

## A Study of Clinical Profile of Neurofibromatosis

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**Abstract:** Neurofibromatosis is an autosomal dominant disorder that affects the bone, the nervous system, soft tissue, and the skin. At least 8 different clinical phenotypes of neurofibromatosis have been identified and are linked to at least two genetic disorders. Clinical manifestations increase over time. Neurologic problems and malignancy development may supervene. The commonest clinical features were café au lait macules and lisch nodules seen in 90% patients each, multiple neurofibromatosis in 86.6% patients, axillary freckling was seen in 80% patients, learning disabilities in 33.3% patients, tumours of brain and spinal cord in 23.3 % patients, hearing defects in 20% patients, endocrinal abnormalities in 16.6% patients, schwannomas in 6.6% patients and plexiform neurofibromatosis in 2.5% patients.

### INTRODUCTION

Neurofibromatosis (NF) is a genetic disorder that affects the bone, soft tissue, skin and nervous system. It is classified into 2 distinct types, neurofibromatosis 1 (NF1) and neurofibromatosis 2 (NF2). NF1 occurs in about 1 in 3000 births whilst NF2 only occurs in about 1 in 50,000 births.<sup>1</sup>

NF1, also known as von Recklinghausen disease, is characterised by the presence of:

- 6 or more café-au-lait spots (defined oval-shaped light brown patches greater than 0.5cm in diameter)
- Multiple neurofibromas (tumours on, under, or hanging off the skin)
- Freckling (under the armpits and areas of skin folds such as the groin)
- Lisch nodules (tiny tumours on the iris of the eye)

NF2, also known as bilateral acoustic neurofibromatosis, is characterised by multiple tumours and lesions on the brain and spinal cord. Tumours growing on the auditory nerves that lead to hearing loss is usually the first symptom of the disease. Often this is not apparent until the late teens or early 20's. NF1 and NF2 occur as a result of defects in different genes. NF1 is caused by a mutation on a gene located on chromosome 17 and NF2 on chromosome 22. The mutated gene can be inherited from a parent who has NF or in some cases you could be the founder of a spontaneously mutated gene. A parent with NF has a 50% chance of passing the gene on to each of their children<sup>2</sup>. Aims was to study the epidemiology and clinical features of 30 patients of neurofibromatosis.

### MATERIAL AND METHODS

30 patients of type 1 and type 2 neurofibromatosis were selected for the study. Informed consent of all the patients was taken for the study and prior approval of the hospital ethical committee was taken for the study. The patients were made to undergo a thorough clinical examination and routine investigations of the patients were done. Xray of the skull, spine and long bones was done in all the cases. MRI examination of spine and brain was done in all the patients. A woods lamp examination was done in patients with very pale skin in an effort to view café-au-lait macules slit lamp examination was done to confirm the presence of lisch nodules. Histopathological examination of neurofibromatosis was done wherever the diagnosis was in doubt.

### RESULTS

The above table shows that maximum percentage of patients (50%) were between 21-30 years of age followed by 33.3% patients between

**Table 1 :** Table Showing Age Distribution Of Patients

S. No.	Age Distribution (Years)	Number of Patients	Percentage
1	0-10	1	3.3
2	11-20	10	33.3
3	21-30	15	50
4	31-40	2	6.6
5	41-50	1	3.3
6	>50	1	3.3

11-20 years of age, 6.6% patients were between 31-40 years and 3.3% patients were between 0-10 years, 41-50 years and more than 50 years each. There were 18 males and 12 females. Positive family history was seen in 27 of 30 cases (90%).

