Brain Tumors and Neurofibromatosis Type 1

Virginia L. Harrod, MD, PhD

November 13, 2021

dell children's | ASCENSION

The University of Texas at Austin
Dell Medical School

The Brain and NF-1

- Other Brain/Neurological Concerns (Dr. Moodley)
  - Headaches
  - Hydrocephalus
  - Epilepsy, stroke, Moyamoya
  - Neurocognitive concerns

The Brain and NF-1

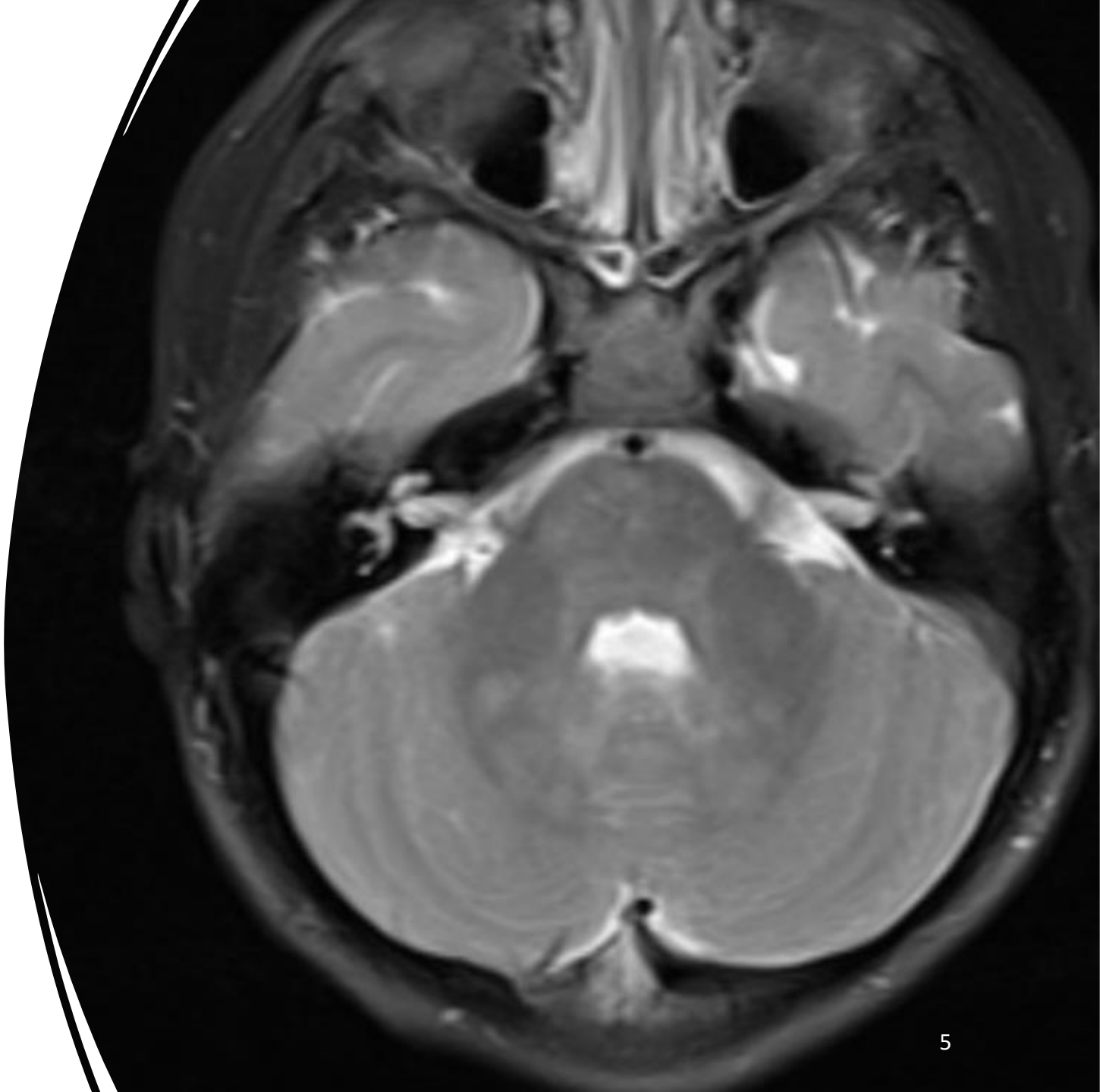
- Evaluations for NF-1 patients; when to look at the brain
- Imaging Recommendations
- Tumors of the Brain in NF-1
  - Optic pathway tumors
  - Low grade gliomas (Brainstem gliomas)
  - High grade gliomas
  - Intraspinal tumors
  - MPNST (in CNS and outside CNS) – covered by other presentation
- Treatment and Outcomes

Evaluations of the Brain in NF-1

- Routine screening?
  - Physical evaluations - YES
  - Neuropsychological evaluations - YES
  - Radiographic evaluations – DEPENDS – be careful what you look for
    - UBOs/FASIs
      - Unidentified bright objects
      - Focal Areas of Signal Intensity
  - Any abnormality tends to lead to more scans/anesthesia/contrast administration, etc; these are not without toxicity

FASI/UBOs

- Not ‘pathological’ BUT
  - Perhaps connected to cognitive impairment (especially in thalamic area)
- 86% of children have this finding (<10yo)
- Myelin changes with no inflammatory component (water component)
- Sometimes regress (over 10yo)



Indications for MRI (brain) in NF1 patients

- Neurological symptoms (decreased sensation/function)
- Seizures
- Headaches (increasing in severity and/or frequency)
- Stroke/TIA
- Vision changes (ophthal exam)
- Precocious puberty (early puberty)
- Head/neck plexiform neurofibroma increasing in size/pain
- Cognitive decline
- Leg length discrepancy/asymmetric extremities

Miller, et al;. Health supervision for children with NF1; Pediatricss May 2019.

Brain MRI: Positive or Negative?

