Calvarial defects associated with neurofibromatosis Type 1

Report of two cases

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In Calvarial osteolysis is a relatively rare finding in patients with neurofibromatosis. The authors describe two patients with neurofibromatosis Type 1 (NF1) and extensive cranial defects associated with underlying dural ectasia. Cranioplasties were performed in both patients with mixed results. One patient underwent cranioplasty using titanium mesh and methylmethacrylate. The other patient underwent an extensive cranioplasty with autogenous iliac crest grafting, and after initial healing has since had further bone resorption. In conclusion, the results of cranial reconstruction in patients with NF1 and dural ectasia are unpredictable because of the tendency for further bone resorption; techniques that protect the graft material from cerebrospinal fluid pulsations via a rigid mesh should be considered.

KEY WORDS • calvarium • skull defect • neurofibromatosis • pediatric neurosurgery

NEUROFIBROMATOSIS Type 1 is a neurocutaneous disorder affecting approximately one in 3000 persons worldwide.16 The main clinical features are cutaneous neurofibromas, café au lait spots, and Lisch nodules. Less common manifestations include axillary or inguinal freckling and neural sheath tumors.6 Neurofibromatosis Type 1 is caused by mutations in the NF1 tumor suppressor gene, located on chromosome 17q11.2. Neurofibromin, the NF1 gene product, is a potent down-regulator of Ras proteins, which control cellular functions such as proliferation, differentiation, and apoptosis. Loss of heterozygosity for the NF1 gene results in elevated levels of Ras–guanosine triphosphate in cells and the formation of neurofibromas, a characteristic lesion in patients with NF1.7,35 Inheritance is autosomal dominant, although more than 50% of cases represent new mutations and 80% of inherited cases are of paternal origin.6

Osseous manifestations have been reported in approximately 50% of patients with NF1.4,18 The most common anomalies are scoliosis (10–26% of patients), absence of the greater sphenoid wing (3–11.3%), tibial pseudarthrosis (1–4%), short stature, spinal meningocle, and macrocephaly.6 Calvarial involvement in patients with NF1 is uncommon, however there have been several reports of defects in the occipital and parietal cranium.9,17,18,21,33 In most of these cases, it was unclear whether the bone gap was congenital or acquired. We present the cases of two patients with NF1 who experienced progressive, massive calvarial osteolysis and were treated with different operative strategies. The disparate outcome of each cranioplastic method provides insight into the pathogenesis of these lesions.

Case Reports

Case 1

History and Examination. This 15-year-old boy with neurofibromatosis and Noonan syndrome was evaluated for two enlarging occipital defects. He was born at 37 weeks of gestation via spontaneous vaginal delivery after an unremarkable pregnancy. His parents and two older siblings were healthy and there was no family history of neurofibromatosis. When he was 5 years of age, he had a neurosurgical evaluation for two previously undetected calvarial defects. On physical examination, he was noted to be short for his age and had obvious developmental delays (IQ testing revealed that his full-scale IQ was in the first percentile for his age, according to the serial Wechsler Intelligence Scale for Children, Third Edition). He had other features seen in patients with NF1 including multiple café au lait spots and a large plexiform neurofibroma involving the left ear and occipital scalp. There were palpable bone defects in the left occipital and parietal cranium.9,17,18,21,33

Abbreviations used in this paper: CSF = cerebrospinal fluid; CT = computed tomography; ICP = intracranial pressure; NF1 = neurofibromatosis Type 1.
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ciput and in the left retrosigmoid area. A head CT scan revealed a posterior fossa cyst with partial agenesis of the cerebellar vermis, and ventricular asymmetry with prominence of the left lateral ventricle (Fig. 1A and B). Clinical and imaging follow up were recommended. Over the following decade, the patient participated in sports and other activities and had no symptoms related to the cranial defects. Nevertheless, serial head CT examinations demonstrated that the occipital holes had gradually enlarged to approximately 6 × 6 cm each (Fig. 1C–F).

Operation and Postoperative Course. Given the size of the lesions and his desire to remain active, the patient underwent cranioplasty using titanium mesh and methylmethacrylate when he was 15 years of age (Fig. 2). The patient tolerated the procedure well and at the 2-year follow-up visit the implant appeared clinically and radiographically stable. However, two small defects have since emerged in the surrounding bone.

