The Role of Bone Centers in the Pathogenesis of Craniosynostosis: An Embryologic Approach Using CT Measurements in Isolated Craniosynostosis and Apert and Crouzon Syndromes

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This paper describes the role of the displacement of bone centers, i.e., the tubers, in the pathogenesis of craniosynostosis. This displacement was studied in 54 patients with isolated or syndromic craniosynostosis in the form of CT scans as well as in two dry neonate skulls with Apert syndrome. For comparison, 49 fetal and 8 normal infant dry skulls were studied. Our investigation was restricted to the coronal and metopic sutures. The results showed a significantly more occipital localization of the frontal bone center and a more frontal localization of the parietal bone center at the side of a synostotic coronal suture in the isolated form as well as in Apert syndrome. In contrast, this was not the case in Crouzon syndrome, thus showing that these two syndromes have a different pathogenesis. For trigonocephaly, a more anteromedial localization of the frontal bone centers was found. (*Plast. Reconstr. Surg.* 98: 17, 1996.)

Craniosynostosis is generally considered as a premature closure of cranial sutures resulting in cranial deformity.[1] One of the classifications of craniosynostosis designates the isolated and the syndromic craniosynostoses.[2] In the isolated form, no other abnormalities, except those which may occur secondary to early sutural obliteration, are found, e.g., unilateral or bilateral coronal suture synostosis and metopic suture synostosis. In syndromic craniosynostosis, other primary defects of morphogenesis occur. The Apert and Crouzon syndromes are examples of this latter group.

Little is known about the pathogenesis of craniosynostosis. Genetics plays an important role, and recently, the genes for Apert, Crouzon, Pfeiffer, and Saethre-Chotzen syndromes have been located.[3–6] Craniosynostosis is considered to be a late developmental defect during embryogenesis (≥17 mm crown-rump length).[7–9] Our goal in this study was to explain the etiology of coronal and metopic suture synostosis from an embryologic point of view in both the isolated and the syndromic forms.

Embryology

During normal development of the skull, the frontal bone and both parietal bones are formed by ossification of membrane anlagen. The frontal bone starts to ossify in a pair of bone centers, one left and one right, and each parietal bone in two fusing bone centers.[10,11] According to several authors, the frontal bone centers arise in the developmental stage of 26 to 35 mm crown-rump length,[9,12–15] and the parietal bone centers arise in stage 31 to 45 mm crown-rump length.[9,12–14] Subsequently, ossification extends radially toward the margins with the tubers, being the most prominent portion of the bone, situated in the center of the thus formed radiating growth pattern of the bone.[11,16] According to *Gray's Anatomy*[16] and

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Trotter and Peterson,[17] the original position of the frontal and parietal bone centers is represented by the frontal and parietal tubers, respectively, while Inman and Saunders,[11] Starck,[14] Hinrichsen,[18] and Macklin[19] do not adhere to this statement. Inman and Saunders,[11] for example, situated the frontal bone centers in the superciliary region.

Normally, the metopic suture, formed by the frontal bone centers, ossifies during the second year of life. The coronal suture, developed bilaterally by the frontal and fused parietal bone centers, begins to close at 24 years of age.[20] Apoptosis (programmed cell death) appears to prevent fusion of bone centers and therefore causes the existence of the sutures.[9,21]

On abnormal development of the skull, the literature reports agenesis of the bone centers with subsequent agenesis of the involved bone[7,22–25] and failure of bone centers to fuse where they normally do, resulting in the formation of an extra suture, e.g., the bipartite parietal bone.[26–28] An extra bone center within one bone also can cause an extra suture, as is seen in the bipartite zygomatic bone.[8,9] Trigonocephaly was described as the result of the frontal bone developing from one single bone center.[8] Moreover, Vermeij-Keers[9] has suggested that craniosynostosis could be caused during embryogenesis by direct fusion of bone centers. Describing the infant Apert skull, Kreiborg and Cohen[29] mentioned that proper sutures do not form in the coronal or sagittal areas. Because of this sutural agenesis, adjacent centers of ossification would no longer be prevented from coalescing, resulting in bony fusion across coronal suture areas. Furthermore, Wrete[30] noted the lack of both the frontal and parietal tubers in bilateral synostosis of the coronal suture and the lack of frontal tubers in trigonocephaly, but without drawing any conclusions from his finding.

