ARTICLE ORIGINAL

The eyelid plexiform neurofibroma in neurofibromatosis type 1: report of 10 cases and literature review

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Keywords
Neurofibromatosis type 1, Plexiform neurofibromatosis, Ptosis, Astigmatism, Resection.

Abstract

Purpose. To describe the clinical and therapeutic features of plexiform neurofibromas in patients with neurofibromatosis type 1.
Methods. This was a retrospective study over a period of 10 years including 10 patients with von Recklinghausen's disease and having an eyelid plexiform neurofibroma. All patients were treated in the department of Ophthalmology of Farhat Hached University Hospital in Sousse, Tunisia.
Results. The age of our patients at diagnosis ranged from 18 months to 42 years. Six women and 4 men were involved. The eyelid plexiform neurofibroma was unilateral in all cases. This lesion appeared at birth in 3 patients and between 3 to 5 years in 7 patients. The upper eyelid was the site of the lesion in 100% of cases. A mechanical ptosis was present in 9 patients. Various eye lesions were: Lisch nodules (8 patients), facial hemihypertrophy (5 patients), external canthal dystrophy (2 patients), and one case for each of the following injuries: ectropion of the lower lid entropion of the lower lid, congenital glaucoma and hypertrichosis brow. Seven patients underwent surgical treatment: 4 had received tumor resection associated with the treatment of ptosis and the others had only ptosis surgery. Resection of plexiform neurofibroma was followed by an anatomic success in 100%. The surgery of ptosis was followed by a good postoperative outcome in all patients.
Conclusion. The plexiform neurofibroma is a suggestive sign of neurorofibromatosis type 1. The polymorphism of its clinical associations, as well as the risk of their malignant transformation means that the knowledge of this disease is important for any practitioner.

Introduction

Von Recklinghausen's disease (VRD) or neurofibromatosis type 1 (NF1) is the most frequent of phacomatosis [1]. It is an autosomal dominant transmitted disorder with a high penetrance and a variable expressivity. Among oculopalpebral manifestations, the plexiform neurofibroma (PNF) is an important diagnosis criteria. Its frequency ranges from 30% to 39 % [2]. It is a benign nervous tumor in which neurofibromas arise from multiple nerves as bulging and deforming masses involving also connective tissue and skin folds. There are two types of PNF: the diffuse PNF and the nodular PNF. Surgical management is the key treatment. Lesions can have a persistent aesthetic and psychological impact which leads to consultation and surgical management.
The aim of our study was to describe the clinical and therapeutic features of plexiform neurofibromas in patients with neurofibromatosis type 1.

Methods

This is a retrospective study over a period of 10 years interesting a series of 10 patients with von Recklinghausen's disease and having an eyelid plexiform neurofibroma. All were hospitalized in the department of Ophthalmology of Farhat Hached Hospital in Sousse Tunisia for therapeutic management.
Diagnosis criteria for this disease were given by the National Institutes of Health in 1987.
All the patients were examined by ophthalmologist, dermatologist and neurologist. Visual field test was conducted for one patient to rule out glaucoma.
Orbital radiography was performed in 5 cases. All patients underwent orbito-cerebral computed tomography scan (CT scan). One patient underwent orbito-cerebral magnetic resonance imagery (MRI).
Surgical treatment was performed in 7 patients because of aesthetic or visual problems. Visual indications were amblyopia and astigmatism.
Three patients were not operated on. The first patient had a small PNF and there is no esthetic or visual impact. He was under observation. The second patient had a congenital glaucoma which has caused blindness in this eye. The third patient refused to undergo any surgery.
Surgical protocol was dictated by the size of the tumor. When the PNF is small, the surgical treatment was limited to the ptosis surgery (3 patients). When the tumor is big in size, PNF resection was firstly conducted. In the second time the ptosis is treated (4 patients).
The PNF resection was the first step of surgery. The surgery was ruled under general anesthesia with a local adrenal xylocaine infiltration. The tumor excision was very hemorrhagic in 3 cases.
The excision prevailed a temporalis jugal tumor, the outer canthus and the outer third of the upper and lower eyelid in one case. It prevailed the outer third of the eyelid and a part of lacrimal gland in one case and the temporalis muscle aponeurosis in other case. In all cases tumor resection was incomplete because there is no cleavage plan between the tumor and the surround tissue. Two patients were reoperated on because of tumor relapse. Histological examination of the tumor was performed in all the patients.
Ptosis surgery was performed in all the patients. When tumor excision had been needed, ptosis surgery was performed for a second time. Two methods were carried out: levator resection (two

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patients), frontalis suspension using fascia lata (5 patients). Two patients were reoperated on because of ptosis relapse. The used method was frontalis suspension.

