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REVIEW

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The neurofibromatoses. An overview

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Abstract The last two decades have seen clinical and molecular delineation of the different forms of neurofibromatosis. Differentiation of these forms is not just an academic exercise: their natural history, management and genetic counselling are quite different. Of the numerical classifications of neurofibromatosis proposed in the past, only neurofibromatosis type 1 (Nf1) and neurofibromatosis type 2 (Nf2) are now well delineated clinically and have been shown to be distinct at the molecular level. For both forms of neurofibromatosis, patients with clinical generalised disease have been demonstrated to be mosaic at the molecular level, and features of segmental or mosaic Nf1 and Nf2 have been delineated. Other reported forms of neurofibromatosis are rarer; they include Watson syndrome, hereditary spinal neurofibromatosis, familial intestinal neurofibromatosis, autosomal dominant café-au-lait spots alone, autosomal dominant neurofibromas alone, and schwannomatosis, the latter believed to be a variant of Nf2. Further delineation is needed for individuals having overlapping features of Noonan's syndrome and neurofibromatosis (the so-called Noonan/neurofibromatosis syndrome) and the syndrome of "multiple naevi, multiple schwannomas and multiple vaginal leiomyomas". In this article we review the forms of neurofibromatosis which we believe are true clinical entities. Particular attention is given to the neurological manifestations of neurofibromatosis.

Key words Neurofibromatosis • Nf1 • Nf2 • Mosaic/segmental neurofibromatosis • Variants • Classification • Neurological manifestations • Genetics • Childhood • Adulthood

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Introduction

The last decade has seen major developments in our knowledge of the different forms of neurofibromatosis. Evidence-based clinical diagnostic criteria and management guidelines have been developed. The genes for the two major forms, neurofibromatosis type 1 (Nf1) and type 2 (Nf2), have been cloned and the respective gene products, neurofibromin and merlin (sometimes called schwannomin) have been fully characterised [1-4].

Until the late 1970s, however, many clinicians did not distinguish the different forms of neurofibromatosis and used the terms von Recklinghausen disease or multiple neurofibromatosis to describe all patients with variable combinations of café-au-lait (CAL) spots and tumours of the peripheral or central nervous system (CNS). As systematic clinical research began, it became clearer that within this umbrella term there were several distinct diseases. The differentiation of these disorders is not simply an academic exercise – the natural history and management of the different forms of neurofibromatosis are very different.

In this article we review these developments and focus on the neurological aspects of the different forms of neurofibromatosis, trying to answer the questions that neurologists most often ask "neurofibromatologists".

Classification of the different types of neurofibromatosis

The definition of the different forms of neurofibromatosis depends on the occurrence, number and distribution of CAL spots, tumours of the nervous system (neurofibromas and schwannomas) and ophthalmologic findings (which are frequently asymptomatic) [1, 3]. Riccardi in 1982 [5, 6] proposed a classification of neurofibromatosis which included seven different types and an eighth category for cases "not otherwise specified". This classification has not come into general use partly because type III "mixed", type IV "vari-

ant" and type VII "late onset" forms are not defined sufficiently to permit their general use [3, 7]. Gorlin et al. [8] later added two further categories of type VIII "gastrointestinal" and type IX "neurofibromatosis/Noonan" forms. Viskochil and Carey [9] proposed in 1992 an alternative classification which laid the basis for differentiation by combining clinical and molecular knowledge. They divided the different forms of neurofibromatosis into two broad categories:

1. *Alternate* forms having some of the respective clinical features of either Nf1 or Nf2 yet not demonstrating the "typical" presentation; these included mixed type, localised types (segmental and gastrointestinal neurofibromatosis, and multiple CAL spots only) and schwannomatosis;
2. *Related* forms having classic clinical features of neurofibromatosis in addition to distinctive clinical features not typically seen in either Nf1 or Nf2, including Noonan/neurofibromatosis, Watson syndrome, duodenal/carcinoid/phaeochromocytoma/Nf1 and juvenile xanthogranuloma/Nf1.

At present, however, the most widely used classification continues to be that recommended in 1987 by the NIH Consensus Conference on Neurofibromatosis [10]. This is a numerical rather than descriptive or eponymic nomenclature, with Nf1 replacing the terms von Recklinghausen, peripheral neurofibromatosis or multiple neurofibromatosis, and Nf2 replacing bilateral acoustic or central neurofibromatosis. The consensus statement acknowledges that there are other types which, at that time, were not defined well enough to be part of the formal classification. Apart from mosaic/segmental Nf1 (formerly type V of Riccardi's classification) they are all extremely rare [3, 7]. In this article we review the forms of neurofibromatosis which we believe are true clinical entities.

Neurofibromatosis type 1

Nf1 is the most common form of neurofibromatosis and one of the commonest autosomal dominant disorders in man, with an estimated birth incidence of 1/2500 and a disease prevalence in population-based studies of 1/4500 [1, 2, 6, 11]. Nf1 is an extremely variable disease, even within families. From the patient's perspective, it is this variability, as well as the unpredictability of what will happen and when, that makes Nf1 a difficult disease for families to come to terms with and for clinicians to manage.

Historical perspective on Nf1

Possible illustrations of Nf1 sufferers with plexiform neurofibromas may date back as far as the second century [1, 6, 12], and a thirteenth century drawing of a man with skin nodules by a Cistercian monk named Heinricus seems to depict a patient with neurofibromatosis [13, 14]. However, the first clinical description of a case is attributed to Ulisse Aldovrandi, an Italian physician and naturalist, who in the sixteenth century described a man of short stature with large tumours growing from the left side of his head and upper trunk resembling plexiform neurofibromas [13, 14]. Drawings of a child with skin tumours and pigmented lesions from the eighteenth century can be seen in Buffon's *Histoire Naturelle,* while illustrations of pathological studies of Nf1 are found in *Cruveilhier's Anatomie Pathologique du Corps Human* [1, 12]. The first English language clinical report is that of Akenside in 1768, while Virchow's classification of neuromas and fibromas on a pathological basis laid the groundwork for the landmark presentation of one of his students and youngest assistant, Friedrich Daniel von Recklinghausen, who in 1882 in his report entitled *On Multiple Cutaneous Fibromas and Their Relationship to Multiple Neuromas* was the first to confirm the origin of skin tumours and to name them neurofibromas [1, 12-14].

Clinical features of Nf1

The clinical features of Nf1 are diverse and can affect almost any organ system [1, 2, 6, 11, 15-17]. We find it useful to consider them in three main groups major defining features, minor features, and disease complications [3, 7].

Major defining features of Nf1

The characteristic features of Nf1 are CAL spots, freckling in specific places, peripheral neurofibromas and Lisch nodules. These are present in the vast majority of affected individuals and form the basis for the diagnostic criteria (Table 1).

Table 1 National Institutes of Health diagnostic criteria for neurofibromatosis type 1. A positive diagnosis requires the presence of two or more of the listed criteria. (Modified from [2, 10])

Six or more café-au-lait macules > 5 mm in greatest diameter in pre-pubertal individuals, or > 15 mm in greatest diameter in post-pubertal individuals
Two or more neurofibromas of any type or one plexiform neurofibroma
Freckling in the axillary or inguinal region
Optic glioma
Two or more Lisch nodules (iris hamartomas)
A distinctive osseous lesion such as sphenoid wing dysplasia or thinning of the long bone cortex with or without pseudarthrosis
First degree relative (parent, sibling or offspring) with Nf1 diagnosed by the above criteria

Café-au-lait spots

Café-au-lait (CAL) spots are macules varying in diameter from 0.5 to 50 cm, having typically a smooth contour or, when large, irregular outlines. Their colour varies with background skin pigmentation. They are not unique to Nf1 patients and 11%-25% of individuals in the general population have one or two such skin lesions. Clinically, there are no differences between CAL spots in Nf1 patients and those in the general population; it is the increased number that is significant (Table 1). Few other conditions, however, give rise to more than six typical CAL spots, and are all extremely rare [1, 3, 17, 18]; they include ring chromosome syndrome and Schimke osseous dysplasia [1, 3, 18]. The other conditions that are confused with Nf1 largely fall into two groups: (1) those associated with abnormal skin pigmentation confused with CAL spots, such as McCune-Albright syndrome and Leopard syndrome; and (2) those associated with cutaneous or subcutaneous tumours including Proteus syndrome and congenital generalised fibromatosis [1, 3]. CAL spots may be present at birth or develop within the first 1-2 years of life. They increase in number in early childhood, but tend to fade with age or become obscured by numerous dermal neurofibromas. Hence, in adulthood it may be difficult to recognise or count a number greater than six. CAL spots are not found on the scalp, eyebrows, palms and soles.

