Diagnosis of sporadic neurofibromatosis type 2 in the paediatric population

Geetha Anand,[1] Grace Vasallo,[2] Maria Spanou,[2] Saumya Thomas,[1] Michael Pike,[3] Didu Sanduni Kariyawasam,[3] Sanjay Mehta,[1] Allyson Parry,[4] Juliette Durie-Gair,[5] James Nicholson,[6] Karine Lascelles,[7] Vanessa Everett,[7] Frances Mary Gibbon,[8] Nicola Jarvis,[9] John Elston,[10] Dafydd Gareth Evans,[9] Dorothy Halliday[11]

For numbered affiliations see end of article.

Correspondence to
Dr Dorothy Halliday, Oxford Centre for Genomic Medicine, Nuffield Orthopaedic Hospital, Windmill Rd, Oxford University Hospitals NHS Trust, Oxford, UK; dorothy.halliday@ouh.nhs.uk

Received 4 April 2017
Revised 12 December 2017
Accepted 12 December 2017
Published Online First
13 March 2018

ABSTRACT

Objective Onset of symptoms in severe sporadic neurofibromatosis type 2 (NF2) is typically within childhood; however, there is poor awareness of presenting features in young children, potentially resulting in delayed diagnosis and poorer outcome. We have reviewed presentation of sporadic paediatric NF2 to raise awareness of early features, highlighting those requiring further investigation.

Design Patients diagnosed with NF2 at age ≤16 and seen between 2012 and 2015 were notified via the British Paediatric Neurology Surveillance Unit or identified through the English NF2 service.

Results Epidemiological data estimate that 1 in 110 611 births are affected with childhood-onset NF2. Notes of 32 patients with sporadic NF2 were reviewed. Of those presenting under the age of 5, 89% (17/19) had ocular, 74% (14/19) dermatological and 58% (11/19) neurological signs; in 84% (16/19) features were multisystemic. Sixty-six per cent (21/32) had ≥1 atypical feature, including cerebellar hypoplasia in three cases (9%) and focal cortical dysplasia in five out of seven seizure-related presentations. Five cases presented with a sometimes transient or intermittent cranial nerve mononeuropathy. The mean delay to diagnosis was 3.16 years; in eight cases (25%) this exceeded 6 years. Most significant delay occurred in mononeuropathy, ophthalmological and/or seizure presentations, with a mean delay of 3, 4.5 and 6 years, respectively. Eighty-four per cent (27/32) of cases needed intervention in childhood.

Conclusions All non-vestibular schwannoma NF2 presentations in childhood had significant diagnostic delay. We emphasise the importance of detailed assessment of skin and eyes in unusual presentations and propose an aide to prompt timely referral to specialist services.

What is already known on this topic?

- Neurofibromatosis type 2 (NF2) is a severe debilitating disease caused by *NF2* mutations and diagnosed using the NF2 diagnostic criteria.
- Childhood presentation differs from adults, with fewer symptoms related to vestibular schwannoma and a greater number with spinal, ocular and dermatological features.
- There is frequent diagnostic delay, with the potential for greater morbidity, delayed or unnecessary treatment.

What this study adds?

- Despite increased awareness of NF2 and a national NF2 service, there remains significant diagnostic delay, most marked in ophthalmological, mononeuropathy and seizure-related presentation.
- Most presentations are multisystemic, emphasising the importance of detailed history and examination.
- Patients potentially affected with sporadic NF2 should have genetic referral to allow confirmation of the diagnosis and access to specialist care.

INTRODUCTION

Neurofibromatosis type 2 (NF2) is an autosomal dominant disorder caused by mutations in the *NF2* gene, with a birth incidence of 1 in 25 000–33 000[1] and prevalence of 1 in 60 000.[2] It is characterised by the development of multiple tumours, in particular bilateral vestibular and other schwannoma, meningioma, and ependymoma. Although predominantly diagnosed in adulthood, 18% of cases present in childhood.[3] There is a high rate of new mutations within the *NF2* gene, with a high proportion of patients (50%–83%) presenting sporadically.[4 5] Lack of family history can lead to diagnostic difficulties in a rare condition.

Adults with NF2 commonly present with vestibular schwannoma (VS)-related hearing loss. In children, presenting features are typically ophthalmic, with reduced visual acuity from cataracts, retinal hamartoma or optic nerve sheath meningioma (ONSM); dermatological, with NF2 skin plaques, subcutaneous schwannomas or hyperpigmented lesions; or neurological, related to non-VS tumours or mononeuropathy.[3 6–11] Adults are often mildly affected, which can occur if the new mutation is not present in all cells, having occurred at a later stage of development. Due to the high proportion of affected adults with no mutation identified in blood, robust diagnostic criteria (box 1)[12] are essential to clarify affected status. In contrast, patients presenting at age ≤16 would typically fulfil the diagnostic criteria through identification of

To cite: Anand G, Vasallo G, Spanou M, *et al*. *Arch Dis Child* 2018;**103**:463–469.