Results

The age of our patients at diagnosis ranged from 18 months to 42 years. Six women and 4 men were involved.
The eyelid plexiform neurofibroma was unilateral in all cases. This lesion appeared at birth in 3 patients and between 3 to 5 years in 7 patients.
The upper eyelid was the site of the lesion in 100% of cases. The tumor reached the temporal region in two cases (**Figure 1**), reached the lower eyelid in two cases and the orbit in 3 cases. One patient had a PNF of the eyebrow (**Figure 2**). On palpation, this tumor was painless and adherent to the deep plan. The free margin of the upper eyelid was deformed by the tumor in 4 cases.

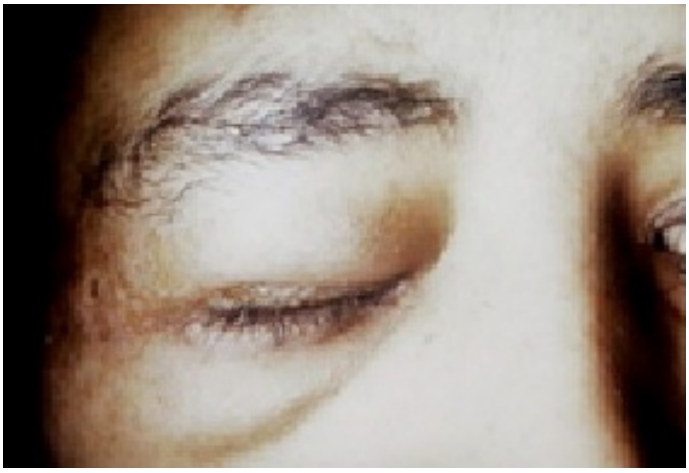

Figure 1. PNF extended to temporal region with major ptosis of the right eye.

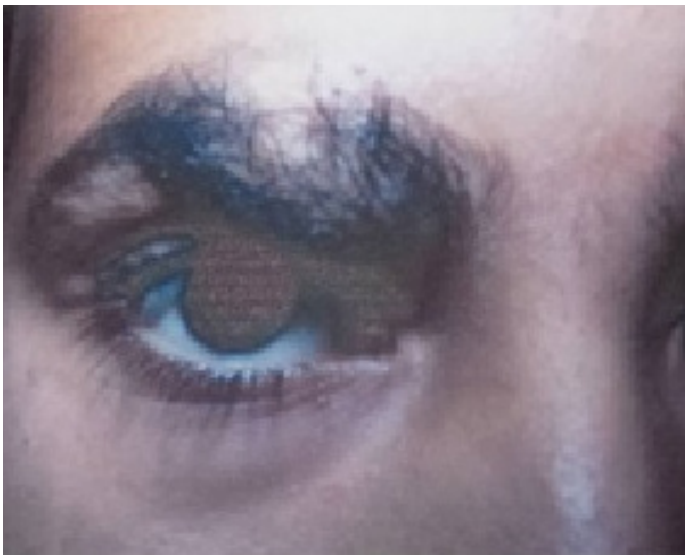

Figure 2. PNF of the eyebrow with hypertrichosis.

A mechanical ptosis was present in 9 patients. It was major in 5 cases (**Figure 3**) and moderate in 4 cases. We found a missing levator function of the upper eyelid in 3 patients.
Direct astigmatism ranging from -1.00 to -2.75 diopters whose average was -2 diopters was found in 5 patients.
Various eye lesions were noted: Lisch nodules (8 patients) (**Figure 4**), facial hemihypertrophy (5 patients), external canthal dystrophy (2 patients) (**Figure 5**), and one case for each of the following injuries: ectropion of the lower lid entropion of the lower lid, congenital glaucoma and hypertrichosis brow. These lesions constitute "Jules Francois" syndrome (**Figure 6**). **Table I** displays patients' characteristics. **Table II** demonstrates different lesions associated with PNF.

Table I. Patients' characteristics.

