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ORIGINAL ARTICLE

Clinical, radiological features and surgical strategies for 23 NF1 patients with intraorbital meningoencephalocele

Jianxing Niu[1,2] · Jianzhen Wang[2] · Daizhong Wang[3] · Xin He[2] · Zhongming Li[2] · Xin Li[2] · Fan Su[4] · Wang Jia[1]

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Abstract

Intraorbital meningoencephalocele is a rare manifestation of neurofibromatosis type 1 (NF1) caused by secondary changes in sphenoid dysplasia, and it seriously affects patients' vision and facial appearance. We retrospectively analyzed the clinical data of 23 patients with NF1 and intraorbital meningoencephalocele, summarized the surgical strategies employed, and evaluated their clinical efficacy in order to better understand its management in clinical practice, establish a reasonable surgical strategy, and assess prognosis. Before surgery, 22 patients had unilateral pulsatile exophthalmos, 18 patients had significant visual impairment, and 13 patients had ptosis associated with an orbital plexiform neurofibroma (PNF). All 23 patients underwent microsurgical craniotomy with skull base reconstruction using a soft titanium mesh. One month after surgery, the degree of exophthalmos in the 22 (95.65%) patients was significantly reduced compared with before surgery ($P < 0.001$), and ocular pulsation had subsided. The visual acuity did not decrease significantly ($P = 0.298$) compared with before surgery. Eleven (47.83%) patients received phase-II eyelid PNF resection and/or oculoplastic surgery, and the degree of ptosis was significantly reduced ($P < 0.001$). There was no recurrence of pulsatile exophthalmos, displacement of titanium mesh, decreased visual acuity, or increased degree of ptosis noted during follow-up. The best strategy is to reconstruct the skull base under microscopy to relieve pulsating exophthalmos and preserve existing visual function. In cases of ptosis caused by an eyelid PNF, surgical resection should be performed as soon as possible to remove the tumor, and/or oculoplastic surgery should be performed to improve the cosmetic outcome.

Keywords Neurofibromatosis type 1 · Intraorbital meningoencephalocele · Sphenoid dysplasia · Pulsatile exophthalmos · Plexiform neurofibroma

Introduction

NF1 is an autosomal dominant genetic disease caused by mutation of the NF1 gene on chromosome 17q11.2. The population incidence is 1:2500–3500 [1–3]. NF1 has a variety of clinical manifestations, which are classified as neoplastic and non-neoplastic phenotypes. The neoplastic phenotype is mainly characterized by neurofibromatosis, malignant peripheral nerve sheath tumors, or other tumors, whereas the non-neoplastic phenotype is characterized by abnormal skin pigmentation (such as café-au-lait spots, freckle-like pigmentation, and pigmented iris hamartomas), learning disabilities, or bone abnormalities [4–6]. Studies have shown that changes in the expression of mutant or wild-type NF1 alleles play an important role in the clinical phenotypes [1, 7–9].

According to the literature, 3–11% of patients with NF1 have sphenoid dysplasia, and imaging in these patients generally reveals oval enlargement of the orbital margin, posterior orbital wall defects, and anteroposterior enlargement of the middle cranial fossa [10–13]. However, not all sphenoid dysplasia results in intraorbital meningoencephalocele [12, 13]. The frontal or temporal lobes and even the brain tissue can enter the orbital area through a large skull base defect and cause intraorbital meningoencephalocele. Pulsation of the

Jianxing Niu and Jianzhen Wang contributed equally to this work.

✉ Wang Jia
jwttyy@126.com

[1] Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China

[2] Department of Neurosurgery, The Third Medical Center of Chinese PLA General Hospital, Beijing 100039, China

[3] Department of Pathology, Taihe Hospital, Hubei University of Medicine, Shiyan 442000, Hubei, China

[4] Institute of Orbital Diseases of The Third Medical Center of Chinese PLA General Hospital, Beijing 100039, China

brain tissue can result in pulsating exophthalmos, eyeball displacement, optic nerve compression, increased axial length, and visual loss [14, 15]. If an eyelid PNF is present, it may cause ptosis. As the eyelid PNF grows, the skin of the eyelids can sag to the cheeks, causing severe facial deformity [16–18].

NF1 with intraorbital meningoencephalocele is rare and has only been described in case reports or small studies. At present, the lack of systematic research on the clinical features and surgical strategies for this condition may affect therapeutic outcomes. In this study, we retrospectively analyzed the clinical features of 23 patients with NF1 and intraorbital meningoencephalocele, summarized the surgical strategies employed, and evaluated the surgical outcomes in order to provide evidence for early diagnosis, establish a reasonable surgical strategy, and assess prognosis in these patients.

Materials and methods

Patients

This study was approved by the Ethics Committee of The Third Medical Center of Chinese PLA General Hospital. Written informed consent was obtained from each patient or their legal relatives. A total of 23 patients with NF1 and intraorbital meningoencephalocele who underwent surgical treatment in our hospital from January 2004 to December 2015 were included in this study. The inclusion criteria were as follows: (1) the clinical diagnostic criteria for NF1 [19] were met; (2) intraorbital meningoencephalocele was confirmed by imaging; (3) patients had no prior history of skull base reconstruction; and (4) patients had complete clinical data (detailed medical history, physical examination, preoperative and postoperative imaging data, and preoperative and postoperative ophthalmic examination). The exclusion criteria were as follows: (1) patients with exophthalmos caused by non-NF1-related tumors; (2) patients without confirmed diagnosis of intraorbital meningoencephalocele; and (3) patients with non-NF1-related skull base or orbital deformity.