Box 1 Revised Manchester criteria for NF2[12]

- Bilateral VS <70, or
- FDR family history of NF2 and unilateral VS <70, or
- FDR family history of NF2 or unilateral VS, and 2 of* meningioma, cataract, glioma, neurofibroma, schwannoma and cerebral calcification (if UVS + ≥2 non-intradermal schwannomas need negative LZTR1 test), or
- Multiple meningiomas (2 or more) and 2 of unilateral VS, cataract, glioma, neurofibroma schwannoma and cerebral calcification, or
- Constitutional or mosaic pathogenic *NF2* gene mutation in blood or identical mutations in two distinct tumours.

*Any 2 includes two of any tumour type such as schwannoma.
FDR, first-degree relative; NF2, neurofibromatosis type 2; UVS, unilateral vestibular schwannoma; VS, vestibular schwannoma.

an *NF2* mutation, emphasising the need for improved understanding of the initial presenting features of affected children, to allow earlier referral for genetic testing.

Objectives

The aim of the study was to review the presentation of children with sporadic NF2 to highlight features that should prompt onward referral for genetic testing to facilitate earlier diagnosis and specialist care.

METHODS

Study design

To raise awareness of NF2, paediatric neurologists registered with the British Paediatric Neurology Surveillance Unit (BPNSU) were requested to send notification and complete a questionnaire on all affected children seen during the surveillance period (November 2012–June 2015). Additionally, data regarding initial presentation were requested retrospectively from the four specialist nationally commissioned English NF2 centres: Oxford, London, Cambridge and Manchester. To determine epidemiology, all sporadic patients known to the NF2 service, diagnosed at age ≤16 years and born between 1998 and 2001, were counted.

Case definition

Children aged ≤16 with sporadic NF2 seen within the surveillance period were included if NF2 was diagnosed using the Manchester criteria,[13] or where a pathogenic *NF2* mutation was identified. Mutation data were used to assign a severity grade, with Grade 1 representing a clinical diagnosis with no *NF2* mutation detected in blood; Grade 2 representing patients with a mild (2A)/moderate (2B) *NF2* mutation detected in blood; and Grade 3 representing those with a severe truncating *NF2* mutation in blood.[5]

RESULTS

During the BPNSU surveillance period, 2864 clinicians responded positively or negatively regarding NF2, of which 4 were confirmed UK cases. The majority of data (n=32) were collected retrospectively from the four NF2 centres. Of the 32 patients with sporadic NF2, the median age of presentation with NF2-related symptoms was 3.5 years (range 0–15); 19 (59%) cases presented at age ≤5, 7 (22%) cases at age 6–10, and 6 cases (19%) at age >10. The initial point of contact involved 12 different specialities: ophthalmology, 16 cases (50%); paediatric neurology/neurosurgery, 5 cases (16%); paediatric Accident & Emergency, 3 cases (9%); paediatrics, 2 cases (6%); and orthopaedics/paediatric oncology/paediatric surgery/dermatology/NF2 clinic and genetics, 1 case each.

Epidemiology

Birth statistics for England (Office for National Statistics) for the 4-year period of 1998–2001 report 2 456 848 births in England and Wales (~2 322 827 in England alone based on proportional populations in UK Census). Twenty-one cases born during this period were diagnosed with de novo NF2 at age ≤16, corresponding to 1 in 110 611 live births. This gives a detection rate of approximately 5.3 cases/year, corresponding closely to previous estimates in England of 4.4 cases/year in England, suggesting high ascertainment.

Genetic data

NF2 mutations in blood were identified in 31/32 cases (97%), grade 3 in 15 cases (47%), and increasing to 62% of those first presenting at age <5. All cases presenting at age ≤10 had a 2B/3 mutation. One case presenting at age >10 had a grade 3 mutation, but had symptoms for the preceding 10 years. In one case, no mutation was identified.

Symptoms and signs at presentation

Three cases (9%) presented with raised intracranial pressure (ICP) requiring urgent intervention (table 1). In the remaining cases, ocular, neurological and dermatological symptoms predominated at presentation. Presentation was multisystemic, with 50% of cases having symptoms or signs in two or more systems, increasing to 88% (28/32) after detailed assessment and NF2 diagnosis.

Ocular features

Twelve cases (38%) presented with visual impairment with or without other symptoms (tables 1 and 2), including squint, nystagmus and ptosis. Features noted included unilateral optic atrophy, dysplastic/hypoplastic optic nerve heads and optic nerve morning glory syndrome (one case). A characteristic NF2 eye manifestation (hamartoma, epiretinal membrane, ONSM and cataract) was seen in 50% (16/32) of cases, with more than one in 22% (7/32).

Skin features

Hyperpigmentation, NF2 plaques (figure 1) and lumps clinically suggestive of subcutaneous schwannomas predominated (tables 1 and 2).

Neurological features

Seven children developed seizures, the presenting feature in three. In five of these, MRI demonstrated focal cortical dysplasia (three frontal and two temporal). In one case, no underlying cause for seizures was established, and in the remaining case seizures occurred after treatment for a central nervous system tumour. Four of the children investigated for seizures had previously presented with significant ocular pathology: posterior subcapsular cataract in two cases, peripheral cataract/macular scarring in one case and unilateral optic atrophy in one case. One case had associated visual impairment on presentation with seizure, and presence of a dysplastic optic disc and ONSM prompted NF2 diagnosis.

