Dysplasia of the Orbit and Adjacent Bone Associated with Plexiform Neurofibroma and Ocular Disease in 42 NF-1 Patients

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Abstract. *Neurofibromas are the hallmark of neurofibromatosis type 1 (NF1). Interestingly, generalised and localised interference or dysfunction of bone is also a key element of the NF1 phenotype. In the skull, NF1-associated orbital dysplasia often results in a severe disfigurement of affected individuals. However, the underlying pathology of orbital dysplasia is a complex phenomenon and up to now poorly understood. This study was performed to describe the orbit in 42 NF1 patients with large, disfiguring soft-tissue tumour of the orbital/eyelid region (plexiform neurofibroma (PNF)). A dysplastic orbit on the affected side was diagnosed in 80.9%. Orbital PNF extension to adjacent regions revealed a significant correlation of orbit and temporal region (0.33, p<0.034), cheek and oral cavity (0.4, p>0.011), oral cavity and nose (0.35, p<0.026), and temporal region and cheek (0.46, p<0.003). Alterations of the optic nerve and adjacent structures were identified on MRI or CT in 14 patients. On plain skull radiographs, only sphenoid wing dysplasia and ipsilateral orbital enlargement were significantly correlated (0.528, p<0.01). This study reveals PNF as the main component of soft tissue affecting eyelids and orbit in those cases, which show a soft tissue mass in the affected orbital region. The oval-shaped orbital rim, typically seen on plain skull radiographs in sagittal projections, seems to be strongly associated with the (lateral and caudal) extension of a PNF and independent from sphenoid wing dysplasia. Several factors constitute the individual orbital dysplasia, including the growth of the invasive PNF.*

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Neurofibromatosis type 1 (NF1) is an autosomal-dominant inherited disease. Alterations of the integument are relevant diagnostic findings in NF1 (1, 2), in particular in childhood (3). Interestingly, generalised and localised interference or dysfunction of bone is also a key element of NF1 phenotype, *e.g.* short stature or pseudarthrosis (4, 5). In the skull, NF1-associated orbital dysplasia is a rare but pathognomonic complication (6, 7) and often results in a severe disfigurement (8). However, the underlying pathology of orbital dysplasia is a complex phenomenon and currently poorly understood. Some reports discuss in detail the dysplastic sphenoid bone and associated malformations of the cerebral membranes as the cause of orbit deformity (9, 10). These findings are in favour of a primary dysplasia of bone and cerebral membranes, resulting in temporal lobe displacement into the orbit and consecutive extension of orbital walls. Indeed, exploration of this region has in some cases revealed malformations of the cerebral membranes (9, 10). The phenotype of orbital defects in NF1, usually affecting the orbital roof, is eventually associated with unilateral pulsating exophthalmos (10-13). Current studies on orbital manifestations of NF1 focus on the incidence and action of optic nerve gliomas (14-17). In contrast, other reports point to the fact that plexiform neurofibroma (PNF), arising in the first and second branches of the trigeminal nerve (7, 18), may also extend into the orbit and contribute to dysplasia (19-21). The synchronic manifestation of orbital PNF, connatal glaucoma, ptosis of the upper eyelid and hypertrophy of the adjacent facial parts is called François syndrome (22, 23). Intraorbital neurofibroma might invade the external muscles of the eye, resulting in strabism. Riccardi (8) assumes that more than 5% of NF1 patients develop a strabism, including those patients with no obvious intraorbital tumour (10). Therefore, orbital dysplasia visible on plain radiographs, computed tomograms (CT) or magnetic resonance imaging (MRI) appears to be associated with multiple signs of NF1 and can be an indicator of a PNF (19-21, 24, 25). Facial surgery for PNF is challenging and should be based on thorough knowledge of associated lesions in the field of

surgery. This study was performed to describe the orbit in NF1 patients with a large cranial nerve sheath tumour of the orbital region, with special reference to surgical therapy.

Patients and Methods

This study comprised physical, radiological and histological findings of 42 patients treated in a single institution (female: 52.4%, male: 47.6%). All patients were diagnosed as being affected by NF1 according to the current diagnostic criteria for NF1 (1, 2). Inclusion criteria for the study were a visible affection of the orbital region by a large soft-tissue tumour of the eyelids or orbit that was histologically proven following maxillofacial surgery. The affected parts of the orbit (muscles, globe, lids, lacrimal gland, optic nerve), the extension of the orbital or eyelid tumour to adjacent regions (lids, orbit, brow, oral cavity, cheek, nose, temporal region), associated skeletal and soft-tissue alterations concerning the third trigeminal nerve branch were determined and the functional defects as a consequence of tumour or as postoperative sequelae, osseous manifestations (orbit, midface and mandible), intracranial alterations and optic pathway pathologies were evaluated. Tumour extension and evidence of optic nerve glioma were determined on MRI and CT. In cases with no MRI or CT images, plain radiographs of the orbit were evaluated to determine bony changes (14, 26, 27). Correlative statistics were carried out to provide evidence for association of lesions. The following patient data were collected: age at the time of first surgery, number of operations, type and frequency of complications, histological type of tumour (neurofibroma), surgery beyond the orbital region, time interval between first symptom and first operation.

Results

Age at time of NF1 diagnosis varied [1 to 5 years: 21 (50%), 6 to 19: 4 (9.5%), 11 to 15: 2 (4.8%), 16 to 20: 4 (9.5%), 21 to 30: 5 (11.9%), > 30: 0, no data: 6 (14.3%)]. The tumours were PNF in all but one patient with no further specification. A family history of NF1 was evident in 14 patients (33.3%). The (peri)orbital pathologies were unilaterally localized in all patients (28). Further affections of the facial skeleton of the same side were noted in 41 patients. In one patient, the orbital pathology was located contralaterally to the extensive PNF that involved the temporo-occipital region, neck and scapula. The right orbital region was affected in 23 patients (54.8%) and the left in 19 (45.2%). The first findings and symptoms were recorded prior to the sixth year of life in the majority of patients.

First findings attributable to NF1 of 16 patients (38.1%) were recorded during the first month after birth (facial swelling (always unilateral): 9, café-au-lait (CAL) spots: 3, glaucoma: 2 (associated with asymmetrical head: 1), fibromatous nodule: 1, CAL spot associated with facial swelling: 1, not specified: 1). During the second to twelfth month after birth, a further 9 patients showed findings in the periorbital region (swelling: 3, CAL spots and swelling: 4, proptosis of the eye associated with temporal lobe prolapse: 1, and asymmetrical head with facial swelling: 1). A further 4 patients (9.5%) showed the first findings during the period of 13 to 36 months after birth (swelling: 3, unspecified statement: 1). In 2 patients (4.8%) CAL spots or localized swelling in the affected facial region were noted up to the 60th month after birth. The first findings of 4 patients (9.5%) were noted later than 60 months of age but prior to their 12th birthday (fibromatous nodule: 1, swelling associated with buphthalmos: 1, swelling: 2). The medical records of 7 patients (16.7%) were inconclusive concerning this item and no classification could be made.

