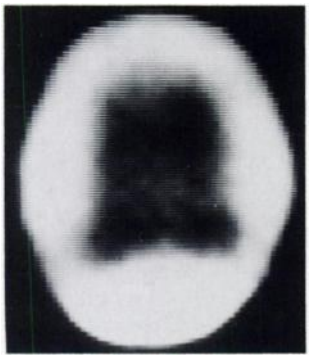

FIGURE 1. Technetium-99m-HMPAO study on a 12-mo-old infant without any evidence of CNS involvement (control). Transverse section. Uniform distribution of radio tracer is noted in the cerebral hemisphere.

FIGURE 2. Technetium-99m-HMPAO study on a 5-mo-old infant (Patient 1) with left plagiocephaly. Transverse section, showing left fronto-parietal perfusion defect.

attenuated dural vessels were seen corresponding to the site of sutural fusion at gross examination (Fig. 4) in three children, while the rest showed normal bilateral dural vasculature.

HMPAO studies for Patients 1–4 revealed disappearance of almost all perfusion defects following surgical decompression (Fig. 5). Only in one child with brachycephaly (Patient 3) did a small perfusion defect persist in the right frontal region. Two other postoperative studies done on Patients 6 and 7 revealed a normal perfusion pattern (Table 2). MPQs were again determined in all children postoperatively and were found to be essentially unaltered as compared to the preoperative values (Table 2).

DISCUSSION

Although craniosynostosis has been known since the days of Virchow (*15*), the etiopathogenesis of calvarial sutural fusion is still not well understood. The anomaly is known to occur both as an isolated event and in association with other anomalies (*1–12*). Some consider craniosynostosis a malformation of suture, whereas others consider it as deformation (*8,16,17*). It is also not clear whether the sutural fusion is the primary pathology or is secondary to basal dysplasia (*1,4,18*). The study of the histopathology of prematurely fused sutures has not been of much help in identifying the primary cause, and as such, many pathologists regard craniosynostosis as a normal developmental process of suture occurring at an abnormally early age, i.e., in the fetus (*18*). During the last century, several etiological factors have been identified or postulated. These factors can be classified into several groups: genetic mutation (*5,6,19*), specific infections (*6*), metabolic abnormalities (*7,20,21*), fetal head constraints and abnormal biomechanical forces (*8,10,22*). Several pathogenetic mechanisms also have been identified, such as defects in mesenchymal blastema, accelerated osseous maturation and lack of growth stretch across the sutures. These do not, however, explain sutural fusion in all cases (*1,18*). Because of the heterogenecity of the etiology and pathogenesis, Cohen postulated the possible relationship between etiology, pathogenesis and craniosynostosis (*23*). Little is known of suture topogenesis and morphogenesis even to this day. It has been suggested that this disorder may be a form of sutural agenesis, and not a fusion of formed sutures due to failure of undermined mechanisms, which prevented contact or fusion of adjacent bone territories (*8,16*).

Experimental approaches to premature synostosis have met with varying success. Experimental sutural fusion have been produced in mammals (rats, rabbits, monkeys) by autotransplantation of mature periosteum (*24*), stripping of periosteum overlying the sutures (*25*), insertion of bone disc into the sutural area (*26*) and application of cyanoacrylate (*27*). However, results have been conflicting and controversial. It is still not clear how these factors induce closure of sutures and the exact mechanism at the molecular level.

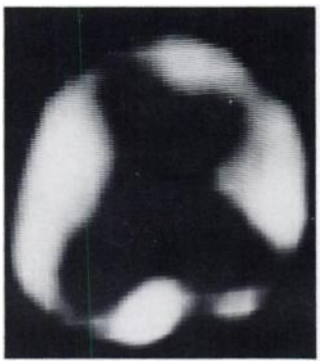

FIGURE 3. Technetium-99m-HMPAO study in a 4-yr-old child (Patient 2) with bilateral coronal, sagittal and bilateral lambdoid sutural synostoses. Transverse section, showing bilateral fronto-parietal and posterior parietal perfusion defects.

