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# Intramedullary tumours in patients with neurofibromatosis type 2: MRI features associated with a favourable prognosis

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AIM: To assess the magnetic resonance imaging (MRI) features and natural history of intramedullary tumours in patients with neurofibromatosis type 2 (NF2).

MATERIALS AND METHODS: Eleven NF2 patients with intramedullary spinal cord tumours were identified from the database of the multidisciplinary NF2 clinic. All the imaging studies of these patients were individually reviewed by two neuroradiologists to evaluate the size, number, location, imaging characteristics, and interval growth of the intramedullary tumours.

RESULTS: Two of the 11 patients had lesions that required surgery. Both these lesions were in the cervical region, and extended over three and five segments respectively. Nine patients with a mean imaging follow-up period of 77 months had lesions that remained stable, apart from the development of small peritumoral cysts in three. The lesions were well circumscribed, often multiple, usually less than 1 cm in diameter, and were most frequently found in the cervical cord.

CONCLUSION: The majority of intramedullary tumours in NF2 patients are very slow growing and share certain MRI features that differ from those of progressive or symptomatic lesions.


## Introduction

Neurofibromatosis type 2 (NF2) is an autosomal dominant disorder with an incidence of 1 in 33-40,000 live births.[1] The disease is caused by mutations of the NF2 gene on chromosome 22q. It is characterized by neoplastic and dysplastic disorders of Schwann cells (schwannomas and schwannosis), meningeal cells (meningiomas and meningoangiomatosis), and glial cells (gliomas and glial microhamartomas). Bilateral vestibular schwannomas are pathognomonic. Further features include posterior lens opacities and cerebral calcifications. Diagnostic criteria have been developed to allow a clinical diagnosis of the condition to be made even before bilateral vestibular schwannomas have developed. The most commonly used of these are the NIH criteria.[2]

NF2 predisposes to both intramedullary and extramedullary spinal tumours. The extramedullary tumours — schwannomas and meningiomas — can cause symptoms due to cord or cauda equina compression and may require surgery. All types of intramedullary glial tumours are more common in NF2 patients than in the general population, with ependymomas and astrocytomas being the most frequent. In addition to glial tumours, intramedullary schwannomas have also been described in NF2. It appears that the type of mutation of the NF2 gene is related to the severity of both the intracranial and spinal disease, with stop mutations leading to patients being severely affected, whereas splice, missense, and large deletions result in a milder disease form.[3]

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**Table 1** Summary of patient characteristics

| Patient | Age/sex | Number of tumours | Size (mm) | Position | Signal change | Follow-up period | Change over time | Any new lesion | Treatment | Mutation of NF2 gene | Histology |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 54/M | 1 | 40 × 10 | C4 to C6 | Syrinx C1 to C7 | 10 years 8 months | Increase in size | 10 × 5 mm nodule at T7/8 | Laminectomy and radiotherapy 8 years into follow-up | Stop codon at 341 | None |
| 2 | 43/F | 1 | 65 × 10 solid, | C4 to T4 | Multiple cavities | 4 years 3 months | Atrophy post-surgery | No | Surgery 6 months into follow-up | Two deletions found in tumour | Ependy-moma WHO grade II |
| 3 | 58/F | 4 | 4 | C2 to T1 | High signal C2 to T1 | 11 years 5 months | No | No | None | | None |
| 4 | 32 at death/M | 14 | 20 × 15 largest, 7 mm others | C0 to conus | None | 6 months | No | No | None | Stop mutation at codon 57 | None |
| 5 | 17/M | 1 | 3 × 3 | C0 | None | 4 years 6 months | No | No | None | | None |
| 6 | 28/M | 6 | 10 × 10 largest C1, 2 mm others | C1 to C7 | None | 10 years 2 months | Yes, solid unchanged, 10 mm cyst at C1 developed | No | None | Duplication exons 12—14 | None |
| 7 | 20/M | 2 | 10 × 8 C2, 3 mm C0 | C0 and C2 | None initially | 4 years | Yes, solid unchanged, cyst C0 to C3 developed | No | None | | None |
| 8 | 59/F | 11 | 6 × 5 largest | C4 to C7 | None | 7 years | No | No | None | Deletion of promoter to exon 1 | None |
| 9 | 18/M | 4 | 10 × 7 largest C0 | C0, C7, T7, T12 | None | 4 years | No | No | None | | None |
| 10 | 38/M | 1 | 10 × 5 | C1 | None | 7 years 10 months | Developed cyst, solid unchanged | No | None | | None |
| 11 | 60/F | 2 | 8 × 4 mm both | C2, T3 | None | 6 years | Small cyst at C2 | No | None | | None |

The imaging findings of the intramedullary lesions are shown over stated follow-up periods.