The swelling and/or tumour infiltration respectively, as initial findings in NF1 was confined to the periorbital region or expanded into larger parts of the face (50% each). In the latter cases, a distinction between eye/orbital manifestation and facial manifestations was impossible due to the initial extension of the tumour. The term 'facial' is used to describe the tumour-invaded region of the integument by one or more branches of the trigeminal nerve of one side. Facial swelling in conjunction with a positive family history and identification of CAL spots led to the tentative diagnosis in 42%. The clinical diagnosis of the syndrome was confirmed by histological investigation of tumour specimen in 45% prior to our therapy. In 13% of patients it was not clear whether the orbital/facial findings paved the way to the diagnosis already established at the time of referral.

First operation in the orbital region. The mean age at the time of the first operation in the orbital region was 15 years (mean age at the time of first facial operation: 11.8 years). Up to their 20th year of age, 66.7% of patients experienced surgery in this region. Ten patients (23.8%) were operated on in the orbital region between their 1st and 5th year of age, 6 (14.3%) between 6th and 10th, 7 (16.7%) between 11th and 15th year, 5 (11.9%) between 16th and 20th, and 6 (14.3%) between 21st and 30th year, >30 years: 6 patients; unknown: 2 (4.8%).

The first operation was performed in 75% of cases in order to reduce the tumour burden in the orbital region or tightening up the ptotic lids. Reduction of intraocular pressure or enucleation of the globe due to extensive and destructive tumour growth was intended in a further 7.1% of cases. There were 3 cases of correction for strabism, debulking for corneal tumour or intended elevation of the globe by augmentation techniques combined with plastic correction of the orbital roof. In 11 patients, the surgery of the orbital region succeeded surgery for other NF1-related pathologies. First surgery of the orbital region was performed within the first 5 years after establishing the diagnosis in 19 patients (45.2%). Four patients (9.5%) experienced surgery in the orbital region prior to NF1 diagnosis, 2 of them to reduce intraocular pressure in the course of glaucoma, in 1 case for blepharoplastic and in 1 case for exploration of

suspected haemangioma. Eleven patients (26.2%) were operated in the orbital region 6 to 32 years after diagnosis (insufficient data: 7 patients, 16.7%).

The number of operations performed per patient varied considerably (up to 17, mean: 3.9 operations) summarized to 164 cumulative surgical interventions across all patients (oral and maxillofacial clinic: 130, others: 34). A single operation in the orbital/eye region was performed in 7 patients (16.7%), two in 10 (23.8%), three to five in 13 (31%), and more than five operations were performed in 10 patients (23.8%). Patients were of all ages in all categories. The time that elapsed between the first and last surgery in the orbital region was a mean of 10.6 years (any first to last operation: 14.1 years). These values correlate to the age of the patients (r=0.75), *i.e.* the older the patient, the longer the time period of treatment lasts, indicating the chronic need for treatment.

Surgery was performed in 67.4% of cases to reduce tumour burden and/or the ptosis. In 32.6% intraorbital tumour reduction was necessary. Twenty-three patients (54.8%) experienced further tumour debulking in the nasal, cheek and lip region of the same side (number of surgical interventions: 1 to 20).

Complications. Complications attributable to surgery were evaluated for 130 interventions (100%). The most frequent and obvious complication was extensive postoperative swelling that lasted for several weeks or months, in particular in those patients who experienced their first operation in the eyelid region. Estimation of the surgical result was impossible for weeks in patients with upper eyelid surgery (ptosis or debulking procedure). Infections were registered in 8.5% of patients. In the following 4 cases (3.1%), the infection resulted in excorporation of foreign bodies (implants): (a) explantation of silastic slings for suspension of the upper lid (after 17 years), (b) excorporation of a palavit implant inserted in the orbital floor for elevation of the globe (after 1 week), (c) excision of a scleral plastic (after 3 weeks) and (d) explantation of a foil (after a few weeks). A noteworthy bleeding after surgery was documented in 7 cases (5.4%) but a dehiscence of the sutures was rare (3.9%). An impaired nerval function was registered: 3 for the facial (2.3%), 2 for the oculomotorius (1.5%), and 1 for the abducens nerve (0.8%). Impaired lid function, at least temporarily noted, was attributable to scary fixation (4, 3.1%). Necrosis occurred in three cases (2.3%) and was restricted to the superficial layers. A keratopathy was noted twice (1.5%).

Intraoperative haemostasis was delayed in the majority of interventions. In 12 interventions (9.2%), haemostasis was extremely deferred. Both the prolonged bleeding and the invasive growth pattern of PNF impeded significantly the intended tumour reduction.

Enucleation of the globe was performed in 5 patients (11.9%). In 2 of them subsidence of the eye prosthesis required repeated corrections. The eyes of both patients were enucleated decades earlier, while they were young. First corrections of the prosthetic base were needed 22 and 33 years after the ablative intervention. Both patients underwent several interventions to stabilize the elevated orbital floor (augmentation material: palavit or hydroxyapatite-ceramic granules: one patient: six corrections within 8 years, and the second: four corrections within 6 years). Both patients had extensive PNF of the orbital region. At the time of writing, 3 patients have had no need for surgery of their eye prosthesis (reasons for enucleation: buphthalmos, cataract with megalocornea, or PNF with invasion of the choroidea and ciliary body). Mean age at the time of enucleation was 27 years.

Topography. Localization of the neurofibroma in 42 patients was: involvement of the lids in 41 (97.6%), specified to involvement of both upper and lower eyelid (27 cases), upper lid (10 cases) and lower lid (4 cases). In 18 cases, the lateral portions of the upper lid were predominantly affected, leaving only 4 cases with predominant medial tumour growth. In 15 cases, the diffuse involvement of both lid and orbit allowed no determination of a preferential site. In 1 patient, the diffuse invasion of the lid was not discernable to the investigator but was proven histologically.

Evidence for orbital invasion (postseptal tumour growth) was verified in 34 patients (81%). However, the tumour extension inside the orbit was inaccurately described in 16 cases. In the remaining 18 patients, the tumour distribution was: retrobulbar or orbital fissure (6), craniolateral (5), cranial (5), lateral (1) or medial (1). In 5 patients (11.9%), the lacrimal gland was invaded and the secretory function was impaired. The region of the eye brow was affected by the PNF in 23 patients (54.8%). Interestingly, in this study patients with no infiltration of the upper lid had no tumour in the eyebrow and frontal region. The temporal region was affected by the PNF in 29 cases (69%), the cheek region in 33 cases (78.6%), and the nose in 21 cases (50%). Intraoral extension of the PNF was diagnosed in 27 patients (64.3%).

