

Recognition and Treatment of Neurofibromatosis Type 1

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Overview:

- Clinical signs/diagnosis of NF1.
- Biology/Clinical Pathways underlying tumor formation.
- Current screening recommendations.
- Ongoing clinical trials.

The Neurofibromatoses

- Genetic neuro-cutaneous disorders which predispose to both benign and malignant tumors.
- Three distinct types:
 - Neurofibromatosis Type 1
 - Neurofibromatosis Type 2
 - Schwannomatosis
- Arise from different genes – lead to different clinical phenotypes.
- No clearly effective medical therapy for any of these three.

Neurofibromatosis Type 2

- Rare - affects 1 in 25,000 individuals.
- Autosomal Dominant, gene located on Ch 22.
- Characterized by:
 - Bilateral acoustic neuromas. Suspicion should be raised in a unilateral acoustic prior to age 30.
 - Can also develop schwannomas on other nerves.
 - Also at risk of Meningiomas, ependymomas
 - Juvenile cortical cataracts
 - Family history
- Often diagnosed in late teens/early adulthood – hearing loss, balance issues or tinnitus in late teens or early twenties can be the first symptom.
- Most patients with NF2 lose their hearing by adulthood.
- Most undergo multiple surgical procedures during their life.
- Avastin is currently being studied in patients with NF2, early trials demonstrated tumor response and/or hearing improvement.

Schwannomatosis

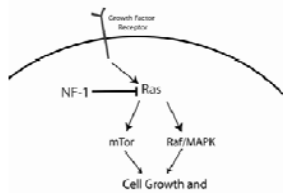
- Schwannomatosis:
 - Rare – 1 in 40,000. Only recently recognized and often considered along with NF2.
 - Genetics are not as clear as NF 1 or NF 2.
 - Most cases have no family history.
 - Gene recently identified – SMARCB1 (IN1) (found in only a subset of patients)
 - Characterized by: multiple schwannomas (not of the VIII nerve) on cranial, peripheral or spinal nerves.
 - Segmental findings in 1/3 of patients
 - No other associated tumors or learning disabilities.
 - Major difficulty is chronic pain.

Neurofibromatosis Type 1

- First described in 1882 by German pathologist Friedrich Daniel von Recklinghausen
- Very common:
 - 1 in 2500 individuals.
 - Affects more than 100,000 Americans and 7000 Texans.
- Worldwide distribution: equally affects males and females; no racial, ethnic or geographic distribution.
- Autosomal dominant disorder:
 - 50% of cases are new (sporadic) mutations.
 - Variable presentation (penetrance) even within families.
 - 60% of patients will have a mild presentation and course.
 - 20% have a very serious course.

NF Genetics

- Mutation in the NF-1 gene on Chromosome 17.
- Is a mutation in a tumor suppressor gene.
 - Requires the loss of the second gene at the cell level for tumor formation.
- No clear correlation between the mutation and the clinical course.
- NF-1 is a negative regulator of growth and survival signaling pathways within a cell.



Identification of NF1 Matters

- Most common cancer predisposition syndrome.
- Places patients at risk for a variety of tumors, benign and malignant.
 - Big risk of optic gliomas is in children less than 8.
 - Malignant peripheral nerve sheath tumor risk is in the early 20s.
- There are consensus guidelines for screening for tumors as well as other associated complications.
- Therapy decisions are influenced by the presence of NF1.
 - Need for treatment as well as the type!

Diagnostic Criteria for Neurofibromatosis Type 1

- Six or more café au lait macules greater than 5 mm in prepubertal and greater than 15mm in postpubertal patients
- Two or more cutaneous neurofibromas of any type or
- One or more plexiform neurofibromas
- Freckling in the axillary or inguinal region
- Optic glioma
- Two or more Lisch nodules
- Osseous lesion such as sphenoid wing dysplasia (orbital wall) or thinning of long bone cortex, pseudoarthrosis
- First degree relative with NF1

Skin Findings in NF

- Café au lait macules:
 - aggregations of melanocytes.
 - Often present at birth, increase in size and number until puberty.
 - 80% of patients with NF1 have 6 or more by 1 year of age.
 - Patients with 6 or more CALMs and no other criteria should be treated as if NF1 – as 95% will go on to meet NF1 criteria.
 - Present in close to 90% of patients with NF1.
 - Often will darken and increase in size as patients age.
 - In general – not associated with tumor growth.
- Skin fold freckling:
 - Typically develops by age 5.
 - Present in 75% of patients with NF1.



