# Medical management of neurofibromatosis

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## Abstract

The neurofibromatoses consist of at least three autosomal dominantly inherited disorders, neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2) and schwannomatosis. For many years these conditions were inextricably linked as part of generalized neurofibromatosis (von Recklinghausen disease). Since 1987 with the separate localization of NF1 to chromosome 17q and NF2 (bilateral vestibular schwannoma) to 22q it has been possible to formally separate them. More recently the *SMARCB1* gene on 22q has been confirmed as causing a subset of schwannomatosis. The last 20 years has seen a considerable improvement in our knowledge of the clinical and molecular features of these conditions. Both NF1 and NF2 provide the clinician with often complex management decisions. Childhood presentation of NF2 in particular presages a usually severe disease course.


**Keywords** ependymoma; glioma; meningioma; MPNST; NF1; NF2; schwannoma; schwannomatosis

## Introduction

The neurofibromatoses have for most of their known existence been united as a single entity. Gradually in the latter 20 years of the 20th century the differences in clinical presentation and genetic cause resulted in the clinical definition of two conditions, NF1, formerly known as von Recklinghausen neurofibromatosis and NF2 as bilateral acoustic or central neurofibromatosis. The clinical and genetic distinction between the two conditions was not fully recognized until 1987 and NF1 and NF2 were frequently intermingled. The conditions were eventually recognized as separate entities with the localization of the respective genes to chromosome 17 and 22. This was followed by the formal clinical delineation at a U.S. National Institutes of Health (NIH) consensus meeting in 1987. The gene for NF1 was cloned on chromosome 17 in 1990 and for NF2 on chromosome 22 in 1993. A third type of neurofibromatosis called schwannomatosis has now also been delineated with clinical and tumour features which overlap with NF2. A separate chromosomal location for the condition was verified in 2003, and mutations in a subset of mainly inherited schwannomatosis cases confirmed in the *SMARCB1* gene 4 years later. In this review I will delineate the clinical, epidemiological and management aspects of NF1 and NF2.

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## Neurofibromatosis 1 (NF1)

### Genetics and epidemiology

A number of studies have addressed the genetics, prevalence and incidence of NF1. The autosomal dominant nature of the condition was recognized in the early part of the last century. Although many cases present as a *de novo* mutation of the gene, and appear as isolated instances, the presence of the disease features in multiple generations and with transmission from male to male, confirmed the presence of the gene as an autosomal disease. NF1 has a birth incidence of one in 2,500–3,300 and a diagnostic prevalence of one in 4,150–4,950. The highest frequency was reported in an Israeli study of military recruits with a prevalence of around one per thousand.

### Pathology and pathogenesis

NF1 is manifested by protean tumour and other clinical features. Most features especially tumours are caused by inactivation of both copies of the NF1 gene leading to loss of the protein neurofibromin in the cell. This loss of tumour suppression gives rise to a high risk of tumours particularly of neural crest origin. Even the common non-tumour features such as skin pigmentation with *cafe au lait* patches is caused by complete inactivation of NF1 (Figure 1).

### Disease course

NF1 is extremely variable in its disease course. Variation is often substantial even within families with the same genetic mutation. As such predicting disease severity is difficult. Children with early manifestation of multiple tumour disease are likely to do worse and this may be a manifestation of an early loss of the normal copy of the NF1 gene a large inherited deletion of the NF1 gene itself or of inheriting a bad combination of modifier genes. Diagnosis of one clinical feature does not usually imply a high risk of another complication although there are exceptions as optic pathway glioma is associated with a higher risk of symptomatic gliomas occurring elsewhere in the brain.

### Clinical manifestations

**Diagnostic criteria:** the diagnostic criteria for NF1 are shown in Table 1 and when used are unlikely to lead to misdiagnosis or confusion. These were originally devised at the 1986 National Institutes of Health (NIH) consensus conference. Patients with segmental neurofibromatosis can fulfil these criteria and clinicians should note any segmental involvement as this may mean the child has only a partial or 'mosaic' form of the disease. Clinicians need to be aware that a subset of individuals and families with multiple *cafe au lait* patches, without other NF1 primary features, have mutations in the *SPRED1* gene: a condition now called Legius syndrome.

**Disease features:** the disease features make up some of the categories for the diagnostic criteria:

- *Café au lait* patches
- Intertriginous freckling
- Cutaneous neurofibromas
- Plexiform neurofibromas
- Lisch nodules

In childhood *Café au lait* patches are smaller as reflected in the diagnostic criteria, but they become larger and may merge. They have a straight rather than ragged border, they are often described as like the "coast of California" in contrast to the "Coast of Maine" seen in McCune–Allbright syndrome. They