Skinfold freckling

These are hyperpigmented macules resembling CAL spots that are 1-3 mm in diameter, not related to sun exposure, and seen in the axillae, groins and around the base of the neck [1, 3, 19]. They can also occur in the inframammary regions and over the trunk. They are unique to Nf1, appearing after CAL spots and usually before dermal neurofibromas develop.

Peripheral neurofibromas

Nearly all adult patients have *dermal* neurofibromas [1, 3, 20]. These lie within the dermis and epidermis and move passively with the skin. Most are discrete nodules that are soft, almost gelatinous in consistency, and violaceous in colour. In older patients they tend to increase in size and become papillomatous. They are rarely painful, sometimes cause itching, and are found mainly on the trunk but can appear on any body part. Their number is only roughly proportional to age, severely and mildly affected individuals being seen in all age groups. At present there is no means of predicting how many neurofibromas a patient will develop. The pattern of growth is unpredictable, with periods of rapid growth followed by relative quiescence. New neurofibromas or increased growth of preexisting lesions are often noted during pregnancy [20, 21]. Dermal neurofibromas rarely, if at all, undergo sarcomatous change, but it is prudent to remove rapidly enlarging or painful lesions [20].

A less common form of peripheral neurofibroma is the *nodular* neurofibroma, present in about 5% of Nf1 patients [1, 17, 20]. These develop subcutaneously on the major peripheral nerve trunks, and have a much firmer consistency and more defined margins. They are palpated under the skin or found in deeper parts of the body. They often give rise to neurological symptoms such as sensorimotor deficit due to pressure on the peripheral nerves and are a source of pain [20].

Histopathology reveals a mixture of cell types including Schwann cells, perineural-like cells, fibroblasts, mast cells, endothelial cells, lymphocytes, and cells with intermediate features. Their growth is initially along the course of nerve fibres which become encased by tumours. Staining for S-100 protein is invariably seen albeit less extensively than in schwannomas (see Nf2); the tumour is epithelial membrane antigen (EMA)-negative.

Lisch nodules

These are harmless, asymptomatic iris hamartomas [22]. They appear on slit-lamp examination as being smooth, dome-shaped, and usually light brown in colour. They develop during childhood, after the appearance of CAL spots but before peripheral neurofibromas. As they are unique to Nf1 and are present in over 90% of adults with Nf1 they are useful to confirm the diagnosis.

Minor features of Nf1

These features are present in a significant proportion of patients but are not so specific to be used as part of the diagnostic criteria.

Macrocephaly of unknown aetiology is seen in about 50% of people with Nf1. A child with Nf1 and macrocephaly, therefore, does not need to be investigated unless there are other symptoms or signs suggestive of intracranial pathology, or when serial measurements of head circumference show progressive enlargement.

Approximately 30% of Nf1 patients are at or below the 3rd percentile in height. When compared with unaffected siblings, Nf1 patients are usually 7-8 centimetres shorter. The cause of *short stature* is unknown.

Multiple juvenile *xanthogranulomas* may develop in 1%-2% of children with Nf1 [23, 24] predominantly on the trunk, head and extremities. They present in early childhood and disappear with age. There is some suggestion in the literature [23, 24] that Nf1 patients with xanthogranuloma are at increased risk for developing juvenile chronic myeloid leukaemia, but this may well just be a coincidental occur-

rence of rare Nf1 features due to report bias.

Angiomas (Campbell de Morgan spots), mostly on the trunk and thighs, are more common in Nf1 patients than in the general population irrespective of age [25].

Hypertelorism and *thoracic abnormalities* including pectus excavatum and pectus carinatum have been documented in 63% and 37.6% of patients in one series, respectively [26]. Documentation of such features may be a helpful aid in assessing the possibility of a diagnosis of Nf1 in children with only CAL spots [26, 27].

Complications of Nf1

We define a complication as any condition that occurs at increased frequency in individuals with Nf1 compared with the general population. Few of the complications are specific to Nf1, and most are also seen as isolated findings in the general population. It is the disease complications which make Nf1 a condition with significant morbidity and mortality. Their occurrence cannot be predicted, even within families. The major Nf1 complications are neurological disorders, plexiform neurofibromas, orthopaedic or opthalmolgic complications, general medical complaints, and malignancy.

Neurological complications

The temptation to accept every neurological occurrence in a patient with Nf1 as part of the Nf1 phenotype should be avoided as recent population-based studies show that neurological involvement is less frequent than previously thought.

Cognitive impairment. The intellectual impairment in Nf1 presents in childhood as learning difficulties and is relatively mild and non-progressive [28, 29]. The majority of Nf1 patients have a mean full-scale intelligence quotient (IQ) in the low-average range (around 90) compared with age-matched or sibling controls. Only around 3 to 8% of the children with Nf1 have mental retardation (defined as an IQ < 70). On psychological assessment, patients with Nf1 perform better on verbal than on performance tests and have particular difficulties with visuospatial orientation, attention span, and short-term memory, writing and calculation, most often leading to disruptive behaviour, poor reading and lack of organisation skills. The situation is further compounded by the high frequency (~ 40%) of impairment of gross and fine coordination in Nf1. Cognitive impairment may improve with age but only early intervention can help the patient avoid functioning below his intellectual capabilities in adulthood. These problems are present in 30%-60% of Nf1 children as compared to 6%-9% of schoolchildren in the general population, and are genetic in origin, albeit not fully penetrant, as recently shown in a mouse model of Nf1 [30]. Several studies have examined the hypothesis that either the number of the hyperintense lesions typically seen with brain magnetic resonance imaging (MRI) in Nf1 patients (discussed below in the section on hyperintense brain lesions on T2-weighted MR images) or altered expression of neurofibromin in the brain may account for cognitive deficits in Nf1, but there has been no consensus of opinion among researchers [31].

All children with Nf1 should have full neuropsychological assessment before school entry. Those infants and toddlers presenting with delay in developmental milestones, hypotonia and incoordination require early referral for appropriate management [1, 2].

Hyperintense brain lesions on T2-weighted MR images. High-signal-intensity lesions on T2-weighted MRI of the brain are a frequent finding in individuals with Nf1 [1, 2, 29, 31]. These are well-circumscribed, round to ovular, non-enhancing hyperintense lesions that usually do not produce mass effect. They are referred to as "unidentified bright objects" (UBOs) and are most commonly found in the basal ganglia, especially in the globus pallidus, internal capsule, thalamus, cerebellum, and brain stem regions. They are generally asymmetrical and occur in about 60% of children and young adults with Nf1 who undergo MRI, but they tend to disappear in adulthood and are seldom observed in patients over 30 years of age. They do not cause overt neurological symptoms. Although they have been postulated to represent foci of abnormal neuronal dysplasia, hamartomas, abnormal myelination, low-grade gliomas or heterotopias, their pathological correlation is yet debated [31-33]. Pathologic analysis of limited tissue specimens has confirmed several of these histologic findings in addition to intramyelinic areas of vacuolar or spongiotic changes with fluid-filled, coalesced or conflated vacuoles (from 5 to 100 μm in diameter) [32]. Although these lesions are distinctive and associated with Nf1, data on their specificity for Nf1 are scarce. Hence, there should be no reason to perform MRI to screen for the presence of UBOs, since they neither are a clinical diagnostic criterion nor have any prognostic or therapeutic significance. Nonetheless, their radiological behaviour is heterogeneous; in one study, the lesions located in the brain stem, thalamus and cerebellar peduncles evolved into true masses [31]. These findings suggest the possibility that there may be different effects of neurofibromin on different CNS locations [31, 34]. Hypometabolism was demonstrated in UBOs in one study [35] but not in others [36, 37]. UBOs must be distinguished from high-signal lesions which displace neighbouring structures and are brighter on T2-weighted images or enhance more intensely after intravenous injection of contrast medium, as the latter may well be low grade gliomas and necessitate continuous monitoring as discussed below in the section on brain tumours.

Brain tumours. Gliomas are a well-recognised complication of Nf1 and may arise in all parts of the brain, although the

sites of predilection are the optic pathway, brain stem and cerebellum [1, 29, 38, 39]. Medulloblastomas and ependymomas have also been described in Nf1 [1]. Conversely, meningiomas do not appear to occur with greater frequency in Nf1 and we did not observe any in ~ 500 Nf1 patients examined at the Oxford Neurofibromatosis Clinic (ONC) nor in the ~ 300 Nf1 children seen at the neurofibromatosis clinic at the Department of Paediatrics of the University of Catania (DPUC). There is no evidence to support an increased incidence of vestibular schwannomas (the hallmark of Nf2) in patients with Nf1.