It is postulated here that during embryogenesis, adjacent bone centers, being displaced toward the synostotic suture, can undergo direct fusion of these bone centers. Subsequently, there is no development of the coronal suture, for example, at this level. This malformation can occur unilaterally in unilateral coronal suture synostosis and bilaterally in bilateral coronal suture synostosis and in Apert syndrome. Basically the same mechanism occurs when both bone centers of the frontal bone are located more anteromedially. Direct fusion between them takes place, without formation of the metopic suture, giving rise to a trigonocephalic skull.

Computed Tomography

Computed tomography (CT) has been shown to be a very sensitive method for detecting craniosynostosis.[31] Sutures of the calvaria are most accurately identified on high-resolution CT scans, using 1.5- or 2.0-mm-thick sections,[32] depending on the type of scanner. Three-dimensional reconstruction from CT images is of great value in understanding the pathologic morphology of the patient and in the preparation for craniofacial surgery.[33–35]

Craniofacial measurements obtained from CT scans are accurate and reproducible.[36,37] The technique is easy to master, and the objective data obtained can be used to assist in diagnosis, guide preoperative planning, and document results after surgical correction.[37–41] Waitzman et al.[42] created a base of normative CT data for the upper part of the craniofacial skeleton. Carr et al.[43] compared these values with measurements derived from patients with Apert and Crouzon syndromes under the age of 1 year and in addition compared Apert with Crouzon syndrome. Data from their study, however, did not show major differences between patients with the Apert and Crouzon syndromes despite morphologic differences. According to Carr et al.[43] and Kreiborg and Pruzansky,[44] measurements in other planes or of other structures are necessary to differentiate the morphology of these syndromes quantitatively.

By studying dry skulls, dry-skull CT scans, and CT scans derived from patients with craniosynostosis, we have evaluated the relationship between tubers and bone centers, as well as their involvement in coronal and metopic suture synostosis in the isolated form, in Apert and Crouzon syndromes. New CT measurements, based on our suggested embryologic etiology for coronal and metopic suture synostosis, are introduced.

Materials and Methods

Subjects

In order to study the involvement of the frontal and parietal tubers and bone centers in coronal and metopic suture synostosis compared with normal, macroscopic observations were performed of 49 normal fetal dry skulls (ranging in age from 15 to 40 weeks), eight normal dry skulls of infants (estimated age 1 to 4 years),

and two dry neonatal Apert skulls of the teratologic collection of the Museum of Anatomy of Leiden University. Unfortunately, no infant dry Crouzon skulls were available.

To trace the tubers on a CT scan in an anteroposterior direction, we first marked the frontal and parietal tubers with clay before taking the axial CT scan. This procedure was done for one normal fetal skull (approximately 6.5 months) and for the two Apert skulls. Based on the findings of these scans, we developed new CT measurements for locating the tubers. This enabled us to locate the frontal and parietal tubers on CT scans of our patients.

To validate this method, a comparison of the results of locating the tubers on the dry-skull CT scans using our new measurements with identifying them by clay marking was made.

A retrospective study of CT scan series of 54 patients with an isolated or syndromic craniosynostosis was undertaken using our new variables. Only complete, good-quality CT series of unoperated children, ranging in age from 1 month to 20 years, were selected. The age and gender distributions of the samples under study are outlined in Table I.

The scans had been made for the purpose of three-dimensional imaging. The population under study was classified according to the synostotic sutures, with Apert and Crouzon syndromes kept separate, the metopic suture being considered synostotic only if it had resulted in a trigonocephalic configuration of the skull (Table II).

