Neurofibromatosis type 2 and related disorders

Dorothy Halliday[a,b], *Allyson Parry*[b,c], *and D. Gareth Evans*[d]

Purpose of review
Neurofibromatosis type 2 (NF2) is a schwannoma predisposition syndrome, alongside schwannomatosis related to germline *LZTR1* and *SMARCB1* pathogenic variants. This review highlights their overlapping phenotypes, new insight into NF2 phenotype and treatment outcomes.

Recent findings
Mosaic NF2 is more prevalent than previously thought. Use of next-generation sequencing and tumour testing is needed to differentiate mosaic NF2 and schwannomatosis. Developing NF2 phenotypic insights include vasculopathy with brainstem infarction and vessel stenosis; focal cortical dysplasia in severe phenotypes; swallowing/speech difficulties and continued debate into malignancy in NF2. Proposed are: use of visual evoked potentials to monitor optic nerve sheath meningioma; potential routine magnetic resonance angiogram in adolescence and a genetic score to cohort patients with similar pathogenic_variants, for natural history/treatment outcome studies. Cohort studies found survival analysis to hearing loss and unilateral visual loss in severe mutation groups was 32 and 38 years; active management gave better outcomes than surveillance in spinal ependymoma; gamma knife, bevacizumab and hearing preservation surgery maintained or improved short-term hearing in selected patients, and gamma knife had a good long-term tumour control in mild patients with small tumours.

Summary
Further long-term outcome studies are needed comparing similar severity patients to allow informed decision making.

Keywords
LZTR1, neurofibromatosis type 2, schwannomatosis, *SMARCB1*

INTRODUCTION

Neurofibromatosis type 2 (NF2), a disorder caused by pathogenic variants in the Merlin encoding, tumour suppressor gene *NF2*, is no longer associated with NF1, but with the schwannoma predisposition syndromes including *LZTR1* and *SMARCB1*-related schwannomatosis. A further related phenotype is meningiomatosis, sometimes caused by pathogenic variant in *SMARCE1*. Next-generation sequencing and routine tumour testing has revealed phenotypic overlap in these conditions. Schwannomatosis birth incidence is approximately one in 69 000, compared with one in 28 000 for NF2, with mean life expectancy of 76.9 years compared with 66.2 in NF2 [1▪]. This review focusses on phenotypic overlap in these related conditions, on emerging NF2 phenotypic features and management outcomes.

DIAGNOSIS OF NEUROFIBROMATOSIS TYPE 2 AND SCHWANNOMATOSIS

The Manchester diagnostic criteria for NF2 were published in 1992 [2]. Recent molecular analysis of 2777 individuals [3▪] revealed their failure to distinguish between schwannomatosis and mosaic-NF2. Schwannomas often involve a three to four molecular hit involving biallelic *NF2* loss of function, with loss of function or haplo-insufficiency of *LZTR1/SMARCB1*. Analysis of 23 tumours from 19 NF2 patients found biallelic *NF2* hits in all tumours, with one additional hit (e.g. *SMARCB1* loss) in 2/17, and two additional hits (*LZTR1* and *SMARCB1* loss) in 15/17 tumours analysed [4].

Two studies estimated the NF2 mosaicism rate higher than previously thought. A study of 142

[a]Genomic Medicine, [b]Oxford NF2 Unit, [c]Department of Neurosciences, Oxford University Hospitals NHS Foundation Trust, Oxford and [d]Ge-Genomic Medicine, Division of Evolution and Genomic Sciences, MAHSC, University of Manchester, St Mary's Hospital, Manchester, UK

Correspondence to Dorothy Halliday, Oxford Centre for Genomic Medicine, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Trust, Windmill Rd, Oxford, UK. Tel: +44 01865 226029; e-mail: Dorothy.Halliday@ouh.nhs.uk