Optic pathways gliomas (OPG) are pilocytic astrocytomas which cause expansion of the optic nerve. OPG may spread posteriorly to the optic chiasm and then either into the contralateral optic nerve, thalami or internal capsule; they may even cause obstruction of the cerebrospinal fluid (CSF) circulation leading to hydrocephalus [40]. The peak-age for developing an OPG in Nf1 is 4.9 years and symptomatic tumours seldom arise after the age of 6 years. Approximately 20% of Nf1 patients can have OPG on MRI but only 1%-5% develop symptoms. Clinical progression, once ophthalmic symptoms appear, is rare (~ 5%). In rare instances spontaneous involution has been documented [41]. Symptomatic patients complain of deterioration in visual acuity and loss of vision in the peripheral fields. Ophthalmologic examination may reveal impaired colour vision, retinal vein tortuosity, optic atrophy, strabismus or pupillary abnormalities. Proptosis or the presence of precocious puberty in a child may suggest rapid enlargement of a tumour [42]. Recent consensus guidelines [40] recommended only annual, full ophthalmologic evaluation in all newly diagnosed cases of Nf1 and in Nf1 children under 6 years by testing visual acuity, colour vision, and visual fields, and by fundoscopy and slit lamp examination. Neuroimaging in asymptomatic children was not recommended. Ophthalmologic evaluation should be repeated at annual intervals until age 10 years, then every alternative year until age 25 years. Early treatment is unnecessary and does not change clinical outcome. However, chemotherapy (carboplatin and vincristine) is the first choice treatment because of less side effects; radiotherapy is initially more effective but does not influence the long-term outcome. Surgery takes a role only with those cases having symptomatic unilateral lesions.

The frequency of *brain stem and cerebellar tumours* is greater in Nf1 than in the general population [29, 38, 43, 44]. These are mostly low-grade gliomas, but are sometimes medulloblastomas or, in the brain stem, ependymomas. On MRI they appear as diffuse enlargements of the brain stem, focal enhancing masses, intrinsic tectal tumours or focal non-enhancing lesions hyperintense on T2-weighted and hypointense of T1-weighted images. The majority do not require specific treatment but approximately 50% of patients may show clinical or radiological progression at some stage and some may experience symptoms or neurological deficits. These tumours seem, however, to have a more indolent course in Nf1 as compared to when they occur in isolation. In a few patients the clinical course is extremely aggressive. Excision and adjuvant radiotherapy, when feasible, resulted in stabilisation of these tumours in one series [43].

Gliomas may also arise at unusual sites, namely either around the third ventricle or in the hypothalamus or thalamus [1, 29]. Multicentric gliomas have been also described. We have seen a few serial MRI studies in asymptomatic Nf1 children, monitored up to five years, revealing extensive non-progressive abnormalities, especially in the basal ganglia, whose pathology is uncertain (unpublished observations).

The routine or screening use of brain MRI with contrast administration does not improve OPG prognosis because the majority of asymptomatic OPGs do not require treatment [29, 40]. This observation and the low prevalence (~ 2%-4%) of non-OPG CNS tumours in Nf1 have led to the consideration that neuroimaging is no longer necessary in Nf1. Instead, routine clinical examination is advised [1, 2, 45]. MRI should be reserved for those Nf1 patients presenting unexplained ophthalmologic or neurological symptoms or signs of precocious puberty.

Intraspinal, intramedullary and paravertebral tumours. Intrinsic low-grade or atypical gliomas and ependymomas of the spinal cord have been occasionally reported in Nf1 patients, although they are more common in Nf2. They usually present with impairment of pain and temperature sensation, reflex loss at the level of the tumour, sphincter disturbances or progressive paraparesis. They may be only slowly progressive but generally have a poor outcome. The usual practice is to confirm the diagnosis by neurosurgical biopsy and to offer irradiation. Total excisional surgery is generally difficult to perform. Spinal root neurofibromas may arise at any level from C1 to the cauda equina and may cause symptoms of spinal cord or spinal root compression.

Seizures and epilepsy. The occurrence of a seizure in an Nf1 patient may well signal the existence of a recognised complication of Nf1 such as tumours, hydrocephalus or cerebrovascular disease, but may, as for seizures in the general population, be idiopathic or consequential to non-Nf-related pathology. There is increased awareness that seizures may be relatively uncommon in Nf1 and not fully explained by underlying CNS lesions [29, 46-50]. The prevalence of seizures in most recent Nf1 population-based studies is 3%-5%, similar to the overall lifetime risk of epilepsy in the general population (2%-5%) [1, 11, 46, 48]. The most common seizures patterns are partial seizures followed by idiopathic generalised seizures and typical absences; infantile spasms can also occur [49, 50]. At the ONC, most Nf1 patients presented with idiopathic, generalised tonic-clonic seizures: only three out of the 19 having seizures had a structural cause (cerebral or cerebellar gliomas) for their epilepsy (M. Ruggieri, S.M. Huson, manuscript in preparation). Seizures were related to

underlying Nf1 specific causes (CNS gliomas and aqueductal stenosis) in 3 out of 13 Nf1 children with seizures followed-up at the DPUC (M. Ruggieri et al., manuscript in preparation). Overall, the clinical course, causes, response to treatment and prognosis are similar to seizures in the general population.

Headache. There is some suggestion in the literature and it is the experience of those who examine large numbers of Nf1 patients that some individuals with Nf1, especially children, may experience migraine headaches, characterised by steady or throbbing cephalalgia, nausea or abdominal pain [1-3, 11, 29, 51]. Abdominal pain can be accompanied by headache. These patients should have a careful physical and neurological examination to exclude other underlying Nf1 complications. By contrast, the use of neuroimaging or other diagnostic study will depend on the history, signs, and persistence of symptoms.

Aqueductal stenosis. Hydrocephalus due to aqueduct stenosis is a true, albeit rare, complication of Nf1 [29, 52, 53]. In some cases the pathologic basis consists of non-progressive proliferation of subependymal glial cells around the acqueduct. When symptomatic it requires immediate neurosurgical intervention by shunting.

Cerebrovascular disease. There is an increasing number of reports in the literature on intrinsic abnormalities of the intracranial vasculature in association with Nf1 [54]. However, the assumption of increased prevalence of this pathology in Nf1 has to be carefully interpreted since cerebrovascular disease is common in the community at large. Usually, presentation is with subarachnoid haemorrhage or as an incidental finding, but a miscellany of symptoms is not uncommon. Most cases affect the internal carotid artery, the proximal portions of the anterior and middle cerebral arteries, or rarely the posterior cerebral or vertebral arteries. The Moya Moya phenotype has been reported to occur at an increased frequency in Nf1 children [1]. Multiple arteries are often involved. Management is conservative.

Spinal meningoceles. In Nf1, spinal meningoceles are predominantly lateral herniations of the theca in the thoracic or cervical regions [55]. Most are incidentally found during radiological investigations, but neurological symptoms have been also reported.

Neurofibromatous neuropathy. Rare cases of progressive sensorimotor peripheral neuropathy in association with Nf1 have been reported: the neurological deficit was due to accumulation of multiple peripheral neurofibromata on the nerve roots. Electrophysiology can easily distinguish this occurrence from hereditary neuropathies [56, 57].

There are few cases of Nf1 patients with peroneal muscular atrophy due to an axonal form of hereditary motor and sensory neuropathy. This has been called neurofibromatous neuropathy and presents with foot drop and generalised weakness, mostly after intense exercise. Pathological findings reveal neurofibroma-like tissue in a subperineurial sleeve showing interlacing bundles of collagen fibrils with blood vessels surrounding a central core of more normal endoneuronal tissue. The progression is slow.

Multiple sclerosis. An increased frequency of multiple sclerosis has been reported in Nf1 patients [1, 11, 58]. Mutations in the oligodendrocyte-myelin glycoprotein (OMGP) gene which predispose to MS and is embedded within the *Nf1* gene were postulated but not yet detected [58].

Malignant peripheral nerve tumours. Malignant peripheral nerve sheath tumours (MPNSTs) are a true Nf1 complication [1, 6, 29]. These may occur at any site in the peripheral nervous system but are most common within plexiform neurofibromas (see below in the section on plexiform neurofibromas); rarely they occur in the dermis. In approximately 10% of patients they develop at a site that has been previously irradiated for another neoplasm. These tumours correspond to World Health Organization (WHO) grade III or IV, and about 50% of patients with MPNSTs have Nf1. The prognosis is usually poor and the tumours tend to occur in younger subjects [59, 60]. Wide excision is the only favourable prognostic factor; when not feasible radiotherapy is performed. Histopathology reveals fibrosarcoma-like, haemangiopericytoma-like or unusual histological features with fasciculated growth of tightly packed hyperchromatic spindle cells. In 50%-70% of cases, scattered tumour cells express S-100 protein. The majority of MPNSTs show positive staining for p53, in contrast to neurofibromas.