In order to compare the measurements for the synostotic with those for open coronal and metopic sutures, each suture was classified as being open, synostotic, or uncertain. Four of the 54 patients had a synostotic metopic suture,

TABLE I

Age and Gender Distribution of Patients

Age Category	Females	Males	Total
0–3 months	6	5	11
4–6 months	5	8	13
7–9 months	2	3	5
10–11 months	2	5	7
1 years	5	4	9
2 years	2	1	3
3 years	–	1	1
4 years	–	1	1
5 years	1	–	1
7 years	1	–	1
13 years	–	1	1
20 years	1	–	1
TOTAL	25	29	54

TABLE II

Population Under Study, Classified According to the Synostotic Sutures, Apart from Apert and Crouzon Syndromes

Synostotic Suture(s)	No. of Patients	Syndrome Involved
	9	Apert
	7	Crouzon
Coronal, unilateral	10	
Coronal, bilateral	8	
Sagittal	10	
Lambdoid	6	
Metopic	3	
Lambdoid + metopic	1	
TOTAL	54	

resulting in a trigonocephalic skull. Of the remaining 50 patients, 100 coronal sutures were classified; 42 were synostotic, 43 were open, and for 15 ossification was uncertain (Table III). Since no CT scans obtained by the same procedures were available of normal, age-matched controls, we compared open with synostotic sutures within our population of patients.

Computed Tomographic Procedures

The axial CT scans of the dry skulls were taken with a Siemens Somatom Plus VD30 CT scanner using 2.0-mm slices (Department of Radiology, University of Rotterdam). Axial CT scans of the patients were obtained with a Philips Tomoscan LX CT scanner and a Philips Tomoscan 350 using 1.5-mm contiguous slices. General anesthesia was used for children under age 12 (Department of Radiology, University of Utrecht).

Measurements

The four new variables in the cranial region (Table IV) were measured and standardized with reference to the 5-cm scale bar on each film. For that purpose, we first made a copy of the required slice in order to measure more precisely. To obtain data, the slice transecting the most anterolateral points of the lateral ven-

TABLE III

Classification of the Studied Coronal Sutures after Separating Patients with Trigonocephaly (n = 100)

	Synostotic	Open	Uncertain
Apert	18	–	–
Crouzon	3	5	6
Other	21	38	9
TOTAL	42	43	15

TABLE IV
Computed Tomographic Measurements of the Bone Centers

Measurement	Description
Frontal bone center angle	Sharpest angle, left and right sides, at the frontal bone (see Fig. 4*a*)
Frontal bone center distance	Distance between the frontal bone center angle and the most frontal point of the outer table of the skull (see Fig. 4*b*)
Parietal bone center angle	Sharpest angle, left and right sides, at the parietal bone (see Fig. 4*c*)
Parietal bone center distance	Distance between the parietal bone center angle and the most frontal point of the outer table of the skull (see Fig. 4*d*)

tricles and the occiput above the inion was used, according to Waitzman et al.[42]

Measurements of the four variables were repeated by the same person on two separate occasions to check intraobserver reproducibility.

Statistical Analysis

Statistical differences between group means were tested by Student's *t* test. Group means, standard deviations, and 95 percent confidence intervals were calculated for the measurement variables. Test statistics associated with probabilities of 0.05 or less were considered significant, and all probability (*p*) values were two-sided.

Results

Macroscopic Observations

Macroscopic observations of the fetal and infant skulls clearly showed the radiating growth pattern of the frontal and parietal bones with, respectively, the frontal and parietal tubers in the center, as can be seen in Figure 1. This radiation was seen best in the fetal skulls, remaining visible until the age of approximately 1½ years with respect to the frontal bone and 4 years for the parietal bones. The position of the tubers, however, was very consistent.

Both Apert skulls clearly showed an abnormal radiating growth pattern of both frontal and parietal bones (Fig. 2) and a displacement of the tubers, being situated in the center of this pattern. The frontal tuber is situated more posterocaudally and the parietal tuber more anterocaudally. In between the frontal and parietal tubers the radiating growth pattern is absent, and fusion of the bones took place, instead of the expected normal development of the coronal suture. The coronal suture was formed cranial and, to a much lesser extent,

FIG. 1. Dry skull of a fetus showing the radiating growth pattern of the frontal and parietal bones with the frontal and parietal tubers in the center.

