Scientific Research Publishing

Open Journal of Ophthalmology, 2022, 12, 407-415
https://www.scirp.org/journal/ojoph
ISSN Online: 2165-7416
ISSN Print: 2165-7408

# Neurofibromatosis Type 1: About a Series of 5 Cases

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**How to cite this paper:** Laminou, L., Kadidia, I.K., Adam, N.D., Kaka, Y.A. and Abdou, A. (2022) Neurofibromatosis Type 1: About a Series of 5 Cases. *Open Journal of Ophthalmology*, **12**, 407-415.
https://doi.org/10.4236/ojoph.2022.124038

**Received:** September 8, 2022
**Accepted:** November 18, 2022
**Published:** November 21, 2022



## Abstract

We report in this series 5 cases of neurofibromatosis type 1 (NF1). The mean age of the patients was 14.8 years (±9.65) with extremes ranging from 3 to 27 years. Three patients were female (60%) and two were male (40%). Three of our patients (60%) had no history of NF1 and two were monophthalmic because of plexiform neurofibromas involving the eyelid. Both cutaneous and plexiform neurofibromas were found in all our patients. The latter were of variable location: one on the chin, two on the left temporofacial region and two on the left upper eyelid. They were the cause of complications such as blindness in two patients. Café au lait macule (CALMs) was also present in all our patients. No cases of optic nerve glioma were found in the 3 patients (60%) who underwent an orbitocerebral CT scan. Lish nodules were observed in 4 patients (80%). With the exception of the 3-year-old female patient who was not old enough to go to school, all the other four patients dropped out of school because of the stigma attached to them.

## Keywords

Neurofibromatosis Type 1, Monophtalmic, Stigma, Zinder, Niger

## 1. Introduction

Neurofibromatosis type I (NF1) belongs to a heterogeneous group of diseases characterized by a genetically determined predisposition to the development of benign or malignant tumors that can affect several sites in the body, including the eye [1]. In 1882, Friedrich Daniel Von Recklinghausen described for the first time the nervous origin of the tumors observed in the disease that bears his

name [2]. NF1 or peripheral neurofibromatosis is one of the most frequent genetic diseases with an estimated prevalence between 1/7800 and 2000 [3]-[8]. In Niger the prevalence of this disease is not known, but cases have been reported by some authors [9]. The diagnosis of neurofibromatosis type 1 is clinical (**Table 1**), based on diagnostic criteria established following the National Institute of Health (NIH) consensus statement in 1988 [10]. We report a series of 5 cases of neurofibromatosis type 1 diagnosed in the ophthalmology department of the National Hospital of Zinder.

## 2. Ethical Aspects

This study was conducted in accordance with the ethical rules of the Declaration of Helsinki. Each patient was free to participate or refuse to participate after informed consent.

### 2.1. Observation 1

B.I., male, 21 years old, dressmaker by profession, referred from the department of stomatology and maxillofacial surgery for ophthalmologic consultation because of a left temporofacial swelling responsible for a mechanical ptosis. On examination, no personal or family medical or surgical history of any pathology was found. On ophthalmological examination, the uncorrected distance visual acuity was 9/10 on the right and 8/10 on the left. The adnexa were normal on the right, on the left there was a ptosis due to the weight effect of the mass. The corneas were healthy, the anterior chambers calm and Lish nodules were found with a normal fundus bilaterally. The dermatological examination noted café-au-lait macules (CALMs) (**Figure 1(a)** blue arrow), numerous skin nodules (**Figure 1(a)** red arrow) and plexiform nodules in the left temporofacial region (**Figure 1(b)** black arrow) which palpation noted a kind of rope. X-ray of the leg bones (**Figure 1(c)**) noted thinning of the cortex and on CT (**Figure 1(d)**) both optic nerves were normal in size with a left temporal mass (green arrow). The diagnosis of neurofibromatosis was made and surveillance was instituted.

**Table 1.** Panel: NIH consensus criteria for diagnosis of neurofibromatosis type 1 (1988). Two or more the following clinical features are sufficient to establish a diagnosis of neurofibromatosis type 1.

| |
|---|
| 1) Six or more café-au-lait macules (>0 - 5 cm at largest diameter in a prepubertal child or >1 - 5 cm in post-pubertal individuals) |
| 2) Axillary freckling or freckling in inguinal regions |
| 3) Two or more neurofibromas of any type or one or more plexiform neurfibromas |
| 4) Two or more Lish nodules (iris harmatomas) |
| 5) A distinctive osseous lesion (sphenoid wing dysplasia, lon-bone dysplasia) |
| 6) An optic pathway glioma |
| 7) A first degree relative with neurofibromatosis type 1 diagnosed by the above criteria |

NIH: National Institute of Health.