Number of Patients	10 patients
Mean age	21 years (18 to 42 years)
Gender	6 women , 4 men
Anatomic localization of the tumor	Unilateral: 10 patients Upper eylid: 10 patients
Age at diagnosis	At birth : 3 patients Between the age of 3 and 5 years : 7 patients

Table II. Ocular lesions associated to PNF.

Associated ocular lesion	Number of Patients
External canthal dytrophy	2
Lower eyelid entropion	1
Lower eyelid ectropion	1
Hemifacial hypertrophy	5
Eyebrow hypertrichosis	1
Congenital glaucoma	1
Lisch nodules	8

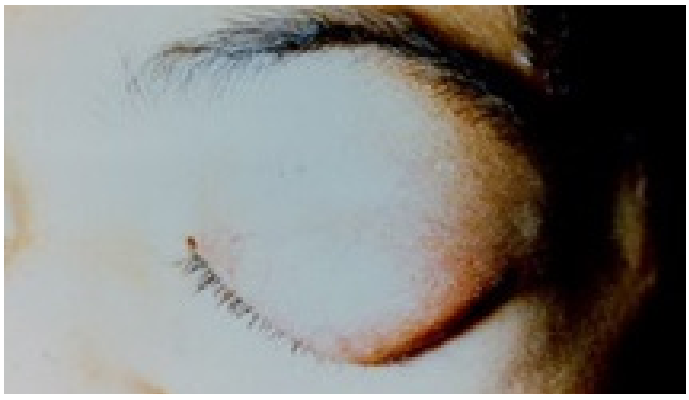

Figure 3. Major ptosis due to a PNF of the upper eyelid.

Orbital radiography was conducted in two cases and showed enlargement of the orbit in 2 cases (**Figure 7**), and thinning of the occipital bones in the other case. CT scan showed that the density of the PNF is similar to muscle density. On CT Scan, the size of PNF was measured. Extensions of the tumor and bone destruction were reported on the CT Scan. Spheno-orbital dysplasia was noticed in 4 cases (**Figure 8**). On MRI, PNF was heterogeneous T1 hypointense signal and heterogeneous hyperintense T2 signal (**Figure 9**). MRI, in addition to CT Scan, was helpful to analyze tumor extension.

