

Comparison of outcomes of peripheral nerve schwannoma excision in neurofibromatosis type 2 patients and non-neurofibromatosis type 2 patients – a case control study.

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This work has been presented at the International Federation of Societies for Surgery of the Hand (IFSSH) in Delhi 2013, at the European Federation of Societies of Surgery of the Hand (FESSH) in Antalya 2013, and at the Society of Academic and Research Surgery (SARS) Annual Meeting in London 2013. Part of this work has been presented in poster form at the 15th European Neurofibromatosis Meeting, Istanbul 2012, and in abstract form in the Journal of Hand Surgery – European Volume and British Journal of Surgery.

Summary

Background

Patients with neurofibromatosis type 2 (NF2) are an important subgroup of patients undergoing peripheral nerve schwannoma excision, however data on their outcomes are lacking. Co-existing peripheral neuropathy can complicate the clinical presentation and recovery in NF2. We designed a study to compare outcomes of peripheral nerve schwannoma excision in NF2 patients with excision of isolated, sporadic schwannomas in non-NF2 patients.

Methods

30 peripheral nerve schwannoma excisions from 15 NF2 patients were compared to 30 excised isolated schwannomas. These were matched for age, size, nerve and level of involvement. Final outcomes were scored on a scale of 0 (no improvement) to 3 (complete symptom resolution). Data were analysed by McNemars test and Wilcoxon matched pairs test.

Results

NF2 patients had multiple lesions and more pre-operative weakness ($p=0.041$) and sensory loss ($p=0.133$) compared to controls. Post-operative neurological morbidity occurred in both groups after schwannoma excision. Final outcome scores of 2.4 in NF2 and 2.2 in controls indicate great improvement or complete resolution in the majority.

Conclusions

Outcomes in the NF2 group are not different to controls, despite NF2 patients having more significant pre-operative deficit and co-existing neuropathology. These findings suggest that surgical intervention should be offered to NF2 patients with peripheral nerve schwannomas.

Keywords: Type 2 neurofibromatosis, schwannoma.

Introduction

Neurofibromatosis type 2 (NF2) is an autosomal-dominant disorder associated with multiple central and peripheral nervous system tumours. Schwannomas are the most common peripheral nerve lesions, and they cause morbidity secondary to nerve compression¹. Peripheral neuropathy is increasingly recognised as a common clinical feature of NF2, affecting 6-66% of patients during the course of their disease. It may occur independently of nerve compression by tumours^{5, 6, 10, 11}.

NF2 patients are an important subset of patients with peripheral schwannomas, yet the outcomes of schwannoma excision in this complex group are unknown. There has been concern that these patients would do poorly due to their other associated peripheral neuropathies, resulting in reluctance to intervene. Surgery may also be delayed further when priority is given to their central disease.

We present case control data on the outcomes of peripheral nerve schwannoma excisions in patients with NF2, and sporadic peripheral nerve schwannomas. Our data suggest that outcomes of surgical excision in NF2 are not different.

Methods

We reviewed the records of 98 patients under the NF2 service in Oxford for all peripheral nerve schwannoma excisions performed in the unit since the introduction of plastic surgery to the NF2 multidisciplinary team in April 2010. These patients had an established diagnosis of NF2 from genetic analysis or clinical criteria^{3,5}. We sought controls from our records of all isolated schwannoma excisions performed in the plastic surgery unit between 1995 and 2011. Controls were only selected if they did not have a diagnosis of neurofibromatosis (type 1 or 2) or multiple schwannomatosis. Schwannoma excisions in NF2 patients or controls were included if the following criteria were met:

1. Schwannoma associated with a major named nerve. Intramuscular and cutaneous schwannomas were excluded.
2. Peripheral nerve lesions, excluding spinal cord or spinal nerve root lesions.
3. Histological diagnosis of a benign schwannoma. Malignant peripheral nerve sheath tumours and other lesions such as neurofibromas were excluded.
4. Patients' information and follow-up available.

Controls were selected and matched to NF2 schwannoma excisions based on the criteria below, in the following order of preference:

1. Involvement of the same named peripheral nerve
2. Involvement at the same site/level
3. In a patient of the same or similar age
4. A tumour of the same or similar size

Schwannoma excisions were performed by 4 different surgeons in the plastic surgery unit. In all cases excision was undertaken by exposure of the nerve above and below the tumour, epineurial incision, and blunt dissection of the nerve sheath off the tumour. Extirpation of the tumour was usually achieved by dividing the sole fascicle from which the tumour had arisen, while preserving the other fascicles of the nerve (figure 1). Data were collected on the macroscopic characteristics of excised schwannomas, including the tumour site, nerve involved, and lesion size.

