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Case Report

Impaired wound healing following cranial vault reconstruction in a patient with an atypical phenotype of Marfan syndrome: A case report

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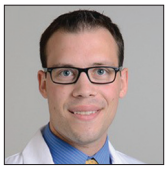

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ABSTRACT

Background: Marfan syndrome (MFS) is an autosomal dominant disorder of the connective tissues caused by mutations in the FBN1 gene which can result in widespread systemic involvement. Loeys-Dietz syndrome (LDS) is a related autosomal dominant disorder of connective tissue with widespread systemic involvement which has phenotypic overlap with MFS. LDS is caused by heterozygous pathogenic variants in six different genes, the most common of which involve transforming growth factor beta-receptor 1 or 2. While LDS is commonly associated with craniofacial manifestations, MFS is not typically characterized by craniosynostosis.

Case Description: We present a 7-month-old female patient with MFS and metopic craniosynostosis with an unusual clinical presentation who underwent cranial vault reconstruction with fronto-orbital advancement and anterior cranial vault remodeling. Her course was complicated by impaired wound healing after surgery, requiring return to the operating room.

Conclusion: Phenotypic overlap between genetic disorders can confound clinical diagnosis as illustrated in this case. Genetic testing can be highly valuable in the diagnosis of clinically variable disorders. Patients with MFS who undergo cranial surgery may be at increased risk for wound healing complications.

Keywords: Craniofacial abnormalities, Craniofacial dysostosis, Craniosynostosis, Marfan syndrome, Pediatrics

INTRODUCTION

Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder that is characterized by varying combinations of skeletal, cardiovascular, pulmonary, dermatologic, and ocular malformations.[4,13] The disorder is caused by pathogenic variants in the FBN1 gene, encoding fibrillin-1 protein, which provides force bearing structural support in elastic and nonelastic connective tissue.[13,15] The prevalence of the disease has been reported as 0.02–0.03%, and approximately, 25.0% of cases are sporadic occurrences due to *de novo* pathogenic variants.[10,13] Typical clinical manifestations of MFS include ocular anomalies (ectopis lentis and myopia), skin findings (striae), and cardiovascular phenotypes (aortic root aneurysm and mitral valve prolapse).[13] Craniofacial abnormalities are not typical of MFS, although they have

occasionally been reported.[8] MFS shares phenotypic overlap with a number of other connective tissue disorders including Loeys-Dietz syndrome (LDS), Shprintzen-Goldberg syndrome, and the MASS phenotype among others.[8,13]

LDS is a related autosomal dominant disorder of connective tissue with widespread systemic involvement. It is caused by heterozygous pathogenic variants in six different genes, the most common of which are transforming growth factor beta-receptor 1 or 2 (TGFBR1 or TGFBR2).[12] The triad of hypertelorism, cleft palate or bifid uvula, arterial/aortic aneurysms, and/or arterial tortuosity typically characterize the syndrome. Approximately 75% of LDS patients present with typical facial dysmorphic features (cleft palate, craniosynostosis, and/or hypertelorism), which are termed LDS type 1. The recent identification of TGFBR2 pathogenic variants in patients suspected to have MFSII and of TGFBR1 and TGFBR2 pathogenic variants in patients suspected to have LDS demonstrates the phenotypic overlap of these conditions and provides direct evidence of abnormal signaling in transforming growth factors b (TGF-b) in the pathogenesis of MFS.[8] TGF-b signaling has a prominent role in vascular and craniofacial development, and perturbations of TGF-b signaling occurs in many human phenotypes including craniosynostosis, cleft palate, arterial aneurysms, congenital heart disease, and mental retardation.[12] It is in the light of this significant phenotypic overlap of MFS and LDS that we present the case of an infant found to have clinical manifestations typically associated with LDS, but whose genotype was positive for a pathogenic variant in the FNB1 gene considered diagnostic of MFS.

