Chapter 4
Neurofibromatosis

D. Gareth R. Evans

Abstract Neurofibromatoses are made up 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 generalised neurofibromatosis as first delineated by von Recklinghausen. In 1987 the separate localisation of the NF1 gene to chromosome 17q and NF2 (bilateral vestibular schwannoma) to 22q led to a consensus conference at the National Institutes of Health. At this conference the two main neurofibromatoses, NF1 and NF2, were formally separated. More recently, the *SMARCB1 and LZTR1* genes both on 22q have been confirmed as causing a subset of schwannomatosis. The last 28 years have seen a great improvement in understanding 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 predicts a severe multi-tumour disease course. Malignancy is rare in NF2 particularly in childhood; however, there are significant risks in NF1. NF1 is associated with a risk of juvenile myelomonocytic leukaemia (JMML), rhabdomyosarcoma and malignant peripheral nerve sheath tumour as well as a substantial risk of noninvasive pilocytic astrocytoma particularly affecting the optic pathway. The malignancy risk in schwannomatosis is not well defined but may include an increased risk of malignant peripheral nerve sheath tumour.

Keywords Neurofibromatosis · Schwannomatosis · NF1 · NF2 · Café au lait macules · Lisch nodules · Plexiform neurofibroma

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4.1 Introduction

Neurofibromatoses have for most of their known existence been lumped together as a single entity. This was largely due to the highly influential Harvey Cushing describing that bilateral tumours of the "nervus acusticus" was part of von Recklinghausen disease in the early part of the twentieth century [1]. The clinical and genetic distinction between the two conditions was not fully recognised until the last three decades, and NF1 and NF2 were frequently intermingled in prior reports [2]. Gradually in the latter 20 years of the twentieth century, the differences in clinical presentation and genetic cause resulted in the definition of two distinct conditions, NF1, formerly known as von Recklinghausen neurofibromatosis, and NF2 as bilateral acoustic or central neurofibromatosis. The conditions were eventually recognised as separate entities with the localisation of the respective genes to chromosomes 17 and 22 [3, 4]. This was followed by the formal clinical delineation at a US National Institutes of Health (NIH) consensus meeting in 1987 [5]. The gene for NF1 was cloned in 1990 [6] and the NF2 gene in 1993 [7, 8]. Since 1987 there has been no evidence that either classical NF1 or NF2 fulfilling NIH criteria were anything but homogeneous conditions. Thus far there is no evidence of exclusion of classical NF2 (bilateral VS) from the *NF2* locus on 22q [9] or of NF1 from the locus on 17q. There is nonetheless phenotypic overlap, and families with multiple café au lait patches and macrocephaly without neurofibromas or other typical NF1 features may either have a three-base-pair deletion in *NF1* [10] or a *SPRED1* pathogenic variant (PV) [11]. A third type of neurofibromatosis called schwannomatosis is now accepted [12] with clinical and tumour features which overlap with NF2. A separate chromosomal location for the condition was identified in 2003 [13], with a gene causing at least a proportion of schwannomatosis, *SMARCB1* identified in 2009 [14]. In this chapter, I will delineate the clinical, epidemiological and molecular aspects of NF1, NF2 and schwannomatosis and particularly how they manifest in childhood.

4.2 Neurofibromatosis 1 (NF1)

4.2.1 Genetics and Epidemiology

A number of studies have addressed the genetics, prevalence and incidence of NF1. The autosomal dominant inheritance pattern of NF1 was recognised in the early 1900s. Although many cases present as a de novo mutation of the gene and appear as isolated cases, the presence of the disease features in multiple generations and with transmission from male to male confirmed the gene as an autosomal dominant [2]. NF1 has a birth incidence of 1 in 2052–3300 [2, 15–17] and a diagnostic prevalence of 1 in 4088–4950 [15–17]. The highest frequency was reported in an Israeli study of military recruits with a prevalence of around 1 per 1000 [18]; however, this

was based largely on the presence of ≥6 café au lait patches and could represent a founder effect for the three-base-pair deletion in *NF1* or *SPRED1* PVs [10, 11, 16, 19]. Indeed only two-thirds of children with ≥6 café au lait patches and no tumour features of NF1 had an *NF1* PV [19].