- Negative
  - This is just a moment in time and doesn't predict the future
  - Doesn't change the need for routine screening

- Positive
  - Doesn't mean treatment is indicated
  - Does usually lead to more scans, more anesthesia, more contrast administration, more anxiety

Oncological Complications of the Brain and NF-1

- Tumors
  - Optic pathway tumors
  - Low grade gliomas (Brainstem tumors)
  - High grade gliomas
  - Intraspinal neurofibromas
  - MPNST – covered by other presentation
- Treatments
- Outcomes/Prognosis

NF-1 and Brain Tumors

- 15-20% of NF1 children will develop OPG/CNS tumors
- OPGs
  - Of these, 30-50% will be symptomatic
  - 1/3 require intervention (treatment)
  - Most commonly occur prior to age 6yo
  - Develop anywhere on the optic pathway
  - Location determines symptoms

Optic Pathway Gliomas (OPG)

- NF screening – ophthal annual evals (possibly every 6 months) from diagnosis of NF-1
- Most will present prior to 6 years of age; ophthal exams hard (but not impossible for pediatric ophthalmologists knowledgeable about NF)
- MRI for screening is not recommended (NF-OPG Task Force recs[1])
  - Risk: anesthesia, contrast allergies/reactions, stress/anxiety
  - Benefit: early detection – but still no intervention unless vision loss/changes, so ophthal evals should theoretically 'catch' these cases
- <50% of patients with OPG have vision changes

1.Miller, et al; Health Supervision for Children with NF Type 1; Pedicatrics, 143(5); 1 May 2019

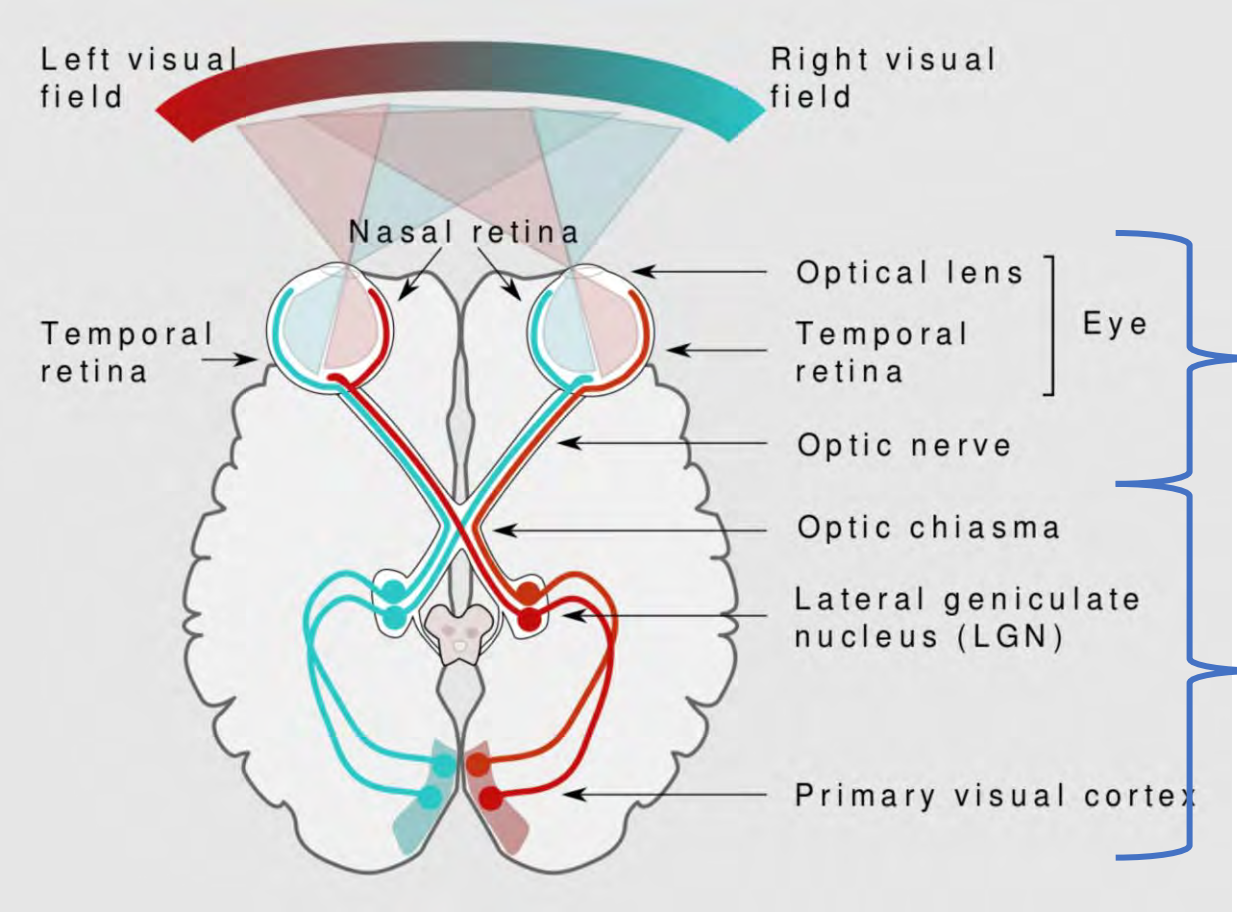
Optic Pathway Gliomas (OPG)

- Chemotherapy can help stop further vision loss; doesn't always regain vision (30 % might improve vision)

- Risk factors for vision loss
  - Young age (< 2 yo) or older age (>10yo)
  - Optic tract/radiation involvement
  - female

Campain, et al, CNS Tumors in Neurofibromatosis; J Clin Oncol. 2017 35(21): 2378-2385

