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Neurofibromatosis Type 1 Diagnostic Updates and Plexiform Neurofibroma Treatment Options

Racheal Bingham, DNPc, MSN, RN, CPNP, CPON

Pediatric Nurse Practitioner Neurology/NeuroOncology/NF Clinic
rebingha@mdanderson.org

Disclosures

- I have no actual or potential conflict of interest in relation to this presentation.

Objectives

- Understand the definition of Neurofibromatosis type I (NF1)
- Review the current diagnostic criteria and potential updates
- Review the common manifestations of NF1 in the pediatric population and how it can affects growth and development
- Review the associated risks of cancer development with NF1
- Review treatment options for unresectable plexiform neurofibromas with targeted therapy such as MEK inhibitors
- Discuss a challenging case study from clinical experience

What is Neurofibromatosis Type 1?

- Neurofibromatosis (NF1) type 1 is a ***progressive*** autosomal dominant disorder that affects 1/3000 people worldwide
- 50 % of all NF1 patients are spontaneous mutations
- The NF1 gene neurofibromin, located on chromosome 17 (17q11.2), is a protein that is defective or missing and stimulates the overgrowth of cells
  - Ras protooncogene, protein expressed 10 days post fertilization
  - Can produce hundreds of variations in the mutation *producing a variety of clinical symptoms*
  - Active role in pathological embryogenesis or pathological cellular function after birth
  - Participates in oncogenesis when paired with a 2nd oncogene

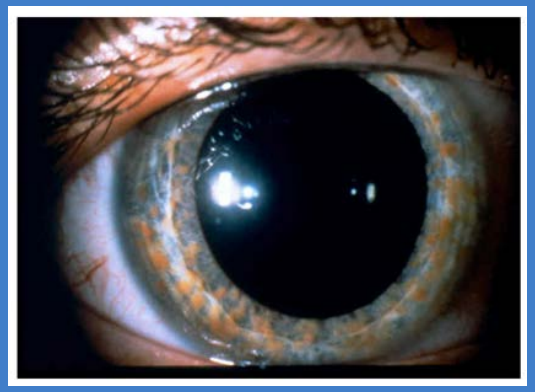
NF1 diagnostic criteria

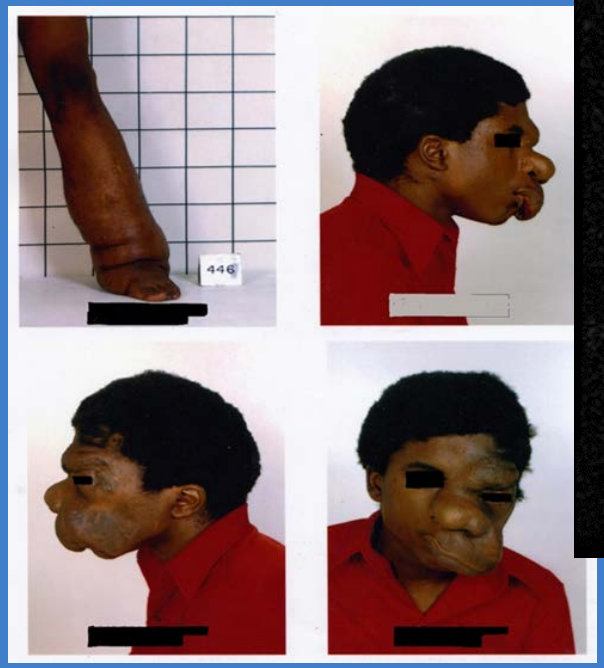
- **NIH 1987 Diagnostic Criteria:**
- six or more café-au-lait spots over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals,
- two or more neurofibromas ***or*** 1 plexiform fibroma,
- Axillary or inguinal freckling,
- optic glioma,
- two or more Lisch nodules (pigmented hamartoma of iris),
- osseous lesion, and
- 1st degree relative (parent, sibling, or offspring) with the diagnosis with NF1.

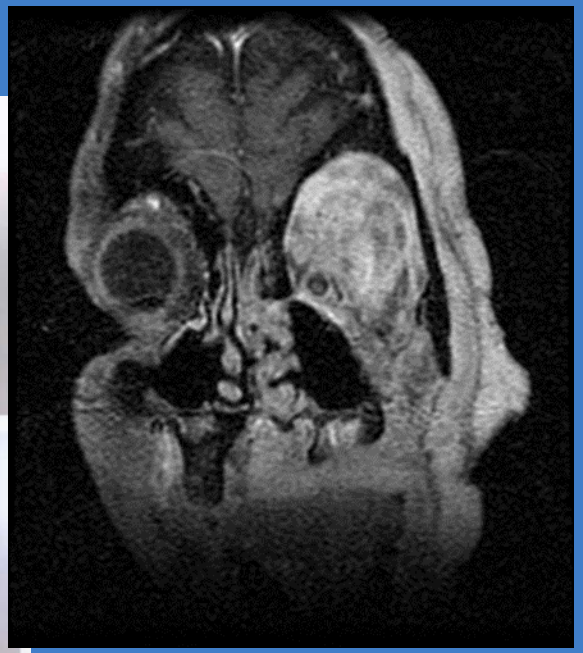
Potential updates to criteria:

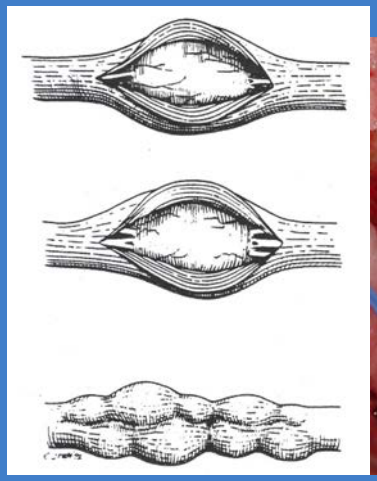
- Confirmed genetic testing of NF1 pathogenic variant, not required and will NOT stand alone without other features (90%)
- update verbiage on diagnostic list
- Choroidal abnormalities
- Sphenoid wing dysplasia, tibial dysplasia, and pseudoarthrosis of a long bone→ distinctive osseous lesions

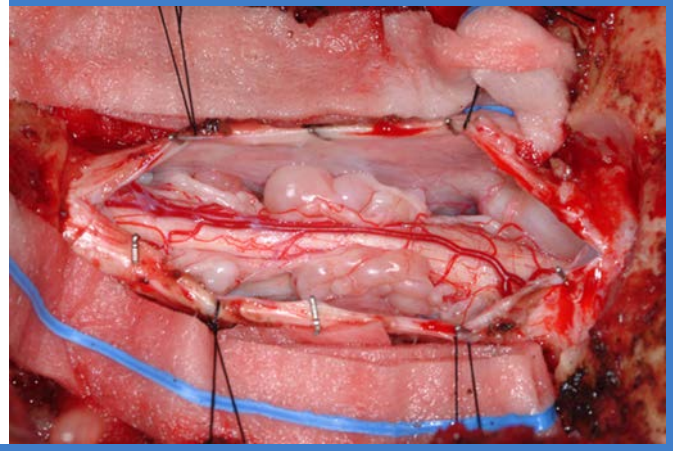
What does NF1 look like?