4.2.2 Pathology and Pathogenesis

NF1 is characterised by multiple site tumour and other clinical features [2, 20, 21]. Most features especially tumours are caused by inactivation of both copies of the *NF1* gene leading to loss of the NF1 protein (neurofibromin) in the causative cell. This causes loss of tumour suppressor function leading to a high risk of tumours particularly of neural crest origin. Even the common non-tumour features such as café au lait patches are caused by complete inactivation of *NF1*.

4.2.3 Disease Course

NF1 is widely variable in disease course. This variation is frequently great even within families with an identical *NF1* PV. Such predicting disease severity is difficult. Children with early manifestation of multiple tumour disease are likely to have a more severe disease course, and this may be a manifestation of an early loss of the normal copy of the *NF1* gene or due to a germline large inherited deletion of the *NF1* gene itself or of inheriting a pattern of modifier genes that alter the phenotype. 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 [22].

4.2.4 Clinical Manifestations

4.2.4.1 Diagnostic Criteria

The diagnostic criteria for NF1 are shown in Table 4.1 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 +/− axillary/inguinal freckling, without other NF1 primary features, have PVs in the *SPRED1* gene: a condition now called Legius syndrome [11, 16, 19]. One study showed that 8% of children with no family history or

Table 4.1 NIH diagnostic criteria for NF1

Two or more must be present
1. Six or more café 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

personal tumour features of NF1 who only had pigmentary criteria harboured a *SPRED1* PV [19]. While the criteria have stood the test of time, they are currently being modified by an international group to recognise the overlap with Legius syndrome and incorporate molecular criteria.

4.2.4.2 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 typically have a straight rather than ragged border, and they are often described as like the "coast of California" in contrast to the "coast of Maine" seen in McCune-Albright syndrome. They often fade in later life against the generally darker "dirtier"-looking skin and may be less easy to recognise without a Wood's light. They are flat with no associated hair and have no propensity for malignant transformation. Freckling usually occurs in non-sun-exposed skin with the axilla more frequently affected than the groin. Freckling usually appears later than café au lait patches. Neurofibromas on and under the skin are the characteristic feature of NF1. These often start as pink−/purple-raised soft lesions that can then transform into more "wart"-like growths (Fig. 4.1). Plexiform tumours, which represent an early potentially embryonic tumour, 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 [22]. 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,

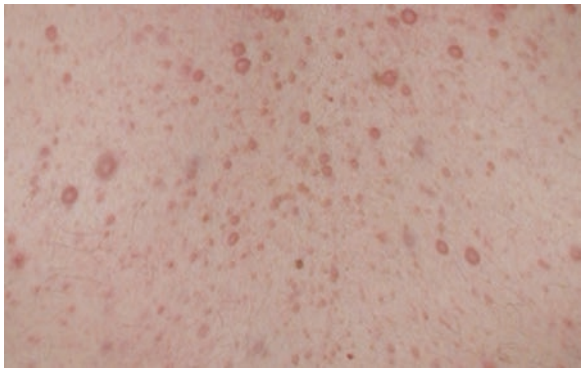

Fig. 4.1 Cutaneous neurofibromas in NF1. Pinkish/purple skin lesions and papillomatous lesions

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 brown-orange out-swelling from the latticework of the iris. In contrast to iris nevi which are flat and usually dark brown or black. Ophthalmic slit lamp examination is therefore a useful diagnostic aid in equivocal cases.

4.2.5 History

Clinicians should take a family history for features of NF1 especially relating to the parents of the child. The presence of skin pigmentation (birth marks, Fig. 4.2) 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.

4.2.6 Examination

Full cutaneous examination of the child and their parents is important looking for cutaneous tumours, café au lait, freckling, and possible bony malformations [23]. Slit lamp examination of the irides may also be helpful, and choroidal abnormalities using infrared monochromatic light have been identified as a possible additional method of differentiating NF1 from Legius syndrome [24]. About 5% of children develop xanthogranulomas (small orange-coloured nodules that appear in clusters on the skin) aged 2–5 years, and these were thought to have been associated with an increased risk of juvenile chronic myeloid leukaemia. NF1 patients may also be

