Congenital giant plexiform neurofibroma with occipital calvarial dysplasia in association with meningoencephalocele in neurofibromatosis Type 1 and segmental neurofibromatosis

Report of 2 cases

RAVI DADLANI, D.N.B.,1 VENKATRAMAN SADANAND, M.D., PH.D.,1,2 NANDITA GHOSAL, M.D.,3 AND ALANGAR S. HEGDE, M.CH., PH.D.1

Departments of 1Neurosurgery and 3Pathology, Sri Sathya Sai Institute of Higher Medical Sciences, Bangalore, India; and 2Department of Neurosurgery, Loma Linda University, Loma Linda, California

Giant plexiform neurofibroma (GPNF) of the scalp is an extremely rare lesion reported in association with neurofibromatosis. Occipital location of GPNF is even more infrequent, especially in association with occipital dysplasia (OD). The authors report 2 pediatric cases of GPNF associated with OD. The first case had an associated meningoencephalocele, and the second had large vascular channels within the lesion and the dominant ipsilateral transverse sinus lying in the center of the calvarial defect. The authors present these 2 unusual cases with a review of literature and discuss the radiological findings, theories of etiopathogenesis of the OD, and management dilemmas.

(http://thejns.org/doi/abs/10.3171/2013.8.PEDS12624)

KEY WORDS • plexiform neurofibroma • occipital dysplasia • meningocele • segmental neurofibromatosis • pediatric neurosurgery • oncology

NEUROFIBROMATOSIS Type 1 (NF1) is an autosomal dominant disorder affecting 1 in 2500–3500 individuals.5,13 It has a penetrance of almost 100%.5 The fact that it is a progressive disorder and that almost 50% of cases are sporadic mutations multiplies its clinical magnitude severalfold.5 Among its varied clinical presentations, plexiform neurofibromas (PNFs) form one of the cardinal signs of this disorder.5

Kurimoto et al.6 discuss a report by Ricardi et al. in which they described and classified 7 different types of NF. Of these, NF1 and NF2 are distinct forms and the rest represent variants. Segmental neurofibromatosis (SNF) corresponds to the NF5 of the original classification. It is a distinct relative of NF1, but is 10%–20% rarer, accounting for approximately 1 case in 36,000–80,000 individuals.5,6

Skeletal dysplasias are well documented in NF1.5 Scoliosis is the most common.13 Skull dysplasias do occur but are almost always restricted to the orbit. Occipital dysplasias (ODs) are extremely rare and very few cases have been reported in the literature.5,13

We present 2 pediatric cases of giant PNF (GPNF) associated with OD. In the first case there was NF1 with a meningoencephalocele, and in the second case there was an SNF.

Illustrative Cases

Case 1

The first case was a 17-year-old boy who had presented with a progressive, painless swelling of the occiput since early childhood. The parents had noticed it when the child was a few months old. The boy’s mother had NF1 with all the diagnostic criteria. On examination, the swelling was large (15 × 12 × 13 cm), and he had grown his hair long enough to partly cover it (Fig. 1a). The swelling was fluctuant but not transilluminant. The margins of the bone defect were only partly palpable. He had cutaneous stig-
mata of NF1 with more than 15 café-au-lait patches and several cutaneous neurofibromas on the forehead (Fig. 1b). His radiological findings are depicted in Fig. 2. There was a large heterogeneous lesion with a giant underlying meningoencephalocele. A large portion of the visible swelling consisted of a giant neurofibroma (Fig. 2a), which was excised completely. The meningocele sac was repaired (Fig. 3b and d) and a cranioplasty was performed using polymethylmethacrylate (Fig. 1c–e). A “V-Y” plasty was done for the scalp and excess tissue was excised (Fig. 3c).

Case 2

This 14-year-old boy presented with history of a gradually progressive painless swelling in the occipital region, first noticed by his parents at the age of 2 years. The swelling gradually increased in size and developed a reddish hue. The patient was from a rural area and the parents were apprehensive about surgery; he finally presented to us at the age of 14 years. On examination he had a large occipital swelling (Fig. 4a and b) that was soft and nonfluctuant, and transillumination was negative. The swelling had a red telangiectatic hue (Fig. 4a and b), but no bruit was auscultated. The margins of the bone defect were palpable. The boy had no neurological deficits and no signs or family history of NF1. The neuroimaging revealed a large (12 × 12 × 10 cm) swelling in the occiput, on the right more than on the left (Fig. 5). There was an underlying defect of 8 × 6 cm. The dominant right transverse sinus was located in the middle of the lesion (Fig. 5c and f); this was confirmed on the MR venogram (Fig. 5f). The excision was subtotal, due to the presence of the venous sinuses and the vascularity of the lesion. The residual lesion was left adherent to the sinus, and the use of intraoperative ultrasound and Doppler studies prevented any injury to the sinus. A formal cranioplasty was avoided due to the residual lesion.

