NF1 plexiform neurofibroma growth rate by volumetric MRI

Relationship to age and body weight

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Abstract—*Objective:* To longitudinally analyze changes in plexiform neurofibroma (PN) volume in relation to age and body growth in children and young adults with neurofibromatosis type 1 and inoperable, symptomatic, or progressive PNs, using a sensitive, automated method of volumetric MRI analysis. *Methods:* We included patients 25 years of age and younger with PNs entered in a natural history study or in treatment trials who had volumetric MRI over ≥16 months. *Results:* We studied 49 patients (median age 8.3 years) with 61 PNs and a median evaluation period of 34 months (range 18 to 70). The PN growth rates varied among patients, but were constant within patients. Thirty-four patients (69%) experienced ≥20% increase in PN volume during the observation period. PN volume increased more rapidly than body weight over time ($p = 0.026$). Younger patients had the most rapid PN growth rate. *Conclusions:* Volume increase of plexiform neurofibromas is a realistic and meaningful trial endpoint. In most patients plexiform neurofibroma growth rate exceeded body growth rate. The youngest patients had the fastest plexiform neurofibroma growth rate, and clinical drug development should be directed toward this population. Age stratification for clinical trials for plexiform neurofibromas should be considered.

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Plexiform neurofibromas (PNs) in individuals with neurofibromatosis type 1 (NF1) are a major source of morbidity and, in some cases, undergo malignant transformation.[1-3] Surgery is the only standard treatment for PNs, but complete resection is difficult due to the large size and location of PNs, and regrowth of PNs after surgery is common.[4,5]

PNs may present at birth, and growth has been described as erratic.[1] An ongoing natural history study of PNs in NF1 will provide data regarding the longitudinal growth of PNs using volumetric MRI analysis.[1,6]

Several agents have been evaluated in clinical trials for PNs.[7,8] The large size and complex shape of PNs, the limited understanding of their natural history, and their slow growth rate compared to solid cancers make quantitative evaluation of benefit from medical interventions challenging. Standard one- and two-dimensional solid tumor response criteria have limited value in detecting small changes in the size of PNs.[9,10]

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Table 1 *Equivalent percentage of change in diameter (RECIST), product of perpendicular diameters (WHO), and volume for spherical lesions (e.g., increasing the diameter of a sphere by 6% results in a 20% increase in the volume)*

Percentage of change in tumor size		
RECIST diameter (1D)	WHO product (2D)	Ongoing NF1 studies volume (3D)
6	13	20*
12	25*	40
20*	44	73

* The definition of progression according to the standard RECIST and WHO criteria, and the definition for progression by volumetric measurements used on several currently ongoing clinical trials for NF1-related plexiform neurofibromas. The volumetric method can more sensitively detect tumor progression.

RECIST = Response Evaluation Criteria in Solid Tumors; WHO = World Health Organization; NF1 = neurofibromatosis type 1; 1D = one-dimensional; 2D = two-dimensional; 3D = three-dimensional.

To more sensitively and reproducibly monitor the growth of PNs as the primary endpoint in clinical trials, we developed a method of automated volumetric MRI analysis of PNs.[11] This method has been used at the National Cancer Institute to centrally evaluate time to tumor progression in several multicenter trials for patients with NF1 and PN. In these trials, tumor progression is defined as a ≥20% increase in PN volume, a change that cannot be reliably detected with one- or two-dimensional measurements (table 1). In this study, we sought to describe the growth rate of PNs and to analyze the relationship of tumor growth to age and body weight.

Methods. *Inclusion criteria.* Patients who were enrolled in one or more of several ongoing trials (table 2) were included in this study if they had NF1 and a measurable PN (longest diameter ≥3 cm), were 25 years of age or younger at the time of the first evaluation, had volumetric MRI analysis of their PNs at the Pediatric Oncology Branch between September 1999 and December 2005, had been followed with repeated MRI scans for a period of at least 16 months, and gave informed consent for serial MRI scans when enrolled in a clinical trial (table 2).