Ocular Manifestations

- Lisch Nodules
 - Iris Harmartomas
 - Benign - do not impact vision.
 - Initially light colored, darken with age
 - Seen in 50% of 5-6 year olds, >90% of adults.
 - May not be seen prior to age 4.
 - Visible with slit-lamp examination.



Picture: Kotagal et al., 2002

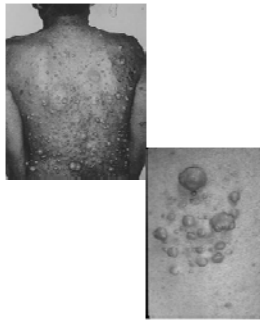
Bone abnormalities

- Scoliosis:
 - seen in up to 30% of patients, incidence increases with age.
 - Most often is mild.
- Congenital bone defects:
 - Absence of orbital wall (sphenoid wing)
 - Bowing of tibia/fibula.
 - Pseudoarthrosis
 - Scalloping of vertebral bodies.
 - Bone thinning – esp in spine and pelvis
 - Bony overgrowth
 - Bone cysts



Benign Neurofibromas

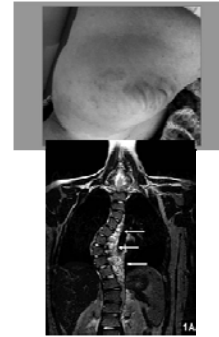
- Cutaneous and subcutaneous neurofibromas are present in 95% of adults with NF1.
- Can appear at any age, but numbers and size usually increase with puberty and pregnancy.
- Are proliferations of Schwann cells, endothelial cells and fibroblasts at a nerve root.
- Are benign but can be disfiguring.
 - Can have pain, itching.
- Do not appear to carry a risk of malignant transformation.



Picture: www.nf1.org

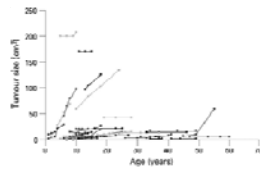
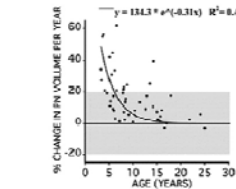
Plexiform Neurofibromas

- 25-30% of patients with NF-1.
 - Masses of Schwann cells, fibroblasts, mast cells and endothelial cells around nerves.
 - Grow due to a positive feedback loop with the nerve, blood vessels, fibroblasts, infiltrating mast cells.
 - Highly infiltrative, disfiguring
 - Potentially life threatening.
 - Can be deep, nodular and not visible.
 - Often felt to be congenital.
- No known effective medical therapy!!



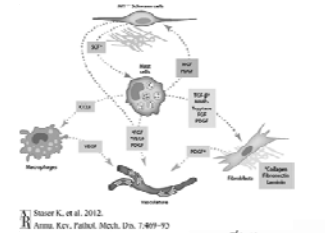
Plexiform Neurofibromas

- Growth can occur throughout childhood, but often have long periods of stability.
- Surgical resection is still the standard therapy.
 - Often necessary when the neurofibroma is impinging on airway, etc.
 - Complete resection is often difficult without major complications.
 - 44% grow back if sub-totally resected – particularly in young children.
 - Often have major sequelae.
 - Chemotherapy is not effective.
 - Radiation therapy not effective.
 - Associated with a clearly increased risk of secondary malignancy.

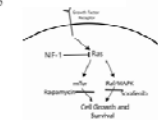


Medical Treatments for Plexiform Neurofibromas

- New therapies aimed at blocking the signaling cascades involved and/or interaction of the microenvironment.
- Increased MAPK and mTOR signaling in plexiform neurofibromas as a result of loss of NF1.
- Growth signals from the microenvironment – haplo-insufficient for NF1 are necessary.



