Clinical Characteristics and Surgical Decision Making for Infants with Metopic Craniosynostosis in Conjunction with Other Congenital Anomalies

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Background: Metopic craniosynostosis can occur in isolation or in conjunction with other congenital anomalies. The surgical decision making and outcomes between these 2 groups are analyzed.

Methods: A retrospective review of all children evaluated in the craniofacial clinic at Seattle Children's Hospital for metopic craniosynostosis between 2004 and 2009 was performed. Physical examination and CT scan characteristics were analyzed as were the treatment decisions and surgical outcomes.

Results: From 2004 to 2009, 282 patients were evaluated and 100 were determined to have metopic craniosynostosis. Of these, 19 patients were found to have additional congenital anomalies. Review of these patients' CT scans revealed 13 with classic trigonencephaly, 3 with microcephaly, and 3 with narrow frontal bones, abnormal orbits, and small anterior fossa. Patients (90%) with isolated metopic craniosynostosis underwent cranial vault expansion, whereas only 63% of the complex group did so. The complex metopic group had a longer hospital stay (5 d vs 3.4 d), more intraoperative complications, and required more repeat surgery.

Conclusion: Patients with metopic craniosynostosis and additional anomalies require special consideration when deciding upon surgical intervention and should be cared for by a multidisciplinary team to address their additional needs. *(Plast Reconstr Surg Glob Open 2013;1:e62; doi: 10.1097/ GOX.0b013e3182a87e9b; Published online 25 October 2013.)*

Craniosynostosis occurs in 0.4 to 1 per 1000 children,[1] and metopic craniosynostosis (MCS) represents 10–25%[2,3] of all single-suture synostoses. MCS is associated with a characteristic skull shape, known as *trigonencephaly*, which is characterized by forehead narrowing and triangulation, biparietal widening, and hypotelorism.[4–13]

MCS can occur in isolation, in combination with other suture synostoses, and/or as part of a syndrome.[14] The etiology of MCS is unknown for most patients and is likely heterogeneous, possibly resulting from fetal constraint,[15] abnormal suture biology,[16] lack of typical brain growth,[17] and various genetic causes.[18,19] Trigonencephaly has been associated with syndromes such as Saethre-Chotzen,[20,21] Opitz C trigonencephaly syndrome,[22–24] Say-Meyer trigonencephaly syndrome,[25] Christian syndrome,[26] and Floating-Harbor syndrome.[27] It has also been associated with several chromosomal anomalies such as Jacobsen syndrome (del 11)[28–31] among others.[32–37]

We recommend cranial vault expansion for infants with isolated craniosynostosis to avoid the development of elevated intracranial pressure (ICP) [38,39] and subsequent developmental delay.[40–42] Yet, the mechanism of suture fusion may be different for infants with isolated MCS and those with MCS in combination with other anomalies, and it is unclear whether surgical intervention provides the same benefit in these patients.[43] Henceforth, we refer to patients with MCS in conjunction with other anomalies and or medical conditions as "complex MCS" and those without other conditions as "isolated MCS." Surgery is not without risks,[44–46] and the decision to operate can be difficult for patients with associated medical conditions. The purpose of this study is to assess the clinical characteristics among children with complex MCS. In addition, we sought to compare characteristics between infants with isolated vs complex MCS and to evaluate factors involved in surgical decision making and surgical outcomes for patients with complex MCS.

METHODS

Study Population

All patients seen in the Seattle Children's Hospital Craniofacial Center for evaluation of MCS between the years of 2004–2009 were identified through our clinical database. Pediatric and surgical clinic notes were reviewed. Patients with a diagnosis of MCS by their treating craniofacial pediatrician or plastic surgeon were included in the study. All patients with MCS had physical examination findings consistent with our craniofacial team's established characteristics for diagnosing MCS,[47] including trigonencephaly; palpable ridge overlying the metopic suture; narrow forehead; pterional constriction; pseudohypotelorism; and epicanthal folds. Of the initial 282 patients who were evaluated for possible MCS, 100 had (1) a clinical examination consistent with MCS and (2) a closed metopic suture on CT scan.

A craniofacial geneticist (A.H.) evaluated the medical records of the 100 patients with MCS for the presence of neurologic anomalies, chromosomal abnormalities, associated anomalies, syndromic diagnoses, and/or teratogenic exposures. Individuals with MCS and one of the above characteristics were considered to have "complex MCS" and all others were considered to have "isolated MCS." Of the 100 patients with MCS, 19 patients were considered to have complex MCS and 81 patients were considered to have isolated MCS.