Curr Opin Oncol 2019, 31:562–567
DOI:10.1097/CCO.0000000000000579

KEY POINTS

- The phenotype of mosaic-NF2 and schwannomatosis overlaps; paired molecular testing of *NF2/LZTR1/SMARCB1* from tumour and blood can help with diagnosis.
- Rare vascular features in NF2 include rupture of intracranial aneurysm, mid-brain/brainstem infarction and vascular stenosis; consideration of magnetic resonance angiogram in adolescence may be warranted.
- Malignancy in two NF2 cases with no prior radiation suggests it may be a rare feature in NF2.
- Survival analysis to loss of useful hearing and vision in one eye (logmar >1.0) was age 32 and 38, respectively, in those with truncating *NF2* pathogenic variant, but unimpaired in the genetically mild group.
- Further long-term studies are needed to compare hearing outcomes with different interventions.

patients meeting Manchester criteria, found 58% had confirmed or presumed mosaic-NF2 [5▪] as did 59% of 1055 NF2 patients [6]. Vestibular schwannoma is now recognized in LZTR1-schwannomatosis. Of 50 NF2 patients with unilateral vestibular schwannoma and at least two other non-intradermal schwannoma five had likely/highly likely germline *NF2* pathogenic variants but additionally, five had *LZTR1* pathogenic variants [7▪].

In 15 schwannomatosis patients with multiple schwannomas but no vestibular schwannoma or dermal schwannomas, 7/15 had *LZTR1* pathogenic variants but in three of the remaining eight cases (37.5%), analysis of two independently arising tumours confirmed mosaic NF2 with identical *NF2* pathogenic variants [8▪] however this also occurred in the presence of a constitutional *LZTR1* pathogenic variant. Of 39 patients with meningiomatosis *SMARCE1* pathogenic variant were found in three (8%) patients [4].

A clinical way to differentiate NF2 and schwannomatosis reported was volumetric analysis of the dorsal root ganglia. In 16 schwannomatosis patients there was no difference to 26 controls, contrasted to hypertrophy seen in 14 NF2 cases [9]. Other clinical differences were the more peripheral/spinal schwannoma distribution in schwannomatosis [1▪] with higher pain levels. Pain was associated with *LZTR1*-schwannomatosis more than *SMARCB1*-schwannomatosis [10▪].

An isolated meningioma/schwannoma may represent the initial manifestation of a tumour predisposition syndrome. A 14 year old with an isolated vestibular schwannoma had a constitutional *LZTR1* pathogenic variant identified [11]. In 16/42 (38.1%) individuals presenting with an isolated meningioma under age 25 a pathogenic variant was identified: *NF2* in 7/42 and *SMARCE1* in 9/42 cases [12▪]. 44/153 (29%) with an isolated schwannoma under 25 had a pathogenic variant but 55% of those with a spinal compared with 18% with a cranial schwannoma. 4/106 (3.8%) with a cranial schwannoma (vestibular schwannoma in three of the four cases) had an *LZTR1* pathogenic variant, and 9/106 (8.5%) an *NF2* pathogenic variant identified. By contrast, in familial isolated vestibular schwannoma 0/28 families had a constitutional pathogenic variant in *NF2/LZTR1* and in nine cases with available tumour the two tumour *NF2* hits were absent from the germline, suggesting chance occurrence [13].

Widening of the *LZTR1* and *SMARCB1* phenotype has been reported. *SMARCB1* is associated with two distinct phenotypes. 53/422 (12.5%) of schwannomatosis cases have *SMARCB1* pathogenic variants [1▪] as do at least 30% of rhabdoid tumour predisposition syndrome atypical teratoid/rhabdoid tum. Families have been reported previously with both phenotypes; recently co-occurrence in the same individual was reported. A proband previously treated for atypical teratoid/rhabdoid tumour age 2, with an inherited *SMARCB1* exon 8–9 deletion, presented age 22 with multiple spinal schwannomas [14]. Mouse models indicate that the timing of smarcb1 loss is critical, with early loss in the neural crest cells being required for tumorigenesis with rhabdoid histology; whereas later loss in schwann cells, combined with NF2 loss, generated schwannomas [15]. Similarly, *LZTR1* pathogenic variants, found in 78/422 (18.5%) of schwannomatosis cases have recently been reported in both autosomal dominant and recessive Noonan syndrome [16,17].