Optic Pathway Gliomas (OPG) – Location/Loss



Unilateral (one side) vision loss

Bilateral (both sides) vision loss

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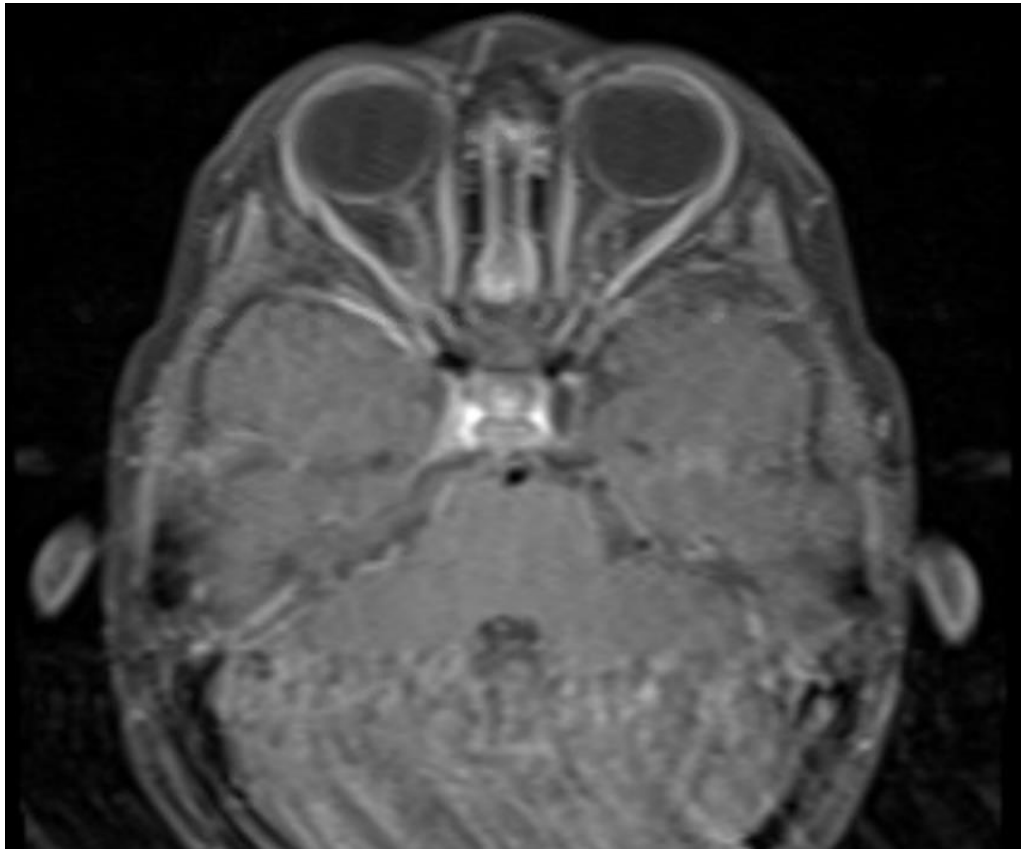
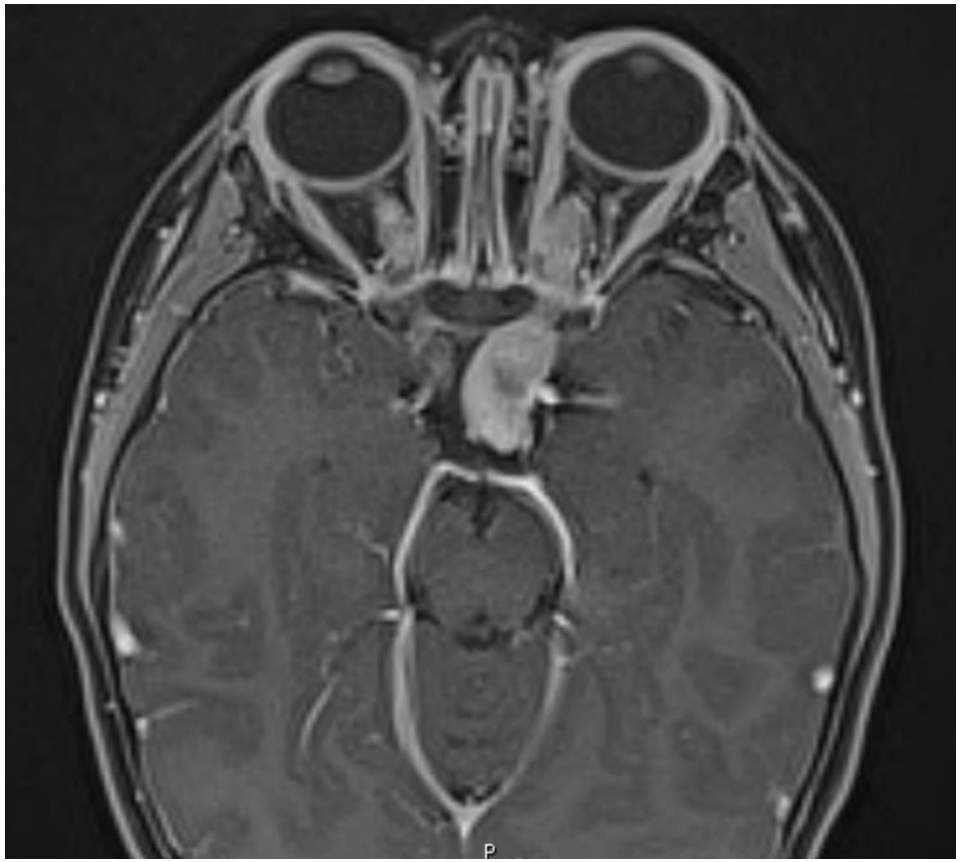
Optic Pathway Gliomas (OPG)

Chiam location – bilateral loss of vision;
precocious puberty possible



Bilateral Optic nerve involvement L>R



Optic Pathway Gliomas (OPG) - Treatment - for VISION LOSS or INCREASING SIZE***

- Pilocytic astrocytomas (though usually not biopsied)
- Chemotherapy
  - Carboplatin/Vincristine
    - Hearing loss, peripheral neuropathies (pain in hands/feet; change in walking ability)
  - Vinblastine
  - Other
- Treatment lasts 12-15 months
  - Requires weekly IV infusions of medications/lab checks
  - Surgery to have Port-A-Catheter placed for blood work
  - MRI scans every 3 months