Imaging

All patients underwent preoperative and postoperative head CT scan with 3D skull reconstruction. The three-dimensional reconstructed images of the head CT were measured on the imaging system software, and the maximum diameter of the defect was recorded. Diagnosis of intraorbital meningoencephalocele was confirmed by the head CT and brain MRI. All patients underwent preoperative and postoperative MRI on a MAGNETOM Trio Tim 3.0 T (Siemens, Erlangen, Germany). Patients simultaneously underwent gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA)–enhanced scanning, in which neurofibromas present homogeneous enhancement with clear boundaries. Tumor locations were determined based on MRI data. The presence of neurofibromas identified on MRI scan was confirmed by pathological examination.

Ophthalmologic examination

Evaluation of ocular impairment: all patients underwent preoperative and postoperative ophthalmologic examination, including assessment of visual acuity, eye pressure and intraocular pressure, diopter measurement, and slit lamp examination of the fundus. Patients with refractive interstitial pathology or fundal pathology that might affect vision were excluded. The patients' best-corrected visual acuity (BCVA) was measured using an international standard eye chart. The degree of exophthalmos was measured using a Hertel exophthalmometer. The degree of upper ptosis was quantified using the internationally accepted Marginal Reflex Distance One (MRD1) value, i.e., the distance between the center of the pupillary light reflex and the upper eyelid margin.

Surgical procedure

Preoperative routine examination showed that all patients could receive general anesthesia, who were free from cardiopulmonary diseases and hemostasis disorders. All patients underwent microsurgical craniotomy with skull base reconstruction using a soft titanium mesh under microscopic visualization (Carl Zeiss GmbH, Oberkochen, Germany). Surgical approach should take into account the requirements of reconstruction of the skull base and resection of PNF in the adjacent region.

Follow-up

During follow-up, patients underwent outpatient CT scans with three-dimensional skull reconstruction, eye examinations, and telephone surveys. During follow-up examinations and imaging, the presence or absence of the following factors was assessed: recurrence of meningoencephalocele, resorption and displacement of the titanium mesh, decreased visual acuity, recurrence of exophthalmos, eye movement disorders, and worsening ptosis.

Statistical analysis

Statistical analyses were performed using SPSS version 22.0 software for Windows (IBM Corp, Armonk, NY). Quantitative data with a normal distribution are expressed as the mean ± standard deviation. Quantitative data without a normal distribution are expressed as the median and interquartile range. Independent sample and paired sample *t* tests were used to compare the means between groups for normally

distributed data. The Mann-Whitney *U* test was used to compare the means for data without a normal distribution. The Pearson correlation coefficient was determined to verify the correlation between the duration of the disease and the diameter of the skull base defect. Categorical variables with small samples were compared using the Fisher exact probability test. All statistical analyses used two-tailed tests, and values of $P < 0.05$ were considered statistically significant.

Results

Patient characteristics

Twenty-three patients were diagnosed with NF1 complicated by intraorbital meningoencephalocele before surgery via clinical and imaging examinations. These patients accounted for 9.22% of the cases of orbital and cranial disease with NF1 (212 cases) treated in our hospital during the study period. The clinical features of the 23 patients with NF1 who met the diagnostic criteria for NF1 are shown in Table 1.

Clinical data are summarized in Tables 2 and 3. A total of 22 (95.7%) patients had sought medical advice in other hospitals. Fifteen patients had been diagnosed with NF1 before admission, and 5 (21.7%) patients had been diagnosed with intraorbital meningoencephalocele in another hospital. Eight (34.8%) patients had a history of surgery in NF1-affected sites.

Table 1 Characteristics consistent with NF1 diagnosis criteria ($n = 23$)

NF1 diagnosis criteria	Frequency (%)
Family history	13 (56.5)
Pigment anomaly	
Café-au-lait spots on the skin	20 (90.0)
Axillary or inguinal freckles	17 (74.0)
Iris hamartomas	9 (39.1)
Osteopathy	
Sphenoid dysplasia	23 (100)
Calvarial bone dysplasia	13 (56.5)
Pseudarthrosis of the tibia	1 (4.3)
Neoplastic phenotype	
Somatic neurofibroma	18 (78.3)
Orbital and cranial PNF	19 (82.6)
Optic pathway glioma	0
Meningioma	1 (4.3)
Congenital heart disease	
Ventricular septal defect	1 (4.3)
Patent ductus arteriosus	1(4.3%)

NF1, neurofibromatosis type 1; *n*, number; *PNF*, plexiform neurofibroma

Imaging features

All patients underwent preoperative (Fig. 1d–f) and postoperative (Fig. 1g–i) CT with three-dimensional skull reconstruction. The images showed an absence of the greater wing of the sphenoid bone, elevation of the lesser wing of the sphenoid bone, and partial or complete absence of the anterior clinoid process, resulting in obvious defects of the anterior or middle skull base. The meninges and brain tissue entered the eye socket through the skull base defect. Protrusion and downward displacement of the eyeball were present in 22 patients. One patient had slight invagination of the eyeball due to a periorbital PNF (anterior orbit), which can prevent displacement of orbital contents. This patient also had an abnormal sphenoid bone that caused anterior and posterior enlargement of the eye socket. All intraorbital meningoencephaloceles were unilateral: on the left in 11 patients and on the right side in 12 patients. The maximum diameter of the skull base defect ranged from 3.8 to 6.1 cm, with an average of 4.9 ± 0.7 cm. Seventeen (73.9%) patients had arachnoid cysts in the temporal lobe of the affected side, and 6 (26.1%) patients had significantly enlarged subarachnoid space in the temporal lobe.

