Multiple schwannomas in the peripheral nerves

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Multiple tumours of peripheral nerves are often seen in patients with neurofibromatosis of type 1 or 2. Multiple schwannomas may occur without other manifestations of neurofibromatosis.

We have reviewed 12 patients with multiple schwannomas arising from peripheral lesions who did not fulfil the criteria for either type of neurofibromatosis. Four had spinal and one an intracranial lesion in addition to the peripheral tumours. Two patients had one and three *café-au-lait* spots, respectively, and another had a probable family history. The largest tumours were 45 to 250 mm in size. Three patients had been referred as having von Recklinghausen's disease.

The large size of tumours, the difficulties of histological diagnosis on biopsy, and the confusion with neurofibromatosis can lead to overtreatment. Malignant change seldom, if ever, occurs in patients with multiple schwannomas.

J Bone Joint Surg [Br] 1998;80-B:657-661.

Received 7 November 1997; Accepted after revision 19 January 1998

Benign schwannomas and neurofibromas are common in peripheral nerves. A schwannoma is usually a solitary lesion, but neurofibromas are seen as multiple lesions in neurofibromatosis (NF) type 1.¹ Multiple schwannomas have been observed in peripheral nerves in rare instances, some in association with NF2, formerly known as bilateral acoustic neurofibromatosis.² Patients with multiple schwannomas in the spine or periphery are occasionally seen without acoustic tumours,³⁻⁸ and may be misdiagnosed as

having NF1.⁸ We present the clinicopathological details of 12 patients with multiple peripheral schwannomas but without other stigmata of NF1 or NF2.⁹

Patients and Methods

We have reviewed all cases diagnosed as a schwannoma or neurofibroma of the spine, soft tissue or skin seen at our centre. There were 246 patients with schwannoma, 15 of whom had multiple lesions. Three of them were diagnosed as having NF2 (Table I) and were excluded from this study. The clinical notes and histological slides of the other 12 were reviewed.

Results

Clinical findings. The clinical features of the 12 patients (six men and six women) are summarised in Table II. Their mean age was 43 years (19 to 77), and the number of schwannomas in each varied from two to 16. The sciatic nerve and the brachial plexus were the most common peripheral sites. Four patients had spinal schwannomas and six had skin lesions. The mean size of the largest tumour in

Table I. Criteria for diagnosis of neurofibromatosis 1 and 2⁹

Neurofibromatosis 1

Two or more of the following are required:

- Six or more *café-au-lait* spots over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in adults
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Freckling in the axillary or inguinal regions
- Optic glioma
- Two or more Lisch nodules
- A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudarthrosis
- A first-degree relative (parent, sibling, or offspring) with NF1 diagnosed by the above criteria

Neurofibromatosis 2

One of the following is required:

- Bilateral tumours of the eighth nerve seen with appropriate imaging techniques such as CT or MRI
- A first-degree relative with NF2 and either a unilateral mass of the eighth nerve, or two of the following; neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacity

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0301-620X/98/48532 \$2.00

Table II. Details of patients with peripheral schwannomatosis

Case	Age (yr)	Gender	Location of tumours and number			Total number of tumours	Size* (mm)	Diagnosis before excision
			Peripheral nerve	Intraspinal	Skin			
1	67	M	2 left brachial plexus 1 left ulnar 1 left digital			4	50	
2	39	F	2 left brachial plexus		7	9	60	
3	54	M	1 right brachial plexus 1 left brachial plexus	2	2	6	Unknown	
4	50	M	1 left sciatic 4 right sural			5	170	Sarcoma†
5	52	M	1 left sciatic		4	5	45	Neurinoma‡
6	24	M	1 left sciatic 1 left peroneal	2		4	60	Sarcoma†
7	77	F	11 left sciatic	2	3	16	90	Benign tumour†
8	19	M	4 right brachial plexus 1 left radial 1 left ulnar	2	8	16	250	
9	64	F	2 right sciatic 1 right tibial			3	100	Neurinoma§
10	37	F	1 left peroneal 1 left radial			2	150	Sarcoma‡
11	42	M	1 left saphenous		1	2	50	
12	43	M	5 right sciatic			5	120	Fibrosarcoma§

* the longitudinal length of the largest tumour

† by aspiration cytology

‡ frozen section

§ open biopsy

Fig. 1a

Fig. 1b

Case 4. Axial MRI showing a) a large schwannoma (arrows) of the left sciatic nerve (the T1-weighted image, with enhancement, shows heterogeneous and intense contrast with clear margins) and b) two schwannomas (arrows) of the right sural nerve.

individual cases was 104 mm (45 to 250). A large schwannoma of the left sciatic nerve and two schwannomas of the right sural nerve, all from case 4, are shown in Figure 1.