The constellations of individually registered tumour extensions were investigated for correlations (Kendall Tau B). Manifestations of the eyelids correlated to no other topographic unit: they are independent findings in the setting of facial NF1. Correlations of other findings are small but significant. Correlation of PNF of the orbital and temporal region is 0.33 ($p<0.034$), cheek and oral cavity 0.4 ($p<0.011$), oral cavity and nose 0.35 ($p<0.026$), and temporal region and cheek 0.46 ($p<0.003$). All other correlations proved to be not significant ($p>0.05$).

A dysplastic orbit was diagnosed on radiographs in 34 patients (81%). An enlarged orbit was found in 20 patients (47.6%), a narrowed orbit in 3 patients only (7.1%; unchanged: 6 (14.1%), not determinable: 2 (5%)). An

enlarged orbit was associated with PNF. However, the diminished orbit found in 3 cases showed a peculiar growth pattern of PNF in 2 (PNF restricted to the temporal fossa/lateral border of the orbit: 2; shrunken orbit following exenteration in childhood: 1). Affection of the maxillary sinus of these 3 patients appeared to be coincidental: in each case the sinus was of the affected side was narrowed, enlarged or not altered compared to the non-affected side. However, in the group of 20 patients with enlarged orbit, 11 (55%) showed a narrowed maxillary sinus. In one patient, beside the enlarged orbit, the maxillary sinus also appeared enlarged, probably due to the extensive facial PNF with severe facial scoliosis. In 75% of cases the enlarged orbit was associated with sphenoid wing dysplasia. On plain radiographs only the sphenoid wing dysplasia and ipsilateral orbital enlargement were significantly correlated (0.528, $p<0.01$).

Associated malformation of the mandible in patients with orbital PNF. The aim of this analysis was to assess the malformation of the mandible in patients with orbital neurofibromatosis. Clinical and histological investigations intended to reveal the presence of tumour adjacent to the bone in cases of relevant osseous alterations and malpositioning of teeth. In 18 patients (42.9%), neither apparent tumour nor osseous alterations were detectable. Sixteen patients (38.1%) had tumour and ipsilateral osseous mandibular defect or at least severe malpositioning of mandibular teeth. Three patients (7.1%) had alteration of the bone but no visible tumour, and 5 patients (11.9%) had tumour but apparently no bony defect (r=0.622 for tumour and mandibular alteration).

Topography of PNF related to the trigeminal nerve branches. The trigeminal nerve (N V) divides into 3 branches, the ophthalmic (N V1), maxillary (N V2) and mandibular (N V3) branch. The descriptive analysis intended to delineate the facial tumour extension (photographs of all patients, medical and operative reports, MRI and CT) and to match the field to the topography of the branches. The determination was dichotomous (yes/no) with no further specification. In 25 patients (59.5%), the orbital tumour extension matched with the spreading of the mandibular nerve. The trigeminal nerves were affected as follows: N V1: 6 patients, N V2: 2 patients, N V1+2: 9 patients, N V2+3: 3 patients, and N V1+2+3: 22 patients.

Functional deficits of the nerves. Functional deficits were found in 41 patients. Due to the long lasting history of many patients with repeated surgical interventions both tumour- and surgery-related causes must be taken into account. However, the retrospective analysis allowed no clear distinction of this factor in the majority of cases. Facial nerve paresis was documented in 22 patients (52.4%). In 4 cases, the impaired facial nerve function was first diagnosed after facial surgery for PNF on the affected side.

Lid function was impaired in 35 patients (83.3%) due to ptosis of the upper lid. Opening and closing of the lids were impossible or severely afflicted in 25 patients (59.5%). Lower lid ectropion, frequently associated with conjunctivitis and epiphora, was diagnosed in 14 patients (33.3%). In 14 patients (33.3%), the mobility of the eye was also impaired, ranging from 'slightly impaired' to 'completely walled in and immobile'. An altered position of the globe was recorded in 20 patients (inferior: 6, inferior and exophthalmos: 4, exophthalmos: 3, enophthalmos: 3, superior: 1, superior and exophthalmos: 1, medial dislocation and exophthalmos: 1, lateral dislocation: 1).

A reduced vision of the eye of the affected side was diagnosed in 36 patients (85.7%), indicating the severe consequences of an orbital PNF. Bilateral reduction of sight was noted for 4 patients, 2 of them with chiasma opticum glioma. In the other 32 patients, the reduction of sight was restricted to the tumour-affected side. The results of vision tests of these eyes were evaluable in 24 patients (Landolt rings), referring to the most recent results: 0.0 to 0.5: 18 patients, 0.6 to 0.9: 6 patients). Diagnosis of optic nerve glioma was difficult in these cases. Reports from CT or MRI were available for 30 patients. In 19 patients, only CT scans were performed, 6 patients had only MRI and 5 patients were subjected to both imaging techniques. A total of 6 patients were diagnosed as having an optic nerve glioma of the affected side. Diagnosis of glioma was rare despite relevant findings indicating this alteration of the optic nerve (thickening of the nerve: 5 cases, optic nerve atrophy: 2 cases, enlargement of optic canal: 4 cases, irregular borders of the optic canal: 1 case, glioma: 3 cases, glioma including the chiasma opticum: 3 cases). A total of 14 patients showed alterations of the optic nerve or the adjacent osseous structures to allow the suspected diagnosis of optic nerve glioma.

Discussion

This study detailed the associated findings in patients with orbital and eye lid PNF of the craniofacial region and indicated the therapy for patients with this condition, with special reference to complications and long-term follow-up control.

The main result of this study is the evidence for a direct connection between NF1-associated alterations in the region of orbit and eyelid with a PNF. The spectrum of these tumour-indicative soft-tissue alterations is wide: discrete swelling of the lids (29), intensified hairiness of the brows (30) or lateral deformation of the lid's rim (31) up to destruction of the globe consecutive to invasive PNF and deeply to the cheek extending ptosis (7, 8). Diseases of the globe may also emerge, independently of the orbital PNF (*e.g.* buphthalmos) (32-34). The malformation of the orbital

roof is an independent diagnostic finding in NF1 (1), but appeared in this study to be associated in about 50% of patients with orbito-facial PNF. Indeed, extensive osteolysis of the orbit and adjacent bone associated with PNF in the course of NF1 are well known (35). However, NF1 is a genetic skeletal disease (36). Whereas sphenoid wing dysplasia as part of NF1-associated orbital deformations is an independent and indisputable finding, the malformation of the orbital entrance, in particular the subsidence of the lateral part of the infraorbital rim resulting in an oval shape of the orbit in posterior-anterior radiographic projection, appears to be associated with a PNF.