All patients underwent preoperative and postoperative MRI on a MAGNETOM Trio Tim 3.0 T (Siemens, Erlangen, Germany). These scans showed a simple skull base defect in 4 patients, and a skull base defect with a cranio-orbital PNF in 19 patients (82.6%). Figure 1 depicts one representative case.

Surgical findings and postoperative outcomes

A unilateral frontotemporal approach was used in 17 patients and a coronal frontotemporal approach was used in 6 patients. Seventeen patients underwent only skull base reconstruction. Six (26.1%) patients underwent resection of either a posterior orbital PNF (3 patients) or a cranio-orbital PNF (3 patients). The PNF was located in the area of the skull base defect in these only 6 patients. Sixteen patients underwent skull base reconstruction via an incision of the dura mater, and skull base reconstruction with separation of the orbital content from the meninges was performed in 7 patients. Eleven (47.8%) patients underwent resection of an eyelid tumor and/or oculoplastic surgery at 3 months after the reconstruction of the skull base. Five patients of which underwent anterior orbit tumor resection concurrently, and the pathological examination after surgery confirmed the diagnosis of PNF.

All surgeries were performed by the same team. None of the patients had serious complications after surgery. In 22 patients with preoperative pulsatile exophthalmos, the ocular protrusions were significantly improved after reconstruction of the skull base, and the pulsation symptoms subsided. In one patient with preoperative ocular invagination who underwent skull base reconstruction, eyeball invagination remained

Table 2 Clinical, radiological features and operative method for 23 cases of NF1 with intraorbital meningoencephalocele

Case no.	Age (years), sex	Course of disease (years)	Skull base defect	Side	Size (cm)	Pulsating exophthalmos	Arachnoid cyst	Location of PNF	Surgical strategies		Periop outcomes
									First	Second	
1	54, M	54	Yes	Rt	5.8	Yes	Yes	Scalp	A		Improved
2	20, F	15	Yes	Lt	5.1	Yes	Yes	Eyelid, scalp	A	B + E	Improved
3	17, F	10	Yes	Lt	5.9	Yes	Yes	Scalp, posterior orbit	A + C		Improved
4	17, F	14	Yes	Lt	5.0	Yes	Yes	Scalp, eyelid	A	B + E	Improved
5	17, M	17	Yes	Rt	5.8	Yes	NO	Scalp, eyelid, cranio-orbital	A + D	B + E	Improved
6	21, F	21	Yes	Lt	5.3	Yes	Yes	Scalp,	A		Improved
7	19, M	19	Yes	Lt	5.1	Yes	Yes	Eyelid, anterior orbital	A	B + C + E	Improved
8	23, M	23	Yes	Rt	4.5	Yes	Yes	None	A		Improved
9	14, F	14	Yes	Rt	4.2	Yes	Yes	Scalp	A		Improved
10	13, F	10	Yes	Lt	4.0	Yes	Yes	Scalp, eyelid	A	B + E	Improved
11	29, M	10	Yes	Rt	4.5	No	No	Eyelid, anterior orbital	A	B + C + E	Improved
12	25, M	20	Yes	Rt	5.0	Yes	No	Eyelid, anterior orbital	A	B + C	Improved
13	18, M	18	Yes	Rt	6.1	Yes	No	Scalp, eyelid, cranio-orbital	A + D		Improved
14	20, M	20	Yes	Rt	5.0	Yes	Yes	Eyelid, anterior orbital	A	B + C + E	Improved
15	42, F	10	Yes	Lt	4.9	Yes	Yes	None	A		Improved
16	36, M	16	Yes	Rt	5.2	Yes	Yes	Scalp	A		Improved
17	72, F	72	Yes	Lt	5.9	Yes	Yes	Eyelid, posterior orbital	A + C		Improved
18	26, F	24	Yes	Rt	4.4	Yes	No	Scalp, eyelid, anterior orbital	A	B + C	Improved
19	14, F	2	Yes	Lt	4.0	Yes	No	Eyelid,	A		Improved
20	10, M	10	Yes	Lt	5.0	Yes	Yes	Scalp, eyelid, cranio-orbital	A + D	B + E	Improved
21	7, M	5	Yes	Rt	4.2	Yes	Yes	Slalp, eyelid, posterior orbital	A + C	B + E	Improved
22	1, F	1	Yes	Rt	3.8	Yes	Yes	None	A		Improved
23	9, F	4	Yes	Rt	4.7	Yes	Yes	None	A		Improved

