

01-C-0027: Natural History of Plexiform Neurofibromas in Neurofibromatosis Type 1 (NF1)

Plexiform neurofibromas in patients with NF1 are a significant cause of morbidity but little is known about the natural history of these lesions. The purpose of this study is to monitor the natural history of plexiform neurofibromas and to evaluate the usefulness of volumetric MRI tumor measurements in this disease. Other goals of the study are to provide a body of normative data on the growth rate of plexiform neurofibromas and to establish a tissue repository and pathology review center to allow future studies of the pathogenesis of neurofibromas and clinical trials of potential therapeutic agents. This study is being coordinated by Dr. Bruce Korf at the Partners Center for Human Genetics, Boston, MA.

ELIGIBILITY CRITERIA:

Diagnosis of Neurofibromatosis:

All study subjects will fulfill two or more of the diagnostic criteria for NF1 listed below, as stated by the NIH Consensus Conference³⁴ and annotated by Gutmann *et al.*³⁵. It is expected that approximately equal numbers of males and females will be recruited, representing a diversity of ethnic and racial backgrounds.

- Six or more *café-au-lait* macules
- 1.5cm or larger in postpubertal individuals
- 0.5 cm or larger in prepubertal individuals
- Two or more neurofibromas of any type *or* 1 or more plexiform neurofibroma
- Freckling in the axilla or groin
- Optic glioma (tumor of the optic pathway)
- Two or more Lisch nodules (benign iris hamartomas)
- A distinctive bony lesion
- Dysplasia of the sphenoid bone
- Dysplasia or thinning of long bone cortex
- A first degree relative with NF-1

Plexiform Neurofibroma:

- A plexiform neurofibroma fulfilling entry criteria for the study will be defined as a diffuse soft tissue or nerve enlargement in a patient with NF1 that is causing or has potential to cause disfigurement or functional disability.
- Distribution of Plexiform Neurofibromas by Site
- A total of 300 plexiform neurofibromas will be studied, consisting of 100 tumors in the following three groups (based on region of maximal involvement):
 - Head and Neck
 - Trunk and Limbs (externally visible)
 - Trunk and Limbs (internal) [spinal plexiform neurofibromas involve two or more levels with connection between the levels or extending laterally along the nerve]

Distribution of Study Subjects by Age:

In order to include subjects representing a broad distribution of ages, the 100 patients in each group over all consortium sites will include 50 subjects from birth to age 18 years and 50 subjects over 18 years of age (age determined at time of recruitment into the study).

Study Groups:

The three tumor sites and two age ranges define 6 study groups, as defined in the table:

Tumor Location	< 18 years	> 18 years
Head and Neck	IA	IB
Trunk and Limbs (Externally Visible)	IIA	IIB
Trunk and Limbs (Internal)	IIIA	IIIB

EXCLUSION CRITERIA:

- Presence of metallic implant that will make the patient unable to have MRI studies
- Presence of medical or psychological condition that will make the patient unable to tolerate MRI studies or anesthesia (if needed)
- Inability to image tumor or define tumor margins by MRI (which may be determined after the initial study)
- Failure to obtain initial MRI within 60 days of enrollment
- Previous radiation therapy to site of plexiform neurofibroma
- Surgery involving the plexiform neurofibroma (excluding biopsy) within a six month period before enrollment
- Current antineoplastic therapy
- Entry of more than one member of the same family into the study is not permitted.

PROTOCOL DESIGN:

A total of 300 patients with plexiform neurofibromas will be studied, consisting of 100 tumors in the following three groups (based on region of maximum involvement):

- Head and Neck
- Trunk and Limbs (externally visible)
- Trunk and Limbs (internal) [spinal plexiform neurofibromas involve two or more levels with connection between the levels or extending laterally along the nerve]
- Participants will be grouped by age; 50 subjects ≤ 18 years of age and 50 subjects > 18 in each tumor location grouping.

EVALUATION ON STUDY:

- History and physical examination at the start of study and at 6 month intervals during the three year study period
- Photography: plexiform neurofibromas that are visible on the body surface will be photographed every six months
- MRI at the time of study entry; at one year and at three years. (More frequent if clinically indicated)
- Research blood for possible genetic studies in the future. This sample will be sent to a central tissue repository at Washington University in St. Louis and banked there – patients who do not wish to give blood will not be excluded from the study
- Tumor sample for central tumor repository from already existing specimen or if surgery becomes necessary; patients who do not wish to contribute a tumor sample will not be excluded from the study.

ACCRUAL:

- Open to accrual.