Probability of bilateral disease in people presenting with a unilateral vestibular schwannoma

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Abstract

***Background*—Some 4%-5% of those who develop vestibular schwannomas have neurofibromatosis type 2 (NF2). Although about 10% of these patients present initially with a unilateral vestibular schwannoma, the risk for a patient with a truly sporadic vestibular schwannoma developing contralateral disease is unknown.**

***Methods*—A United Kingdom survey of 296 patients with NF2 was reviewed for laterality of vestibular schwannoma at presentation and the presence of other NF2 related features. The time to presentation of bilateral disease was calculated for patients presenting with a unilateral tumour. Mutation analysis of the NF2 gene was carried out on all available cases presenting initially with unilateral disease.**

***Results*—Of 240 patients with NF2 with vestibular schwannomas, 45 (18%; 32 sporadic, 13 familial) had either a unilateral tumour or delay in detection between the first and contralateral tumours. Among those tested for NF2 mutations, eight of 27 and nine of 13 were identified among sporadic and familial cases respectively. Sporadic cases showed a high female to male ratio and 19 of 32 have not as yet developed a contralateral tumour (mean 4.1 years after diagnosis of the first). Thirteen of 32 sporadic patients developed a contralateral tumour (mean 6.5 years after the first tumour diagnosis, range 0–22 years) compared with 11 of 13 familial patients (mean delay 5 years, range 0–16 years). Seven of the 45 patients had neither a family history of NF2 nor evidence of related tumours at initial presentation (six before the age of 35 years).**

***Conclusion*—The risk of patients with sporadic unilateral vestibular schwannomata developing a contralateral tumour in the absence of family history or other features of NF2 is low, but those presenting with other neurogenic tumours in addition to vestibular schwannoma are at high risk of harbouring an NF2 mutation in at least a proportion of their somatic cells.**

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Type 2 neurofibromatosis (NF2) is an autosomal dominant inherited condition characterised by development of bilateral vestibular schwannomas, schwannomas of other cranial, spinal, and cutaneous nerves, and cranial and spinal meningiomas.[1–3] The National Institutes of Health (NIH) defined diagnostic criteria for NF2 in 1987[4] and modified criteria to allow for sporadic cases have since been published.[2] According to NIH criteria (table 1) a person with bilateral vestibular schwannomas is assumed to have NF2 and 50% of offspring would be predicted to be affected. As the isolation of the NF2 gene in 1993[5 6] mutation studies have included reports of germ line mutations.[7–9] Detection rates using routine methodology have been disappointingly low even in classically affected patients and cannot therefore be used as a means of excluding the condition.

At presentation, 10%-20% of patients with NF2 have a unilateral vestibular schwannoma, although other features of the disorder may be identified.[2 3 10] However, the clinical details of such patients have not been fully reported before now. Previously we reported a series of such patients with unilateral vestibular schwannomas and other features suggestive of NF2.[11] The risk to a patient who presents with a sporadic unilateral vestibular schwannoma of developing further tumours is uncertain. Unless it can be minimised by exclusion of a germline mutation, such patients and their children may need ongoing screening. We have analysed a large group of patients with NF2 who had unilateral vestibular schwannomas to determine the risk of developing contralateral disease.

Patients and methods

Since 1989 our multidisciplinary team has ascertained cases of NF2 from throughout the United Kingdom, 296 cases fulfilling modified criteria for NF2 (table 1). Thirty four died before the study, 21 since referral. Two hundred and seventy five of 296 patients had a history of vestibular schwannomas (21 patients diagnosed on DNA analysis alone or fulfilled criteria in other ways), 240 had clinical details concerning the diagnosis of each vestibular

Table 1 Diagnostic criteria for NF2

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

Table 2 Age at onset of unilateral vestibular schwannoma and time to bilaterality in 45 patients with NF2