Current imaging recommendations of the spine are for an initial magnetic resonance imaging (MRI) to be carried out at around age 10—12 years, or earlier if there are specific symptoms, and for follow-up spinal imaging to be carried out every 2—3 years.[4] In the routine follow-up of this patient group in the quarterly multidisciplinary NF2 clinic, we have noticed that intramedullary lesions often do not have the imaging characteristics or show progression on follow-up imaging typical of ependymomas seen in the general population, and yet they are often labelled as such. Due to the nature of these lesions and the symptomatology of this patient group, they rarely undergo surgery, and thus histological confirmation is usually not obtained. In order to better characterize the natural history of these lesions, a retrospective review of the spinal MRI images was conducted in the NF2 patient cohort.

## Materials and methods

NF2 patients were identified from the database of the multidisciplinary NF2 clinic. We identified 47 patients in whom follow-up imaging had been performed, all confirmed as having NF2. All patients had bilateral vestibular schwannomas, and all had undergone at least one spinal MRI examination. By systematically reviewing the radiology reports and clinic records of these patients, 11 patients with intramedullary spinal cord tumours were found. This patient group consisted of seven men and four women with a mean age of 39 at time of review (range 18—60 years). The patients all had their follow-up imaging performed using a 1.5 T GE Signa Excite MRI (Wisconsin, USA), or a 1.5 T Siemens Vision (Erlangen, Germany). Initial imaging was performed either on these MRI machines, or at other centres. Typical imaging protocols varied slightly, but generally included sagittal T2 and T1 post-gadolinium images of the whole spine, with axial T2- and gadolinium enhanced T1-weighted sequences. All the available neuroimaging studies were reviewed independently by two neuroradiologists. Consensus was reached in cases of disagreement. Data was collected on the position, size, number, and imaging characteristics of intramedullary lesions, and how these changed over time. Search for mutations of the NF2 gene was performed on all 11 patients.

Local ethics committee agreement was deemed not to be necessary as the study was entirely retrospective, and did not generate any additional imaging or follow-up.

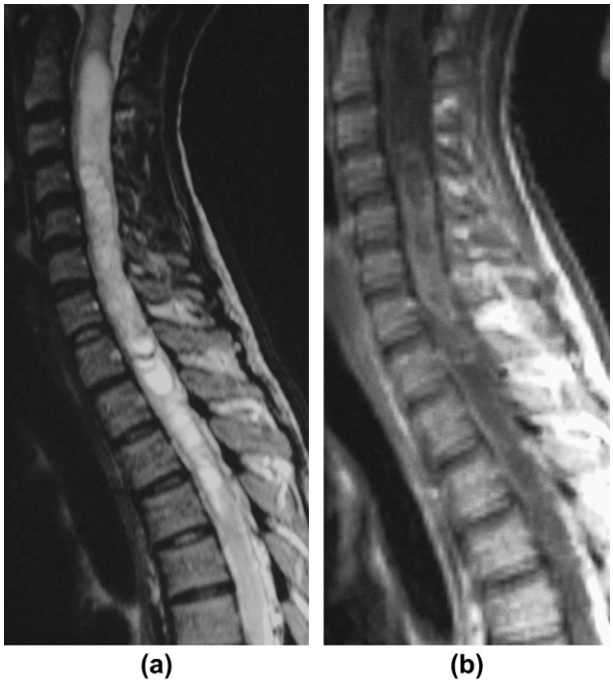


**Figure 1** Patient 2: A sagittal T2-weighted image (a) shows cord expansion by a heterogeneous mass in the cervical cord with increased signal extending up to C2 and hydromyelic changes inferior to the tumour extending to T4. A sagittal T1-weighted gadolinium enhanced image (b) shows heterogeneous enhancement of the tumour extending from C4 to T1. This lesion was excised, with the histology confirming ependymoma.