Data were collected retrospectively by a trainee surgeon who was not involved in the surgery. Records from the first post-operative follow-up consultation were reviewed for evidence of a new neurological deficit secondary to surgery. An outcome score was assigned based on the data recorded at the final post-operative follow-up, compared to the recorded pre-operative neurological deficit, according to a pre-defined scoring system (Table 1). When resolution of pre-operative symptoms was accompanied by a new, persistent neurological deficit secondary to the surgery, an outcome score was assigned based on the overall relative severity of neurological morbidity at the pre-operative and final follow-up consultations, taking both into account. Data on tumour recurrence were not included in the outcome score, but were considered separately according to clinical evidence of recurrence confirmed by intra-operative findings at re-exploration and/or MRI results. Data from NF2 patients and controls were analyzed by McNemars test for nonparametric, categorical, paired data, and Wilcoxon matched pairs test. A correction for multiple comparisons was calculated by the Sidak-Bonferroni method based on a familywise

significance level of 0.05 and 14 comparisons, giving a statistically significant p value <0.0037. Mean data are presented with corresponding 95% confidence intervals (CI) and ranges. Institutional approval for the study was granted by Oxford University Hospitals.

Results

We reviewed 30 cases of peripheral nerve schwannoma excisions in 15 patients with NF2, which were matched to 30 sporadic schwannoma excisions in 28 patients without NF2 (Table 2). 22 NF2 schwannomas and 22 control schwannomas were associated with a mixed sensory and motor nerve. One control schwannoma was associated with a motor branch to extensor carpi radialis longus, with no sensory component, and the remainder were sensory nerves. The mean size (maximum diameter) of excised schwannomas was 30.0 mm in NF2 (range 10.0 mm – 83.0 mm), and 24.1 mm in controls (range 3.0 mm – 46.0 mm). The mean duration of post-operative follow-up was 17.8 months in NF2 (95% CI 4.1 – 31.5), and 7.0 months in controls (95% CI 2.5 – 11.4). Although we aimed to match for age, patients with NF2 were younger (mean age 46.9 years 95% CI 41.1 - 52.8) compared to controls (mean age 58.8 years, 95% CI 51.8 – 65.8). NF2 patients were more likely to have multiple schwannomas, with an average 2.0 lesions per patient in NF2 (95% CI 1.2 – 2.8) compared to 1.0 in controls (95% CI 1.0 – 1.2).

Schwannomas presented with symptoms and signs secondary to nerve compression including pain, paraesthesia, sensory loss and weakness (Table 3). In addition, one NF2 patient presented with macrodactyly in the territory of the digital nerve schwannoma⁽²⁾. NF2 schwannomas had a higher prevalence of pre-operative weakness ($p=0.041$) and sensory loss ($p=0.133$) than control tumours, which presented more commonly with paraesthesia ($p=0.013$), however this was not

statistically significant when a Sidak-Bonferroni correction for multiple comparisons was applied.

Neurological morbidity at the initial post-operative review was a common finding in both groups. We classified this into two categories: a pre-existing deficit that failed to resolve immediately, or a new neurological deficit secondary to the schwannoma excision. Despite higher rates of pre-operative weakness in NF2 cases (Table 3), post-operative weakness was more common after excision of sporadic schwannomas in the control group ($p=0.013$) (Table 4), although this was not statistically significant after a Sidak-Bonferroni correction. All post-operative weakness could be attributed to a pre-existing deficit in the NF2 cases, however the majority of post-operative weakness appeared to develop secondary to the surgical intervention in controls. Overall, the rates of neurological morbidity secondary to surgery did not differ significantly between groups, and there was a trend towards more favourable results in the NF2 group (Table 4). When present, pre-existing or new pain and paraesthesia resolved during the follow-up period in the majority of NF2 cases and controls, but recovery of sensory loss and weakness was less reliable in both groups (Table 5).

The mean outcome scores at final follow-up assessment were 2.4 in NF2 (95% CI 2.1 – 2.7), and 2.2 in control schwannoma excisions (95% CI 1.8 – 2.6), corresponding to a great improvement or complete resolution of pre- and post-operative neurological deficit (Table 1), without a significant difference between groups ($p=0.264$), despite NF2 patients having a more severe pre-operative neurological deficit (Table 3)

Recurrence occurred in 3/30 NF2 schwannoma excisions and 2/30 controls

($p=1.000$).

Discussion

Peripheral nerve schwannomas cause neurological morbidity in NF2¹, and although these patients form an important subset of those undergoing surgical intervention for peripheral nerve sheath tumours, studies focussing specifically on the outcomes in NF2 are lacking. Our data suggest that surgical excision of peripheral nerve schwannomas results in improvement or complete resolution of associated neurological deficit in the majority of cases. Furthermore we were unable to demonstrate a difference in outcomes between NF2 patients and matched cases of sporadic schwannomas.

Patients with NF2 begin to develop characteristic nervous system lesions from childhood⁴ however intervention for peripheral disease may be delayed as a result of diagnostic uncertainty in the presence of other central and peripheral nervous system pathology^{5,6,10,11}, and where priority is given to the management of central lesions. These challenges are reflected in our data. Although patients with NF2 presented with peripheral nerve schwannomas at a younger age, there was a trend towards higher rates of pre-operative weakness and sensory loss compared to controls, suggesting a more severe compressive neuropathy and earlier onset of a more advanced neurological deficit in NF2-associated schwannomas. Despite this, our data suggest that with surgical intervention these patients do as well as patients with sporadic schwannomas.