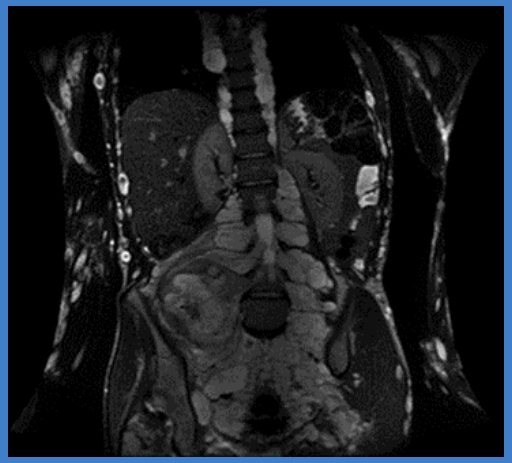




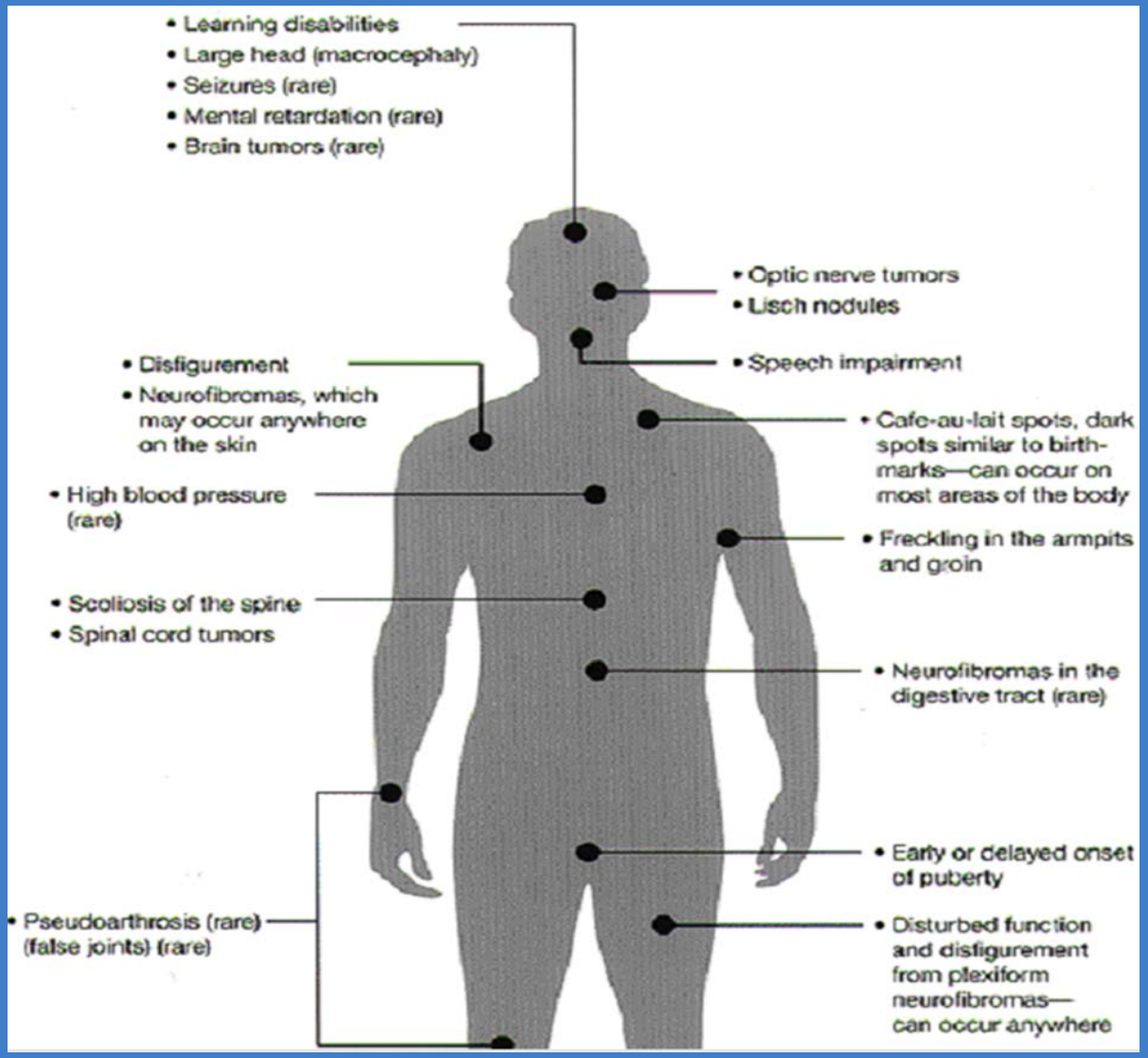


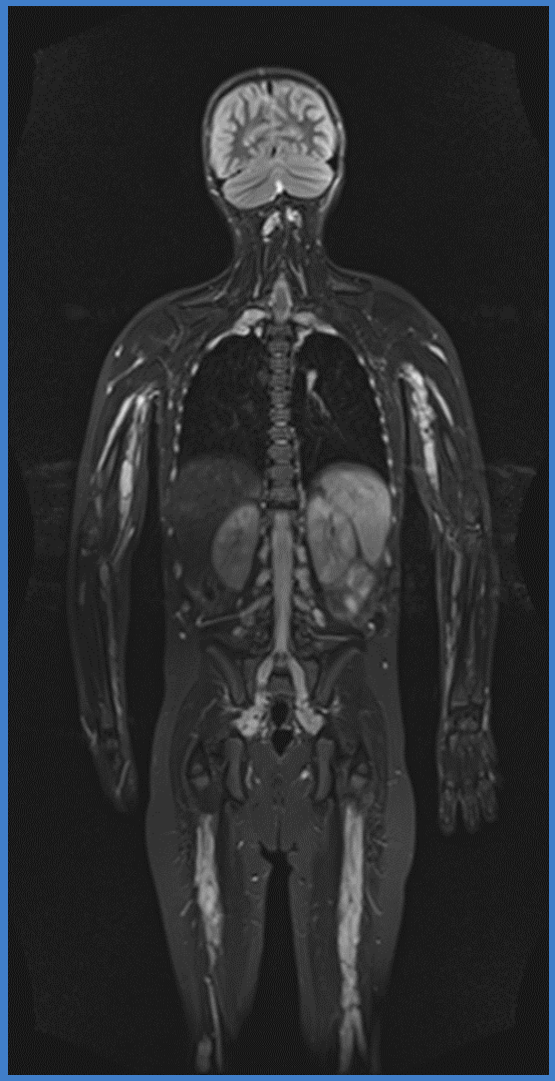






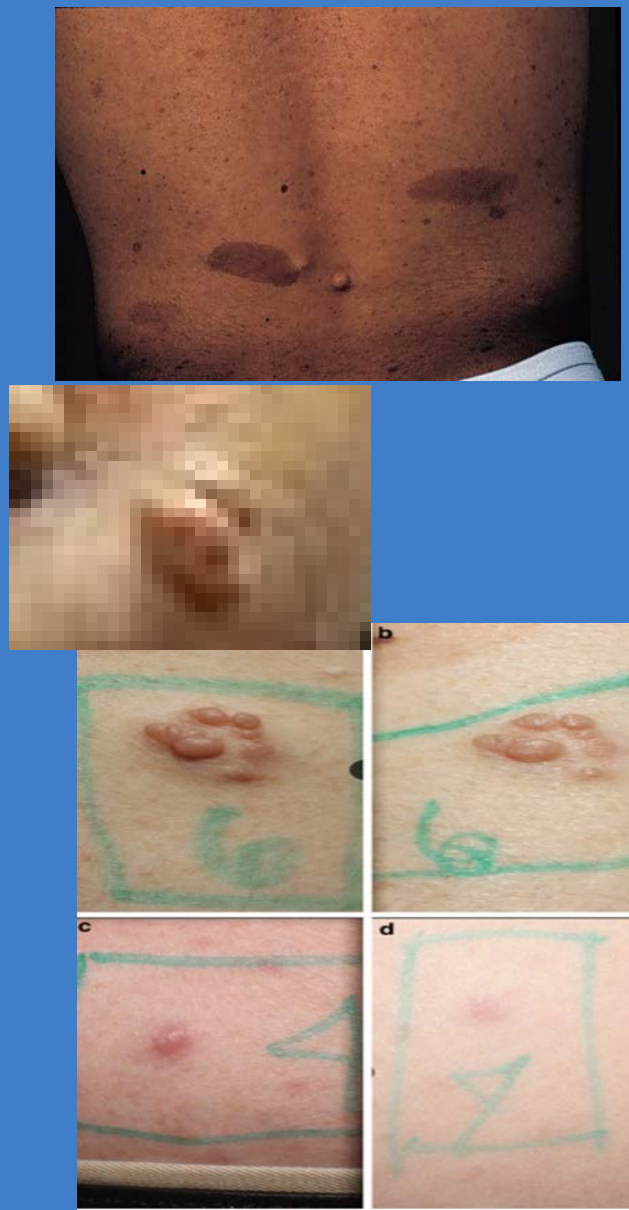
NF1 affects many systems





NF1 and skin

- **Common presenting pediatric symptom is a café au lait spot**
  - # of café au lait spots does not correlate with disease severity
  - recommends following younger pts with >6 CALs spots only as if they have NF1; other signs could develop over time
- **Cutaneous neurofibromas are not a risk for malignancy but does significantly impact quality of life**
  - Mast cells are abundant in cutaneous neurofibroma, releasing histamine excessively in NF 1→ pruritus common symptom
  - Can not predict future skin burden as an adult



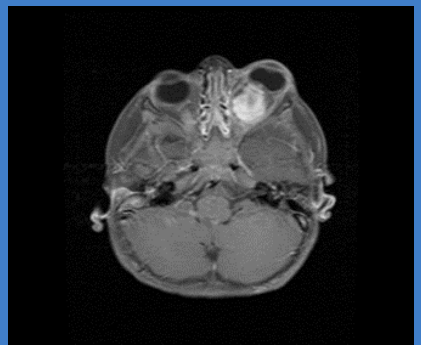
NF1 and cancer significance

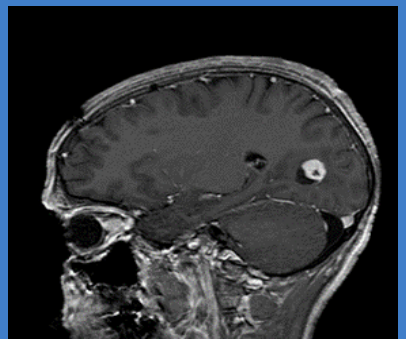
- NF1 children are 7x more likely to develop myeloid type leukemia but treatment is typically the same
- Optic gliomas usually in NF1 children younger than 7 years old.
  - Can be asymptomatic, treatment not required
  - Treatment is warranted when vision is affected with chemotherapy such as carboplatin and vincristine
  - Surgery not an option due to location
  - Radiation not an option in pts with NF1 due to risk to develop second malignancies, vascular abnormalities (Moya Moya), and neuropsychological difficulties

	Lifetime risk
Glioma of the optic pathway	15–20%
Other brain tumour	More than fivefold increase
Malignant peripheral nerve-sheath tumour	8–13%
Gastrointestinal stromal tumour	4–25%
Breast cancer	About fivefold increase
Leukaemia	About sevenfold increase
Phaeochromocytoma	0·1–5·7%
Duodenal carcinoid tumour	1%
Rhabdomyosarcoma	1·4–6%

Table: Lifetime risk of different tumours in children and adults with neurofibromatosis type 1