**Table 2 :** Table Showing Clinical Features of Neurofibromatosis

S. No.	Clinical Features	Number of Patients	Percentage
1	Café-Au-Lait Macules (> 5 in number and > 0.5 cm in diameter)	27	90
2	Multiple Neurofibromas	26	86.6
3	Axillary Freckling	24	80
4	Lisch Nodule	27	90
5	Learning Disabilities	10	33.3
6	Hearing Defects	6	20
7	H/O Epileptic Fits	5	16.6
8	Tumours Of Brain And Spinal Cord (Gliomas, Astrocytomas, Schwannomas, And Meningiomas)	7	23.3
9	Schwannomas	2	6.6
10	Endocrinal Abnormalities, (Short Stature, Gh Deficiency And Sexual Precocity)	5	16.6
11	Plexiform Neurofibromatosis	1	2.5

The above table shows that the commonest features were café-au-lait macules and lisch nodules seen in 90% patients each, multiple neurofibromatosis in 86.6% patients, axillary freckling was seen in 80% patients, learning disabilities in 33.3% patients, tumours of brain and spinal cord in 23.3 % patients, hearing defects in 20% patients, endocrinal abnormalities in 16.6% patients, schwannomas in 6.6% patients and plexiform neurofibromatosis in 2.5% patients.

## DISCUSSION

In our study, maximum percentage of patients (50%) were between 21-30 years of age followed by 33.3% patients between 11-20 years of age, 6.6% patients were between 31-40 years and 3.3% patients were between 0-10 years, 41-50 years and more than 50 years each. Male : Female = 3: 2 and males outnumbered females. It was seen that positive family history was seen in 90% patients with neurofibromatosis. The commonest clinical features were cafe au lait macules (Fig 1) and lisch nodules seen in 90% patients each, multiple neurofibromatosis in 86.6% patients, axillary freckling was seen in 80% patients, learning disabilities in 33.3% patients, tumours of brain and spinal cord in 23.3 % patients, hearing defects in 20% patients, endocrinal abnormalities in 16.6% patients, schwannomas (Fig 2) in 6.6% patients and plexiform neurofibromatosis (Fig 3) in 2.5% patients.

Neurofibromatosis is a neurocutaneous condition that can involve almost any organ system. Thus, the presenting signs and symptoms may vary widely. Two major subtypes exist: type 1 neurofibromatosis, which is the most common subtype and is referred to as peripheral neurofibromatosis, and type 2 neurofibromatosis, which is referred to as central neurofibromatosis. These descriptions are not especially accurate because type 1 neurofibromatosis often has central features.



**Fig. 1:** Type 1

neurofibromatosis with cafe au lait macules

**Fig. 2:** Type 2

neurofibromatosis with acoustic neuroma

**Fig. 3:** Figure

showing plexiform neurofibromatosis of the hand

A third variant is known as segmental neurofibromatosis; this term is used to describe disease limited to a single body region. Segmental neurofibromatosis may be related to mosaicism or segmental hyperexpression of the condition. Loss of heterozygosity may create the clinical impression of segmental lesions.<sup>3</sup> Worldwide, type 1 neurofibromatosis occurs in approximately 1 of 2,500-3,300 live births, regardless of race, sex, or ethnic background. The carrier incidence at birth is 0.0004, and the gene frequency is 0.0002. The incidence of type 2 neurofibromatosis is 1 case per 50,000-120,000 population.

Neurofibromatosis can involve various body systems over time. Signs can range from benign cutaneous manifestations to profound disfigurement. The mortality rate is higher than that of the healthy population because of the increased potential for malignant transformation of diseased tissues and the development of neurofibrosarcoma. Patients with type 1 neurofibromatosis have an estimated 3-15% additional risk of malignant disease in their lifetime. The extent and severity of manifestations of NF vary greatly from person to person and varies within the same family. Although isolated cafe-au-lait spots can be found in many people without NF, individuals with more than 5 of these have a good chance of also having NF1, particularly if they appear on the skin within the first 5 years of life. More than 5 cafe-au-lait spots are found in 1.8% of newborns, 25-

40% of children and 14% of adults with NF1. Freckling under the armpits is a clear sign of NF1. After puberty, Lisch nodules are present in 97-100% of patients with NF1. Clinically, they do not cause any problems but help to confirm diagnosis. There are basically 4 types of neurofibromas found in NF1:

- Cutaneous: superficial, soft button-like tumours with no malignant potential
- Subcutaneous: tumours in the dermis that may cause localised pain or tenderness
- Nodular plexiform: large network of tumours involving the dorsal nerve roots
- Diffuse plexiform: invasive tumours that may involve all layers of skin, muscle, bone and blood vessels