NEUROFIBROMATOSIS TYPE 2 NATURAL HISTORY

Contrasted to adult disease, paediatric NF2 is overwhelmingly from constitutional *NF2* pathogenic variants. A total of 32 children presenting with de-novo NF2, had a 3.1 year mean delay from symptom onset to diagnosis [18▪]. Presenting features were multisystemic in 84%, with ophthalmological, dermatological and neurological features in 89, 74 and 54%. All 81 children with NF2 under the English NF2 service had a detectable pathogenic variant in blood: 91% constitutional and 9% mosaic. Correspondingly, phenotype of NF2 in children is typically severe, with multiple tumours (usually schwannoma, ependymoma and meningioma) occurring at young ages [19]. In those with severe

NF2 (caused by truncating *NF2* pathogenic variants between exons 2 and 13) mean age of first manifestation was 4.3 years and almost half (48%) had undergone cranial/spinal tumour resection or bevacizumab treatment by the last review (mean age 12.9 years).

NF2 has strong genotype-phenotype correlations. Validation of a score to account for both the *NF2* pathogenic variant type and proportion of affected cells now allows comparison of phenotypic trends according to genotype [5▪]. Use of this score showed that the severe group had greater frequency of optic atrophy, epiretinal membrane, combined hamartoma and cataract. Survival analysis to loss of vision in one eye (logmar >1.0) was age 38 in the severe group, but unimpaired in the mild group with no *NF2* pathogenic variant in blood [20▪]. Of those under age 18, 12/31 (43%) in the severe group had Logmar more than 1.0 in their worst eye [19]. Similarly, survival analysis to loss of hearing in 147 NF2 patients followed for 10 years was 32 years in the severe group, but age 80 in the mild group [21▪].

Optic nerve sheath meningioma

Natural history of optic nerve sheath meningioma (ONSM) is poorly defined. Three cases were presented where associated visual loss was swift and irreversible and where MRI did not show objective evidence of progression. In the three cases change in multifocal visual evoked potential was an objective measurement of optic nerve functional loss which correlated with visual decline. This was proposed as an adjunct to MRI to monitor ONSM, giving an objective measure of progression earlier than changes seen on MRI [22▪].

Voice and swallowing dysfunction

A total of 42 NF2 patients treated at Johns Hopkins were assessed with self-reported questionnaires and formal assessment with laryngoscopy/swallowing assessment in 31. 71% had vocal cord paralysis/paresis (55% unilateral and 16% bilateral) and flexible endoscopic assessment of palate function showed 45% had velopharyngeal insufficiency. When graded by blinded assessors, 71% had an abnormal voice. Vocal fold movement impairment was strongly associated with ipsilateral cerebellar pontine angle surgery, and with impaired voice/swallow-related quality of life [23▪].

Malignancy in neurofibromatosis type 2

There continues debate on the risk of malignancy in NF2. From 1253 NF2 cases in the English NF2 register malignant transformation of vestibular schwannoma occurred twice and one malignant glioma developed, all after radiation treatment [24▪,25▪]. Malignancy in confirmed NF2 cases has recently been reported twice, neither time after radiation. One 8 year old with a germline exon 11 *NF2* truncating pathogenic variant, developed a malignant peripheral nerve sheath tumour (MPNST) in the cervical nerve roots/brachial plexus [26]. Second, a 22 year old, with a germline *NF2* exon 8 splice site pathogenic variant, developed an epithelioid MPNST with additional *SMARCB1* loss in the tumour [27].

Emerging neurofibromatosis type 2 vascular phenotype

MRI review of 289 NF2 patients in Germany found symptomatic ischaemic brainstem stroke in three NF2 patients (age 7–22), as the presenting feature [28▪]. Lascelles reported three cases: a 13 year old with a symptomatic pontine infarct; a child with a small, tortuous internal carotid artery; and narrowing of the left internal carotid artery in a 4 year old with additional gliosis of the right middle cerebellar peduncle suggesting previous infarction [29]. Of the 6/7 cases of ischaemic stroke now reported, this occurred in the midbrain/brainstem with no obvious reason established for the stroke. In a retrospective review of NF2 paediatric MRI reports (by NF2 specialist radiologists), brainstem/cerebellar lacunar infarcts were noted in 3/81 (4%) cases [19].