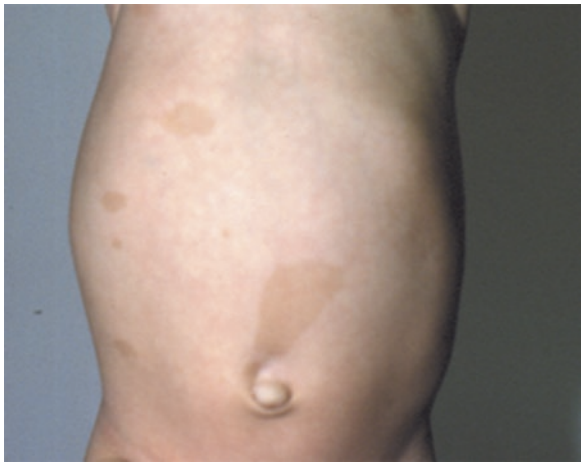

Fig. 4.2 Cafe au lait patches in an infant with NF1

present in childhood with complications from an optic glioma, in particular with 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 <1%.

4.2.7 Complications

The frequency of disease features and complications is outlined from two UK studies in Table 4.2.

4.2.7.1 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 [25]. 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% and 6% [20–22]. Tumours usually present between birth and 6 years of age peaking at around 3–4 years [25, 26], but adult onset of symptoms does occur. Other brain stem gliomas are less frequent affecting around 2–3% 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

Table 4.2 NF1: clinical features, with typical ages at presentation and childhood risk

	Disease feature in percentage (%)	Frequency (paediatric risk) presentation	Age of
Patients in series	**135**	**523**	
Major defining features			
Café au lait spots	>99	98 (98–99)	Birth-puberty
Freckling	67	88 (60–88)	Birth-puberty
Peripheral neurofibromas	>99	60 (20–60)	≥7 years
Lisch nodules	90–95	63 (20–60)	≥3 years
Complications			
Plexiform neurofibromas			
All plexiforms	30	15 (15)	0–18 years
Large lesions of the head and neck	1.2	6 (6)	0–3 years
Limbs/trunk lesions associated with significant skin/bone hypertrophy	5.8	5 (5)	0–5 years
Intellectual handicap			
Severe	0.8	0.5	
Moderate	2.4	2	0–5 years
Minimal/learning difficulties	29.8	35	
Epilepsy			
No known cause	4.4	4.9 (3–5)	
Secondary to disease complications	2.2	0.7	Lifelong
Hypsarrhythmia	1.5	1	0–5
CNS tumors			
Optic glioma	1.5	5 (5–6)	Childhood (usually)
Other CNS tumors	1.5	2.0 (1)	Lifelong
Spinal neurofibromas	1.5	2.0 (0.2)	Lifelong
Aqueduct stenosis	1.5	1.2	Lifelong
Malignancy			
Malignant peripheral nerve sheath tumors	1.5	5 (0.2)	Lifelong
Pelvic rhabdomyosarcoma	1.5	0.2 (0.2)	0–5
Orthopaedic complications			
Scoliosis, requiring surgery	4.4	2.6	0–18
Scoliosis, less severe	5.2	12	
Pseudarthrosis of the tibia and fibula	3.7	2.3	0–5
Vertical scalloping	10.0		Lifelong
Gastrointestinal tumors (neurofibromas and GISTs)	2.2	2.0 (0)	Lifelong
Renal artery stenosis	1.5	0.6	Lifelong
Pheochromocytoma	0.7	0.4 (0.2)	≥10 years
Duodenal carcinoid	1.5	2 (0.1)	≥10 years

(continued)

Table 4.2 (continued)

	Disease feature in percentage (%)	Frequency (paediatric risk) presentation	Age of
Congenital glaucoma	0.7	0.6	0–1
Juvenile xanthogranuloma	0.7	0.6	0–5
Sphenoid wing dysplasia	0	0.6	Congenital
Atypical forms of childhood leukaemia	0	0.2	0–18
Cerebrovascular disease	0	0.6	Childhood (usually)
Glomus tumours in nailbeds	0	0.2 (0.1)	Adults (usually)

stenosis (<1%) and unidentified bright objects (UBOs) on T2-weighted MRI (33%). About 3% of NF1 patients have epilepsy [20, 21].

4.2.7.2 Bony Lesions

Bony abnormalities are frequently congenital and therefore are present from birth. While scoliosis typically advances at puberty, there are often underlying congenital bony abnormalities of the vertebrae. Scoliosis occurs in about 5–9% of cases, with about half requiring surgery. Pseudoarthrosis of the tibia/fibula occurs congenitally in around 1–2%. Sphenoid wing dysplasia and lambdoid suture defects occur in about 1%.