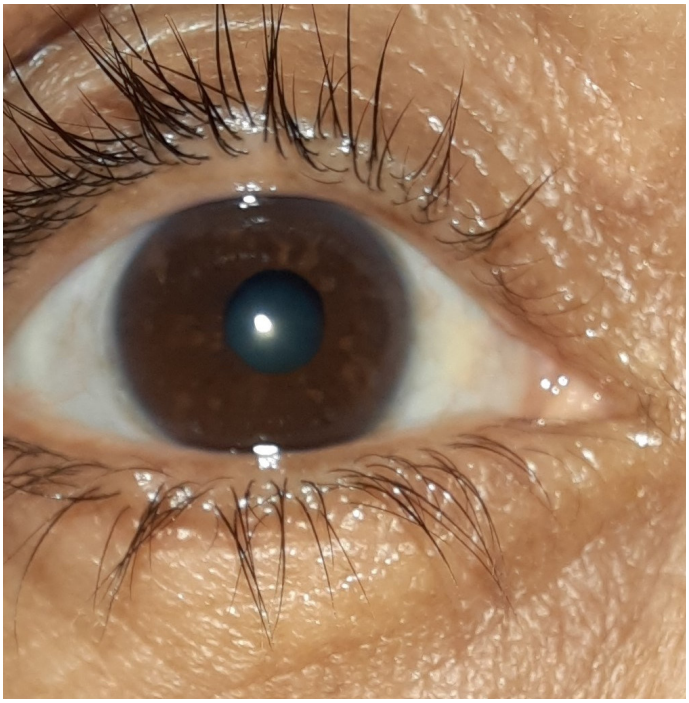

Figure 4. **Lisch nodules.**

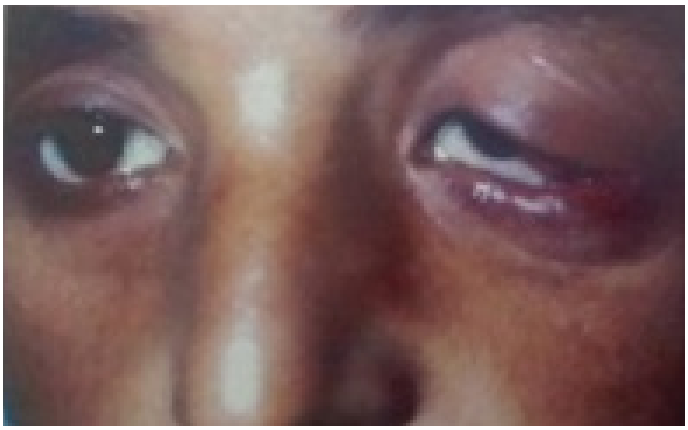

Figure 5. **External canthal dystrophy with lower eyelid ectropion.**

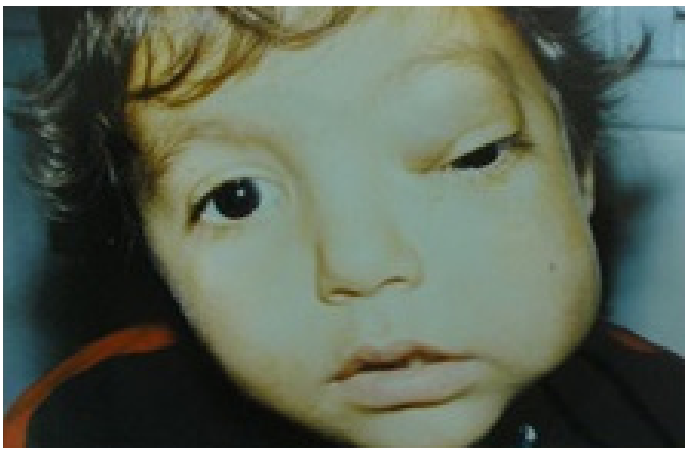

Figure 6. **Oculorobital dystopia with congenital glaucoma, a case of Jules Francois syndrome.**

The age at surgery ranged from 4 to 26 years with an average of 16.5 years. Seven patients underwent surgical treatment: 4 had received tumor resection associated with the treatment of ptosis (Groupe 1) and the others had only ptosis surgery (Groupe 2).

For group 1, resection of plexiform neurofibroma was followed by an anatomic success in 100%: PNF excision reduced the tumor size. The esthetic result was good in 3 cases. For the other patient, 3 times excision complement was needed and the final result was good (**Figures 10a, 10b, 10c, 10d**). The cure of ptosis was followed by a good postoperative outcome in all patients.
Surgery was complicated by peroperative bleeding in 3 cases and postoperative hematoma in 3 cases. Histological examination of the surgical specimen confirmed the diagnosis of PNF, but the tumor resection was incomplete in all cases. On histological examination, fusiform cells were found medium in size. Their nuclei were dense without atypia, with fibrillary cytoplasmic eosinophilia. The tumor had an intradermal proliferation and was not well limited. In the second group, ptosis surgery was performed in all cases and was followed by a good outcome in all patients. In one case ptosis relapse was noticed and a second surgery was needed. The final postoperative outcome was good.

Discussion

Plexiform neurofibroma is a benign nervous tumor. It affects mainly the cephalic region because of its rich innervation. It is considered as a pathognomonic sign of neurofibromatosis type 1 [3]. Frequency of PNF associated to NF type 1 varies from 18 to 75% [4]. This tumor is often unilateral. Curi reported bilateral lesions in 8.3% [5]. The lesion appeared in the first year, and became apparent between 2 and 6 years. On teenager period lesion grew fast then remained stable. [4]. PNF affects mainly females which is concordant with our result [5].
The tumor affects predominantly the upper eyelid. This localization is very evocative of NF1 [6].
PNF is responsible for modification of the upper eyelid margin. It has become sinusoid like an S. Lee et al reported that 85% of their patients have a ptosis resulting from the infiltration of the upper eyelid levator muscle by the PNF. The ptosis was mechanic in 9% of cases, related to a large and nodular PNF [4]. Dotan and al reported that moderate myopia and astigmatism were the most common ametropia [7]. In our series astigmatism was found in 50% of cases.
The tumor leads to the displacement of palpebral ligament complex. Then occurs a canthal dystrophy which affects mainly the outer canthus [8]. Tumor eyelid infiltration leads to ectropion which affects the upper or the lower eyelid [8]. Entropion and trichiasis are reported but remain rare.
Conjunctival infiltration by the PNF or excess of surgical excision leads to dysfunction of the lacrimal system. In these cases, dry eye syndrome occurs. We reported in our study one case of partial lacrimal gland excision. The patient had no dry eye problem. Lacrimal secretion may be affected by palpebral drooping too [4].
The PNF is often associated to orbitofacial malformation: ipsilateral hemifacial hypertrophy which can lead to elephantiasis [9, 10].
Sphenoorbital dysplasia was reported in some series [11].This malformation occurs in nearly 100% according to Zimmermann [12].
Congenital glaucoma associated with VRH disease was reported [13]. Jules Francois syndrome associates PNF, buphtalmia and hemifacial hypertrophy. We reported such a case. This syndrome is pathognomonic of NF type 1 [14].
Imaging is useful to precise the localization, extension and hemorrhagic complication [15].
PNF naturally increases: skin becomes thicker forming multiple folds covering the cheek. This sign is called pachydermatocele. Intraorbital extension appears in 25% of cases [13], 30% in our study. PNF is encapsulated. When the tumor invades the retrobulbar area, it leads to exophthalmia, compressive optic atrophy and widened orbit.
Sarcomatous transformation is rare. It is ranging from 5% to 8%. Peack age for transformation is between 10 to 20 years [16]. The risk of such transformation is increased by surgery according to