The association of PNF and optic nevre glioma (ONG) was already assumed by Davis (40), based on the description of a clinical course and necropsy of the orbit in a neurofibromatosis patient with PNF of this region. He described an ONG of the affected side in close proximity to the orbital PNF and further ophthalmologic pathologies. In this case, the orbital walls remained intact but the orbit was increased in size. Davis postulated that defects were not present due to the fact that the deceased patient was a child and the elapse of time during a longer lasting life would probably have resulted in an orbital defect, as already described by others (29, 37, 38). He referred to the capability of PNF to invade and destroy bone and argued for the PNF as the cause of bony defects of the orbit in neurofibromatosis. However, reference should be made to the reports of authors who noted congenital absence of the orbital roof (with pulsating exophthalmos) (37, 41). These findings are interpreted as primary malformations of the bone, not necessarily associated with a PNF (9, 10).

Gender-independent manifestation. Twenty-two female and twenty male patients represent a balanced ratio of NF1-affected individual with orbito-facial PNF (1:1.1). There is every indication that the risk of developing NF1 is equally distributed between men and women (8). The risk for orbital affection in NF1 is also not influenced by gender (42). Results from this study add the information that PNF of the orbital region show no preference for gender.

Initial findings and symptoms of NF1 in the region of the eyelid and orbit. In the literature only a few reports exist addressing the item 'first findings and symptoms' in NF1 (43). The present investigation found facial swelling as the predominant finding preceding the diagnosis. This result is obviously biased due to the selection criteria of this study. However, many of the patients were young at the time of diagnosis, supporting the current theory that PNF develops in the perinatal period and becomes symptomatic in early childhood. Exceptions of this course of the disease appear to be rare (43). CAL spots are relevant indicators for NF1 diagnosis in early childhood (3). Whitehouse (44) identified CAL spots in 81% of affected individuals at birth. The remaining 19% of NF patients developed CAL spots during their first year of life. These studies were performed prior to the distinction of NF subtypes. However, Riccardi (8) confirmed the presence of CAL spots of NF1 patients early in their life, frequently soon after birth. In this study, CAL spots were rarely the first diagnostic finding in NF1. Probably this discrepancy can be explained by the topography of the CAL spots that develop more frequently in the skin of the trunk and extremities. An inexplicable facial swelling is more conspicuous than a confluent hyperpigmentation of the skin that might also appear in the general population, without any hazard. Indeed, solitary CAL spots are not diagnostic of NF1 (2). Social contact and self-confidence are more restricted due to a facial PNF than CAL spots. Henderson (42) confirms the assumption that orbital and eyelid manifestations are registered as a serious finding by parents of patients much earlier than are CAL spots, based on his long-lasting experience in a major ophthalmological center. The low frequency of CAL-spots (76.2%) in this study compared to the frequencies of other reports (White *et al*.: 95% (45), Overveg *et al*.: 98% (46), Cnossen *et al*.: 96.7% (47)) is likely to be attributable to the confinement of the surgical exploration to the relevant region of the body.

Exophthalmos and enophthalmos. Exophthalmos and deep position of the globe were the most frequent topographic alterations. A deep position of the globe was associated with exophthalmos in 40% of cases. This dislocation does not allow the precise localisation of the tumour inside the orbit but serves as an indicator of the tumour-associated facial scoliosis, *i.e*. the associated skeletal malformation (10). Enophthalmos was diagnosed in 3 patients with preserved eye. In all these patients a large PNF of the orbit was associated with the subsided eye. In 2 out of 3 patients the orbital volume was enlarged. Enlargement of the orbit as the solely findings might cause an enophthalmos (48). Enophthalmos in NF1 is only occasionally noted (49).

The presented functional deficits show interrelationships, *e.g*. exophthalmos can be associated with impaired lid function. A ptosis was diagnosed in 35 out of 42 patients and can impair the elevation of the lid, in particular in cases with subsidence of the globe. Furthermore, the visual acuity can be impaired by ptosis of the eyelid and optic nerve glioma (8). This study revealed impaired vision in 36 patients, including 6 patients with diagnosis of optic nerve glioma.

Ptosis. Ptosis in NF1 without any detectable nerve sheath tumour occurs in about 9% (50). In a subsequent study, 3 out of 81 NF1-patients showed this type of ptosis (3.7%, (51)). Ptosis emerges more frequently unilaterally than bilaterally (50). The pathophysiological basis for this phenomenon is

unclear (31). In this study the ptosis was associated with tumour and in many cases with orbital malformations. Recurrent eyelid surgery was mandatory in many patients to improve the visual field of the seeing eyes.

Origin and growth pattern of eyelid neurofibroma. It is widely believed that orbital PNF arises in the eyelids and invades in a centripedal fashion into the orbit (31). The appreciation of the formal pathogenesis of PNF of this region is severely hampered due to the facts that the predominant finding 'swelling' in orbito-facial region is ambiguous, the progress of the disease often proceeds with time, and the time of diagnosis does not match with the time of tumour onset. In many cases, the tumour growth is already far advanced and the orbital infiltration manifest. Causally intended ablative surgery as a means to stop invasive (centripedal) growth is restricted to single cases in an early stage of tumour development (52).

Family history and high percentage of spontaneous mutations. A family history of NF1 was proven in 14 patients (33.3%). In 27 patients, no relatives were NF1 affected or the data allowed no conclusion about this item (*e.g.* adoption). This percentage of NF1 patients with family members also affected by the disease is remarkable lower than those from earlier reports (3): 50%, (53): 64%). A 50% rate of spontaneous mutations in NF1 is generally accepted (53). The divergence between the data of this study and data in the literature is probably attributable to the retrospective study design. Based on the experience of these authors, it was recorded several times that these patients had not discussed their disease, neither with their children, nor with their parents. Therefore, the delay in NF1 diagnosis also applies to relatives of patients with orbito-facial PNF. Furthermore, the high variability of NF1 phenotype hampers the accurate diagnosis in sparsely affected individuals, facilitating the diagnosis of 'spontaneous' cases in their offspring. In an earlier report, it was proposed that the first diagnosis of NF1 might be delayed even for decades despite extensive tumour growth (elephantiasis, (54)). The recommendation to investigate parents of NF1 patients at least for CAL spots, Lisch nodules and cutaneous neurofibromas should be followed (55).