CASE DESCRIPTION

A 7-month-old female presented to the Craniofacial Center of Western New York (John R. Oishei Children's Hospital, Buffalo, NY) following a genetics consultation that raised concern for LDS with possible craniosynostosis. The parent's chief complaint was the appearance of the patient's head shape and orbits, which they felt had been abnormal since birth. The parent's denied any constitutional symptoms. They denied any apparent visual disturbances, abnormal gaze, signs of headache, head banging, unexplained vomiting, or other symptoms classically associated with increased intracranial pressure. The patient was noted to be tracking above average on her growth curve and was noted to be meeting all developmental milestones. Physical exam revealed a well-appearing, tall infant. She had a pectus excavatum deformity, arachnodactyly, and long narrow feet with long toes. Her craniofacial examination was remarkable for ridging along the metopic and left coronal sutures with bitemporal narrowing and mild trigonocephaly, a flat anterior fontanel, and prominent supraorbital ridges [Figure 1]. She was also noted to have a narrow pointed Menton. There was no apparent compensatory anterior translation of the ears or forehead. An initial echocardiogram was normal, but a follow-up study disclosed mitral valve prolapse, mild-to-moderate mitral valve regurgitation, and mildly dilated aortic sinuses and ascending aorta.

Although the patient had presented to the Craniofacial Clinic at 7 months of age, there was concern for the child's abnormal head shape early in life and on presenting to the child's physician, a posterior-anterior skull radiograph was taken at 7 weeks of age. The skull radiograph skull radiograph

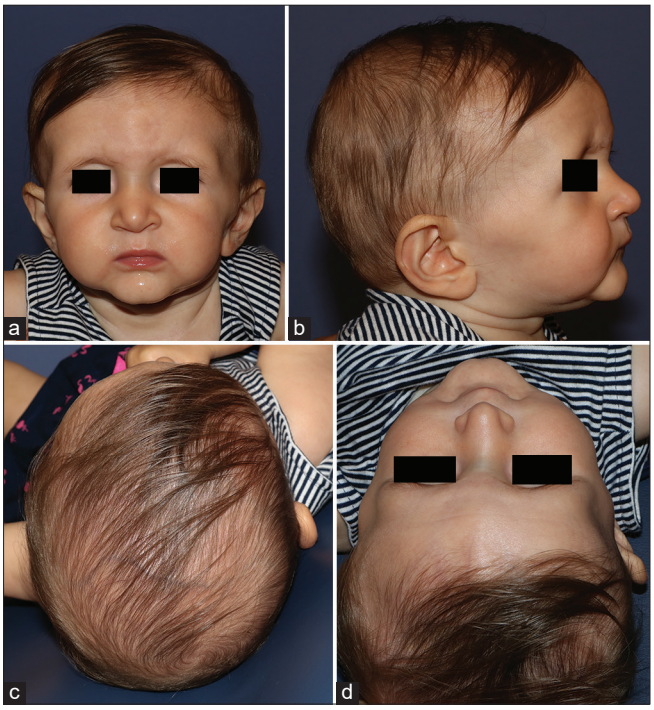

Figure 1: Frontal (a), side profile (b), bird's-eye view (c), and modified bird's-eye views (d) of the patient displaying a pointed and prominent menton, ridging of the supraorbital rims, mild metopic ridging, hypotelorism, and relative bitemporal narrowing.

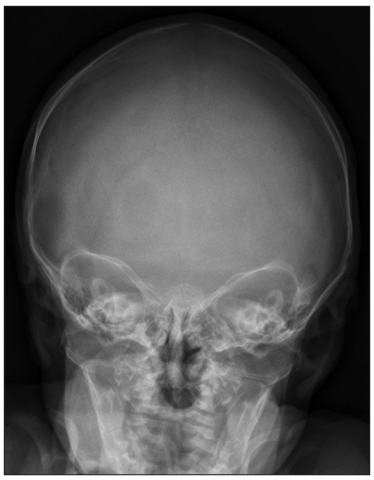

Figure 2: Posterior-anterior skull radiograph obtained at 7 weeks of age demonstrating metopic suture synostosis.

identified metopic suture craniosynostosis [Figure 2]. After evaluation at the Craniofacial Clinic at 7 months of life, a CT scan of the head revealed very mild hypotelorism, bitemporal narrowing, and prominent ridging with complete synostosis of the metopic suture [Figure 3]. Metopic indices were taken from the CT and found to be within normal range.[3,5,6,16] The midfronto-zygomatic diameter was 70.4 mm, the eurion-eurion diameter was 115, resulting in a metopic index of 0.61. In addition, the endocranial bifrontal angle was 139 degrees. After a detailed discussion with the multidisciplinary craniofacial team regarding the risks and benefits of surgery, the parents elected to proceed with fronto-orbital advancement and anterior cranial vault expansion and remodeling.