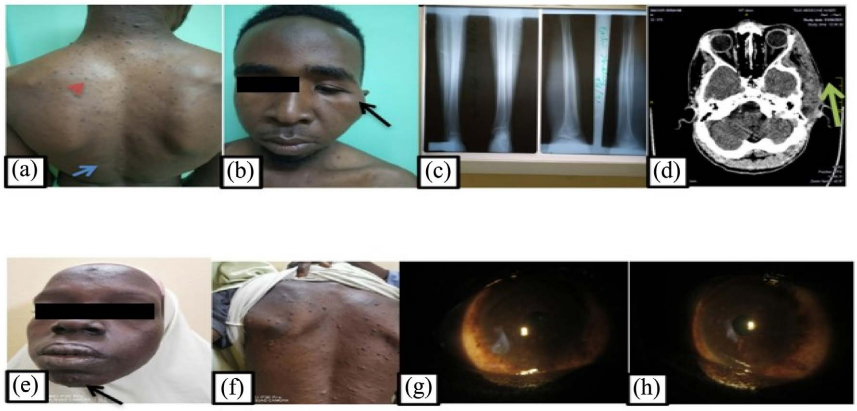


**Figure 1.** (a) Cafe au lait stain (blue arrow), Cutaneous neurofibroma (red arrow), (b) Plexiform neurofibroma (black arrow), (c) Leg bone radiograph showing cortical thinning, (d) Oritocerebral CT scan, absence of optic nerve gioma, but left temporofacial mass of plexiform neurofibroma (green arrow), (e) plexiform neurofibroma of the cheek (black arrow), numerous skin nodules and cafe-au-lait spots, (g) and (h) lish nodules of right and left eye.

### 2.2. Observation 2

D. S female, 27 years old, fatherless, economically disadvantaged, consulted for lacrimation, pruritus. On ophthalmologic examination, visual acuity was 10/10 bilaterally, adnexa normal, cornea clear and anterior chamber deep, Lish nodules bilaterally (**Figure 1(g)** and **Figure 1(h)**). Dermatological examination noted café au lait spots (**Figure 1(f)**), skin nodules (**Figure 1(f)**) and plexiform nodules on the chin (**Figure 1(e)**). Orbitocerebral CT was normal. The diagnosis of neurofibromatosis type 1 was retained. It should be noted that no family history of NF1 was found.

### 2.3. Observation 3

A.B, male, 15 years old, who dropped out of school due to the stigma of his disease by the children of his school, consulted for swelling involving the orbit and hanging from the left hemiface, with facial dysmorphia (**Figure 2(a)** and **Figure 2(b)**). No family history of disease was reported. On ophthalmologic examination, visual acuity was 10/10 on the right and at finger count 2 meters on the left. Biomicroscopic examination of the right eye revealed normal adnexae, a healthy cornea with a good quiet anterior chamber, Lish nodules (**Figure 2(d)**) with a normal fundus. Examination of the left eye, hampered by swelling, revealed conjunctivitis, a 360˚ corneal pannus with a corneal opacity that made examination of the anterior segment impossible. The dermatological examination noted café au lait spots, skin nodules and a plexiform neurofibroma (**Figure 2(a)** and **Figure 2(b)**) and axillary lentigines (**Figure 2(c)**). The diagnosis of neurofibromatosis type 1 was retained.