Differential diagnosis of ONG and PNF. Differential diagnosis of orbito-facial NF1 with proptosis has to consider a space-occupying glioma of the optical nerve (14). The ONG is an essential diagnostic criterion for NF1 (2). Earlier studies even proceeded to the assumption that ONG in almost every case is associated with neurofibromatosis (40, 56). However, this assessment is refuted by studies based on modern imaging techniques (57). ONG arising in early childhood is associated with NF1 in about 70% (16). At least bilateral ONG are believed to be a sure sign that the individual is NF1 affected (42). Lewis and Riccardi (55) state a prevalence of ONG in 12% consecutive studies (53, 58), even in 15% of NF1 patients. According to Henderson (42) there is no correlation between ONG and a PNF of the orbit and eyelids in NF1 patients. Evidence of occult ONG and inconspicuous orbits and eyelids in ophthalmological studies support this judgement ((14), CT study). In contrast, the association between ONG and orbital neurofibroma in this entity was already noted at the beginning of the last century (59). The characteristic proptosis of the globe, already symptomatic in children (16), can also be caused by a PNF with intraorbital or retrobulbar extension (60, 61). The standard methods of orbital diagnostics for ONG is CT (14, 24, 25) or MRI (62, 63). PNF is best visualized with the aid of CT (24) or MRI (64). CT is preferentially used to detect associated skeletal malformations (21). MRI and CT were not performed in all patients and the findings must therefore be interpreted with caution (long interval of patient recruitment and long history of recurrent therapy in the affected region). The large number of histologically verified PNF (41 of 42 cases) allows the assumption that the space occupying lesions of eyelids and orbit were caused by this neoplasm. The correct histological diagnosis of the orbital tumour is mandatory to discuss skeletal alterations properly (21). Recent CT and MRI studies on NF1-associated tumours (65) and the experience of other authors show that neither the evidence for tumour can be stated safely (66), nor can a histological diagnosis be derived distinctly from these imaging modalities (67). The pathogenetic assignment of orbital dysplasias to glioma, PNF or a combination of both entities is further impaired following the reports of spontaneous regression of ONG in the course of NF1 (63, 68, 69). Therefore, it cannot entirely be excluded that an ONG might have developed in early childhood, associated with dysplasia of the orbit (in particular the orbital apex), but regressed during the years, leaving an expanded passage through the skull base. Indeed, evidence for an enlarged optical canal is indicative of ONG but insufficient to determine the proximal extension of the tumour (26).

The proportion of clinically unapparent findings of the orbit appears to be high (70, 71). Radiological investigations refer to the detection rate and course of ONG in NF1 by means of MRI or CT, without histological proof of diagnosis (63). Korf (72) refers to the recommendation of the US national NF Foundation to investigate NF1 patients with ONG annually and to adjust the intervals adequately in relation to alterations of findings and symptoms (16). In this study, at least 13 patients with a PNF of the affected side show findings that are frequently addressed in the diagnostic process of ONG (26) and therefore make this diagnosis likely (30.9%, see Results). In 6 patients, the diagnosis was confirmed by MRI (14.3%). The prevalence of ONG in NF1 was estimated to be 10% (73). Recent studies, based on CT

and MRI, allowed the calculation of 15% of NF1 individuals as being affected by this tumour (14, 58, 74), or even up to 20% (17). The number of potential ONG is higher. The standard for ONG imaging and neurofibroma is MRI with contrast enhancement (75, 76).

According to Wright *et al*. (26), conventional radiographs performed for the diagnosis of ONG revealed an expanded optical canal in 15 out of 16 (93.5%, 10 out of 17 patients with neurofibromatosis; the findings were collected in both solitary and NF1-associated lesions). These tumours were also seen on CT scans. However, no clear distinction could be drawn between glioma and arachnoideal ectasia (surgical exploration and histologically proven tumour in 7 patients).

Reduced visual acuity of the eye of the affected side was diagnosed in all patients. Proptosis (n=15) and atrophy of the optic nerve (n=11) were frequent findings. The expansion of the optic canal can be due to ONG (27). On the other hand, it was argued that the malformation of the optic canal and optic foramen could be primary skeletal malformations resulting in enlarged osseous passages (NF1-associated primary mesodermal malformation (9)). Binet *et al*. (9) recommended the differential diagnosis of ONG in cases with consecutive reduced visual acuity. It is noteworthy to refer to Goalwin's radiological study of the optic canal using plane radiographs (77). Based on the investigation of 1000 optic canals, he found symmetry between both canals in healthy individuals in only 45%. Other authors detail findings such as thickening of the optic nerve (5 patients) and optic nerve atrophy (2 patients) giving rise to the suspicion of a nerve sheath tumour (26, 78). Glioma grows slowly and is asymptomatic over a long period of time (48). The rate of presumptive ONG associated with PNF of the eyelids and orbit is higher than previously estimated, based on MRI studies. Having due regard to these presumptive cases of ONG (30.9%) this finding is more frequent in NF1 patients with these orbito-facial manifestations than in the NF1 population in general (17). This result should be validated in consecutive studies. On the other hand, this study provides evidence for the association of skeletal malformations of the orbital ring with adjacent PNF. According to Jacquemin *et al*. (21), infiltrations of the optic nerve seen on MRI or CT can also be due to invasive growth of a PNF. Histological proof for this judgement was not presented. However, the presented figures supported this assumption (21). Our surgical experience supports these radiological estimations on the basis of histologically proven evidence of PNF inside the orbit. The fact that there are other causes to explain the radiological findings make routine MRI or CT diagnosis in cases with facial PNF necessary. However, diagnosis might not be definitive despite these efforts. Age at diagnosis of ONG is usually less than 12 years (79, 80), or even below 7 years, according to recent studies on NF1 patients (17). In the present study, the ONG diagnosis was established in 5 out of 6 patients during childhood. Only one patient was diagnosed as having an ONG later (48 years, accidental finding, NF1 diagnosis was established many years earlier) and was not included to determine the mean value (6.2 years). The mean age of our NF1 patients at the time of MRI-based ONG diagnosis is similar to data of other reports on this topic. These comparisons allow postulation of the use of imaging techniques for the estimation of orbito-facial PNF and also for the detection of ONG. In this study, it was not possible to substantiate the experience of Henderson (42) who noted less severe effects on other body parts in patients with disfiguring orbito-facial PNF.

Malignancy. In no case did a malignancy arise in the region of the PNF (follow-up control: up to 12 years). Indeed, the transformation of orbital PNF to malignant peripheral nerve sheath tumours appears to be very rare (81).