Moyamoya from stenosis of the left middle cerebral artery in a child with an intragenic *NF2* exon 2–6 duplication was reported [30]. In the English paediatric NF2 series 3/81 had vascular stenosis including renal artery and aortic coarctation (both with truncating *NF2* pathogenic variants); and vertebral artery (with 22q deletion encompassing *NF2*) [19].

In the German NF2 series, a 17 year old presented with a ruptured subarachnoid haemmorrhage, taking the reported total to four in those under age 25. In addition, a 16 year old had two unruptured aneurysms of the middle cerebral artery [28▪]. While the larger German series did not find an increased incidence of aneurysm in NF2, in contrast to the earlier report from Afridi *et al.* [31]; the number of young NF2 patients with ruptured aneurysm potentially suggests this is a greater risk in NF2. Routine magnetic resonance angiogram in adolescence with treatment of lesions identified was proposed given this finding.

Cortical dysplasia

In the English paediatric NF2 series, atypical MRI features occurred in 30/79 cases (38%), notable was

cerebellar hypoplasia in 3/32 (9%) along with focal cortical and cerebellar dysplasia, seen in 26 and 22%, respectively, of patients with truncating pathogenic variants, and in 15% and 11% of the whole cohort [19].

VESTIBULAR SCHWANNOMA TREATMENT FOR HEARING PRESERVATION: BEVACIZUMAB, GAMMA KNIFE AND SURGERY

Retaining serviceable hearing and effective hearing rehabilitation is an NF2 management goal [32] utilizing surveillance, surgery, gamma knife and bevacizumab. Data on hearing preservation rates have been reported after bevacizumab [33▪,33▪], decompression of the internal auditory meatus [35▪], and gamma knife [36▪,37].

Of 17 patients treated with bevacizumab (median of 14 months, range 3–60 months) nine had impaired hearing at baseline. Five had gains in word recognition scores lasting longer than 1 year, in two cases over 40% improvement, two showed hearing stability and two had hearing decline on treatment. 40% reported improvement in tinnitus, vestibular symptoms, headache and ability to use a telephone [33▪]. Of 14 patients (median age 30), treated for 48 weeks and followed for a further 24 weeks, patient reported measures found speech understanding/auditory quality improved on treatment and 50% had improved word recognition [34▪].

Short-term hearing response in 12 NF2 patients (mean age 28 years) who underwent decompression of the internal auditory canal (IAC) to preserve hearing/prevent further deterioration was reported. Assessing all 12, hearing improved from 85% mean preoperative speech discrimination score (SDS) to 92.5% postoperation. In the four patients with progressive hearing loss preintervention, three had improved hearing after with mean SDS increasing from 55 to 77.5%. The authors conclude that IAC decompression can be beneficial in selected patients but emphasise that further studies are needed to assess longer term hearing response [35▪].

Large series assessing gamma-knife outcomes in sporadic vestibular schwannoma are available, but it is unknown if this data can be extrapolated to NF2. In 576 vestibular schwannoma (of which 87% of tumours received 18 G over three doses), including 18 NF2 patients with 21 vestibular schwannoma, 50% of treated vestibular schwannoma had the same level of hearing after 3 years, however at 5 and 10 years posttreatment less than 40% and less than 20% maintained pretreatment hearing. Large tumour volumes pretreatment had poorer hearing outcomes [37]. Outcome of gamma knife in 34 NF2 patients with 47 growing vestibular schwannoma (median marginal dose 11 G) matched 1 : 1 to sporadic vestibular schwannoma were reported. While tumour control rates at 1/3/5/8 years were 98, 89, 87 and 87%, rates of serviceable hearing preservation at 1/3/5/7 years were 95, 82, 59 and 33%. Of 22 ears with serviceable hearing pretreatment, 10 (46%) had serviceable hearing after, in four (18%) hearing worsened but remained serviceable but eight cases (36%) lost hearing, in half within 7 months posttreatment. A good outcome was achieved with milder Gardner phenotype and smaller tumour volume ($<6\,cm^3$) while larger tumours in the Wishart phenotype responded poorly. There was no difference between NF2 and control vestibular schwannoma for tumour control, hearing or complications [36▪]. Further outcome studies are still needed using comparable assessment tools, longer follow-up periods, and comparing similar phenotypes.