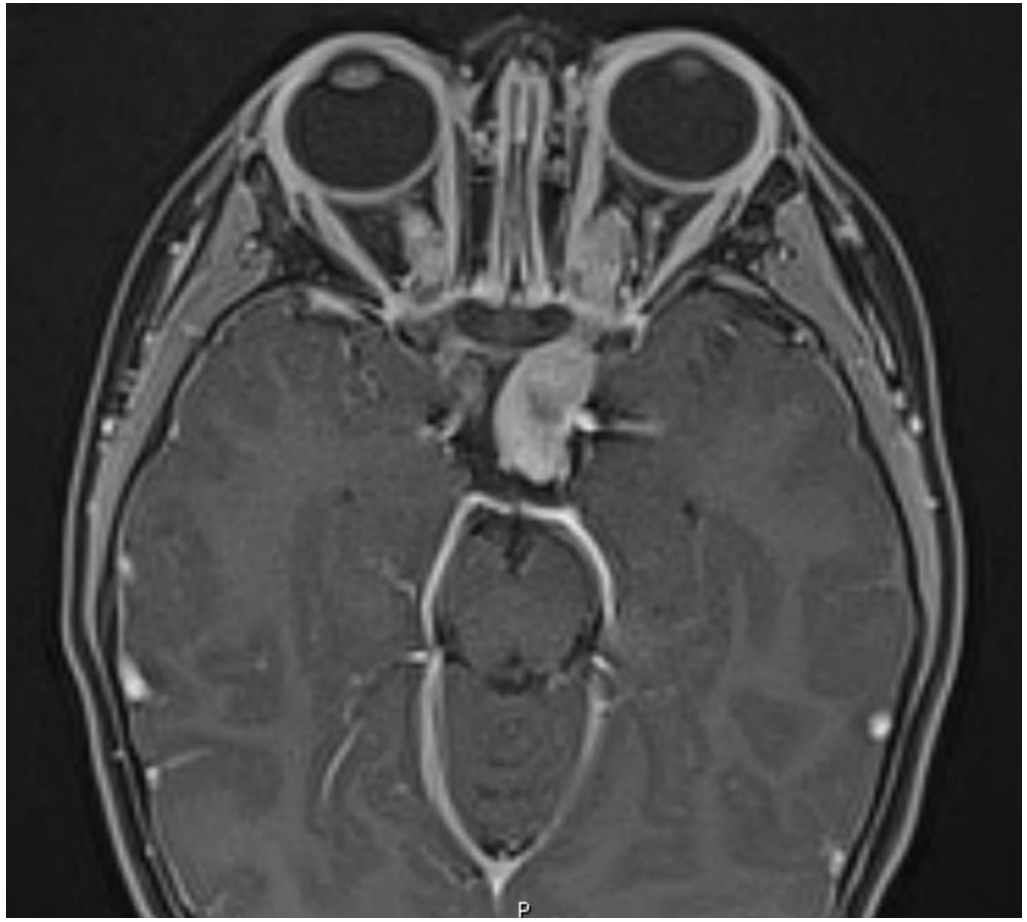
Optic Pathway Gliomas (OPG).- Treatment

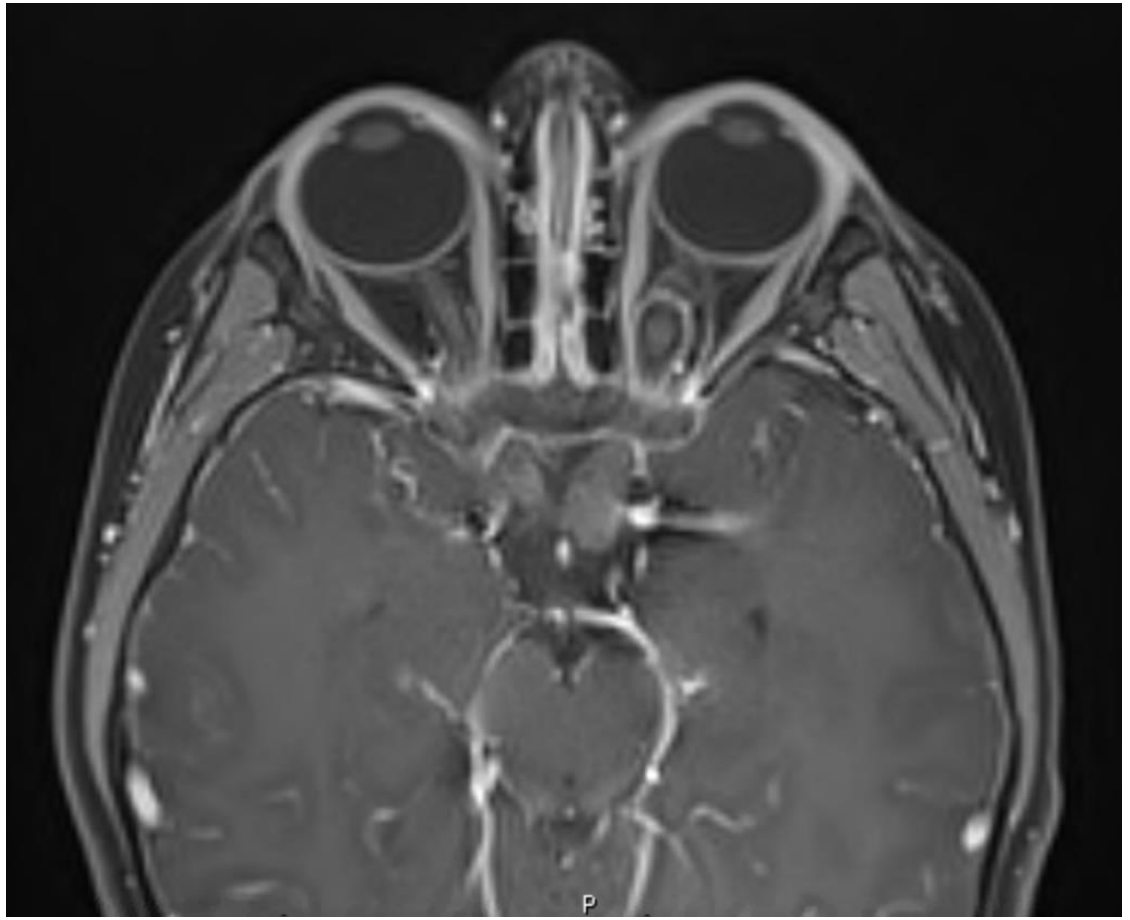
- New Drug therapies (especially NF-1 Plexiform Neurofibromas)
    - MEK inhibitors
        - Selumetinib/Koselugo (AstraZeneca) – FDA approval April 2020
        - 66% response (shrinkage) in PNs
        - Testing in over 10 different types of tumors (including brain tumors)
- Other Drug therapies
    - mTOR inhibitors (Everolimus, Serolimus)
    - EGFR target (Avastin (bevacizumab))

Optic Pathway Gliomas (OPG) - Treatment

- Children's Oncology Group
  - Phase 3 study (for OPG and other brain tumors)
  - Historical chemotherapy against MEK inhibitor (selumetinib)
    - RANDOMIZED 1:2 (2/3 get selumetinib)
  - OPENED 10/2019
  - Ongoing patient enrollment (expect about 5 years to enroll)

OPG before/after treatment (Carbo/VCR)





Optic Pathway Gliomas (OPG) - Outcomes

- Carbo/Vincristine (Historical)
  - 5 yr Event Free Survival = 69% (lower for non-NF patients)
    - EFS is not the same as OS
  - 20% side effects of peripheral neuropathies
  - 10% hypersensitivity reactions to carboplatin
  - 32% some vision improvement; 40% with vision stabilization; 28% worsening*
- Goals of therapy: preservation of VISION
  - Radiographic outcomes do not predict visual outcomes*