some authors. Currently, there is no evidence for this [17].
Surgical treatment has a double aim: to avoid visual dysfunction caused by astigmatism or amblyopia and to improve esthetic condition of children who risk psychological disorders.

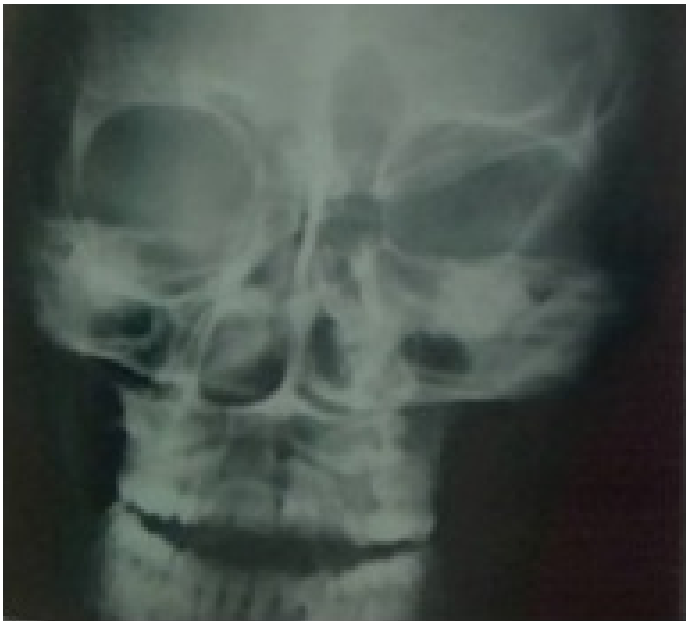

Figure 7. **Orbital radiography showing right orbital enlargement.**

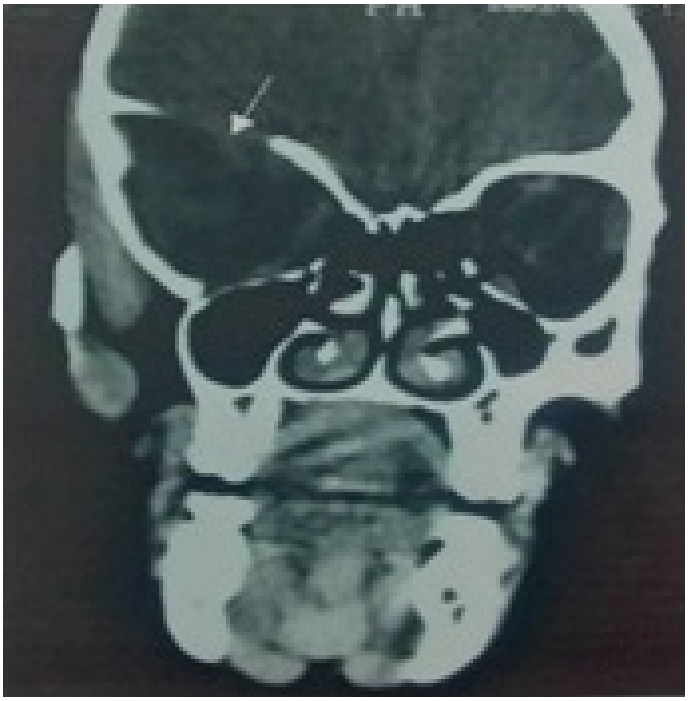

Figure 8. **Orbital scan showing right orbital roof defect with meningoencephalocele.**