Volumetric MRI method. Axial and coronal short T1 inversion recovery (STIR) MR images were obtained to encompass the entire PN using a slice thickness of 5 to 10 mm with no skips between slices.[6] MRIs were performed at baseline, and then every 3 to 6 months for patients in treatment studies and every 6 to 24 months for patients in the NF1 natural history study. PN volume was determined as previously described using the MEDx software platform.[11] This method, which differs from the method used to measure PN volume in the current ongoing natural history study, is based on 1) contrast, defined by intensity in the tumor (high signal intensity) compared to the surrounding tissue (low signal intensity); 2) intensity gradient, defining the outside border (margin) of the lesion; and 3) size of the lesion. PNs are substantial in size, and small isolated areas of high signal intensity can be ignored because their contribution to the PN volume is insignificant. The steps of volumetric analysis are outlined in figure 1. This automated method is sensitive (detects volume changes as small as 10%) and reproducible (coefficient of variation 0.6 to 5.6%), and yields results similar to those of manual tumor tracings ($R = 0.999$).[11]

When automated volume measurement was not feasible, the reason was recorded and manual tumor tracings using the drawing tool of the MEDx software were used to define tumor volume as previously described.[11]

Data collection. At each evaluation, patient age (years), weight (kilograms), and tumor volume (milliliters) assessed by automated or, if not applicable, manual volumetric MRI analysis as described above were recorded.

Table 2 *Use of automated volumetric (three-dimensional) MRI analysis of plexiform neurofibromas (PNs) in children and young adults with neurofibromatosis type 1 enrolled in multi-institutional clinical trials*

Agent	Trial design	Eligibility for PN	Age, y	Trial endpoints	No.*	PI/trial status
Tipifarnib	Phase I	Inoperable	2–18	MTD, pharmacokinetics	3	F. Balis/completed
Tipifarnib/placebo†	Phase II, double-blind, placebo-controlled, crossover	Inoperable, progressive‡	3–25	Time to progression§	32	B. Widemann/ongoing
Pirfenidone†	Phase I	Inoperable	3–21	MTD, pharmacokinetics	10	R. Packer/completed
Pirfenidone†	Phase II	Inoperable, progressive‡	3–21	Time to progession§	10	R. Packer/ongoing
Peg-interferon alfa-2b†	Phase I	Inoperable, progessive, or symptomatic	1.5–21	MTD	2	R. Jakacki/ongoing
—	Natural history	No current medical treatment for PNs	No limits	Growth rate of PNs	17	B. Korf/ongoing

* Of 49 patients included in this report, 31 participated in one, 11 in two, and seven in three trials.
† Centralized volumetric MRI analysis of PNs from all patients is performed at the National Cancer Institute Pediatric Oncology Branch.
‡ Defined as ≥20% in three-dimensional, ≥13% in two-dimensional, or ≥6% in one-dimensional tumor measurements within approximately 1 year of trial entry or between the last two consecutive MRI studies.
§ Progression defined as ≥20% in tumor volume compared to baseline MRI.

MTD = maximum tolerated dose.

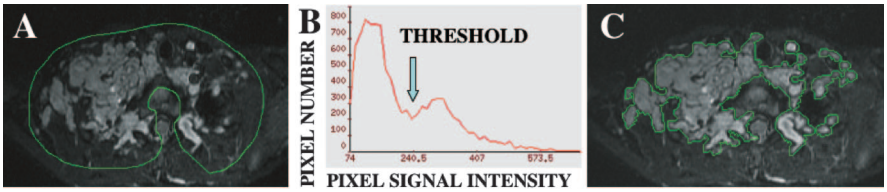

Figure 1. Steps of automated volumetric MRI analysis of plexiform neurofibromas (PNs): (A) Original axial short T1 inversion recovery MRI of a neck PN. The PN appears bright vs normal surrounding tissue. During the analysis, a region of interest including the tumor and some low signal intensity surrounding tissue is manually outlined on each MRI slice. (B) The program derives a histogram of pixel signal intensity and identifies a threshold that separates the PN from surrounding tissue. (C) The program automatically defines the tumor contour.

Data analysis. PN volumes were calculated in milliliters. For patients who had more than one PN imaged, the volumes of the individual tumors were summed to obtain a total tumor volume and only time points with complete data were included. Tumor volume (milliliters) was converted to tumor weight (grams) using a density of one (1,000 mL = 1 kg). Changes in tumor volume, body weight, and tumor weight expressed as a percentage of body weight over time were calculated. PN growth and body growth rates were expressed as the percentage of change in tumor volume and body weight per year.