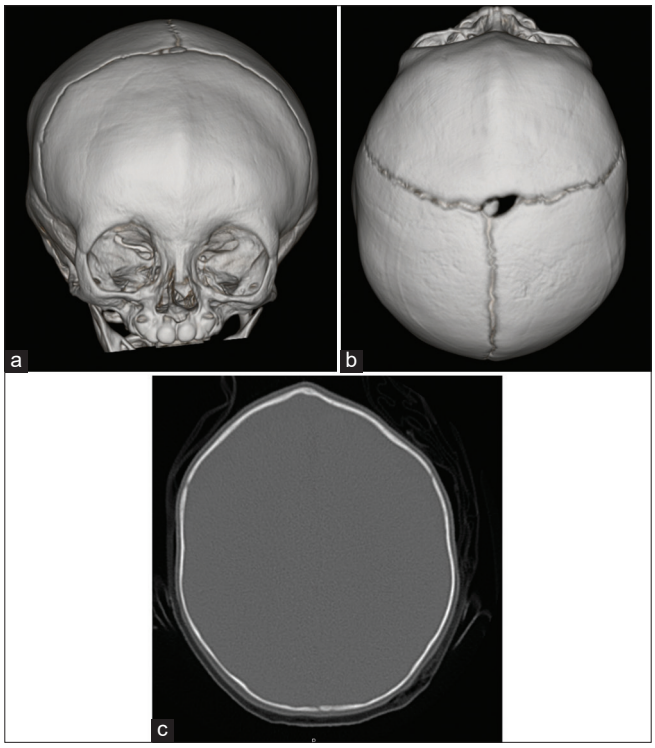

Figure 3: Frontal (a) and bird's-eye (b) three-dimensional views, as well as an axial view (c) of a noncontrast computed tomography scan obtained at 7 months of age displaying metopic synostosis, mild hypotelorism, and mild bitemporal narrowing.

The patient was taken to the operating room at age 9 months for fronto-orbital advancement and anterior cranial vault expansion and remodeling. A standard curved coronal incision extending bilaterally to 2 cm superior of the postauricular area was made. An avascular subgaleal was then dissected up to 1.5 cm superior to the supraorbital rims. Next, an anteriorly based pericranial flap exposing the frontonasal suture and frontozygomatic sutures was dissected in the subperiosteal plane [Figure 4a]. The temporalis muscles were released bilaterally just to below the squamosal suture. After marking the orbital and cranial osteotomies with prefabricated cutting guides, a bifrontal craniectomy was performed followed by osteotomies of the orbital bandeau. The orbital bandeau was then taken to the back table and osteotomized and shaped to match the preoperative plan using positioning guides. A full-thickness cranial bone graft was also harvested and fixated between the two halves of the bandeau to correct the patient's hypotelorism. The bandeau was then applied and fixated to the patient. Next, the frontal bones were osteotomized, applied, and fixated in position to match the preoperative plan [Figure 4b]. Significant abnormalities noted during surgery included the thin and fragile nature of the patient's dura and weak and friable dermis of the scalp. The galea and dermis were closed with 3-0 Coated polyglactin 910 Braided Absorbable Suture (Vicryl, Ethicon, Inc., Johnson and Johnson Co, Raritan, NJ). During closure, the galea and dermis tolerated only minimal tension before stitches would pull-through. The dermis appeared atrophic to almost nonexistent. Skin was closed with 4-0 Vicryl RAPIDE™ suture (Ethicon, Inc., Johnson and Johnson Co, Raritan, NJ) in a running fashion. Primary closure was achieved [Figure 4c]. The patient underwent an uneventful immediate postoperative course and was transferred to the pediatric intensive care unit for close postoperative monitoring, as is the protocol at our institution. The patient was transferred from ICU to floor on postoperative day 2 and discharged to home on postoperative day 4.