4.2.7.3 Cardiovascular Lesions

Renal artery stenosis (1%) is a much-quoted NF1 complication and is one of the reasons for regular blood pressure checks. However, recently it is becoming clear that vascular events in early adulthood including bleeds and cerebrovascular events are more common than once thought. Indeed the frequency of these events causing death in those aged <30 years was three times the national rate in North America [27]. A male preponderance of early cardiovascular deaths also appears to be the case [28]. Moyamoya disease following radiotherapy is another complication of note particularly for those having received radiotherapy for optic glioma [22].

4.2.7.4 Malignancy

Malignant peripheral nerve sheath tumours (MPNST) are rare tumours occurring in only 1 per million annually in the general population; between 20 and 50% are NF1-associated [29]. NF1 patients have an 8–15% lifetime risk of MPNST [29, 30], but

these are rare in childhood (aged <16 years–~1%), although cumulative risk to age 20 years has been estimated at 2.7% [31]. Nonetheless a rapidly growing deep-seated tumour with pain or neurological deficit needs to be investigated. PET scans are useful in differentiating a benign plexiform tumour from malignant change.

High-grade gliomas occur at increased frequency in NF1 and are often associated with the presence of an optic pathway glioma. Overall they occur in <1% of patients [22, 27], and only 2/45 childhood gliomas in a population-based series were high grade [31]. Juvenile myelomonocytic leukaemia (JMML) is a definitive NF1 complication. It is generally thought to be incurable (autologous bone marrow transplantation seems to offer some promise) but only occurs in about 1 in 300 NF1 patients [28] and was absent from a population series of 524 children followed from birth to 20 years [31].

4.2.7.5 Endocrine Tumours and Other Tumours

Duodenal endocrine (carcinoid) tumours and pheochromocytoma occur in NF1 with a frequency of around 1%, but they are rare in childhood. "Glomus" tumours *can* occur as painful swellings in the nail beds are being increasingly recognised [32]. Gastrointestinal stromal tumours (GIST) were previously called gastrointestinal neurofibromas which occur in around 2% of NF1 patients but again rarely in childhood.

4.2.7.6 Educational Problems

Although a significant proportion of children with NF1 have learning difficulties particularly with reading and/or minimal intellectual handicap, this rarely causes severe handicap and therefore is not usually a presenting feature. Although some studies have shown a large proportion (8–11%) with an IQ < 70 indicating mental handicap population-based studies suggest that less children have moderate or severe handicap (3%) or need special schooling [33]. Learning difficulties improve with extra education, and IQ in adulthood is better. More recently it has been recognised that around 30% of NF1 children are in the autistic spectrum [34].

4.2.8 Investigations

- *In general practice*
- In general terms NF1 patients only need investigations if a complication is suspected. Annual blood pressure checks are advisable, and checking of the skin and back for early scoliosis is important in childhood. MRI scans of the head and

spine should generally only be performed if optic glioma or another CNS tumour is suspected [35].

- *In out-patient (specialist clinic) or community clinic*
- Checks should be more frequent in childhood with at least annual checks of the bone structure (scoliosis, pseudoarthrosis), vision and growth (optic glioma), blood pressure, neurology/intellectual development, and skin. Because of the risk of optic glioma particularly in the first 6 years of life, regular 6–12 monthly visual field checks are suggested [35].

4.2.9 Differential Diagnosis

The main causes for confusion and potential mis-labelling with NF1 are conditions which are associated with pigmentary abnormalities and multiple cutaneous/subcutaneous lumps. If the NIH criteria are used strictly, then misdiagnosis should be extremely unlikely unless only pigmentary criteria are met [19]. Therefore a biopsy of a subcutaneous tumour in multiple lipomatosis or proper assessment of cutaneous pigmentation in conditions such as Fanconi disease, McCune-Albright, congenital mismatch repair deficiency (CMMRD) and LEOPARD syndromes should be conclusive [35]. The more recent cause for confusion has been the recessive forms of inheritance of the Lynch syndrome mismatch repair genes *MSH2*, *MLH1*, *MSH6*, and *PMS2*. Children with homozygous PVs (CMMRD) present with café au lait patches (rarely typical for NF1 or fulfilling NIH criteria) and paediatric malignancy including brain tumours. Cutaneous neurofibromas have also been reported [35]. Perhaps now the greatest chance of misdiagnosis is with Legius syndrome, although again strict application of the NIH criteria will not usually give a problem [19].