Image Review

A pediatric radiologist, craniofacial surgeon, and craniofacial pediatrician reviewed all available clinical photographs and CT scans. The following CT scan findings were recorded: presence of a closed metopic suture, straight frontal bones, posteriorly displaced frontal bones, upper orbital narrowing, interorbital narrowing, and the presence of the omega sign.

Medical Record Review

Results of available genetic testing were reviewed by the craniofacial geneticist. We recorded whether the patient underwent cranial vault surgery and the type of surgery performed. Factors that led to this decision not to pursue surgery were also recorded. Surgical complications and the need for revision surgery were also noted.

This study was approved by Seattle Children's Institutional Review Board (#13126).

RESULTS

Patient Characteristics

Of the 19 patients with complex MCS, 11 (57%) were male and the average age at diagnosis was 12.8 months (range = birth to 13 y). Patients with complex MCS were divided into 5 subgroups (Table 1) based on the following associated characteristics: 1) neurologic abnormality ($n = 8$; 42%); 2) chromosome imbalance ($n = 6$; 32%); 3) multiple congenital anomalies ($n = 3$; 16%); 4) syndromic diagnosis ($n = 1$; 5%); and 5) teratogenic exposure in utero ($n = 1$; 5%).

Medical and Genetic Characteristics of Individuals with Complex MCS

The 8 patients with neurologic abnormalities had various combinations of microcephaly, developmental delay, and epilepsy (Table 1).Four patients from the neurologic subgroup had normal genetic testing (Table 1). Of the 6 patients with chromosome abnormalities, 2 had Jacobsen syndrome (chromosome 11q25 deletion) and one each had: 1q duplication, 7p deletion, partial trisomy 13, and an unbalanced 8:15 translocation (Table 1). Three patients had multiple congenital anomalies without chromosome abnormality or a recognizable syndrome. One child was given clinical diagnosis of Simpson-Golabi-Belmel syndrome and 1 patient had an in utero exposure to valproic acid (Table 1).

Radiographic Characteristics

All patients with isolated MCS and most patients ($n = 13$) with complex MCS demonstrated the classic signs of MCS on CT scan, which included a trigon-encephalic head shape on CT images with forehead narrowing, biparietal widening, a keel deformity of the mid forehead, and a decreased interorbital

Table 1. Distribution of Additional Diagnoses among Children with Complex Metopic Craniostosis Seen at Seattle Children's Hospital between 2004 and 2009

| Case	Additional Craniofacial Diagnoses	Age at Time of Surgery	Associated Health Concerns	Genetic Studies
Neurologic abnormalities				
1	Chiari malformation, hydrocephalus, seizures	2 y	Developmental delay, left hydronephrosis, short stature, perinatal asphyxia	None reported
2	None	9 mo	Developmental delay	None reported
3	Microcephaly	16 mo	Developmental delay, early adrenarche	None reported
4	Microcephaly	None	Developmental delay, hip dislocation	None reported
5	None	8 mo	Developmental delay	None reported
6	None	No surgery	Developmental delay	Normal karyotype and fragile X test
7	Microcephaly	No surgery	Developmental delay, athetoid hand movement, exotropia	Normal array CGH, normal metabolic studies
8	None	15 mo	Developmental delay	Normal array CGH, normal metabolic studies
Chromosomal imbalance				
1	Nystagmus, strabismus, seizures	13 mo	Developmental delay, ventricular septal defect	Chromosome 1q32.1-q43 dup
2	Esotropia	13 mo	Developmental delay, atrial and ventricular septal defects, duplicated renal collecting system, cavovarus feet, thrombocytopenia	Chromosome 11q2-qter deletion (Jacobsen syndrome)
3	Ptosis, ear canal stenosis, hearing loss	9 mo	Developmental delay, adducted thumbs, hemangioma	Chromosome 7p15-p21 deletion
4	Cleft palate, seizures	No surgery	Developmental delay, bicuspid aortic valve, vesico-ureteral reflux, microphthalmia, peter's anomaly	Partial trisomy 13
5	Schizencephaly, ptosis	No surgery	Developmental delay, hypoplastic left heart, pyloric stenosis, platelet dysfunction	Unbalanced chromosome 8;11 translocation
6	Cryptotia, cleft palate, hearing loss	No surgery	Developmental delay, double-outlet right ventricle, cryptorchidism, thrombocytopenia	Unbalanced chromosome 8;15 translocation
Multiple congenital anomalies				
1	Cleft palate	12 mo	Ventricular septal defect, short stature, hypoplastic fifth digits	Normal karyotype, normal array CGH
2	Cleft lip and palate	9 mo	None reported	Normal karyotype
3	Preauricular pits	12 mo	Ventricular septal defect, cleft mitral valve, Duane anomaly, hypoplastic right thumb, duodenal atresia	Normal array CGH, normal Fanconi chromosome breakage
Syndromic diagnosis				
1	Simpson Golabi Behmel syndrome, macroglossia, cleft palate	11 mo	Atrial septal defect, pulmonary stenosis, hydronephrosis, cryptorchidism, macrosomia	None reported
Teratogenic exposure				
1	Exotropia, valproate embryopathy	4 mo	Ventricular septal defect, radial ray hypoplasia, vertebral anomaly	Normal karyotype