Histopathological Findings

The H & E staining of resected tissue specimens clinched the diagnosis (Fig. 6). The lesion was a neurofibroma showing focal myxoid generation and spindle cells, with serpentine nuclei and wispy cytoplasmic borders.

Discussion

As discussed by Scott,\textsuperscript{15} in 1906 Helmholtz and Cushing first reported PNF of the scalp. Subsequently, as detailed by Ohaegbulam,\textsuperscript{11} Rakshit et al. identified 2 scalp neurofibromas in a review of 256 patients with NF. In general, PNFs are found in association with NF (in 26.7% of patients).\textsuperscript{17} PNF is usually found along the course of a major nerve trunk, the ophthalmic division in the face.\textsuperscript{1} It is an unencapsulated lesion and infiltrates the surrounding soft tissue to produce a fusiform appearance.\textsuperscript{1} GPNFs have been described very rarely in the literature.\textsuperscript{1,4,6,7,9,11,13,15–17}
SNF is a mosaic form of NF.\textsuperscript{5,6} It usually involves one large segment of the body and may involve both sides of the body either symmetrically or asymmetrically.\textsuperscript{5} Early embryological mutations are usually indistinguishable from NF1, but later somatic mutations restrict the disease to one segment of the body. The pathogenesis is a post-conception mutation of somatic cells rather than germ cells.\textsuperscript{6} The varied distribution of the lesions reflects different cell clone lines. That SNF is a mutation in the NF1 gene has been proven in molecular studies recently. In general SNF carries a very low risk of disease-associated complications and of having a child with generalized NF.\textsuperscript{5,6} SNF has been very rarely described in the scalp.\textsuperscript{5,6} The diagnosis of SNF is based entirely on clinical signs.\textsuperscript{6} The second patient in this report had a GPNF with OD and with telangiectatic discoloration of the overlying skin, but with none of the other cutaneous stigmata of NF1. Review of the literature on SNF revealed only a few recent reports, including one as recent as 2011, and discussed that OD has been reported by only one other paper,\textsuperscript{1,17} so we ran a PubMed search and found to our surprise that the first occipital plexiform neurofibroma with an occipital bone defect was described in 1966.\textsuperscript{9,15} We have summarized the review of the literature in Table 1.
Giant plexiform neurofibromas with occipital dysplasia in NF1

Only 11 reports were found in the literature, of which 10 were in English and 1 was in Japanese. Of these, 2 cases had nonoperative management and 2 had only a biopsy. In the initial description by Helmholtz and Cushing, as detailed by Scott, the location of the PNF was at the forehead and temporal region. It was suggested then that there was a propensity for the forehead and the temporal region, especially the area of the scalp innervated by the trigeminal nerve. Although the forehead and the distribution along the course of the trigeminal nerve is the most common location, there have been a few reports of the PNF occurring at the occiput. The defect of the occipital bone was not mentioned in 5 reports. One patient had multiple areas of bone loss. Two patients in this report had giant ODs. There were only 4 other cases describing meningoencephalocele in association with OD. Of these, only 1 had SNF and the remaining 3 had NF1. All of these lesions were associated with calvarial dysplasia.

Spinal meningocele associated with NF is relatively common, and may occur in between 60% and 85% of all cases of NF. There have been several theories to explain the occurrence of the associated meningocele in the spine. The occurrence of the meningocele is probably part of the mesodermal dysplasia. The enlargement of the sac is generally believed to be due to the pulsating motion of the CSF. Some authors believe that meningocele may be a forme fruste of neurofibromas. This would explain the coexistence of the 2 pathologies, even in the cranium. Another theory assumes that trauma is the inciting event for the meningocele. It would seem probable that the cranial meningocele would occur as part of the mesodermal dysplasia and that CSF pulsations would gradually enlarge the sac. This theory would lend credence to the progressive enlargement of the sac, as seen in most of the cases.