Meningioma and ependymoma

Outcome of gamma knife to 99 meningioma (medial marginal dose 13 G) in 35 NF2 patients was reported. 90.6% local control rate was achieved: four patients with treatment failure needed surgery to the treated lesion (median time 52 months). 6/35 patients (17%) developed radiation necrosis and oedema treated with medication (at median 7 months after treatment). No posttreatment malignancy was reported in relatively short-term follow-up [38▪].

Differing management between two European centres allowed comparison of outcomes of spinal ependymoma managed conservatively or surgically [39▪]. 27% of the conservatively treated group deteriorated during follow-up, compared with 11% actively managed in a specialist NF2 centre. Although bevacizumab may be the preferred option in those with a significant disease burden, surgery should be considered for growing or symptomatic ependymoma.

SUMMARY/CONCLUSION

Revised criteria are needed to differentiate between NF2 and schwannomatosis. With larger cohorts, further aspects of NF2 phenotype are emerging. Due to the wide phenotype of NF2, similar outcome measures must be used in groups of similar patients to provide valid comparisons.

Acknowledgements

None.

Financial support and sponsorship

D.G.E. is supported through the NIHR Manchester Biomedical Research Centre (IS-BRC-1215-20007).

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
- ■ of special interest
- ■■ of outstanding interest

1. Evans DG, Bowers NL, Tobi S, *et al.* Schwannomatosis: a genetic and ■ epidemiological study. J Neurol Neurosurg Psychiatry 2018; 89:1215–1219.

Point prevalence and birth incidence were calculated from regional birth statistics. Within the North-West England population, schwannomatosis has half the birth incidence and prevalence of neurofibromatosis type 2 (NF2).

2. Evans DGR, Huson SM, Donnai D, *et al.* A clinical study of type 2 neurofibromatosis. Q J Med 1992; 84:603.

3. Evans DG, King AT, Bowers NL, *et al.* Identifying the deficiencies of ■ current diagnostic criteria for neurofibromatosis 2 using databases of 2777 individuals with molecular testing. Genet Med 2019; 21:1525–1533.

Two large databases were interogated and diagnosis reviewed. The strong overlap between mosaic NF2 and schwannomatosis was identified. In contrast ependymoma was found to be highly specific for NF2. The term glioma was not accurate and use of the term ependymoma in the criteria advocated.

4. Louvrier C, Pasmant E, Briand-Suleau A, *et al.* Targeted next-generation sequencing for differential diagnosis of neurofibromatosis type 2, schwannomatosis, and meningiomatosis. Neuro Oncol 2018; 20:917–929.

5. Halliday D, Emmanouil B, Pretorius P, *et al.* Genetic Severity Score predicts ■ clinical phenotype in NF2. J Med Genet 2017; 54:657–664.

This was a validation study of the UK-NF2 genetic severity score whereby patients with no *NF2* pathogenic variants in blood were designated as group 1, with mild/moderate constitutional or mosaic *NF2* pathogenic variants in blood as group 2A/2B, and those with constitutional truncating *NF2* pathogenic variants in exon 2–13 as group 3. The score showed significant difference in phenotype across 10 measures encompasing tumour burden and intervention.

6. Evans DG, Hartley CL, Smith PT, *et al.* Incidence of mosaicism in 1055 de novo NF2 cases: much higher than previous estimates with high utility of next-generation sequencing. Genet Med 2019; https://doi.org/10.1038/s41436-019-0598-7.

7. Smith MJ, Bowers NL, Bulman M, *et al.* Revisiting neurofibromatosis type 2 ■ diagnostic criteria to exclude LZTR1-related schwannomatosis. Neurology 2017; 88:87–92.

In this study, the Manchester database was assessed for those presenting with one vestibular schwannoma and two other (nonvestibular schwannoma) lesions. The most likely cause was mosaic NF2, but germline *LZTR1* mutations were equally common as *NF2* germline variants, indicating that LZTR1 must be excluded when no germline NF2 pathogenic variant is identified.

