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Skull Base and Calvarial Deformities: Association with Intracranial Changes in Craniofacial Syndromes

Aya M. Tokumaru, A. James Barkovich, Samuel F. Ciricillo, and Michael S. B. Edwards

PURPOSE: To analyze the skull and brain malformations in patients with craniofacial syndromes. **METHODS:** A retrospective analysis of imaging studies of 21 children with craniofacial anomalies (8 with Apert syndrome, 6 with Pfeiffer syndrome, 4 with Crouzon syndrome, 1 with Robert syndrome, 1 with Coffin-Lowry-syndrome, and 1 with Saethre-Chatzen syndrome) was carried out using CT (21 patients), MR imaging (9 patients), and MR venography (2 patients). A series of qualitative and quantitative assessments of the skull base and intracranial structures was performed. **RESULTS:** Skull base abnormalities were present in all patients. Intracranial abnormalities included ventriculomegaly, frank hydrocephalus, callosal anomalies, hypoplasia/absence of the septum pellucidum, hypoplasia/dysplasia of the hippocampus, dysplasias or distortions of the cerebral cortex, and parenchymal hemorrhage. The anomalies of the corpus callosum, septum pellucidum, and hippocampus appeared primary, whereas the others may have been the result of brain distortion by the calvarial anomaly. MR imaging was more useful than CT for evaluating brain abnormalities. In the two patients in whom it was performed, MR venography showed anomalies of the venous system, indicating that venous anomalies, possibly related to the skull base hypoplasia, may contribute to the intracranial abnormalities. **CONCLUSION:** A wide range of neuroimaging abnormalities are present in the craniofacial syndromes. Some of these are clearly primary, whereas others appear to be related to the small skull base and sutural synostoses. MR venography may prove useful in defining the cause of some of the associated anomalies.

Index terms: Brain, abnormalities and anomalies; Children, diseases; Skull, abnormalities and anomalies

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Craniofacial anomalies are developmental abnormalities of the face and skull that are frequently associated with malformations of the central nervous system. From an embryologic perspective, most of these disorders are believed to result from insufficient formation, or inadequate migration, of mesenchyme to the skull base and the face (1, 2). Anomalies of the brain are particularly important, as studies have

shown that those patients with brain anomalies have poorer clinical outcomes (3, 4). The purpose of this study was to analyze the skull base, calvaria, and intracranial contents of patients with these disorders using computed tomography (CT), magnetic resonance (MR) imaging, and MR venography. We briefly discuss the clinical manifestations and theories of the pathophysiology of these disorders.

Materials and Methods

A review of records in the pediatric neurosurgery division and radiology file room at our institution revealed that neuroimaging studies were available for 21 children who had undergone craniofacial surgery over the past 10 years. A retrospective analysis of imaging studies of these children (8 with Apert syndrome, 4 with Crouzon syndrome, 6 with Pfeiffer syndrome, 1 with Robert syndrome, 1 with Coffin-Lowry syndrome, and 1 with Saethre-Chatzen syndrome) was carried out. Patients ranged from 1 day to 9 years old at the time of the study. Standard axial CT

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examinations were performed using 3- to 5-mm-thick sections and processed with both bone and soft-tissue algorithms in all of the 21 patients. Two patients, both with bilateral external auditory canal atresia, had temporal bone CT studies with 1.5-mm axial and coronal sections through the petrous portions of the temporal bones using a bone algorithm. MR examinations were performed in 9 patients, all at 1.5 T. MR imaging parameters included a 256×128 or 192 matrix; 3- to 7-mm section thickness (with an intersection gap of 1 to 3 mm). Axial 4-mm spin-echo sequences at 2500–3000/30–60,80–120/1 (repetition time/echo time/excitations), and sagittal spin-echo sequences at 600/11/1 were obtained in all 9 patients. Coronal spin-echo sequences at 600/11/1 were obtained in 5 patients. A three-dimensional gradient-echo sequence with gradient spoilers was obtained in 2 patients at 36/8, theta = 35° , and 1.5-mm partition size. Two-dimensional time-of-flight MR venography (45/8, theta = 40° , 1.5-mm partition size, matrix = 256×128) was performed in 2 patients. The initial MR venogram was obtained to ascertain a possible venous cause for a temporal lobe hemorrhage. The second venographic study was done as part of a new protocol for examining patients with craniofacial syndromes.

The following qualitative features and quantitative measurements were assessed: (a) The number and location of fused sutures. Sutural fusion was identified by careful examination of the entirety of the suture on the bone algorithm thin-section images. Continuity of bone across the suture line on any image was considered diagnostic of fusion. (b) The appearance of the orbit, in particular the degree of proptosis in relation to the interzygomatic line and lateral orbital angle. (c) The appearance of the skull base (appearance of skull base synchondroses, size of the clivus and posterior fossa, craniozygomatic measurements (5), relationship of normal skull base structures). The craniozygomatic measurements were made on the preoperative CT scans obtained in the patients who were less than 1 year old; the values obtained were compared with normal control values listed in Carr et al (5). (d) The appearance of the calvaria, in particular thinning or irregularity of bone and presence of pseudoencephaloceles. (e) The appearance of the brain, in particular anomalies of the corpus callosum, septum pellucidum, and cerebral cortex, ventricular size, configuration of the hippocampus, optic nerve size, tonsillar or transtentorial herniation, and evidence of parenchymal damage.

All of these features impact on the severity of the craniofacial deformity or on neurologic psychological development (3, 6, 7). Qualitative assessments, such as clival hypoplasia and optic nerve atrophy, were determined by consensus of two of the authors, both experienced neuroradiologists. Only those structures that were agreed upon by both authors as definitely abnormal were graded as abnormal (hypoplastic, small, and so on). Questionable cases were considered normal. The findings are summarized in Table 1.