Thirteen children developed a mononeuropathy/cranial nerve palsy (CNP), the presenting feature in five. One transient VI CNP resulted from raised ICP; one unexplained unilateral VI

Table 1 Presenting features and features documented at last review, according to age at presentation (no value indicates the symptom was not documented at presentation or at last review)

	Presenting at ≤5 (19)		Presenting at 6–10 (7)		Presenting at >10 (6)		Total (32)	
	Presenting symptom n (%)	Patients affected at last review, n (%)	Presenting symptom n (%)	Patients affected at last review, n (%)	Presenting symptoms n (%)	Patients affected at last review, n (%)	Presenting symptoms n (%)	Total number with features n (%)
Ocular features								
Total number affected with ocular symptoms	16 (84)	17 (89.4)	2 (28.5)	4 (57)	3 (50)	5 (83.3)	21 (66)	26 (81)
Visual impairment	10 (52.6)	16 (84)	1 (14.2)	2 (28.5)	1 (16.6)	4 (66.6)	12 (37.5)	22 (68)
Ptosis	2 (10.5)	3 (15.7)					2 (6)	3 (9)
Nystagmus	3 (15.7)	3 (15.7)					3 (9)	3 (9)
Squint	6 (31.5)	6 (31.5)			1 (16.6)	2 (33.3)	7 (21.8)	8 (25)
Optic meningioma		4 (21)		1 (14.3)				5 (16)
Epiretinal membrane		5 (26.3)				2 (33.3)		7 (22)
Cataract		4 (21)		1 (14.3)		2 (33.3)		7 (22)
Retinal hamartoma		5 (26)		2 (28.5)		3 (50)		10 (31)
Other visual problems		9 (47.3)		2 (28.5)		1 (16.6)		12 (37.5)
Optic atrophy		3 (15.7)						3 (9)
Relative afferent pupillary defect		1 (2.6)		1 (14.3)				2 (6)
Dysplastic optic nerve/disc		1 (5)		1 (14.3)		1 (16.6)		3 (9)
Retinal detachment		1 (5)						1 (3)
Combined hamartoma of the retina and retinal pigment epithelium (CHRRPE)		1 (5)						1 (3)
Optic nerve morning glory syndrome*		1 (5)						1 (3)
Macular scarring		1 (5)						1 (3)
Neurological features								
Total number affected with neurological symptoms	3 (15.7)	11 (58)	4 (57)	6 (85.7)	1 (16.6)	2 (33.3)	8 (25)	19 (59)
Cranial nerve palsy (third, sixth & seventh lower CNP)	4 (21)	9 (47.3)		3 (42.8)	1 (16.6)	1 (16.6)	5 (15.6)	13 (40.6)
Scoliosis		3 (15.7)						3 (9)
Seizures	1 (5)	5 (26.3)	2 (28.5)	2 (28.5)			3 (9)	7 (21.8)
Gait disturbance/weakness/ wasting			3 (42.8)	7 (100)	1 (16.6)	1 (16.6)	4 (12.5)	8 (25)
Dermatological features								
Total number affected with dermatological symptoms	1 (5)	14 (73.6)	2 (28.5)	4 (57)	1 (16.6)	3 (50)	4 (12.5)	21 (65.6)
Hypopigmentation		3 (15.7)						3 (9)
Hyperpigmentation	1 (5)	10 (52.6)		1 (14.2)		1 (16.6)	1 (3)	12 (38)
Skin lumps	1 (5)	10 (52.6)	1 (14.2)	1 (14.2)	1 (16.6)	1 (16.6)	3 (9)	12 (38)
NF2 plaque		6 (31.5)	1 (14.2)	1 (14.2)		1 (16.6)	1 (3)	8 (25)
VS-related features								
Total number affected with VS symptoms		3 (15.7)			2 (33.3)	3 (50)	2 (6)	6 (18.75)
Hearing loss/tinnitus /imbalance		3 (15.7)			2 (33.3)	3 (50)	2 (6)	6 (18.75)
Raised ICP (vomiting, unsteadiness, headache)	2 (10.5)	2 (10.5)				1 (16.6)	2 (6)	3 (9)
Pathognomonic NF2 tumours documented within childhood		17 (89.4)		5 (71.4)		6 (100)		28 (88)
Bilateral VS		17 (89.4)		5 (71.4)		6 (100)		28 (88)
Meningioma		12 (63)		3 (42.8)		3 (50)		18 (56)
Spinal lesions		14 (73.6)		5 (71.4)		4 (66.6)		23 (71.8)
Other schwannoma		13 (68.4)		4 (57)		4 (66.6)		21 (65.6)
Atypical features (other than ocular)								
Total number affected with ≥1 atypical feature		9 (47.3)		1 (14.2)		2 (16.6)		12 (37.5)
Vascular anomalies								2 (6)
Coarctation		1 (5)						