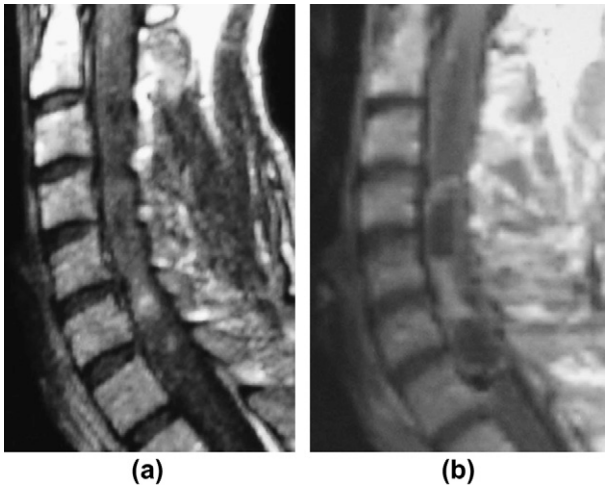


**Figure 2** Patient 1: A gadolinium enhanced sagittal T1-weighted image (a) shows a heterogeneously enhancing lesion extending from C4 to C7. Gadolinium enhanced sagittal T1-weighted image (b) 5 years later shows a slight increase in size with increased cord expansion. The patient had progressive symptoms and underwent decompressive laminectomy and radiotherapy.

## Results

A summary of patients and imaging findings of their intramedullary lesions is shown in Table 1. The total period of follow-up ranged from 6 months to 11 years 5 months, with a mean of 6 years 5 months and a median of 6 years. The shortest follow-up in the cohort was 6 months. This patient died due to causes unrelated to the NF2 before further follow-up was performed. Although a post-mortem was performed on this patient, specific examination of the spinal cord by a neuropathologist was not performed.

Out of the 11 patients, two had lesions to which progressive symptoms could be attributed. Both of these patients required surgical intervention. In one (patient 1, see Table 1) symptoms progressed over 8 years of follow-up, before decompressive laminectomy and radiotherapy was performed. In this patient there had been little change in the imaging appearances before treatment. In the other patient (patient 2) excisional surgery was performed 6 months after the initial imaging. In this patient the presentation had been with symptoms attributable to the cord lesion. In both of these cases the lesions caused expansion of the cord with high signal on T2-weighted images extending over three and five spinal levels, respectively. Both lesions showed heterogeneous enhancement following gadolinium administration (Figs. 1 and 2). The histology of the patient who underwent