Neurofibromatosis is generally considered to be a neurocutaneous disorder of neural crest origin with very little emphasis on osseous abnormalities, although osseous dysplasia is 1 of the 7 criteria for diagnosing NF1. Neurofibromatosis is generally considered to be a neurocutaneous disorder of neural crest origin with very little emphasis on osseous abnormalities, although osseous dysplasia is 1 of the 7 criteria for diagnosing NF1. However, recent evidence has proven mesodermal involvement in this syndrome. There may be primary or secondary involvement of the skeletal system. The skeletal involvement is compounded by osteoporosis and poor bone healing. Most of the osseous lesions are thought to be secondary to the altered functioning of the NF1 gene.
Besides true dysplasias, secondary involvement of the bones may be due to compression of the malignant tumors seen in association with this disorder, such as malignant peripheral nerve sheath tumors and rhabdomyosarcomas.

Osseous manifestations in NF1 are relatively common and occur in up to 50% of patients with NF1.1,2,6,7–11,13,15–17 These lesions are usually found in long bones and may include scoliosis (10%–26%), sphenoid bone dysplasia (3%–11.3%), pseudarthrosis, and macrocephaly.8 Cranial osteolysis in NF1 is very rare.1,6–11,13,17 There are only a few cases reported, and in most it is difficult to ascertain whether the osteolysis was a result of the erosion secondary to the giant tumor or was merely associated as part of the disease syndrome.9 It is generally accepted that if there are no sclerosing margins of the bone defect and there is hypoplasia of the ipsilateral mastoid air cells, then the dysplasia is a true dysplasia and probably not due to the overlying defect.10,14

There have been a few theories outlining the etiopathogenesis of osteolysis in NF. The first and simplest explanation for osteolysis appears to be the associated mass lesion causing erosion of the overlying calvaria.1,2,6–11,13,14,16,17 The problem with this hypothesis was that none of the reports demonstrated radiological evidence of progression. Calvarial osteolysis without mass lesions in NF has been described.8,14 Inherent dural ectasia and ballooning of the dura mater and subsequent erosion of the overlying calvaria has also been proposed. The exact mechanism, however, is a matter of conjecture.8

Defective mesodermal and neuroectodermal development has been proposed as an embryological mechanism.8 A few molecular mechanisms have been postulated. NF1 is caused by heterozygous mutations in the NF1 tumor suppressor gene at 17q11.2.5 Its product neurofibromin has several important interactions. It has an important role as ras signal regulator and thus for osteoblast function. Data from research in mouse models has elucidated that NF1 haplosufficiency is most likely associated with generalized neurofibromin bone remodeling defects. On the other hand, total loss of the NF1 gene is probably related to focal dysplastic events, perhaps not unlike those seen in OD.

PNFs usually have a very indolent course and enlarge gradually.1,2,5–7,9,11,13,15–17 as evidenced in both our cases. The indications for surgery are pain, cosmetic disfigurement, and neurological involvement.5 There have been re-
Giant plexiform neurofibromas with occipital dysplasia in NF1