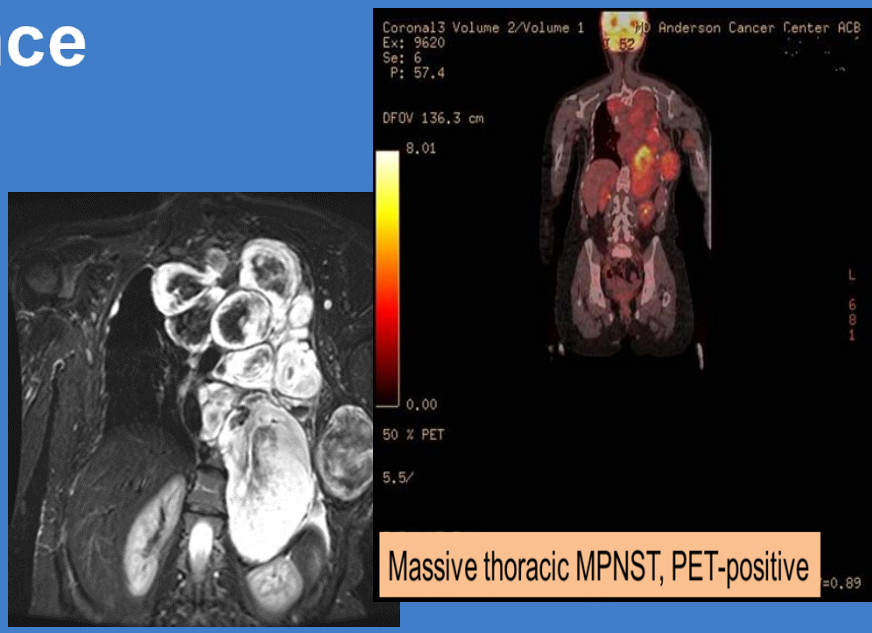
Hirbe & Guttmann, 2014

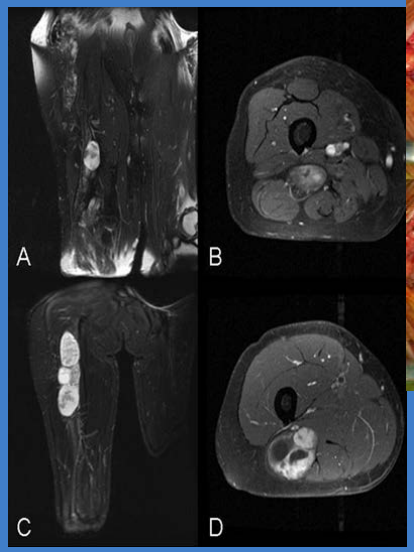


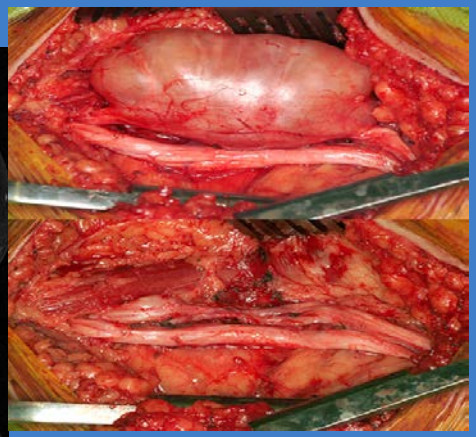


NF1 and cancer significance

- NF1 5x more likely for brain tumors, such as low grade gliomas or glioblastoma grade IV
- Plexiform neurofibromas (PN) is linked with 50% of persons with NF1, often diagnosed in children, with a 15% risk for malignant transformation
- Malignant peripheral nerve sheath tumor (MPSNT) mortality rate is 50% at one year, usually fatal if invasive and not encapsulated
  - MPSNTs are painful, fast growing
  - PET scans are helpful to diagnose
  - Surgery is the only curative option
  - Radiation beneficial as palliative options to for symptom management
  - Chemotherapy has not proven to cure