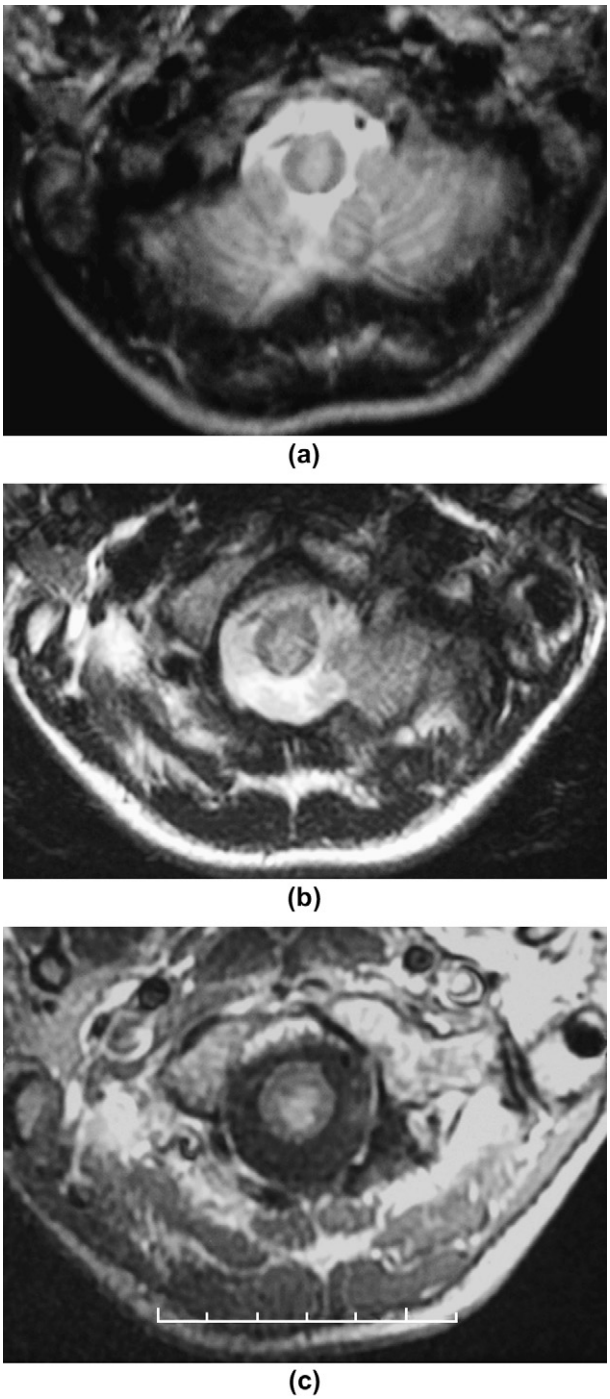


**Figure 3** Patient 9: Axial images of the cranio-cervical junction. The lesion returns high signal on a T2-weighted image (a), and is centrally placed within the cord. Four years later there has been no change (b). A gadolinium enhanced T1-weighted image (c) demonstrates uniform enhancement.

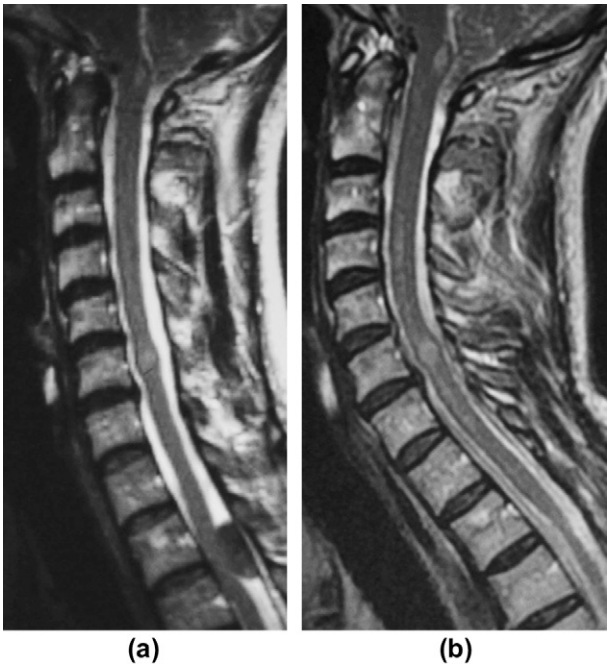


**Figure 4** Patient 8: A sagittal T2-weighted image (a) shows multiple intramedullary nodules within the cerivical cord. The highest lesion is at the level of the obex. The low signal, extramedullary lesion at T2/3 was a meningioma. A sagittal T2-weighted image of the same patient performed 7 years later (b) demonstrates no change in the intramedullary lesions. The patient has undergone surgery to remove the meningioma.

excisional surgery revealed an ependymoma [World health Organisation (WHO) grade II].

The imaging characteristics of the intramedullary lesions in the remaining nine patients differed in a number of respects from the two patients who underwent surgery. The lesions were centrally placed within the cord and generally small, with a mean size of 6 mm (range 2—20 mm; Fig. 3).