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Clinical Features</th>
<th>Associated Lesions</th>
<th>Tumor Size (cm)</th>
<th>Skull Defect (cm)</th>
<th>Outcome</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott, 1966</td>
<td>27, F</td>
<td>PPS, no NF (probable SNF)</td>
<td>venous malformation of scalp</td>
<td>6 × 6</td>
<td>Thinning of OB</td>
<td>GTR</td>
<td>15 yrs; no rec</td>
</tr>
<tr>
<td>Maroun et al., 1969</td>
<td>21, M</td>
<td>PPS &amp; sudden hem</td>
<td>meningocele &amp; encephalocele</td>
<td>6 × 5</td>
<td>Size NR</td>
<td>GTR</td>
<td>NR</td>
</tr>
<tr>
<td>Ohaegbulam, 1977</td>
<td>13, F</td>
<td>PPS, no NF venous malformation of scalp</td>
<td>perineural fibromas of nerve</td>
<td>20 × 16 × 17</td>
<td>Size NR</td>
<td>GTR</td>
<td>18 mos; no rec</td>
</tr>
<tr>
<td>Nakasu et al., 1981†</td>
<td>42, M</td>
<td>NR meningocele &amp;/or encephalocele</td>
<td>gliomatous meningioma, meningocele &amp; encephalocele</td>
<td>NR +, size NR</td>
<td>Size NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mohamed, 1986</td>
<td>17, F</td>
<td>PPS, NF giant</td>
<td>meningocele &amp; encephalocele</td>
<td>Size NR +, size NR</td>
<td>Size NR</td>
<td>GTR</td>
<td>6 mos</td>
</tr>
<tr>
<td>Wakuta &amp; Mitani, 1988</td>
<td>19, M</td>
<td>PPS, no NF (probable SNF) telangiectasia (bruit present)</td>
<td>interhemispheric meningioma, meningocele &amp; encephalocele</td>
<td>26 × 19</td>
<td>Thinning of OB</td>
<td>GTR</td>
<td>7 yrs</td>
</tr>
<tr>
<td>Chen et al., 1991 NR (young adult)</td>
<td>PPS plexiform neurofibromas of liver</td>
<td></td>
<td></td>
<td>10 × 8 × 3.5</td>
<td>Size NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Renshaw et al., 2003</td>
<td>54, F</td>
<td>PPS, NF meningioma &amp;/or encephalocele</td>
<td>venous sinus thrombosis</td>
<td>NR +, size NR</td>
<td>Size NR</td>
<td>GTR</td>
<td>1 mos</td>
</tr>
<tr>
<td>Bodhey &amp; Gupta, 2006</td>
<td>28, M</td>
<td>PPS, NF neurofibrosarcoma, meningocele &amp;/or encephalocele</td>
<td></td>
<td>10 × 12 × 10</td>
<td>Size NR</td>
<td>GTR</td>
<td>NR</td>
</tr>
<tr>
<td>Kurimoto et al., 2008</td>
<td>34, F</td>
<td>PPS, SNF venous sinus meningioma &amp; encephalocele</td>
<td></td>
<td>16 × 12 × 13</td>
<td>Size NR</td>
<td>GTR</td>
<td>5 yrs</td>
</tr>
<tr>
<td>Yoshida et al., 2011</td>
<td>17, M</td>
<td>PPS, NF perineural fibromas of nerve</td>
<td></td>
<td>20 × 10</td>
<td>Size NR</td>
<td>GTR</td>
<td>10 × 8</td>
</tr>
<tr>
<td>Present study</td>
<td>14, M</td>
<td>PPS, SNF intracranial meningioma &amp; encephalocele</td>
<td></td>
<td>12 × 12 × 10</td>
<td>Size NR</td>
<td>GTR</td>
<td>6 mos</td>
</tr>
<tr>
<td></td>
<td>17, M</td>
<td>PPS, NF intracranial meningioma &amp; encephalocele</td>
<td></td>
<td>12 × 12 × 10</td>
<td>Size NR</td>
<td>GTR</td>
<td>6 mos</td>
</tr>
</tbody>
</table>

* Bx = biopsy; GTR = gross-total resection; hem = hemorrhage; NR = not reported; OB = occipital bone; PPS = progressive painless swelling; rec = recurrence; STR = subtotal resection; + = present.
† Article in Japanese.

Conclusions

Plexiform neurofibroma associated with OD in patients with NF and SNF is extremely rare. Early surgical management should be the treatment of choice, not just for cosmetic considerations but also for the theoretical risk of malignant transformation. However, the occurrence of osteolysis may also be prevented if it is indeed secondary to the pressure effects of the lesion, which cannot be disproven conclusively. Surgical management also needs to be individualized because of the varied coexisting lesions. The outcome is generally good. However, further genetic studies specifically related to neurofibromin cellular functions and downstream signaling pathways would be needed for a better understanding of the origin of these tumors.
and predilection of skeletal dysplasias for certain anatomical sites and other related conditions and to further elucidate the ramifications of this genetically challenging disorder.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Dadlani, Sadanand. Acquisition of data: Dadlani, Sadanand, Ghosal. Analysis and interpretation of data: Dadlani, Ghosal, Hegde. Drafting the article: Dadlani, Sadanand. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Dadlani. Administrative/technical/material support: Dadlani, Hegde. Study supervision: all authors.

References


R. Dadlani et al.

Manuscript submitted December 24, 2012. Accepted August 7, 2013.

Please include this information when citing this paper: published online September 13, 2013; DOI: 10.3171/2013.8.PEDS12624.

Address correspondence to: Ravi Dadlani, D.N.B., Department of Neurosurgery, Sri Sathya Sai Institute of Higher Medical Sciences, EPIP area, Whitefield, Bangalore 560 066, India. email: ravi.dadlani@gmail.com.