8. Kehrer-Sawatzki H, Kluwe L, Friedrich RE, *et al.* Phenotypic and genotypic ■ overlap between mosaic NF2 and schwannomatosis in patients with multiple nonintradermal schwannomas. Hum Genet 2018; 137:543–552.

A total of 15 patients meeting clinical criteria for schwannomatosis with no vestibular schwannoma, intradermal schwannomas or ocular features had paired lmphocyte and schwannoma analysis. 3/8 cases without a schwannomatosis mutation had confirmed mosaic NF2, confirming the diagnostic overlap.

9. Godel T, Mautner VF, Farschtschi S, *et al.* Dorsal root ganglia volume differentiates schwannomatosis and neurofibromatosis 2. Ann Neurol 2018; 83:854–857.

10. Jordan JT, Smith MJ, Walker JA, *et al.* Pain correlates with germline mutation in ■ schwannomatosis. Medicine (Baltimore) 2018; 97:e9717.

A total of 37 patients with a clinical diagnosis of schwannomatosis were assessed for tumour load and distribution and pain scores. Spinal tumours were more common in LZTR1 patients, and LZTR1 was associated with higher pain scores than SMARCB1.

11. Gripp KW, Baker L, Kandula V, *et al.* Constitutional LZTR1 mutation presenting with a unilateral vestibular schwannoma in a teenager. Clin Genet 2017; 92:540–543; 11.

12. Pathmanaban ON, Sadler KV, Kamaly-Asl ID, *et al.* Association of genetic ■ predisposition with solitary schwannoma or meningioma in children and young adults. JAMA Neurol 2017; 74:1123–1129.

The cohort study analysed patients referred to the Manchester diagnostic lab for isolated maningioma under 25 (42 patients) or schwannoma under 25 (135 cases). Patients with schwannoma were screened for *NF2, SMARCB1* and *LZTR1*, and meningioma were screened for *NF2*, *SMARCB1, SMARCE1* and *SUFU*. 16/42 (38%) had a predisposing mutation to meningioma and 27/135 (20%) had a predisposing mutation to schwannoma.

13. Evans DG, Wallace AJ, Hartley C, *et al.* Familial unilateral vestibular schwannoma is rarely caused by inherited variants in the NF2 gene. Laryngoscope 2019; 129:967–973.

14. Kehrer-Sawatzki H, Kordes U, Seiffert S, *et al.* Co-occurrence of schwannomatosis and rhabdoid tumor predisposition syndrome 1. Mol Genet Genomic Med 2018; 6:627–637.

15. Vitte J, Gao F, Coppola G, *et al.* Timing of Smarcb1 and Nf2 inactivation determines schwannoma versus rhabdoid tumor development. Nat Commun 2017; 8:300.

16. Yamamoto GL, Aguena M, Gos M, *et al.* Rare variants in SOS2 and LZTR1 are associated with Noonan syndrome. J Med Genet 2015; 52:413–421.

17. Johnston JJ, van der Smagt JJ, Rosenfeld JA, *et al.* Autosomal recessive Noonan syndrome associated with biallelic LZTR1 variants. Genet Med 2018; 20:1175–1185.

18. Anand G, Vasallo G, Spanou M, *et al.* Diagnosis of sporadic neurofibroma- ■ tosis type 2 in the paediatric population. Arch Dis Child 2018; 103:463–469.

The retrospective chart review analysed the presentation of 32 children with de-novo NF2. The multisystem presentation was noted with a marked delay in diagnosis in nonvestibular schwannoma presentations. In 8/32 cases the diagnostic delay was more than 6 years. Unusual factors reported were cerebellar hypoplasia in 3/32 (9%) and focal cortical dysplasia in 5/7 cases presenting with seizure.

19. Halliday D, Emmanouil B, Vassallo G, *et al.* Trends in phenotype in the English paediatric neurofibromatosis type 2 cohort stratified by genetic severity. Clin Genet 2019; 96:151–162.

20. Painter SL, Sipkova Z, Emmanouil B, *et al.* Neurofibromatosis type 2-related ■ eye disease correlated with genetic severity type. J Neuroophthalmol 2019; 39:44–49.