Psychiatric consequences in Nf1

Suggestions that patients with Nf1 suffer from psychiatric disease more than the rest of the population have to be evaluated with care. Hospital-based and population studies including case control groups [1, 6, 11] found that diagnosed psychiatric illness was no more common in Nf1 sufferers than in age- and sex-matched controls and that the scores of the Nf1 patients on a formal test of depression and anxiety were no different from those of the controls. Therefore, although patients with Nf1 may have somatic symptoms that cause them concern, most seem to cope with such symptoms as well as the rest of the community.

Plexiform neurofibromas

The second most common Nf1 complication, after learning difficulties, is plexiform neurofibroma (PNF), [1, 3]. PNFs

are clinically and pathologically distinct from dermal neurofibromas and usually appear within the first year or two of life although they may rarely manifest in young adulthood. They usually present as large subcutaneous swellings, soft in consistency, with ill-defined margins, varying from a few centimetres in diameter to a whole area of the body. Much less frequently, PNFs are nodular with nerve trunks developing discrete nodular tumours. The overlying skin is often hyperpigmented and hypertrophied or shows excessive hair growth. This often produces disfiguring, localised gigantism causing psychological problems. Surgery is difficult because of the massive involvement of soft or nervous tissue or both. MRI should always be considered to delineate the extent of internal involvement and to monitor lesion progression. PNFs may undergo sarcomatous degeneration or sarcomas may also occur *de novo* [60]. The current recommended management is conservative unless the PNFs are particularly unsightly causing functional problems, or if there is concern for sarcomatous degeneration [61].

Orthopaedic complications

Bone abnormalities are common in Nf1 and usually arise from intrinsic abnormalities of the skeletal system, from bony overgrowth or destruction caused by underlying PNF [1, 6, 62-64]. *Scoliosis* is present in 10% of Nf1 patients and is of two main varieties of curve:

1. *Dystrophic* scoliosis involves 4-6 segments and causes severe wedging and rotation of the vertebral bodies, rib thinning and scalloping. This form of scoliosis usually appears early in childhood, is rapidly progressive, is uncontrolled by bracing, and requires early fusion;
2. *Idiopathic* scoliosis may be convex to the left or to the right, and can be managed in the same way as conventional idiopathic scoliosis by an instrumented posterior fusion.

Pseudarthrosis of the long bones (usually of the tibia or fibula), due to a congenital defect of bone formation, is seen in 2% of Nf1 patients. Bowing, constriction or a defect in the affected long bone may present at birth. Spontaneous recurrent fractures or fractures following minor trauma manifest in early childhood and usually do not heal spontaneously. Other congenital deformities may be also present. Prognosis varies largely and several surgical techniques have been employed. In severe cases amputation of the affected limb may be needed.

Ophthalmological complications

Besides OPGs, ophthalmological complications include:

- Neurofibromas involving the eyelids or the orbit,
- Sphenoid wing dysplasia often associated with disruption of the posterior, superior wall of the orbit leading in turn to herniation of the temporal lobe into the orbit and pulsating exophthalmos,
- Idiopathic congenital ptosis (sometimes referred to as part of the so-called Noonanoid phenotype),
- Congenital or acquired glaucoma (usually unilateral),
- Choroidal hamartomas, and
- Diffuse or nodular enlargement of the corneal nerves (not pathognomonic of the disease) [1, 17, 22].

General medical complications

The commonest general medical disorder associated with Nf1 is hypertension usually secondary to the increased incidence of phaeochromocytoma and renal artery stenosis. For this reason, an annual blood pressure check is recommended for all Nf1 patients [1, 3, 11]. There is increasing evidence that congenital heart disease may occur with increased frequency in Nf1 [16]. Stenosis or aneurysms of the coronary arteries, as well as any other vascular district including those previously mentioned, have been reported in Nf1. Respiratory problems are infrequent in Nf1 but intrapulmonary neurofibromas or significant scoliosis may cause lung disease.

Carcinoid tumours, gastrointestinal neurofibromas, gangliocytic paragangliomas and ganglioneuromas have been, albeit rarely, reported in Nf1 [65]. They may cause pain, dyspepsia, haematemesis and melaena, abdominal distension, discomfort or constipation, and they must be taken into high consideration when dealing with gastrointestinal problems in Nf1 patients.

Malignancy

Malignant tumours occur four-times more frequently in Nf1 patients than in the general population. Cross-sectional and retrospective cohort studies give credible evidence for the validity of the association of Nf1 with some central nervous system tumours (especially glioma of the optic pathway), neurofibrosarcoma and phaeochromocytoma whose relative risk is surely high, but the absolute risk is low [11, 60]. The common adult cancers, however, do not seem to be associated with Nf1. By contrast, certain leukaemias (especially non-lymphocytic leukaemias of childhood) are validly associated tumours. The prognosis in Nf1 malignancies is not different from that of non-Nf1 individuals with the same tumour and stage and, therefore, there are no reasons to modify therapy just because the patient has Nf1.

Pathogenesis of Nf1

Nf1 has virtually 100% penetrance by the age of 5 years; the majority of patients develop six or more café-au-lait spots in the first two years of life. Approximately 50% of cases represent new mutations; the mutation rate is one of the highest recorded in humans [11, 66].

The *Nf1* gene was mapped in 1987 to chromosome 17 by linkage analysis [67, 68] and cloned in 1990 [69-71]. It spans over 350 kb of genomic DNA and encodes an RNA of 11-13 kb with at least 59 exons. Its protein product has been named neurofibromin, contains 2818 amino acids, and has an estimated molecular mass of 220 kDa [72]. The *Nf1* gene has four alternatively spliced transcripts, three of which have been studied in detail and show, to some extent, differential expression in various tissues. A portion of the coding sequence of the *Nf1* gene (about 13%) shows close homology to the GTPase-activating protein (GAP) family. This region is known as the GAP-related domain (Nf1-GRD). GAP proteins are involved in the regulation of *ras*, and the presence of this domain supports a tumour suppressor function for *Nf1*. Some but not all tumours associated with Nf1 show loss of heterozygosity at the *Nf1* locus, providing further evidence for a tumour suppressor action. Neurofibromin is involved in control of cell growth and differentiation by at least three possible mechanisms: as an upstream down-regulator of p21 *ras*, as a downstream effector of p21 *ras*, and as a link between tubulin and p21 *ras* [66].

The mouse *Nf1* gene shows strong similarity to the human locus [11]. Transgenic mice homozygous for a mutation in the *Nf1* gene lack neurofibromin in all tissues and do not survive beyond the day-14 embryo stage. The embryos show widespread developmental anomalies, and embryonic death is attributable to severe heart malformation. Heterozygote mice do not show classic Nf1 disease features but appear to have increased susceptibility to some of the tumours seen in the human disease, such as phaeochromocytoma and myeloid leukaemias [11, 66].

The large size of the *Nf1* gene has made mutation analysis difficult. No hotspot for mutation has emerged, the identified changes being spread throughout the gene. No obvious genotype/phenotype correlation has emerged except in the small minority of patients who have either large *de novo* deletions or a deletion of the whole Nf1 gene [73]. Distinctive features of these patients are that they have more severe intellectual handicap than normally seen in Nf1, facial dysmorphism (although a specific phenotype has not yet emerged), large hands and feet, and the development of cutaneous neurofibromas at a much earlier age than normal [74, 75].

The phenotypic variation of *Nf1*, however, may be largely determined by the action of modifying genes, which may vary from one disease feature to another. Thus, the pathogenesis of Nf1 is likely to be a complex process [11, 66]. Research is now being concentrated on the function of the other domains of the *Nf1* gene and on the genes which modify its action [11].

Management of Nf1 and genetic counselling

The diagnosis of Nf1 can be made by a careful clinical examination and detailed history. Family history should minimally include information on tumours and skin lesions in first- and second-degree relatives. Physical examination is directed at determining whether Nf1 diagnostic criteria are present; the examinations at different ages should be geared to particular complications (Table 2). Laboratory or imaging tests are dictated only by the findings on clinical examination. Routine screening by any means of investigation is not warranted in the management of Nf1. Genetic counselling should be provided for all at-risk family members.

Longitudinal care of Nf1 patients should be provided by clinicians familiar with neurofibromatosis. In our respective centres, we run specialist neurofibromatosis clinics offering co-ordinated care and follow-up by a group of specialists, including a paediatrician, ophthalmologist, neurologist, dermatologist, neurosurgeon and neuroradiologist.

The recommended protocol for children with Nf1 calls for an annual review to monitor disease progression, particularly with respect to the development of complications. Examination should be geared appropriately, as the majority of Nf1 complications present with symptoms either in childhood or not at all. Annual review at all ages must include blood pressure measurements. The follow-up of adults with uncomplicated Nf1 should include annual review of symptoms and blood pressure. More frequent re-evaluation should only be dictated by unusual symptoms.