Case 2

History and Examination. This 18-year-old woman with NF1 presented with large progressive occipital bone defects. The patient had been born of an uncomplicated full-term pregnancy. There was a strong maternal history of NF1 in her family and she received the diagnosis early in childhood. Physical findings included axillary freckles, multiple café au lait spots, and minor facial asymmetry with right orbital proptosis. When the patient was 4 years of age, bone defects were noted in the area of the right lambdoid suture; these were closed at another institution using titanium plates. At 8 years of age, she presented to Children’s Hospital Boston with a palpable fullness in the right occipital–parietal area. Results of a CT scan confirmed that the plates had become unstable due to peripheral bone erosion. She was also noted to have a large right orbitosphenoidal osseous deficiency. The plates were removed and the defects were repaired using split calvarial bone graft secured with titanium plates. A follow-up CT scan obtained 1 year postoperatively confirmed osseous healing. This scan also revealed a sulcal prominence within the right side of the cerebrum, a mega cisterna magna, and encephalomalacia in the distribution of the right distal posterior cerebral artery (Fig. 3A and B).

The patient remained symptom-free until she was 18 years of age, when she began to complain of headaches and temporary visual loss after being struck lightly on the back of her head. Physical examination revealed a large, compressible soft mass in the right occiput with several small cranial defects cephalad to this area. The results of her neurological examination were normal, and no papilledema was noted. Another CT scan was obtained which confirmed the presence of a new 10 × 5–cm posterior calvarial aperture with a large protruding meningocele that connected to the

Fig. 2. Case 1. Operative photograph obtained in the patient at 15 years of age demonstrating the titanium mesh covering the skull defects prior to application of methylmethacrylate. Lower arrowhead corresponds to left parietooccipital skull defect and upper arrowhead corresponds to left retrosigmoid skull defect.

Fig. 1. Case 1. Axial noncontrast head CT scans. Images obtained in the patient at 4 years of age (A and B) demonstrating a large posterior fossa cyst with hypoplasia of the cerebellar vermis. Other findings include an increase in the CSF space anterior to the left temporal lobe, prominence of the left lateral ventricle, thinning of the squamous portion of the left occipital bone in the retrosigmoid area, and a small skull defect in the left parietal bone. Repeat imaging was performed when the patient was 10 (C and D) and 15 (E and F) years of age, demonstrating progressive enlargement of the occipital and parietooccipital skull defects with prominent underlying CSF spaces.
cisterna magna (Fig. 3C and D). There were multiple smaller defects toward the vertex, presumably at the sites of her previous operations. Although there was extensive dural protrusion through the calvarial defect, encephalomalacic changes were stable. Because the right greater sphenoid wing was absent and there was a large occipital defect, 3D imaging of the skull afforded a remarkable view through the calvarium via the patient’s right orbit (Fig. 4). There was no mass in the surrounding area on magnetic resonance imaging.

Operation and Postoperative Course. Due to the size of, and symptoms related to, her cranial defect, the patient underwent another cranioplasty using split thickness iliac crest

![Fig. 3. Case 2. Axial noncontrast head CT scans. A and B: Images obtained in the patient at 10 years of age demonstrating an enlarged retrocerebellar CSF collection, asymmetry of the lateral ventricles, and early signs of bone irregularities. C and D: Repeat imaging obtained when the patient was 18 years of age. An interval increase in ventricles and CSF spaces and continued bone erosion is demonstrated. E and F: Further erosion is revealed in the suboccipital region despite previous repair with split thickness autograft material.](image)

![Fig. 4. Case 2. Three-dimensional CT renderings of the cranium in the patient at 18 years of age. A–D: Anteroposterior views of cephalocaudal rotation, demonstrating multiple bilateral frontal and parietal repairs along the vertex. The absence of the left greater sphenoid wing provides a remarkable view through the calvarium via the occipital defect. E–H: Posteroanterior views of left–right rotation, demonstrating numerous parietooccipital, occipital, and suboccipital defects.](image)
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grafts secured with resorbable plates (Fig. 5). The ectatic dura was plicated prior to the cranioplasty. Her postoperative recovery was uncomplicated, and her occipital area was firm 6 weeks postoperatively. At 3 months postoperatively, however, there was clinical evidence of small recurrent bone gaps. A CT scan demonstrated a small osseous defect (2 × 2 cm) near the cranioplasty site (Fig. 3E and F). The defect gradually enlarged and at the 15-month follow-up examination it measured 6 × 4 cm. The iliac bone graft material was still visible in central and peripheral parts of the defect, but the size and thickness of the remaining material had progressively decreased.