Orbital dysplasia. Orbital lesions (dysplasia and osteolysis) were detected in 34 of 42 patients (81%). The umbrella term 'orbital dysplasia' includes not only enlargement or reduction of the orbital volume, but all irregularities of the orbital walls (25). The cause of orbital dysplasia is unknown and seems to be the result of different pathogenetic factors. Binet *et al*. (9) assume in patients with generalized NF a connatal dysplasia of growth centres of the sphenoid bone, resulting in an enlargement of the orbit and the medial cranial fossa. These malformations might result in different grades of hypoplasia of sella turcica, minor and major sphenoid wing (9). Holt and Wright (82) described a case with complete absence of the sphenoid bone in an adult who was known to have neurofibromatosis since childhood. This constellation seems to be very rare. Binet *et al*. (9) detected a simultaneous ipsilateral sphenoid wing dysplasia in 7 consecutively investigated patients with consistently enlarged orbits. Van der Meulen (48) also described a relationship between sphenoid wing dysplasia and orbital enlargement. Enlargement of the orbit was diagnosed in 20 patients of this study, 15 of them with sphenoid wing dysplasia. Farris and Grove (32) investigated 10 patients with orbital neurofibromatosis. Eight out of 10 patients had an enlarged orbit (intra-individual comparison of orbital diameter), associated with sphenoid wing dysplasia in 8 patients. However, simultaneous occurrence of sphenoid wing dysplasia and orbital dysplasia was restricted to 6 patients. It is remarkable that the orbital volume was reduced in 3 patients of this study. In one patient, the cause of the phenotype was probably the enucleation of the globe during childhood and the consecutive surgery for adjustment of the prosthetic base. Reduction of the orbital volume following enucleation is a well known consequence of this therapy and

not specific for osseous malformation in NF1 (70). Two patients also showed a narrowed orbit. Both patients had large PNF of the temporal region extending to the lateral margin of the eyelids and known to be present since childhood. It is fair to assume that the interference of the tumour with the bone resulted in the narrowed orbit. However, this cannot explain the pathomechanism. Some reports suggest that osseous alterations might be the result of pressure exerted by the tumour (83). Burrows (84) detected in an enlarged orbit regularly in neurofibroma and postulated the tumour growth as the cause for the widening of the bone. Binet *et al*. (9) did not reveal neurofibroma after exploration of the orbit in their neurofibromatosis patients. Therefore, several factors (tumour-associated growth factors, brain pressure in cases with defects of the orbital roof) seem to contribute to the form of orbital dysplasia, without evidence of neurofibroma (10). On the other hand, 17 out of 20 patients with enlarged orbit showed intraorbital space occupying lesions (neurofibroma, temporal lobe). A pulsating exophthalmos as an indicator of sphenoid wing dysplasia in NF1 was repeatedly noted in the literature (11, 13, 21).

Plexiform neurofibroma and orbital dysplasia. The frequency of PNF of this study exceeds by far the prevalence of this tumour in population-based studies in NF1 (47, 53). In those studies, the frequency of PNF was calculated to be 26.6% (47) and 32% (53), and was predominantly encountered on the trunk and extremities. In the study of Huson *et al*. (53) 3 patients had developed a PNF of the head and neck region. The reason for the high number of PNF in this study is the selection of patients, who were required to have a (peri)orbital tumour. This tumour is almost always a PNF. Association of PNF with orbital dysplasia is noted but statistically not significant. This result coincides with the information provided by Kaste and Pivnick (70), who studied the orbital volume in NF1 patients dependent on the presence of an ONG (58 patients, CT, axial scans). In their study, several deviations of the orbital geometry were noted in patients with both with and without ONG. They found no specific pattern of orbital dysplasia. Two patients had a sphenoid wing dysplasia. The authors did not address the presence of a PNF in their study. In contrast to the findings of Kaste and Pivnick (70), some NF1 patients with PNF of this study demonstrated characteristic dysplasias of the orbit (oval shaped macro-orbit).

Frequency of PNF in the eye lids and orbital region. The facial PNF predominantly arises in the orbital region, with a preference for the upper eyelid (85). However, PNF are predominantly located in the trunk and extremities concerning their distribution over the whole body in NF1 patients (43). White *et al*. (45) investigated 257 patients with neurofibromatosis. Forty-two patients (17%) had a PNF of the head and neck region. Eighteen of these 42 patients had a PNF in the regions of the orbit and eye lids (7% of the total collective, 42.8% of the subgroup). The preferential location of facial PNF in the eyelid and orbital region are supported by this study (45). Evidence of PNF is almost always diagnostic for NF1; exceptions are very rare (86). The evaluation of orbital and eyelid PNF of patients treated in the ophthalmologic centre of the Mayo clinic revealed neurofibromatosis in only 21 out of 27 consecutive patients (42). Solitary facial neurofibroma preferentially arises in the orbit and eyelid regions, but appears to not be PNF (42).

Point in time of plexiform and cutaneous neurofibroma development. The demand for surgical therapy is usually less extensive in cases with cutaneous neurofibroma compared to PNF, because the functional deficits of the eye and eyelids are not or only slightly impaired by these tumours. Cutaneous neurofibromas of this region are not associated with orbital malformations. Sphenoid wing dysplasia develops independently of tumour type. Clearly, the differences in orbital geometry compared to values obtained from healthy individuals were obtained in patients with cutaneous (disseminated) neurofibromas (70). Cutaneous neurofibromas arise during or after puberty (55). On the other hand, PNF are frequently present at birth (1). This study confirms these findings. First findings were noticed during the first months of life in 16 patients, and a further 9 patients developed first NF1-associated findings within the second and twelfth month after birth. Age at the time of diagnosis reflects the perinatal manifestation of PNF in this location. In 50%, the diagnosis was established between the first and fifth year of life (excluding 14.3% of patients with inconclusive data). The mean age at the time of diagnosis was 8.5 years and is lower than that reported by Fienman and Yakovac (87) and Holt (80), who calculated 12 and 15 years, respectively. Both studies considered the time points of diagnosis in their institution only, whereas this study recorded all time points of diagnosis, irrespective of institution.

Misdiagnosis of plexiform neurofibroma. Delay in diagnosis was noted for orbito-facial neurofibromatosis. The main reason for diagnostic delay was ignorance of the diagnostic criteria for NF1. One further reason was the non-specificity of the facial swelling and the similarity of PNF imaging to lymphangioma and hemangioma on MRI or CT due to the dense vascularity of PNF mimicking these entities. The observation to regard PNF as a highly vascularised tumour goes back to descriptions of Tauber (25) and others (89). The widening of vessels inside the tumour (88), the infiltration of the vessel walls by tumourous cells (89) and the resemblance of PNF and lymphangioma in imaging (67) hamper the correct diagnosis in some cases. In this study,

suspected diagnosis of lymphangioma or hemangima prior to the diagnosis of orbito-facial PNF was noted in 4 patients. In one patient, the swelling was erroneously diagnosed as haemangioma and corrected at 20 years of age. In the second patient the suspected diagnosis was lymphangioma and NF was proven at the age of 10 years. In the third patient the suspected diagnosis was lymphangioma at the age of 6 years. A biopsy was rejected and the diagnosis of PNF was established at the age of 24 years. In the final patient, a lymphangioma was diagnosed at the age of 14 years. PNF was diagnosed at the age of 27 years.