Our results, including rates of initial post-operative neurological deficit, also compare favourably to outcomes reported elsewhere in the literature for schwannoma excisions (not specifically associated with NF2). In one series of 20 patients with benign peripheral nerve schwannomas of the upper limb, neurological deficit was reported to occur in 75% following tumour excision⁹. Although much higher than our rates of initial post-operative deficit, data on outcomes at final follow-up were superior, with 93% of affected patients achieving complete recovery of their neurological deficit. A lower incidence of post-operative neural deficit has been reported in another series of 87 cases of peripheral nerve schwannomas, with only 25.3% of excisions associated with post-operative neurological morbidity; 17.2% with sensory disturbance and 8% motor deficit⁸. However a different analysis of the outcomes of 30 lower limb peripheral nerve schwannoma excisions revealed a higher incidence of post-operative neurological deficit occurring in 76.7% of cases, and only 52% of those affected had recovered by their final follow-up at an average of 58.8 months⁷. There is clearly much variation in outcomes reported in the literature.

From the data generated by our small case-control study we were not able to demonstrate a difference in the outcomes of peripheral nerve schwannoma excisions between the two groups. It is possible that closer post-operative surveillance in the NF2 group could account for the slightly superior outcome scores in NF2, with a trend towards a longer period of post-operative follow-up for NF2 schwannoma excisions. Our study supports the concept that despite their complex associated neurological pathology, surgical intervention should still be offered to patients with NF2 who have symptomatic, peripheral nerve schwannomas.

Conflict of interest statement

None to declare

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Figures



Figure 1. Surgical technique of excision of a sciatic nerve schwannoma in a patient with NF2. A: Peripheral nerve schwannoma, still contained within the nerve sheath. B: Appearance of the schwannoma after dissection of the nerve sheath off the tumour. The association with a single nerve fascicle is shown.

Tables

Table 1: Scoring system to assess final outcomes in cases and controls.

Final outcome	Score
No improvement	0
Some improvement	1
Great improvement	2
Completely resolved, no neurological symptoms	3

Table 2. Schwannoma characteristics. This table shows the distribution of NF2 schwannomas included in the study (level of involvement and named nerve involved), and corresponding data on matching of sporadic schwannomas in controls.

Nerve involved	NF2 (number of cases)	Controls (number of cases)
Digital nerve	4	4
Median nerve	4	4
Ulnar nerve	3	6
Radial nerve	3	3
Musculocutaneous	2	1
Suprascapular	2	0
Brachial plexus root	2	4
Brachial plexus trunk	2	2
Brachial plexus cord	1	0
Sciatic	1	1
Common peroneal	1	2
Tibial	3	2
Sural	1	0
Median plantar nerve	1	1
Site of lesion	NF2 (number of cases)	Controls (number of cases)

Upper limb	23	24
Neck/axilla	11	7
Arm/elbow	2	7
Forearm	2	4
Wrist/hand	4	2
Finger	4	4
Lower limb	7	6
Thigh/popliteal fossa	3	2
Leg	2	1
Ankle/foot	2	3

Table 3. Pre—operative neurological deficit. Comparison of the number of schwannomas associated with a neurological deficit (pain, paraesthesia, sensory loss and weakness, subjective or objective on clinical examination) out of 30 NF2 schwannomas and 30 matched sporadic schwannomas included in the study.

Pre-op symptoms	NF2	Controls	p
Pain	25	26	1.000
Paraesthesia	1	9	0.013
Sensory loss	6	2	0.133
Weakness	8	2	0.041

Table 4. Initial post-operative morbidity. New neurological deficit secondary to surgery, recorded at the first post-operative follow-up.

Neurological morbidity	NF2 cases	Controls	p
Pain	0	1	1.0000
Paraesthesiae	3	7	0.1336
Sensory loss	6	8	0.4795
Weakness	0	8	0.0133

Table 5. Outcomes at final follow-up. Neurological deficit, pre existing or new, which resolved at final follow-up.

All neurological deficit	NF2	Controls	p
Pain			
All cases affected	25 / 30	27 / 30	
Cases resolved / affected	25 / 25	25 / 27	
All symptom free cases final	30 / 30	28 / 30	0.4795
Paraesthesia			
All cases affected	4 / 30	16 / 30	
Cases resolved / affected	3 / 4	11 / 16	
All symptom free cases final	29 / 30	25 / 30	0.1336
Sensory loss			
All cases affected	12 / 30	10 / 30	
Cases resolved / affected	3 / 12	6 / 10	
All symptom free cases final	21 / 30	26 / 30	0.0736
Weakness			
All cases affected	8 / 30	10 / 30	
Cases resolved / affected	3 / 8	6 / 10	
All symptom free cases	25 / 30	26 / 30	0.1336

final			
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