Longitudinal study of neurofibromatosis 1 associated plexiform neurofibromas

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ABSTRACT

Background: Plexiform neurofibromas are benign tumours that occur in more than half of people with neurofibromatosis 1 (NF1). These tumours can cause serious complications and can also progress to malignant peripheral nerve sheath tumours (MPNSTs), one of the leading causes of death among NF1 patients. Plexiform neurofibromas are clinically heterogeneous, and knowledge of their natural history is limited. In order to characterise the growth of plexiform neurofibromas better, we performed serial magnetic resonance imaging (MRI) in NF1 patients with such tumours.

Methods: MRI was done on 44 plexiform neurofibromas in 34 NF1 patients (median age 10 years; range 1–47 years). Each tumour was measured in two dimensions from the MRI scan, and the area and growth rate were calculated. The median length of follow-up was 6 years, with an average interval of 3 years between scans.

Results: 36 tumours remained stable in size throughout the period of follow-up. 8 tumours increased in size; all occurred in patients who were under 21 years of age when first studied. The single exception was a man who developed rapid tumour growth and pain in a plexiform neurofibroma that had been followed for 10 years. Biopsy showed the presence of an MPNST.

Conclusion: Longitudinal MRI is a valuable means of monitoring the growth of plexiform neurofibromas in individuals with NF1.

Neurofibromatosis 1 (NF1) is an autosomal dominant disease affecting 1 in 3500 individuals.[1] Benign neurofibromas are the defining feature of NF1. Plexiform neurofibromas, which may occur almost anywhere in the body, develop in about half of individuals with NF1.[2–4] Plexiform neurofibromas are benign, but can be seriously disfiguring, may erode adjacent bone or blood vessels, may cause obstruction of the respiratory or gastrointestinal tract[5] or they can progress to malignancy, producing malignant peripheral nerve sheath tumours (MPNSTs), one of the leading causes of premature death in people with NF1.[6]

Although plexiform neurofibromas are rarely diagnosed at birth, many are thought to be congenital,[7] while others appear to develop later in life.[8] Very little objective data exist on the growth of plexiform neurofibromas, in part because their irregular shape and frequent location deep within the body have made accurate longitudinal measurement of tumour size over time difficult. However, magnetic resonance imaging (MRI) has been shown to be an effective means of visualising plexiform neurofibromas[9 10] and can be used to follow them longitudinally.[11] In order to learn more about the natural history of plexiform neurofibromas, we performed longitudinal MRI scans of 44 tumours in 34 patients with NF1.

METHODS

Inclusion criteria

Between 1990 to 2006, 41 NF1 patients with clinically apparent plexiform neurofibromas were examined with serial MRI as part of their routine clinical care. All patients met the National Institutes of Health Diagnostic Criteria for NF1.[12] MRIs were performed every 1 to 4 years, depending on clinical indication, except during the last 3 years of the study, when annual MRI examinations were done on 27 of the patients. The investigation was approved by the ethical committee of the medical chamber in Hamburg.

For the purpose of this study, a tumour was diagnosed as a plexiform neurofibroma on the basis of characteristic external appearance or typical MRI features, such as strong signal intensity on T2 weighted STIR (short-tau inversion recovery), medium signal intensity on T1 weighted native images and variable enhancement with contrast. Histopathological confirmation was not available for these tumours. In order for a plexiform neurofibroma to be included in this study, all of the following imaging criteria were required:

- either axial/coronal or sagittal/axial scans
- reproducible measurability in two dimensions
- a measurement of >10 mm in at least one dimension
- comparable slice thickness (4 mm), slice gap (0–25%), and slice orientation on at least three MRI examinations.

All plexiform neurofibromas included in our analysis were followed for at least 3 years in adults or at least 2 years in children. Seven of the 41 patients originally enrolled in the study were excluded from the analysis because their tumours could not be followed for this length of time. The reasons for exclusion were surgical removal of the tumour in three cases, development of an MPNST in one case, and loss to follow-up in three cases.