Patient	*Onset HL*		*Diagnosis UVS (y)*	*Current age (y)*	*Age at BVS (y)*	*Delay (y)*	*Other NF2 features*	*Mutation*
	Years	*Sex*						
Sporadic:								
1	15	M	15	16	—	1	1M, 3Sp	No
2	35	F	36	38	—	2 (3)	2M, 2Sp	No
3	22	F	22	26	—	4	2Sp	ND
4	27	F	28	30	—	3	3M	No
5	19	M	20	20	—	1 (2)	1M, 1Gl	Yes
6	16	F	29	37	—	8 (11)	2M, 2Sp	ND
7	25	M	26	28	—	2 (3)	4M, 1sp	Yes
8	26	F	26	29	—	3	2M, OM	No
9	43	M	50	51	—	1 (8)	8cut	Yes
10	44	F	46	47	—	1 (3)	3M	No
11	22	M	24	27	—	3 (5)	4M, 2Sp, Ep	Yes
12	19	F	38	46	—	8 (27)	3M	Yes
13	42	F	43	49	—	6 (7)	3M	No
14	25	F	25	30	—	5	OM, 1Sp, XII	No
15	48	F	49	53	—	4 (5)	5M, 1cut, X	ND
16	29	F	28	33	—	5 (4)	1sp,3cut,Ep	No
17	57	F	59	62	—	3 (5)	3M	No
18	29	M	39	54	—	15 (25)	2Sp	No
19	50	F	50	56+	—	6	3M, 2cut	No
20	34	F	36	52	42	6 (8)	Nil	No
21	44	F	48	63	61	13 (17)	Nil	ND
22	21	F	23	52	45	22 (24)	1Sp	No
23	16	F	16	20+	18	2	5M, nSp, Ep	No
24	18	M	17	25	21	8 (7)	6M, 3Sp	Yes
25	24	M	24	42	32	8	Nil	No
26	23	M	36	45	37	1 (14)	OM, 6M Sp	No
27	16	F	22	37	29	7 (11)	Nil	No
28	15	F	15	33	20	5 (5)	1sp, 2M	No
29	11	M	11	15	13	2	1M, 7cut, PLO	No
30	33	F	36	44	40	4 (7)	2M	ND
31	6	F	23	36	23	0 (16)	1Sp, 1cut	Yes
32	14	F	16	25	23	7 (9)	Nil	No
Familial:								
Affected child:								
P1	28	M	56	62	56	0 (15)*	Nil	Yes
P2	37	F	53	62	57	4 (20)	4M, 1Sp	No
P3	31	M	36	49	45	9 (14)	Nil	Yes
P4	17	M	18	39	25	7 (8)	M, Sp, Gl	Yes
P5	27	M	32	42	39	3 (8)	4M	Yes
P6	27	F	27	45	43	16	4M, 3Sp, PLO	Yes
Affected parent:								
C1	19	M	18	22	—	4 (3)	3cut, X	Yes
C2	29	F	29	32	—	3	Nil	Yes
C3	13	M	11	17	16	5 (3)	Nil	No
C4	19	M	18	25	24	6 (5)	Nil	Yes
C5	14	F	12	18	16	4 (2)	2ct, PLO	No
C6	13	F	20	26	22	2 (9)	1M, 6cut, PLO	No
C7	21	F	27	33	29	2 (7)	3M, 4cut, PLO	Yes

M=meningioma; OM=optic nerve meningioma; cut=cutaneous tumours; PLO=posterior lenticular opacity; Gl=glioma; Ep=ependymoma; Sp=spinal tumours, X=cranial nerve tumour; HL=hearing loss.
(n) Symptomatic delay between ears in years.
*Symptomatic delay before onset of bilateral hearing loss.

schwannoma. Of patients presenting with symptomatic vestibular schwannoma to our neuro-otological unit from a defined region (north west England population 4.1 million) between May 1989 and May 1998, 26 of 500 (5.2%) had bilateral disease.

We analysed patients presenting with a unilateral vestibular schwannoma—either those with initial CT or MRI showing evidence of unilateral involvement, or those with unilateral symptoms for more than 10 years before diagnosis. In the second group delay in diagnosis between sides was defined. Other features of NF2 such as family history, other neurogenic tumours, cataracts, and cutaneous findings such as cafe au lait patches were noted and DNA from peripheral blood was analysed for mutations in the NF2 gene using methodology previously described.[8] In patients in whom a mutation was not identified tumour material was subjected to molecular analysis. For all patients age at follow up was taken as the last detailed clinical examination or scan.

