# Neurofibromatosis type 1– unpredictable disease?

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## Abstract

Neurofibromatosis type 1 (NF1), also known as Von Recklinghausen's disease, was first described in 1882, and it is the most frequent of the neurocutaneous syndromes.

It is one of the most common genetic disorders, which responsible gene is located in the long arm of chromosome 17, with a 1/2500 incidence rate, with dominant autosomal transmission, being half of the cases familial and the other half sporadic.

The diagnosis is based on the presence of at least 2 of 7 criteria established on the National Institute of Health Consensus Conference of Bethesda in 1987.

Although in adults the diagnosis is rather easy, when it comes to children the café-au-lait spots may be, for a long period of time the only sign, keeping the disease undiagnosed.

Besides the typical café-au-lait and neurofibromas there is an aggravated risk of developing malignant neoplasms, namely malignant peripheral nerve sheaths tumors also referred to as schwannomas or neurofibrosarcomas.

These neurofibrosarcomas have a smaller response to the conventional cancer treatment, and it is believed that many genetic factors are responsible for their higher aggressiveness.

Malignant tumors are the main cause of death by NF1, being associated to mortality at tender age. The case we describe is such an example.


Key words: Neurofibromatosis type 1, von Recklinghausen's disease, NF1, neurofibromin, café-au-lait spots, neurofibromas, neurofibrosarcomas.

## INTRODUCTION

It is reported the case of a female patient, 20 years old, Black, born in Guinea-Bissau, without any relevant personal or family background.

Brought to Lisbon in March 2008 to evaluate an exuberant mass on the posterior side of the left thigh, painful, leading to functional impotence and bed restriction.

The NF1 diagnosis was made based in the presence of over six café-au-lait spots, more than 15mm in diameter located on the face and trunk, inguinal and axillary ephelides and multiple neurofibroma.

The left lower limb tumor biopsy has revealed a neurofibrosarcoma.

After three successive hospitalizations within a context of paraneoplastic pleural effusion she died due to breathing failure.

NF1 is a pathology with a clinical wide spectrum, ranging from skin lesions within a mere aesthetic implication, to malignant neoplasm evolving inexorably to death.

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## CLINICAL CASE

Female patient, 20 years of age, black race, with irrelevant personal background, born and residing in Guinea-Bissau until March 2008, time she was referred to Lisbon (North Lisbon Hospital Center – Santa Maria Hospital) to evaluate the mass on the posterior side of the left thigh, painful, leading to functional impotence and bed restriction for about an year.

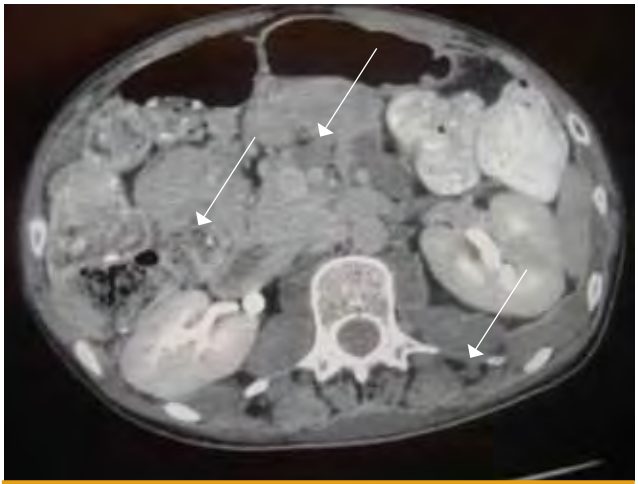
In his hospital she was evaluated in the Oncology Clinic, being subject to nuclear magnetic resonance (NMR) of the thighs revealing diffuse multinodular alteration in both thighs, and of notice, on the left, areas of necrosis and hemorrhage suggesting a malignant degenerative lesion, most likely a node sarcomatosis.

A vacuum puncture of the said mass was made being the cytology compatible with a neural tumor without atypia or mitosis, probably with degenerative cystic areas, and also a left supraclavicular node revealing a neural tumor, probably benign.

As there was not a malignant transformation she was not bound as an Oncology outpatient, and she was instead referred to the Intra-hospital team for the support of palliative care due to the need of symptomatic control of pain.