MRI measurement method

MRI was performed using a 1.5 Telsa Siemens Magnetom 63 SP/Symphony/Avanto scanner. Sagittal and coronal 4 mm slices were examined. T1 weighted images had an echo time of 15–25 ms and a repetition time of ⩽600 ms, and T2 weighted images had an echo time of 80–120 ms and a repetition time of >2000 ms. T1 weighted coronal and sagittal images were obtained before and after intravenous administration of 0.1 mmol/kg or 0.2 ml/kg of gadopentetate dimeglumine.

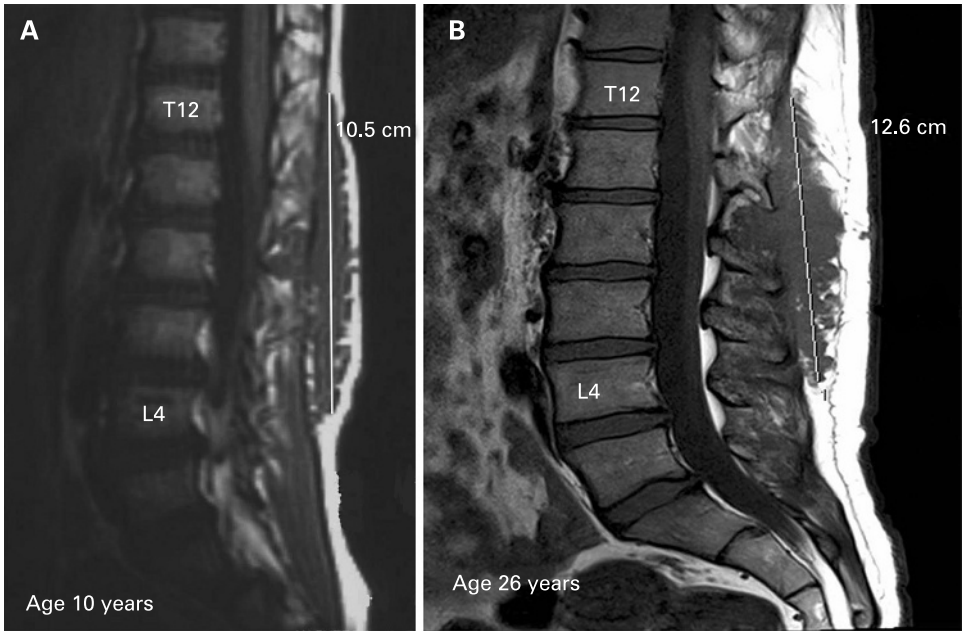

Figure 1 An example of tumour measurement for a thoracic plexiform neurofibroma in a patient with NF1. The size was measured in two orthogonal directions (called "horizontal" and "vertical"). This tumour increased in vertical length from 10.5 cm in 1990 (A) to 12.6 cm in 2006 (B). The area of the tumour is determined from the product of the largest horizontal and vertical measurements.

Data collection

All patients underwent a comprehensive physical and neurological examination at the time of each visit. MRI examinations were performed over a period of 16 years, during which the quality of available imaging improved substantially (see, for example, fig 1). Volumetric tumour measurements were not available at the beginning of this study, so two dimensional box models were used to estimate tumour size throughout the study. We initially performed MRI scout views in two or three directions to identify fixed anatomical reference points to define the region of interest. The target area was measured in the slice with the largest tumour area (fig 1). Tumour size was determined as the product of the largest diameter in each direction (horizontal and vertical). If multiple conglomerating nodular tumours were present, only the most clearly demarcated one was selected for measurement.