A total of 83 patients were reviewed for NF2 eye abnormalities, to relate eye disease to genetic severity. Presence of NF2 eye features including optic atrophy, epiretinal membrane, retinal hamartoma and cataract significantly correlated with genetic severity. Median age to survival of significantly impaired visual acuity was related to genetic severity at 38 in the severe group. The eye pathology in the severe group was largely untreatable, but treatable eye disease must be sought and treated early to preserve vision.

21. Emmanouil B, Houston R, May A, *et al.* Progression of hearing loss in Neurofibro- ■ matosis type 2 according to genetic severity. Laryngoscope 2019; 129:974–980.

The retrospective cohort study assessed 147 patients with NF2 followed for 10 years in a National NF2 centre. The patients were stratified by the UK-NF2 genetic severity score. Significant differences in timing of hearing loss with genetic severity was seen.

22. Jayanetti V, Klistorner AI, Graham SL, *et al.* Monitoring of optic nerve function ■ in neurofibromatosis 2 children with optic nerve sheath meningiomas using multifocal visual evoked potentials. J Clin Neurosci 2018; 50:262–267.

Optic nerve sheath meningioma in five eyes in three patients were assessed over a period of 5–12 years. Visual evoked potentials were assessed, along with serial MRI and visual acuity, and were able to demonstrate decline in optic nerve functional loss in keeping with visual decline, suggesting that visual evoked potential could be a useful tool in assessing progression of optic nerve sheath meningioma.

23. Best SR, Ahn J, Langmead S, *et al.* Voice and swallowing dysfunction in ■ neurofibromatosis 2. Otolaryngol Head Neck Surg 2018; 158:505–510.

The cross-sectional study used both self rated voice and swallow questionnaires in 40 patients, and a swallow and voice assessment in 31. Voice and swallow impairment was highly prevalent in NF2, strongly related to surgery in the cerebellopontine and caused significant impairment in quality of life.

24. King AT, Rutherford SA, Hammerbeck-Ward C, *et al.* High-grade glioma is not ■ a feature of neurofibromatosis type 2 in the unirradiated patient. Neurosurgery 2018; 83:193–196.

The Manchester database of 1253 patients was reviewed for presence of high-grade gliomas, covering 11 123 years of follow-up. There was one report of a grade VI glioblastoma multiforma in a patient who had previously received gamma knife for vestibular schwannoma. No grade-III glioma was reported.

25. King AT, Rutherford SA, Hammerbeck-Ward C, *et al.* Malignant peripheral ■ nerve sheath tumors are not a feature of neurofibromatosis type 2 in the unirradiated patient. Neurosurgery 2018; 83:38–42.

The Manchester database of 1253 patients (11 123 patient years of follow-up) were reviewed for notification of malignant peripheral nerve sheath tumour (MPNST). Two cases developed proven or presumed MPNST 3 years after radiotherapy to a vestibular schwannoma; one after gamma knife, and one after fractionated radiotherapy. There were no MPNST reported in nonirradiated patients.

26. Agresta L, Salloum R, Hummel TR, *et al.* Malignant peripheral nerve sheath tumor: transformation in a patient with neurofibromatosis type 2. Pediatr Blood Cancer 2019; 66:e27520.

27. Linder C, Smith MJ, Bulman M, *et al.* Sarcoma in neurofibromatosis 2: case report and review of the literature. Fam Cancer 2019; 18:97–100.

28. ■ Gugel I, Mautner VF, Kluwe L, *et al.* Cerebrovascular insult as presenting symptom of neurofibromatosis type 2 in children, adolescents, and young adults. Front Neurol 2018; 9:733.

MRI scans of 298 NF2 patients were retrospectively reviewed for aneurysm or iscaemic stroke. Five patients were found under age 25 with aneurysms or iscaemic stroke, particularly located in the brainstem. The need for multicentre studies on large cohorts was stressed.

29. Lascelles K, Afridi S, Siddiqui A, *et al.* Cerebral vasculopathy in childhood neurofibromatosis type 2: cause for concern? Dev Med Child Neurol 2018; 60:1285–1288.

30. Santoro C, Palladino F, Bernardo P, *et al.* Report on a child with neurofibromatosis type 2 and unilateral moyamoya: further evidence of cerebral vasculopathy in NF2. Neurol Sci 2019; 40:1475–1476.