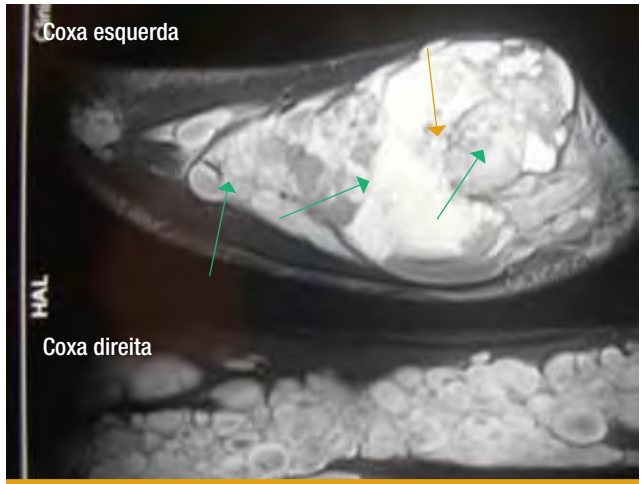
The pain was controlled with morphine, gabapentin, amitriptyline, paracetamol, lorazepam and dexamethasone.

Aiming to get a more precise diagnosis it was



Pelvic CT presenting multiple neurofibroma.

FIG. 1




Thighs RMN showing several neurofibroma and neurofibrossarcoma in the left thigh.

FIG. 2

planned a biopsy by excision of the mass on the lower left limb, being the patient admitted electively to the Orthopedic service.

As she was presenting tachypnoea (breathing rate: 27 bpm) and tachycardia (heart rate: 111 ppm), showing hypoxaemia ($PaO_2$: 7.8 mmHG in room temperature), with an $O_2$ saturation kept of (95.7%) and radiographically she has shown a bulky pleural effusion on the right, being transferred on the following day to the biopsy for the Medicine 1 Service.

On admission into the Service, she showed several café au lait spots in the face and trunk with a diameter above 15 mm, axillary and inguinal ephelides several subcutaneous neurofibromas, discreet and widespread.

She presented also semiology of the pleural effusion located on the lower two thirds of the right hemithorax.

Based on the existence of more than six café au lait spots, over 15 millimeters in the widest diameter, of axillary and inguinal ephelides and of multiple neurofibromas it was made the diagnosis of neurofibromatosis type I.

Thoracocentesis was performed removing 1100 cc serohematic fluid with features of polymorphonuclear exudates. Cultures, Koch´s bacilli search and neoplastic cells were negative.

Subsequently a thorax CT scan was carried out revealing several tumor formations suggesting neurofibromas in the supraclavicular fossa, mediastinum and mesenterium root.

The abdominal and pelvic CT scan has documented multiple solid nodular lesions located in the retroperitoneal compartment, namely in retro-crural and para-vertebral topography, filling almost completely the pelvic cavity and conditioning a marked distortion of the adjacent organs, pushing forward the bladder and intestinal loops. It was also verified also a sacrum lytic commitment.

During in the hospitalization a physiotherapy program was started aiming to improve the quality of life.

The biopsy result documented a malignant tumor (neurofibrosarcoma) on the peripheral nerves sheath in continuity with plexiform neurofibromas, being the malignant grade 2 in 3.

The case was debated with the Oncology Service, who considered not being an indication for direct therapy, namely chemo- and/or radiotherapy, due to the stage of evolution of the disease.

After clinical and laboratorial stabilization the patient was discharged being followed up in the Palliative Care Clinic.

She was readmitted after a month, in a context of low urinary infection due to *Escherichia coli* being discharged after favorable response to the implemented experimental antibiotic therapy.

About a month later she came again to Santa Maria Hospital due to intense dyspnoea, presenting O2 saturation of 60% (in the environment air).

Objectively she was aware, cooperative and orien-

ted although rather prostrated. She was apyretic (tympanic temperature of 36.9°C), with a blood pressure of 146/73 mmHg and Heart Rate of 140 bpm. Mucosa and skin were pale and dehydrated. Pulmonary auscultation revealed no vesicular murmur in the lower two thirds of both hemi-thorax and crackles in the upper one third of the right hemi-thorax.

The blood tests revealed leukocytosis (25.900/mL) with neutrophilia (91.4%), high CPR (38.7 mg/dL) then also high LDH (1102 U/L).

The X Ray showed extensive bilateral pleural effusion.

The electrocardiogram documented sinusal tachycardia.

She was readmitted into Medicine 1C Service, where she was kept in oxygen therapy ($FiO_2$ 100%) and started antibiotic therapy in the context of respiratory and urinary infection.

Therapeutic thoracocentesis was also carried out extracting 500 cc of haematic fluid, suspended due to the patient intolerance.

In the uroculture it was isolated *Pseudomonas aeruginosa* sensitive to the current antibiotic therapy.