4.2.10 Management

NF1 children with little or no problems can be managed by the community paediatrician or a specialised GP. Emphasis is important in childhood on the educational difficulties in NF1.

Hospital management of NF1 may be necessary for disease complications in childhood. Long-term follow-up will be required after optic glioma diagnosis or bony dysplasia. Children with complex NF1 involving a major disease complication should be referred to an NF specialist service for long-term planning.

It is advisable for NF1 patients to be sent to a specialist NF1 clinic aged 15 years so that their transition care can be determined. Most patients will be able to have long-term follow-up by their primary care physician. However, in patients with a

major complication or large tumour, burden follow-up in specialist clinics is advised in adulthood.

4.2.11 Prognosis

Most children and their parents can be reassured that they may never develop a serious complication of the condition. Life expectancy is reduced largely due to MPNST risk in adulthood [27, 28], but this is more likely if there is substantial tumour burden aged 15–20 years and/or the patient has a large NF1 deletion [29]. NF1 children will have a 50% risk of transmission to their offspring, but disease course is usually to variable to predict severity.

4.2.12 Follow-Up

Follow-up should usually be annual in childhood (6 monthly eye checks to 6 years) unless a serious complication [35].

Tests including MRI scans are usually only necessary if the patient is symptomatic. Investigation for rare complications such as leukaemia will depend on presentation and should be suspected when a child has xanthogranulomas although the link is not conclusive [35]. Early breast screening for increased risk of breast cancer [35, 36] in women with NF1 is probably warranted and FDG PET to investigate suspicious lesions for MPNST [35, 37]. Those with large deletions should have a low threshold for PET investigation [38].

4.2.12.1 Predictive Testing

A child may present brought in by concerned parents who are worried; their child may have inherited NF1 from themselves (they have the disorder) or that the child has disease features suggestive of NF1. The requirement for pre-symptomatic testing in NF1 is limited as the condition is usually identifiable in first-degree relatives by about 5–6 years [39]. There are cases for mutation analysis in children with multiple café au lait patches, although the great majority with 6 or more typical patches will have NF1 [19]. The greatest sensitivity of mutation analysis [19, 40] gives the best negative predictive value, and there is some demand for prenatal testing. However, the variableness of disease course even within families [41] makes counselling in this situation problematic.

4.2.13 Treatment

Generally treatment of a malignancy in NF1 is the same as for non-NF1 patients although radiation should be avoided if at all possible [22]. However, a treatment paradigm has been developed with treatment of plexiform tumours with MEK inhibitor drugs which now have FDA approval [42]. These are likely to also find a place in treatment of optic pathway glioma [43] and potentially other tumour manifestations.

4.3 Neurofibromatosis 2

4.3.1 Genetics and Epidemiology

In the UK, a large population-based estimate of birth incidence for NF2 showed that 1 in 28–33,000 people would be born with a PV in the *NF2* gene [16, 44, 45]. Overall diagnostic disease prevalence is less at 1 in 50–56,000 but would be less than 1 in 150,000 in children.

NF2 like NF1 is an autosomal dominant disorder with >50% cases having no family history [16, 45]. Although the transmission rate is 50% in the second generation and beyond, the risk of transmission in an apparently sporadic case of NF2 is less than 50% due to the high rate of mosaicism, which affects >50% of de novo cases [46, 47].

4.3.2 Clinical Manifestations

NF2 is characterised by the development of benign nerve sheath tumours (schwannoma) and meningiomas [48]. The hallmark of NF2 is the development of bilateral vestibular schwannoma (VS) causing deafness and/or tinnitus. Schwannomas also occur on other cranial, spinal, and peripheral nerves. Meningiomas both intracranial (including optic nerve meningiomas) and intraspinal occur more in women than men although boys are more at risk than girls in childhood [49]. There is also a risk of low-grade central nervous system (CNS) malignancies (ependymomas). The Manchester (modified NIH) diagnostic criteria for NF2 are shown in Table 4.3. The original NIH criteria were expanded to include patients with no family history who have multiple schwannomas and/or meningiomas but who have not yet developed bilateral eighth nerve tumours. These criteria have been shown to be more sensitive [50], but a new point-based system has also been developed that may improve sensitivity in childhood [51].