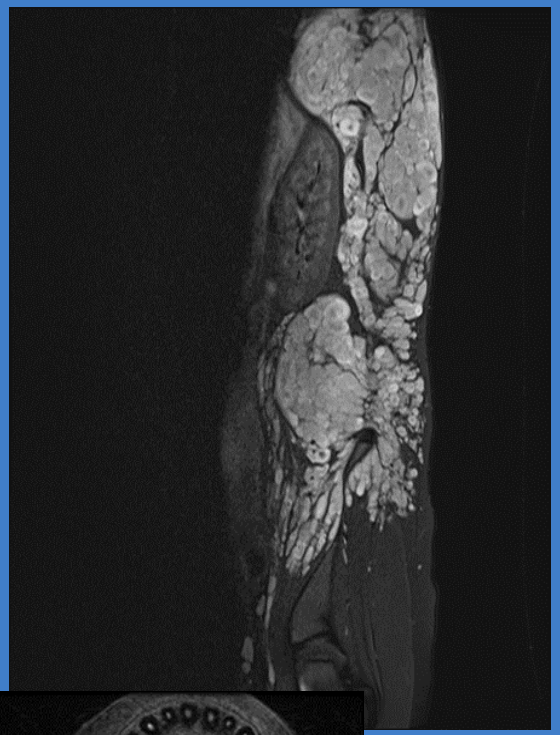


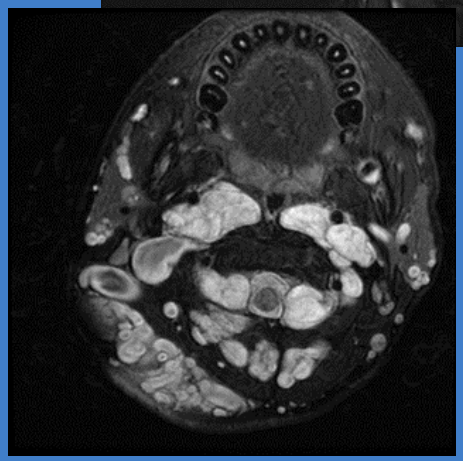


Complete resection of MPNST from sciatic nerve By Dr. Ian McCutcheon

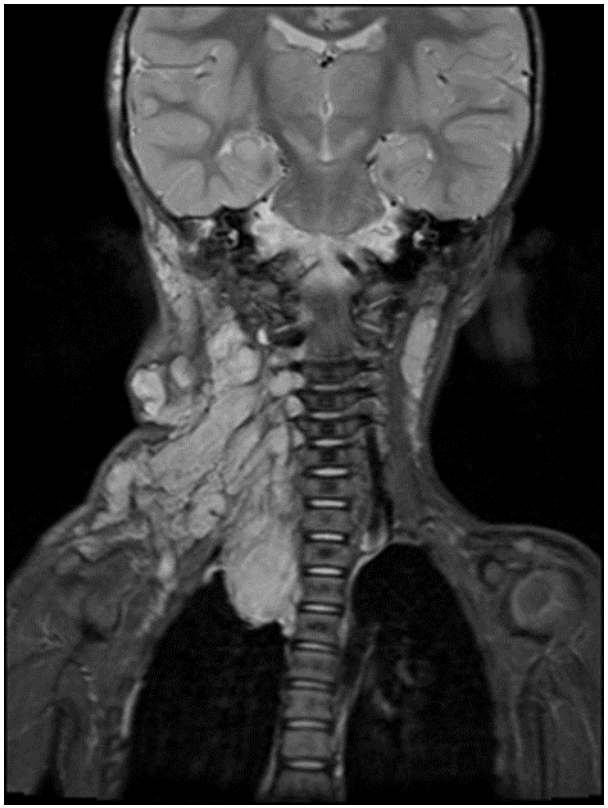
Benign tumors plexiform neurofibromas

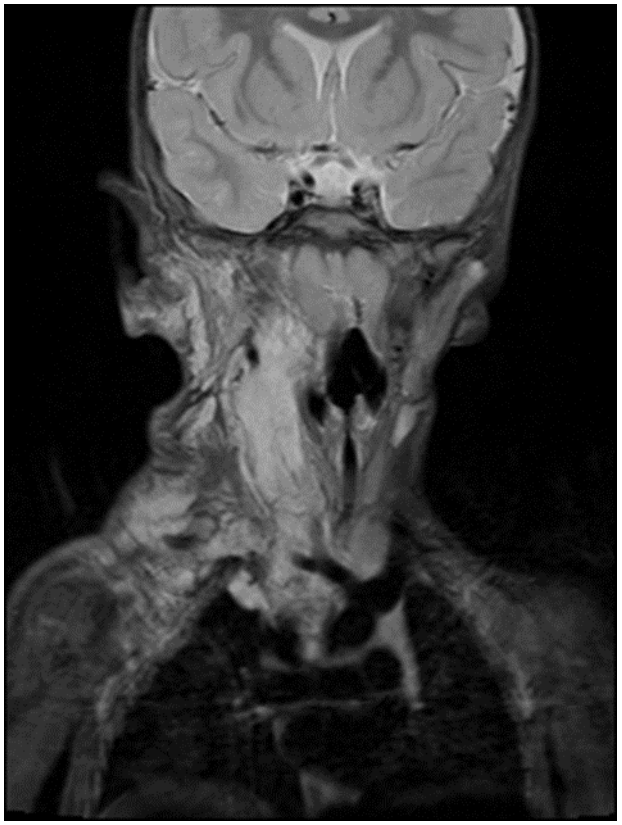
- During childhood growth and development there can also be rapid growth of PNs significantly affecting QOL
- Complications include: pain, disfigurement, functional impairment, and potential fatal malignant transformation
- Surgical resection is not always option for PNs due to their location and comorbid risks or regrowth after resections
    - Non resectable: complex head and neck, facial/orbital, complex masses of the brachial and lumbosacral plexus, and diffusely invasive masses



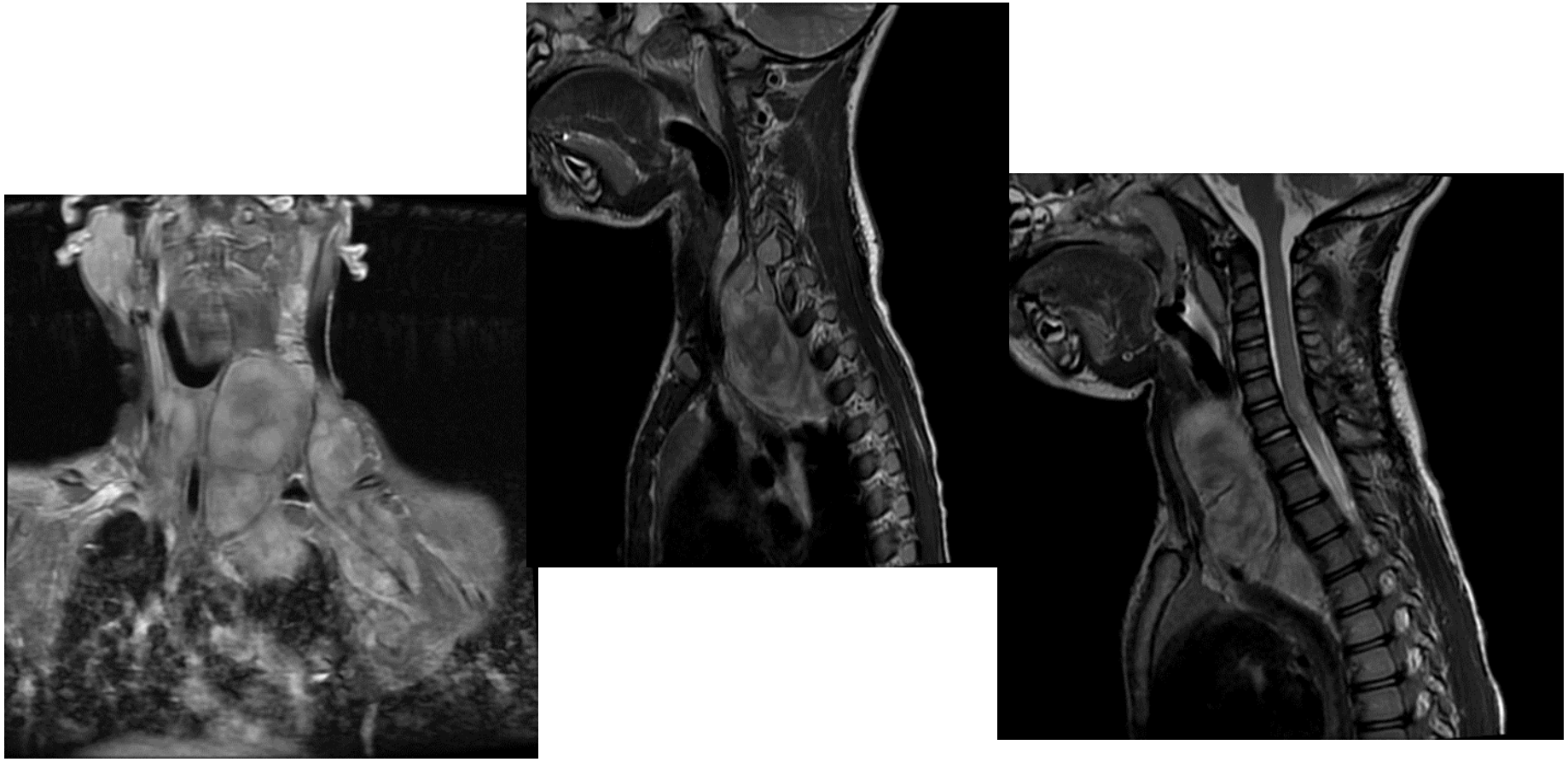


4 year old child- Complex Neurofibroma crosses multiple anatomic boundaries Inoperable-surgical morbidity is excessive