The mainstay of care is anticipatory guidance and surveillance for treatable complications. As most of the patients with Nf1 will never develop major complications, it is not advocated that all patients need to attend a specialist clinic. Specialist assessment, however, can be helpful at the time of initial diagnosis, in the care of patients with unusual symptoms or complications, and in the management of Nf patients not easily classified as having Nf1 or Nf2.

As Nf1 is a dominant condition, patients have a 1 in 2 risk for having children with the disease. However, the severity of the disease in affected children is unpredictable. Thus, a parent with one particular complication will not necessarily have children with Nf1 and that complication. The child's expected risk of developing one of the Nf1 complications is 1 in 12 (8%), and the lifelong risk of malignant neoplasms is 1 in 20 (5%).

Mosaicism in neurofibromatosis

It is increasingly recognised that both Nf1 and Nf2 can arise from somatic mosaicism [7, 76]. For both forms of neurofibromatosis, patients with clinical generalised disease have been demonstrated to be mosaic at the molecular level. We will briefly describe features of segmental or mosaic Nf1 and the findings in patients with mild generalised Nf1 and mosaicism for the *Nf1* gene. In the Nf2 section, we will discuss features of segmental or mosaic Nf2.

Table 2 Major features and most frequent age-related complications in neurofibromatosis type 1. (Modified from [3])

Period of life	Major features	Complications
Birth - 2 years of life	Café-au-lait spots	Plexiform neurofibroma
	Macrocephaly	Sphenoid wing dysplasia
	Short stature	Pseudarthrosis
	Thoracic abnormalities	Hypertension (renal artery stenosis or phaeochromocytoma)
	Hypertelorism	Glaucoma
		Optic pathway glioma (unusual)
		Scoliosis (unusual)
Pre-school children	Café-au-lait spots ±	Learning difficulties
	Skinfold freckles	Optic pathway glioma (peak incidence 4-6 years)
	Macrocephaly	Other central nervous system tumours
	Short stature	Scoliosis (unusual)
		Hypertension (renal artery stenosis or phaeochromocytoma)
		Cerebrovascular disease
Late childhood and adolescence	Café-au-lait spots ±	Learning difficulties
	Skinfold freckling	Optic pathway glioma
	Lisch nodules	Other central nervous system tumours
	Occasional neurofibromas	Scoliosis
	Macrocephaly	Hypertension (renal artery stenosis or phaeochromocytoma)
	Short stature	Cerebrovascular disease
Adulthood	Café-au-lait spots ±	Spinal neurofibromas
	Skinfold freckling	Malignancy secondary to Nf1
	Lisch nodules	Endocrine tumours
	Neurofibromas	Hypertension (phaeochromocytoma)
	Macrocephaly	Duodenal carcinoma
	Short stature	

Mosaic/segmental Nf1

Patients with the signs of Nf1 limited to one or more body segments are usually referred to as having segmental Nf1 (Figs. 1 and 2) [76, 77]. This condition is being reported with increasing frequency [78, 79], and in a recent literature review we identified 150 cases up to 1997 [76, 80]. The frequency of cases referred to the ONC and PCUC appears to be 1 in 70 000-80 000 (0.0014%).

The first case of mosaic Nf1 was reported in 1931 by Gammel [81] who referred to it as "localised neurofibromatosis". Crowe et al. [82] termed the disease "sectorial neurofibromatosis" and postulated somatic mosaicism of the Nf1 gene as the likely cause. In 1977 Miller and Sparkes [83] suggested the term "segmental neurofibromatosis". Roth et al. in 1987 [84] divided the condition into four subtypes: (1) true segmental Nf or unilateral segmental Nf; (2) bilateral segmental Nf; (3) segmental cases with deep involvement; and (4) hereditary segmental Nf describing cases where parents with segmental Nf had transmitted the full-blown disorder to their offspring. In 1992 Viskochil and Carey [1, 9], following the somatic mutation hypothesis, proposed four phenotypic categories for mosaic Nf1.

We followed a group of 90 patients with mosaic Nf1 over a four-year period beginning 1995 and we classified them according to their Nf1 lesional patterns (M. Ruggieri, C. Moss, M. Upadhyaya, S.M. Huson, manuscript in preparation). We found patients with: (1) pigmentary anomalies only (Fig. 1); (2) neurofibromas (dermal and/or nodular) only (Fig. 2); (3) combination of pigmentary lesions and neurofibromas; and (4) plexiform neurofibromas only.

Age at onset of Nf1 manifestations varies according to the presence of pigmentation anomalies only (from birth until the first 2 years of life) or neurofibromas only (from around puberty to young adulthood). In cases with pigmentary changes, but also in those with pigmentary anomalies and neurofibromas, often the whole segment of affected skin had a darker background (seen either at naked eye or most often by Wood's lamp examination) than the unaffected parts of the body. In some patients the involved segment seemed to be more severely affected than that usually seen in the generalised disease [85, 86]. Most cases only had cutaneous involvement: in only 5% of cases in the literature and 11% of our cases was there an associated Nf1 complication.

The majority of reported cases of segmental Nf1 have no affected relatives with the disease. From our data, and from

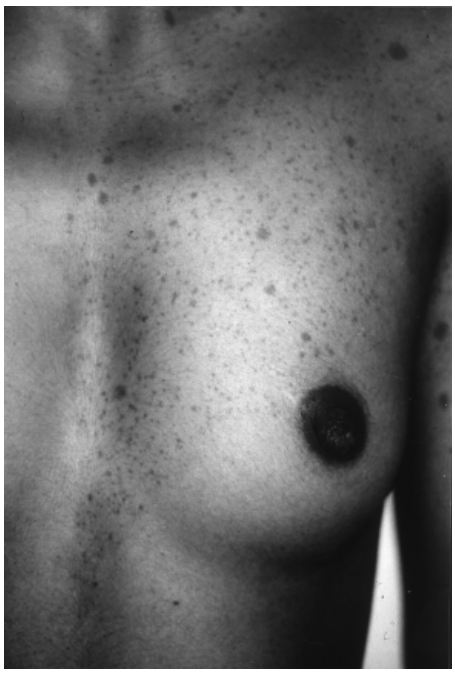

Fig. 1 *Mosaic/segmental Nf1 in a 20-year-old woman.* Circumscribed segment (left upper thoracic region, axilla and left forearm) of skin with multiple café-au-lait spots and freckles within. Note the sharp midline cut-off over the midthoracic region

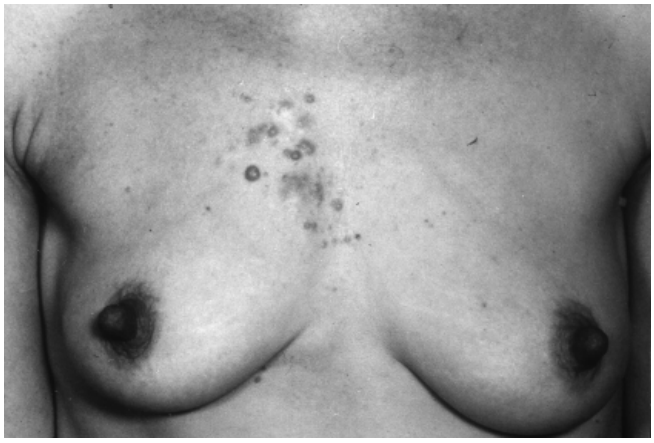

Fig. 2 *Mosaic/segmental Nf1 in a 40-year-old woman.* Circumscribed segment of skin with a cluster of dermal neurofibromas only over the right upper thoracic region

data in the literature [77, 87-91], there are a handful of cases where parents with segmental Nf1 have children with full-blown disease or with mosaic Nf1. It is assumed that these cases represent gonosomal mosaics with involvement of both somatic and gonadal tissue. From the clinical viewpoint, these cases emphasize the importance of examining both the skin and irides of parents of apparently isolated cases of Nf1 [77]. It is also important to realise that even though the segment of the body affected is distant from the gonads, there can be gonadal involvement [92]. Therefore, it is difficult to fully reassure individuals with apparent segmental Nf1 that there is no risk of Nf1 occurring in their offspring.

"Mild" generalised mosaic Nf1

Ainsworth et al. [93, 94] described a patient with multiple CALs, neurofibromas (NFs) and bilateral Lisch nodules but without family history of Nf1. Colman et al. [95] reported a 31-year-old female who was diagnosed with Nf1 at age 27 years after pathological examination of an excised NF. Her parents as well as her two children, aged 5 and 7 years, had no signs of Nf1. Loss of heterozygosity analysis performed on blood samples, NFs and skin samples obtained from affecetd and unaffecetd areas determined that both patients [93-95] were mosaic for a large deletion in the Nf1 region of the maternal-derived allele.