Table 4.3 Diagnostic criteria for NF2 (these include the NIH criteria with **additional criteria**)

Bilateral vestibular schwannomas *or* family history of NF2 *plus*
(1) Unilateral VS *or*
(2) Any two of meningioma, glioma, neurofibroma, schwannoma and posterior subcapsular lenticular opacities
Additional criteria: Unilateral VS *plus* any two of meningioma, glioma, neurofibroma, schwannoma and posterior subcapsular opacities
Or
Multiple meningioma (two or more) *plus* unilateral VS *or* any two of glioma, neurofibroma, schwannoma and cataract

"any two of" refers to individual tumours or cataract, not to tumour types

4.3.3 Presentation

The majority of adults with NF2 present with hearing loss, which is usually unilateral at time of onset. A significant proportion of cases (20–30%) present with an intracranial meningioma, spinal tumour, or cutaneous tumour. Indeed, the first sign of more severe multi-tumour disease in early childhood is often a non-eighth nerve tumour [52]. This has been re-emphasised by a recent study of 53 paediatric meningiomas [53] in which five unsuspected cases of NF2 were uncovered in addition to the nine already known, giving a frequency of 14/40 (42%) of the meningioma series. Adult presentation is therefore often very different to paediatric presentation, in which VS accounts for as little as 15–30% of initial symptoms [52]. There also appears to be a tendency to mononeuropathy, particularly affecting the facial nerve causing a Bell's-like palsy, which does not fully recover years before the detection of a tumour. Some children present with a polio-like illness with wasting of muscle groups in a lower limb, which again does not fully recover. Ophthalmic features are also prominent in NF2. Between 60% and 80% of patients have cataracts, which are usually presenile posterior subcapsular lenticular opacities that rarely require removal. However, cortical wedge opacities may be present from near birth. Optic nerve meningiomas can cause visual loss in the first years of life, and extensive retinal hamartomas can also affect vision. The frequency of various features of NF2 in 4 studies is shown in Table 4.4.

4.3.4 Examination

Cutaneous features are useful in diagnosis; however, skin features in NF2 are much more subtle than in NF1. About 70% of NF2 patients have skin tumours, but only 10% have more than ten skin tumours [46]. The tumours appear to be of at least three different types. The most frequent type is a plaque-like lesion, which is intracutaneous, slightly raised and more pigmented than the surrounding skin, often with excess hair (Fig. 4.3). More deep-seated subcutaneous nodular tumours can often be

Table 4.4 Clinical characteristics of NF2 patients in four clinical studies

	Study			
	Kanter et al.	Evans et al.	Parry et al.	Mautner et al.
	1980	1992	1996	1996
Setting	USA	UK	USA	Germany
Number of cases	73	120	63	48
Number of families	17	75	32	44
Sporadic cases	0	45	17	44
Mean age at onset (years)	20 (of 59)	22	20	17
Onset in childhood	NK	25%	NK	NK
Intracranial meningiomas	18%	45%	49%	58%
Spinal tumours	NA	26%	67%	90%
Skin tumours	32%	68%	67%	64%
>10 skin tumours	NK	10%	NK	NK
Café au lait macules	42%	43%	47%	NK
Cataract	NK	38%	81%	62%
Astrocytoma	NK	4.1%	1.6%	NK
Ependymoma (%)	NK	2.5%	3.2%	6%
Optic sheath meningioma	NK	4.1%	4.8%	8%

NK not known/not assessed

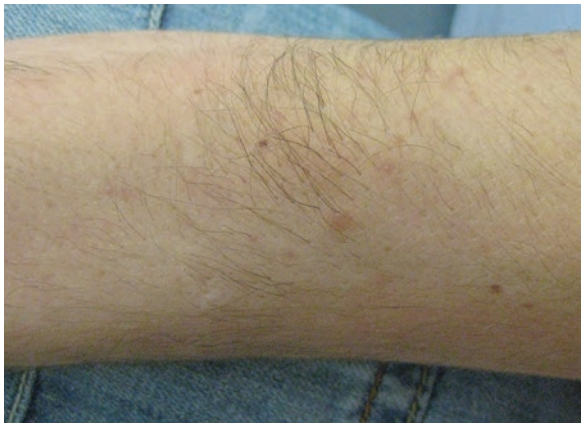

Fig. 4.3 Plaque-like lesions on the arm of a patient with NF2. These are slightly raised, often slightly pigmented lesions that are also frequently hairy