Results

A single suture was involved in 2 patients and multiple sutures in 19 patients. CT evidence of bilateral coronal synostosis was recognized in 8 of 8 patients with Apert syndrome, in 2 of 4 patients with Crouzon syndrome, and in 1 of 6 patients with Pfeiffer syndrome. CT findings in patients with bilateral coronal synostosis included duplication of the sphenoid ridge, thickening of the bone around the frontozygomatic suture, foreshortened anteroposterior length of the anterior cranial fossa, shallow orbits, apparent anterior and superior displacement of the sphenoid bones, and anterior displacement of the petrous bones.

Patients with Apert, Crouzon, Pfeiffer, and Saethre-Chotzen syndrome all had widening of the lateral orbital angle, more protrusive globes, and shorter medial and lateral orbital walls than the others in this series.

Deformity of the skull base was recognized in almost all the patients. Craniozygomatic measurements were outside the 95% confidence limits established from the control group reported by Carr et al (5) in 178 (87%) of 205 total measurements. The anterior orbital distance was outside the 95% confidence limits in 12 of 13 patients in whom it was measured, the midinterorbital distance in 11 of 13, the lateral orbital angle in 9 of 13, the intertemporal distance in 14 of 14, globe protrusion in 10 of 14, medial orbital wall protrusion in 13 of 13, lateral orbital wall angle in 14 of 14, medial orbital wall length in 14 of 14, lateral orbital wall length in 10 of 14, interzygomatic arch distance in 12 of 13, interzygomatic buttress distance in 9 of 13, zygomatic arch length in 8 of 12, intercoronal length in 14 of 15, skull length in 13 of 15, and interparietal width in 15 of 15. Seven patients with Apert syndrome had expansion of the middle cranial fossa with elevation and forward bowing of the sphenoid ridge and lateral bowing of the temporal squamosa (Figs 1 and 2). One patient with Apert syndrome and one patient with Crouzon syndrome had bilateral atresia of the external auditory canals and distortion of the middle ear structures (Fig 3). Four patients had hypoplasia of the clivus, especially the basiocciput, and an apparently small posterior fossa manifest by tonsillar or transtentorial herniation of the cerebellum (Figs 2 and 4); this was most severe in patients with Crouzon syndrome (Fig 5). Widening of the orbital angle (Fig 2) was

TABLE 1: Imaging findings in 21 children with craniofacial anomalies

Patient	Syndrome	Suture Synostoses	Orbit		Skull Base Deformity	Calvaria		Nasal Skew	Paranasal Sinuses	Ventricles
			Proptosis	Wide Lateral Orbital Angle		Thinning, Irregularity	Pseudoencephalocele			
1	Apert	Bilateral coronal	Y	Y	Y	N	N	N	Hypoplastic	Large
2	Apert	Bilateral coronal	Y	Y	Y	N	N	N	Hypoplastic	Large
3	Apert	Bilateral coronal, L lambdoid	Y	Y	Y	N	N	N	Hypoplastic	Large
4	Apert	Bilateral coronal, L sphenoccipital	Y	Y	Y	Y	N	N	Hypoplastic	Large
5	Apert	Bilateral coronal	Y	Y	Y	Y	N	N	Hypoplastic	Large
6	Apert	Sagittal, metopic, L coronal	Y	Y	Y	Y	Y	Y	Equivocal	Large
7	Apert	Bilateral coronal	Y	Y	Y	Y	N	N	Hypoplastic	Large
8	Apert	Cloverleaf	Y	Y	Y	Y	Y	Y	Hypoplastic	Large
9	Crouzon	Bilateral coronal	Y	Y	N	N	N	N	Normal	Normal
10	Crouzon	Metopic, R lambdoid	N	N	Y	Y	N	N	Hypoplastic	Normal
11	Crouzon	Cloverleaf	Y	Y	Y	Y	Y	Y	Hypoplastic	Large
12	Crouzon	Sagittal	Y	Y	Y	N	N	N	Hypoplastic	Normal
13	Pfeiffer	Bilateral lambdoid	Y	Y	Y	N	N	Y	Hypoplastic	Large
14	Pfeiffer	Bilateral coronal, metopic	N	N	Y	N	N	Y	Equivocal	Large
15	Pfeiffer	Cloverleaf	N	N	Y	Y	Y	Y	Hypoplastic	Large
16	Pfeiffer	Metopic, bilateral coronal, lambdoid	Y	Y	Y	Y	Y	Y	Hypoplastic	Large
17	Pfeiffer	Metopic, sagittal, L coronal	Y	Y	Y	Y	Y	N	Hypoplastic	Large
18	Pfeiffer	Coronal, lambdoid, metopic, L sphenofrontal	Y	Y	Y	Y	Y	Y	Hypoplastic	Large
19	Robert	L lambdoid	N	N	N	N	N	N	Normal	Large
20	Coffin-Lowry	Metopic, sagittal	N	N	N	N	N	N	Normal	Normal
21	Saethre-Chatzen	R coronal	Y	Y	Y	Y	N	N	Normal	Normal

Note.—Y indicates yes; N, no.

identified in 16 patients, all of whom had associated deformity of the superior orbital fissure.

Fourteen patients had thinning and irregularity of the calvaria. This consisted of apparent spicules of bone extending centrally from the inner table, perpendicular to the calvarial surface (Figs 4 and 5). Thinning of the bone, creating the appearance of a calvarial defect, was noted in 3 of these patients; frank herniation of intracranial contents through the defect was seen in 2 (Figs 4B and 5B). Seven of 14 patients with thinning and irregularity of the calvaria had associated tonsillar and/or transtentorial herniation (Figs 4 and 5).