### 2.4. Observation 4

M.B., female, 8 years old, with a family history of neurofibromatosis. She was

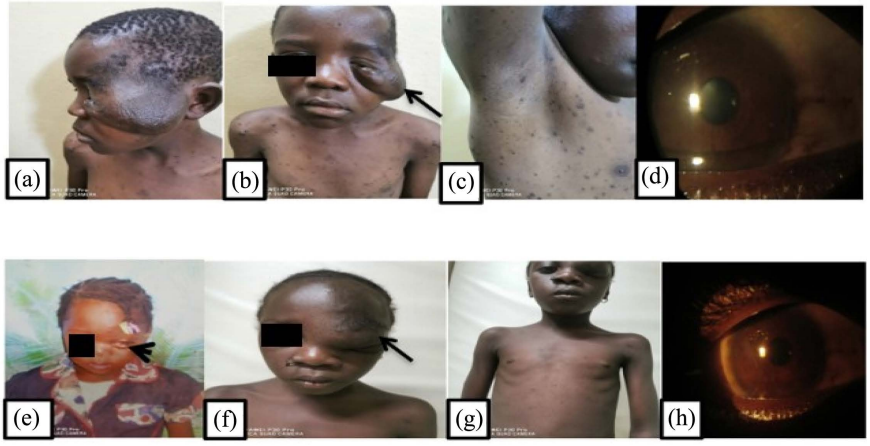


**Figure 2.** (a) and (b) Suspended plexiform neurofibroma of the left temporal region, CALMs, (c) Axillary lentigine, (d) Right eye Lish nodules, (e) Left unilateral congenital glaucoma (small black arrow), (f) Left upper eyelid plexiform neurofibroma; (g) Numerous CALMs and skin nodules, (h) Lish nodules on right eye.

dropped out of school in the first grade because of the stigma attached to her disease by children her age. She had undergone evisceration of her left eye at the age of 5 years after failed trabeculectomy treatment at the age of 2 years for unilateral congenital glaucoma of the left eye (**Figure 2(e)**). On ophthalmologic examination, the distance visual acuity on the right eye was 10/10 and there was no light perception on the left eye (**Figure 2(f)**). The adnexa examination showed purulent conjunctivitis and total ptosis in the left eye (2N), normal adnexa in the right eye, a clear cornea, a quiet anterior chamber, and Lish's nodules with a reactive pupil (**Figure 2(h)**). Dermatologic examination noted several café au lait macules (CALMs) (**Figure 2(g)** arrow), numerous skin nodules (**Figure 2(g)** arrow), and a plexiform neurofibroma on the left upper eyelid (**Figure 2(f)**). A CT scan of the orbitocerebrum was requested and was unremarkable except for the palpebral mass. The diagnosis of neurofibromatosis type 1 was retained and referred for reconstructive surgery.

## 2.5. Observation 5

H. S. female, 3 years old, brought in consultation by her parents for left unilateral ptosis. She had a first degree history of neurofibromatosis type 1 through her mother. She presented numerous café au lait spots, a tumoral process of the left upper eyelid producing a mechanical ptosis. The examination of the right eye appeared normal under magnification, but the examination of the left eye was difficult because of the ptosis. The diagnosis of neurofibromatosis type 1 was retained and surveillance was instituted.

On analysis of the observations, our series included 5 patients with an average age of 14.8 years (±9.65) with extremes ranging from 3 to 27 years. Three patients were female (60%) and two were male (40%). Three of our patients (60%) had no history of NF1 and two were monophthalmic because of plexiform neu-

rofibromas involving the eyelid. Both cutaneous and plexiform neurofibromas were found in all our patients. The latter were of variable location: one on the chin, two on the left temporofacial region and two on the left upper eyelid. They were the cause of complications such as blindness in two patients. Café au lait spots were also present in all our patients. No cases of optic nerve glioma were found in the 3 patients (60%) who underwent an orbitocerebral CT scan. Lish nodules were seen in 4 patients (80%). With the exception of the 3-year-old patient who was not old enough to go to school, all the other four patients dropped out of school because of the stigma of the students.

## 3. Discussion

Neurofibromatosis type 1 is an autosomal dominant genetic neurocutaneous disorder. In 1990, the gene responsible for the mutation was located on chromosome 17 in the 17q11.2 region, it codes for neurofibromin, a protein involved in the control of cell proliferation and differentiation by inhibiting the pRas activation pathway. [6] [7]. Its penetrance is close to 100% around the age of 5 years and de novo mutations occur in about 50% of cases [11]. There is no gender, age or race predilection and in our study 60% of patients were female. The diagnosis of neurofibromatosis type 1 is clinical based on criteria (**Table 1**) established in 1988 by the National Institute of Healh (NIHCDC) consensus conference [10].

**Café-au-lait macules (CALMs)** are the most frequent signs, found in more than 90% of cases during adolescence. Often congenital, they rarely appear after the age of 2. They are brown spots with clear contours, becoming slightly paler in adulthood if they do not disappear permanently. They are not specific to NF1 as they are found in 10% to 25% of the general population without NF1 [12] [13]. All patients in our series had café au lait spots, as reported by some authors [8] [9].