Neurofibromatosis type 2

Nf2 was not established as a distinct entity until 1970. The clinical overlap with Nf1 arises because CAL spots and peripheral nerve tumours occur in both conditions. However, it is extremely unusual for Nf2 patients to have six or more CAL spots and the nerve tumours are schwannomas not neurofibromas. Iris Lisch nodules do not occur in Nf2 but specific, usually asymptomatic, eye changes are seen.

Nf2 is inherited as an autosomal dominant trait, and about half the cases have no family history. Nf2 is much less common than Nf1, with an estimated birth incidence of around 1 in 33 000 and a symptomatic prevalence of 1 in 210 000 [1, 2, 96-98].

Historical perspective on Nf2

The first probable case of Nf2 was reported by Wishart in 1822 [99], predating the publications of von Recklinghausen on Nf1 by over half a century. Henneberg and Koch in 1903 [100] described the condition in detail. Following the description of von Recklinghausen disease, however, many subsequent authors reviewing cases of bilateral acoustic neuromas recognised that the cutaneous features were similar in both conditions and tended to label patients as having the same disorder. However, Gardner and Frazier in 1930 [101] suggested that bilateral vestibular schwannomas represented a separate entity. When Young, Eldridge and Gardner in 1970 [102] reported a follow-up of the original family of Gardner and Frazier, Nf2 at last became established as a distinct entity.

Clinical features of Nf2

Nf2 causes significantly more morbidity and mortality than other forms of neurofibromatosis and this is largely due to vestibular schwannomas and other cranial or spinal tumours [96-98]. Patients with Nf2 may be clinically subdivided into a severe (Wishart) type and a mild (Gardner) subtype. Individuals with the *severe-Wishart form* of the disease usually present before age 25 years, develop numerous tumours (> 3), require repeated surgical intervention, and often do not survive past 50 years of age [103]. Patients with the *mild-Gardner subtype* usually present with symptoms later in life (> age 25 years), develop a smaller number of more slowly growing tumours (often only bilateral vestibular schwannomas), and generally survive beyond the 5th decade [1, 2, 96-98]. The most recent Nf2 diagnostic criteria [2] recommend two categories of patients, those with definite Nf2 and those with presumptive or probable Nf2 (Table 3). The purpose of the latter group is to identify individuals who need to be kept under long-term surveillance for the development of other disease features. The frequencies of Nf2 features in the largest series so far reported are shown in Table 4.

Table 3 Diagnostic criteria for neurofibromatosis type 2. (Modified from [2, 10])

Confirmed (definite) Nf2

– Bilateral vestibular schwannomas (VS) or
– A family history of Nf2 (first-degree relative) plus:

Unilateral VS diagnosed at less than 30 years of age
Any two of: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract

Presumptive or probable Nf2 (should be evaluated for Nf2)

– Unilateral VS diagnosed at less than 30 years of age *plus* at least one of the following: meningioma, glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract
– Multiple meningiomas (2 or more) *plus* unilateral VS diagnosed at less than 30 years of age *or* one of the following: glioma, schwannoma, juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract

VS, vestibular schwannoma

Table 4 Clinical features and frequency of symptomatic lesions of neurofibromatosis type 2. (Modified from [1, 96-98]

Feature	Frequency (%)
Central nervous system tumours	
Bilateral vestibular schwannomas	85
Unilateral vestibular schwannomas	6
Meningiomas	45
Spinal tumours (meningiomas, schwannomas)	26
Astrocytomas	4
Ependymomas	2.5
Peripheral neurofibromas	
Overall	68
> 10 peripheral tumours (> 27 tumours)	10
Nf2 plaques	48
Nodular schwannomas	43
Nf-like cutaneous neurofibromas	27
Other nervous system features	
Peripheral neuropathy	3
Café-au-lait spots	
1-6 spots	43
1 spot	24
2 spots	11
3 spots	4
4 spots	3
6 spots	1
Cataract	
Overall	81
Posterior subcapsular	72
Cortical	41
Both types	33
Retinal hamartoma	9

Central nervous system tumours

Vestibular schwannomas. Representing the hallmark of the disease, vestibular schwannomas are bilateral in 85%-90% of cases [96-98, 104, 105]. Early symptoms include mild to moderate, progressive hearing loss accompanied by tinnitus or vertigo related to pressure on the cochlear nerve. These symptoms are the presenting features of Nf2 in the majority of affected patients. Other symptoms are imbalance, unilateral facial weakness, or disorientation when swimming underwater. Vestibular schwannomas are usually diagnosed synchronously, but there may be a time interval in their development with a mean interval of 7.5 years (range, 0.5-20 years). Sometimes, hearing may be preserved initially on one side in patients with bilateral lesions. Histopathology shows within a globoid and encapsulated mass the typical Schwann cells with abundant, eosinophilic cytoplasm; their growth reveals cellular (Antoni A) and hypocellular (Antoni B) patterns with strong and diffuse expression of S-100 protein or Leu-7 or, focally, glial fibrillary acidic protein (GFAP). In contrast to sporadic unilateral vestibular schwannomas, the tumours in Nf2 tend to present symptoms at a relatively young age, usually in the late teens or early 20s (average, 25.2 years; range, 7-50 years). Other differences between the tumours in Nf2 and their sporadic counterparts are the size of the tumours at diagnosis (larger in Nf2) and their appearance at operation (multi-

lobulated with the facial and cochlear nerves often directly entering the tumour in Nf2) [60]. The rate of growth of vestibular schwannomas in Nf2 is extremely variable and this has important implications for management.

Other cranial and spinal tumours. *Schwannomas* can also develop on other cranial nerves (except CI and CII) and on the dorsal roots of the spinal cord [1, 96-98]. The latter tumours are often multiple. The presenting features of the tumours are related to their anatomical localisation. With improved neuroimaging techniques, asymptomatic schwannomas (and meningiomas) are often detected incidentally on screening or during intracranial surgery for other tumours in Nf2 patients. It is of note that the presentation and MRI appearance of spinal schwannomas can be similar to that of spinal root tumours in Nf1, but in Nf1 these are neurofibroma and not schwannoma.

Meningiomas are relatively common in Nf2 and their symptoms are related to location [96-98]. These include headache of increasing frequency or severity, weakness, seizures, sensory changes, visual disturbances, changes in memory or personality, hoarseness, dysphagia, disequilibrium, and even transient ischaemic attacks. Often intracranial meningiomas are multicentric. In terms of pathological features they do not differ from those occuring sporadically. In children with severe Nf2, meningiomas or other CNS tumours often become symptomatic before the vestibular schwannomas. Meningiomas can occasionally involve the optic nerve and be confused as optic nerve gliomas, leading to misdiagnosis as Nf1. Spinal meningiomas can present with weakness, cramping and numbness, especially of the legs, radiating pain, and changes in bladder function.

Meningoangiomatosis is a distinctive, dysplastic, hamartomatous rather than neoplastic process, with a meningothelial component that can be associated with Nf2. When symptomatic, symptoms are related to location, and the most frequent site of involvement is the cerebrum [1]. This disease is usually fatal over a number of years.

Glial tumours, much less common in Nf2, include pilocytic astrocytomas or ependymomas of the brain and spinal cord [1, 96-98].

Other associated CNS lesions. These are usually asymptomatic and include intramedullary and perivascular schwannosis, discrete ependymal ectopias and glial microhamartomas. Syringomyelia can develop in association with intramedullary tumours [96, 98].

Peripheral nerve tumours

There are three types of peripheral nerve tumours associated with Nf2 [96-98, 106]:

1. Nf2 plaques (Fig. 3) are discrete, well-circumscribed, slightly raised, roughened, pigmented or hairy cutaneous lesions, usually less than 2 cm in diameter. These lesions should be carefully looked for when evaluating a patient with suspected neurofibromatosis because they are pathognomonic of Nf2;
2. Nodular schwannomas are similar to their counterpart lesion in Nf1 and present as subcutaneous, often spherical lesions in the large peripheral nerve;
3. The so-called Nf1-like dermal neurofibromas, similar to their counterpart in Nf1, are violaceous in colour, but much fewer in number than would be normally seen in adults with Nf1.