The frequency of ventricular dilatation was high, identified in 16 patients. However, progressive ventricular enlargement, leading to a diagnosis of hydrocephalus and ventriculoperitoneal shunt placement (Fig 4), was detected in only 4 of the 15; enlarged anterior third ventric-

ular recesses (Fig 2B) were identified in these patients. MR venography in one patient with hydrocephalus showed obliteration of bilateral transverse and sigmoid sinuses. Five patients with ventricular enlargement did not have enlargement of the anterior recess of the third ventricle, which suggested that these patients had "distortion" ventriculomegaly (see "Discussion") rather than hydrocephalus. Six patients with Apert syndrome had a characteristic configuration of ventriculomegaly in which the frontal horns of the lateral ventricles were disproportionately dilated (Fig 1).

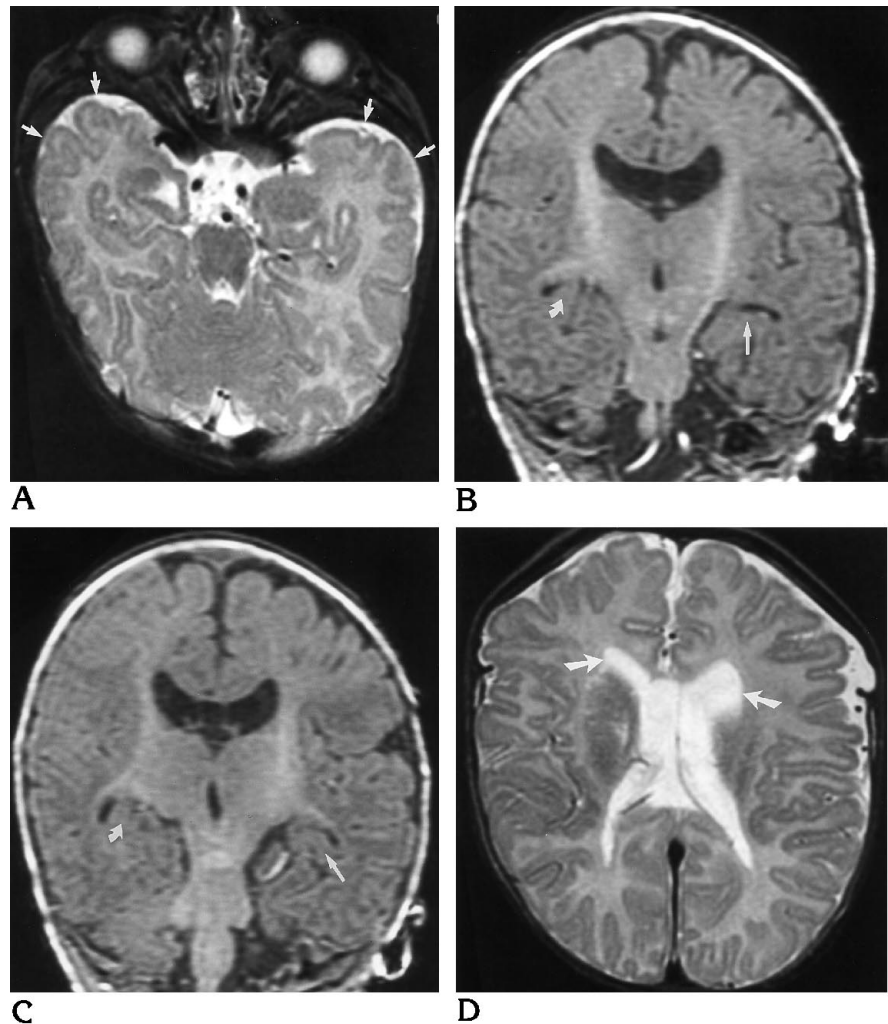
Brain anomalies were frequently identified. Callosal anomalies (Fig 6) were identified in three patients and defects of the septum pellucidum (Fig 1) were recognized in six patients. These anomalies were especially common in the patients with Apert syndrome. An anomaly of the temporal lobe, including the hippocam-

Fig 1. Patient 4. Apert syndrome.

A, Axial spin-echo (3000/120) MR image shows expansion of the middle cranial fossae (*arrows*) with elevation and forward bowing of the sphenoid ridges and lateral bowing of the temporal squamosa.

B and C, Coronal spoiled gradient-echo (36/8) images show abnormality of the hippocampus and partial absence of the septum pellucidum. The right hippocampus (*curved arrow*) is abnormally elevated and vertical, whereas the left hippocampus (*straight arrow*) appears hypoplastic. The gyral patterns of both temporal lobes are abnormal. Both leaves of the septum pellucidum appear absent in B but present in C.

D, Axial spin-echo (3000/120) image shows disproportionate enlargement of the frontal horns (*arrows*) of the lateral ventricles and absence of the right leaf of the septum pellucidum.



pus and adjacent temporal horn (Figs 1 and 6), was identified on thin-section coronal and sagittal MR images in four patients; three of these patients had associated septal defects (Fig 1) and one of them had associated callosal agenesis (Fig 6). In addition, patient 4 had an atypical gyral pattern in the temporal lobes bilaterally (Fig 1) without an obvious neocortical anomaly. We were unable to detect abnormalities of the olfactory system in any of the patients.

Optic nerve atrophy was detected in five cases. In all, our findings were verified by fundoscopic examination. Two of these five had marked hydrocephalus (Fig 2), suggesting the presence of high intracranial pressure. Sagittal and coronal MR images revealed obviously stretched optic nerves and chiasm in three patients. The optic canals appeared normal in size in all of these patients.