We performed two analyses to explore the relationship between tumor growth rate and increase in body weight of patients over time. 1) For each patient, tumor weight expressed as a percentage of body weight was plotted as a function of time since the initial MRI was performed. The resulting individual patient slopes, which were determined by linear regression, would be estimates of the change in tumor weight as a percentage of body weight. These slopes would be positive if the percentage of body weight made up of tumor were increasing over time and negative if the percentage of body weight made up of tumor were decreasing over time. The Wilcoxon signed rank test was used to determine whether there was a significant change in tumor weight as a percentage of body weight over time. If these slopes were centered on zero, this would indicate that there was no overall change over time in the percentage of body weight made up of tumor. 2) For each patient, linear regression was used to obtain the slopes for the percentage of change in tumor volume and percentage of change in body weight as a function of time since the initial MRI. If the percentage of change in tumor volume and body weight changed at the same rate, the ratio of the slopes would equal 1. The Wilcoxon signed rank test was used to determine whether the ratio centered around 1.

To analyze the relationship of age to PN growth rate and body growth rate, the percentage of change in tumor volume and the percentage of change in body weight per year were each plotted against the patient age. The relationship between PN growth rate and age was well described by fitting an exponential equation.

Finally, the Wilcoxon rank sum test was used to compare PN volume increase per year in children younger and older than the median age (8.3 years) at study entry.

All p values are two tailed.

Results. *Patient characteristics.* Fifty-six patients with NF1 and PNs had been followed with MRI for at least 16 months. We were unable to evaluate seven of the 56 patients in this study because of incomplete MRIs or inconsistent MRI coverage of the PN preventing longitudinal volumetric analysis (n = 4) or debulking surgery to the PN (n = 3). One of the seven unasssessable patients also had evidence of a growing lesion within a stable PN. This raised suspicion of malignant degeneration, and the lesion was subsequently confirmed at surgery to be a low-grade malignant peripheral nerve sheath tumor. Thus, 49 patients with 61 PNs were included in this study. Eight patients had two and two patients had three PNs.

The median (range) age of the 49 evaluated patients was 8.3 years (3.3 to 25 years), 30 were male, and 19 were female. The diagnosis of NF1 in these patients was based on fulfilling the NIH Consensus Criteria.[12] Thirty-seven of these patients who had large, symptomatic PNs were evaluated at the National Cancer Institute Pediatric Oncology Branch. Twenty-eight (57%) of the 49 evaluated patients had measurable PN progression as defined in table 2 within 1 year prior to their first evaluation, as required by the clinical trial eligibility criteria. Patients were evaluated as part of their participation on the clinical trials outlined in table 2. In addition, two patients received treatment with thalidomide, not as part of a clinical protocol.

Volumetric MRI analysis. The median duration of follow-up with MRI was 34 months (range 18 to 70 months), the median number of MRI evaluations per patient was seven (range 2 to 14), and the median interval between MRI studies was 3.9 months (range 0.6 to 35.3 months). A total of 373 MRI studies were analyzed in the 49 evaluated patients. Automated volumetric MRI analysis was not feasible for eight patients due to artifacts resulting from spinal metal implants (n = 4) and lack of contrast between tumor and surrounding nontumor tissue (n = 4). For these patients, manual volume determinations were performed.

PN volumes expressed in milliliters and as a percentage of body weight at the start and end of the longitudinal observation period by patient, by PN, and by location of the PN are shown in tables E-1 and E-2 on the *Neurology* Web site at www.neurology.org. Tumor burden was substantial in most patients (median PN volume at baseline 471 mL) and extreme in some patients, reaching up to 21% of body weight at baseline evaluation.

The growth of PNs over time in this longitudinal study was well documented using the volumetric MRI method. Overall, the PN volume increased by a median of 14.3% per year (table E-1), but this rate varied widely among patients (−3.1 to 68.3% per year). Over the course of the longitudinal observation period, PN volume increased by as much as 218%. There was no relationship between the PN growth rate and the site of the PN or the volume of the PN at baseline. Ten patients had more than one PN (table E-3). Among eight patients with two PNs, the median PN growth rate per year of the slower growing PN was 11.8% (range −3.6 to 63.6%), and the rate of the more rapidly growing PN was 25% (range 7.7 to 70.9%). In two patients with three PNs each, the PN growth rates per year ranged from 16 to 72% for Patient 9 and 12.9 to 18.4% for Patient 10 (table E-3).