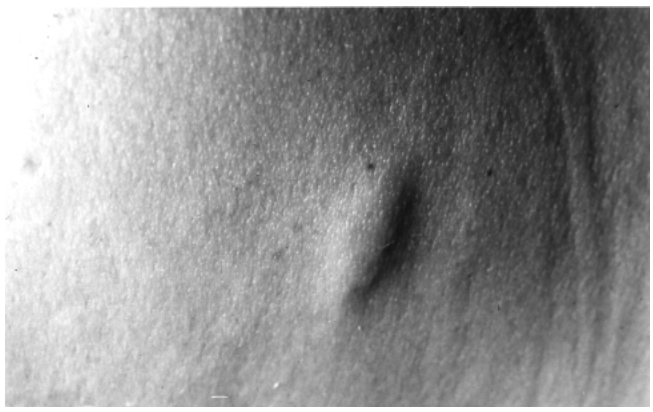

Fig. 3 *Nf2 plaque.* The characteristic Nf2 skin change is easily missed on examination. It is a small, slightly raised lesion. The skin is roughened, may be hairy and is usually orange-brown in colour

Café-au-lait spots

These simply occur more frequently in Nf2 patients but are not associated with other pigmentary abnormalities (e.g. skin-fold freckling), and only occasionally can be six or more in number (Table 4) [96-98].

Ophthalmologic findings

Posterior capsular or cortical (or both) cataracts are found in most affected Nf2 individuals [107, 108]. These lesions, however, cause significant visual disturbance only in a minority (2%) of Nf2 patients. Other ocular features which can cause significant visual loss include retinal hamartomas, epiretinal membranes, combined hamartomas of the retina and retinal pigment, and optic disc gliomas [108].

Other disease features

Mild, mixed peripheral motor and sensorineuropathy or motoneuritis multiplex occurs infrequently in some patients

with Nf2. The clinical features are glove and stocking sensory loss and peripheral weakness. The lesions have a characteristic appearance at nerve biopsy [1, 96, 98].

Intracranial calcifications on computed tomography (CT), not due to tumours and somewhat similar to those seen in tuberous sclerosis complex (TSC), have been reported in a number of Nf2 patients without any features of TSC. Their exact frequency and histopathology is unknown [1, 11].

Pathogenesis of Nf2

The *Nf2* gene was provisionally localised to chromosome 22 through studies of loss of heterozygosity of chromosome 22 DNA markers in acoustic neuromas in 1986 [109]. This was confirmed by linkage studies the following year [110]. The identification of germ-line deletions in Nf2 patients in the critical area of chromosome 22 facilitated the cloning of the diseased gene in 1993 [111]. The *Nf2* gene is a tumour suppressor gene which spans 110 kb and comprises 16 constitutive exons and one alternatively spliced exon. The *Nf2* gene sequence is homologous to the highly conserved protein 4.1 family. The protein encoded by *Nf2* is most similar to moezin, ezrin and radixin, so it was named merlin in abbreviation for moezin-ezrin-radixin-like protein [112]. The primary role of the protein 4.1 family appears to be mediating communication between the extracellular milieu and the cytoskeleton.

A wide variety of different mutations have been identified in the *Nf2* gene. Protein-truncation mutations have been correlated with the severe-Wishart form of Nf2, while a predominance of mild-Gardner Nf2 has been found in splice-site mutation carriers [113, 114]. Still, the role of *Nf2* mutations in the development of presenile lens opacities is unclear [113].

Management of Nf2 and genetic counselling

The successful management of Nf2 involves co-ordination between several different specialties, mainly neurosurgery, otolaryngology, ophthalmology and genetics. In comparison with Nf1, the follow-up of at risk family members is complex.

The standard for identification of vestibular schwannomas is MRI of the head with 3-mm cuts and fat saturation (suppression) in both axial and coronal views through the internal auditory canals with and without gadolinium administration. Full brain and spinal MRI, with and without gadolinium administration, however, should be obtained in all patients with a new diagnosis of Nf2.

Individuals at risk for Nf2 need genetic counselling and pre-symptomatic testing if feasible. A normal MR image at 16 or 18 years of age indicates a reduced risk of having inherited the condition. A normal MR image at age 30 years makes inheritance very unlikely, except in late-onset families, and may justify cessation of formal screening. Those at high-risk should have an ophthalmological check in the first year or two of life, clinical assessment in the early years only if symptoms occur, and MRI screening for cranial and spinal tumours usually beginning when the patient is a young teenager. Otolaryngological (including audiometry and evoked potential studies) and full ophthalmological examinations must be part of the protocol for newly diagnosed Nf2 individuals at all ages. Moreover, given the confusion regarding neurofibromas and schwannomas in individuals with Nf2, part of the evaluation of an individual suspected of having Nf2 should include a careful review of pathology reports and of the original tumour sections.

Follow-up for affected individuals includes an annual neurological evaluation with cranial MRI and audiological studies for those with any functional hearing, as well as ophthalmological evaluation and spinal imaging for those with specific problems in those areas.

The surgical treatment of individuals with Nf2 is complex and should probably be limited to specialised centres with experienced otolaryngologists and neurosurgeons. The decision to operate early on vestibular schwannomas or wait until symptoms or complete deafness ensue is complex. The tumour rate of growth must be monitored by MRI every 6-12 months. Stereotactic radiosurgery has been offered as an alternative to surgery in some selected patients, but one must take into consideration that radiation exposure may lead to malignant transformation in Nf2.

Genetic counselling

As clinical and radiological screening cannot reassure at-risk individuals that they have not inherited the condition until 30 years of age, molecular genetic testing for Nf2 has had a major impact on clinical practice. Mutation testing for Nf2 is available and mutations are found in about half the families tested. Identified mutations can be used for presymptomatic testing and the latter is warranted even in children.

Schwannomatosis

This condition, originally described in Japanese patients, was labelled as neurilemmomatosis [115-119]. It consists of multiple cutaneous schwannomas, central nervous system tumours, and various neurological deficits without other signs of neurofibromatosis. The overlapping features of schwannomatosis and neurofibromatosis consist of CNS tumours commonly found in Nf2. Of the 14 patients reported by MacCollin et al. [117], none had acoustic nerve involvement, three had lesions localised on one limb suggesting somatic mosaicism, two had only peripheral nerve

schwannomas, six had peripheral and spinal schwannomas, one had peripheral and cranial nerve schwannomas, one had spinal and cranial nerve schwannomas, and one had only spinal involvement. Symptoms included disabling pain and neurological disability related to cord compression. Only one patient had a positive family history. The authors assumed the most likely pathogenetic mechanism to be an autosomal dominant tumour suppressor gene possibly allelic to the *Nf2* gene.

Among the 21 cases followed up by Evans et al. [119], there were 5 families and 7 isolated cases. These authors emphasized the overlap between schwannomatosis and Nf2, as in their familial cases the majority of affected members only had multiple peripheral and spinal schwannomas, but one or two members in each case had either a unilateral acoustic neuroma or a meningioma. Moreover, in one of their families a brother and sister were considered to have the classic phenotype of schwannomatosis for many years, until one of them developed bilateral acoustic neurofibromas at the age of 44; this patient's son had a more typical course of classic Nf2 with bilateral acoustic neurofibromas diagnosed at the age of 22 years. DNA markers for the *Nf2* gene segregated with the disease in the two largest families. The authors concluded that schwannomatosis is likely allelic to Nf2 with particular mutations predisposing to this relatively specific phenotype [116, 119].

Patients with suspected schwannomatosis must be carefully screened for other signs of Nf2 and offered long-term follow-up for monitoring the development of further lesions. They should also be referred for genetic counselling.

Mosaic/segmental Nf2

Little is known about the outlying phenotypes of mosaic Nf2. Thirteen individuals with such phenotype have been identified and clinically characterised by MacCollin et al. [120]. Eight of these thirteen had unilateral vestibular schwannoma and other ipsilateral tumours suggestive of Nf2 mosaicism; in five additional cases, unilateral vestibular schwannoma was accompanied by other features of Nf2 without clear anatomic localisation. None of these individuals had a preceding family history of neurofibromatosis. There was a marked female preponderance, a relatively late age at onset of symptoms and a lack of transmission to offspring.

Molecular analysis on genomic DNA extracted from tumour specimens in three of the thirteen individuals demonstrated mutations in the *Nf2* gene which were present at low levels in leukocytic DNA, suggestive of somatic mosaicism. In two of the four patients with the mutation this observation was confirmed by identification of the same mutation in second tumours; "second hits" not present in the other tumours or blood were also identified in two further tumour specimens.

Other forms of neurofibromatosis

The outlying phenotypes and the molecular genetics of other, rarer, types of neurofibromatosis have been recently delineated. The main clinical features and the genetic aspects are summarised in Table 5.