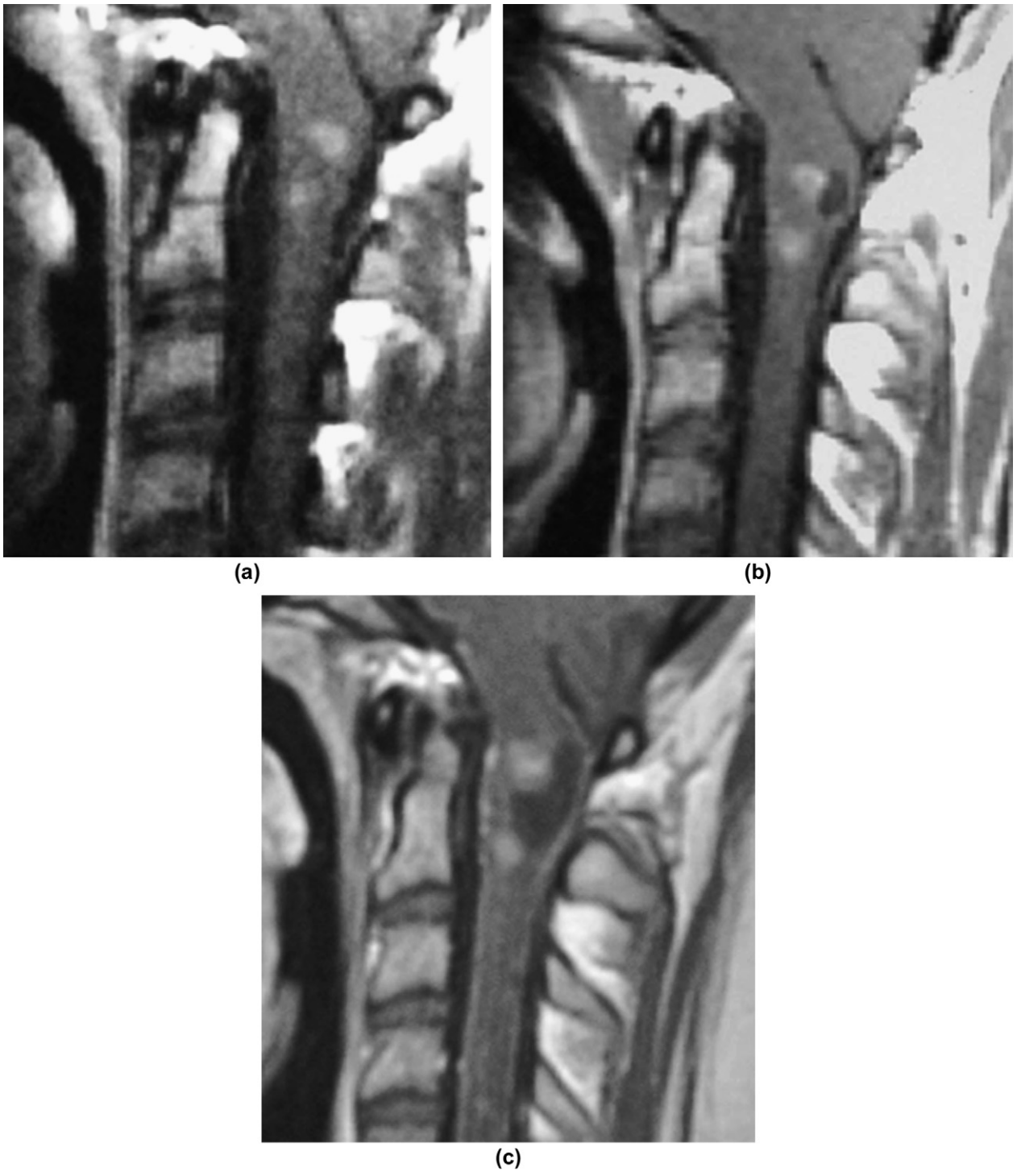


**Figure 5** Patient 6: Three sagittal T1-weighted post gadolinium images in the same patient taken at presentation (a), after 3 years (b), and after 10 years (c). They show a cyst developing and growing, related to the most superior enhancing lesion at C1. Numerous small lesions more distally within the cord, best demonstrated on image (c), remain unchanged.

They returned uniform high signal on T2-weighted images and showed avid, homogeneous enhancement after intravenous administration of gadolinium (Figs. 4 and 5). In six of the nine patients, at least one lesion was present at the craniocervical junction. Of the remaining three patients, two had lesions at C2, and the third had a C4 lesion. Most of the lesions (80%) were in the cervical cord. The mean number of lesions per patient was five (range 1—14). Over the follow-up period none of these enhancing lesions increased in size. However, in three patients a cyst related to the enhancing nodules either developed or grew over the follow-up period (Figs. 5 and 6). None of these three patients developed symptoms attributable to the enlarging cysts.

Table 2 lists the other intracranial and spinal tumours demonstrated in the patient cohort. The patients mostly had numerous intracranial and spinal tumours in addition to bilateral vestibular schwannomas. Imaging follow-up demonstrated enlargement in some or all of the intracranial tumours in all but two patients. Five patients developed new tumours over the follow-up period.

Mutational analysis revealed five patients with mutations of the NF2 gene (see Table 1). Both patients with lesions typical for ependymomas have had mutations found. Of the other nine patients, three have had mutations detected.