Continued

Table 1 Continued

	Presenting at ≤5 (19)		Presenting at 6–10 (7)		Presenting at >10 (6)		Total (32)	
	Presenting symptom n (%)	Patients affected at last review, n (%)	Presenting symptom n (%)	Patients affected at last review, n (%)	Presenting symptoms n (%)	Patients affected at last review, n (%)	Presenting symptoms n (%)	Total number with features n (%)
Renal artery stenosis		1 (5)						
Neuroradiological anomalies								11 (34.3)
Cerebellar hypoplasia		3 (15.7)						
Prominent perivascular spaces with white matter loss†		1 (5)						
Prominent choroid plexus						1 (16.6)		
Focal cortical dysplasia		4 (21)		1 (14.2)				
Cerebellar hamartoma		1 (5)						
Mild learning difficulty (mainstream school)†		1 (5)	1 (14.2)		1 (16.6)			3 (9)
Attention deficit hyperactivity disorder†		1 (5)						1 (3)
Pilocytic astrocytoma		2 (10.5)						2 (6)
Other								2 (6)
Macrodactyly‡		1 (5)						
Hip dysplasia§				1 (12.5)				

*Optic nerve morning glory syndrome: a specific congenital funnel-shaped excavation of the posterior fundus (usually sporadic and unilateral) that includes the optic disc, which is enlarged, elevated (or recessed), with a characteristic retinal blood vessel appearance and occasionally pigmented. Vision is often poor, consequently presenting with a squint in childhood. There are, to our knowledge, two case reports of morning glory optic disc in NF2, in one of which it was bilateral.[31 32]
†Significance unknown.
‡Digital plexiform schwannoma.
§Likely coincidental.
CNP, cranial nerve palsy; ICP, intracranial pressure; NF2, neurofibromatosis type 2; VS, vestibular schwannoma.

CNP developed in a child aged 1; and four cases developed an intermittent or persistent III CNP, aged 1.3, 2, 4 and 8 years. Four cases, aged between 1 and 11, presented with a unilateral VII CNP, which was transient and recurrent in two cases. Three cases developed hoarseness/dysphonia; in one case, it was the presenting symptom and a vagal schwannoma was demonstrated.

Eight children developed features related to spinal or peripheral nerve lesions, the presenting features in four. Presenting cases included foot drop at age 6 from a lumbosacral schwannoma; toe-walking and wasting of the right calf at age 5 (with spinal schwannoma and T5/S1 nerve root lesions later apparent on MRI); and two children aged 6 and 8 with leg weakness/abnormal gait from spinal tumours. Those with an established NF2 diagnosis included foot drop at age 10 from a lumbar nerve root schwannoma; a partial femoral nerve palsy from an L3/L4 lesion; and arm symptoms from a brachial plexus lesion and signs of a right radial neuropathy, with loss of the finger extensors, at age 10. In addition, three children developed scoliosis from an underlying spinal schwannoma. In some children with neurological symptoms or signs, imaging demonstrated an accountable lesion; in others a schwannoma/nerve enhancement was not identified, or only apparent on subsequent imaging.

Other features

Nineteen per cent (6/32) had symptoms related to VS, such as hearing loss, tinnitus or imbalance. Sixty-six per cent (21/32) had an atypical feature noted, detailed in tables 1 and 2.

Age at presentation and diagnostic delay

The median age of symptom onset, presentation and diagnosis was 2.5 years (range 0–15), 3.5 (0–15) and 9.5 (1–16), respectively. The median (range)/mean time from presentation to diagnosis was 0.9 (0–15)/3.16 years. Most (25/32, 78%) cases presented to medical care at symptom onset; in 12 cases (38%) it took >12 months from presentation to diagnosis, and in this group the median delay in diagnosis was 8 years (range 1–15).

The features at presentation differed according to age, with ocular symptoms predominating (16/19, 84%) in those presenting at ≤5 years and none presenting with VS-related symptoms. In contrast, in those aged >10, 33% (2/6) had presenting symptoms suggestive of VS. In those presenting at age 6–10, notable were features attributable to spinal lesions or CNP.

All non-VS childhood NF2 presentations had a mean diagnostic delay of >12 months; most significant delays were in cranial nerve mononeuropathy, focal cortical dysplasia and ophthalmological presentations, with mean delays of 3, 4.25 and 4.5 years, respectively.

Paediatric phenotype

At the last assessment, after a mean follow-up interval of 5.5 years from diagnosis, bilateral VS, meningioma and spinal lesions were identified in the majority (table 1). Twenty-seven cases (84%) required intervention within childhood, including 19 (59%) undergoing neurosurgery, 16 (50%) receiving bevacizumab, 5 (16%) undergoing other surgery and 3 (9%) receiving a hearing implant. Ninety-one per cent (29/32) of the cohort and 95% (18/19) of cases presenting at age ≤5 reported impaired vision, hearing, ambulation or learning.