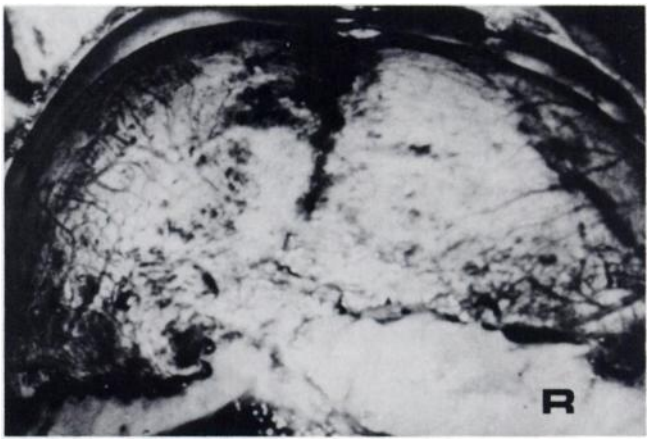

FIGURE 4. Frontal craniectomy in a child with right plagiocephaly. Both frontal lobes are in view. Note: Paucity of blood vessels on the dura (R) corresponding to the synostosed suture.

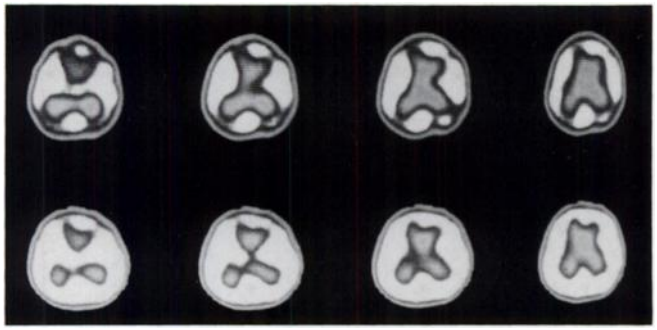

FIGURE 5. Technetium-99m-HMPAO study on a child with bilateral coronal, sagittal and bilateral lambdoid sutural synostoses. Transverse sections. Top row: preoperative study showing multiple frontoparietal and posterior parietal perfusion defects. Bottom row: postoperative study. Corresponding transverse sections showing normal distribution pattern indicating normalization of perfusion following surgical decompression.

Moss suggested hypovascularity or hypervascularity of sutures as possible causes of synostosis (*9*). Abnormalities of vascular development and vascular insult in intrauterine life has been known to produce failure of organogenesis or agenesis such as in neural tube defect, acardic monstor, jejunal and ileal atresia, gastroschisis, sirenomelia, defects of branchial arch derivatures, limb reduction defects, anomalies of aortic arch and cleft lip (*28,30*). Therefore, it is possible that similar ischemic processes may be responsible for premature fusion of cranial sutures in fetal life. In an experimental study at this institute a high incidence (37%) of ipsilateral sutural fusion was observed in Swiss albino rats, when hypovascularity was induced by right common carotid artery ligation or heat cauterization (*14*).

Dura and an endocranial part of sutures receive blood supply from the dural component of cerebral vessels (*31*). Anatomically dura is adherent to calvaria and more so at the site of sutures. The dural vessels carry cerebral blood to the endocranial part of the sutures along the sites of dura-sutural adhesion. Smith and Tondury (*32*) reported that in patients where the brain deformity antedated the development of the dura and calvaria, major dural reflections conformed to the anatomical variations of the aberrant brain and the sutures, in turn, were directly related to the unusual dural reflections. It was also reported that wherever dural bands were missing the corresponding sutures were absent (e.g., holoprosencephaly) and in the absence of dural development (e.g., craniopagus), neither the bone nor the sutures were present. Since the development of cranial sutures is dependent on dura (dural bands or fold) and the blood supply to the dura and endocranium is from the dural vasculature (*31*), it is possible that any aberration to dural vasculature or poor cerebral perfusion would cause ischaemic changes in the endocranial part of the cranial sutures and produce synostosis.

Scanty and attenuated dural vessels were seen on the affected side in four out of the six children who were operated in this study (Fig. 4). Besides, HMPAO SPECT studies revealed hypoperfusion in the corresponding cerebral hemispheres in all children studied preoperatively. Similar results have also been reported in the past by Satoh et al. by ^{123}I IMP SPECT (*13*). These findings strongly suggest that in craniosynostosis there is cerebral hypoperfusion at the microvascular tissue level. The disappearance of these perfusion defects in the follow-up scans in all but one child is similar to what has already been reported in literature. This 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, especially in Plageocephalies.

Why this hypoperfusion exists and whether this is the cause or the effect of sutural tension still remains unanswered. Whether this hypoperfusion is due to function impairment of the brain due to lack of space, craniostenosis, or is a part of aberrant mesenchymal blastema forming a defective neurocapsule causing sutural fusion and hypovascularity of the dural vessels and hypoperfusion of the cerebral cortex, still cannot be answered.

It may also be noted that none of these children demonstrated any significant change in the levels of their mental performance. However, early surgery and release of the craniostenosis appears to be mandatory to achieve optimum perfusion, brain development, cosmetic repair and arrest further deterioration of mental performance.

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