Rt, right; *Lt*, left; *PNF*, plexiform neurofibroma; *A*, reconstruction of skull base defect; *B*, resection of eyelid PNF; *C*, resection of orbital PNF; *D*, Resection of cranio-orbital PNF; *E*, oculoplastic surgery

unchanged after surgery. This patient subsequently underwent resection of eyelid and orbital tumors and oculoplastic surgery and achieved a significant improvement in eyeball invagination. In 22 (95.65%) patients, the degree of exophthalmos (the difference between the affected side and the contralateral eye) was significantly reduced after skull base surgery compared with before surgery ($P < 0.001$). In 17 patients, the visual acuity was not significantly changed or was slightly improved 1 month after surgery. The visual acuity in 2 patients was slightly lower than before surgery. There was no significant difference between preoperative visual acuity and postoperative visual acuity ($P = 0.298$). Of the 11 patients with ptosis who underwent the second phase of treatment, the degree of ptosis as quantified by the MRD1 value was significantly reduced 1 month after surgery compared with before surgery ($P < 0.001$). Ocular and facial preoperative and postoperative features of another representative case are shown in Fig. 2.

Comparison between adult and pediatric patients

Patients were divided into a pediatric group (≤ 14 years old) and an adult group (> 14 years old) according to their age. Table 4 shows the comparison between adult and pediatric patients. The duration of disease (22.7 ± 8.2 months) in the adult group was significantly longer than that in the pediatric group (6.6 ± 4.8 months) ($P < 0.001$). The follow-up period in the adult group (52.6 ± 35.3) was significantly longer than that in the pediatric group (22.0 ± 16.8) ($P = 0.024$). The range of skull base defects in the adult group (5.2 ± 0.5 cm) was significantly higher than that in the pediatric group (4.3 ± 0.4 cm) ($P = 0.001$). There was no significant difference in gender, lesion location, or the number of surgeries between the two groups ($P = 0.371$, $P = 0.667$, $P = 0.067$).

Table 3 Clinical and demographic characteristics of 23 patients with NF1 with intraorbital meningoencephalocele

Variable	Value
Age (years)	22.8 ± 15.4
Sex	
Male	11 (47.8%)
Female	12 (52.2%)
Duration from onset to admission (years)	17.8 ± 15.9
Prehospital diagnose	
NF1	15 (65.2%)
Intraorbital meningoencephalocele	5 (21.7%)
Initial manifestation	
Pulsating exophthalmos	22 (95.7%)
Visual impairment (blind)	18 (78.3%)(3)
Ptosis	13 (56.5%)
Ocular movement disorder	6 (26.1%)
Eye pain	6 (26.1%)
Intracranial hypertension	1 (4.3%)
Enophthalmos	1 (4.3%)
Sides affected	
Left	11 (47.8%)
Right	12 (52.2%)
Sizes of defects (cm)	4.9 ± 0.7
Arachnoid cyst	
Yes	17 (73.9%)
No	6 (26.1%)
Location of PNF	
Scalp	13 (56.5%)
Eyelid	13 (56.5%)
Anterior orbit	5 (21.7%)
Posterior orbit	3 (13.4%)
Cranio-orbit	3 (13.4%)
Surgical strategies	
One	12 (52.2%)
Two	11 (47.8%)
Follow-up (month)	42.4 ± 33.3
Long-term outcome ($n = 18$)	
Recurrence of exophthalmos	0
Recurrence of visual impairment	0
Recurrence of ptosis	0

Long-term follow-up data were available in 18 patients after surgery

NF1, neurofibromatosis type 1; *PNF*, plexiform neurofibroma; *n*, number

Discussion

In this study, we found that most of the patients developed progressive pulsating exophthalmos soon after birth and had decreased visual acuity, which suggests that the disease may be related to congenital malformation [20]. In addition, we noticed that more than half of the patients in this study did not undergo meningoencephalocele-specific surgery, which could prevent exophthalmos and loss of visual acuity. This likely resulted in reduced visual acuity or even blindness in patients. The reason why patients did not undergo surgery may be that the incidence of NF1 with meningoencephalocele is low, and thus, clinicians may have an insufficient understanding of the disease and struggle to implement timely and effective treatment.

The pathogenesis of NF1 with intraorbital meningoencephalocele remains unclear and may be related to sphenoid dysplasia caused by congenital ectoderm and mesoderm dysplasia [20] and cranial abnormalities caused by the interaction of PNFs and the sphenoid bone [12, 13]. Elefteriou suggested that sphenoid dysplasia is unique to NF1 and is due to the defects in bone primordial cells, leading to skeletal system lesions in the sphenoid bone, long bones, and vertebral bodies in patients with NF1 [21]. Craniofacial measurement of 101 patients with NF1 revealed a shorter sphenoid bone in patients with NF1, consistent with intrinsic bone cell defects. This makes the fragile sphenoid bone more susceptible to secondary damage, leading to skull abnormalities [10]. Although numerous studies have reported that sphenoid dysplasia is probably caused by invasion and destruction of PNFs in the adjacent area, only 6 (26.1%) patients in this group had a PNF in the skull base defect area. This is not enough evidence to conclude that skull base abnormalities are caused by PNF damage to adjacent bones. Our results support the idea that NF1-related bone dysplasia is the intrinsic basis of skull base defects. The pulsating impact of brain tissue on abnormally weak bone and the destruction of peripheral bone by PNF may be additional factors in the development of skull base defects [10, 12, 13].