Stover K, et al. 2012. Annu. Rev. Pathol. Mech. Dis. 7:489-92

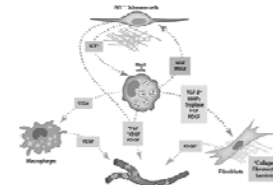
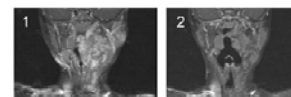


Sirolimus (Rapamycin)

- Phase II clinical trial currently open at CTF Clinical Consortium Centers.
 - Enrolled patients older than 3 years of age.
 - Stratum 1: inoperable, progressing
 - Stratum 2: High risk
- Preliminary evidence:
 - Time to progression around 10 months.
 - Stratum 1: Closing accrual. Awaiting last imaging for results
 - Stratum 2: 13 enrolled – all removed after 6 cycles.
 - 11 without response, 1 with progression.
 - Toxicity noted.
 - Decreases in doses, 3 removed for toxicity.

Imatinib (Gleevac)

- Drug initially designed for leukemia.
- Inhibits cell surface receptors in the microenvironment which are involved in the development of plexiform neurofibromas.
 - Work done in Luis Parada's lab at UT Southwestern and Wade Clapp's lab at IU the basis for this trial.
 - 1 patient had >50% reduction in tumor size of a neck plexiform neurofibroma.
 - Yang et al., 2008 Cell 135 (3)



Stover K, et al. 2012. Annu. Rev. Pathol. Mech. Dis. 7:489-95

Imatinib – Phase II Clinical Trial

- 36 total patients enrolled (pediatric and adult).
 - Looking for changes of 5% or more.
- 24 patients evaluated.
 - 38% demonstrated tumor reduction (>5%).
 - 3/3 pelvic plexiforms and 3/3 head and neck tumors responded.
 - 8% stable tumors
 - 54% progressive tumors
 - Symptomatic improvement in 55%
 - 12 patients withdrew prior to 6 months
 - Most common toxicities: weight gain, liver function tests, blood counts.

PEG-Interferon

- Inhibits growth.
 - Inhibits blood vessels.
 - Immune modulation.
 - Not specific.
- In early trials with α -interferon:
 - 5/27 patients reported clinical improvement.
 - 26/27 had stable plexiforms on MRI scan.
 - Few objective clinical responses.
 - Can get rebound growth after stopping.
- Administered under the skin once per week.
- Open to patient 18 months to 21 years.
 - Plexiforms increasing in size or in dangerous locations.
 - Recent results show a doubling of the time to growth (progression) in PNS growing prior to starting.
 - Can go on and off – appears to still have activity.
- Currently open in Pittsburg, NCI, Chicago and Seattle.

Malignant Peripheral Nerve Sheath Tumors

- Plexiform neurofibromas have a significant risk of progression to malignancy – malignant peripheral nerve sheath tumors
 - 10% risk over a patients lifetime, 3% risk in pediatrics.
- Concerning signs: rapid growth or dull, constant pain.
 - Pain that wakes at night.
- Treated with combination chemotherapy – but outcomes are poor.

Patients with NF1 and MPNST Fair Poorly

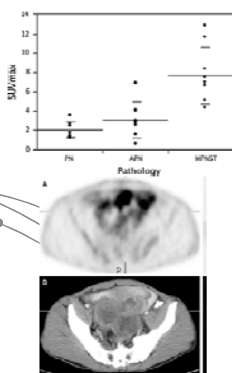
- Patients with NF1 tend to do worse overall.
- Patients with NF1 tend to have larger tumors or be metastatic at presentation.
- Patients with NF1 present with MPNSTs at a younger age.
 - 20 instead of 40-50s.
- Patients with NF1 and MPNSTs have less response to chemotherapy.
 - In combined Italy/Germany experience:
 - 126 patients over 25 years
 - Response to chemotherapy was 55% without NF1; 18% in patients with NF1
 - Overall survival at 5 years was 55% vs 32%.

*Zou et al., 2009

FDG-PET scans can be of benefit

- Significant difficulty in distinguishing symptomatic plexiform neurofibromas from MPNSTs on conventional MRI/CT scans.
- Biopsies can be difficult and may have sampling error.
- Early detection may benefit NF patients.
- ^{18}F -Fluorodeoxyglucose positron emission tomography (FDG-PET) – initial studies in adults by R. Ferner.
- PET has 95% sensitivity and 87% specificity in detecting MPNSTs.