CGH, .

distance with narrowing of the superior aspect of the orbits (Figs. 1B, E, H). The frontal bones tended to be straight, rather than curved, and were retrusive in relation to the lateral orbits, giving the appearance of bilateral pterional constriction. Intracranially, thumbprinting and the omega sign (Fig. 2) were frequently present.

Three patients with complex MCS (2 from the neurologic subgroup and 1 from the chromosomal imbalance subgroup) had CT scan findings consistent with trigonencephaly although their forehead and orbital shapes differed from that seen in isolated MCS (Figs. 1C, F, I). The frontal bones were small and narrow, and there was some curvature to these bones rather than the nearly straight frontal bones seen in classic MCS. On profile, the frontal bones were noted to slope back abruptly from the orbits and the orbits were spaced widely rather than narrowed. The orbits were also flat and rectangular in shape rather than the upsloping, trapezoid shape commonly observed in isolated MCS (Figs. 1B, C, E, F, H, I). Intracranially, the anterior fossa was very small, but thumbprinting was absent and there was no evidence of an omega sign.

Three patients were found to have microcephaly with a closed metopic suture (Figs. 1A, D, G).
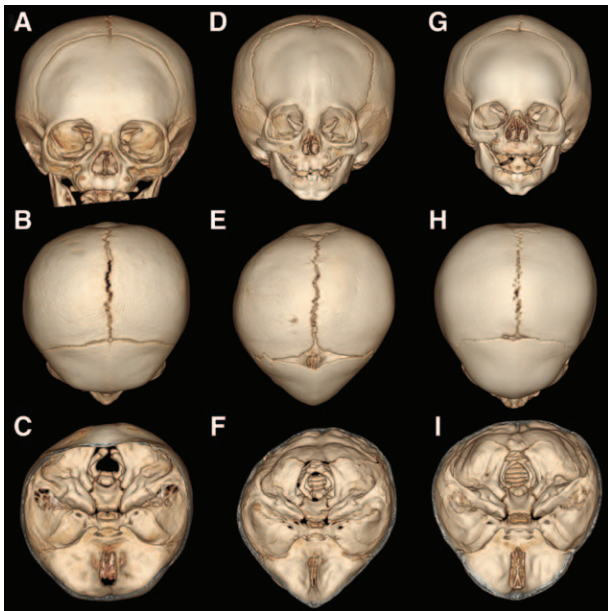
Fig. 1. Three-dimensional CT scans of patients evaluated for MCS. A, B, and C, CT findings for patients with microcephalic head shapes and palpable metopic ridges. D, E, and F, CT findings associated with isolated MCS. Patients with isolated MCS display classic trigonencephaly with straight, narrowed frontal bones, orbital narrowing, and temporal constriction. G, H, and I, CT from an individual with complex MCS and underlying neurological condition. Patients with complex MCS associated with neurologic conditions or genetic abnormalities tended to display a narrow forehead with small anterior cranial fossa. But, the frontal bones are curved, not straight and the interorbital distance is widened, not narrowed. Additionally, the vertical height of the orbits is reduced as compared patients with isolated MCS or complex MCS without neurologic abnormalities.
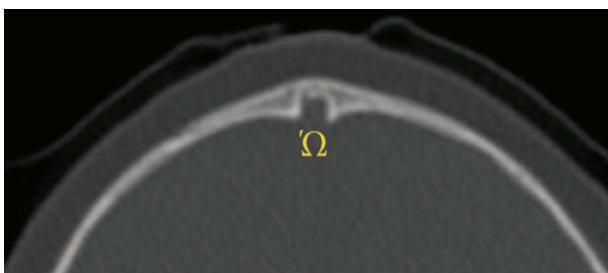
Fig. 2. The omega sign. On axial CT scan, the prematurely fused metopic suture forms an invagination intracranially that is termed the "omega sign." This is one CT scan finding that may help diagnose MCS.

