# Repair of Occipital Bone Defects in Neurofibromatosis Type 1 by Means of CAD/CAM Prefabricated Titanium Plates

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## Abstract

Certain skeletal defects may develop in neurofibromatosis type 1 (NF1), a common tumor-suppressor syndrome, such as cranial lesions confined to the lambdoid suture region. Here, we report on the repair of osseous defects of occipital bone in a NF1 patient with history of skull trauma and tumorous hemorrhage. Computer-aided design and computer-aided manufacturing (CAD/CAM)-assisted devices were applied to safely close the bone defects. The variable phenotype of NF1 in the occipital skull region is discussed and a brief review is presented on NF1-related therapies for tumors and malformations of the occipitoparietal skull region.

**Keywords**

- neurofibromatosis type 1
- lambdoid suture
- calvarial defect
- plexiform neurofibroma
- CAD/CAM reconstruction

Neurofibromatosis type 1 (NF1) is a tumor-suppressor syndrome that can present with a plethora of alterations affecting organs and body systems.[1] Neurofibromas of the skin are the hallmark of the disease which is classified as a neurocutaneous syndrome.[2] However, NF1 is also a bone disease and certain skeletal findings are regarded pathognomonic features allowing diagnosis of the syndrome.[1] A less frequent finding of the skull in NF1 patients is occipital calvarial defects.[3] Some of these defects can be assigned to the course of the lambdoid suture and preferentially occur on one side.[3] In the majority of reported cases, additional peripheral nerve sheath tumors, in particular plexiform neurofibroma (PNF), are diagnosed.[4] The phenomenon of lambdoid suture defect is rare and larger series on this item are seldom reported.[4] Here, we describe the closure of occipital bone defect in a NF1 patient and discuss indication for surgery as well as pertinent literature on this subject.

## Case Report

*Medical history and diagnostics.* A 26-year-old man was admitted to the oral and craniomaxillofacial outpatient clinic to treat a symptomatic calvarial defect. On admission, the patient showed a palpable impression of his right occipitoparietal region. The defect roughly correlated with the expected course of lambdoid suture. Integument was intact and the skull completely covered with hair. Hair line extended deep to the neck, was asymmetrical with deeper line on the affected side, and showed spotty hyperpigmentation (►**Fig. 1a**). The scalp was easily moveable above the defect and showed a soft-tissue surplus extending to the temporal region. The anterior contour of the right orbit was ovally deformed and showed a caudal displacement of the lateral infraorbital rim. Scleral show of the right eye was more pronounced than on the left (►**Fig. 1b**). A PNF was expanded externally visibly into the lateral neck and

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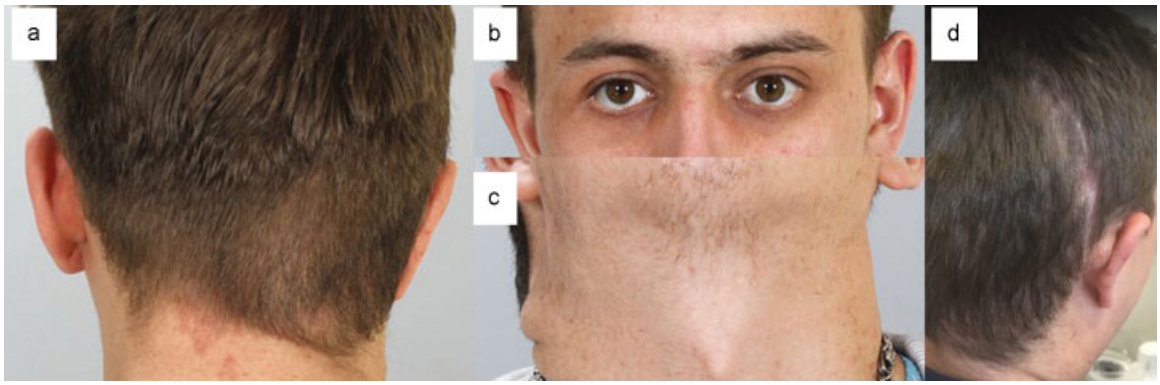