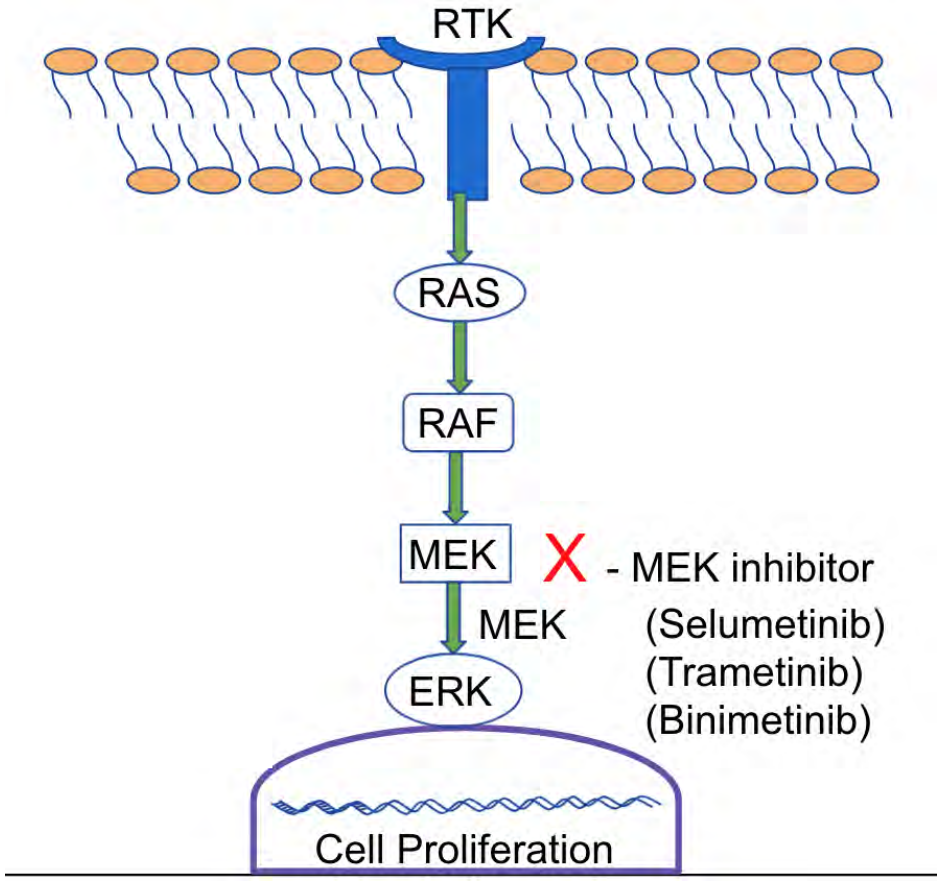
*Fisher, et al, Neuro Oncol 14: 790-797; 2012

Optic Pathway Gliomas (OPG)

- Goals of Study
  - Do better with fewer toxicities

- MEK inhibitor
  - Ease of use (oral pill)
  - Difficulty of use (pill swallowing)
  - Daily use
  - 2 years of treatment
  - Long term outcomes not known but with PN→ sometimes tumors regrew when med stopped

MEK inhibitors – not an automatic home run (for brain tumors)



Side Effects

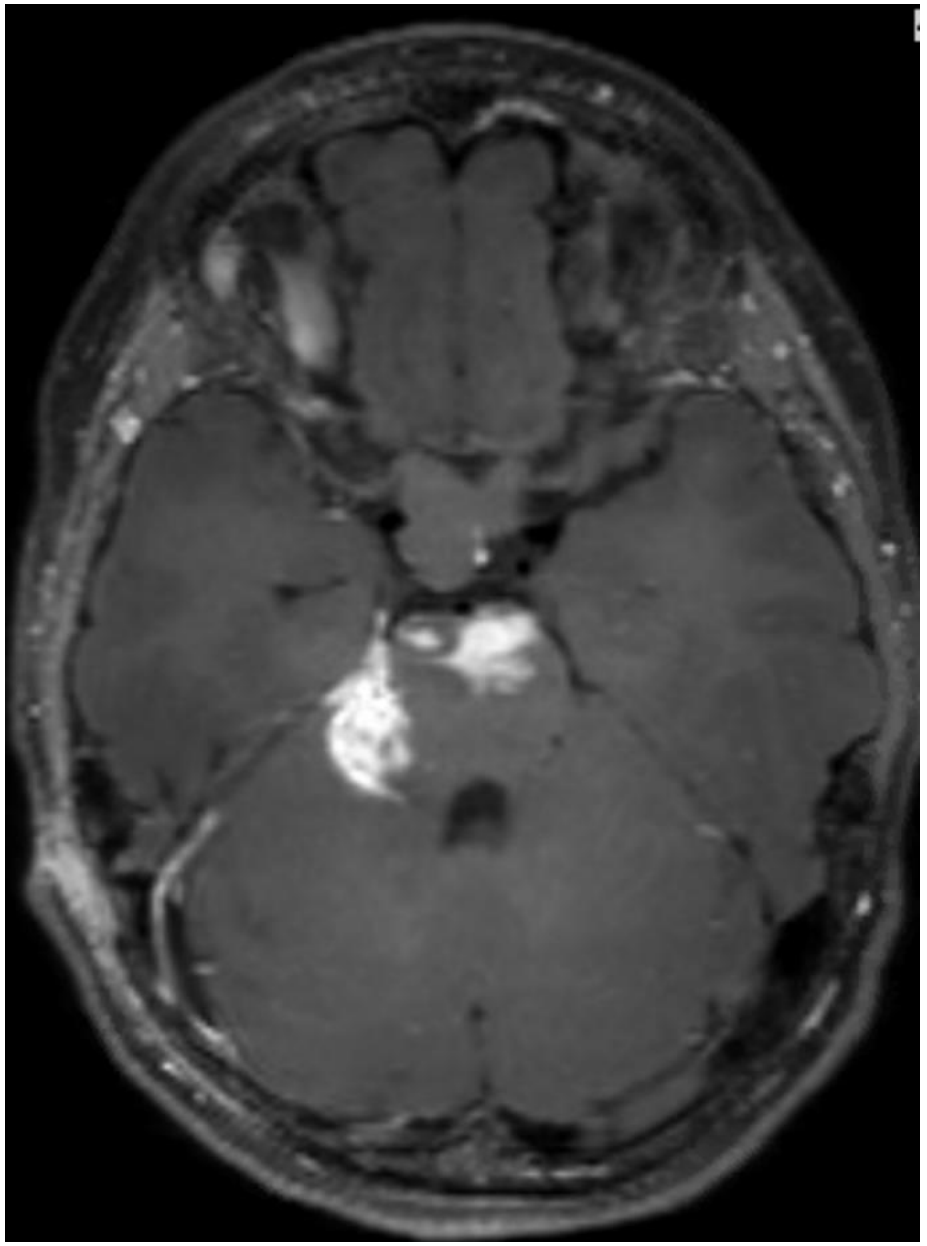
- GI disturbance (70%)
- skin toxicity (50-90%)
- eye toxicity (retinal detachment) 15-20%
- cardiac toxicity (20-25%)

NF-1 and Brain Tumors

- 15-20% of NF1 children will develop OPG/CNS tumors
- OPGs
- Other CNS tumors
  - Low Grade Gliomas (Brainstem Gliomas)
  - High Grade Gliomas
  - Intraspinal neurofibromas/tumors
  - MPNST (covered in another lecture)