On the second day of hospitalization, in spite of the implemented therapy, the condition deteriorated and the patient died.

## DISCUSSION

Neurofibromatosis type I (NF1) or Von Recklinghausen, described for the first time in 1882, it is the most frequent of the neurocutaneous syndromes.

In spite of being known for over a century, all in the last four decades, it was established as a nosological entity on its own, with well defined clinical, image and genetics.

On Table I is made a historic summarized review of NF1.

This is one of the most common genetic diseases, with a prevalence calculated between 1/400 to 1/3000 individuals, having a homogeneous global distribution, without predominance of race, ethnics or gender and incidence around 1/2500 births.[1]

N F1 has a dominant autosomal character, being half of the cases hereditary and the reminder occasional.[2]

In the reported cases we can presume to be a new mutation as there was no family history for NF1.

New mutations occur in paternal chromosomes, although the reasons justifying such phenomenon are not well clarified.[3]

**TABLE I**

**Important milestones in NF1 history**

| |
|---|
| 1882 Von Recklinghausen describes the disease for the first time |
| 1970 to 1980 NF1 and NF2 are recognized as distinct clinical entities |
| 1978 The National NF Foundation is created (at present called Children's Tumor Foundation) |
| 1987 NF1 diagnosis criteria are established by the National Institute of Health |
| It is located in the NF1 gene in the chromosome 17 |
| 1990 Gene NF1 is cloned |
| 2000 Genetic study enables to identify the mutation in over 95% of patients |

Penetrance is total and at 8 years of age, almost all those affected have a clinical manifestation of the disease.[4]

The identification of the NF1 gene is a milestone of the utmost importance to the understanding of this pathology pathogenesis. It is also a tumoral suppressor located on the pericentrometric region of chromosome 17 long arm, more specifically on locus 17q 11.2.[5]

NF1 gene codifies neurofibromin belonging to the Gap family (protein activating GTPase), responsible for inhibiting the Ras system, namely the proto-oncogenesis p 21 – ras.[6,7]

A NF1 gene mutation originates a deficient neurofibromin, implying a high Ras activity, conditioning an exacerbated cell proliferation and tumoral formation.[8,9]

Mutations on the NF1 gene generate a wide variety of inter- and intra-family phenotypes.[10]

There is not a reliable correlation between genotype and phenotype, but in cases where big deletions were detected on the NF1 gene, the incidence of intellectual disability, facial malformation and earlier presentation of neurofibromatosis are increased.[5]

It is also presumed a higher risk of neurofibromas malignancy in such cases, having consequently a worst prognosis.[11]

NF1 diagnosis is based on 7 criteria (represented on Table II) set up in the conference for the Consensus of the National Institute of Health (NIH) of Bethesda

**TABLE II**

**Conference on Consensus by NIH 1988**

| Criteria | |
|---|---|
| 1. > = 6 café-au-lait spots | > 5 mm wider diameter before puberty<br>> 15 mm wider diameter after puberty |
| 2. Ephelides | Axillary, inguinal |
| 3. Neurofibromas | ≥ 2 neurofibroma of any type or a plexiform neurofibroma |
| 4. Typical bone lesion | Sphenoid dysplasia and/or cortical thinning of a long bone with or without pseudarthrosis |
| 5. Lisch nodes | ≥ 2 |
| 6. Optical glioma | By image (RMN) |
| 7. NF1 1st degree relative | Parents, siblings, children |

in the United States of America, in 1987.

The competition of at least two of such criteria, confirmed the diagnosis.

The patient presented the typical café au lait spots in a number and diameter meeting the diagnostic criteria, inguinal and axillary ephelides and several neurofibromas, among which are the plexiform neurofibroma documented by biopsy.

The presentation of different clinical manifestation depends on the age (shown on Table III), and it is necessary sometimes to follow the patient for several years to document the disease. If the diagnosis in the adult is easy, in the child the café au lait spots can be for a long time the only sign keeping sometimes the diagnosis suspended.

Around 90% of those affected present two or more diagnostic criteria at six years of age, 97% at eight years of age and all of them at 20 years. [12]

The sequence of the typical presentation of clinical criteria starts with café au lait spots, followed by the ephelides, Lisch nodes and neurofibromas. [12]

The café au lait spots, colored macules darker then the skin, are a cardinal sign of NF1, being present in around 99% of cases in the first year of life. [12]

They can be present in the new born, having an oval shape and a diameter between 1 to 4 cm, being distributed randomly and tend to increase in size and number until the adult age, time in which they start to disappear.