**Fig. 1** Inspection findings. (**a**) Occipital view on the patient's head. Hair line is deeper on the right side. Right pinna is in more caudal position compared with the left side. Hyperpigmentation area of neck skin does not respect midline and extends to the left side of the body. (**b**) Curvature of right lower eyelid is in slightly more caudal position. Scleral show of right eye is greater on right side. (**c**) Skin folding of right side of the neck due to plexiform neurofibroma extending to this region. (**d**) Occipital scarring 4 months after surgery.

developed a fold-forming tumorous elevation below the angle of the jaw in close contact to the mandibular angle deformation (►**Fig. 1c**).

The constellation of clinical findings has been evaluated as evidence of the presence of an extensive PNF ranging from the occipital region to the frontal and parotid regions.

The patient knew about the skull defect ever since childhood. He was diagnosed as being NF1 affected some years ago. He showed typical stigmata of the disease, such as café-au-lait spots of the skin and axillary freckling.

About a year ago, the patient accidentally hit his head on a wall and immediately afterward developed an extensive hematoma over the skull defect. The patient did not develop neurological deficits due to this injury. The resorption of the hematoma lasted several weeks. Since then the patient was afraid of brain injuries following minor head trauma.

*Imaging*. Physical examination revealed only one defect. However, further cranial vault defects became visible on computed tomographies (CTs), both in the line of lambdoid suture and at the base of occiput (►**Fig. 2**). Further dysplasia of right lateral skull in the region of the PNF was seen: a mastoid reduced in size compared with the other side, narrowing of the zygomatic arch and reduction of the glenoid fossa in the transverse diameter, impression of the lateral orbital border of the sphenoid, and oval bulge of the lateral infraorbital rim in the caudal direction (►**Fig. 2a, b**). It was noticeable that the styloid of the side affected by the tumor was unusually long and thinned out compared with the contralateral side. The angle of the jaw had developed a bony deformation in the caudal direction (►**Fig. 2a, b**). Intracranially, a meningoencephalocele was visible in close proximity to the lambdoid suture defect (►**Fig. 2c, d**). The right hemisphere of the cerebellum showed some T2-weighted hyperintensities on magnetic resonance image (MRI) in the cortical region and distortion, particularly close to the skeletal defects (►**Fig. 2e–g**). Pneumatization of sphenoid bone reached dorsum sellae. However, the right side of this sinus was less pneumatized in more dorsal parts (►**Fig. 2d**).

*Therapy*. We decided to cover the defects with computer-aided design and computer-aided manufacturing (CAD/CAM)-generated titanium plates (DePuy Synthes Deutschland, Umkirch, Germany; ►**Fig. 3a, b**). The coverage was planned as three single workpieces with a safety distance of at least 1 cm between each plate. Overlap of the plate edges over the bone was planned approximately 1 cm. Single, small lattices were preferred to a large bowl-shaped covering of the occipital, because the tolerance of the soft tissue against foreign bodies in the PNF is very low in the craniofacial region, according to our own experience. Therefore, we estimated smaller workpieces as it is easier to incorporate and as less mechanically stressful for covering the soft tissue. In general anesthesia, the occipital bone was exposed via semicoronal incision. The cross-section of the scalp presented the typical view of a diffuse infiltrating, plexiform tumor, which was traversed by nodes. The upper lambdoid suture defects were smaller than expected from CT. However, careful investigation of the expected defect sites revealed substantial thinning of bone allowing only low retention of the screw turns in regions closer to the defects. Planned osteosynthesis plate area and positioning of screw holes allowed the secure fixation of the implants. The planned dimensions of this implant thus proved to be appropriate (►**Fig. 3c**). The implant for coverage of the large lateral defect fitted to the site of insertion. However, for the cranial prefabricated retention of the osteosynthesis screws, a slightly larger distance to the defect edge was preferred, leaving a narrow defect margin (►**Fig. 3d**). It was decided during the procedure that only the dorsal aspect of the caudal defect close to the foramen magnum should be covered, because injury to the brain was judged unlikely to occur deep below the muscular coverage of the bone defect. The trimming of the third workpiece was performed quickly in the operating room, whereby the maintenance of the specified fixing points had to be ensured (►**Fig. 3d**). Healing was uneventful. Four months after the treatment, the patient is free of complications and feels very satisfied with his choice of therapy. The soft-tissue surplus was only slightly reduced at the time of follow-up, probably as a result of scarring. We are concerned about a tightening of the scalp in the area of PNF because, according to our experience, hair loss can occur relatively quickly in this area following surgical interventions (►**Fig. 1d**).