Radiologists had access to all previous scans and measurements for comparison at each reading. Tumours were classified by location (superficial or deep) and type (displacing, invasive or simple superficial) as previously described.[9 10] Plexiform neurofibromas were considered to be *superficial* if they were located cutaneously or subcutaneously, respected the epifascial membrane, and did not penetrate into muscle. Tumours that were located below or penetrated through the subcutaneous tissue into deeper tissue layers were classified as *deep*. Plexiform neurofibromas were considered to be *displacing* if they were multinodular, had smoothly defined borders, and compressed adjacent structures. Neurofibromas were classified as *invasive* if they consisted of conglomerating tumours that could not be divided from each other and that penetrated into adjacent tissue.

Data analysis

For each tumour, size was plotted as a function of the patient's age, and tumour growth rate was determined from the slope of the linear regression for each individual plexiform neurofibroma. The distributions of tumour size and growth rate were highly skewed, so the non-parametric Kruskal–Wallis test was used for multi-class comparisons, and the Mann–Whitney U test for binary comparisons. Non-parametric correlations were used to compare initial age at exam and tumour features. All calculations were performed with SPSS version 11.0 software (SPSS, Inc, Chicago, Illinois, USA). A value of $p \leqslant 0.05$ was considered to be significant.

RESULTS

Patient characteristics

Thirty-four patients (19 males and 15 females with NF1 and at least one plexiform neurofibroma that could be measured on MRI) were included in this study. There was no significant difference in the age at first examination between males (mean (SD) 17.3 (12.2) years, range 1–45 years) and females (13.5 (13.0) years, range 1–47 years).

All patients received at least three MRI scans, and 13 patients (29%) received four MRI scans. Altogether, 145 MRI scans were evaluated on the 44 tumours studied. The median length of follow-up was 6.0 years (range 1–15 years), and the average interval between scans was 3.0 (1.9) years (range 1–9 years). Supplemental table 1 summarises the findings on each of the patients and tumours.

Tumour characteristics

Table 1 shows a breakdown of the 44 tumours studied by type and main anatomical location. Fourteen neurofibromas presented with symptoms that included pain (5), discomfort with movement (4), paralysis (4), or impairment of vision (1). Four

Table 1 Location and type of 44 neurofibromas studied longitudinally by magnetic resonance imaging

	Tumour location				
Tumour type	Head	Spine	Trunk	Extremity	Total
Deep and invasive	2	4	3	2	11
Deep and displacing	1	7	0	1	9
Superficial and invasive	3	1	0	3	7
Superficial and displacing	0	1	2	7	10
Superficial only	5	0	2	0	7
Total	11	13	7	13	44

Table 2 Summary of median (range) of magnetic resonance imaging (MRI) measurements for neurofibromas classified by location, type and anatomical site

Classification		Median age (years) at first MRI exam (range)	Median tumour size (cm^2) at first exam (range)	Median tumour size (cm^2) at final exam (range)	Median change in tumour size (cm^2) over period of study (range)	Median growth rate (cm^2/year) (range)
Location	Deep (n = 20)	11 (1–47)	6.1 (0.8–170.0)	8.5 (0.8–170.0)	0.2 (0–53.2)	0.0 (0–12.9)
	Superficial (n = 24)	10 (3–45)	8.2 (0–200.0)	12.5 (1.8–208.0)	3.5 (0–75.0)	0.6 (0–10.6)
Type	Invasive (n = 18)	9 (7–16)	3.0 (0–97.8)	9.0 (2.4–125.1)	2.9 (0–27.3)	0.4 (0–5.3)
	Displacing (n = 19)	10 (3–41)	7.6 (0.8–170.0)	14.6 (1.8–170.0)	3.4 (0–53.2)	0.6 (0–12.9)
	Superficial (n = 7)	10 (1–47)	7.1 (0.8–200.0)	11.7 (0.8–208.0)	0.5 (0–75.0)	0.1 (0–10.6)
Site	Head (n = 11)	10 (1–47)	5.0 (0.3–97.8)	9.0 (2.2–125.1)	3.9 (0–27.3)	0.7 (0–5.3)
	Spine (n = 13)	26 (8–41)	7.1 (0.8–16.5)	8.5 (0.8–21.0)	0.0 (0.8–8.8)	0.0 (0–1.5)
	Trunk (n = 7)	9 (4–11)	82.2 (0–170.0)	69.3 (2.4–170.0)	2.4 (0–75)	0.5 (0–12.9)
	Extremity (n = 13)	8 (3–45)	8.0 (1.4–200.0)	20.0 (1.8–208.0)	3.2 (0–52)	0.5 (0–7.7)

superficial and displacing, three superficial and invasive, two deep and displacing, and five deep and invasive tumours were symptomatic.