The age at surgery is discussed. Marchac et al support that PNF excision at an early stage when the tumor is still small prevents bones deformation [18]. According to Conley, acting later surgery, after puberty, gives better results because the tumor did not progress [19]. We recommended, before surgery, to evaluate tumor progression, functional disorder and esthetic condition.
PNF is generally a benign tumor. Sarcomatous transformation may not be prevented by the tumor excision. Surgery is really a symptomatic treatment. In some cases surgery is not needed.
Surgical technique has some particularities. Total tumor excision is sometimes impossible because of the non cleavage plan between the tumor and the surround tissue [20]. Authors report that surgical outcomes are generally good [17, 20]. In our study anatomical success was reported in 4 cases. Surgery was often difficult and causing bleeding. Wound healing delay is usual [21] but not reported in our study. Meningoencephalocele or orbital management may be necessary [20, 22].

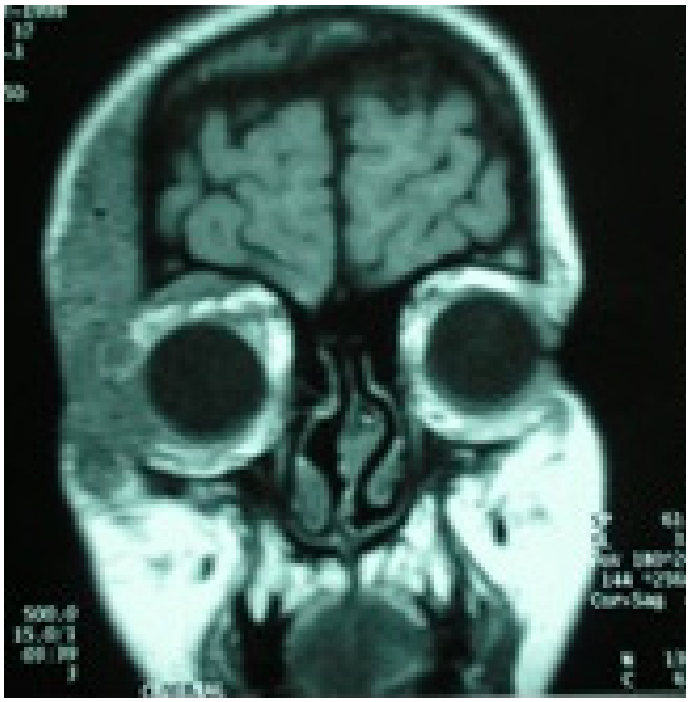

Figure 9. **T1 weighted MRI showing PNF extended to temporal right bone.**

Ptosis surgery has some particularities because of the dysfunction of eyelid levator and thickening of upper eyelid. Ptosis can affect visual function when the visual axis is blocked. Ptosis surgery aims to prevent amblyopia [23]. Surgical technique is discussed: Lee [23] and Marchac [18] reported that eyelid levator preserve good function although it is infiltrated by the tumor. Thus, they rarely recommended frontal suspension. Pentagonal resection of the upper eyelid is recommended for megalocornea. It is useful for nodular NF resection [23].
In our study frontal suspension was practiced in 3 patients. In these cases eyelid levator was not individualized, therefore, very infiltrated by the tumor. Before operation, it is difficult to specify tumor infiltration so limits of excision are difficult to determine before operation. Surgical outcomes of eyelid levator are often good [23]. All our outcomes were good despite the fact that one patient needed 3 reoperations because of ptosis relapse. No postoperative complication was noticed (corneal exposure or conjunctival prolapsus) [23]. Same cases of PNF were treated by CO2 laser with good outcomes [24].

Conclusion

Among the oculopalpebral manifestations of NF type 1, the PNF is an important diagnosis criteria. The PNF is a suggestive sign of NF type 1. The polymorphism of its clinical associations, as well as the risk of their malignant transformation, mean that the knowledge of this disease is important for any practitioner. It is a benign nervous tumor in which neurofibromas arise from multiple nerves as bulging and deforming masses involving also connective tissue and skin folds.
Surgical management is the key treatment. Lesions can have a persistent aesthetic and psychological impact which leads to consultation and surgical management.