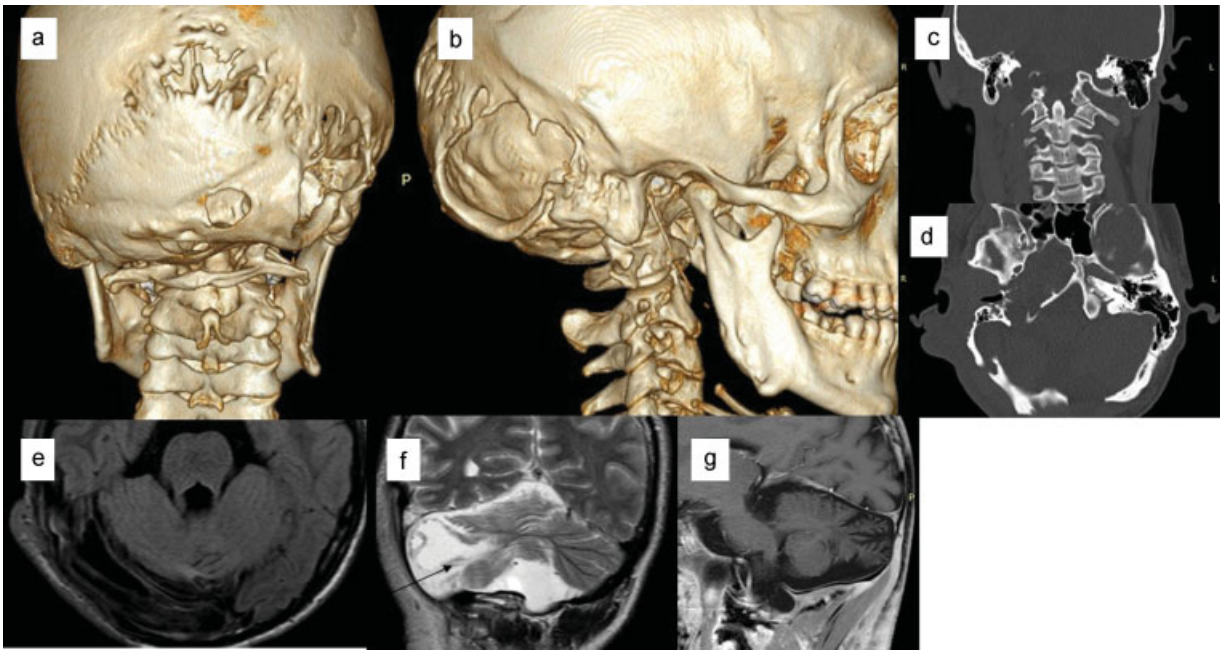


**Fig. 2** Imaging of cranium and brain. Computed tomographies (CTs) of the patient's skull with three-dimensional reconstruction of skull surface. (**a**) Occipital view of the skull discloses dehiscence of right lambdoid suture with some bone bridges. Further defects of occipital bone are located caudally and not associated with the suture. There are further skeletal findings on the PNF-affected side: dysplasia of the upper vertebrae, extension of the right mandibular angle in caudal direction, and small volume of mastoid. (**b**) Lateral view on the bone surfaces shows deformation of glenoid fossa, and thin styloid ligament. (**c**) Coronal view discloses the asymmetrical pneumatization of mastoid and associated concavity of the calvaria. Soft-tissue thickness of the scalp is clearly greater on the right side. (**d**) Multiple occipital skull defects are associated with soft-tissue mass covering, in this CT sectional image, the entire right side of the skull. Note distance of pinna to the bone. (**e–g**) Magnetic resonance images (MRIs) of calvarial extension of plexiform neurofibroma and associated malformations of the brain. (**e**) Axial section of cerebellum region on T1-weighted MRI shows cyst-like extension of subarachnoidal space. (**f**) The right cerebellar lobe shows hyperintense stimulation preferentially in the gyri on T2-weighted coronal MRI. (**g**) Sagittal T1-weighted MRI identifies cyst-like space occupying lesion surrounding circularly the cerebellum.

*Histology*. On microscopic investigation, the scalp showed invasion by diffuse-dermal neurofibroma with intercalated PNF (►**Fig. 4**).

## Discussion

This report describes the successful cranial vault reconstruction using CAD/CAM-fabricated titanium osteosynthesis plates, and dealing with new intraoperative findings.

*Localization of cranial vault defects*. The skeletal defects of the cranial vault in NF1 show a certain regularity in their topography. Evidently, most reports are about bone defects in the region of the lambda suture,[3,5–10] but similar osseous lesions are found at the foramen magnum,[11,12] the parietal,[13–15] and the frontotemporal region.