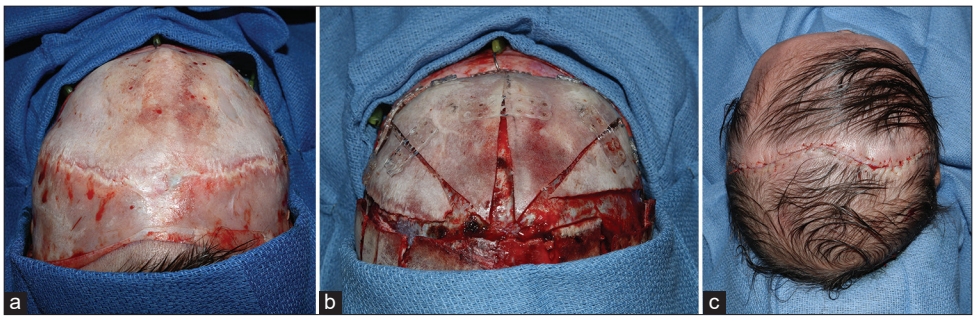

Figure 4: Bird's-eye view of the patient after subperiosteal dissection and bilateral reflection of temporalis muscles (a). Bird's-eye view after reconstruction (b) and closure (c).

The patient followed up 3 days later (postoperative day 7) displaying adequate head shape and good wound healing. Her scalp incision appeared well approximated with no signs of infection or dehiscence [Figure 5]. At 4 week follow-up, the patient was noted to have a small area of dehiscence at the right scalp incision. There was no active infection and wound care was stressed to the patient's parents in hopes of secondary wound healing. The patient presented 1 month later for follow-up and was noted to have a 2 cm × 2 cm area of ulcerated skin at the lateral aspect of the right scalp flap [Figure 6]. Again, this did not appear to be actively infected, but was failing to heal. The patient was taken to the operating room for wound debridement and scalp closure, after which the wound healed well without further complication.

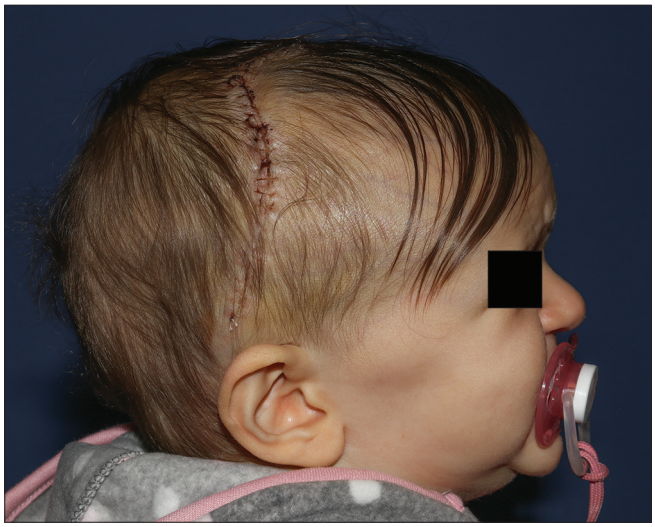

Figure 5: Right side profile view showing adequate wound healing at postoperative day 7.

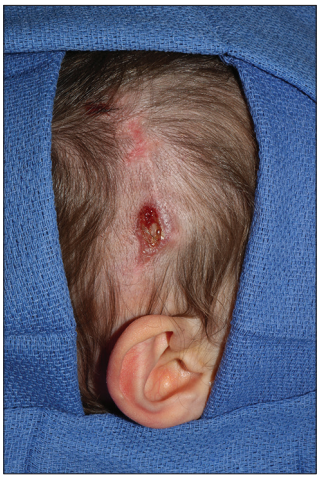

Figure 6: Right side profile view showing superficial wound breakdown along the scalp incision.

The patient underwent genetic testing which disclosed a variant in a highly conserved region of the FBN1 gene denoted as c.3152T>C(p.phe1051ser). This variant is classified as a variant of unknown significance, but this mutation in combination with the patient's phenotype was considered to be pathogenic and diagnostic of MFS. There were no variants detected in the other six genes analyzed. Results of follow-up parental studies were negative for the FBN1 variant detected in our patient, confirming that the variant was *de novo*.