**Cutaneous neurofibromas** are benign tumors of the peripheral nerve sheath and are a major cause of morbidity in NF1 patients. They are small tumors of elastic consistency, soft, mobile with skin that may be sessile or pedicled. They are found in 95% of adults with NF1 [12] and 100% in our patients.

**Lentigines** are part of the diagnostic criteria of NF1. They are diagnosed between 3 and 7 years of age in 90% of cases. They are found in undiscovered areas, especially in the axilla and inguinal regions, but can also be seen in other parts of the body [14].

**Plexiform neurofibromas** occur in 30% - 50% of patients with NF1 [15] [16]. Formerly called plexiform neuromas or "royal tumor", they are the most common palpebral manifestation of NF1 localizing most frequently and unilaterally to the upper eyelid [17]. Although congenital, this lesion undergoes rapid growth in the first years of life before stabilizing. They have been reported in all our patients with various locations. Unilateral congenital glaucoma was often associated with NF1, as was the case in our 2nd patient. Its treatment involved

surgery with disappointing results. In the majority of cases, this glaucoma occurs on the same side as the palpebral plexiform neurofibroma with the secondary appearance of a buphthalmos [18]. In the case of plexiform neurofibroma, an exophthalmos was present in 25% of cases. It was found in one of our patients (20%). Orbital involvement due to the growth of the plexiform neurofibroma is rare and has been given several names: Orbitotemporal neurofibromatosis, orbitofacial neurofibromatosis, cranioorbital neurofibromatosis, cranioorbital-temporal neurofibromatosis and its variety is considered pathognomonic of neurofibromatosis type 1 [19]. And recently a working group had suggested the term orbital-periorbital plexiform neurofibromas (OPPNs) to encompass all sites of localization [18].

**Lisch's nodules,** whose association with neurofibromatosis was demonstrated by Prof. Lisch in 1937 [20], are the most frequently reported ophthalmological manifestations, accounting for 73% to 95% of cases in adults according to the authors [21] [22], compared with 80% in our series, with the exception of the youngest patient aged 3 years. They are a valuable aid to diagnosis and correspond to small pigmented tumors of the iris (iris hamartomas) without causing a symptomatic manifestation, they are quasi-pathognomonic of NF1 [12] [13]. Lisch nodules are frequently found in the lower half of the iris and their presence correlates with age and severity of NF1. Thus, before the age of 3 years, Lisch nodules are found in 5%, 42% between 3 and 4 years of age, and 55% between 5 and 5 years of age and in 100% of cases in adults over 21 years of age [18].

**Optic nerve gliomas (ONG)** are associated with NF1 in 25% to 50% of cases. Imaging, of which MRI remains the gold standard, will show an enlargement of the optic nerve or chiasma in T1 hypersignal, T2 hypersignal with constant uptake of contrast product such as gadolinium. GNO occurs in children between 3 and 7 years of age and should be suspected in the presence of any decrease in visual acuity, exophthalmos, hydrocephalus, intracranial hypertension (ICH) with headaches and early puberty [6] [23]. For this reason, annual radiological surveillance, including MRI, is recommended in NF1 to detect complications [10]. No case of optic nerve glioma was found in our patients who had a CT scan due to the absence of MRI. It should be emphasized that outside the optic nerves these gliomas can extend to any part of the optic tract and even outside the optic tract, into the brain stem. Other ocular manifestations have also been described that were not part of the diagnostic criteria for either the anterior or posterior segment. Refractive errors including mild to moderate myopia have been reported more frequently in NF1 than in the general population [18].

## 4. Treatment

Several treatments including surgery, chemotherapy and radiotherapy have been tried with often mixed results. No curative treatment is yet available [24], it is so far symptomatic [2] [9] [10] [18] [25]. The management of NF1 is multidisciplinary, involving ophthalmologists, dermatologists, maxillofacial surgeons, neu-

rosurgeons and plastic surgeons [19]. Considering the stigmatization and psychological suffering of NF1 patients, psychiatric and psychosociological care offers should accompany NF1 patients and promote their social integration [26].

## 5. Conclusion

The ophthalmologist has a central role in the diagnosis, management and monitoring of patients with NF1. Of clinical diagnosis, his management remains multidisciplinary and oriented according to the occurrence of complications. Because of the stigmatization of which they are victims, a psychological support must accompany not only the patients reached of NF1 especially in the early childhood to avoid the school deprivations. Genetic disease, in case of NF1 a genetic advice must be considered to decrease the incidence of this pathology.

## Conflicts of Interest

No potential conflict of interest was reported by the authors.

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