31. Afridi SK, Thomson S, Connor SEJ, *et al.* Aneurysms in neurofibromatosis type 2: evidence for vasculopathy? Am J Med Genet A 2017; 173: 1562–1565.

32. North HJD, Lloyd SKW. Hearing rehabilitation in neurofibromatosis type 2. Adv Otorhinolaryngol 2018; 81:93–104.

33. ■ Sverak P, Adams ME, Haines SJ, *et al.* Bevacizumab for hearing preservation in neurofibromatosis type 2: emphasis on patient-reported outcomes and toxicities. Otolaryngol Head Neck Surg 2019; 160:526–532.

A total of 17 patients were treated with Bevacizumab and assessed for tumour control and hearing response. Nine had impaired hearing at baseline and could be assessed for a hearing response. Five had an improvement in word recognition scores, two remained stable and two declined. Responses in hearing lasted for over 1 year.

34. ■ Huang V, Bergner AL, Halpin C, *et al.* Improvement in patient-reported hearing after treatment with bevacizumab in people with neurofibromatosis type 2. Otol Neurotol 2018; 39:632–638.

A total of 14 patients with NF2 (median age 30) and hearing impairment (median baseline word recognition scores 60%) were treated with Bevacizumab (7.5 mg/kg 3 weekly) for 48 weeks followed by surveillance for 24 weeks. Half had an objective hearing response and patient reported outcomes of speech understanding and auditory quality improved.

35. ■ Bonne NX, Risoud M, Hoa M, *et al.* Hearing response following internal auditory canal decompression in neurofibromatosis type 2. Neurosurgery 2019; 1–8; DOI:10.1093/neuros/nyz057.

This was a retrospective chart review of 12 cases of middle fossa osteotomy for internal auditory canal osteodural decompression in NF2-related vestibular schwannoma, for hearing progression or stability. Over a short-term follow-up (2–3 years post surgery) in three of four cases operated on for hearing progression hearing improved and in all eight cases operated for hearing stability, no case deteriorated. In the hearing progression group 1 still had 90% speech discrimination score (SDS) 6 years after surgery and one 24%. In the hearing maintenance group, at 3 years post treatment six had maintained 100% SDS.

36. ■ Kruyt IJ, Verheul JB, Hanssens PEJ, Kunst HPM. Gamma knife radiosurgery for treatment of growing vestibular schwannomas in patients with neurofibromatosis type 2: a matched cohort study with sporadic vestibular schwannomas. J Neurosurg 2018; 128:49–59.

This was a retrospective analysis of 47 tumours in 34 patients who underwent gamma knife (median 11-G marginal dose). 5 year hearing preservation rate was 59%. Long-term control was good in mild phenotype patients with small tumours, whereas patients with a severe phenotype and/or larger tumour volumes had poorer tumour control rates.

37. Santa Maria PL, Shi Y, Gurgel RK, *et al.* Long-term hearing outcomes following stereotactic radiosurgery in vestibular schwannoma patients-a retrospective cohort study. Neurosurgery 2018. doi: 10.1093/neuros/nyy407.

38. ■ Gao F, Li M, Wang Z, *et al.* Efficacy and safety of gamma knife radiosurgery for meningiomas in patients with neurofibromatosis type 2: a long-term follow-up single center study. World Neurosurg 2019; 125:e929–e936.

A total of 35 patients who received gamma knife were followed-up from 25 to 224 months. Local 5 year control was 90% however 17% had radiation-related complications.

39. ■ Kalamarides M, Essayed W, Lejeune JP, *et al.* Spinal ependymomas in NF2: a surgical disease? J Neurooncol 2018; 136:605–611.

A total of 24 patients with spinal ependymoma greater than 1.5 cm were followed from Manchester and 46 from Lille and assessed for neurological decline using the Modified McCormic outcome score. In Manchester management was conservative and in Lille surgery was actively considered. 27% of the conservatively managed group deteriorated compared with 23% of the surgically managed group, but only 11% in the group managed surgically in a specialist centre. As the outcome was significantly better in the surgically managed group in a specialist centre, surgery should be considered as a management option for growing or symptomatic tumours.