NF1 often causes complex orbital and facial malformations due to sphenoid dysplasia and PNF of orbit and eyelid, and the location of individual lesions varies greatly. It is difficult to solve all problems at the same time with any one surgical approach and in a single procedure. In addition, the timing of surgery plays an important role in surgical outcomes. The therapeutic outcomes depend on the severity of the lesion in the eye and the appearance of the face [22], and a timely and reasonable surgical strategy is necessary to guarantee the best effect. In this study, the diameter of the skull base defect in the adult group was significantly larger than that in the pediatric group, and the diameter of the skull base defect was positively correlated with the duration of the disease. As the disease progresses, the range of the skull base defect increases, with irreversible development of pulsatile exophthalmos and a progressive decline in visual acuity. Early reconstruction of the bony barrier between the meningeal tissue and the eye socket is necessary to eliminate the pulsating impact on the eyeball [23].

With the development of neurosurgical techniques, craniotomy with reconstruction of the skull base has become a standardized surgical method that can be carried out with

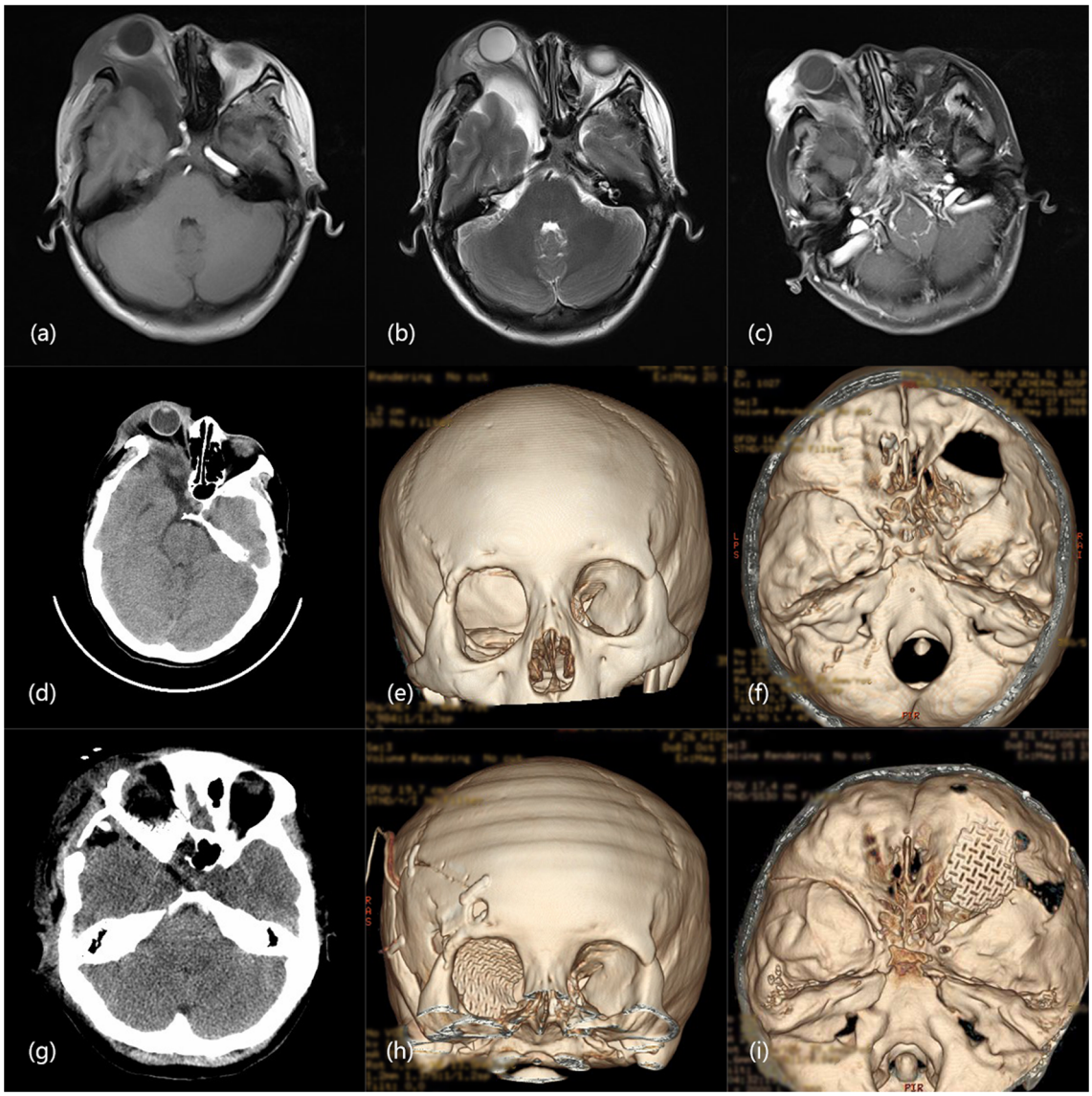

Fig. 1 Imaging features (preoperation and postoperation) of case 18: **a** (T1-weighted MRI image), **b** (T2-weighted MRI image) showing the significantly widened subarachnoid space in the right temporal pole, which enters in the right eye socket to compress the extraocular muscles, and the right eyeball obviously protruding outward; **c** Enhanced MRI scan showing significant enhancement of plexiform lesions in the right eyelid and orbit; **d** Plain CT scan of the head showing the absence of the right greater wing of the sphenoid bone; **e** Anteroposterior view of the three-dimensional skull reconstruction of the head CT showing oval enlargement of the right orbit and obvious defects of the posterior orbital wall; **f** Three-dimensional skull base reconstruction of the head CT showing the absence of the greater wing of the right sphenoid bone and obvious defect of the skull base; **g** Plain CT scan of the head after skull base reconstruction showing good positioning of the right titanium mesh and reduced herniated intraorbital meningeal tissue; **h**, **i** Three-dimensional reconstruction of the skull CT after skull base reconstruction showing good positioning of the titanium mesh with a satisfactory shape and incomplete coverage of the titanium mesh in the repaired region of the anterior clinoid process and the superior orbital fissure to avoid compressing the nerves and blood vessels