The severity of cutaneous involvement in NF1 is not an indicator of the extent of the disease as internal manifestations are common and are often more serious. Problems may occur in other parts of the body including:

- Malformation of the long bones (below the knee and elbow) and curvature of the spine (scoliosis)
- Short stature and growth hormone deficiency
- Learning difficulties (speech problems) and behavioural problems (25-40% have learning disabilities, 5-10% may have mental retardation)
- Tumours on the optic nerve which can cause visual loss
- High blood pressure and other blood problems
- Tumours on the spine and brain: increase risk of epilepsy
- Tumours or lesions on the gastrointestinal tract that may cause bleeding or obstruction
- Hearing defects

NF2 does not have as many outwardly signs as NF1 and in most instances substantial hearing loss is the first sign of possible NF2. The main problem of NF2 is the development of tumours on the brain and spinal cord. Most tumours in both NF1 and NF2 are non-cancerous (benign). But benign tumour enlargement can interfere with vital functions. It is estimated that a person with NF1 has a 3-15% increased risk for developing cancerous tumours.

Neurofibromas are the most common benign tumor of type 1 neurofibromatosis. These tumors are composed of Schwann cells, fibroblasts, mast cells, and vascular components. They can develop at any point along a nerve. Three subtypes of neurofibroma exist: cutaneous, subcutaneous, and plexiform. Both cutaneous lesions and subcutaneous lesions are circumscribed; neither is specific for type 1 neurofibromatosis. These nodules may be brown, pink, or skin colored. They may be soft or firm to the touch, and they may have the pathognomonic buttonhole invagination when pressed with a finger. Plexiform neurofibromas are noncircumscribed, thick, and irregular, and they can cause disfigurement by entwining important supportive structures. The plexiform subtype is specific for type 1 neurofibromatosis.<sup>4,5</sup> Neurofibromatosis is often diagnosed because of unusual pigmentary patterns.<sup>6,7</sup> Cafe au lait spots are irregularly shaped, evenly pigmented, brown macules. Most individuals with neurofibromatosis have 6 or more spots that are 1.5 cm or greater in diameter. In young children, 5 or more cafe au lait macules greater than 0.5 cm in diameter are suggestive of neurofibromatosis and should be pursued. Less than 1% of healthy children have 3 or more such spots, although 1 or 2 cafe au lait macules are commonly encountered in healthy individuals without disease. Lisch nodules are hamartomas of the iris that appear dome shaped and are found superficially around the eyes on slit lamp examination. They are

asymptomatic, but they help in confirming the diagnosis of neurofibromatosis. Axillary freckling (as well as freckling on the perineum), known as the Crowe sign, is a helpful diagnostic feature in neurofibromatosis. Both axillary freckling and inguinal freckling often develop during puberty. Areas of freckling and regions of hypertrichosis occasionally overlay plexiform neurofibromas. Bone involvement can include pseudoarthrosis of the tibia, bowing of the long bones, and orbital defects. Occasionally, pulsating exophthalmos can be encountered due to dysplasia of the sphenoid wings. Mild scoliosis may be encountered, and localized bony hypertrophy, especially on the face, may be identified. Whether these bony changes are caused by diffuse neurofibromas or other kinds of mesodermal defects is not entirely clear. Various neurologic abnormalities may occur. Acoustic nerve involvement and deafness may be seen, and gliomas of the optic nerve also occur. Various tumors, such as astrocytoma, meningioma, intramedullary glioma, and ependymoma, occur with greater frequency in these patients. Tumors may cause increased intracranial pressure, seizure, ataxia, or cranial nerve abnormalities. Schwannomas are uncommon in patients with type 1 neurofibromatosis, but they can present on spinal nerve sheaths. However, in type 2 neurofibromatosis, they are the most common tumor, involving cranial and peripheral nerves. The presence of a unilateral vestibular schwannoma (formerly known as an acoustic neuroma) should mandate inclusion of type 2 neurofibromatosis in the differential diagnosis. Many individuals with neurofibromatosis have below average intelligence. Of patients with type 1 neurofibromatosis, 25-40% may have learning disabilities, while 5-10% may have mental retardation. Types of learning disabilities may include neuromotor dysfunction and attention deficit hyperactivity disorder, as well as deficits in visuospatial processing. Endocrinologic problems associated with neurofibromatosis are common. Short stature and growth hormone deficiency are more common in these patients than in the general population, although the exact incidence is not known. Also, sexual precocity occurs in 3-5% of children who are affected, usually associated with an intracranial tumor. As mentioned, pheochromocytoma can occur.