DISCUSSION

We present a case of MFS and metopic craniosynostosis with notable atypical findings. First, our patient's clinical phenotype suggested a diagnosis of LDS. Her genetic test results, however, were compatible with a diagnosis of MFS. Our patient's craniofacial findings, particularly her craniosynostosis, confounded our initial diagnostic impression. Although there is currently no standard or widely accepted craniometric measurement for the diagnosis of metopic craniosynostoses, several have been proposed in the contemporary literature.[3,5,6,16] Many of our patient's measured craniofacial parameters align more closely with reported controls rather than those of patients with metopic craniosynostosis, which is consistent with the very mild, even subtle, features of metopic craniosynostosis she displayed. We certainly acknowledge that her case did not demonstrate a classic phenotypical appearance for metopic craniosynostosis. However, we feel that her morphology and craniometric analysis is confounded by her phenotypic features of MFS/LDS, which may invalidate the reported indices in her case. Specifically, these disorders are associated with hypertelorism, while metopic craniosynostosis typically causes hypotelorism. On initial physical examination, our patient did not appear grossly hyperteloric or hypoteloric. We also believe that her prominent brow and relative enophthalmos, observed in MFS, likely masked the degree of trigonocephaly and bitemporal narrowing she developed, especially in the lower forehead. X-ray imaging obtained at 7 weeks of age confirmed metopic suture metopic suture craniosynostosis. This is well below the lower limit of 3 months, which reported as the earliest age of metopic fusion in large anthropometric studies.[9,14,16,17] The presence of metopic craniosynostosis, in combination with her overall dysmorphology and desire from the family to pursue improved cosmesis, influenced the decision to proceed with surgical intervention.

Ozyurt *et al*. reported two cases of early onset MFS.[7] One of these cases was a 2-month old with a clinical phenotype strikingly similar to our case. Features included arachnodactyly, pectus excavatum, similar facial features, and craniosynostosis. Similar to our patient, this patient

also had aortic root dilatation. Ades *et al*., in their review of MFS and related craniosynostosis and mental retardation disorders, reported another case that shared similar findings with our patient.[1] Findings included tall stature, arachnodactyly, pectus excavatum, and cranial deformity with craniosynostosis. Craniofacial examination was notable for a broad flat forehead, ridging of the anterior sagittal suture, a beaked nose, and a prominent pointed chin. Similar to our patient, this patient's cardiac findings included mitral valve prolapse.

These cases, in conjunction with the case presented herein, further demonstrate the wide clinical spectrum of MFS. There appears to be a phenotypic continuum among patients clinically diagnosed with MFS, marfanoid features-craniosynostosis, or marfanoid features-mental retardation spectrum. The underlying genetic variants in patients with MFS who have craniofacial abnormalities are likely related to abnormal TGF-b signaling, affecting craniofacial morphogenesis. Our findings indicate that craniosynostosis does not exclude a diagnosis of MFS, although it is not a typical finding.

Another interesting aspect of the patient in this report is her poor postoperative healing. It is reported in the general surgery literature that patients with MFS tend to develop hernias, which can be difficult to repair, because the soft tissue can fail to retain sutures.[2] We had a similar experience in closing our patient's scalp flap as suture tended to pull through deeper tissue layers.

Classical Ehlers–Danlos syndrome (EDS), a disorder affecting collagen structure and processing, is characterized by abnormal wound healing. Affected patients demonstrate skin fragility and often experience delayed wound healing. Surgical recommendations include that dermal wounds be closed in at least two layers, and sutures should be left in place twice as long as usual. In addition, some recommend reinforcement of the wound with adhesive tape.[2,8] The application of a similar protocol may be indicated in other connective tissues disorders such as MFS.

Van Camp *et al*. performed a large retrospective study of patients with classical EDS and MFS who presented to the Oral and Maxillofacial surgery department at their institution.[11] They found no difference in postoperative complications in the study population compared to the general population and posited that this could be due to strict precautions taken at the time of surgery and meticulous postoperative instruction. For both MFS and EDS patients, they used a greater number of subcutaneous sutures, and more closely spaced transcutaneous sutures. They also allowed nonresorbable sutures to stay in place twice as long as patients who did not have EDS or MFS. They also recommended additional fixation of the adjacent wound edges with adhesive tape to prevent scar stretching.[2,11]

Our patient differed from the aforementioned protocols in that our patient's coronal flap was closed with absorbable sutures (Vicryl RAPIDE™ polyglactin 910 suture). Perhaps, nonresorbable sutures may have been warranted in this situation; however, in a young child, this may necessitate a return to the operative room for suture removal. In either case, meticulous wound care must be practiced.