The ephelides are also pigmented findings which are characteristic and harmless, differentiating themselves from the café au lait spots for being smaller and concentrated in aggregates in the axillary and inguinal region.

They can also be located in the infra -mammary region, on the neck posterior region and on the skin folds, suggesting an eventual environmental modulation. [13]

Another NF1 characteristic almost pathognomic are the Lisch nodes, iris pigmented hamartomas, without a clinical repercussion, detected by a slit lamp. [14]

The optical nerve glioma are the most frequent tumors of the central nervous system in NF1, and are usually present before the six years of age, being rare after such age. [15]

The low grade pilocytic astrocytoma, uni- or bilateral, involving the optical nerve, the optical chiasm, the hypothalamus (frequently associated to early or late puberty [16]), the cerebellum or the cerebral trunk. [17]

From around 15% of patients presenting such tumors, half develop symptoms (reduced visual acuity, dyschromatopsia, proptosis, afferent pupillary defect).

Such lesions present a higher risk of a second CNS tumor (cerebral trunk glioma, astrocytoma) more frequently manifested by intracranial hypertension.

Around 70% of the optical nerve glioma is associated to NF1, for which its identification justifies that this pathology is excluded. [18]

Its exclusion and the follow-up can be made through an annual ophthalmological evaluation, reserving the brain and orbital nuclear magnetic resonance for the cases in which it is difficult due to the lack of cooperation from the child and when alterations are seen in the exam, as it is recognized by the *Children's Tumor Foundation* and the French Association of Neurofibromatosis.

It was verified that sporadic cases of optical nerve have and earlier and more aggressive presentation than those associated to NF1 [19] and in these, sometimes it occurs a spontaneous regression. [17]

NF1 presents several characteristic bone changes, such as sphenoid dysplasia which is usually unilateral and asymptomatic.

**TABLE III**

**NF1 typical evolution[12,18,25]**

| Symptoms | Presentation age | Frequency |
|---|---|---|
| Café-au-lait spots<br>Ephelides | Before 2 years of age<br>From the 3-5 years of age | 99%<br>>90% |
| Lisch nodes<br>Cutaneous neurofibromas | Aadolescence<br>Variable | 95%<br>0-9 anos: 14%<br>10-19 anos: 44%<br>20-29 anos: 85%<br>>30 anos: 95% |
| Diffuse plexiform neurofibroma<br>Optical nerve glioma | Congenital<br>Before 6 years of age | 25%<br>15% |
| Tibia/sphenoid dysplasia | 1 year of age | 1-4%: tíbia<br>3-7%: sphenoid |

Complications are rare translated in facial asymmetry, enophthalmos and herniation of the brain through the orbit. [20]

The congenital thinning of the cortex in the long bones, predominantly of the tibia, is clinically translated by an arching and fractures during childhood (50% occurs before the two years of age), causing pseudarthroses or false articulations.

NF1 is the main cause of long bones pseudarthroses justifying its exclusion when such lesions are identified.

Pseudarthroses lead sometimes to the limb amputation.

The deformation of long bones and osteolytic lesions can be caused by the expansion of neurofibromas as seen in the case presented.

All this setting increases the risk of osteoporosis and osteopenia in NF1. [21]

Neurofibroma is benign tumors, with random distribution, originating from superficial peripheral nerves, or less frequently, deep ones.

They present a multicellular constitution, being made by Schwann, axons, fibroblasts, mastocytes, endothelial and perineural cells.[22]

Its presentation is often preceded by skin rash.

They are classified as discrete and plexiform neurofibroma. [14]

Discrete neurofibromatosis appears usually during puberty, tending to increase in number and size throughout the life, particularly during pregnancy, regressing sometimes after child-birth. [23]

Its clinical importance arises mainly of the compression they exert on the underlying structures.

They are subdivided in cutaneous (the most common type of neurofibromatosis) and subcutaneous.

Cutaneous discrete neurofibromas are small painless protuberances, of soft consistency and color similar to the skin, pinkish, or violet, predominantly in the trunk.

They imply problems of aesthetics nature, can be destroyed by laser $CO_2$ or surgically removed when go beyond 1 centimeter in diameter.

Subcutaneous discrete neurofibroma is originated from sub-epidermical nerves, changing from a pea size of several centimeters, being more easily visible then palpable and can cause pain by radicular compression.

Plexiform neurofibroma are classified in diffuse (congenital, although they are only identified when acquiring a considerable dimension, more often located on the head, neck and abdomen) and nodal (rarer, involving usually the spinal nerves).