intraoperative navigation and 3D printing technology. However, we believe that we still need to pay attention to certain details related to the surgery in order to achieve the best surgical results. First, the superior orbital fissure disappears in most patients, and our attention should be paid to identify and protect the nerve structures, which has been displaced under microscopic visualization. Second, we recommend using epidural dissection, which can avoid exposure and damage to the brain tissue and reduce the possibility of epidural effusion, intracranial infection, and cerebrospinal fluid leakage. However, when there is a huge arachnoid cyst in the skull base or when there is also an intracranial PNF, it is still necessary to perform dissection after dural splitting decompression. Third, we recommend using a soft titanium mesh during the operation, as it can be re-shaped according to actual need. Preoperative three-dimensional shaping is closer to the actual shape of the skull base, but it is necessary to reserve sufficient room to tailor the mesh according to the

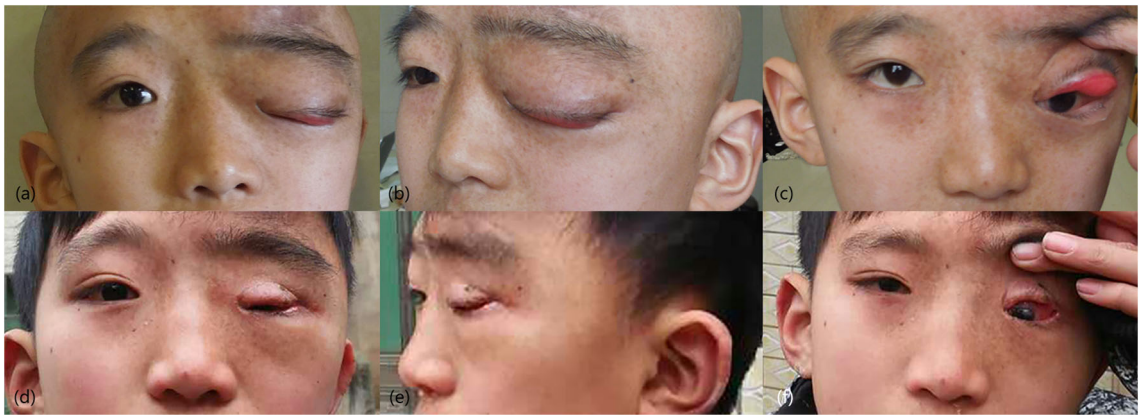

Fig. 2 Ocular and facial features of case 20: **a**, **b** Preoperative anteroposterior and oblique views showing hypertrophy and ptosis of the left upper eyelid; **c** Anterior protrusion and anteroinferior displacement of the left eyeball; **d**, **e** Postoperative anteroposterior and oblique views showing a significant improvement in ptosis of the left upper eyelid; **f** Significant reduction in the left eyeball protrusion

actual need during operation. Fourth, it is necessary to fully expose the edge of the skull base defect before fixation. In fact, it is not necessary to cover the defect aspect, and a sufficiently large area should be prepared to avoid compression of the skull base nerves. Titanium mesh displacement may be related to poor fixation or the lack of a suitable position for fixation [22, 24–29]. We prefer to fix the titanium mesh with screws on the skull base lateral to the defect. Some researchers used a reverse-shaped titanium mesh technique that did not require fixation with screws in 4 patients, and no titanium mesh displacement occurred [27]. However, using the pressure of the brain tissue to fix the titanium mesh may be unstable, as the pulsating impact of the brain tissue may cause displacement of the titanium mesh. In this study, pulsatile exophthalmos subsided after skull base reconstruction in 22 patients, without a significant decrease in visual acuity. In 18 patients who underwent follow-up examinations, no displacement of the titanium mesh and no recurrence of pulsating exophthalmos were reported during follow-up.

Reconstruction of the skull base cures the pulsatile exophthalmos caused by meningoencephalocele and prevents deterioration of existing visual acuity. However, patients with NF1

Table 4 Comparison of the features of cases stratified by patient age

Variable	> 14 years ($n = 16$)	≤ 14 years ($n = 7$)	P value
Age	28.5 ± 15.6	9.7 ± 4.7	0.005
Gender			0.371
Male	9 (9/16)	2 (2/7)	
Female	7 (7/16)	5 (5/7)	
Course of symptoms (years)	(22.7, 8.2)	6.6 ± 4.8	< 0.001
Positive family history of NF1			0.405
Yes	8 (8/16)	5 (5/7)	
No	8 (8/16)	2 (2/7)	
Sides affected			0.667
Left	7 (7/16)	4 (4/7)	
Right	9 (9/16)	3 (3/7)	
Sizes of defects (cm)	5.2 ± 0.5	4.3 ± 0.4	0.001
Arachnoid cyst			0.621
Yes	11 (11/16)	6 (6/7)	
No	5 (5/16)	1 (1/7)	
Surgical strategies			0.667
One	8 (8/16)	4 (4/7)	
Two	8 (8/16)	3 (3/7)	
Follow-up (month) ($n = 18$)	52.6 ± 35.3	22.0 ± 16.8	0.024