Low-density areas in the cerebral white matter were detected on CT scans in seven patients. Small high-density areas were recognized in the immediate periventricular region in one patient with Apert syndrome. Another patient with Apert syndrome and a cloverleaf skull had hemorrhage within the lateral temporal lobe, considered to be the result of venous infarction. MR venography in this patient (Fig 2C) did not show either the transverse or the sigmoid sinus, suggesting obliteration of venous flow.

Discussion

The number of identified craniofacial syndromes is large and growing (8–11). A summary of several of the most common inherited forms and their essential features is presented in Table 2 (12). Most affected patients may be

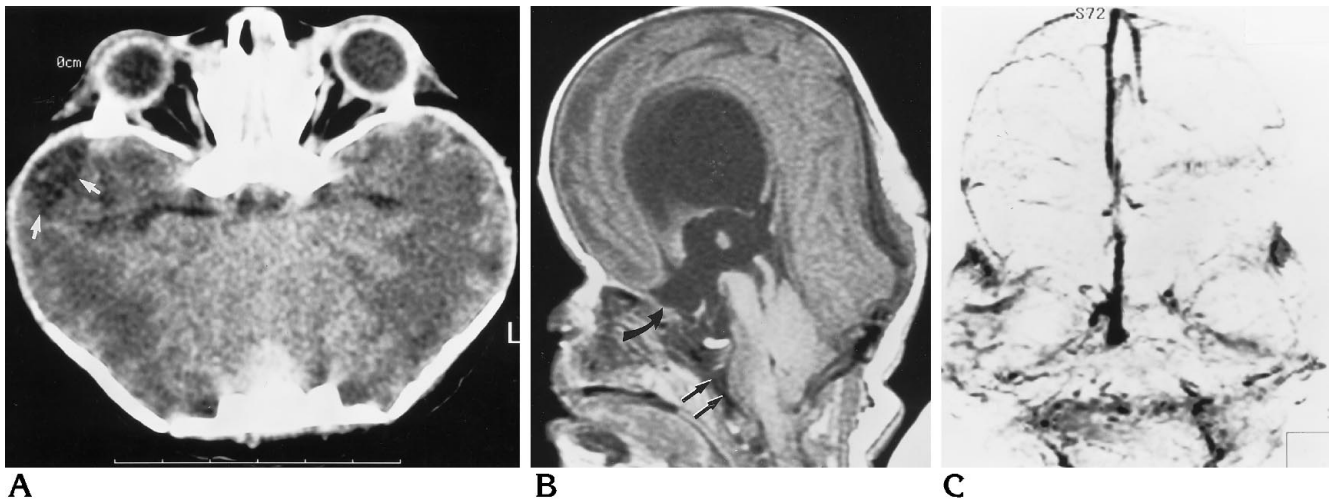


Fig 2. Patient 8: Apert syndrome.

A, Axial CT scan shows expansion of the middle cranial fossae with elevation and forward bowing of the sphenoid ridges and lateral bowing of the temporal squamosa. The orbital angle is widened and the optic nerves are small. Low attenuation (*arrows*) is from a venous infarct in the right temporal lobe.

B, Sagittal spin-echo (600/11) MR image shows oxycephaly caused by bilateral coronal synostosis and hydrocephalus, the latter manifest as enlargement of the anterior recesses of the third ventricle (*curved black arrow*). The posterior fossa is small, in part because of the small clivus (*small arrows*).

C, Maximum intensity projection from a two-dimensional time-of-flight MR venogram shows absence of flow in both transverse and sigmoid sinuses.

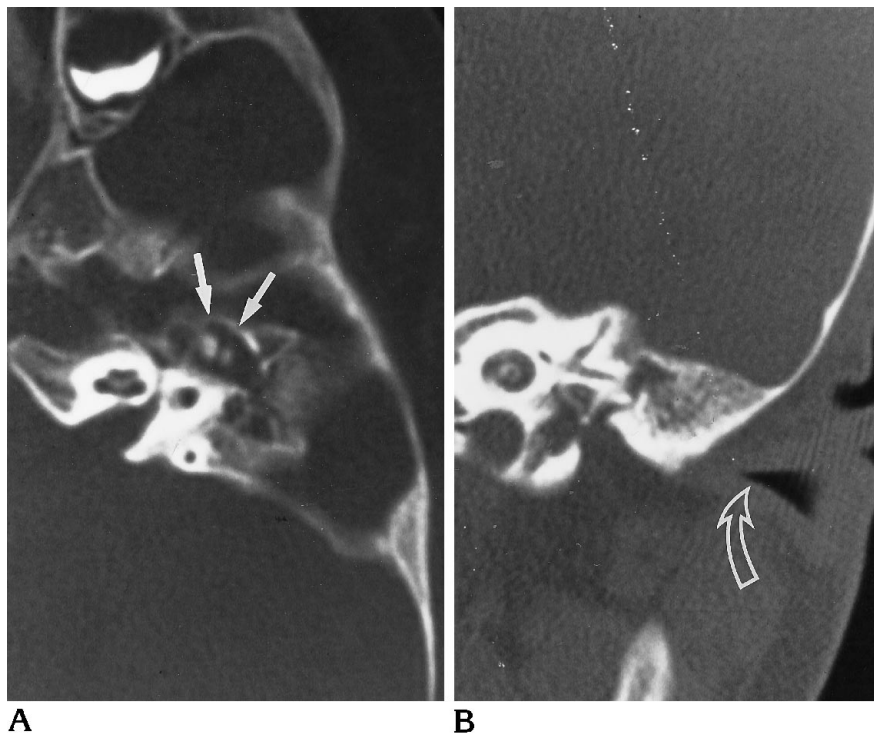


Fig 3. Patient 10: Crouzon syndrome.

A, Axial and B, coronal CT scans show atresia of the external auditory canal (*curved arrow*). The middle ear is filled with fluid. The configuration of the epitympanum (*straight arrows*) is unusual, as it curves anteriorly and medially with respect to the vestibule.