Surgery. The listing of the number of operations and complications illustrates the difficulties of surgery for orbito-facial PNF. Recurrence of PNF is well known (83, 90-96). The major surgical intentions are debulking procedures adjusted to the topography of the affected region, frequently associated with face-lift procedures (90-95). The psychological burden as a consequence of a disfiguring tumour is high in particular in cases with facial PNF (8). Prevention of blindness or maintenance of residual vision is the main reason for recurrent eyelid surgery in these patients.

In more than 50% of cases, the first surgery in the eyelid and orbit region was performed prior to their 15th year of age. This mean age appears to be high, having regard to the frequently noticed severe facial disfigurement caused by a tumour, detectable in early childhood. Many patients did not seek surgical therapy until adulthood. Needle *et al*. (96) calculated a mean age of 10 years at the time of first surgery for NF1. This study was based on a large number of patients and included all body regions. The mean age at the time of first surgical intervention of the patients in this study in consideration of all body sites was 12 years and similar to the information provided by Needle *et al*. (96).

The maximum number of surgical procedures of the eyelids and orbit was 17, with a mean of 3. Twenty-three patients had between 1 and 20 operations outside the orbito-facial region (mean 6.5). The mean value of 3 operations per patient in the facial region (97) falls below the number of our operations per patient. It is reasonable to assume that the long-term follow-up provided in a large referral centre is a selection factor of severely affected cases (98). There is a slight correlation between age of patient and treatment interval. This correlation points to the life-long need for surgical treatment, in particular in facial PNF cases where tumour reduction is the only therapeutic option and tumour recurrence must be expected (83, 90-95, 97).

Ten interventions intended to reduce the intraocular pressure, confined to 3 patients with hydrophthalmia, were recorded. Despite recurrent interventions, all 3 patients lost complete vision of the affected eye and later on the eye was destroyed by tumour. Both the site of tumour manifestation and the neuroectodermal developmental disorder resulting in buphthalmos appeared to be pathogenetic factors in these cases (99). Congenital glaucoma (hydrophthalmia) is estimated to occur in about 0.5% of NF1 (8).

François syndrome. The delineation of a syndrome as a means to single out several groups of findings from a plethora of phenotypes might facilitate medical communication, in particular between fields of medical specialization. The designation of a syndrome by the name of the author who described this grouping is popular but gives no information about the actual findings. In particular, it does not allow the appellation of the syndrome in orbito-facial PNF a reference to the clinical course of the disease (preservation of the eye inside the tumourous orbit, visual acuity associated with grade of ptosis, extension of the tumour to other parts of the skull, *etc*.). Furthermore, the constitutive findings of the syndrome should be reviewed (22, 23): besides evidence for a PNF, ipsilateral glaucoma with buphthalmos, the syndrome also includes unilateral facial hemihypertrophy. This hemihypertrophy is not specified (soft or hard tissue or both) and the description of facial nerve function is not included in the syndrome. The group of constitutive findings of this syndrome have already been published (7). Modern imaging techniques allow the conclusion that a true skeletal hypertrophy of the affected region is very rare (100) and the effect of a prominent zygomatic complex is attributable to severe facial scoliosis (with severely thinned out bones). Therefore, the term 'François Syndrome' should not be used to describe orbito-facial PNF.

Complications. Excluding the extensive oedema following surgery as a postoperative complication (all cases) from the evaluation, the complication rate was around 33%. General risks were low in number (infection: 11 cases, bleeding: 7 cases, dehiscence of wound: 5 cases). All complications were recorded during the patients' stay in hospital and immediately treated. A further aspect was the presence of neurological deficits attributable to surgery or the disease. In 6 cases (4.6%), a cranial nerve deficit was recorded after surgery. Needle *et al*. (96) investigated permanent neurological deficits following 302 operations. These authors also listed 4.6% of their cases as having a neurological deficit. In contrast to the current study, the data of Needle *et al*. (96) are based on the evaluation of all operations performed on the whole body of their NF1 patients and did not address the deficits of cranial nerves. Lee *et al*. (95) reported about persistent ptosis, overcorrection of ptosis, deformation of eyelids, xerophthalmia, scleral show and entropion or ectropion in follow-up control of their patients. This detailed description emphasises the difficulties of performing adequate surgery in a tumourous region. Indeed, the progress of the tumour has to be considered as a

powerful factor in the estimation of the postoperative aspect. Prolonged bleeding impedes therapy, in particular in the facial region. Preoperative angiography of the carotids was recommended 24 to 48 h prior to surgery for facial PNF and to embolize the tumour-feeding arteries (91). This procedure was not applied in any case in this study.

Besides the orbit and eyelids, other facial regions were affected in 40 out of 42 patients. This extension of PNF was also registered in another study in 80% of their cases (32) and substantiates the need for thorough investigation of every patient with orbito-facial PNF. The unilaterality of the findings is remarkable. Friedrich *et al*. (100) had already noted this unilateral tumour growth but noted a slight transgression of the PNF beyond the midline in some of their cases. This marginal transgression might be due to locally invasive tumour growth and/or the overlap of the terminal branches of the trigeminal nerve in the midline region. However, in no case did the non-affected side show any neurological deficit or tumour invasion of muscles.

Associated manifestations. It is notable that in 27 patients (64.3%), the ipsilateral buccal region was also involved in the neurofibroma spread (penetrating infiltration of the cheek). Friedrich *et al*. (100) expected that for NF1 patients with facial affections referred to a specialized maxillofacial surgery clinic, about 50% would have an intraoral manifestation of (plexiform) neurofibroma. The most frequently affected regions of oral NF1 are the cheek, tongue and alveolar process (101). This study revealed the frequent association of oral manifestations in patients selected for their orbito-facial PNF. These findings are confined to the ipsilateral side. The characteristic of the nerve sheath tumour following the branches of the trigeminal nerve is confirmed by the frequent and statistically significant involvement of the ipsilateral side of the nose.

'Sigmoid course' (29), (horizontal) 'paragraph symbol' or 's-type course' of the upper lid rim (32) of the affected side are variants of the description of the predominant lateral manifestation of PNF in this location. The tumour extended up to the temporal region in 16 of 18 patients with a PNF in the lateral upper lid. Despite the fact that only 18 out of 34 patients with intraorbital tumour proven by adequate imaging techniques had a complete description of intraorbital tumour extension, the findings correspond to the results of an earlier analysis provided by Henderson (42), who described a preference of the space occupying lesion in cranial parts of the orbit.