P values were corrected for multiple testing by controlling the false discovery rate of 5%

n, number; *NF1*, neurofibromatosis type 1

and intraorbital meningoencephalocele have multi-site lesions that can be found in both cranial and orbital regions. Because the sphenoid bone abnormality can also cause orbital malformation and orbital volume changes, it is difficult to completely achieve the ideal position of the eyeball in the eye socket by skull reconstruction alone. Moreover, patients with NF1 often have orbital PNFs. Because of the rapid growth of children's facial PNF lesions, ptosis may cause deprivation amblyopia and refractive amblyopia in children. Therefore, it is necessary to monitor the development of PNFs to determine when surgical intervention is needed [30, 31]. Adult PNFs are relatively stable, and surgical treatment can achieve reliable results [32]. In this study, ptosis was significantly improved 1 month after surgery, and the patients also had better facial appearance than before surgery. Because eyelid PNFs invade the orbital muscles, ptosis is significantly improved after surgery, but the function of the levator palpebrae superioris muscle is difficult to restore. In the 11 patients (8 adults and 3 children) who underwent phase II surgery, neither recurrence of the PNF in the eyelid and orbit nor aggravation of ptosis was reported during follow-up. Since the follow-up period was too short (8–12 months) in the 3 children, the follow-up data cannot be used to explain the difference in outcomes between children and adults.

Conclusions

In conclusion, we analyzed the clinical features, radiological features, and surgical strategies employed for 23 patients with NF1 complicated by intraorbital meningoencephalocele and evaluated the surgical efficacy based on ocular characteristics. This study may improve clinical practice by helping surgeons implement timely and reasonable surgical interventions to improve patient symptoms and facial appearance.

Compliance with ethical standards

This study was approved by the Ethics Committee of The Third Medical Center of Chinese PLA General Hospital. Written informed consent was obtained from each patient or their legal relatives.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. McClatchey AI (2007) Neurofibromatosis. Annu Rev Pathol 2: 191–216. https://doi.org/10.1146/annurev.pathol.2.010506.091940
2. Lammert M, Friedman JM, Kluwe L, Mautner VF (2005) Prevalence of neurofibromatosis 1 in German children at elementary school enrollment. Arch Dermatol 141:71–74. https://doi.org/10.1001/archderm.141.1.71
3. Evans DG, Howard E, Giblin C, Clancy T, Spencer H, Huson SM, Lallo F (2010) Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. Am J Med Genet A 152A:327–332. https://doi.org/10.1002/ajmg.a.33139
4. Hirbe AC, Gutmann DH (2014) Neurofibromatosis type 1: a multidisciplinary approach care. Lancet Neurol 13:834–843. https://doi.org/10.1016/S1474-4422(14)70063-8
5. Brems H, Beert E, de Ravel T, Legius E (2009) Mechanisms in the pathogenesis of malignant tumours in neurofibromatosis type 1. Lancet Oncol 10:508–515. https://doi.org/10.1016/S1470-2045(09)70033-6
6. Williams VC, Lucas J, Babcock MA, Gutmann DH, Korf B, Maria BL (2009) Neurofibromatosis type 1 revisited. Pediatrics 123:124–133. https://doi.org/10.1542/peds.2007-3204
7. Zhu Y, Ghosh P, Charnay P, Burns DK, Parada LF (2002) Neurofibromas in NF1: Schwann cell origin and role of tumor environment. Science 296:920–922. https://doi.org/10.1126/science.1068452
8. Carey JC (2017) Phenotype analysis of congenital and neurodevelopmental disorders in the next generation sequencing era. Am J Med Genet C: Semin Med Genet 175:320–328. https://doi.org/10.1002/ajmg.c.31568
9. Diggs-Andrews KA, Gutmann DH (2013) Modeling cognitive dysfunction in neurofibromatosis-1. Trends Neurosci 36:237–247. https://doi.org/10.1016/j.tins.2012.12.002
10. Cung W, Freedman LA, Khan NE et al (2015) Cephalometry in adults and children with neurofibromatosis type 1: implications for the pathogenesis of sphenoid wing dysplasia and the"NF1 facies". Eur J Med Genet 58:584–590. https://doi.org/10.1016/j.ejmg.2015.09.001
11. Arrington DK, Danehy AR, Peleggi A, Proctor MR, Irons MB, Ullrich NJ (2013) Calvarial defects and skeletal dysplasia in patients with neurofibromatosis type 1. J Neurosurg Pediatr 11:410–416. https://doi.org/10.3171/2013.1.PEDS12409
12. Jacquemin C, Bosley TM, Svedberg H (2003) Orbit deformities in craniofacial neurofibromatosis type 1. AJNR Am J Neuroradiol 24: 1678–1682
13. Jacquemin C, Bosley TM, Liu D, Svedberg H, Buhaliqa A (2002) Reassessment of sphenoid dysplasia associated with neurofibromatosis type 1. AJNR Am J Neuroradiol 23:644–648
14. de Vries J, Freihofer HP, Menovsky T, Cruysberg JR (1998) Successful surgical repair of progressive exophthalmos caused by a meningocele in a patient with neurofibromatosis type 1. J Neurosurg 89:1032–1035. https://doi.org/10.3171/jns.1998.89.6.1032
15. Macfarlane R, Levin AV, Weksberg R, Blaser S, Rutka JT (1995) Absence of the greater sphenoid wing in neurofibromatosis type 1: congenital or acquired: case report. Neurosurgery 37:129–133
16. Wise JB, Patel SG, Shah JP (2002) Management issues in massive pediatric facial plexiform neurofibroma with neurofibromatosis type 1. Head Neck 24:207–211
17. Ransom ER, Yoon C, Manolidis S (2006) Single stage near total resection of massive pediatric head and neck plexiform neurofibromas. Int J Pediatr Otorhinolaryngol 70:1055–1061. https://doi.org/10.1016/j.ijporl.2005.10.025
18. Fadda MT, Giustini SS, Verdino GG, Bartoli DD, Mustazza MC, Iannetti GG, Calvieri SS (2007) Role of maxillofacial surgery in patients with Neurofibromatosis type I. J Craniofac Surg 18:489–496. https://doi.org/10.1097/01.scs.0000249349.59096.06
19. Gutmann DH, Aylsworth A, Carey JC, Korf B, Marks J, Pyeritz RE, Rubenstein A, Viskochil D (1997) The diagnostic evaluation and multidisciplinary management of neurofibromatosis 1 and neurofibromatosis 2. JAMA 278:51–57
20. Hunt JC, Pugh D (1961) Skeletal lesions in neurofibromatosis. Radiology 76:1–19
21. Alwan S, Armstrong L, Joe H, Birch PH, Szudek J, Friedman JM (2007) Associations of osseous abnormalities in neurofibromatosis