Analysis of tumour size and growth

The median tumour size was somewhat greater in females than in males, both on first examination (8.7 cm^2, range 0.3–97.8 cm^2, *vs* 7.1 cm^2, range 0–200.0 cm^2) and on the final MRI examination included in the study (15.8 cm^2, range 5–125.1 cm^2, *vs* 8.5 cm^2, range 0.8–208.0 cm^2), but these differences did not reach statistical significance. The median difference between the initial and final tumour size was significantly greater in females (5.1 cm^2, range 0–53.2 cm^2) than in males (0.5 cm^2 range 0–75.0 cm^2) ($p = 0.037$). The tumour growth rate was also greater in females (0.8 cm^2/year, range 0–12.9 cm^2/year) than in males (0.1 cm^2/year, range 0–5.4 cm^2/year), but this difference did not quite reach statistical significance ($p = 0.055$). One patient (patient 14) had a second plexiform neurofibroma identified for the first time on a follow-up examination of another tumour imaged as part of this study.

Tumours classified by location as superficial grew more rapidly than those classified as deep ($p = 0.034$) (table 2). There was no significant difference in initial tumour size, final tumour size, change in tumour size, or growth rate between tumours classified by anatomical site or by type as invasive, displacing, or simple superficial (table 2). Figure 2 shows the tumour size and growth by age for all tumours, classified by both location and type.

Many of the plexiform neurofibromas found in our study were small (<10 cm^2); however, all large neurofibromas (>100 cm^2) were found in children. The median tumour size on initial examination was similar in children under 21 years of age and adults (7.75 cm^2 and 5.2 cm^2, respectively, not significant), although all nine of the tumours that measured >20 cm^2 on initial examination occurred in children. The median age of the NF1 patients included in this study was 10 years. The median initial and final tumour sizes were not significantly different between individuals <10 years of age at initial examination (initial tumour size 4.8 cm^2 and final tumour size 8.5 cm^2) and individuals who were >10 years of age at initial examination (initial tumour size 9.4 cm^2 and final tumour size 13.2 cm^2). However, the difference between the initial and final tumour size was significantly greater in younger individuals (3.2 cm^2) compared to older individuals (0.2 cm^2, $p = 0.031$). In addition, the growth rate of tumours in younger individuals (0.7 cm^2/year) was significantly greater than that of tumours in individuals >10 years of age at initial examination (0.03 cm^2/year, $p = 0.014$). With one exception, all eight tumours that increased in size (≥2.0 cm^2/year) were in individuals who were children or adolescents when first studied. One superficial and invasive plexiform neurofibroma in a man showed substantial growth and became painful between the second and third MRI (patient 25). This tumour was biopsied and was found to be an MPNST.

There was a significant negative correlation between patient age at initial examination and the difference between the initial and final tumour size ($p = 0.003$), and also between patient age at initial examination and tumour growth rate ($p = 0.001$).

To determine if tumour growth among younger NF1 patients could be accounted for by normal growth of the individual, we calculated the tumour size/unit body mass index (BMI) and plotted the values by age (data not shown). All tumours that displayed substantial growth in NF1 patients <13 years of age (fig 2) also increased in size relative to BMI, suggesting that the tumour growth in these individuals was greater than would be expected on the basis of normal body growth.

Seven individuals had more than one plexiform neurofibroma imaged for this study. The growth pattern of multiple tumours within the same individual varied, even when the tumours were of the same type and/or in a similar region of the body (table 3).