## Discussion

NF2 causes severe long-term morbidity, as well as a significant reduction in life expectancy, due to multiple, predominantly benign, neoplasms of the cranial and spinal regions. Repeated cranio-spinal MRI examinations are important in the management and follow-up of NF2 patients and provide useful information to clinicians involved in counselling these patients about their prognosis. Relatively little has been published about the incidence and natural history of intramedullary spinal cord tumours in NF2 patients. Patronas et al.[5] published the largest series describing 26 NF2 patients with intramedullary lesions. Sequential imaging was performed in 16 of their patients with a mean follow-up period of 49 months. In all, but one patient, there was no change in the lesions. Histology was obtained in three, revealing three different tumour types: ependymoma, astrocytoma, and intramedullary schwannoma.

In the present study the MRI features of intramedullary spinal cord tumours in NF 2 patients associated with a good prognosis were investigated. The mean follow-up period of 6 years 5 months is significantly longer than any previous series. The results suggest that there is a distinct category of intramedullary tumour that remains stable over a long period (Table 3). In the present

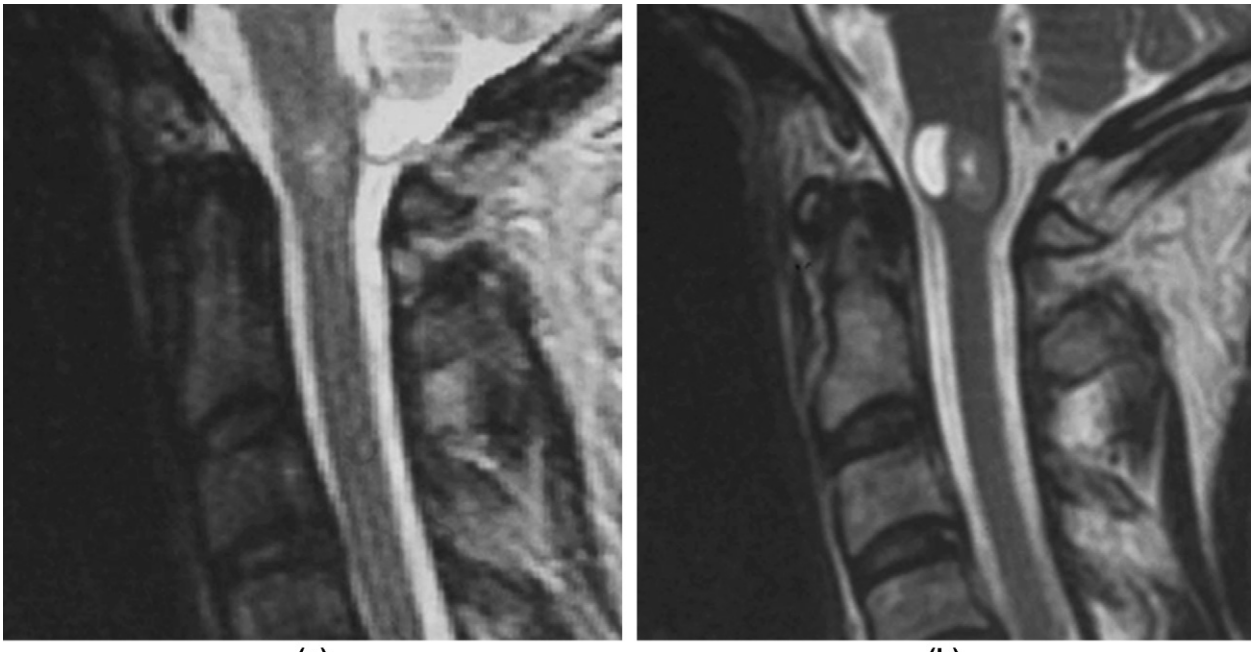


**Figure 6** Patient 10: A Sagittal T2-weighted image (a) shows an intramedullary lesion at C0. Seven years later, a sagittal T2-weighted image (b) shows that a cyst has developed at the anterior aspect of the tumour but the solid component remains unchanged. The patient had no brain stem symptoms.