DISCUSSION

We report the largest series of sporadic paediatric NF2, including all UK children known to the English NF2 service, born since 1998 and diagnosed at age ≤16. We aimed to raise awareness of the multisystemic presentation of childhood NF2, highlighting features that should prompt further investigation and/or specialist referral. The English NF2 service, established in 2010, provides and oversees all NF2 care, via four specialist multidisciplinary clinics. All four cases observed by the BPNSU

Table 2 Presenting symptoms and clinical features for the 32 sporadic cases separated by presentation type to illustrate the multisystemic nature of sporadic paediatric NF2 and predominance of eye, neurological and dermatological features

Age at presentation Median (range)	Age at diagnosis Median (range)	Visual impairment	Ptosis	Nystagmus	Squint	Optic meningioma	Epiretinal membrane, cataract or retinal hamartoma	Cranial nerve palsy	Scoliosis	Seizures	Wasting/weakness/gait abnormality	Hypopigmentation	Hyperpigmentation	Skin lumps/ NF2 plaque	Hearing loss	Imbalance	Raised ICP*	Number with unusual features	Mean number of system†
Acute presentations, n=2																			
2 (2–2)	3.4 (2.8–4)	1	–	–	1	–	–	1‡	–	1	1	–	1	1	–	–	2	1††	2
Eye-related presentation, n=16																			
1.75 (0–13)	10.5 (1–16)	15	2	3	6	4	8	6§	2	4	3	2	7	8	4	–	–	13‡‡	2.5
Neurological-related presentation, n=8																			
6.5 (1–15)	8 (1–16)	2	1	–	–	1	4	5¶	–	2	4	–	3	4	-	-	-	4§§	2.25
Dermatological, n=4																			
8 (3–13)	10 (6–14)	3	–	–	–	–	3	1**	1	–	–	1	1	4	–	–	–	2¶¶	2.25
VS/hearing-related, n=2																			
13.5 (12–15)	14.5 (14–15	1	–	–	1	–	–	–	–	–	–	–	–	–	2	2	1	1***	2

*Vomiting and unsteadiness (underlying tumour: intraventricular meningioma (n=1), posterior fossa meningioma (n=1), pilocytic astrocytoma (n=1)).
†Including ocular, neurological, dermatological and vestibular.
‡Transient VI.
§III, VI, VII, lower cranial nerve.
¶III, VII.
**Lower cranial nerve.
††Pilocytic astrocytoma, optic atrophy, retinal granuloma, attention deficit hyperactivity disorder.
‡‡Pilocytic astrocytoma, optic atrophy (n=2), macular scarring, retinal detachment, congenital myopia, optic nerve morning glory syndrome, relative afferent pupillary defect, iris anomalies, microphthalmia, dysplastic optic disc/optic nerve hypoplasia (n=3), cerebellar hypoplasia, focal cortical dysplasia (n=3), prominence of perivascular spaces and loss of white matter, renal vascular disease, coarctation of aorta, macrodactyly finger.
§§Cerebellar hypoplasia, focal cortical dysplasia (n=2), cerebellar hamartoma, congenital hip dysplasia, calcified choroid plexus.
¶¶Cerebellar hypoplasia, mild learning difficulty.
***Learning difficulty associated with ch22 del.
ICP, intracranial pressure; NF2, neurofibromatosis type 2; VS, vestibular schwannoma.

were managed by the specialist centres, which is associated with improved outcomes.[14 15]

Children of an NF2-affected parent are typically known to an NF2 specialist, and genetic testing or clinical screening can confirm the status of the child at the appropriate time. In contrast, for children lacking a family history, poor awareness of paediatric presenting features can cause diagnostic delay. The varied presenting symptoms indicate the need for an awareness of NF2 among a wide range of paediatric specialists.

All children presenting at age ≤10 had a moderate/severe *NF2* mutation identified, and in only 1/32 cases (3%) was no mutation detected. In contrast, a recent NF2 cohort including adults found 34% of sporadic cases (40/118) had a moderate/severe mutation, and in >50% of cases no mutation was identified in blood, suggesting *NF2* mosaicism.[5] The current study highlights the tendency of severe disease to present at a young age, and from this study 1 in 110 611 live births will present as de novo childhood-onset NF2.

We found a younger mean age of symptom onset and diagnosis, compared with other case series.[16] Those with milder genotypes would typically present symptomatically at age >16. Ascertainment may be incomplete due to diagnostic delay, as of 600 de novo cases on the national NF2 database, 163/600 (27%) presented with symptoms at age ≤16; only 95 of these (57%) were diagnosed in childhood. From the national database there were 44 children without a family history of NF2, diagnosed in the 10 years before the national service (2000–2009). The mean delay for the 32 where information was available on symptoms was 3.2 years, and 22/32 (69%) had a >12-month delay to diagnosis, compared with only 38% (12/32) in the study period. This shows that more sporadic children are getting an accurate diagnosis in childhood, suggesting that the specialist NF2 services have made a difference in reducing the delay in diagnosis. Despite this improvement, it is disappointing to see substantial delays over 20 years from when these were first noted in a large UK study.[17] For the 25% (8/32) with significant diagnostic delay (>6 years), there was the potential for suboptimal management, increased morbidity or unnecessary surgery. In keeping with other studies,[18 19] 68% (22/32) of the cohort had visual impairment at last review. Early diagnosis is paramount to limit preventable loss of vision in patients at risk of bilateral hearing loss. Earlier diagnosis may also allow consideration of options, such as bevacizumab, to limit tumour growth.[20–22]

This study highlights the multisystemic nature of paediatric NF2, where features were seen in a mean of 2.25 system groups. Although in keeping with other studies,[16] nearly 90% (28/32) had bilateral VS noted within childhood, only 19% (6/32) presented with VS features, increasing to 33% of those presenting at age >10. Most VS therefore were asymptomatic at presentation and other features led to the diagnosis. Although acute presentations of NF2 are rare, they have been described previously[3] and were seen in 6% (2/32) of our cohort.