They are different from discrete neurofibroma for being vascularised, making exeresis difficult mainly as they present risk of malignancy.

The transformation in malignant tumor of the peripheral nerve sheath, also known by neurofibrosarcoma or malignant Schwannoma occurs in around 8 to 13% of NF1 cases.[24]

Such tumors represent the most important complication in NF1 and are usually located in the abdomen, para-spinal region, limbs, head and neck. [25]

The malignant transformation can be expressed in pain or neurological signs of appearance or recent deterioration, changing consistency or increase in the size of a plexiform neurofibroma.[13]

In the clinical case the malignant degeneration was expressed by an exuberant mass conditioning pain and functional impotence and by recurrent paraneoplastic pleural effusions culminating with the patient's death.

Neurofibrosarcoma associated to NF1 have an earlier presentation, higher metastatic capacity and worst prognosis comparatively to sporadic neurofibrosarcoma.[17,25]

Although most NF1 neurofibrosarcoma are a result

**TABLE IV**

**NF1 Frequent Manifestation**[30,33,20,34,14,36-42]

| Manifestation | Frequency |
|---|---|
| HTA | 6% |
| Phaeochromocytoma | 1% |
| Renal artery stenosis | 1% |
| Learning difficulty | 20-65% |
| Attention deficit with or without hyperactivity | 38-39% |
| Intellectual disability | 4,8-11% |
| Scoliosis | 10-25% |
| Low stature | 40% |
| Macrocephaly | 20-45% |
| Epilepsy | 3.5-7.3% |

from a malignization of a plexiform neurofibroma new cases can occur.[17,25]

Pointed out as possible explanations for such fact is the abhorrent expression of the epidermal growth factor receiver,[26] the hyperexpression of CD 44[27] and the link protein of cerebral lipid[28] and the homozygotic deletion of the tumoral suppressor P 16. [29]

To the high invasive character of such tumors it is added the fact of presenting a weak response to chemotherapy and radiotherapy and sometimes emerges a second malignant neoplasm (osteosarcoma, myeloid leukemia) with a cancer conventional treatment. Due to such vicissitudes and the evolution stage, it was decided not to start directed therapy.

Life expectancy in NF1 patients is around 15 years less than the general population, being the mortality before the 30 years of age associated to malignant tumors, as verified in the presented case. [31]

Malignancy apart of being an earlier cause of mortality is also the main cause of death. [32]

The clinical spectrum of NF1 is extremely wide, and not restricted to the cardinal diagnostic criteria.

Table IV summarize some of the symptoms and complications more prevalent in NF1.

It is highlighted that cardiovascular complications are an important cause of mortality in patients with NF1 having an earlier presentation comparatively with those in the general population. [35]

It is also verified a high frequency of rhabdomyosarcoma in NF1.

There is a NF1 variation called segmental NF1, different from the classical presentation as it is circumscribed to a part of the body and presents a risk of having descendents with a smaller NF1 generalizes (from 0 to 50%).[40]

A NF1 gene post-zygotic causing somatic mosaicism is at the origin of such process.

Spinal neurofibromatosis is another NF1 variation which can distinguish itself by presenting neurofibroma located mainly in the root of the spinal nerves, manifesting itself often by medullar compression. NF1 remaining typical manifestations are usually rare and minimal mutations of the NF1 gene are usually at the origin of such variation.[8]

Some very rare pathologies present some of theNF1 diagnostic criteria.

As an example is the neurofibromatosis type , that in spite of evolving with neurofibroma and café au lait spots is a distinct clinical entity linked to the mutation of NF2 gene located on chromosome 22. [41]

The great clinical variability and high risk of malignant neo plasmas (5 to 15%, around 2,5 to 4 times higher than the general population) imposes a regular and multidisciplinary follow-up. [42]

The follow-up is usual annual in children from 2 to 5 years old and in adults without complications.

The genetic study enables the identification of the mutation in around 95% of NF1 cases being particularly important in individuals presenting only one diagnostic criterion; although they do not allow foreseeing the disease evolution. [43]

Prenatal diagnosis can be made through the mutation identification, through amniocentesis or by a sample of the chorionic villi, however as mentioned previously the wide variability of the intra familial phenotype makes impossible to predict the seriousness of the disease.

## CONCLUSION

NF1 is a congenital disease, with a multi-organic involvement and unpredictable evolution, with a symptomatic treatment and sometimes only palliative, and the hope to find a more satisfactory approach relies on genetic advances. ■

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