DISCUSSION

Very little information beyond clinical anecdote is available on the natural history of benign tumour growth in NF1. This is the first longitudinal MRI study of plexiform neurofibroma growth in a large series of unselected and untreated (no surgical or drug intervention) NF1 patients to be reported and the age range of the patients reflects that of a general NF1 clinic population.

Most of the plexiform neurofibromas found in our patients were small (<10 cm^2) but the largest tumours seen were all in children. The occurrence of large tumours in children but not in adults with NF1 is unexpected if plexiform neurofibromas are

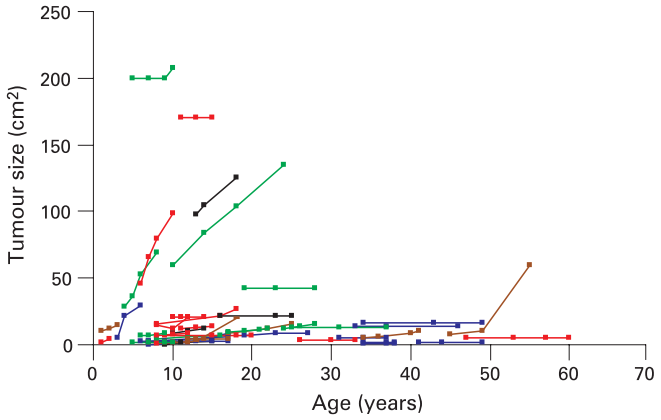

Figure 2 Tumour size by age in 44 plexiform neurofibromas in 34 patients with NF1. Key to graphs: red = deep and invasive; blue = deep and displacing; green = superficial and displacing; brown = superficial and invasive; black = superficial only.

all congenital neoplasms that grow irregularly after birth, as is often stated.[13 14] One possible explanation for our finding is selection bias, whereby young patients with large tumours were more likely than older patients with lesions of similar size to have participated in this multi-year follow-up study. Another possibility is that large neurofibromas in children have a very high risk for malignant degeneration or producing other lethal outcomes and may not live beyond early adulthood. This possibility demands further investigation because of its clinical importance.

The identification of a new plexiform neurofibroma in one individual was incidental, as it was identified on follow-up MRI within a region imaged for another tumour that was part of the study. Because the MRI examinations performed in this study were targeted to the location of suspected or known tumours, it is not possible to draw any conclusions regarding the rate of new plexiform neurofibroma formation.

Superficial plexiform neurofibromas grew more rapidly than the deep plexiform tumours included in our study ($p = 0.034$) (table 2). This novel observation requires independent confirmation but suggests that tumour location may affect tumour growth.

We found no relationship of neurofibroma growth to anatomic site (table 2) or radiological classification as displacing, invasive or simple superficial.[9 10] However, the number of tumours in each of these categories was small, and their size and growth rates were quite variable.

Neurofibromas from younger individuals grew faster than neurofibromas from older individuals. The growth rate of tumours in younger individuals exceeded the increase in their BMI, so the rapid tumour growth we observed in some young NF1 patients cannot be attributed to the expected growth in the child's body with age. This observation is consistent with the findings of a recent study that used volumetric MRI to measure the growth of plexiform neurofibromas in 49 NF1 patients over a median period of 34 months.[11]

We observed growth of 2 cm^2/year or more in 30% of tumours in individuals under 13 years of age. Our patients were recruited from a specialised neurofibromatosis clinic and may have had tumours that tended to be more aggressive than most NF1 associated plexiform neurofibromas. Dombi *et al* recently observed measurable growth in 57% of 61 plexiform neurofibromas in 49 young NF1 patients,[11] but most patients included in that study were selected because they had inoperable or progressive tumours. In addition, the volumetric method used to document tumour growth in Dombi's study is more sensitive than the two dimensional measurements we used.