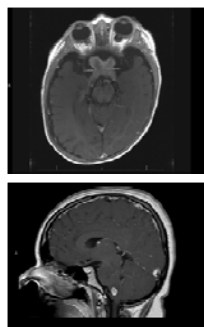
FDG-PET scans and NF1



- Retrospective analysis of NF1 pediatric patients.
- Underwent FDG-PET and biopsy (20 patients, 27 lesions)
- Benign PNs – SUV of 2.49 (SD 1.5)
- MPNSTs – SUV 7.63 (SD 2.96).
- Proposed SUV of 4 for a cutoff with high sensitivity (100%) and specificity (94%).
- Utility in routine screening not yet clear.
- Tsai et al, 2012 – J. NO 108(3).

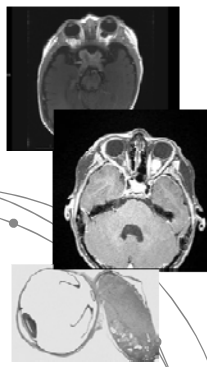
Pilocytic Astrocytomas

- Low grade, benign tumors of the central nervous system.
- Derived from glia, the support cells of CNS.
- 35-40% of childhood brain tumors.
- Overall survival very good - >90% at 5 years.
- Surgical resection usually curative.
- Neurofibromatosis type 1 patients at increased risk, but do better overall.
 - Most common site is the optic apparatus, followed by the brainstem.



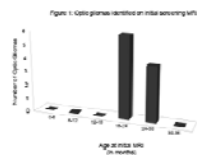
Optic Gliomas

- 5% of all pediatric intracranial tumors
- Present in 30% of patients with NF1.
 - 25% of these patients will require therapy.
- Most commonly presents prior to the age of 8.
 - Peak age of development appears to be age 2-3.
 - Present with decrease in visual acuity or visual field loss.
- Can cause sequelae: including vision loss, neurological symptoms, proptosis.
- Screening by ophthalmologist yearly is critical.
- Visual outcome is variable. May improve even years after therapy.

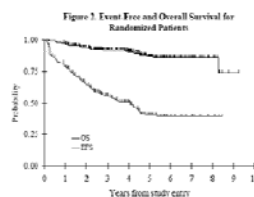


Optic Gliomas and NF1

- Screening Recommendations:
 - Yearly ophthalmology examination until age 8, then every 2 years.
 - Limited evidence in children less than 1 year of age.
 - Changes in visual acuity or visual fields need further evaluation.
- Optic glioma task force does not recommend screening MRIs.
- Overall benign nature – majority halt growth spontaneously.
 - Can regress spontaneously.
- Only clear indication for therapy is vision changes.



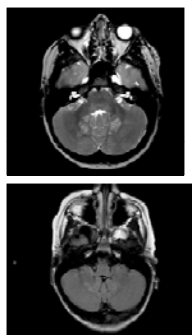
Low-Grade Gliomas: The Influence of Neurofibromatosis-1



COG A9952

Stigmata of NF1

- Also called UBO or myelin vacuolization.
 - Areas of T2 hyper intensity which are common in patients with NF1.
 - Well circumscribed, non-enhancing.
 - Found in over 60% of individuals with NF1.
 - Not tumors, no known clinical significance.
 - Often come and go – tend to disappear by adulthood.
 - Are not a diagnostic feature of NF1.



Current Therapy for OPG

- When to treat:
 - No clear guidelines.
 - Loss of vision.
 - Radiographic progression, endocrine changes, patient age.
- Often watchful waiting.
- First line treatment: Chemotherapy.
 - Carboplatin and vincristine.
 - Second line – vinblastine, avastin/irinotecan.
- Radiation Therapy:
 - Felt to have unacceptable long term consequences.
 - 9 of 18 NF pts with progressive OG treated with radiotherapy had 12 secondary malignancies. (Sharif et al., JCO 2006).
 - Also at risk for significant cerebral occlusive vasculopathy (Grill et al., Ann Neurol 1999).

NF1 Associated with Increased Risk of Malignancy

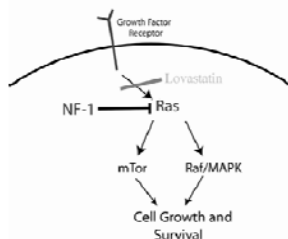
- At higher risk of MPNST and astrocytomas.
- Rarer, but still at higher risk than the general population:
 - High grade gliomas
 - Pheochromocytoma (1-4%)
 - Juvenile Myelomonocytic Leukemia
 - <1% of NF1 patients
 - 200X the risk of non-NF1 patients
 - Risk greatest in <4 year olds.
 - Breast Cancer
 - Increased risk, particularly in women under 50.