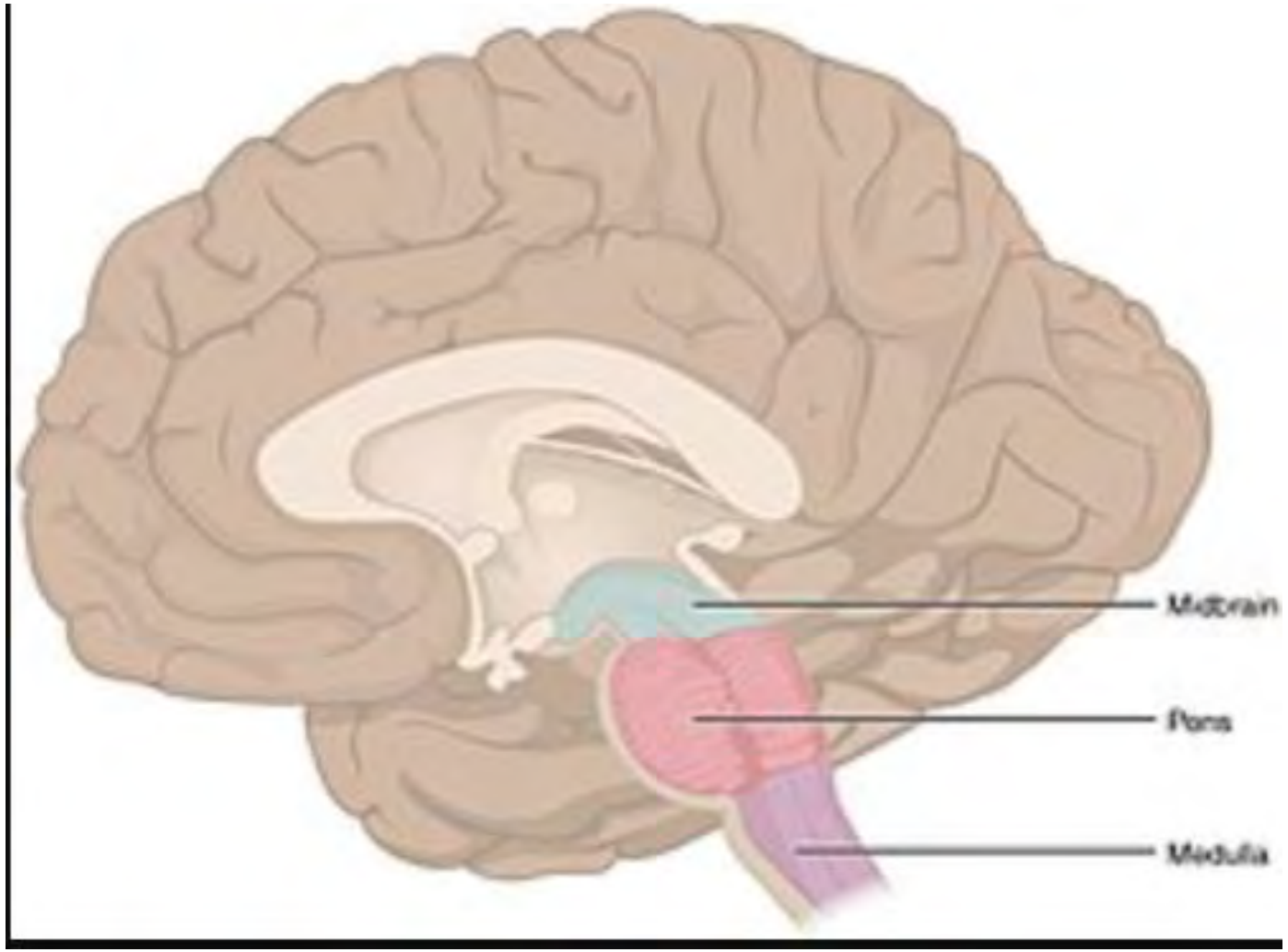
Low Grade Gliomas

- Location: most commonly brain stem (Brainstem Glioma)
- Poorly studied (vs OPG)
- Usually indolent; discovered incidentally (following OPGs)
- Often Pilocytic astrocytomas
- Age: avg 7-8yo



1. Selt, et al, J. Neurooncol 2020
2. Fagusaro, et al, Lancet Oncol, 2019

Brainstem Gliomas in NF-1



Common Symptoms

- Headache
- Nausea/vomiting

Often a/w hydrocephalus

Other possible symptoms

- Cranial nerve palsies (abnormal facial movements)
- Ataxia (balance difficulty)

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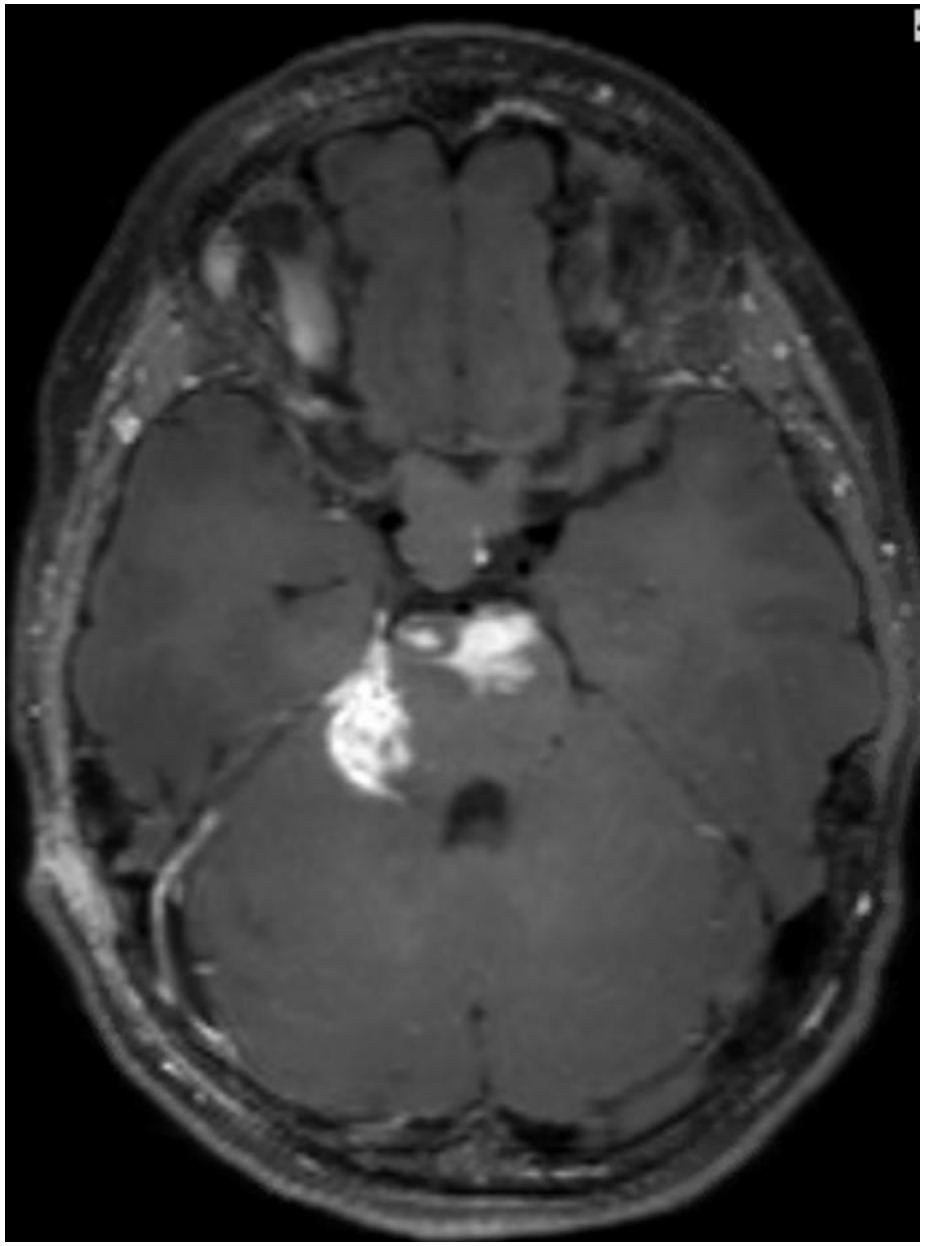
Brainstem Gliomas