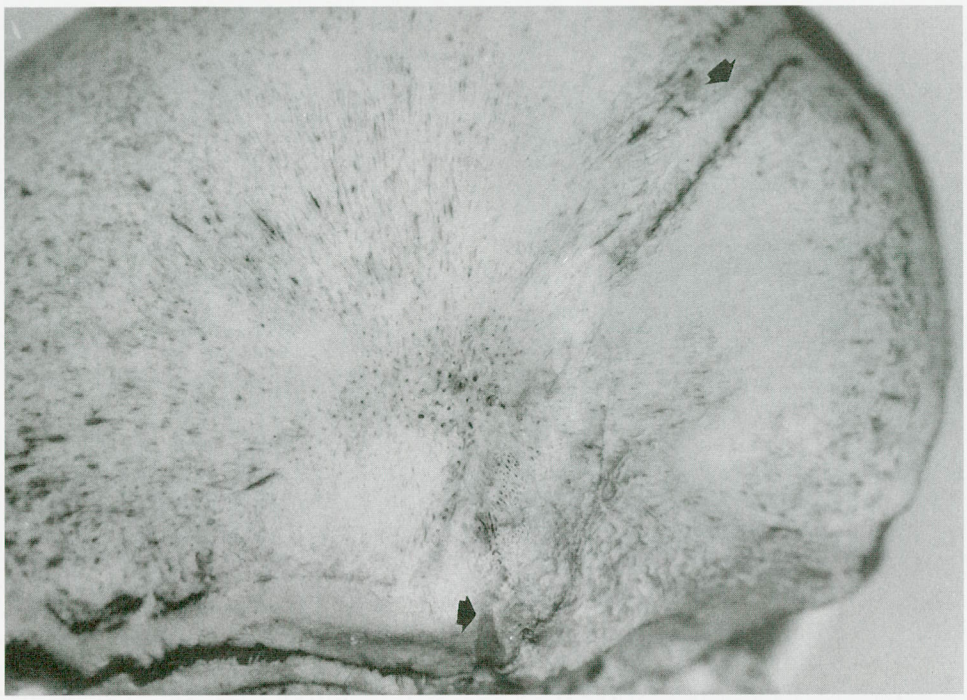

FIG. 2. Dry skull of Apert syndrome. Note the abnormal radiating growth pattern of both frontal and parietal bones in the Apert skull compared with normal (Fig. 1). The coronal suture had been developed only cranial and caudal to the side of fusion (*arrows*).

caudal to the locus of fusion. All abnormalities described were seen bilaterally.

Computed Tomography

On all scans of the three dry skulls, the clay-marked tuber, i.e., bone center, was found near the sharpest angle of the bone concerned (Fig. 3). This suggests that the frontal and parietal tubers can be located on a CT scan at the site of the sharpest angle of the frontal bone and the parietal bone, respectively, on the left and right sides. We measured this *bone center angle* as well as the distance between this point and the most frontal point of the outer table of the skull, the *bone center distance* (see Table IV).

In order to validate this method of measurement for locating the bone centers, the distance between the clay and the most frontal point of the outer table of the skull also was measured on the CT scan and compared with the previously described bone center distance (Table V).

The preceding comparison between both methods of measurement resulted in a mean difference of 0.3 mm with a 95 percent confidence limit of −1.2 to 1.9. This indicates that by identifying the bone center angle on CT scan, a good method for marking the position of the bone center in the anteroposterior direction has been obtained. These variables enabled us to locate the bone centers on the CT scans of our 54 patients.

Figure 4 shows how measurements were taken from the CT scans of patients with isolated unilateral synostosis of the coronal suture (*4.1*), Apert syndrome (*4.2*), Crouzon syndrome (*4.3*), and isolated synostosis of the metopic suture (*4.4*).

Means and standard deviations were computed for each variable for gender. There were no significant differences for gender; with respect to the frontal bone center distance, the mean difference was 4.2 mm with 95 percent confidence limits of −0.7 to 9.1, and for the parietal bone center distance, the mean difference was 5.5 mm with 95 percent confidence limits of −2.3 to 13.3, so data were pooled.

The mean frontal bone center angle was 157 degrees, and the mean parietal bone center angle was 164 degrees. Intraobserver measurements of the frontal bone center distance resulted in a mean difference of 0.4 mm with a 95 percent confidence interval of 0.0 to 0.9. For the parietal bone center distance we found a mean difference of 0.2 mm with a 95 percent confidence interval of −0.4 to 0.8. Bone center distances and age did not correlate.