Fig 4. Patient 17: Pfeiffer syndrome.

A, Sagittal spin-echo (600/11) MR image shows tonsillar herniation through the foramen magnum (*large curved arrow*). The basiocciput (*small arrows*) appears very small.

B, Axial bone window CT scan shows spicules of bones extending from the irregular calvarial surface. A calvarial defect is noted in the right occipital region, with frank herniation of intracranial contents (*arrows*) through the defect.

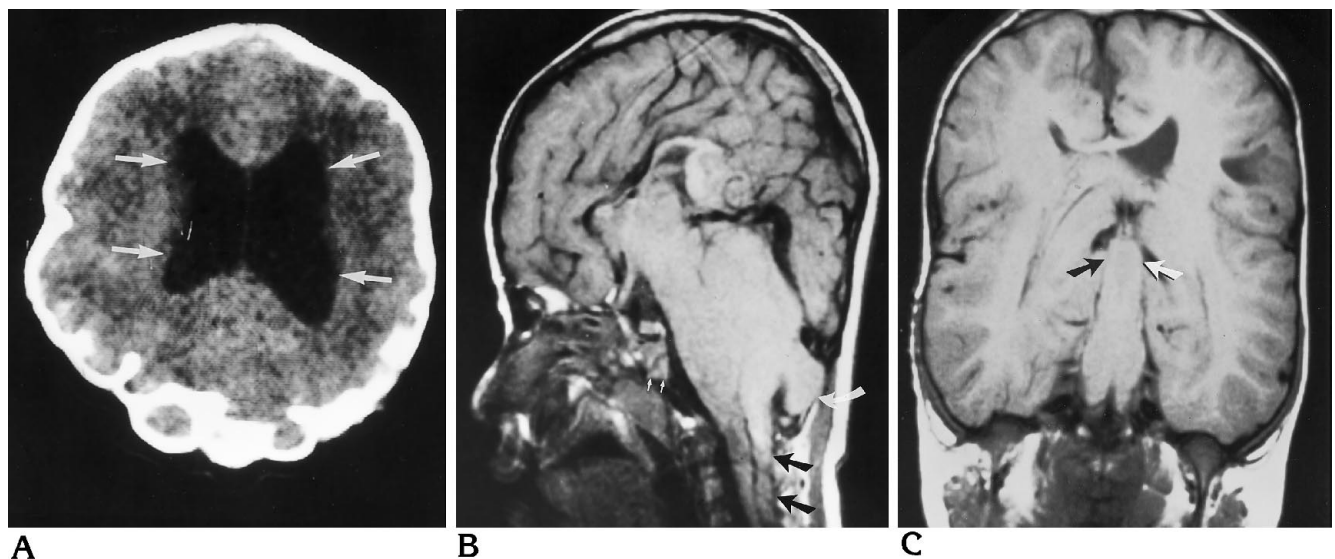
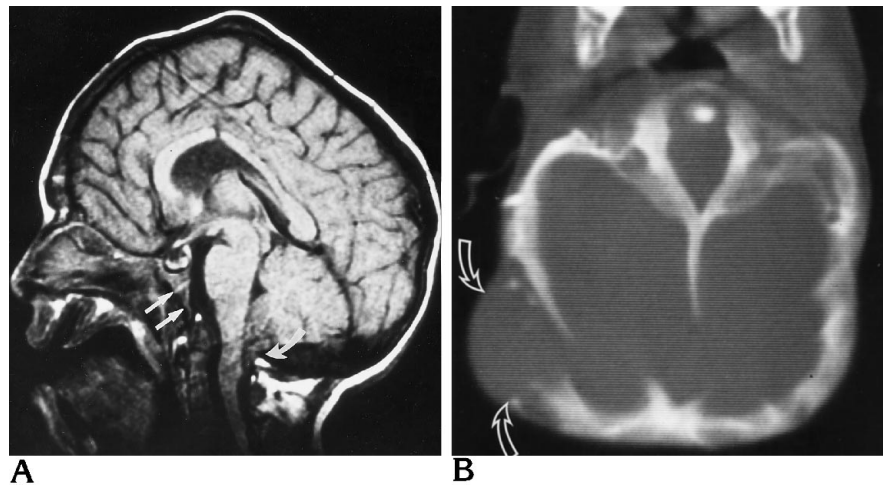


Fig 5. Patient 11: Crouzon syndrome.

A, Axial CT scan shows spicules of bone extending inward from irregular calvarial surface. Lateral ventricles (*arrows*) are enlarged. This patient had progressive hydrocephalus that required ventriculoperitoneal shunting.

B, Sagittal (600/11) MR image shows a vary hypoplastic clivus, especially the basiocciput (*small white arrows*). The posterior fossa is very small, with consequent herniation of the cerebellum (*black arrows*) into the cervical subarachnoid space. Herniation (*curved white arrow*) of cerebellum through a calvarial defect is seen posteriorly. The abnormality of the corpus callosum was attributed to the shunted hydrocephalus.

C, Coronal spin-echo (600/11) MR image shows upward herniation of the cerebellum (*arrows*) through the tentorial incisura and a diffusely abnormal gyral pattern; however, the cortical thickness appears normal. It cannot be determined from this imaging appearance whether the gyral pattern is distorted from a combination of the abnormal calvarial shape and hydrocephalus or whether the cortex is inherently abnormal.

categorized according to syndromes on the basis of characteristics of associated anomalies of the hands and feet, cardiovascular system, or pedigrees in which relatives have been identified as having specific syndromes (8–11, 13). However, as the genetic basis of these syndromes are uncovered, the separation of these patients by specific syndromes remains tenta-

tive, difficult, and, at times, confusing (14, 15). In patients with craniofacial disorders, it is important to know the number and location of sutural synostoses precisely; according to Cohen, a clear description of which suture or sutures are involved and the extent of involvement is more important anatomically and therapeutically than is the genetic classification (8, 9).