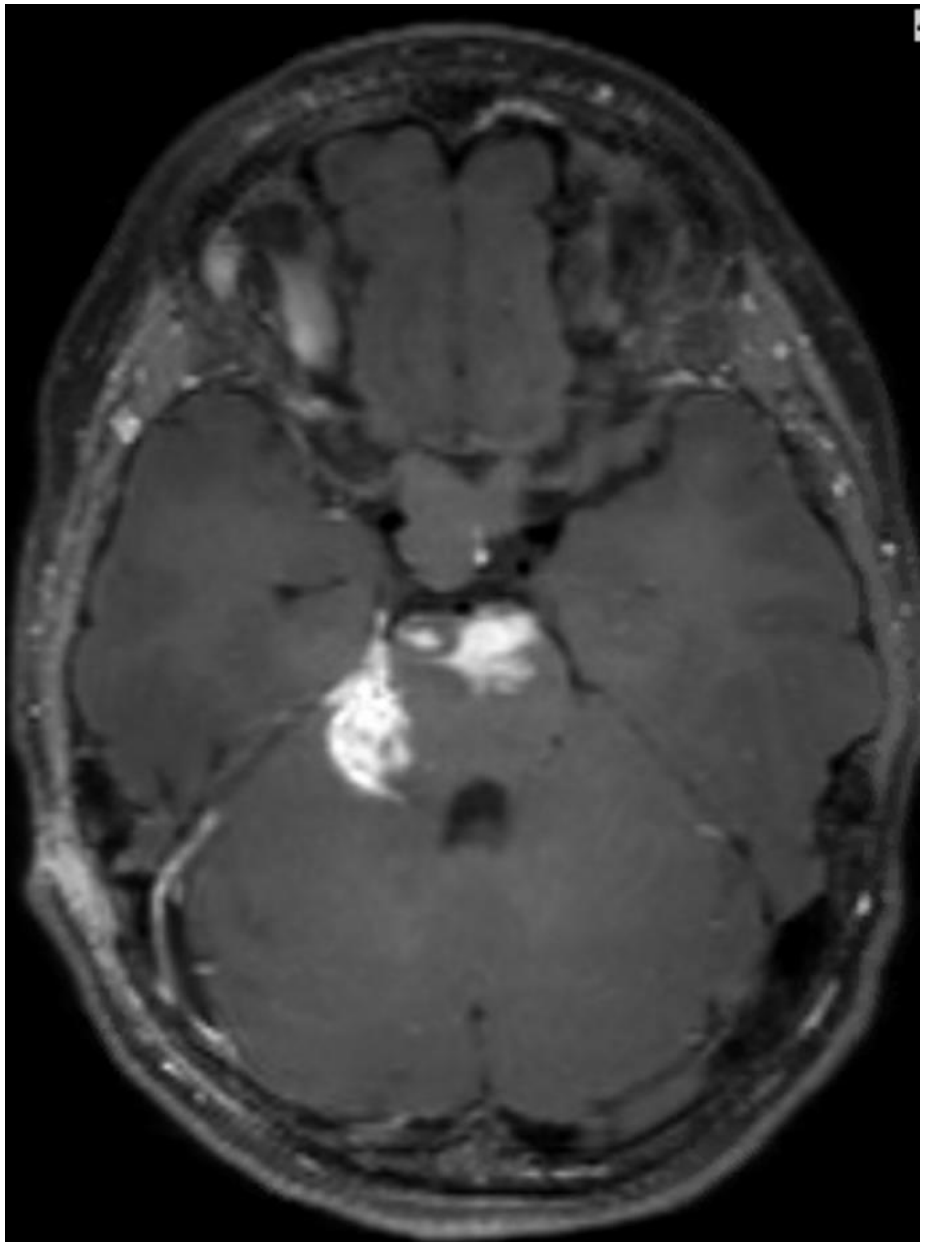
- Treatment:
- Not always needed [1]
  - 7 patients with DIFFUSE involvement
  - 4 with symptoms
  - 4 followed without treatment; all alive and neurologically stable (median=40 months);
    - Note: diffuse pontine tumors in non-NF patients has dismal prognosis