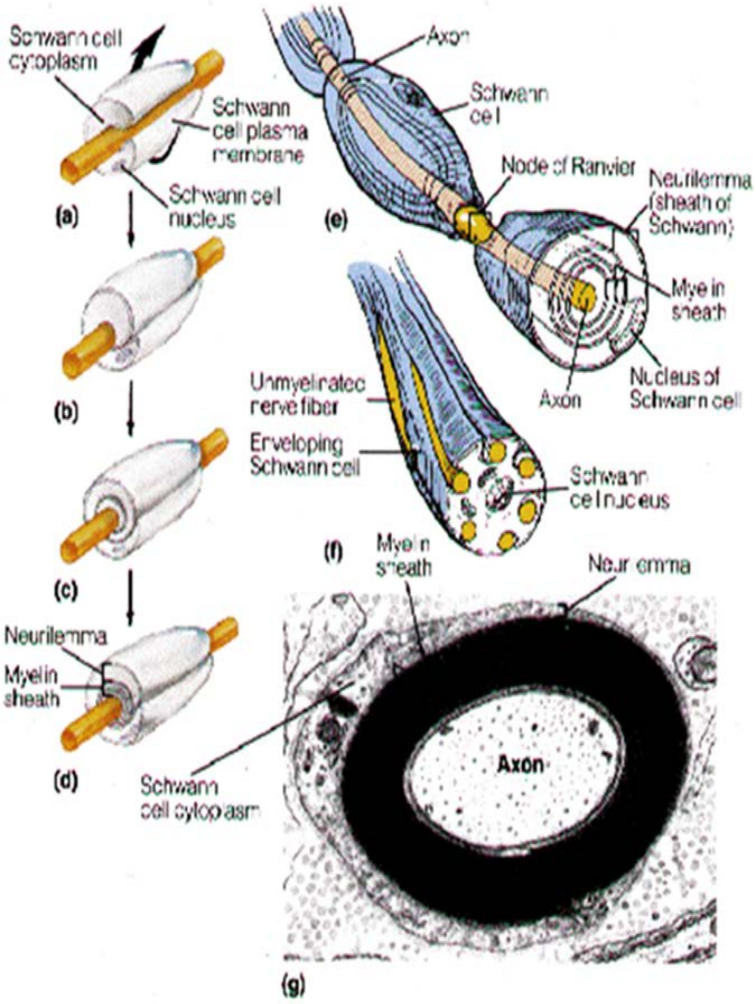


4 year old with neck and paraspinal plexiform neurofibroma



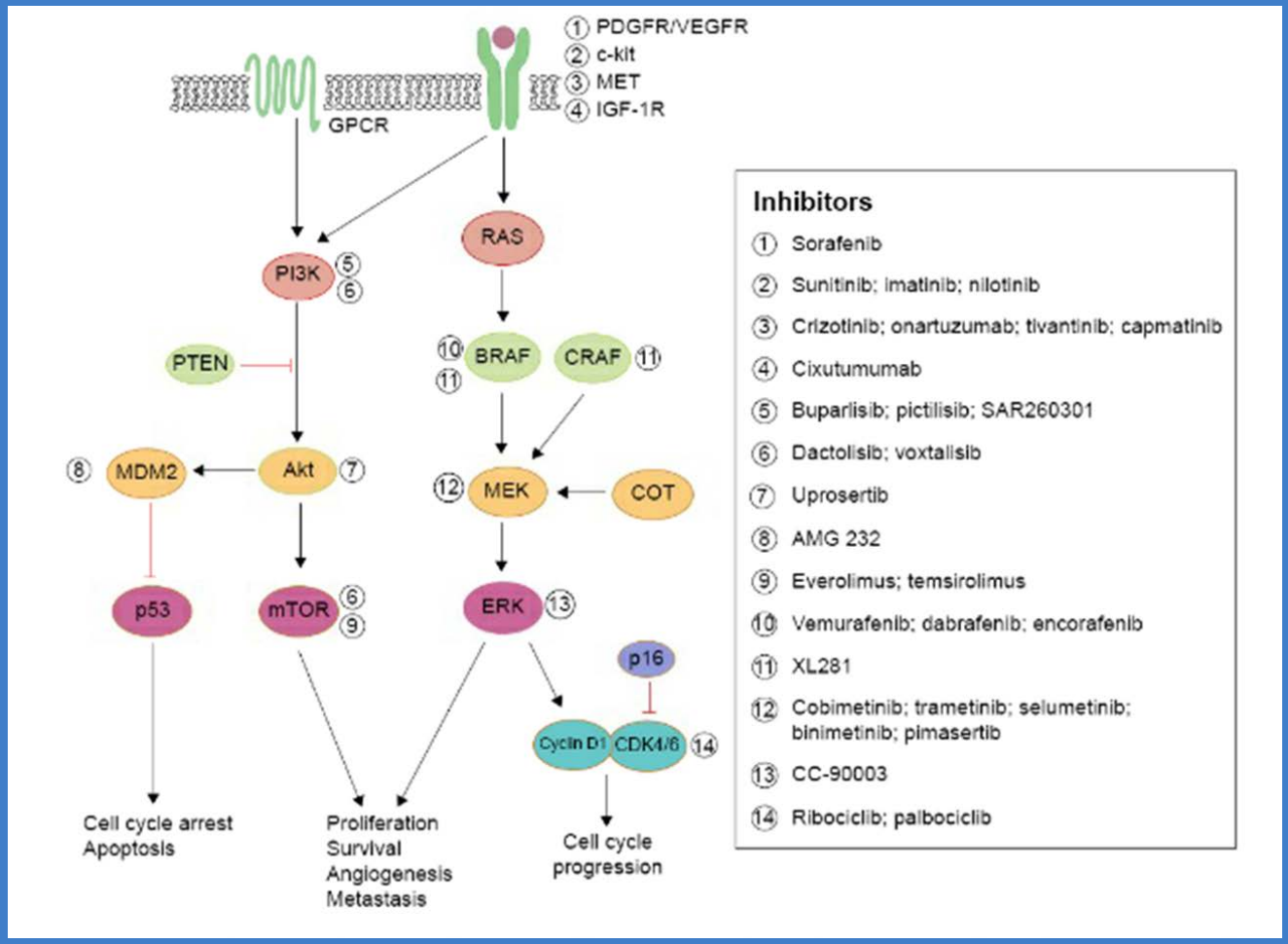
NF1 gene mutations

- The NF 1 mutation can be active in a pathological process virtually anywhere in the body from conception to birth to end of life
- Mutations include missense, nonsense, deletions, frame shifts, all leading to variable mutated/truncated protein “Neurofibromin”
- Several hundred distinct mutations/mutation patterns identified by DNA sequencing, more identified each year



Treating NF1 with MEK inhibitors

- Any reduction in size of NF1 PNs can be beneficial to quality of life, ie., less pain, decrease in degree of disfigurement, and an increase in motor function of affect body part
- Use MEK inhibitor if symptomatic, or inoperable PN causes morbidity
- MEK inhibitors are convenient, oral medications that is currently the most promising treatment for benign NF1 tumors
- MEK inhibitors have proven to reduce volume of low grade gliomas
- All MEK inhibitors are not exclusive; okay to try another MEK inhibitor with recurrence or with dose limiting toxicities
- Koselugo (Selumetinib) is 1st FDA approved MEK inhibitor for NF1 related PN


① PDGFR/VEGFR
② c-kit
③ MET
④ IGF-1R
GPCR
RAS
PI3K ⑤ ⑥
PTEN
⑩ ⑪ BRAF
CRAF ⑪
⑧ MDM2
Akt ⑦
⑫ MEK
COT
p53
mTOR ⑥ ⑨
ERK ⑬
p16
Cyclin D1
CDK4/6 ⑭
Cell cycle arrest
Apoptosis
Proliferation
Survival
Angiogenesis
Metastasis
Cell cycle
progression
Inhibitors
① Sorafenib
② Sunitinib; imatinib; nilotinib
③ Crizotinib; onartuzumab; tivantinib; capmatinib
④ Cixutumumab
⑤ Buparlisib; pictilisib; SAR260301
⑥ Dactolisib; voxtalisib
⑦ Uprosertib
⑧ AMG 232
⑨ Everolimus; temsirolimus
⑩ Vemurafenib; dabrafenib; encorafenib
⑪ XL281
⑫ Cobimetinib; trametinib; selumetinib; binimetinib; pimasertib
⑬ CC-90003
⑭ Ribociclib; palbociclib