[16] There were reports of both unilateral[5,17,18] and bilateral[10,15,19] defects of the occiput. An association with a PNF was found in the majority of cases, but was not always present.[4] This variable association applies both to the different localizations of the cranial vault and to the defects of the cranial base.[4] The eccentric localization of the tumor to the bone defect, as it has occurred in our case, is well recognized in the literature[9] and already indicates that the tumor can be associated with the bone defect but must not be a direct cause of the osseous alteration.[12]

*NF1 and segmental neurofibromatosis*. Similar defects with topographically associated PNF have been reported for patients with generalized neurofibromatosis as well as in some patients whose skeletal/soft-tissue disease has been shown to occur without any further findings that would require the diagnosis of NF1.[12,16,20,21]

*Soft-tissue pathology associated with cranial vault defects*. Although the topography of osseous defects apparently occurs in some preferred regions of the vault, extension of the associated PNF to adjacent regions and also the quality of associated pathologies appear to be random.[11,12,19,22–24] For example, in one case the bony defect was associated with occipital tumor and neck invasion, but physical impairment was apparently restricted to reducible torticollis.[11] On the other hand, lambdoid bone defect can occur combined with ipsilateral temporofrontal PNF.[25] Furthermore, meningoceles associated with the occipital bone defects may cause severe symptoms, such as dysphagia.[26] In contrast to these variable associations of soft-tissue and bone pathology, there are also reports of extensive PNF in this region without any form of bone alteration,[13] including cases that are likely to describe a segmental neurofibromatosis.[27] Hair can be thinned out over the scalp tumor.[13]

*Phenotypical characteristics of PNF in the craniofacial region*. The neurofibroma is predominantly of the diffuse-invasive type. The tumor tends to agglomerate to bulky, baggy masses, which cause considerable disfigurement of the body contours due to its own weight, the slowly increasing volume, and the lower elasticity against normal soft tissue. The age of the patient is another factor which affects the invasive PNF

