Progressing Research and Improving Care in Neurofibromatosis Type 2

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Introduction

- Neurofibromatosis Type 2 (NF2) – Disorder that results from mutation in NF2 gene
  - Loss of merlin – tumor suppressor protein
- Autosomal Dominant
- Mutation predisposes patients to:
  - Central Nervous System (CNS) tumors:
    - Vestibular schwannomas
    - Ependymomas
    - Meningiomas
  - Peripheral tumors
- Morbidity determined by location of tumor and age of clinical manifestations

- NIH is an NF2 center of excellence
- Clinical Trial NCT 00598351
  - 5 year natural history study of 169 patients was completed in 2019
    - Patients followed annually to view progression of clinical manifestations
  - Re-opened in 2020 as a 10 year natural history study for enrollment of additional 100 patients
    - Additional research aims include natural history of speech and swallow function and peripheral neuropathy associated with NF2

	Additional findings needed for diagnosis
Bilateral vestibular schwannomas	None
Family history	Unilateral vestibular schwannoma or two NF2-associated lesions (meningioma, glioma, neurofibroma, schwannoma, or cataract)
Unilateral vestibular schwannoma	Two NF2-associated lesions associated with the disorder (meningioma, glioma, neurofibroma, schwannoma, or cataract)
Multiple meningiomas	Unilateral vestibular schwannoma or two other NF2-associated lesions (glioma, neurofibromas, schwannoma, or cataract)

Data from Evans and co-workers.[21]

Table 2: **Manchester criteria for clinical diagnosis of neurofibromatosis type 2 (NF2) according to primary finding**

Asthagiri et al. Lancet, 2009

Study Objectives

Primary Objective: To determine the natural history (clinical and radiographic) of nervous system tumors in NF2

Secondary Objectives:

1. To identify the underlying causes, and patterns of progression of speech and swallowing problems in patients with NF2
2. To identify imaging biomarkers of hearing loss in patients with NF2
3. To identify the etiology of peripheral neuropathy in patients with NF2
4. To identify serum biomarkers of NF2 disease progression.

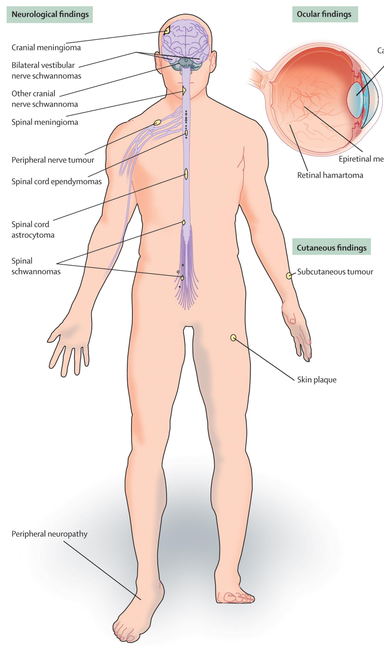
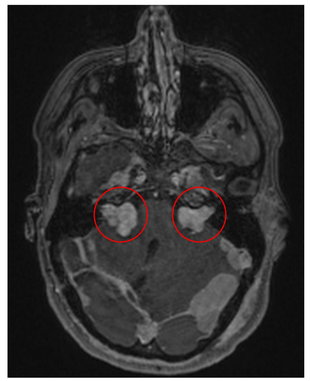
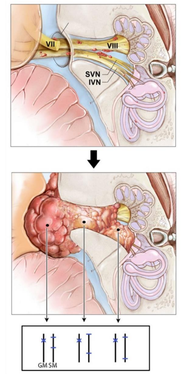


Figure 1. Clinical Manifestations of NF2

NIH Surgical Neurology Branch (SNB) Service	# of NF2 Patients
NF2 Patients enrolled to SNB protocols	193
NF2 related Surgeries performed	147



Bilateral Vestibular Schwannomas



Dewan et al. Neuro-Oncology. 2014

Clinical Evaluations

- Neurosurgery clinic visit
- Neuro-otology clinic visit
- MRI imaging – brain/spine with contrast. Right upper extremity without contrast
- Neurophysiology testing (optional) – electromyography and nerve conduction study
- Audio-vestibular testing (if clinically indicated)
- Clinical laboratory evaluation
- Speech and swallowing evaluation

Lessons Learned

- Data from surgical resection of tumors:
  - Tumors made up of different population of tumor cells
  - CNS tumors grow in stepwise growth pattern

- Vestibular Schwannomas
  - Risks include hearing loss
    - Not necessarily related to tumor size or growth rate
  - Larger tumors
    - Compression of Cranial Nerve VIII
    - Place mass effect upon brainstem and lower cranial nerves
  - Smaller tumors
    - Potential mechanism of hearing loss due to blockage of internal auditory canal
      - Could lead to accumulation of increased protein content in perilymph
    - Management prior to NF2 5 year study:
      - Translabrynthine surgery
      - Round window sampling
    - Management after NF2 5 year study:
      - FLAIR hyperintensity MRI imaging
        - Less invasive
        - Predicts hearing loss

- Peripheral Neuropathy
  - Caused by either primary neuropathy or compression of peripheral nerves from schwannomas

- Speech and Swallowing Difficulties
  - NF2 5 year Natural History Study
    - Suggests association with lower cranial nerve neuropathy

Future Endeavors

- Peripheral Neuropathy
  - New NF2 Natural History Study gives patients the option to undergo baseline and annual EMG/NCS testing, if indicated
- Speech and Swallowing Difficulties
  - Will further investigate hypoglossal weakness, speech, and swallowing dysfunction with new cohort

Surgical Neurology Branch

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