Commonly seen were pigmented lesions (which in NF2 are larger, more irregular and fewer in number than those seen in neurofibromatosis type 1 (NF1),[8 9 16 17] and NF2 plaques, which are typically raised, pigmented and hairy.[6 17] The 25% (8/32) of patients in whom NF2 plaques were seen may be an underascertainment, in a retrospective study. Presence of neurocutaneous stigmata not typical for NF1 should prompt consideration of NF2.

In our cohort, 59% (19/32) presented with neurological symptoms. As noted in previous studies,[3 16 19] common neurological presentations in our series related to cranial/peripheral nerve palsy, seizures or suggested spinal tumour involvement.

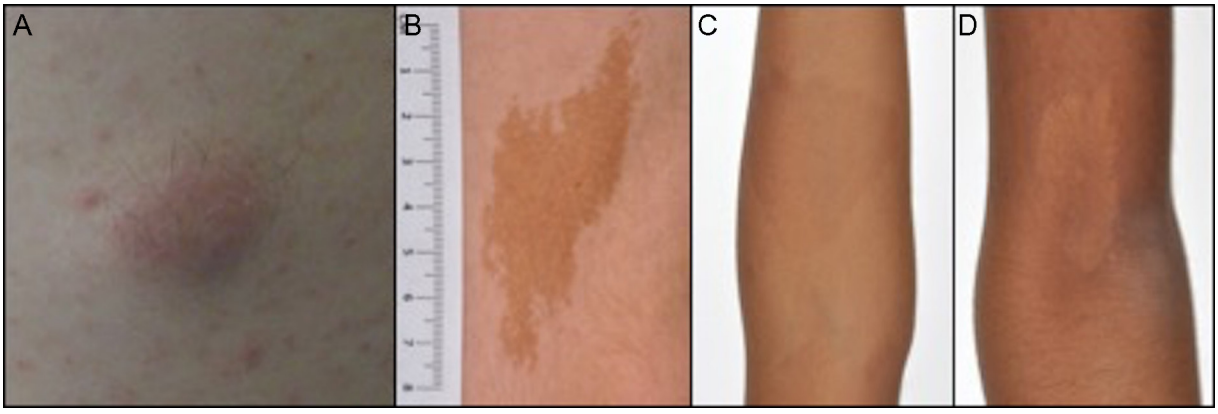

Figure 1 NF2 skin features: (A) NF2 plaque, an intradermal schwannoma appearing as a raised, hairy and dark intracutaneous lesion; (B,C) typical NF2 hyperpigmented areas with irregular outlines, typically larger than neurofibromatosis type 1 café au lait patches; (D) hypopigmented area. NF2, neurofibromatosis type 2.

Being non-specific, CNP and seizure-related presentations had the most significant diagnostic delay. In five of seven cases, seizures were associated with focal cortical dysplasia. Two-thirds of those presenting with seizure had previous ophthalmological pathology, emphasising the importance of medical history and assessment of skin and eyes, when evaluating atypical neurological presentations.

Many (66%) (21/32) had atypical, possibly coincidental features, highlighting the variability in presentation. One previously reported case of renal vascular disease with associated hypertension,[23] an established association with NF1, was seen, as was coarctation of the aorta, also reported in NF1 but not previously in NF2.[24 25] Hypertension is associated with NF2 in adults, potentially suggesting an association with vascular disease.[26] Atypical neuroradiological abnormalities not previously associated with NF2 included cerebellar hypoplasia, a feature recently linked to NF1,[27] and calcified prominent choroid plexus, described once previously in NF2.[28] Focal cortical dysplasia has been previously reported in children with NF2.[29] One case had learning difficulty, secondary to a chromosome 22 deletion extending beyond the *NF2* gene. Two cases needed additional help within a mainstream school and one child had attention deficit hyperactivity disorder. Some of these atypical features may have contributed to diagnostic delay.

Weaknesses of the study are that retrospective data may lack accuracy compared with prospectively collected data, and that radiological images were not specifically reviewed for the study. In addition, specific details were not collected with respect to types of seizure and electroenchephalogram (EEG) findings. Although percentages are given, the small sample size makes conversion to percentages problematic. One weakness is that there may be some children known to the NF2 clinics who have not been included, as they do not fulfil the diagnostic criteria for NF2 nor have an *NF2* mutation. A proportion of this group may be mosaic for an *NF2* mutation,[4] and in time fulfil the NF2 diagnostic criteria, but in excluding them, this analysis has focused on those severely affected.