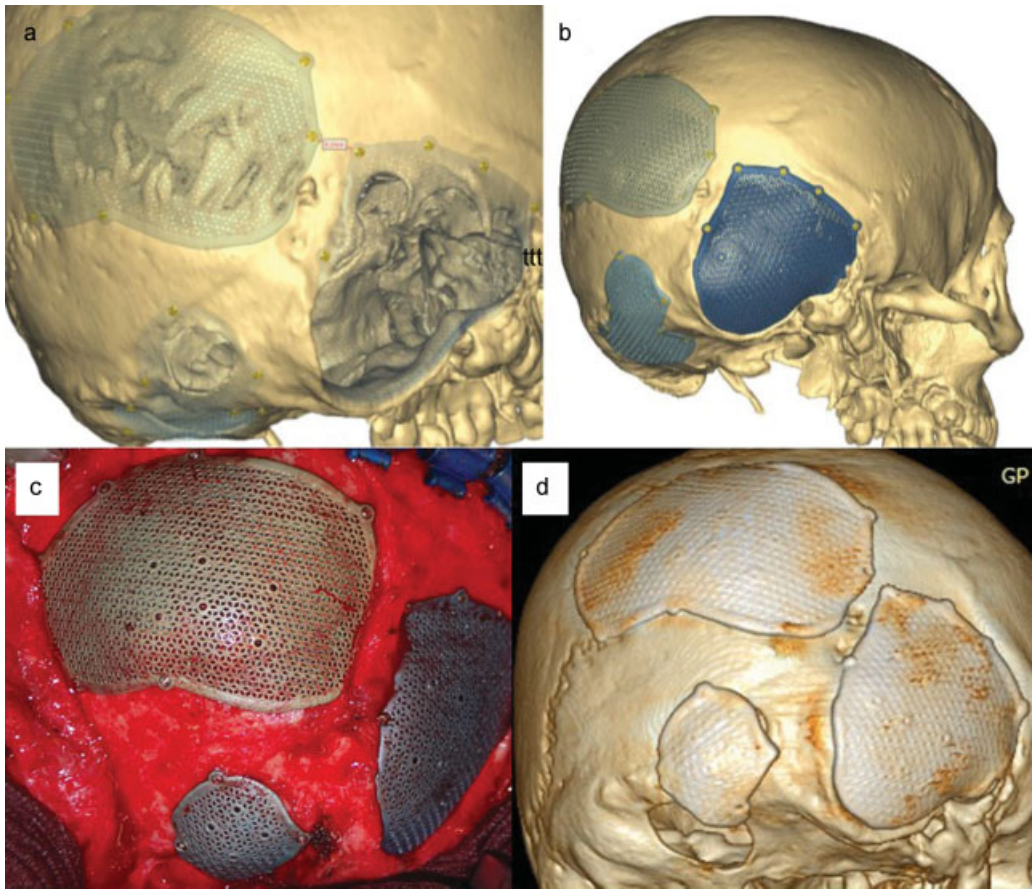


**Fig. 3** Reconstruction of the occipital skull. (**a**) Virtual planning of osteosynthesis plates' dimensions and positioning on transparent plate models. Completed osteosynthesis plates are shown in the virtual model (**b**) and in situ (**c**). (**d**) Skull surface CT model showing position of plates. Caudal plate was intraoperatively trimmed.