Groundbreaking NF1 Selumetinib Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Selumetinib in Children with Inoperable Plexiform Neurofibromas

A.M. Gross, P.L. Wolters, E. Dombi, A. Baldwin, P. Whitcomb, M.J. Fisher, B. Weiss, A.R. Kim, M. Bornhorst, A.C. Shah, S. Martin, M.C. Roderick, D.C. Pichard, A. Carbonell, S.M. Paul, J. Therrien, O. Kapustina, K. Heisey, D.W. Clapp, C. Zhang, C.J. Peer, W.D. Figg, M. Smith, J. Glod, J.O. Blakeley, S.M. Steinberg, D.J. Venzon, L.A. Doyle, and B.C. Widemann

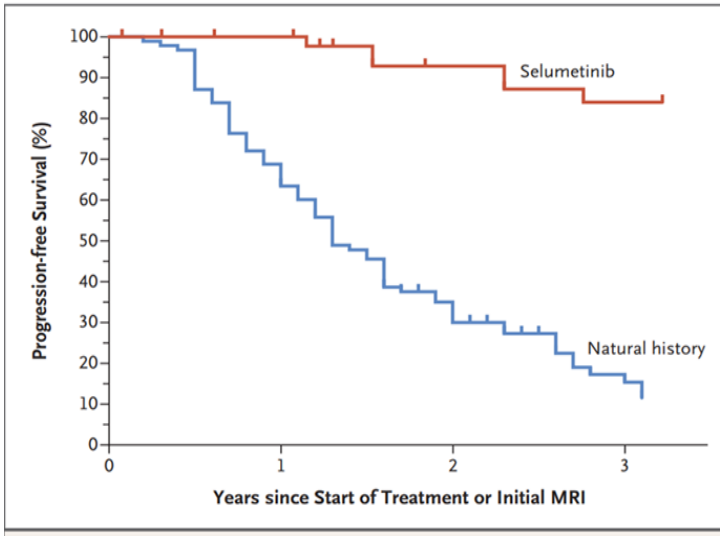


Figure 1. Target Plexiform Neurofibroma Progression–free Survival during Selumetinib Treatment as Compared with Natural History of Neurofibromatosis Type 1.

At 3 years of follow-up, the progression-free survival was 15% in the natural-history group and 84% in the selumetinib group.

Selumetinib 25mg/m2 bid phase 2 trial n=50 children, median age 10.2 (3.5-17.4) years old

35 of 50 pts (70%) had PR, 28 had durable response ≥ 1 yr

Median decrease in pain score 2 points

HRQOL improved 48% per child report and 58% per parent report, functional strength 56%, range of motion 38%

6 patients had disease progression

Most common toxicities: N/V, diarrhea, CK increase, acneiform rash, paronchyia

Selumetinib is safe to reduce symptoms and tumor burden in pediatric patients with NF1 related PNs with acceptable DLTs.

Nursing Considerations on MEK inhibitors

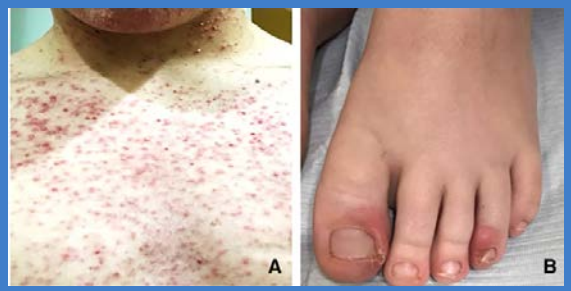
- Anticipatory guidance and education is needed to inform families of the most common, dose-limiting toxicities (DLTs) related to MEK inhibitors involves skin, eyes, or GI symptoms. Most DLTs are reversal
- Take medication on an empty stomach; avoid fried/fatty/spicy foods, increase fluid intake to minimize GI upset and diarrhea
- Stress the importance of good skin hygiene with daily baths with mild cleansers, maintain adequate skin moisture, maintain sun skin safety, etc.
- Baseline ECHOs are suggested prior to starting MEK inhibitors to determine any baseline NF1 anomalies to differentiate potential DLTs
- Encourage patients to report any ophthalmic changes with blurry vision, photophobia, dry eye, etc.
- For Koselugo: avoid aspirin containing products due to increased risk for bleeding because capsule made with Vitamin E. In animal studies, there were concerns with embryo-fetal toxicity so pregnancy tests are recommended.

Table 2. Summary of the most common side effects of individual MEK inhibitors

Side effect	Mirdametinib	Selumetinib	Trametinib
Cardiac (decreased EF/SF)	NRD	38% (Gr 1–2); 2% (Gr 3)	NRD
Diarrhea	NRD	54% (Gr 1–2); 4% (Gr 3)	NRD
Fatigue	26% (Gr ≥2)	56% (Gr 1–2)	NRD
Nausea/ vomiting	21% (Gr ≥2)	44% (Gr 1–2)	NRD
Ophthalmologic	No DL toxicity	No DL toxicity	NRD
Paronychia	NRD	38% (Gr 1–2); 6% (Gr 3)	50%
Rash/skin toxicity	53% (Gr ≥2)	52%–58% (Gr 1–2); 4%–10% (Gr 3)	40%

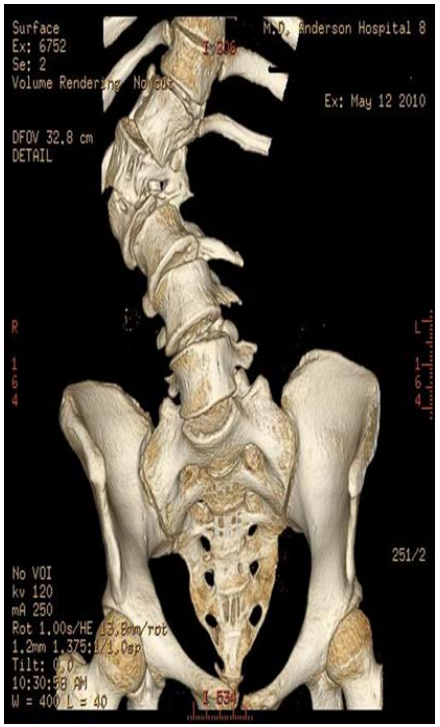
Percentages represent percentages of patients for each grade.
Abbreviations: DL, dose limiting; EF, ejection fraction; Gr, grade; NRD, not reported to date; SF, shortening fraction.