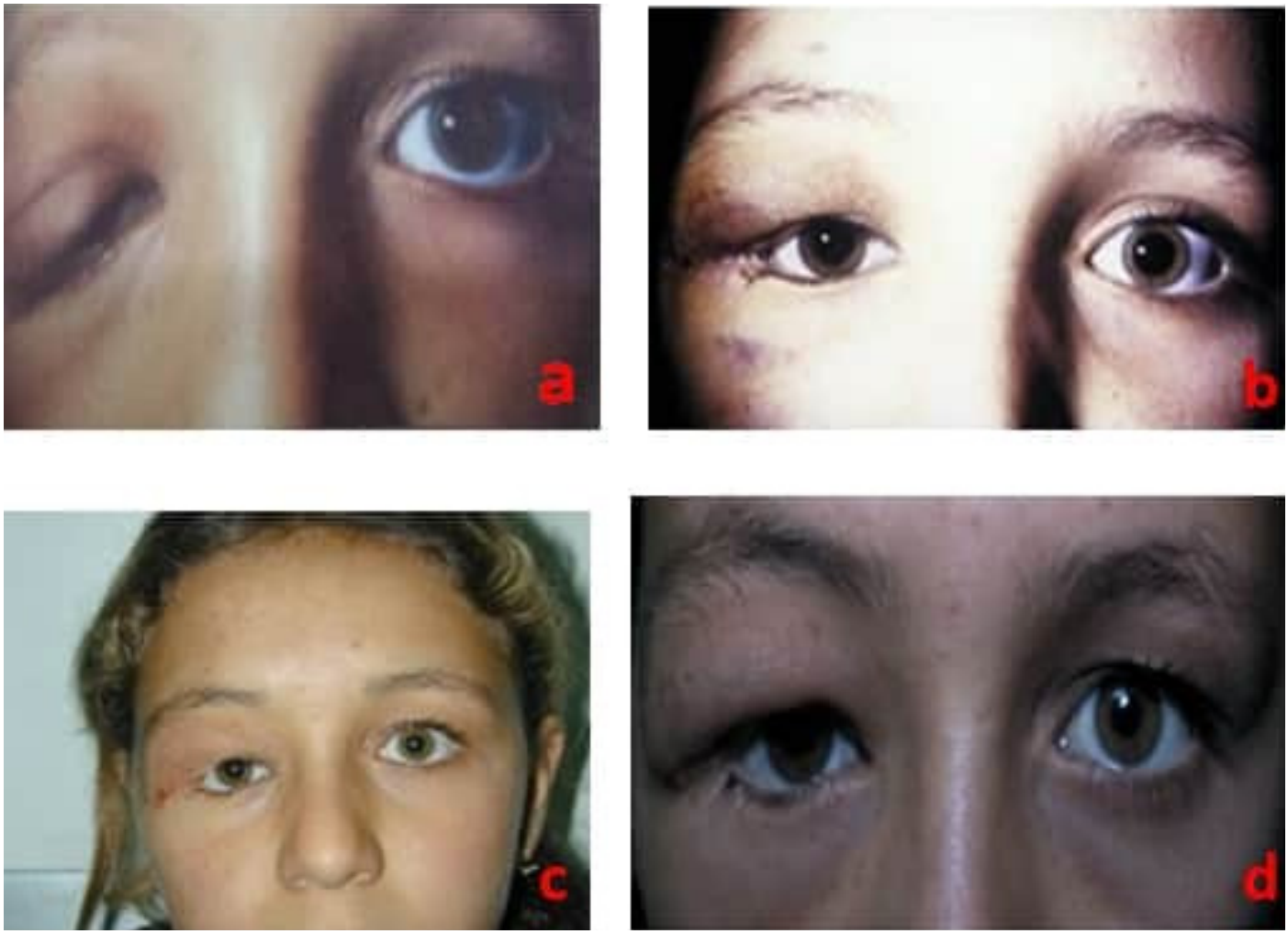

Figure 10. Photography of a girl with PNF (our study) (a) Preoperative photography. (b) Immediate good surgical outcomes: PNF resection frontal suspension. (c) PNF and external canthus recidivum. (d) Final aspect : anatomic success after 3 reoperations.

Competing interests

The authors declare that there is no conflict of interest regarding the publication of this article.

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