Results

Forty five of 240 (18.2%) patients with NF2 fulfilling modified criteria for NF2 have experienced a delay in the onset of vestibular schwannomas on each side (table 2). According to NIH criteria 26 of 221 (12%) had such a delay. In all but two patients (sporadic 31 and P1) the initial scan showed unilateral involvement. However, in both these patients the delay in symptoms between each side was longer than 10 years: it is likely that an early scan would have shown unilateral involvement. The mean delays and the ranges of delay for those developing bilateral tumours are presented in table 3

Neurofibromatosis type 2 affects males and females equally and the male:female ratio in the overall NF2 dataset was, as expected 1:1. However, of 32 sporadic patients with unilateral tumours there was a male:female ratio of 10:22 compared with 7:6 in the familial patients (χ^2=1.16, p=0.28). Although there was no skewing for most other features of the condition,

Table 3 Mean age at hearing loss and interval between diagnosis in sporadic and familial cases

	M/F	Age (y) HL	Age (y) VS	FU (y)	Interval 1st to 2nd	Mutation detected Yes/No
		Mean (range)				
Sporadic:						
UVS (S1–19)	6/13	31.2 (15–57)	34.4 (15–59)	4.2 (1–15)	—	5/11
BVS (S20–32)	4/9	21.6 (6–44)	25.1 (11–48)	12.9 (4–29)	6.4 (0–22)	2/9
Familial:						
BVS						
Parent (P1–6)	4/2	27.8 (17–37)	37.0 (18–56)	12.8 (6–21)	6.5 (0–16)	5/1
Child (C3–7)	2/3	16.0 (13–21)	17.6 (11–27)	6.0 (5–7)	3.8 (2–6)	2/3
UVS:						
Child (C1–2)	1/1	24 (19–29)	23.5 (18–29)	3.5 (3–4)	—	2/0

Table 4 NF2 mutations identified in 45 patients with NF2 presenting with unilateral vestibular schwannoma

Individual mutation		Exon	UVS/BVS
Nonsense mutations:			
S5	G100>T, Glu34>stop	1	UVS
S9	C784>T, Arg262>stop	8 (mosaic)	UVS
S24	C169>T, Arg57>stop	2	BVS
S31	C1612>T, Gln538>stop	15	BVS
P3	G1570>T, Glu524>stop	14	BVS
P5	C1408>T, Gln470>stop	13	BVS
P6	C784>T, Arg262>stop	8 (mosaic)	BVS
C4	G1570>T, Glu524>stop	14	BVS
Frameshifting deletions:			
S7	40 delCT	1	BVS
C7	855 delT	9	BVS
Frameshifting insertions:			
S11	1191 insT	12	UVS
Missense:			
S12	A317>G, Glu106>Gly	3	UVS
P4	C1055>T, Thr352>Met	11	BVS
C2	T1604>C, Leu535>Pro	15	UVS
Splice site:			
P1	516+1G>A	5	BVS
C1	676−7T>G	8	UVS

BVS=Bilateral vestibnular schwannoma; UVS=unilateral vestibnular schwannoma.

13 of the 22 females (59%) had two or more meningiomas at diagnosis of the unilateral vestibular schwannomas whereas only four of 10 men did so (40%; p=0.5). Furthermore, of 21 patients who remained with unilateral tumours, meningiomas were even more overrepresented among women with 10 of 12 having two or more.

Presymptomatic people among the familial group with affected parents were analysed for laterality of diagnosis. Four of seven had presymptomatic unilateral tumours detected on MRI of whom two patients are still to develop contralateral tumours 3–4 years after diagnosis.

Mutations of all varieties except large deletions have been identified (table 4). Mutations were detected in only 26% (seven of 27) of the sporadic patients compared with 69% (nine of 13) of the familial patients. Within the sporadic group 59% (16 of 27) did not fulfil NIH criteria and mutations were detected in 31% (five of 16). Mutation detection was successful in only 18% (two of 11) of those fulfilling the criteria. Tumours from patients S9, S10, S18, and S19 were subjected to molecular analysis and both mutational events in the NF2 gene were identified in S9 and S18. A second tumour from S9 showed an identical nonsense mutation to the first (table 4).

Discussion

There is a low but significant risk that a person presenting with a unilateral vestibular schwannoma will eventually develop a contralateral tumour (or other related tumours) and some means by which those people who are at high risk could be identified would be extremely valuable. The results of surgery are much improved by the smaller size of tumour at operation,[10 12 13] and an indication that a patient is likely to develop a contralateral tumour may even influence the type of surgery or other treatment for the initial side.[10 14] Relatives may also benefit from screening and genetic counselling. We have highlighted some factors useful for identification of those at risk of further tumours.

It will always remain a matter for speculation whether certain patients (for example, patients S1–19) actually have NF2 and will develop bilateral disease. However, it must be realised that these patients are indistinguishable at the time of presentation. In our survey, even excluding those diagnosed presymptomatically through affected parents, over half of those who presented with a unilateral vestibular schwannoma developed a contralateral tumour. Therefore given the relatively short follow up time in S1–19 many of these patients may yet develop a contralateral tumour.