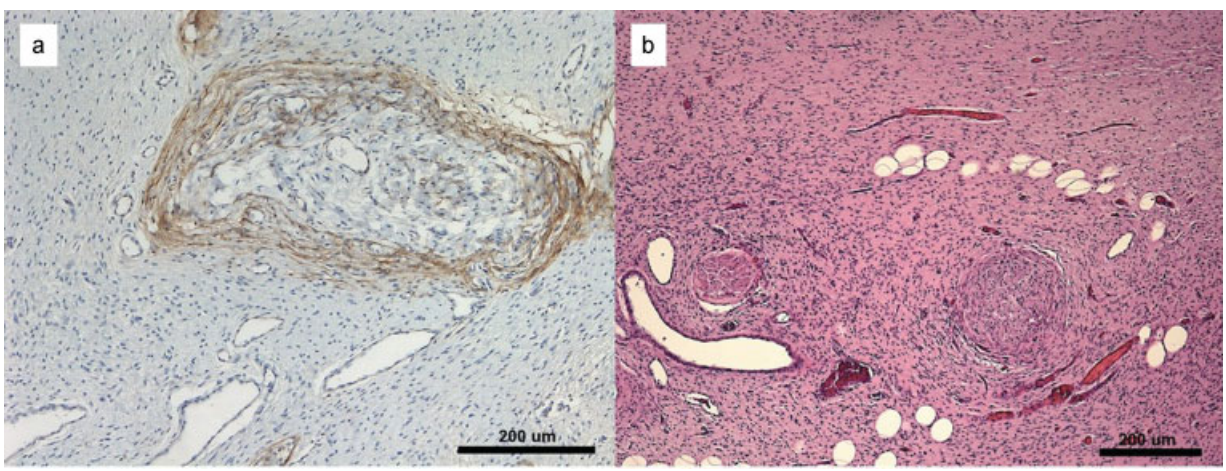


**Fig. 4** (**a**) Hematoxylin eosin stain of the occipital scalp shows diffuse-invasive plexiform neurofibroma with nodular structures. (**b**) Immunohistochemical identification of the perineurium with antibody against epithelial membrane antigen (brown color) in nodular structures of the tumor.

phenotype in the craniofacial region, because the elasticity of the child's connective tissue in most cases is resistant to the limpous tumor mass for a long time, thus delaying the formation of the baggy tumor regions to later periods of life. Typically, the tumors passively follow the gravitational force as a sagging mass at least in late adolescence or early adulthood. However, nodular tumors giving on palpation the association of worm-like aggregate may trespass the diffuse tumor mass.[13,25] From our own experience, we are aware that spontaneous ulceration can occur in these regions of extended diffuse PNF, or defect covers made of alloplastic material lose their soft-tissue cover.

*Pathogenesis of calvarial bone defects in NF1*. Occipital bone defects may occur as a defect in the articulation of bone plates, for example, in the lambda suture. This can be interpreted as a primary connectivity error of the connective tissues involved in suturing of the cranial vault. Increased intracranial pressure can be suspected as further cause of incomplete cranial vault closure, which hinders the ossification. However, neither a local developmental disturbance of the brain or the cerebral membranes is to be demonstrated in several cases, nor is a general increase in pressure of the brain plausibly justified for a localized disturbance of the ossification. Furthermore, these occipital defects also occur outside of the lambdoid suture,[11] as also shown in the present case. The defects differ in size and some with inclusion of the lambdoid suture appear to involve the suture rather randomly.[15] We consider the extensive distortions of the cranial sutures as characteristics of disturbed ossification during cranial growth. Some dysplasia of the neighboring brain structures has been detectable radiologically (►**Fig. 2**). However, local trophic effects of the tumor may also cause bone resorption.[11,28] Some authors consider disturbances of the mineral microenvironment as further factors of the defect development, which they compare with the findings obtained in "growing fracture" of the skull.[10] Interestingly, eight of twelve patients with calvarial defects also had a topographically associated overlying PNF, but only four out of twelve had adjacent dural ectasia. The authors explicitly deny associated soft-tissue pathology in three patients with calvarial defects.[4] Davidson had already pointed out that occipital bone defects can occur both with and without PNF. However, in the case of lack of detection of a PNF, other pathologies causing locally altered bone structure may occur.[5] Nine of twelve patients had further bony pathologies of the skull and vertebral column.[4] Associated skull findings were also registered in the presented case. All these findings, individually or in combination, have been repeatedly reported as skeletal changes in topographical relationship with PNF.[3–7] Mislow et al[15] discussed the requirement of progressive bone resorption associated with a PNF to establish a causal link between tumor and bone pathology. This association already was described in a case report covering a long-lasting history of craniofacial PNF and severe skull resorption.[28] However, the heavy tumor weight must be considered for the estimation of osteolysis. In addition, skull defects in NF1 without evidence of associated tumor were reported.