As the main overt manifestations of NF2 in children are ocular, dermatological and neurological, knowledge of these NF2-associated features can prompt appropriate onward referral, even if the NF2 criteria are not fulfilled. In adult patients, 30%–50% of cases meeting the diagnostic NF2 criteria have no *NF2* mutation detectable on blood testing,[30] emphasising the importance of robust clinical diagnostic criteria. In contrast, in this cohort of paediatric patients, 97% had an *NF2* mutation detectable in blood, confirming the diagnosis. To allow earlier diagnosis, therefore, the challenge is to concentrate on raising awareness of the features that may suggest NF2 in young children, thereby prompting earlier referral for genetic testing. Features that should prompt referral to a clinical geneticist are given in box 2.

NF2 is a disabling condition. In our cohort, 84% (27/32) required intervention within childhood and almost 90% (29/32) had a functional impairment particularly affecting sight, hearing and ambulation. Due to the morbidity of NF2, early detection of children presenting with sporadic NF2 is important. This study highlights the need for awareness across a wide variety of specialists of those symptoms and signs that may suggest NF2 and should prompt onward referral.

Box 2 Indications for referral to clinical genetics in suspected sporadic paediatric neurofibromatosis type 2 (NF2).

Eye features

Retinal hamartoma, epiretinal membrane, optic nerve meningioma.

Posterior subcapsular cataract.

Optic nerve disc abnormalities.

Dermatological features

Characteristic NF2 plaques; subcutaneous schwannoma.

Hyperpigmentation (but not sufficient for neurofibromatosis type 1)/hypopigmentation or both together.

Unexplained skin lumps.

Neurological features

Schwannoma, meningioma.

Ependymoma.

Cranial or peripheral nerve palsy.

Focal cortical dysplasia in association with ocular features listed above.

Features marked in bold: genetic referral for NF2 indicated if one or more features identified.
Features in italics: careful clinical review of neurology, eyes and skin with consideration of NF2 and clinical genetic referral if other additional features suspicious for NF2 are found.

Author affiliations
[1]Department of Paediatrics, Oxford Children's Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[2]Department of Paediatric Neurology, Royal Manchester Children's Hospital, Central Manchester University Hospitals NHS Foundation Trust, Oxford, UK
[3]Department of Paediatric Neurology, Oxford Children's Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[4]Department of Neurosciences, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[5]Department of ENT, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[6]Department of Paediatric Oncology, Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
[7]Department of Paediatric Neurology, Guy's and St Thomas' NHS Foundation Trust, London, UK
[8]Department of Paediatric Neurology, University Hospital of Wales, Cardiff, UK
[9]Genomic Medicine, Division of Evolution and Genomic Sciences, MAHSC, University of Manchester, St Mary's Hospital, Manchester, UK
[10]Department of Ophthalmology, Oxford Eye Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[11]Oxford Centre for Genomic Medicine, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Trust, Oxford, UK

Acknowledgements We would like to thank the clinicians who contributed cases: Dr Tony McShane, Dr Sandeep Jayawant, Dr Saleel Chandratre, Dr Kate Lamb and Dr Dimitrios Zafeiriou.

Contributors Study design/writing of the manuscript was by GA, MP and DH, with suggestions from AP. Data were collected and analysed by GA, ST and DH. GV, MS, JD-G, JN, KL, VE, FMG and NJ provided completed clinical questionnaires. DGE offered data and expertise. JE provided expertise on the eye findings. SM, DSK, JN, DGE, JE and KL contributed to drafting and revision of the manuscript.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The study was approved by the British Paediatric Neurology Surveillance Unit (BPNSU) Executive Committee and the National Research Ethics Service (NRES) Committee-South-West (12/SW/0042).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Data on familial NF2 cases collected as part of this study will be presented separately.