felt, sometimes on major peripheral nerves. These tumours occur as a fusiform swelling of the nerve with thickened nerve palpable on either side (Fig. 4.4). There are also occasional intracutaneous tumours similar to those in NF1. The great majority of these tumours are schwannomas, but occasional definite neurofibromas do occur. Café au lait patches are more common in NF2 than the general population but will only rarely cause confusion with NF1. Ophthalmic examination by a specialised ophthalmologist is important in childhood.

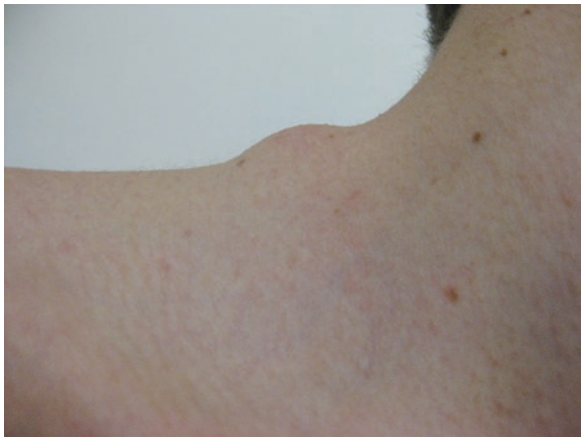

Fig. 4.4 Subcutaneous schwannoma neck angle in a patient with NF2

4.3.5 Radiographic Findings

MRI with gadolinium enhancement (with 1 mm cuts through the internal auditory meatus) will now detect tumours as small as 1–2 mm in diameter on cranial and spinal nerve roots [54]. In children these may already be multifocal at the first investigation [54]. Many of the small spinal tumours will never lead to symptoms. Spinal MRI will detect evidence of spinal tumours in 70–90% of NF2 patients but probably only 50% of children at presentation. There is also increasing recognition of intramedullary tumours, often associated with a syrinx, that predominate in the upper cervical spine and brainstem. On biopsy these tumours are usually low-grade ependymomas. Although these can initially be very worrying for the radiologist or paediatrician, the great majority of these tumours do not progress. Another common finding is schwannomas on other cranial nerves. These occur most commonly on the fifth nerve, but every cranial nerve (bar olfactory and optic) can be affected in NF2 [46]. Nonetheless it is rare for cranial nerve schwannomas other than VS to grow to a size where removal is necessitated. Meningiomas can easily be detected on MRI as enhanced areas on the meninges around the spinal cord, brain or optic nerves (Table 4.4).

There are several groups of individuals who should be considered at risk and investigated further. These groups include those with a family history of NF2, children or young adults presenting with a unilateral VS or meningioma, schwannomas at other sites or retinal hamartoma [55–57]. MRI scanning is vital in their further assessment.

4.3.6 Molecular Genetics

The *NF2* gene was isolated by the simultaneous discovery of constitutional and tumour deletions in a 595 amino acid cell membrane-related gene, which has been called merlin or schwannomin [7, 8]. Large studies have determined genotype/

phenotype correlations with truncating PVs conferring a more severe disease course than missense PVs, splice site mutations or large deletions [58–64]. Position of the PV also correlates with mutations in the 3′ end of the gene (exons 14/15) being associated with fewer meningiomas [49]. Some milder cases have mosaic disease, in which only a proportion of cells contain the mutated *NF2* gene [36, 65–67]. The initiating PV occurs after conception, leading to two separate cell lineages. The proportion of cells affected depends how early in development the mutation occurs. The evidence suggests that up to 58% of NF2 cases without a family history of the disease are mosaic [47], many carrying the mutation in a too small proportion of their cells to be detected from a blood sample [47], and this can be the case even with childhood presentation. Although mosaicism is less in childhood, it still occurs even in a classically affected individual [47, 54, 65]. Mosaicism accounts for the milder disease course in many individuals with unfound mutations, and since only a subset of germ cells will carry the mutation, there is less than a 50% risk of transmitting the disease to their offspring. The risk of transmitting to the next generation will be dependent on the proportion of germinal cells affected. If the mutation is undetectable in blood lymphocytes (only found in tumour cells), then the risk of transmission is low and probably <2% [47, 54]. However, if an offspring has inherited the PV, they will be more severely affected than their parent, since the offspring will carry the mutation in all of their cells.