*Differential diagnosis of cranial vault tumors in NF1*. Differential diagnosis of calvarial defect in NF1 patients can be demanding. In one case with extensive occipital bone destruction and associated head and neck PNF, the bone tumor proved to be of different histology than the apparent cranial vault's nerve sheath tumor: diagnosis was giant cell tumor of the occipital bone.[29] Another case disclosed atypical meningioma as the cause for osteolysis of cranial vault in a patient with NF1 who had developed an extensive scalp tumor mimicking a PNF.[30] A further case disclosed multilocular astrocytoma as the cause of multiple skull defects in a NF1 patient.[31] Transformation of PNF to malignant peripheral nerve sheath tumor preferentially occurs in the trunk and extremities, but occasionally develop also in the cranial vault.

*Imaging of occipital bone defects in NF1*. The imaging of the skull is necessary in patients with cranial PNF to determine soft- and hard-tissue alterations. Plain radiographs and sectional images may disclose further bone pathology.[4,6]

Arrington et al[4] investigated eight cases with lambdoid suture defects both with CT and MRI. Laterality of findings was in favor of right side (5/3). Occipital bone defect as shown on CT was closely related to the suture or included the suture. MRI imaging of soft tissue in the defect region revealed lobulated T2 hyperintensities equivalent to PNF either in close proximity to the defect or covering the defect. Associated dysplasia of other bones such as cranial base, mandible, or vertebrae was noted in 9 of 12 patients with calvarial defects. Nine of these 12 patients were diagnosed to have associated PNF. This collection of findings underlines the close association of PNF with calvarial defects in NF1. However, only seven patients underwent debulking procedures of calvarial PNF.[4]

*Treatment recommendation*. There are no general recommendations as to whether this defect is to be closed.[32] Severe general diseases can exclude the indication for occlusion of the bone defect.[21] There is also no consensus as to which material is most suitable for the closure of the defect. Some authors apply titanium mesh.[15] Minor head trauma can cause hemorrhage in PNF.[33] As a precautionary measure, this implantation was planned because severe intracranial injuries could result with a renewed hemorrhage. Severe hemorrhages with life-threatening situations are well documented for NF1 patients with craniofacial PNF.[34–36] NF1 is also a disease of the vascular system.[22] A definite supply appeared to us feasible because the patient had already grown out and therefore no changes of the implant position in the growing skull had to be taken into account.[21,32] We chose a CAD/CAM-planned coverage of the defects in this case because we expected this procedure to allow precise design of the implants, the surface of which should optimally deburred and smoothed by the industrial working process.[37] Therefore, the tissue tolerance against the foreign bodies should not be overloaded.

The extent of the defect and the characteristics of the malformation can also depend on the time at which the malformation occurs in prenatal physical development or later in life.[8] Recurrent dehiscence of osteoplasty-occluded bone defects has been described in the growing skull.[4] In the present case, distortions and displacements of the suture are visible on the CT-reconstructed skull surface in an adult. Imaging proved evidence for associated meningoencephalocele, but severe brain dysplasia[11,16] was not associated with this osseous malformation. However, the adjacent cerebellum was somewhat deformed (►**Fig. 2**). These topographical relationships between malformations of the occipital skull and the occipital brain regions in NF1 have already been highlighted by Eickhoff and Fischer.[38]

Enlargement of the plates' areas beyond the osseous defect is justified to cover also thinned calvarial bone regions adjacent to apparent defects both to protect brain from external forces and also to secure the mechanical support and fixation of the plate in loadable and retentive bones.

Indeed, epicranial growth of PNF may cause further bone thinning.[35,39,40] Pulse-synchronous brain pressure was thought to be an important factor in the low stability of bone cranial grafts. Metal implants showed better stability.[41] Alternative therapy concepts according to the assessment of the intraoperative findings are to be realized with prefabricated metal plates only with restrictions.

## Conclusion

Repair of calvarial bone defects should be considered in NF1 patients with history of hemorrhage in the region of the bone defects. CAD/CAM-assisted surgery enabled a safe and fast definitive patient care. Intraoperative alternatives to surgical defect cover can only be implemented with limitations by modifying the prefabricated workpieces. The careful investigation of associated pathologies is indispensable in the preparation of the procedure.

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