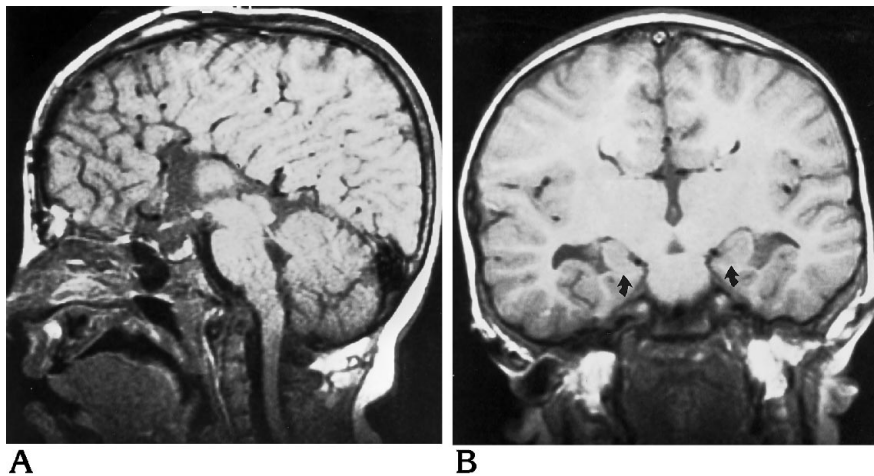


Fig 6. Patient 7: Apert syndrome.
 A, Sagittal spin-echo (600/11) MR image shows absence of the corpus callosum.
 B, Coronal spin-echo (600/11) image shows dysplastic hippocampi (arrows), with associated dilated temporal horns bilaterally.

TABLE 2: Craniosynostosis syndromes

Syndrome	Essential Features	Inheritance
Apert, Apert-Crouzon	Craniosynostosis, severe syndactyly of hands and feet, down-turned mouth, hypertelorism	Autosomal dominant
Saethre-Chotzen	Craniosynostosis, facial asymmetry, low-hairline ptosis, deviated nasal septum, syndactyly of second and third fingers	Autosomal dominant
Pfeiffer, Noack	Craniosynostosis, malformed enlarged thumb and great toe, soft-tissue syndactyly of second and third digits, normal intelligence	Autosomal dominant
Crouzon, craniofacial dysostosis	Craniosynostosis, maxillary hypoplasia, shallow orbits with proptosis, bifid uvula or cleft palate	Autosomal dominant
Craniosynostosis, fibular aplasia, Lowry Jackson-Weiss	Craniosynostosis and fibular aplasia	Autosomal recessive
Carpenter	Craniosynostosis with midface hypoplasia, mild syndactyly of feet, broad great toes	Autosomal dominant
	Oxycephaly, mild syndactyly of fingers, preaxial polydactyly of feet, hypogenitalism, obesity, congenital heart disease	Autosomal recessive

Sutures and Skull Base

In this study and in previous reports (9, 11, 16), bilateral coronal synostosis is the most common combination of synostoses in craniofacial syndromes, especially in Apert syndrome (3, 11). We found that patients with bilateral coronal synostosis also had findings of duplication of the sphenoid ridge, foreshortened anteroposterior length of the anterior cranial fossa, shallow orbits, anterior displacement of the petrous bones, abnormal craniozygomatic measurements, and an abnormally acute angle be-

tween the lateral orbital wall and the lateral wall of the middle cranial fossae (Figs 1A and 2A); all of these are considered to be the result of early closure of the coronal sutures.

Three-dimensional reconstructions from the CT data were not evaluated in this study because, although the three-dimensional images were created for some of the patients included in this report, they were not available to us at the time this study was performed. Previous reports suggest that three-dimensional reconstructions are useful for surgical planning and more precise evaluation of the cranial sutures (17).

Bilateral coronal synostosis is a characteristic finding in Apert syndrome and may result from specific developmental derangements of the skull base. Kreiborg and Cohen (4) and Kreiborg et al (17) have reported that coronal sutures are completely fused at birth in Apert syndrome, despite widely patent sagittal and metopic sutures. They suggested that this sutural fusion results from the close approximation of the frontal, sphenoid, and parietal bones, which permits rapid ossification of the coronal area. In contrast, the gap across the sagittal and metopic sutures in patients with Apert syndrome is so wide that it takes a long time for bony islands to form within the gap, coalesce, and, eventually, completely bridge the gap. This difference in sutural closure may result from known anatomic and physiological differences between the midline (sagittal and metopic) sutures and the off-midline (coronal and lambdoid) sutures (11, 17, 18). Closure of the midline sutures is end-to-end, whereas the nonmidline sutures close by overlapping (beveled type). In addition, the attachment of the falx and the dura of the superior sagittal sinus to the skull vault immediately beneath the sagittal suture may protect it from the direct remodeling influence of elevated intracranial pressure, in contrast to the coronal suture, which directly overlies the dura and pulsating brain.