Relationship of PN growth rate and changes in body weight. The percentage of change in tumor volume and body weight over time for the 49 evaluated patients is shown in table E-1 and figure 2A and B. During the evaluation period, 34 (69%) patients experienced ≥20% increase in PN volume, and 15 patients had less change in PN volume. The rate of PN growth varied among patients but

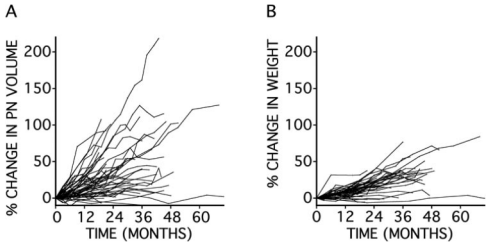

Figure 2. Percentage of change in plexiform neurofibroma (PN) volume (A) and body weight (B) over time in 49 patients with neurofibromatosis type 1 and PN.

appeared to be constant within patients. Erratic PN growth was not observed during the evaluation periods (figure 2A). Similarly, body growth appeared to be constant within most patients. The percentage of increase in body weight during the evaluation period was less than the percentage of increase in PN volume (table E-1, figure 2A and B).

The slopes resulting from the linear regression analysis of change in PN volume as a percentage of body weight over time were positive in 34 patients and negative in 15, indicating that PNs represented a greater proportion of body weight over time in most patients. The Wilcoxon signed rank test on the actual slopes had a two-tailed p value of 0.0015, indicating a tendency for PN volume (weight) to increase faster than body weight (and thus to represent a greater percentage of body weight) over time.

The relationship between the slopes representing the rate of PN growth and the rate of increase in body weight per year is shown in figure 3A. If the rate of PN growth equals the rate of increase in body weight, points will fall on the 45-degree line and the ratio of the slopes centers around 1. Thirty-three of the 49 patients (67%) had values above the 45-degree line, indicating that the PN volume increased more rapidly than the body weight. The Wilcoxon signed rank test of whether the slopes had a ratio that was equal to 1 had a two-tailed p value of 0.026. Thus, there was a tendency for the percentage of change in tumor volume over time to increase faster than the percentage of change in body weight over time in this population of patients, most of whom were selected for clinical trials based on demonstrated PN growth prior to enrollment.

Relationship of PN growth rate and age. The relationship between age and PN growth rate per year is shown in figure 3B. Younger children had a more rapid PN growth rate (percentage of change in PN volume per year) (R^2 = 0.4), and in a subset of these patients, the PN volume increase per year exceeded 20%. For the ongoing clinical trials in patients with NF1 and progressive PNs, disease progression is defined as a 20% increase in PN volume from baseline. In the group of 49 evaluated subjects, there was also a tendency for patients younger than the median age of 8.3 years to have a greater increase in PN volume per year (median percentage of change per year 21.1%) vs older children (median percentage of change per year 8.4%, p = 0.0010 by the two-tailed Wilcoxon rank sum test). In contrast, the percentage of increase in body weight per year did not appear to be greater for very young children (figure 3C), but young adults, as expected, showed no increase in body weight over time. When PN growth rate is expressed relative to the rate of increase in body weight, PN growth still appears to be more rapid in younger children. Seventy-six percent (19/25) of children 8.3 years of age or younger had PN growth rate to the rate of increase in body weight ratios >1 vs 58% (14/24) of patients older than 8.3 years, indicating that most young children had a PN growth rate exceeding the body growth rate.

Discussion. The clinical development of medical treatments for individuals with NF1 and PNs will depend on accurate measurement of the change in size of the PN over time to assess the effect of new treatments. However, the limited understanding of the natural history of PNs, their often large and complex shape, and relatively slow growth rate confound the accurate measurement of PNs. The natural history of PNs in NF1 is currently under study in a clinical trial,[5,6] and, as shown here, reproducible volumetric MRI methods for measuring PNs have been developed.[6,11] In addition, based on the expanding knowledge of the biology of PNs,[5] several novel targeted agents, which are under development for cancers and other diseases, have been identified as rationale agents for clinical evaluation in NF1, and these evolving imaging methods will likely serve as an important outcome measure in the clinical trials of new targeted agents.[5,13]

Our longitudinal study of volumetric MRI in patients with progressing PNs documents the variation in size and growth rate of PNs among patients, although some of this variability in growth rate could have been related to treatment effects in patients on one of several clinical trials. The PN growth rate