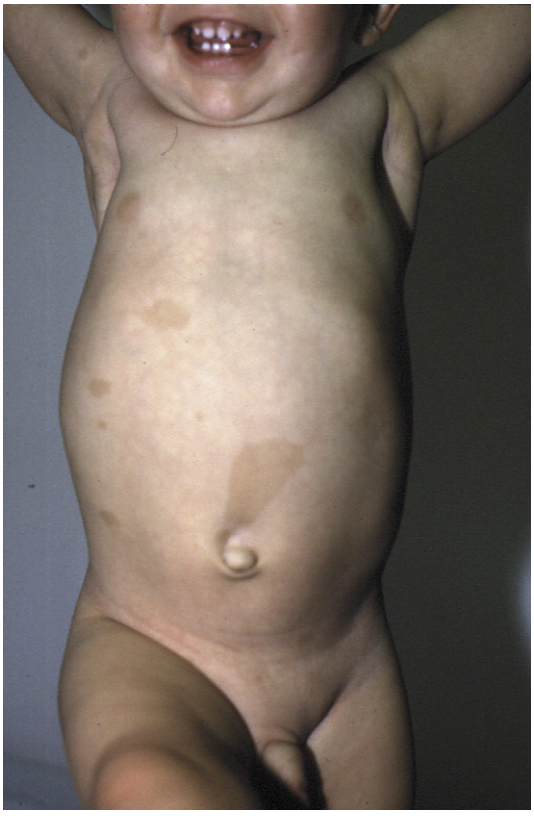

**Figure 1** *Cafe au lait* patches in an infant with NF1.

often fade in later life against the generally darker "dirtier" looking skin and may be less easy to recognize. They are flat and not associated with hair or malignant transformation. Freckling occurs in non-sun exposed skin typically in the axilla more frequently than the groin, and this usually appears later than the *café au lait*. Neurofibromas on and under the skin are the characteristic feature of NF1. Plexiform tumours are often visible from birth with diffuse involvement of the skin and underlying structures. About 2–3% of patients have unsightly plexiform tumours affecting the head and neck. The overlying skin is often hyperpigmented and loses elasticity, this often leads to a gravity effect of "sagging" of the tumour. Cutaneous tumours usually start as soft purplish coloured areas on the skin, but can evolve into unsightly warty outgrowths. Subcutaneous nodular tumours occur as growths on peripheral nerves, which are separate from the overlying skin. They may appear as fusiform swellings on more major nerve routes and can be painful to touch. The deeper fusiform subcutaneous and plexiform tumours may undergo malignant change to Malignant Peripheral Nerve Sheath Tumour (MPNST), although this is uncommon in childhood. Iris Lisch nodules (benign hamartomas) occur early in childhood and usually precede the appearance of cutaneous neurofibromas. They appear as a light browny-orange out-swelling from the latticework of the iris. In contrast to iris naevi which are flat and usually dark brown or black. Ophthalmic slit lamp examination is therefore a useful diagnostic aid in equivocal cases.

**Diagnostic criteria for NF1. Two or more must be present**

1. Six or more *cafe au lait* macules, the greatest diameter of which is more than 5 mm in prepubertal patients and more than 15 mm in postpubertal patients.
2. Two or more neurofibromas of any type, or one plexiform neurofibroma.
3. Axillary or inguinal freckling.
4. Optic glioma.
5. Two or more Lisch nodules.
6. A distinctive osseous lesion such as sphenoid dysplasia or pseudarthrosis.
7. A first degree relative with NF1 according to the preceding criteria.

**Table 1**

### History

Clinicians should take a family history for features of NF1 especially relating to the parents of the child. Presence of skin pigmentation (birth marks) from early life is usual with cutaneous lumps occurring around puberty or later. Most NF1 adults will not be in a high earning profession and 40% will have had educational problems.

### Examination

Full cutaneous examination of the child and the parents is important looking for cutaneous tumours, *café au lait*, freckling and for possible bony malformations. Slit lamp examination as above may be helpful. About 5% of children develop xanthogranulomas (small orangy nodules that appear in clusters on the skin) aged 2–5 years and these were thought to be associated with an increased risk of Juvenile Chronic Myeloid leukaemia. NF1 patients may also present in childhood with complications from an optic glioma, particularly visual loss. The tumours themselves are often very benign and vision may not deteriorate at all from presentation. Other features of optic glioma include precocious puberty with a rapid growth spurt or appearance of secondary sexual characteristics and ocular proptosis. Another rare presenting feature in the eye is congenital glaucoma in less than 1%.

### Complications

The frequency of disease features and complications are outlined from two UK studies in Table 2.

**CNS lesions:** large studies where children with NF1 have been screened with MRI or CT scans indicate that around 15% have at least a unilateral optic glioma. It is unclear how many children who have a scan detected glioma will ever develop symptoms as studies which have not specifically screened with imaging find much lower rates of between 0.7–5%. Tumours usually present between birth and 6 years of age peaking at around 3–4 years, but adult onset of symptoms does occur. Other brainstem gliomas are less frequent affecting around 1–2% of patients, but are more frequent in those with optic glioma. About 2% of NF1 patients present with symptoms from spinal tumours that require surgery, but on MRI imaging more than 60% appear to have spinal nerve root involvement. It is not clear why so few spinal tumours present symptomatically and this is in contrast to NF2 (see later). Other CNS lesions include macrocephaly (45% above 97th centile) aqueduct stenosis (less than 1%) and Unidentified Bright Objects (UBOs) on T2-weighted MRI (33%). About 3% of NF1 patients have epilepsy.