4.3.7 Management

NF2 presents complex management issues, and a child with NF2 should be managed by a multidisciplinary team consisting of a paediatric neurosurgeon, otolaryngologist, audiologist, ophthalmologist, neuroradiologist and geneticist. An adult neurosurgeon specialising in NF2 is also usually involved. There is clear evidence of reduced mortality benefit [68] with a significantly increased life expectancy for NF2 patients managed at three specialty centres in the UK (RR 0.3, 95% CI 0.12–0.98). This approach was adopted by the highly specialised commissioned service in England and has led to further improved life expectancy with 900 NF2 patients being managed by just four centres [69]. It is important to balance the use of microsurgery and radiation treatment, which can have a role in patients who have particularly aggressive tumours, or who are poor surgical risks, or who refuse surgery. Although radiation treatment has received a great deal of attention and short-term results show good "tumour control", this has to be balanced against longer-term risks such as malignancy especially in childhood [70, 71] and the fact that tumours grow slowly and sometimes not at all for periods of time. Teams experienced in the positioning of brainstem implants can offer partial auditory rehabilitation to those who are deaf, although results are still behind those achievable for cochlear implants. Although the cochlear nerve may be left initially intact after surgery, its blood supply may be damaged; nonetheless a few patients can be rehabilitated successfully with a cochlear implant. Because detection of tumours at an early stage is effective

in improving the clinical management of NF2, pre-symptomatic genetic testing is an integral part of the management of NF2 families. Recently the use of targeted treatments has been highlighted [72–75]. The VegF antibody bevacizumab has been shown to shrink schwannomas and has been used in children [72–75]. However, use in children should be guarded as tumours rebound when treatment is stopped and potential side effects on growth and fertility are still a concern, with renal toxicity another issue [76].

4.3.8 Differential Diagnosis

The main possible diagnostic dilemma with NF2 occurs in isolated patients with multiple non-cranial schwannomas. The *SMARCB1* and more recently *LZTR1* genes have been found to cause this schwannomatosis in a proportion of families [14, 77, 78]. Confusion with NF1 is unlikely since only 1–2% of NF2 patients have six or more café au lait patches and Lisch nodules are extremely rare in NF2, but review of tumour histology is a wise precaution in equivocal cases. The presence of a schwannoma in a patient who does not fulfil NIH criteria for NF1 makes NF1 extremely unlikely, while the presence of multiple neurofibromas makes NF2 very unlikely.

4.3.9 Management and Follow-Up

Management and follow-up should be arranged through a specialised multidisciplinary team [79, 80].

4.4 Schwannomatosis

Schwannomatosis is less common than NF2 and is rare in childhood [45, 80, 81]. Unless a *SMARCB1* or *LZTR1* PV is identified, it is a diagnosis that is made after NF2 has been excluded usually by a combination of cranial imaging to show no evidence of VS, blood *NF2* molecular testing and potentially tumour analysis [45, 80]. Tumours show different *NF2* mutations rather than identical ones which would indicate mosaicism in a patient with negative blood analysis [47, 54]. Nonetheless testing for *SMARCB1* and *LZTR1* is suggested in any child with an isolated schwannoma in addition to NF2 testing as 12% of apparently isolated schwannomas <16 years old have germline PVs in the schwannomatosis genes [56, 80]. Indeed 4% of apparently isolated vestibular schwannomas aged <25 years have germline *LZTR1* PVs [57]. The likelihood of vestibular schwannoma in LZTR1-related schwannomatosis does now cause some overlap with NF2 when using the

Manchester criteria as patients with a unilateral vestibular schwannoma and two or more additional non-intradermal schwannomas are as likely to have a germline constitutional *LZTR1* PV as an *NF2* constitutional PV [82]. This has led to an international group revising the criteria for NF2 and schwannomatosis with a publication date likely in 2021. Risks of childhood schwannoma still appear higher in the less common *SMARCB1* schwannomatosis, and a baseline MRI of the spine and brain is probably justified in children at around puberty [80]. Life expectancy is not usually affected unlike NF2 although pain is a prominent feature [45].

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