Associated skeletal alterations.

Maxillary sinus. In 55% of patients with enlarged orbit, the ipslateral maxillary sinus was narrowed. Caudal dislocation of the orbital floor with associated reduced volume of the flattened maxillary sinus was already reported by Bruwer and Kierland (11). Gurland *et al*. (102) described the intraorbital neurofibroma invading the maxillary sinus via the resorbed orbital floor in 3 patients. In this study, associated skeletal alterations of the skull base were noted in 24 patients.

Mandible. The association is moderate between tumour spread in the periorbital region (total group) and alterations of the mandible (dysplasia, arrosion). Atrophic or hypotrophic regions of the bone and displacement of teeth were predominantly seen. Enlargement of the mandibular foramen was found in 4 patients. It is reasonable to assume the pressure of the PNF as the cause for bone resorption, similar to the orbital conditions. In the case of (unilateral) malformation of the bone, all but one case showed a hypoplasia. In 25 patients (59.5%), alterations in the course of the mandibular nerve were recognised that should be attributed to the genetic disposition of these patients. Patients of this study with a (peri)orbital NF1 were frequently affected in the mandible. In 17 patients, the extension of the PNF was restricted to the first and second branch of NV. Several authors noted that the PNF approximately follows the distribution of the trigeminal nerve branches (100). Riccardi (8) distinguished two types of facial PNF: 1st and 2nd or 3rd branch of the trigeminal nerve. This classification is attributable to many NF1 patients with facial PNF. However, it does not cover the variable phenotype. Koch (103) assumed that the PNF is preferentially located in the region of the 1st and/or 2nd trigeminal branch of one side. The descriptive analysis of the patients of this study revealed different combinations of unilateral trigeminal nerve affections thus providing arguments to reject Riccardi's classification. With the exception of the combination of 1st and 3rd trigeminal branch of PNF, all combinations of PNF affecting this nerve can be found. This finding is new and is based on different results (physical investigations, radiology, histology). Friedrich *et al*. (98) identified the involvement of all 3 trigeminal nerve branches in more than 50% of NF1 patients with facial PNF. Concerning 41 patients with PNF of this study, more than 50% of patients were also affected in all 3 nerve branches. Oral soft tissue tumours and dentoalveolar alterations are frequently found in patients with facial PNF (98).

Discrete malformations of the orbit in NF1 patients can be recognized without evidence for neurofibroma in the orbito-facial region (100). On the other hand, in very rare instances, NF1 diagnosis cannot be established in a case of orbital PNF with arrosion of adjacent orbital roof (86). Preoperative imaging is not adequate in all cases to distinguish between tumour and anomalies of meninx (26). Verification of the suspected diagnosis by adequate histology should forego conclusions regarding pathogenesis. However, differential diagnosis of the biopsies from the optic nerve can be inconclusive and were not recommended for differential diagnosis (26). Imaging techniques are the preferred

diagnostic methods in this region (16). A primary skeletal lesion of the orbital roof can be accompanied with neurological deficits, *e.g.* impaired mobility of the eye.

Knowledge of the literature prevents overestimation of own findings. More than 100 years ago and without the diagnostic aids of current times, Michel (7) outlined the orbito-facial manifestations of von Recklinghausen's disease in 3 categories that resemble the prevailing classification: plexiform neurofibroma (angioneuroma), fibroma molluscum and unilateral facial hyperplasia with or without buphthalmos. The facial hyperplasia might involve all facial structures and can invade into the oral cavity (7). This description needs to be completed with the diagnosis of sphenoid wing dysplasia (25), ONG (6) and associated findings of the viscerocranium (100).

Conclusion

Manifestations of NF1 in the orbit and eyelid regions often cause severe disfigurement. Different tissues can be affected: bone, eye, nerves, muscles and skin. Combinations of affected organs are frequently encountered. However, these combinations appear to be variable but not random. Indeed, the facial appearance of NF1 patients with orbito-facial manifestations is often quite characteristic. Some of the manifestations (sphenoid wing dysplasia and optic nerve glioma) are recognised to arise independently and are even main diagnostic criteria of the entity. From a facial surgeon's viewpoint, it was interesting to learn about associated tumours and malformations of this region in these disfigured patients. Hence, NF1 patients were investigated who fulfilled the inclusion criteria of a visible tumour of the orbito-facial region. This tumour had to be different from the well-defined cutaneous neurofibroma. Usually the tumour's border was ill-defined and involved more than one aesthetic unit. Thorough histological investigation revealed a plexiform neurofibroma in almost every case (in particular diffuse and invasive tumour growth pattern). Associated malformations were numerous. The independent appearance of sphenoid wing dysplasia was confirmed (8). However, deformations of other parts of the orbit were strongly associated with adjacent PNF. Exceptions from this association are obviously rare and result in a different deformation of the orbit, compared to PNF-associated ones (10). The frequent diagnosis of optic nerve glioma in association with PNF is remarkable but needs to be confirmed by other studies (17). The number of patients with reduced visual acuity is very high. This knowledge is essential for the planning of facial surgery in this region. Correlations of NF1-associated findings reveal a statistically significant association of orbito-facial PNF with extension of the tumour to the temporal region. Reference to this phenotype goes back beyond the time of defining this entity (104, 105). The preference of tumour manifestation may be the cause to delineate the orbital neurofibromatosis (90) from orbito-temporal neurofibromatosis (93). However, the correlation of tumour extension in our patients revealed that the cheek and oral cavity are also affected as frequently as the temporal region. These new findings are relevant for planning of facial surgery in NF1. Physical investigation of orbito-facial PNF patients should also be directed to oral findings.

Up to now, the current hypothesis that PNF acts as a main factor of orbital dysplasia has been based on radiological assumptions and usually lacks histological evidence. This study reveals PNF as the main component of soft tissue affecting eyelids and orbit in those cases, which show a soft tissue mass in the affected orbital region. The invasive growth of PNF into the orbit is likely to result in orbital disfigurement, in particular in patients with growth spurts of the tumour in early phases of life. The oval-shaped orbital rim, typically seen on plain skull radiographs in sagittal projections, seems to be strongly associated with the lateral extension of a PNF and independent from sphenoid wing dysplasia. This oval shape is frequently associated with facial scoliosis, indicating the large extension of the trigeminal tumour. The optic pathway glioma is a further independent finding and a main diagnostic feature of NF1. The study shows that the coincidence of PNF with an optic glioma is likely to occur more frequently than previously expected and supports previous reports that supposed this relationship (6). Several factors constitute the individual orbital dysplasia, including the growth of the invasive PNF.

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