Learning Disabilities

- Neurodevelopmental problems found in over 50% of NF patients
 - Only a very small proportion have severe mental retardation (8%)
- Learning Disabilities overall 5 times more common in NF patients than the general population.
 - Speech abnormalities (esp. articulation issues).
 - Attention deficient disorders.
 - Impaired performance in at least 1 area of academic achievement.
 - Visual-spatial-perceptual problems.
 - Motor disorders.

Lovastatin in NF1

- Commonly utilized for cholesterol control.
- Well tolerated.
- Inhibits ras activation.
- Currently in phase II study for patients 8-16 years of age, open at 9 sites including Children Medical Ctr/UTSW.
- Looking at the effect of Lovastatin on attention and spacial learning primarily.



Other Complications

- Endocrine:
 - Short stature – tend to be below average in height –
 - 31% of patients (and above average in head circumference)
 - Increased risk of growth hormone deficiency - rare
 - Precocious puberty (associated with tumors of optic chiasm)
- Renal:
 - Essential Hypertension – 4% of patients.
 - Renal Artery Stenosis (proliferation of spindle cells)
- Neurological:
 - Seizure disorder – 7% of patients
 - Must evaluate for an intracranial cause.
 - Stroke – patients are at higher risk for moya-moya.

Associated Disorders

- Legius Syndrome (SPRED 1 mutations)
 - Autosomal dominant, resembles NF1 with café au lait macules, freckling, macrocephaly and some learning disabilities.
 - No malignancy risk.
 - Genetic testing is available.
- Segmental NF
 - Café au lait macules or neurofibromas in a single, unilateral segment of the body.
 - No evidence of systemic involvement.
 - Less risk of passing on to offspring.

Current Treatment Recommendations

- Yearly examinations:
 - Evaluation for new or progressive lesions.
 - Reassurance that café au lait spots may increase in number and size, but have no functional significance besides cosmetic.
 - Reinforce the benefits of sunscreen.
 - Yearly blood pressure examinations.
 - Evaluation of skeletal changes.
 - Evaluation of signs of precocious puberty.
 - Evaluation of neurodevelopmental progress.
 - Early intervention when delay is detected.
 - Hearing screen as warranted – NF1 patients are not at increased risk of hearing loss.

Current Treatment Recommendations

- Ophthalmology examinations:
 - Evaluation yearly by ophthalmologist until age 8, then every 2 years.
 - Critical for patients with known optic gliomas.
 - Often are indolent – treatment is indicated in light of progression or visual changes.
 - In patients without known gliomas – changes in visual acuity, color vision or visual field defects need CNS imaging.

Current Neuropsychological Recommendations

- For evidence of early neuro-developmental delays – early intervention is necessary and beneficial.
- Formal evaluation if difficulties become evident at school age.
 - Often done in school system.
 - Necessary for appropriate placement and school services.
- Evaluation every 2 years as warranted.

What about annual or screening MRIs?

- The NF Optic Glioma Task force and NIH Consensus Development Conference do not recommend routine screening MRI or CT examinations of asymptomatic NF1 patients.
 - Stigmata of NF1 is not specific and is not used for diagnosis.
 - Most optic gliomas or other CNS lesions have a very indolent course and do not require therapy.
 - Benefits do not outweigh risk of sedations, expense.
- There are times where “screening” MRIs maybe warranted.
 - Inability to get a good visual exam in young children.
- MRIs should absolutely be obtained in symptomatic children or children with a new neurological finding (including decrease in visual acuity).

Role of genetic testing

- Is technically difficult as the gene is very large.
- Often not warranted as 95% of patients can be diagnosed clinically by age 11.
 - May consider in patients with possible Legius (SPRED1) mutation.
- Can currently identify mutations 95% of the time.
 - Use an RNA based approach.
 - Testing can also be done on biopsies and can be done prenatally.
 - Average cost of \$1200.

Conclusions

- NF1 is a common genetic predisposition to cancer syndrome.
- Screening and identification is important.
- As the understanding of the biology improves, the number of targeted clinical trials increase.
- Children's Tumor Foundation (CTF) designated affiliate clinics are increasing.

For more information:

- About NF:
 - Children's Medical Center Dallas NF website
 - Texas NF Foundation
 - www.texasnf.org
 - Children's Tumor Foundation
 - www.ctf.org
- About clinical trials:
 - www.clinicaltrials.gov

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