1. Am J Med Genet A 143A:1326–1333. https://doi.org/10.1002/ajmg.a.31754
22. Lotfy M, Xu R, McGirt M, Sakr S, Ayoub B, Bydon A (2010) Reconstruction of skull base defects in sphenoid wing dysplasia associated with neurofibromatosis I with titanium mesh. Clin Neurol Neurosurg 112:909–914. https://doi.org/10.1016/j.clineuro.2010.07.007
23. Dandy WE (1929) An operative treatment for certain cases of meningocele (orencephalocele) into the orbit. Arch Ophthalmol 2:123–132
24. Friedrich RE, Heiland M, Kehler U, Schmelzle R (2003) Reconstruction of sphenoid wing dysplasia with pulsating exophthalmos in a case of neurofibromatosis type 1 supported by intraoperative navigation using a new skull reference system. Skull Base 13:211–217. https://doi.org/10.1055/s-2004-817697
25. Dale EL, Strait TA, Sargent LA (2014) Orbital reconstruction for pulsatile exophthalmos secondary to sphenoid wing dysplasia. Ann Plast Surg 72:S107–S111. https://doi.org/10.1097/SAP.0000000000000090
26. Snyder BJ, Hanieh A, Trott JA, David DJ (1998) Transcranial correction of orbital neurofibromatosis. Plast Reconstr Surg 102:633–642
27. Concezio DR, Amir S, Gianpiero T, Luca M, Mario G (2017) Sphenoid dysplasia in neurofibromatosis type 1: a new technique for repair. Childs Nerv Syst 33:983–986. https://doi.org/10.1007/s00381-017-3408-z
28. Niddam J, Bosc R, TSuffee TM, Le Guerinel C, Wolkenstein P, Meningaud JP (2014) Treatment of sphenoid dysplasia with a titanium-reinforced porous polyethylene implant in orbitofrontal neurofibroma: report of three cases. J Craniomaxillofac Surg 42:1937–1941. https://doi.org/10.1016/j.jcms.2014.08.004
29. Wu C-T, Lee S-T, Chen J-F, Lin K-L, Yen S-H (2008) Computer-aided design for three-dimensional titanium mesh used for repairing skull base bone defect in pediatric neurofibromatosis type 1. Pediatr Neurosurg 44:133–139. https://doi.org/10.1159/000113116
30. Avery RA, Dombi E, Hutcheson KA, Acosta MT, Baldwin AM, Madigan WP, Gillespie A, FitzGibbon EJ, Packer RJ, Widemann BC (2013) Visual outcomes in children with neurofibromatosis type 1 and orbitotemporal plexiform neurofibromas. Am J Ophthalmol 155(6):1089–1094. https://doi.org/10.1016/j.ajo.2013.01.011
31. Avery RA, Katowitz JA, Fisher MJ, Heidary G, Dombi E, Packer RJ, Widemann BC, Hutcheson KA, Madigan WP, Listernick R, Liu GT, Berland JE, FitzGibbon EJ, Korf BR (2017) Orbital/periorbital plexiform neurofibromas in children with neurofibromatosis type 1: multidisciplinary recommendations for care. Ophthalmology 124:123–132. https://doi.org/10.1016/j.ophtha.2016.09.020
32. Lee V, Ragge NK, Collin JR (2004) Orbitotemporal neurofibromatosis. Clinical features and surgical management. Ophthalmology 111:382–388. https://doi.org/10.1016/j.ophtha.2003.05.029