There was no statistical difference found between isolated synostotic coronal sutures and

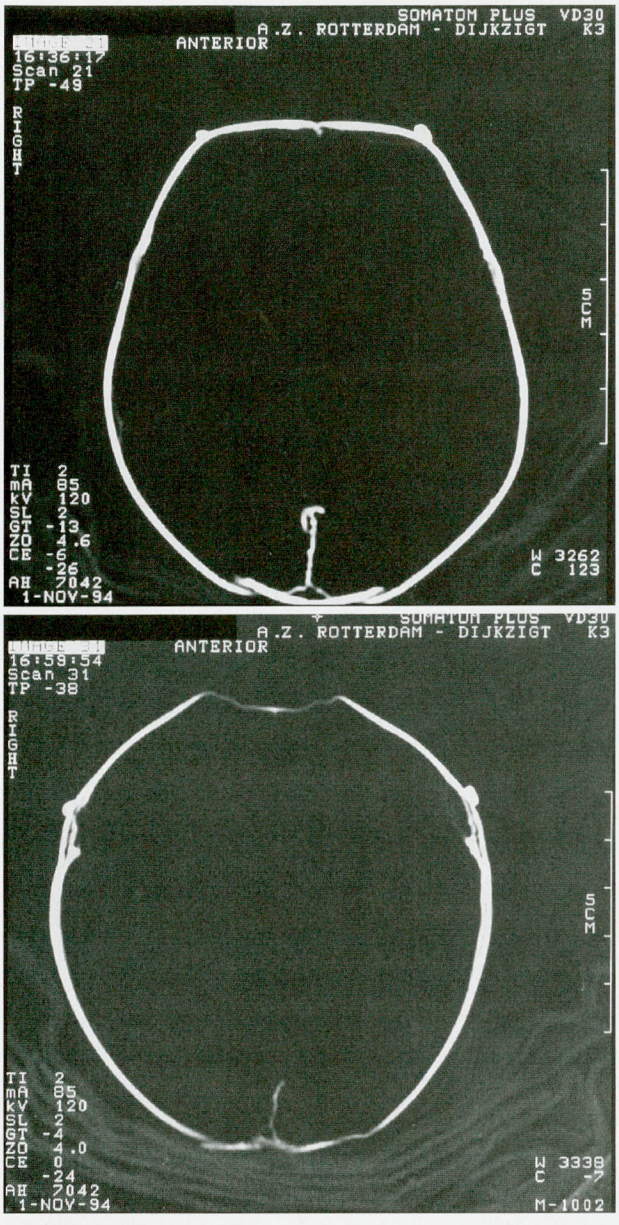

FIG. 3. CT scans taken from a normal fetal dry skull (*above*) and an Apert dry skull (*below*) with the clay indicating the frontal tuber, i.e., bone center.

Apert syndrome for both mean frontal and mean parietal bone center distances (the 95 percent confidence interval of the mean difference in frontal bone center distance was −0.6 to +11.0 mm; for parietal bone center distances the confidence interval was −3.1 to +20.1 mm). Therefore, data on isolated synostotic coronal sutures and Apert syndrome were pooled, collectively forming the synostotic group (Table VI).

Table VI presents the mean values for measurements of the frontal and parietal bone centers. The 95 percent confidence intervals for the frontal and parietal bone center distances for synostotic coronal sutures were not overlapping with those for open coronal sutures. This implies a statistically significant more posterior localization of the frontal bone center and a more anterior localization of the parietal bone center at the side of the synostotic coronal suture in the isolated form as well as in Apert syndrome. In contrast, this was not the case in Crouzon syndrome. The observed synostosis of the coronal sutures in Crouzon syndrome can therefore not be explained by a displacement of the bone centers.

For trigonocephaly, a more medial localization of the frontal bone centers was found, with a normal position of the parietal bone centers in an anteroposterior direction.

DISCUSSION

The combination of an abnormal radiating growth pattern and displaced tubers together with fusion of the frontal and parietal bones in between these tubers instead of coronal suture development, found bilaterally on the dry Apert skulls, shows a close relationship between the localization of the tubers and bone centers involved. This finding suggests that the tubers do indicate the original position of the bone centers, as was stated in *Gray's Anatomy*[16] and by Trotter and Peterson.[17]

The presented CT measurements enabled us to locate the frontal and parietal bone centers on CT scans in an anteroposterior direction. The results of these measurements are in line with our theory that synostosis of coronal and metopic sutures can be explained by an abnormal localization of the bone centers involved.

