# Neurofibromatosis Type1

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# Introduction

Neurofibromatosis type 1 (NF-1) is a genetic syndrome

It is characterized by clinical manifestations of systemic and

Progressive involvement that mainly affect the:

- the skin, nervous system, bones, eyes, and

- can affect any other organ

*S.F Aves Junior et al.2019*

NF-1 traditionally exhibits autosomal inheritance

It results from a mutation in the NF1 tumour-suppressor gene

This gene is located on the long arm of chromosome 17 (at locus 17q11.2)

This encodes a cytoplasmic protein called neurofibromin

This protein is a negative a negative regulator of *Ras* proto-oncogene

It is predominantly expressed in neurons, Schwann cells oligodendrocytes and astrocytes

Basically, NF1 is caused by autosomal dominant loss-of-function mutations in the *NF1* gene.

# Incidence and Prevalence

**NF1 is the most common neurocutaneous syndrome, and the most common autosomal disorder**

**NF1** has an incidence of 1 in 3,000 live births

Its prevalence is approximately 1 in 3000–4000 individuals worldwide

All ethnic groups and sexes are affected with equal frequency

Approximately 50% are inherited from an affected parent,

The other 50% result from a sporadic gene mutation

46% of patients with sporadic mutations do not meet the diagnostic criteria by Age 1 year

*Ramanjan V et al 2005*

*L Ina Ly et al 2019*

# Clinical diagnosis according to the NIH Consensus Developmental Conference (1988)

1. Six or more CALMs ≥ 5 mm in longest diameter in pre-puberty, and 15 mm in longest diameter in after puberty patients

2. Two or more neurofibromas of any type or 1 plexiform neurofibroma

3. Freckling in the axillary or inguinal regions (Crowe sign)

4. Optic glioma (OPG)

5. Two or more iris hamartomas (Lisch nodules)

6. A distinctive osseous lesion, such as sphenoid wing dysplasia or long-bone dysplasia (with associated cortical thickening and medullary canal narrowing), with or without pseudoarthrosis

7. A first-degree relative (parent, sibling, or child) with NF1 according to the criteria

# Revised diagnostic criteria for neurofibromatosis type 1 (NF1).

A: The diagnostic criteria for NF1 are met in an individual who does not have a parent diagnosed with NF1 if two or more of the following are present:

Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in post-pubertal individuals

Freckling in the axillary or inguinal region

Two or more neurofibromas of any type or one plexiform neurofibroma

Optic pathway glioma

Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging

A distinctive osseous lesion such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone

A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells

B: A child of a parent who meets the diagnostic criteria specified in A merits a diagnosis of NF1 if one or more of the criteria in A are present

If only café-au-lait macules and freckling are present, the diagnosis is most likely NF1 but exceptionally the person might have another diagnosis such as Legius syndrome. At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral.
Sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital plexiform neurofibroma.

*Legius E, et al. Nature 2021*

# Management approach

Neurofibromatosis 1 is a progressive disease

It is important that NF1 patients are followed up regularly

A multidisciplinary approach is critical in managing patients with NF

RXH utilizes this approach in managing patients with neurocutaneous disorders.

There is a dedicated clinic specifically for neurocutaneous disorders

*V. Ramanjan, et al. 2005*

# Multidisciplinary approach (cont'd)

The service is coordinated by staff from:

- paediatric neurology,

- neurosurgery,

- neurodevelopment,

- genetics.

- radiology

- Other important teams include ophthalmology, dermatology, plastic surgery, and orthopaedic clinics.

*V. Ramanjan, et al. 2005*

# Study at RXH

Report published in 2005 from RXH, n= 48 patients included in a study which reviewed:

**Clinical Phenotype of South African Children With Neurofibromatosis 1 (**Veruschka Ramanjam; Colleen Adnams; Alvin Ndondo; Graham Fieggen; Karen Fieggen; Jo Wilmshurst. JCN)

**At the time**: The policy was to perform brain neuroimaging on each patient after 8 years of age.

This age was selected because most optic gliomas develop in early childhood.

MRI screening in all patients allowed for appropriate counselling, and

Follow-up of patients with optic pathway tumors.

Similarly, patients with no optic pathway glioma were reassured that the probability of developing such a lesion was low.

# Current practice

While the clinical diagnostic criteria remains.

There is debate about the use of neuroimaging in all children with NF1

Some physicians still advocate for neuroimaging in all young children with NF1.

**However,** the consensus is that neuroimaging (MRI scan) should focus on children who are symptomatic

As such, from 2008, routine imaging of children with NF1 at RXH was discontinued with preference on the symptomatic group.

# Current Practice (Cont'd)

Currently, the neurocutaneous clinic registry at RXH has almost 200 children with neurofibromatosis.

These children are regularly followed up at the clinic

An important challenges:

Delays persist in identifying preschool children, limiting early cognitive development assessment and interventions

How does our service and patient load compare to current practice internationally?

# Aims:

1. Updating of the current NF1 registry, including

- Long term follow-up of the outcomes of pre-school children who underwent neurocognitive assessments

2. Audit of the current clinical practice

- Focus on neuroimaging practice

3. **Specific focus on the clinical profile, complications and long-term outcomes of children with giant plexiform neu**romas.

# My research for M.Phil

My research will focus on:

1. Audit of the current practice

**Hypothesis:**

The current practice of NOT routinely doing MRI for all children with NF is valid.

# The Study

1. Updating of the current NF registry with focus on Optic Pathway gliomas (OPGs)

- Its natural history, course and audit of patients diagnosed with OPG

2. Extracting the MRI scans previously done routinely, to look at the number of patients diagnosed with OPG

3. To also look at comparing the assessment of the ophthalmologist and the MRI scans

# Conclusion

- We hope that it will assist in looking at the lessons learnt and further lessons to be learned.
- Detailed literature review is in ongoing.
- A protocol for the study to follow soon.

**The End**