The importance of the skull base in the genesis of the calvarial deformities of craniosynostosis was first stressed by Moss (19), who postulated that spatial malpositioning of the basal points of dural attachment is the primary underlying anomaly in craniosynostosis; this malpositioning theoretically results in the transmission of aberrant tensile forces upward through the dura to produce synostosis of the overlying suture. Evidence is accumulating to indicate that the cartilaginous cranial base is primarily involved in craniofacial anomalies; for example, the synchondroses of the skull base are completely fused at birth in patients with Crouzon syndrome and show early progressive fusion in Apert syndrome (17). However, other reports suggest that the cranial base malformations are, at least in some part, the result of calvarial synostosis (20, 21). Whether primary or secondary, it is of interest to note that deformities of the skull base were commonly recognized in our patients. These anomalies are of clinical importance because of the many vital structures that pass through the skull base. Cranial neuropath-

ies can result from hypoplasia of skull base foramina. As had been described with achondroplasia, a small skull base can cause hydrocephalus in infants and increased intracranial pressure in older children and adults (22-25). It is tempting to postulate that the small skull base was a factor in the hydrocephalus seen in several of the patients in this series. Both upward herniation of the cerebellum through the incisura (Fig 5) and downward herniation through the foramen magnum (Figs 2, 4, and 5) can result from a normal-sized cerebellum in a hypoplastic posterior fossa (26, 27). Deformity of the optic canals and superior orbital fissures may impair visual acuity by compression of the optic nerve (as seen in patient 9) or ocular motility by compression of cranial nerves III, IV, and VI.

Only two patients in our series were noted to have anomalies of the middle ear. However, these two patients had bilateral external auditory canal atresia and were the only two patients in the study in whom dedicated temporal bone studies were performed. Hearing difficulties are common in Apert syndrome and in the other craniofacial disorders (8), but they are usually attributed to the frequent bouts of otitis media that result from the high frequency of cleft palate and bifid uvula and the high arching palate (28, 29). Congenital conductive hearing loss, however, is not rare in these disorders (29, 30). The possibility of congenital hearing loss should not be overlooked because of preoccupation with other more obvious problems in these infants. The radiologist can play a key role in this regard by carefully scrutinizing the middle ear in affected children.

Eight of the patients described in this article had plagiocephaly, with asymmetric fusion of the sutures (see Table 1). This observation confirms once again that patients with the same syndrome may have abnormal fusion of different sutures and that sutural fusion may be asymmetric in the craniofacial syndromes. This asymmetry is most apparent in Saethre-Chotzen syndrome, in which unilateral coronal synostosis is frequently seen (8). However, the fact that asymmetric synostosis is possible in other syndromes, as well, should be kept in mind during the examination of these children. It is essential, therefore, to specifically identify which suture or sutures are involved in each patient.

Ventricular Enlargement and Hydrocephalus

Ventricular enlargement in craniofacial anomalies is a common finding; however, the mechanism of this phenomenon varies and in some cases the pathophysiology is poorly understood (6, 22, 24). Some authors have postulated that hydrocephalus can result from obstruction of cerebrospinal fluid (CSF) pathways at the level of the basal cisterns owing to a small skull base (31, 32); in the present study, four patients had findings of a small skull base with compression of the basal cisterns. Noetzel et al (33) have suggested that hydrocephalus occurs as a result of an intrinsic abnormality in the embryology of the brain related to the defective formation of the cranium. Other authors have suggested that increased resistance to venous outflow may be an important cause of the enlarged ventricles (22–25). Although we did not directly measure venous pressures in this study, the MR venograms dramatically showed dysplasia or occlusion of the transverse and sigmoid sinuses in the two patients in whom they were obtained. This finding suggests that venous anomalies, primary venous occlusions or venous outflow obstruction with secondary venous occlusion, may be a part of these syndromes. The differentiation is significant for understanding the venous flow abnormality and initiating the appropriate management. Verification of these findings and determination of the cause is an important area for future research.

Differentiating benign ventriculomegaly from hydrocephalus in craniofacial syndromes can be difficult (6, 24, 34). Progressive hydrocephalus appears to be more common in Crouzon and Pfeiffer syndromes than in Apert syndrome or other craniofacial anomalies (34, 35). The frequent presence of ventriculomegaly and the difficulty in differentiating it from frank hydrocephalus is another area in which craniofacial syndromes are similar to achondroplasia, another condition in which the skull base is hypoplastic. In both disorders, separate tables of “normal” head circumferences have been created to adjust for the atypical shapes and sizes of infants’ heads (7). In craniofacial syndromes, the diagnosis of hydrocephalus is made by documenting progressive enlargement of the lateral ventricles (3, 24). In five of our patients, ventriculomegaly was recognized without associated enlargement of the anterior recesses of the third ventricle and without progression, thus

indicating that frank hydrocephalus was not present. The mechanism of the ventriculomegaly in these children is unknown. It may be related to the abnormal cranial configuration, a condition that has been called distortion ventriculomegaly (3, 6). In those patients in whom frank hydrocephalus is present, it is possible that restricted venous outflow through the small skull base, as has been demonstrated in achondroplasia (23, 25), plays a role. The restricted venous outflow results in increased dural sinus venous pressure. Because the resorption of CSF into the dural venous sinuses is believed to rely on a CSF-to-venous sinus pressure gradient, elevated venous pressure reduces the gradient and, consequently, impairs CSF resorption.

Our observation of disproportionate enlargement of the frontal horns of patients with Apert syndrome supports the theory of distortion ventriculomegaly. In Apert syndrome, the metopic and sagittal sutures are widely patent at birth; a huge bony defect is present from the glabella to the posterior fontanel (4, 17). As discussed in the previous section, this defect gradually fills in by the formation of islands of membranous bone within it (4, 17). We postulate that the frontal horns of patients with Apert syndrome are disproportionately large because the anterior midline bone defect allows greater expansion of the brain in the anterior cranial fossa; consequently, the ventricles in the anterior region can enlarge more than the posterior parts of the ventricles where the smaller calvaria restricts growth. This hypothesis is in accordance with the observations of Hochwald et al (36) and the calculations of Shapiro et al (37) that ventricular size increases if the “container” of the brain (the skull or dura) is removed. In the case of Apert syndrome, localized expansion of the skull and dura in the frontal area allows localized ventricular enlargement.