Table 2. Comparison of Diagnostic Features and Surgical Outcomes for Children with Isolated and Complex Metopic Synostosis

	Isolated Metopic $n = 81$	Complex Metopic $n = 19$
CT findings	n (%)	n (%)
Classic findings	81 (100)	16 (84.2)
Atypical findings	0 (0)	3 (15.8)
Surgical issues		
Number underwent surgery	73 (90)	12 (63)
None	81 (100)	11 (91.7)
Intraoperative air embolism	0 (0)	1 (8.3)
Average length of pediatric intensive care unit (d)	1	1
Average length of hospital stay (d)	3.4	5
Surgical outcomes		
No-redo necessary	81 (100%)	9 (75)
Repeat FOA	0 (0%)	2 (16.6)
Treatment of skull defects	5 (6%)	1 (8.3)

Surgical Decision Making

Sixty-three percent ($n = 12$) of patients with complex MCS underwent cranial vault surgery compared with 90% ($n = 73$) of patients with isolated MCS (Table 2). All patients who underwent surgery had classic CT findings of MCS, whereas none of the patients with CT findings that were not consistent with classic MCS had surgery. Documented rationale for surgery included 1) prevention of elevated ICP; 2) correction of abnormal orbital morphology; and 3) treatment of symptoms suggestive of elevated ICP (eg, intractable headaches and vomiting). Four patients from the neurologic subgroup and 3 patients with a chromosome imbalance did not pursue surgery after careful consideration by the surgeon, family, and craniofacial team. Reasons given for not recommending surgical expansion included mild skull deformity, elevated risk of surgical complications, and lack of underlying brain growth in patients who displayed significant developmental delays and evidence of decrease brain volume on imaging, suggesting that the abnormal skull shape was the result of brain growth deficiency. One family opted not to pursue surgery due to religious beliefs that precluded perioperative blood transfusion (eg, Jehovah's witness). For the 3 patients with chromosomal imbalance who did not pursue surgery, 2 had major cardiac anomalies that significantly increased surgical risk and 1 had partial trisomy 13 with a guarded prognosis.

Surgical Outcomes

All patients who received surgical correction underwent a frontal orbital advancement (FOA) with forehead reshaping. One patient with pansynostosis underwent a posterior cranial vault expansion at 8 months old followed by a FOA. Intraoperatively, 1 patient had an injury to the sagittal sinus and did not complete the FOA procedure. In this patient, the FOA was completed 6 weeks later. Another patient with complex MCS sustained an intraoperative air embolism that required brief hemodynamic support and monitoring with an uneventful recovery. Comparatively, no patient with isolated MCS experienced

an intraoperative complication. Postoperatively, those with isolated metopic stayed in the ICU for 1 day, with an average hospital stay of 3.4 days, while those with MCS stayed in the ICU for just over 1 day and had an average hospital stay of 5 days. Reasons for the longer stay in the complex metopic group included prolonged intubation (3 d in 1 patient), increased work of breathing in 1 patient, episodes of bradycardia in 1 patient, and urinary retention in 1 patient. All patients in the surgical group experienced correction of abnormal orbital morphology, and no patients have developed signs of increased ICP since surgery. One patient who experienced headaches had improvement in frequency and severity of symptoms after surgery. Two patients (9%) with complex MCS were later treated for signs of elevated ICP such as intractable headaches and vomiting. These 2 patients underwent repeat FOA to re-expand their cranial vaults and treat their elevated ICP. Additionally, 1 patient with complex MCS underwent cranioplasty for treatment of persistent skull defects (Table 2).

We continue to follow-up most patients with complex MCS who did not have surgery, and to date, no patients have developed signs of increased ICP.