All tumours, with one exception, that showed substantial growth were from NF1 patients under the age of 13 years at initial examination. The single exception is remarkable: a previously stable superficial invasive plexiform neurofibroma in a man who developed tumour associated pain and substantial growth on MRI, and the tumour was found to be an MPNST on biopsy. The patient was treated by amputation and is alive 8 years after diagnosis.

MPNSTs generally have a poor prognosis, particularly in people with NF1, with 5 year survival estimated to be only 21–41%.[15 16] Recognition of malignant degeneration within an existing plexiform neurofibroma in a patient with NF1 presents a formidable diagnostic challenge. Differences in the appearance of the lesions on MRI are sometimes apparent,[17 18] and changes that occur over time may be especially informative. Positron emission tomography (PET) appears to be an effective tool for

Table 3 Summary of patients with multiple tumours

Patient number	Tumour number	Tumour type	Anatomic location	Follow-up (years)	Initial size (cm^2)	Final size (cm^2)	Change over period of study (cm^2)	Growth rate (cm^2/year)
3	1	Superficial only	Head	10	3.0	5.9	2.9	0.3
	2	Superficial only	Neck	10	0.3	9.0	8.8	0.9
7	1	Deep, displacing	Spine	7	4.9	4.9	0	0
	2	Deep, displacing	Spine	4	0.8	0.8	0	0
	3	Deep, displacing	Spine	4	1.8	1.8	0	0
10	1	Deep, invasive	Spine	8	7.1	8.5	1.4	0.2
	2	Deep, displacing	Extremity	8	42.5	42.5	0	0
	3	Deep, displacing	Extremity	4	12.0	15.8	3.8	0.9
14	1	Superficial only	Trunk	6	2.5	2.5	0	0
	2	Superficial only	Trunk	4	0	2.4	2.4	0.4
16	1	Deep, invasive	Spine/trunk	4	15	21.0	6.0	1.5
	2	Deep, invasive	Spine/trunk	4	0.8	2.5	1.7	0.4
	3	Deep, invasive	Spine/trunk	4	7.1	8.5	1.4	0.4
21	1	Deep, invasive	Trunk	4	170	170	0	0
	2	Deep, invasive	Trunk	4	12.0	14.0	2.0	0.5
27	1	Superficial, displacing	Extremity	5	200	208	8	1.2
	2	Superficial, displacing	Extremity	5	1.5	2.0	0.5	0.1

distinguishing MPNSTs from most, but not all, benign plexiform neurofibromas in NF1.[19] The findings in this case raise the possibility that longitudinal monitoring of plexiform neurofibroma growth by MRI may permit recognition of malignant degeneration within a benign tumour. Early detection of MPNSTs in patients with NF1 may provide the opportunity for more successful treatment.

In NF1 patients who had more than one plexiform neurofibroma, the growth of different tumours often differed (table 3). This observation suggests that each tumour needs to be followed separately and that one tumour cannot be used to represent the growth rate of all tumours in an individual.

Current guidelines for management of patients with NF1 recommend imaging studies only when indicated on the basis of clinical signs or symptoms.[3 20–22] However, clinical indications for obtaining an MRI to evaluate plexiform neurofibromas have not been established, and the optimal frequency or even the value of follow-up examinations has not been determined. In our study, 23 plexiform neurofibromas were identified on initial MRI examination in 18 NF1 patients under the age of 10 years. Only seven (33%) of these 23 tumours were symptomatic, including only four (57%) of the nine rapidly progressing tumours. Our findings suggest that routine MRI screening of young NF1 patients for plexiform neurofibromas may be valuable. A large scale longitudinal MRI study of an unselected cohort of NF1 patients of various ages needs to be done to define more fully the natural history of plexiform neurofibromas, to determine the risk for developing MPNSTs in patients with rapidly growing tumours, and to find the optimal strategy for use of MRI in the management of NF1 patients.

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Competing interests: None.

Ethics approval: The study was approved by the ethical committee of the medical chamber in Hamburg

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