Because of this displacement, the bone centers fuse, and subsequently, no suture is formed at this level. The partially developed suture, cranial and caudal to the site of fusion, ossifies gradually. Rather than premature ossification of an established suture, as is implied by the term *synostosis*, this process is the result of a direct fusion of adjacent bone centers. *Sutural agenesis*, a term used previously by Kokich,[20] Furtwängler et al.,[21] and Kreiborg and Cohen,[29] seems to be a more accurate description.

In both the isolated form of coronal suture synostosis and Apert syndrome, in which bilateral coronal suture synostosis is a constant finding,[29,45] a more posterior position of the frontal bone centers and a more anterior position of the parietal bone centers were found. In trigonocephalic skulls, the bone centers of the

TABLE V

Computed Tomographic Measurements of Bone Center Distance (mm) by Means of Clay Localization Compared with Bone Center Angle Localization

	Apert Dry Skull 1		Apert Dry Skull 2		Normal Fetal Dry Skull	
	Clay	Angle	Clay	Angle	Clay	Angle
Frontal bone center distance left	20	20	21.3	20	2.2	2.7
Frontal bone center distance right	25	22.5	17.5	15	2.2	2.2
Parietal bone center distance left	33.8	35.6	38.8	36.3	54.3	58.7
Parietal bone center distance right	38.8	38.8	35.0	37.5	53.3	48.9