DISCUSSION

The surgical treatment goals for MCS are to improve the patient's function and to normalize their aesthetics. Single-suture craniosynostosis is associated with a 10–30%[38,39] estimated risk of elevated ICP and its consequences such as blindness and developmental delay. Additionally, the trigonencephalic skull lacks brow projection, leaving the globe exposed to possible injury. These functional concerns are addressed with an FOA that both expands the anterior cranial fossa and projects the lateral brow, providing protection to the globes. Simultaneously, the aesthetics of the brow and forehead are normalized, thereby correcting the stigmata of this congenital disorder and addressing self-perceived quality of life.[48] However, cranial vault expansion is associated with risks, including blood loss,[49–52] infection,[53] air embolism, seizure, and death.[46,54,55] Our study suggests that these risks and benefits must be weighed carefully in children with complex MCS.

Accurate diagnosis can be challenging in patients with genetic syndromes and chromosome abnormalities associated with facial features suggestive of MCS such as epicanthal folds and hypotelorism. Our study also identified atypical CT characteristics in a subset of individuals with complex MCS for whom surgery was not recommended. In addition, the treatment goals must be carefully evaluated for individuals with microcephaly secondary to poor brain growth. It is possible that a lack of underlying brain growth limits the normal "push," allowing the suture to fuse early, which has also been observed in patients with ventricular shunts and hypopressurization of the cranial vault.[56–58] In the presence of abnormal brain growth, the benefits of FOA would be focused on increasing globe protection and normalization of facial and forehead shape rather than treatment of possible elevated ICP because this is less prevalent in these cases. Additionally, this lack of underlying brain "push" could limit the degree to which the abnormal frontal lobe fills the expanded anterior fossa after FOA. Without the support of the underlying brain and dura, the orbital bandeau and frontal bones are less likely to revascularize and more likely to relapse.

Our study also identified a higher number of postsurgical complications and a longer average length of hospital stay in patients with complex MCS compared with those with isolated synostosis. The longer hospital stay was necessary to address the additional medical needs of patients with complex MCS. The reason for the higher rate of complications in this group, however, is unclear. Previous studies have found increased infection rates when intracranial procedures are performed on patients with more complex diagnoses.[59] We speculate that children with complex MCS have differences in anatomy, bone morphology, and medical comorbidities that may increase the risk of surgical complications.

The strengths of this study included a systematic review of clinical examination, imaging, and surgical outcomes from a large cohort of individuals with isolated and complex MCS. However, the small sample size of children with complex MCS prohibited further exploration within this cohort for factors that were associated with optimal surgical outcomes. In addition, our standard of team care requires careful consideration of all potential risks and benefits before recommending surgical intervention for children with complex MCS, and we do not operate on all children with complex MCS. This, in combination with our small sample size, likely contributed to the small differences observed in length of stay between the isolated and complex metopic groups and limits our ability to comment on all of the surgical risks for children with complex MCS for whom we did not proceed with surgery. Future, multicenter, prospective studies of presurgical phenotype and outcomes for individuals with isolated and complex MCS are needed to aid clinicians in factors that could inform accurate diagnosis and surgical decision making in this population.

Prior studies have demonstrated that up to 25% of children with MCS have associated congenital anomalies or genetic syndromes that have implica-

tions for perisurgical care, surgical risk, and long-term prognosis. For example, Jacobsen syndrome is associated with MCS, congenital heart disease, and platelet dysfunction. Treatment for children with complex MCS requires careful consideration of the risks and benefits of surgical intervention and a multidisciplinary craniofacial team for comprehensive, coordinated care. Additionally, coordination of care can be complicated by need for additional subspecialty consultation by an anesthesiologist, a cardiologist, a pulmonologist, a neurodevelopmental provider, a neurologist, and a psychiatrist, among others. Frequently, treatment of comorbid conditions such as complex congenital heart disease delays cranial vault surgery and increases the risk of complications during surgery and the perioperative period. These factors must be taken into consideration when caring for patients with complex MCS. Multidisciplinary team care for accurate diagnosis and treatment is recommended for all patients with craniosynostosis[60,61] and is essential to ensure thoughtful discussion of the risks and benefits of surgical intervention in patients with complex MCS. Future multicenter, prospective studies with larger patient cohorts of children with isolated and complex MCS are needed to clarify which medical comorbidities place children at highest surgical risk and develop methods to minimize these risks.

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