**Table 2** Summary of the intracranial and spinal extramedullary tumour characteristics from the patient group

| Patient | Vestibular schwannoma | Intracranial meningioma | Intracranial schwannoma | Extramedullary meningioma | Extramedullary schwannoma | Follow-up period | Change over follow-up period |
|---|---|---|---|---|---|---|---|
| 1 | 5 × 5 mm R<br>20 × 20 mm L | Falx cerebri, right frontal | R Trigeminal | None | Right L1 | 10 years 8 months | Increase in size of both VIII schwannomas and meningiomas; development of a L L1 schwannoma |
| 2 | 15 × 18 mm R<br>3 × 3 mm L | None | None | T7 and T9 | T11 | 4 years 3 months | Developed R frontal meningioma, slight increase in size of T7 meningioma |
| 3 | 10 × 5 mm R<br>10 × 5 mm L | Multiple falcine, L intraventricular | None | None | None | 11 years 5 months | Post-surgery to left VIII schwannoma, increase in size in the multiple meningiomas (post-surgery to several) |
| 4 | 20 × 20 mm R<br>Post-surgery L | Bilat sphenoid wing and convexity | None | L3/4 | Several small cauda equina | 6 months | No change |
| 5 | 10 × 6 mm R<br>10 × 4 mm L | Torcula | Bilateral trigeminal | None | T1, T10, L1 | 4 years 6 months | Increase in size of both VIII schwannomas and trocula meningioma; development of numerous spinal schwannomas |
| 6 | 20 × 25 mm R<br>25 × 25 mm L | R jugular foramen | L trigeminal/ cavernous sinus | None | None | 10 years 2 months | Increase in size of R VIII schwannoma; development of multiple small supratentorial meningiomas, and R C7 schwannoma |
| 7 | 20 × 10 mm R<br>10 × 6 mm L | R parietal, L falcine | L cavernous sinus | None | T2, T6, T11 | 4 years | Increase in size in VIII schwannomas and meningiomas; development of olfactory groove meningiomas |
| 8 | Post-surgery R<br>30 × 40 mm L | R optic nerve sheath, multiple supra and infratentorial | L cavernous sinus | Cranio-cervical junction,T2/3 | C2 | 7 years | Slight increase in size of supratentorial and cranio-cervical junction meningiomas, surgery to T2/3 meningioma, |
| 9 | 10 × 8 mm R<br>10 × 8 mm L | R sylvian fissure | L trigeminal | None | Multiple cervical and thoracic | 4 years | No change |
| 10 | 20 × 25 mm R<br>15 × 25 mm L | Large R parietal, multiple small parafalcine | R cavernous sinus | None | Numerous C1, C6, T4, T6, T7 | 7 years 10 months | Increase in size in most schwannomas. |
| 11 | 30 × 30 mm R<br>5 × 5 mm L | Multiple involving supra and infratentorial | None | None | None | 6 years | Surgery on right VIII schwannoma and left convexity meningiomas. |

R, right; L, left.

**Table 3** Imaging features of intramedullary lesions in NF2 patients related to prognosis

| Worse prognosis | Better prognosis |
|---|---|
| Ill-defined and diffusely infiltrating the cord | Well-defined and centrally placed in the cord |
| Large, extending over multiple vertebral levels | Small, usually <1 cm in maximum diameter although the largest lesion in our series measured 1.5 × 2 cm |
| Associated signal change in the cord | No surrounding cord signal change (may develop cyst) |
| Heterogeneous enhancement | Enhance homogeneously |

series, at least one of these tumours was present either at the cranio-cervical junction, or high in the cervical cord in each patient. The lesions were centrally located within the cord, returned high signal on T2-weighted images, and enhanced uniformly after gadolinium administration. Multiple tumours were present in most patients and they did not increase in size over time. There was no associated signal change in the surrounding spinal cord, although small, peritumoural cysts developed in three patients. None of these three patients had symptoms attributable to the cysts.

As with previous studies,[5] the histological status of these lesions was not confirmed. None of the patients with non-progressive lesions in the present study underwent biopsy. However, both patients with lesions more typical of ependymomas did undergo surgery, and in the patient who underwent excision, histology confirmed ependymoma. Case studies describing the imaging features of intramedullary schwannomas report marked T2 signal change within the medullary cord surrounding the lesion.[6–8] None of the non-progressive lesions in the present study had surrounding medullary cord signal change, which would make the diagnosis of intramedullary schwannoma less likely. The multiple lesions could represent nodules of a single large lesion or independently occurring multicentric tumours, a point made by previous authors.[5]

In summary, the MRI features characteristic of intramedullary lesions in NF2 patients associated with a good prognosis were noted. Histological confirmation of the nature of any of these lesions could not be obtained, but the indolent behaviour demonstrated in the present study suggests that these lesions probably do not represent true ependymomas. Although annual cranial follow-up imaging is required in this group due to the frequency of intracranial tumour development and growth, repeated follow-up of intramedullary lesions appears to be less important, unless there are specific new symptoms. These findings may influence the information provided to patients and their families.

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