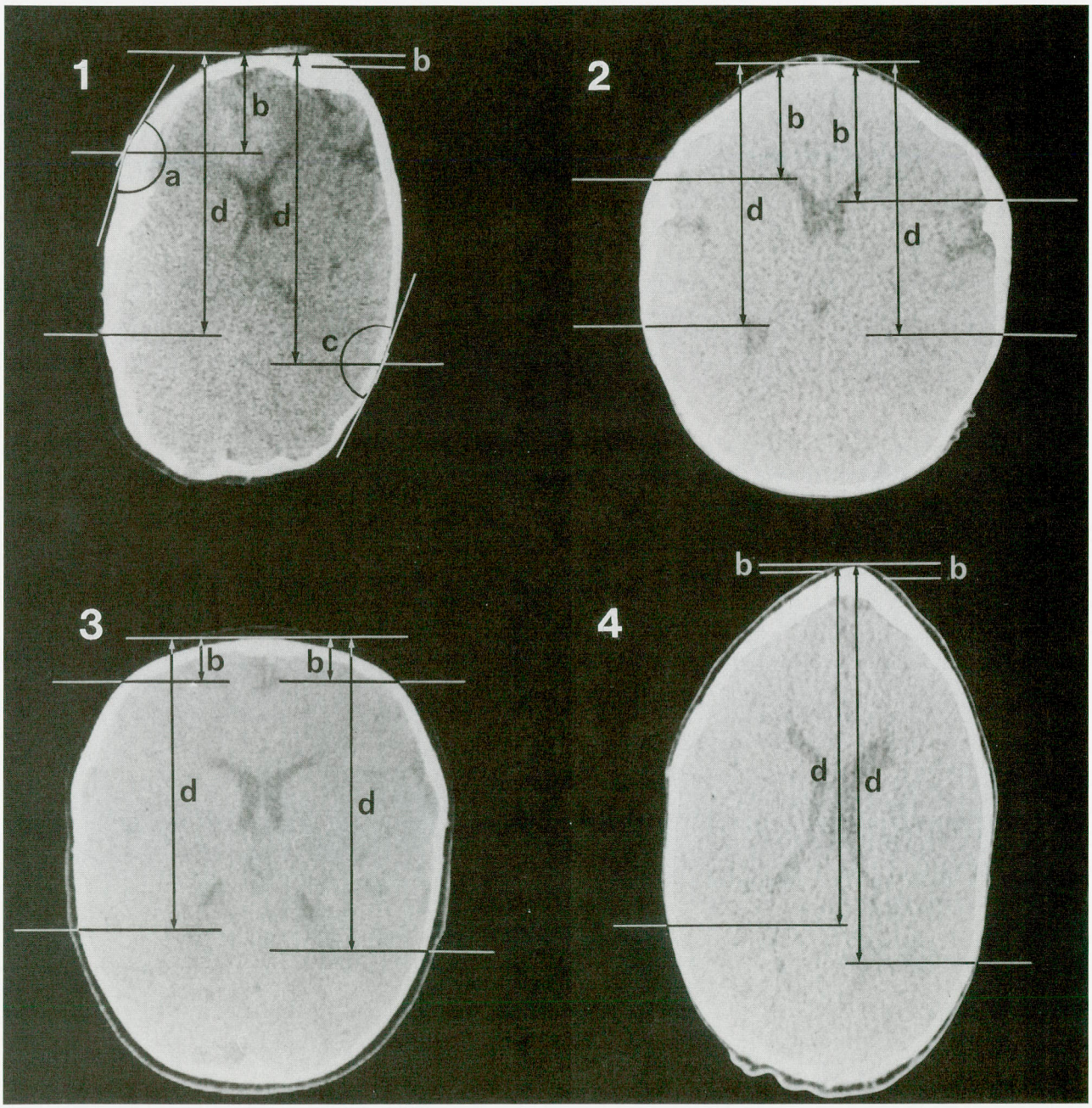

FIG. 4. Bone center measurements from axial CT scans: (*4.1*) plagiocephaly; (*4.2*) Apert; (*4.3*) Crouzon; (*4.4*) trigonocephaly. (*a*) Frontal bone center angle; (*b*) frontal bone center distance; (*c*) parietal bone center angle; (*d*) parietal bone center distance.

TABLE VI
Measurements of the Frontal and Parietal Bone Center Distance

	Open*,† (n = 38)‡	Synostotic* (n = 39)‡	Crouzon (n = 14)‡	Trigonocephaly (n = 8)‡
Frontal bone center distance				
Mean (mm)	7.2	30.6	9.7	1.9
SD	3.3	9.1	5.4	2.2
95% CI (mm)	6.1–8.3	27.7–33.6	6.6–12.8	0.0–3.7
Parietal bone center distance				
Mean (mm)	95.0	71.6	98.3	103.1
SD	13.5	22.6	23.2	10.5
95% CI (mm)	90.5–99.4	64.3–78.9	84.9–111.7	94.3–111.9

* Coronal suture.
† Metopic suture.
‡ Number of measurements.
CI = confidence interval.

frontal bone are localized almost completely in the median plane.

Apart from a displacement in the anteroposterior direction of the bone centers, our macroscopic inspection of the two dry Apert skulls also suggests a more caudal dispositioning. Measuring the bone center distances in this direction requires coronal reformatting of the scans, which we are currently working on. We suggest that the same principle of dislocated bone centers applies to other types of craniosynostosis, which will be studied in subsequent research.

Progressive calcification and fusion of the bones of the hands, feet, and cervical spine are known to occur in Apert syndrome.[46,47] Harris et al.[48] found abnormal epiphyseal ossification centers of the humerus and femur, fusion of calcaneus with cuboid, and fusion of the second and third metatarsal bones with other small bones in Apert syndrome and therefore suggested a more generalized involvement of enchondral ossification. Cohen[49] postulated that the same mechanism responsible for progressive calcification throughout the body is also responsible for the associated craniosynostosis in Apert syndrome. Our findings of a displacement of the ossification centers of the frontal and parietal bones in Apert syndrome make it seem likely that there is one basic ossification disorder for both enchondral and intramembranous ossification in this syndrome, probably leading to all the skeletal abnormalities observed.

The same abnormal localization of the frontal and parietal bone centers in the horizontal plane present in Apert syndrome was found in isolated coronal suture synostosis. However, these patients do not present the calvarial midline defect that is so characteristic of Apert syndrome. The caudal displacement of the bone centers observed in Apert dry skulls combined with true megalencephaly[50] could possibly distinguish and explain the difference in phenotype.

Whereas Carr et al.,[43] using their technique, did not detect any major differences between patients with Crouzon and those with Apert syndrome, our measurements of the new variables presented enabled us to find a distinction. In contrast to Apert syndrome, the bone centers in Crouzon patients were found not to be located significantly different from their normal position, indicating that there is a different pathogenesis involved in causing premature closure of the sutures in Crouzon syndrome. In conclusion, the CT data presented here, differentiating the morphology of the Apert and Crouzon syndromes, show a clear distinction in the pathogenesis of these two syndromes.

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