Discussion

The pathogenesis of calvarial defects in patients with NF1 remains unclear. Because such lesions have been described both in the presence and absence of adjacent tumors, several hypotheses have been put forth. Proponents of one theory suggest that these osseous defects are caused by external pressure, usually from an adjacent neurofibroma or other mass. Indeed, in most of the cases described in the literature there was a contiguous mass including a plexiform neurofibroma, meningioma, meningocoele, or other tumor. Unfortunately, the mere presence of an overlying mass does not establish causation, and none of these reports clearly document progressive bone erosion.

Progressive osseous destruction has been described in the more commonly seen orbitosphenoidal defects. Macfarlane and coworkers used serial CT scans to document progressive erosion of the greater sphenoid wing associated with an enlarging orbital soft tissue mass in a child with NF1. The authors questioned whether growth of the tumor caused expansion of the superior orbital fissure, dural herniation, and subsequent bone erosion from localized CSF pressure. Jacquesmin et al. reviewed CT scans obtained in 31 patients with NF1, and found that 17 of 18 patients with sphenoorbital bone involvement had a contiguous soft tissue tumor, and four had progressive expansion of the middle cranial fossa with bone erosion.

Although both patients in our study had progressive bone loss in the occiput, documented on serial CT scans, only the patient in Case 1 also had an adjacent neurofibroma on clinical examination or magnetic resonance imaging. Both of our patients, however, had large areas of dural ectasia, or ballooning of the dural sac, that could create pressure against the endocortical surface of the cranium. This anomaly is assumed to arise from a congenital or acquired weakening of the dura mater and has been described in patients with NF1, Marfan syndrome, Ehlers–Danlos syndrome, ankylosing spondylitis, and traumatic injuries. Progressive bone defects often arise near these areas of malformed dura. In patients with NF1, dural ectasia is most commonly seen in the thoracic and lumbar spine, although involvement of the optic foramen, internal auditory canal, and calvaria have also been observed. Some authors have speculated that the sphenoidal dysplasia noted in some patients with NF1 may result from dural ectasia of the trigeminal nerve. Although there is a clear association between osseous defects and dural ectasia, the mechanism by which the latter process causes bone erosion remains speculative.

A second theory on the origin of osseous anomalies in patients with NF1 proposes that they are malformations arising from defective mesodermal and neuroectodermal development. Hunt and Pugh advanced this theory to explain cranial lesions that had no adjacent tumor or mass and, therefore, could not be the result of pressure-induced osteolysis. This concept is supported by the following clinical observations: 1) there are several descriptions of patients in whom the surgical specimen or radiographic analysis failed to detect any contiguous tumor; 2) some cases of sphenoorbital dysplasia are clearly present at birth; and 3) the distribution of cranial lesions is remarkably consistent. Orbital lesions of the posterior superior orbit occur in approximately 11% of patients with NF1, while involvement in other areas of the cranial base is extraordinarily rare. The sphenoid is always involved in these orbital defects, and the defect is typically unilateral. Of the 24 lesions in the calvaria reported in other studies, 21 were in the area of the occiput near the lambdoidal suture, and many had hypoplasia and poor pneumatization of the ipsilateral mastoid air cells. Our patients had osseous defects in both the occipital and sphenoorbital regions. Although mechanical explanations have been proposed by several authors, evidence to support these theories is lacking.

Authors of recent molecular studies of neurofibromin, the protein end product of the NF1 gene, suggest yet another hypothesis—that osseous anomalies in patients with NF1 are caused by the abnormal responses of haploinsufficient bone to exogenous mechanical forces. This unifying theory, proposed by Alwan and colleagues, integrates clinical observations with a growing body of literature documenting the vital role of neurofibromin in normal endochondral bone homeostasis and repair. Murine models have demonstrated that neurofibromin acts to modulate mesenchymal stem and progenitor cell differentiation into osteoblasts, and is es-
sential for endochondral bone healing. Elefteriou and co-authors used mice with an osteoblast-specific NFI deletion to show that neurofibromin, through its expression in osteoblasts, is a potent regulator of both bone formation and resorption. Decreased mineral density in the load-bearing areas of the skeleton has been described in patients with NFI and has been cited as indirect evidence that NFI is important in normal human skeletal homeostasis. Although NFI haploinsufficient mice have demonstrated reduced responsiveness to parathyroid hormone and abnormal levels of osteoblastic proliferation, apoptosis, and differentiation, the animals had similar bone density to normal mice. These studies suggest that although the loss of a single allele increases the risk of osteoblast and osteoblastic progenitor malfunction, there are other pathways that preserve bone homeostasis.