Cerebral Abnormalities

Significant cerebral abnormalities—for example, agenesis of the corpus callosum, hippocampal hypoplasia, and septal defects—have been noted in pathologic studies of some patients with craniofacial anomalies (6, 8, 10, 16) and were confirmed by MR imaging in the patients described in this article. On the basis of the limbic system abnormalities identified in their pathologic studies, Maksem and Roessmann (38) suggested that the abnormalities of

the brain parenchyma in Apert syndrome are primary, occurring as early as the sixth week of embryonic life. Others have postulated that the hippocampal abnormalities are related to distortion of the brain by the calvarial deformity (3, 6). Our observation that the septum pellucidum and corpus callosum are commonly anomalous in patients with hippocampal anomalies supports the postulate that the hippocampal anomaly is a primary abnormality related to maldevelopment of the limbic system. The cause of the distortions of the cerebral cortex is less obvious. We found that the most severe gyral abnormalities were in the patients with the most severe cranial malformations (Fig 5). Polymicrogyria has been reported, albeit rarely, in craniofacial anomalies (6); however, most cases of reported gyral anomalies (6, 39, 40) appear to be primarily the result of distortion of the cerebral cortex by the calvarial anomalies, consistent with our observations.

Nonprogressive mental retardation is common in Apert syndrome (3, 24, 41), but the cause is uncertain. Although ventricular dilatation is found frequently in Apert syndrome, clinical signs suggesting a significant degree of hydrocephalus are rarely documented, and it seems unlikely that hydrocephalus is responsible for the retardation (3, 41). Mental retardation is often present in patients (without craniofacial syndromes) with agenesis of the corpus callosum, probably because of the high frequency of associated cerebral malformations (42–44); nevertheless, some patients with callosal agenesis are neurologically and intellectually normal (45). Both agenesis of the corpus callosum (46) and Apert syndrome (6) are often associated with malformations involving limbic structures. Because some structures of the limbic system, in particular the hippocampus, are important in memory, it is tempting to suggest that the limbic system abnormalities are an important component of the intellectual impairment in both conditions.

It is difficult to attribute defects of the septum pellucidum and corpus callosum to secondary events. Septal thinning and necrosis are known to be associated with long-standing hydrocephalus (47); however, as discussed earlier, frank hydrocephalus is uncommon in Apert syndrome, whereas septal absence is rather common (6). Moreover, callosal agenesis is unquestionably a primary anomaly. Therefore, our results seem to confirm an increased frequency

of primary brain anomalies, at least in Apert and Pfeiffer syndromes.

The parenchymal hemorrhage in patient 8 was an interesting finding because it occurred in areas that most commonly hemorrhage in neonates as a result of hemorrhagic infarction from vein of Labbé occlusion (48). MR venography showed occlusion of both transverse sinuses. It is of interest that both infants who had MR venography in this study had venous anomalies or occlusions. If, in fact, the large ventricular size and, when present, hydrocephalus in these patients are the result of venous outflow restriction through the small vascular foramina of the hypoplastic skull base, venous anomalies and occlusions are not surprising and, perhaps, the venous sinuses should be examined routinely in affected patients. MR venography could be a useful method for evaluating venous flow non-invasively both in patients with ventriculomegaly and in those with parenchymal injury.

Abnormalities of the Orbit

Visual loss is the most serious ophthalmologic problem in patients with craniosynostosis. The most frequent causes of visual loss are acquired types of ocular disease, such as optic atrophy and corneal damage, which most commonly result from abnormalities in the bony orbit or skull, and amblyopia resulting from strabismus or refractive differences between the two eyes (3, 10, 16). Thus, it is important to assess the optic nerves, cranial nerves III, IV, and VI, the extraocular muscles, and the orbital fissures precisely. In our study, optic nerve atrophy (Fig 2) was commonly detected. A skewed appearance of the superior orbital fissure was recognized in one patient on CT scans. In patients with hydrocephalus, MR imaging revealed stretching of the optic nerves and chiasm associated with enlarged anterior recesses of the third ventricle (Fig 2B). Other patients had evidence of small optic canals, which can result in pressure atrophy of the nerves. Compression of the vascular supply to the optic nerve has been thought to occur in some situations from sudden changes in intracranial pressures (49). Kinking of the optic nerve as it traverses the distorted skull base may also be a factor, as may prolonged papilledema from increased intracranial pressure (16, 50).

It is important to analyze the extraocular muscles themselves in patients with craniofa-

cial anomalies because ocular motility disturbances of differing causes frequently occur (8). Deformity of the orbital fissure may result in cranial nerve impairment, whereas dysplasia of the orbit contributes to disturbed function of the muscles themselves. Gobin (51) and Morax (52) have shown that the hypoplastic maxilla in patients with craniosynostosis can cause an alteration of mechanical forces of the inferior oblique muscle, enhancing its effect and correspondingly diminishing action of the superior oblique muscle. Hypoplasia of the maxilla, which was a common occurrence in this study, is therefore an important finding to report and repair.

Proptosis (Fig 2) is frequently recognized in craniofacial anomalies and was present in 16 of the patients in this series. Proptosis can be produced by many factors in these patients, including arrested growth of the maxilla, shortened anterior cranial base, depressed planum sphenoidale, and forward displacement of the greater wing of the sphenoid bone. Imaging does not significantly contribute to the diagnosis or management of proptosis.

Summary

To summarize, we have reviewed the cranial imaging findings of 21 patients with a variety of craniofacial syndromes. We have analyzed and discussed a number of the features of this disorder and the imaging manifestations of both the skull and brain. Radiologic assessment is an important component of the clinical evaluation of affected patients. An understanding of these disorders and their basic pathophysiology is essential for appropriate management and correct interpretation of the imaging studies.

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