CONCLUSION

Phenotypic overlap between genetic disorders can confound clinical diagnosis, as illustrated in this case. Genetic testing can be highly valuable in the diagnosis of clinically variable disorders. Patients with MFS who undergo cranial surgery may be at increased risk for wound healing complications.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Ades LC, Sullivan K, Biggin A, Haan EA, Brett M, Holman KJ, *et al*. FBN1, TGFBR1, and the Marfan-craniosynostosis mental retardation disorders revisited. Am J Med Genet A 2006;140:1047-58.
2. Beyene RT, Derryberry SL Jr., Barbul A. The effect of comorbidities on wound healing. Surg Clin North Am 2020;100:695-705.
3. Chandler L, Park KE, Allam O, Mozaffari MA, Khetpal S, Smetona J, *et al*. Distinguishing craniomorphometric characteristics and severity in metopic synostosis patients. Int J Oral Maxillofac Surg 2021;50:1040-6.
4. Gray JR, Davies SJ. Marfan syndrome. J Med Genet 1996;33:403-8.
5. McEwan TW, Martin AL, Tanaka T, Aldridge K, Muzaffar AR. Evaluating children with metopic craniosynostosis: The cephalic width-intercoronal distance ratio. Cleft Palate Craniofac J 2016;53:e95-100.
6. Naran S, Mazzaferro D, Wes A, Vossough A, Bartlett SP, Taylor JA. A craniometric analysis of cranial base and cranial vault differences in patients with metopic craniosynostosis. J Craniofac Surg 2017;28:2030-5.
7. Ozyurt A, Baykan A, Argun M, Pamukcu O, Halis H, Korkut S, *et al*. Early onset marfan syndrome: A typical clinical presentation of two cases. Balkan J Med Genet 2015;18:71-6.
8. Sood S, Eldadah ZA, Krause WL, McIntosh I, Dietz HC. Mutation in fibrillin-1 and the marfanoid-craniosynostosis

(Shprintzen-Goldberg) syndrome. Nat Genet 1996;12:209-11.
9. Teager SJ, Constantine S, Lottering N, Anderson PJ. Physiologic closure time of the metopic suture in South Australian infants from 3D CT scans. Childs Nerv Syst 2019;35:329-35.
10. Tsang AK, Taverne A, Holcombe T. Marfan syndrome: A review of the literature and case report. Spec Care Dentist 2013;33:248-54.
11. Van Camp N, Aerden T, Politis C. Problems in the orofacial region associated with Ehlers-Danlos and marfan syndromes: A case series. Br J Oral Maxillofac Surg 2020;58:208-13.
12. Van Hemelrijk C, Renard M, Loeys B. The loeys-dietz syndrome: An update for the clinician. Curr Opin Cardiol 2010;25:546-51.
13. Verstraeten A, Alaerts M, Van Laer L, Loeys B. Marfan syndrome and related disorders: 25 Years of gene discovery. Hum Mutat 2016;37:524-31.
14. Vu HL, Panchal J, Parker EE, Levine NS, Francel P. The timing of physiologic closure of the metopic suture: A review of 159 patients using reconstructed 3D CT scans of the craniofacial region. J Craniofac Surg 2001;12:527-32.
15. Wagner AH, Zaradzki M, Arif R, Remes A, Muller OJ, Kallenbach K. Marfan syndrome: A therapeutic challenge for long-term care. Biochem Pharmacol 2019;164:53-63.
16. Wang JY, Dorafshar AH, Liu A, Groves ML, Ahn ES. The metopic index: An anthropometric index for the quantitative assessment of trigonocephaly from metopic synostosis. J Neurosurg Pediatr 2016;18:275-80.
17. Weinzweig J, Kirschner RE, Farley A, Reiss P, Hunter J, Whitaker LA, *et al.* Metopic synostosis: Defining the temporal sequence of normal suture fusion and differentiating it from synostosis on the basis of computed tomography images. Plast Reconstr Surg 2003;112:1211-8.

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