Diagnostic criteria for type 1 neurofibromatosis (The diagnostic criteria are met if 2 or more of the features listed are present.)

- Six or more café au lait macules larger than 5 mm in greatest diameter in prepubertal individuals and those larger than 15 mm in greatest diameter in postpubertal individuals
- Two or more neurofibromas of any type or 1 plexiform neurofibroma<sup>8</sup>
- Freckling in the axillary or inguinal regions
- Optic glioma
- Two or more Lisch nodules (iris hamartomas)
- A distinctive osseous lesion, such as sphenoid dysplasia or thinning of the long bone cortex, with or without pseudoarthrosis
- A first-degree relative with type 1 neurofibromatosis according to the above criteria

Diagnosis criteria for type 2 neurofibromatosis (The criteria are met if condition 1 or 2 is present.)

- Bilateral masses of the eighth cranial nerve seen with appropriate imaging techniques (e.g., CT, MRI)
- A first-degree relative with type 2 neurofibromatosis and either (a) a unilateral mass of the eighth cranial nerve or (b) 2 of the following: neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular opacity

Plain radiography may show growth disturbance (ie, hyperplastic bones, "streaky" appearance to the medullary cavity, skull asymmetry, or sphenoid dysplasia), bowing deformities, or pseudoarthrosis of long bones. MRI of the brain and the cervical spine may be helpful in patients with type 1 neurofibromatosis, especially if signs or symptoms suggest lesions. MRI is used to assess the soft-tissue extent of disease and to determine involvement of the adjacent bone and spinal canal. Neurofibromas demonstrate low or intermediate signal on T1-weighted pulse sequences and homogeneously bright signal on T2-weighted sequences. Heterogeneity on T2-weighted sequences raises suspicion for malignant transformation. In patients suspected of having type 2 neurofibromatosis, MRI of the head is recommended in early adolescence. Dedicated MRI of the internal auditory canals is the most sensitive study for the detection of acoustic neuromas, especially small intracanalicular lesions. Optic glioma, a criterion for the diagnosis of type 1 neurofibromatosis, requires imaging for detection. MRI of the orbits is the study of choice. Using MRI to detect optic gliomas in asymptomatic children with type 1 neurofibromatosis is controversial because of the risks associated with the sedation required for an optimal diagnostic MRI. Large optic nerves likely indicate low-grade gliomas in these patients. MRI of the brain may demonstrate scattered foci of high T2 signal in the basal ganglia, thalamus, brain stem, and white matter of up to 50% of children with neurofibromatosis. 18-Fluorodeoxyglucose positron emission tomography (18-FDG PET) may be helpful in determining malignant changes in plexiform neurofibromas in persons with type 1 neurofibromatosis. Typical CT findings in persons with type 1 neurofibromatosis with chest involvement include small well-defined surface neurofibromas, focal thoracic scoliosis, vertebral scalloping, enlarged neural foramina, and characteristic rib notching from adjacent neurofibromas. Dural ectasia, meningoceles, and dumbbell-shaped masses are related to the presence of neurofibromas or abnormal pressure in and around the spinal canal. Dural ectasia is circumferential dilatation of the dural sac with fluid attenuation. The expanding dura can erode the surrounding osseous structures, widening the spinal canal, thinning the lamina, and disrupting the vertebral elements. A Wood lamp examination may be useful in patients with very pale skin in an effort to better view café au lait macules. Slit-lamp examination is recommended for children older than 6 years to confirm the presence of Lisch nodules.

Histologic evaluation of axillary or inguinal freckling reveals increased pigmentation along the basal layer of the epidermis and the presence of macromelanosomes. These macromelanosomes are not usually noted in Albright syndrome. Neurofibromas are characterized by wavy, spindle-shaped nuclei and a loose mucinous stroma.

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