Based on the aforementioned studies, Yu and coworkers proposed that skeletal changes in patients with NFI occur only when haploinsufficient osteoprogenitor cells lose their remaining NFI allele (a “double hit”), sustain changes in an additional modifier gene or genes, or come into close proximity with cytokines from tissues that are NFI-null (such as plexiform neurofibromas). This theory provides a tenable molecular explanation for cranial deficiencies that occur both with and without an adjacent mass. The presence of a localized double hit could account for bone defects that occur without an adjacent tumor. In the long bones, which are developing endochondral ossification, Stevenson et al. found biallelic inactivation of NFI in tissue obtained from human tibial pseudoarthrosis. Additionally, histological analyses of tibial pseudoarthrosis have failed to demonstrate any contiguous neurofibroma.

The response of membranous bones such as the calvaria to inactivation of one or both NFI alleles has not been demonstrated experimentally. However, large parts of the sphenoid and occiput are derived through endochondral ossification. In the sphenoid, the lesser wing forms by endochondral ossification, and the greater wing arises through membranous ossification. The basiocciput and supraoccipital regions of the posterior calvaria are formed from endochondral ossification, whereas the interparietal part of the squamous occiput arises from membranous ossification. Because the endochondral and membranous portions of these bones join in early development, it is conceivable that the limited healing and regenerative capacity of NFI endochondral bone inhibits the normal fusion process. In addition, a double hit of NFI in the cartilaginous precursor of the sphenoid or occiput could result in localized bone agenesis/hypoplasia, similar to what occurs in tibial pseudoarthrosis. Either of these developmental aberrations could account for the preponderance of calvarial defects in the sphenoorbital and occipital regions.

The results of cranioplasty in patients with NFI have been unpredictable. A relatively high incidence of bone resorption and recurrent pulsatile proptosis has been reported following split calvarial reconstruction of sphenoorbital defects. Several authors have described improved graft survival using titanium mesh to reinforce the autogenous bone graft. The patient in Case 2 had partial bone resorption after each cranioplasty attempt—the first attempt used split calvaria (when the patient was 8 years of age) and the second used iliac bone graft material (when the patient was 18 years old). In light of what is now known about endochondral bone healing and regeneration in NFI, it is tempting to assume that the unprotected grafts failed to heal, became unstable, and subsequently resorbed. This would be even more likely if the native occipital bone had loss of heterozygosity, or a double hit. However, there was no clinical evidence that the grafts failed to heal in the early postoperative period, and recurrence of the osseous defects was slow and progressive in each patient. Another hypothesis is that diffusely elevated ICP could contribute to the bone erosion. Although ICPs were not directly measured in either patient, it is unlikely that either patient had clinically significant ICP elevation. The patients were not symptomatic, and had no papilledema on funduscopic examination. It is more likely that the failures were related to the inherent inability of NFI-haploinsufficient bone to withstand exogenous pressure from a large underlying dural ectasia.

Given the unpredictability of autogenous bone graft material in this setting, it is logical to augment reconstruction with other materials. This approach was described by Kuri-mito and coworkers who repaired a large occipital meningocele in a patient with NFI using methylmethacrylate. Unfortunately, long-term follow up was not provided. A similar procedure was effective in the patient in Case 1, although adjacent bone erosion may threaten the long-term stability of the implant. We suspect that the unyielding methylmethacrylate implant redirected pressure from the dural ectasia to adjacent NFI haploinsufficient bone. In light of this, it may be helpful in future cases to place titanium mesh between the abnormal dura and the overlying calvaria (or bone graft material). The protective mesh should extend beyond the involved dura and be stabilized to clinically normal bone.

Conclusions

Calvarial reconstruction in patients with NFI and dural ectasia has a high potential for failure from continued bone resorption. Based on our experience, any cranial reconstruction in such a patient should anticipate resorption of autogenous bone graft material, continued bone erosion around the allograft material, and possible long-term implant instability. It is our opinion that a reconstruction should include wide pressure protection of all endocortical bone surfaces, including autogenous grafts, in the area of abnormal dura.

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