The predominance of females in the sporadic group may be due to the increased frequency of meningiomas in females with NF2.[15] However, it raises the possibility that there is a higher risk of meningiomas among females with mosaic NF2 who would seem to be more likely to present with a unilateral tumour and meningiomas than any other combination.

Mutation analysis is a useful additional investigation but it is not as valuable as detailed clinical assessment in reducing risk estimates of developing a contralateral tumour in those with unilateral disease. Of seven patients without other features of NF2 at presentation only two (P1 and P3) had an identifiable mutation. Low mutation detection rates (40%-60%) have been reported several times.[7–9 16 17] Although the mutation detection rate is generally low it is of note that it was higher at five of 16 (31%) in sporadic unilateral patients compared with two of 11 (18%) in the sporadic patients who went on to develop bilateral disease. The high detection rate in the familial group (nine of 13; 70%) is in keeping with previous reports in which a significant (20%) difference was noted in the likelihood of detection between familial and sporadic patients with classic bilateral disease (55% and 36% respectively).[18] We hypothesised that this difference is due to somatic mosaicism with the NF2 mutation being present in only a proportion of somatic cells. This was the case for patient P6 in whom the mutation was present in only 37% of lymphocytes.[19] A mutation which is present in an insufficient proportion of cells to detect in lymphocyte DNA may nevertheless be found

Table 5 Average risk per decade of patients presenting with vestibular schwannoma having NF2

Age (y)	*% with NF2*	*% with NF2 UVS at diagnosis*	*% with NF2 with no FH and no other NF2 features*
10–19	33% (22–50%)	6% (2.6–9%)	1% (0.3–1.4%)
20–29	15% (8–22%)	2.7% (0.9–4%)	0.45% (0.1–0.6%)
30–39	5% (3–8%)	0.9% (0.3–1.4%)	0.15% (0.03–2.2%)
40–49	2% (1–3%)	0.36% (0.1–0.54%)	0.06% (0.01–0.08%)
50–59	1% (0.5–1.5%)	0.18% (0.06–0.27%)	0.03% (0.007–0.05%)
60–69	—	—	—

UVS= unilateral vestibular schwannoma; FH=family history.

as an identical mutation in all tumours from the same patient (for example, case S9). In addition, previous mutation studies on tumours from those with unilateral vestibular schwannomas and other features of NF2[20] have shown that unless the modified criteria for NF2 are met such patients are unlikely to have a detectable NF2 mutation in blood even when both mutational events were detected in the tumour. Therefore, if mutation analysis is carried out on patients with unilateral vestibular schwannomas (with or without other features of NF2) analysis of tumour DNA is likely to be more reliable than lymphocytic DNA. However, most patients who do not fulfil modified criteria probably represent either chance associations or low level mosaicism, in which the risk of bilateral disease is small.

Of patients with vestibular schwannomas 4%-5%[10 21] have NF2 and from our survey of patients with NF2, 12%-18% are likely to present initially with a unilateral tumour. Thus <1% of patients with unilateral vestibular schwannomas will go on to develop a contralateral tumour. However, of those presenting with a unilateral tumour in this series only seven of 45 had neither an affected parent with NF2 nor other tumours strongly suggestive of the condition. Therefore, after a careful clinical examination for cutaneous tumours and review of a cranial and upper cervical MR less than one in every 500 patients with an isolated unilateral vestibular schwannoma will develop a contralateral tumour.

It is possible to age stratify the risk of a patient with unilateral disease becoming bilateral. Table 5 shows the average risk of a patient with a vestibular schwannoma having NF2 for each decade of age at presentation.[10] By taking 3% of this risk (18%; seven of 45) the chances of a patient developing a contralateral tumour can be derived (table 5). This does not allow for the possibility that not all our patients in table 2 would have eventually developed a contralateral tumour and that more subtle signs of NF2 may have been present at the initial presentation of some of the seven patients with apparently unilateral sporadic vestibular schwannomas. The real risk may, therefore, be even smaller.

Conclusions

The risks for a patient presenting with a unilateral vestibular schwannoma developing bilateral disease are low. In patients over 35 years of age with no relevant family history and no other tumour features of NF2 the risks are insufficient to warrant further follow up for patient or family. A detailed cutaneous and ophthalmic examination in those under 35 years may detect further patients who require monitoring. Risks to young patients (<20 years old) can probably be further modified by molecular analysis of blood and, in particular, tumour material. Overall probably less than 2% of those with unilateral vestibular schwannoma at presentation require ongoing screening for themselves or their offspring.

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