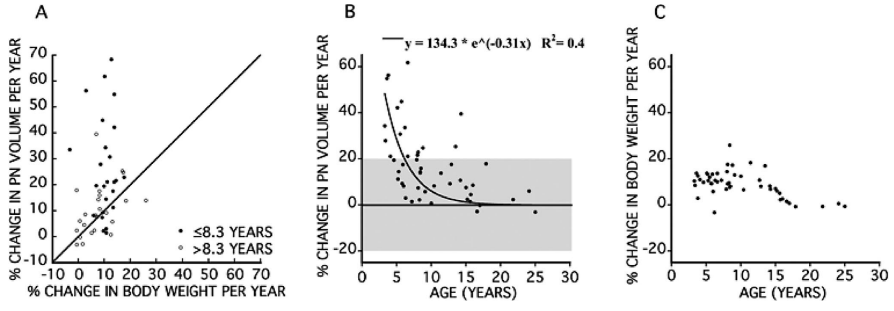

Figure 3. Relationship between the slopes for percentage of change in plexiform neurofibroma (PN) volume and percentage of change in body weight per year (A). Values above the 45-degree line represent ratios of the percentage of change in PN volume to the percentage of change in body weight that are >1. Closed symbols represent patients who are of or younger than the median age (8.3 years) at study entry, and open symbols represent patients who are older than 8.3 years. Percentage of change in PN volume (B) and body weight (C) per year as a function of patient age at baseline. The shaded area indicates the 20% change in PN volume required for documentation of disease progression in ongoing clinical trials. The line in B represents an exponential fit to the data.

within each patient was constant rather than erratic, as previously thought.[1] However, the relatively short evaluation period (median 34 months) and the inclusion of predominantly young patients with symptomatic or progressive PNs limit this observation, and longitudinal volumetric analysis over more prolonged time periods is required to detect changes in PN growth rate as a result of hormonal or other influences.

This automated volumetric MRI analysis[11] was applicable to most PNs, and measurable growth of PNs could be detected in a substantial subset (69%) of patients within 1 year of the first evaluation. Volume increase of PNs therefore is a realistic and meaningful trial endpoint for patients with symptomatic or progressive PNs. However, longitudinal volumetric analysis is only possible if the entire PN is covered by the MRI study and if the same image acquisition protocol including STIR images is used consistently.

PN growth rate exceeded the rate of increase in body weight in most patients. The clinical impression that PNs grow faster in young children was confirmed in our study. We observed the most rapid PN growth rates in the youngest patients. The median age of patients at time of the first evaluation was 8.3 years (range 3.3 to 25 years), indicating that PNs become symptomatic or demonstrate progression at a young age, and the lower age limit of 3 years for participation in three of the clinical trials from which patients on this study came limited participation of even younger children. If effective, new treatments are more likely to prevent the growth of PNs rather than to reduce their size. Therefore, treatments are likely to be most effective if administered at the time of most rapid PN growth in young patients, and clinical drug development should be directed toward this population. In addition, based on the observation of more rapid PN growth rate in young children, consideration should be given to age stratification at trial entry in clinical trials for PNs.

In addition to documenting the natural history of PN growth and to serving as the primary outcome measure in clinical trials of new treatments for PNs, longitudinal volumetric analysis may also be useful for the detection of degeneration of PNs into malignant peripheral nerve sheath tumors. Identifying a change in PN growth rate or a growth rate that significantly exceeds the growth rates demonstrated here or by identifying significant growth of a component within an otherwise stable PN may be potential indicators for malignant degeneration.

Progressive, symptomatic PNs in patients with NF1 are relatively uncommon, and randomized, placebo-controlled trials, such as the tipifarnib study described in table 2, may not always be feasible. Depending on the outcome of the ongoing clinical trials from which patients in this study were drawn, the data presented here may serve as a useful historical control population for future trials using volumetric MRI as the primary outcome measure.

Finally, it should be emphasized that the subjects in this analysis are a heterogeneous group, with subjects treated in several protocols with unknown effects on the natural history of PNs in NF1, including tipifarnib/placebo, pirfenidone, observation (natural history), or a combination of these. Thus, because of the heterogeneity and the fact that for patients in the randomized tipifarnib trial, their treatment assignment is still blinded, the results must be viewed somewhat cautiously and will require confirmation in a larger, more homogeneous group of patients before considering the results definitive.

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