REFERENCES

1 Evans DG, Howard E, Giblin C, *et al*. Birth incidence and prevalence of tumor-prone syndromes: estimates from a UK family genetic register service. *Am J Med Genet A* 2010;152A:327–32.
2 Evans DG. Neurofibromatosis type 2 (NF2): a clinical and molecular review. *Orphanet J Rare Dis* 2009;4:16.
3 Evans DG, Birch JM, Ramsden RT. Paediatric presentation of type 2 neurofibromatosis. *Arch Dis Child* 1999;81:496–9.
4 Evans DG, Raymond FL, Barwell JG, *et al*. Genetic testing and screening of individuals at risk of NF2. *Clin Genet* 2012;82:416–24.
5 Halliday D, Emmanouil B, Pretorius P, *et al*. Genetic severity score predicts clinical phenotype in NF2. *J Med Genet* 2017;54:657–64.
6 Mautner VF, Tatagiba M, Guthoff R, *et al*. Neurofibromatosis 2 in the pediatric age group. *Neurosurgery* 1993;33:92–6.
7 Ragge NK, Baser ME, Riccardi VM, *et al*. The ocular presentation of neurofibromatosis 2. *Eye* 1997;11(Pt 1):12–18.
8 Mautner VF, Lindenau M, Baser ME, *et al*. Skin abnormalities in neurofibromatosis 2. *Arch Dermatol* 1997;133:1539–43.
9 MacCollin M, Mautner VF. The diagnosis and management of neurofibromatosis 2 in childhood. *Semin Pediatr Neurol* 1998;5:243–52.
10 Matsuo M, Ohno K, Ohtsuka F. Characterization of early onset neurofibromatosis type 2. *Brain Dev* 2014;36:148–52.
11 Ruggieri M, Praticò AD, Evans DG. Diagnosis, Management, and New Therapeutic Options in Childhood Neurofibromatosis Type 2 and Related Forms. *Semin Pediatr Neurol* 2015;22:240–58.
12 Smith MJ, Bowers NL, Bulman M, *et al*. Revisiting neurofibromatosis type 2 diagnostic criteria to exclude *LZTR1* -related schwannomatosis. *Neurology* 2017;88:87–92.
13 Evans DG, Huson SM, Donnai D, *et al*. A genetic study of type 2 neurofibromatosis in the United Kingdom. I. Prevalence, mutation rate, fitness, and confirmation of maternal transmission effect on severity. *J Med Genet* 1992;29:841–6.
14 Hexter A, Jones A, Joe H, *et al*. Clinical and molecular predictors of mortality in neurofibromatosis 2: a UK national analysis of 1192 patients. *J Med Genet* 2015;52:699–705.
15 Lloyd SK, Evans DG. Neurofibromatosis type 2 service delivery in England. *Neurochirurgie* 2017;54:657–64.
16 Ruggieri M, Iannetti P, Polizzi A, *et al*. Earliest clinical manifestations and natural history of neurofibromatosis type 2 (NF2) in childhood: a study of 24 patients. *Neuropediatrics* 2005;36:21–34.
17 Evans DG, Huson SM, Donnai D, *et al*. A clinical study of type 2 neurofibromatosis. *Q J Med* 1992;84:603–18.
18 Bosch MM, Boltshauser E, Harpes P, *et al*. Ophthalmologic findings and long-term course in patients with neurofibromatosis type 2. *Am J Ophthalmol* 2006;141:1068–77.
19 Nunes F, MacCollin M. Neurofibromatosis 2 in the pediatric population. *J Child Neurol* 2003;18:718–24.
20 Plotkin SR, Merker VL, Halpin C, *et al*. Bevacizumab for progressive vestibular schwannoma in neurofibromatosis type 2: a retrospective review of 31 patients. *Otol Neurotol* 2012;33:1046–52.
21 Hochart A, Gaillard V, Baroncini M, *et al*. Bevacizumab decreases vestibular schwannomas growth rate in children and teenagers with neurofibromatosis type 2. *J Neurooncol* 2015;124:229–36.
22 Morris KA, Golding JF, Axon PR, *et al*. Bevacizumab in neurofibromatosis type 2 (NF2) related vestibular schwannomas: a nationally coordinated approach to delivery and prospective evaluation. *Neurooncol Pract* 2016;3:281–9.
23 Cordeiro NJ, Gardner KR, Huson SM, *et al*. Renal vascular disease in neurofibromatosis type 2: association or coincidence? *Dev Med Child Neurol* 2006;48:58–9.
24 Pardo R, Somalo L, Málaga S, *et al*. [High blood pressure due to aortic coarctation and renal artery stenosis in a teenager with type 1 neurofibromatosis]. *Nefrologia* 2008;28:216–7.
25 Kimura M, Kakizaki S, Kawano K, *et al*. Neurofibromatosis type 1 complicated by atypical coarctation of the thoracic aorta. *Case Rep Pediatr* 2017;93:235–6.
26 Hornigold RE, Golding JF, Ferner RE, *et al*. Neurofibromatosis 2: a novel risk factor for hypertension? *Am J Med Genet A* 2011;155A:1721–2.
27 Toelle SP, Poretti A, Weber P, *et al*. Cerebellar Hypoplasia and Dysmorphia in Neurofibromatosis Type 1. *Cerebellum* 2015;14:642–9.
28 Ozgür A, Karaman Y, Apaydin FD, *et al*. An uncommon case of neurofibromatosis type 2: a tribute to the intracranial calcifications. *J Clin Imaging Sci* 2013;3:21.
29 Ruggieri M, Gabriele AL, Polizzi A, *et al*. Natural history of neurofibromatosis type 2 with onset before the age of 1 year. *Neurogenetics* 2013;14:89–98.
30 Bijlsma EK, Wallace AJ, Evans DG. Misleading linkage results in an NF2 presymptomatic test owing to mosaicism. *J Med Genet* 1997;34:934–6.
31 Schneider C, Cayrol D, Arnaud B, *et al*. [Clinically isolated Morning glory syndrome]. *J Fr Ophtalmol* 2002;25:178–81.
32 Brodsky MC, Landau K, Wilson RS, *et al*. Morning glory disc anomaly in neurofibromatosis type 2. *Arch Ophthalmol* 1999;117:839–41.