All 12 patients had at least one tumour which caused radiating pain on percussion (Tinel sign), suggesting a lesion of a peripheral nerve. Three patients (cases 6 to 8) had incomplete paralyses due to schwannomas in the spine. The other nine had no motor weakness; one (case 5) had mild dysaesthesia in the distribution of the sciatic nerve.

Only two patients had *café-au-lait* spots on the skin, one in case 5 and three in case 8. A family history suggestive of schwannoma was found in case 7; this patient had 11 lesions in the sciatic nerve, two in the spine and three in the skin (Fig. 2). She also had cataracts and

incomplete loss of hearing but MRI showed no evidence of acoustic schwannoma. Her father and one of four siblings had multiple subcutaneous tumours, but had not received surgical treatment or pathological examination. She had a son aged 51 years and a daughter of 48 years. Although neither had been aware of any tumours, careful physical examination found a soft-tissue tumour 1 cm in diameter in the son's leg. This was enucleated from the peroneal nerve and histological examination showed a schwannoma. No other patient had cataracts, a Lisch nodule (hamartoma of the iris), hearing loss or tinnitus. Three patients (cases 2, 6 and 8) had been referred to us by orthopaedic surgeons as having neurofibromatosis or von Recklinghausen's disease.

Fig. 2a

Fig. 2b

Case 7. Figure 2a – A sagittal MRI showing the multiple schwannomas in the left sciatic nerve. Figure 2b – The 11 schwannomas which were excised from the sciatic nerve; the largest was 90 mm in diameter.

Fig. 3

Case 10. Photomicrograph of a frozen section from a tumour of the peroneal nerve. The highly cellular area with hyperchromatic nuclei was wrongly diagnosed as showing malignancy.

Pathological findings. A histological diagnosis was made before or during operation in seven cases, four of which were thought to be malignant. Two were diagnosed as malignant after aspiration biopsy before operation (cases 4 and 6). One (case 10) was diagnosed as a sarcoma from the frozen section (Fig. 3) and one (case 12) as a fibrosarcoma after a small open biopsy (Fig. 4a).

At final diagnosis on fixed sections, all the tumours had

the typical appearance of a benign schwannoma with Antoni A and B elements. Antoni A areas are composed of spindle cells arranged in short bundles with foci of nuclear palisading and Verocay bodies. Antoni B areas contain spindled or oval cells in a myxoid stroma (Fig. 4b). Immunohistochemical stains for S-100 protein were available for review in nine cases (cases 2 to 7, 9, 10 and 12). All the lesions were diffusely and strongly positive for S-100 protein (rabbit anti S-100 protein antibody; Dako, Denmark) (Fig. 4c).

Treatment and follow-up. Patients were followed for a mean of 7 years 9 months (8 months to 32 years). All but one of the tumours in the peripheral nerves were enucleated. One patient (case 6) developed incomplete palsy of the peroneal nerve, but there were no other complications. One tumour (case 10) was resected *en bloc* with the peroneal nerve, because the frozen section obtained during the operation was thought to show malignancy. There was no local recurrence of the tumours of the peripheral nerves. No patient had an acoustic schwannoma when last seen, but one (case 3) developed an intracranial tumour of the fifth nerve ten years after the excision of a lesion in the axilla.

Discussion

In 1988, the National Institutes of Health Consensus Development Conference Statement defined the diagnostic cri-

Fig. 4a

Fig. 4b

Fig. 4c

Case 12. Figure 4a – Photomicrograph of a tumour of 110 mm diameter in the thigh showing highly cellular spindle-shaped cells with a herringbone-like pattern, diagnostic of fibrosarcoma. Figure 4b – Photomicrograph of the excised tumour showed a hypercellular area (Antoni A) on the left and hypocellular area with a myxoid matrix (Antoni B) on the right. The earlier biopsy (4a) had probably been taken only from an Antoni A area. Figure 4c – Photomicrograph showing diffuse positive staining for S-100 protein.

teria for NF1 and NF2 (Table I).⁹ Both are autosomal dominant disorders. The gene locus for NF1 is on chromosome 17q and that for NF2 on chromosome 22q. The term neurofibromatosis describes two clinically and genetically distinct diseases,^{2,10} previously known as ‘von Recklinghausen’s disease’. This term usually denoted NF1, and NF2 was called ‘bilateral acoustic neurofibromatosis’.² In the peripheral nerves, patients with NF1 usually develop neurofibromas and NF2 is associated with schwannomas.¹