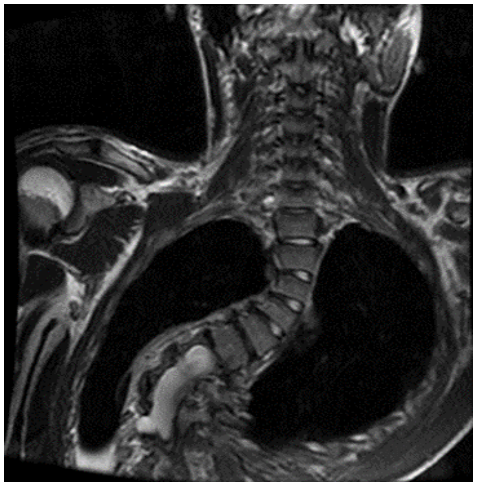
Klesse et al. 2020



NF1 and growth

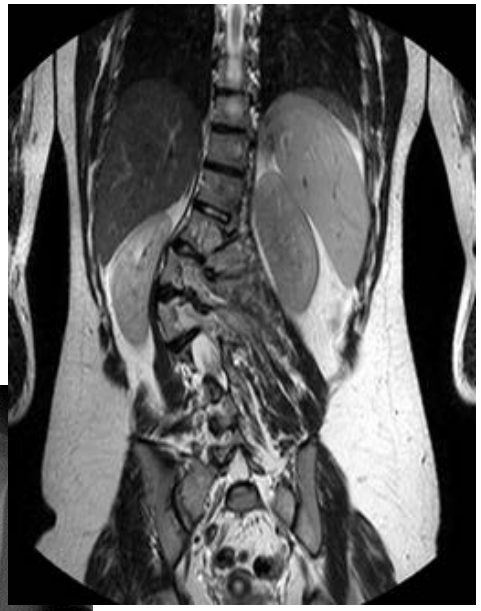
- Macrocephaly and short stature common in NF1, etiology unknown
- Dysmorphic scoliosis is common in up to 25% of NF1 patients requiring close monitoring throughout childhood
  - Treatment can include bracing or surgery for severe cases stabilized spinal/chest wall and to protect lung function.
- NF1 5x more a risk for fractures over age 40 and 3x higher for children 16 years or younger due to low bone density
  - Supplement with vitamin D, calcium and increase exercise
  - Extreme cases may require amputation in cases of pseudoarthosis

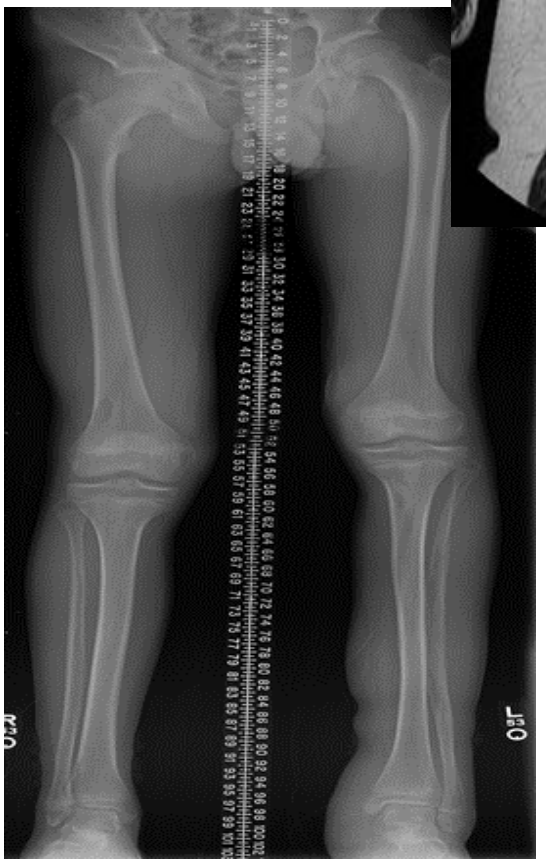




NF1 and growth

- Growth hormone therapy is an option for poor growth velocity and low growth hormone (<3-5% on growth chart)
- Accelerated growth velocity or tall stature can be associated with precocious puberty
  - Consider Endocrine referral for management or consider pituitary (chiasm/hypothalamic) tumor
- Leg length discrepancy (bone growth acceleration) usually associated with underlying plexiform (soft tissue hypertrophy)





NF1 and the heart

- 27% of NF1 patients as associated with ECHO changes confirming cardiovascular abnormalities
- NF1 related vasculopathy can includes renal and cerebral artery stenosis, pulmonary artery stenosis, aortic coarctation, and arteriovenous malformations
- Assess for murmurs, evaluate and manage hypertension, rule out pheochromocytoma
- Pheochromocytomas are catecholamine-secreting tumors of the adrenal medulla or other sites in the sympathetic nervous system
  - Surgery is the curable option
  - Screen with serum metanephrines, diagnostic imaging with PET scan

NF1 and learning deficits

- NF1 is associated with variety of developmental deficits in children and teens
- Reports up to 80% of children with NF1 have at least 1 cognitive deficits and 50% have academic issues
  - Issues to assess include visuospatial abilities, language, learning, adaptive behavior, attention, sleep, executive functioning, motor skills.
- Emphasizes need for early dx of NF to start interventions early for psychosocial needs, such as speech therapy
- Consider need for psychosocial support for caregivers, school accommodations, etc.
- Neurocognitive testing is considered at each major developmental milestone at MDACC

NF1 and mental health

- Suicide attempts 4x more frequent in patients with NF1
- Common links to anxiety, depression, aggression, lowered self esteem, behavioral issues
- 25% of NF1 pts have a dx of autism spectrum disorder
- Risk for bullying, social isolation (even those without disfigurement)

Challenging NF1 Case Study

- Patient presented as a toddler with multiple café au lait spots and one skin biopsy proven juvenile xanthogranuloma (JXG) lesion
- No known family history of NF1, genetic molecular testing confirmed a mutation 204+1G>A on the NF1 gene
- Baseline MRI brain at age 3 due to optic glioma risk. This showed bilateral optic pathway glioma involving the brainstem, central gray matter, and mesial temporal lobes. Visual acuity affected, L>R, light perception only. Treated with 2 different lines of chemotherapy. Repeat MRI brain showed marked improvement in tumor enhancement and no further vision loss was noted.
- 1 year later, he presented to EC with febrile illnesses and CBC smear revealed a rare 2nd myeloid leukemia requiring mismatch unrelated donor bone marrow transplant x2 to maintain remission
- Now almost 3 years out, he is doing well receiving phlebotomy for transfusional iron overload

Conclusions

- NF1 can affect the “whole” person and requires close monitoring by specialists with a multidisciplinary team approach
- NF1 is histologically known as a rare, benign, genetic disorder but it is important spread awareness about the associated risks in pediatric oncology
- MEK inhibitors treatment for benign NF1 tumors are demonstrating positive results with manageable toxicities
- Ongoing research is needed for this rare disorder and pediatric oncology nurses can play a vital role in these future endeavors!

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The University of Texas MD Anderson Cancer Center Children's Cancer Hospital Pediatric Neurofibromatosis Clinic

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- Department Chair: Richard Gorlick, MD