Familial spinal neurofibromatosis

Four families exhibiting a distinct clinical entity of hereditary neurofibromatosis, consisting of extensively and apparently symmetrically distributed, histologically proven, multiple spinal neurofibromas, in association with CAL spots and occasional axillary freckling have been reported to date [115, 121-123]. Lisch nodules were detected only in two affected members of one family. No affected members in any family showed clinical features of Nf2. One of the two families reported by Pulst et al. [121] showed genetic linkage to the *Nf1* locus whereas the other family was most likely linked to *Nf2*. In the family of Poyhonen et al. [122], linkage to *Nf1* was established while linkage to *Nf2* was excluded. A frameshift mutation (8042nsA) in exon 46 resulting in a truncated *Nf1* protein has been detected by Ars et al. [123]. Recently, it has been suggested that spinal neurofibromatosis associated with Nf1 does occur more often than initially thought, its infrequent detection by other investigators being explained by the previous lack of routine spinal MRI studies [122].

Familial intestinal neurofibromatosis

Neurofibromas of the intestine are a recognised although rare feature of Nf1 [115, 124-129]. Sporadic cases of multiple intestinal Nf without cutaneous features of Nf1 have been observed. Hashemian [124] described "familial fibromatosis" of the small intestine, but two of the three cases had other stigmata of Nf1. Lipton and Zuckerbrod [126] described familial intestinal neurofibromatosis (without other features of Nf1). Verhest et al. [128, 129] described a family with localised intestinal neurofibromas with onset of symptoms in adulthood; some gene carriers of this family were asymptomatic into middle or late adulthood. This description fits with a localised expression of phenotype that may be allelic and tissue-specific.

Autosomal dominant café-au-lait spots alone

There have been a handful of families reported world-wide with multiple CAL spots, indistinguishable from those commonly found in Nf1, as the only disease feature segregating

Table 5 Classification of the different types of neurofibromatosis according to the presence or absence of clinical features

	CAL	Freckling	Neurofibromas		Schwannomas	LN	Eyes (other)	Major (or other) clinical features	Inheritance
			Dermal	Nodular					
Nf1	+	+	+	+	-	+	-	Complications affecting all body systems	AD
Mosaic Nf1	+	+	+	+	-	Rare	-	Features of Nf1 limited to one or more body segments (segmental distribution)	Somatic mutation, small risk of classical Nf1 in children
Nf2	> 6 (1%)	-	-	-	+	-	Cataract, Hamart.	Bilateral vestibular schwannomas, meningiomas, multiple CNS tumours	AD
Mosaic Nf2	> 6 (1%)	-	-	-	+	-	Cataract, Hamart.	Unilateral vestibular schwannomas associated with ipsilateral CNS tumours	Somatic mutation, small risk of classical Nf2 in children
Schwannomatosis	-	-	-	-	+	-	-	Multiple schwannomas skin + spinal cord	? (allelic to Nf2)
Spinal Nf	+	+/-	-	+	-	Rare	-	Multiple neurofibromas of the spinal cord	AD (linked to Nf1 gene?)
Intestinal Nf	-	-	-	-	-	-	-	Neurofibromas limited to the GI tract	AD gene not identified
Café-au-lait spots only	+	-	-	-	-	-	-	CAL spots as only disease feature	AD (some families linked to Nf1 gene)
Neurofibromas only	-	-	-	+	-	-	-	Neurofibromas as only disease feature	AD
Waston syndrome	+	-	+/-	-	-	Rare	-	Pulmonary stenosis and dull intelligence	AD (linked to Nf1 gene)

+, present; -, absent; +/-, occasional; ?, unknown; *CAL*, café-au-lait spots; *LN*, Lisch nodules; *AD*, autosomal dominant; *Hamart*., retinal hamartomas; *Nf*, neurofibromatosis; *CNS*, central nervous system; *GI*, gastrointestinal

as an autosomal dominant trait [130-132]. The segregation of DNA markers in the region of the *Nf1* gene has been studied in three of these families. Two families showed evidence of non-linkage [130, 131] while the other appeared to be linked to the *Nf1* locus [132].

When assessing children with multiple CAL spots as the only feature and no family history, Nf1 is by far the most likely diagnosis, although the diagnosis cannot be confirmed until other disease features appear [133].

Autosomal dominant neurofibromas alone

Korf et al. [134] studied 12 affected individuals with multiple subcutaneous and deep peripheral nerve tumours from a kindred of 5 generations. Age at onset ranged over the first two decades. Detailed examination of affected individuals failed to identify clinical features of either Nf1 (CAL spots, freckling or Lisch nodules) or Nf2 (vestibular schwannomas, meningiomas, or cataracts). In addition, the affected individuals were intellectually normal, without evidence of developmental problems or learning disabilities. Tumours from two members of the family were of nerve sheath origin with pathological features intermediate between neurofibroma and schwannoma. Absence of linkage to the *Nf1* or *Nf2* genes using polymorphic microsatellite markers was demonstrated.

Watson syndrome

Watson described autosomal dominant inheritance of pulmonary stenosis, multiple CAL spots and intelligence at the lower end of normal range [135]. The features distinguishing this condition from Nf1 were the pulmonary stenosis and the fact that intellectual problems were found in all family members in the original report. Allanson et al. [136] followed up the original Watson patients and confirmed that their phenotype had remained distinct from Nf1. A few other Nf1 features, namely Lisch nodules and dermal neurofibromas, were present in some of the individuals studied by Watson, but at a lower frequency than usually seen in Nf1. Linkage with markers for the *Nf1* gene and an *Nf1* mutation were subse-

quently demonstrated in these families [137]. The pathogenesis is so far unclear.

Neurofibromatosis-Noonan syndrome

A few patients with Nf1 have clinical features that overlap with mild Noonan's syndrome (NS) with mild ptosis and hypertelorism, down-slanting palpebral fissures, and posteriorly rotated ears. Pectus excavatum can also occur in both conditions. Despite the volume of work and number of cases and families, controversy and conflict still surround the topic of the so-called neurofibromatosis-Noonan syndrome (NFNS) [138]. Various possibilities have been proposed to explain the coexistence of NS and Nf1 in the same patients [138]:

1. Coincidence of two common autosomal dominant disorders with the genes for Nf1 and NS segregating separately;
2. The manifestations of Nf1, specifically the CAL spots, can occur as a component of the classic NS as reported in a family with NS and CAL spots with no linkage to the *Nf1* locus;
3. The manifestations of NS in these patients are simply a variable manifestation of classic Nf1, just like optic gliomas, scoliosis, etc.; or
4. NFNS may represent a discrete entity with the entire pattern running true in some kindreds.

Our clinincal experience and literature review lead us to suggest the third possibility is correct and that this is not a distinct entity.

Multiple schwannomas, multiple naevi, and multiple vaginal leiomyomas

A new syndrome consisting of multiple deep or superficial schwannomas, multiple naevi (compound and melanocytic types), and vaginal leiomyomatosis has been recently reported [139]. Inheritance of the syndrome is dominant, although at the time of the report it had not yet been determined whether autosomal or X-linked. The marker of the syndrome appears to be naevi, although variable in number and not manifest in all the affected members. The tumours develop relatively late (i.e. when patients are over 30 years of age). Although Nf1 and Nf2 were ruled out on clinical grounds alone, linkage studies have not yet been published.

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Sommario *Le ultime due decadi sono state molto importanti per la caratterizzazione clinica e molecolare delle varie forme di neurofibromatosi. La differenziazione di tali forme non rappresenta un mero esercizio accademico, poiché la storia naturale, il tipo di "gestione" dei pazienti ed il consiglio genetico variano a seconda delle diverse forme. Tra le varie classificazioni numeriche delle neurofibromatosi proposte nel passato solo la neurofibromatosi tipo 1 (Nf1) e la neurofibromatosi tipo 2 (Nf2) appaiono oggi ben caratterizzate dal punto di vista clinico e ben distinte dal punto di vista molecolare. Per entrambe le forme di neurofibromatosi in pazienti affetti da malattia generalizzata è stato dimostrato a livello molecolare il fenomeno del mosaicismo; sono state inoltre delineate le principali caratteristiche cliniche della Nf1 e Nf2 a mosaico (segmentale). Altre forme, più rare, di neurofibromatosi sono la sindrome di Watson, la neurofibromatosi spinale ereditaria, la neurofibromatosi intestinale familiare, le così dette forme con "macchie caffè-latte a trasmissione autosomica dominante" e con "neurofibromi a trasmissione autosomica dominante" e la schwannomatosi, quest'ultima ritenuta oggi una variante allelica della Nf2. Ulteriore caratterizzazione necessitano invece le forme con manifestazioni sovrapposte di sindrome di Noonan e neurofibromatosi (la così detta sindrome Noonan/neurofirbomatosi) e la sindrome dei nevi multipli/schwannomi multipli/leiomiomi vaginali multipli. In questo articolo descriveremo le forme di neurofibromatosi da noi ritenute vere entità cliniche approfondendone gli aspetti neurologici.*

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