A schwannoma is an encapsulated, slowly growing tumour of a nerve sheath. It is mobile from side to side but fixed in the long axis of the nerve; a painful Tinel sign can be elicited on percussion. Neurological defects are uncommon in benign schwannomas, but malignant peripheral nerve-sheath tumours (MPNST) often produce loss of peripheral function.^{1,4,5} Enzinger and Weiss¹ noted that a schwannoma almost always occurs as a solitary lesion except in NF. Our patients, however, had multiple peripheral schwannomas with no other stigmata of NF1 or NF2. Of the 246 patients with schwannomas whom we reviewed, 12 (4.6%) had multiple tumours. The multiple occurrence of tumours has been reported in six of 32, and in two of 16 patients with schwannomas in peripheral nerves.^{4,5} Some authors have suggested that multiple schwannomas be

regarded as a distinct clinical entity called neurilemmomatosis or schwannomatosis. Some of these series included patients who would now be classified as having NF2, but others had multiple schwannomas with no evidence of NF.^{8,11-16} The reported lesions were usually less than 5 cm in diameter and were usually superficial, but our patients tended to have larger tumours which were situated deeper.

Histologically, it is sometimes difficult to differentiate in a small biopsy between a benign schwannoma and malignant tumours such as MPNST, fibrosarcoma or a leiomyosarcoma.¹ Diffuse and strong S-100 immunostaining is observed in schwannoma but is seldom seen in fibrosarcoma and leiomyosarcoma. Since this staining is focal and limited to small numbers of MPNST cells it is valuable in the differential diagnosis.¹ MRI characteristics can be useful in the diagnosis of a schwannoma. On a T1-weighted image, the lesion shows an identical or slightly higher signal intensity than muscle. On a T2-weighted image or an enhanced T1-weighted image, a target pattern may be seen with a peripheral hyperintense rim and central low intensity. Malignant soft-tissue tumours and large schwannomas can, however, appear very similar on MRI.¹⁷

MPNST often arise in patients with NF1 and multiple schwannomas are commonly confused with the latter con-

dition.⁸ The large size of the tumours, difficulties in the cytological and histological diagnosis of the biopsy, and confusion with NF1 can lead to overtreatment. The lesions in four of our 12 patients were diagnosed as malignant after examination of biopsies before and during operation and one had an *en-bloc* excision including the peroneal nerve. Malignant change is exceedingly rare in a benign schwannoma and from a practical point of view can be discounted.¹ We have found no reports of such change occurring in cases of multiple schwannoma, and therefore consider that the differential diagnosis between schwannomatosis and NF1 is important.

Six or more *café-au-lait* spots are usually seen in patients with NF1² whereas in schwannomatosis most patients have none.¹¹⁻¹⁵ Two of our patients had such lesions but only one and three, respectively. While less than six *café-au-lait* spots are often seen in patients who do not have NF1, those with the disease usually have more than six.² The presence of six or more spots is a crucial clinical feature in differentiating NF1 from schwannomatosis. Freckling in the axillary or inguinal region and two or more Lisch nodules are also common features of NF1, but have not been reported in schwannomatosis.

It has previously been thought that schwannomatosis is a distinct, non-hereditary condition, but autosomal dominant transmission of schwannomatosis has been described recently and a few reports suggest that it is likely to be a variant of NF2.^{8,18,19} Evans et al.⁸ found that linkage analysis in families with schwannomatosis was consistent with involvement of the NF2 gene. Honda et al.¹⁸ and Pulst, et al.¹⁹ found germline mutations in the NF2 gene in such patients and some cases presenting with schwannomatosis have subsequently developed other signs of NF2.²

None of our patients developed an acoustic schwannoma but one showed a lesion of the fifth nerve ten years after the excision of an axillary tumour. A tumour at this site is seen in 30% of patients with NF2, and our case may therefore represent a variant. In another patient aged 77 years, careful physical examination revealed a very small schwannoma in her 51-year-old son. It is not clear whether all cases of multiple schwannoma are variants of NF2, but careful long-term follow-up and further genetic analysis should be performed.

Patients with multiple schwannomas who present to orthopaedic surgeons tend to have large tumours of the sheaths of peripheral nerves. The condition is easily con-

fused with NF1, which is sometimes associated with malignant tumours at these sites. Malignant change does not occur in schwannomatosis: accurate diagnosis is needed to prevent overtreatment.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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