1. Broniscer, et al. Neurosurgery. 1997 Feb;40(2):331-7

Brainstem Gliomas

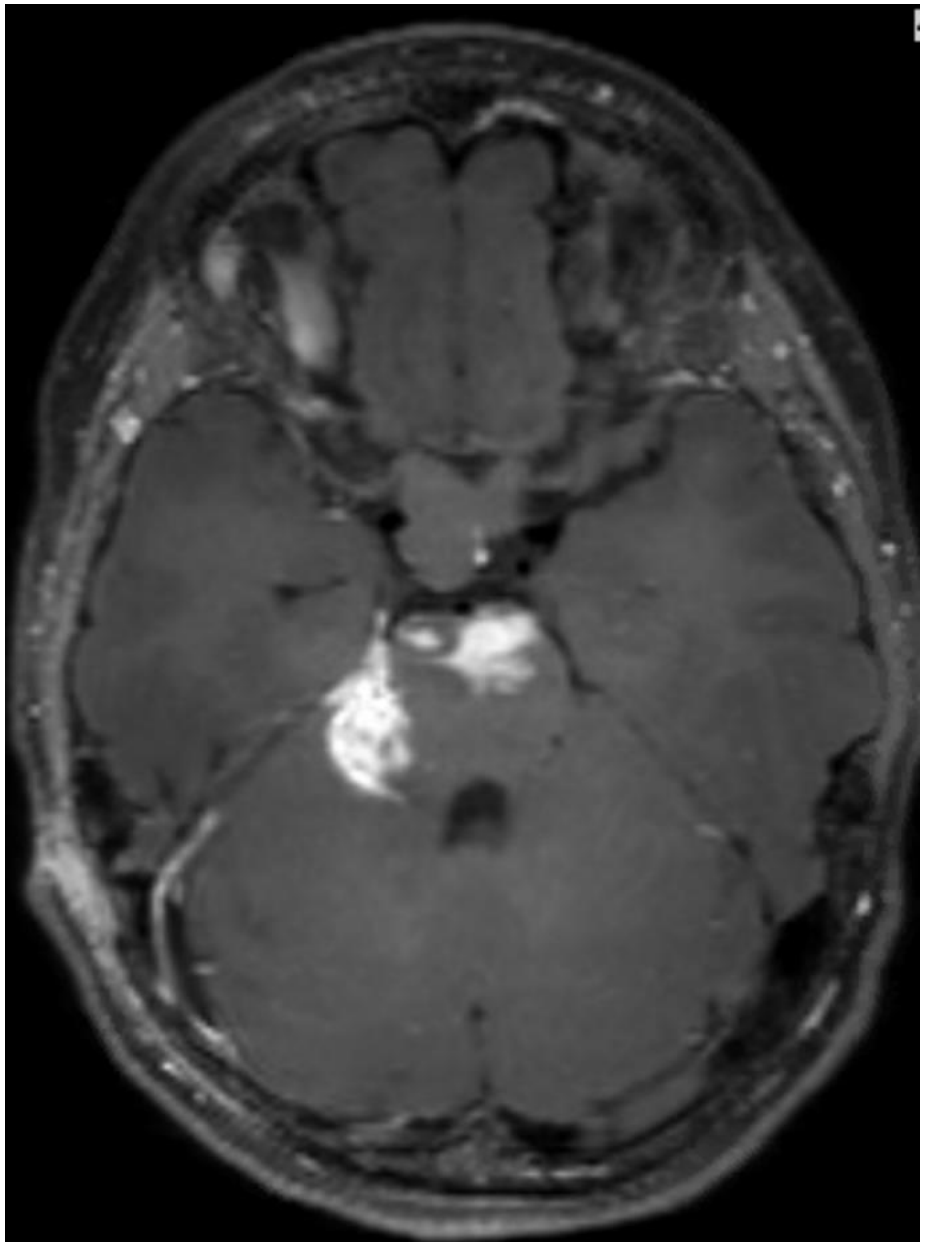
- Treatment:
- Not always needed [1]
  - 21 patients with DIFFUSE involvement
  - 12 with symptoms; 9 without symptoms
  - Followed 3.75 years; 10 showed progression → of these 7 regressed/stabilized without intervention
  - 4 patients received treatment (focal enhancing tumors); stable over 4 years after treatment



1. Pollack, et al; Neurology 1996. Jun;46(6):1652-60

Brainstem Gliomas

- Treatment for rapid growth/clinical worsening
  - Carbo/VCR
- Phase 2 study results
  - Trametinib[1]: 18 patients (8 with NF1)
    - 4 showed stable/improved disease
  - Selumetinib[2]: 50 patients
    - 70% considered partial responders



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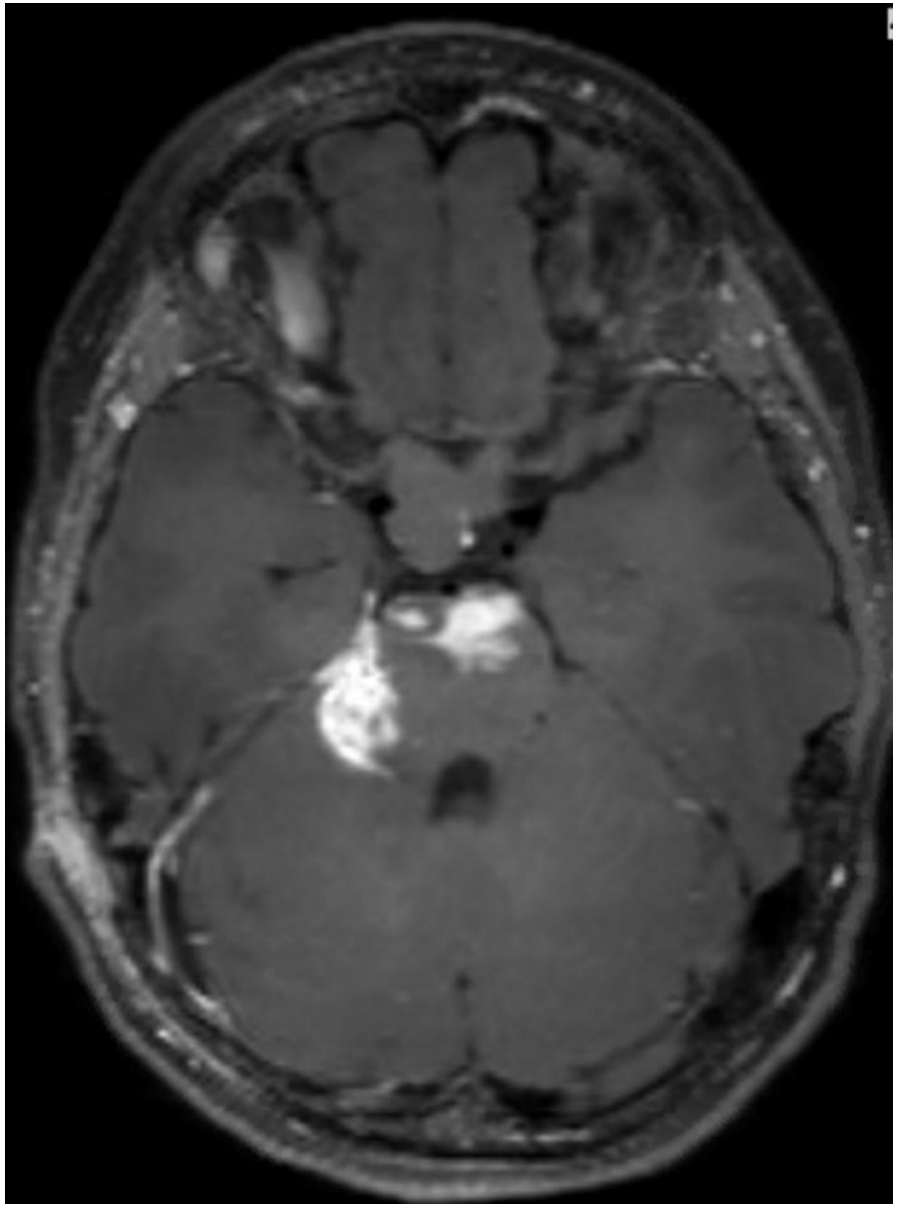
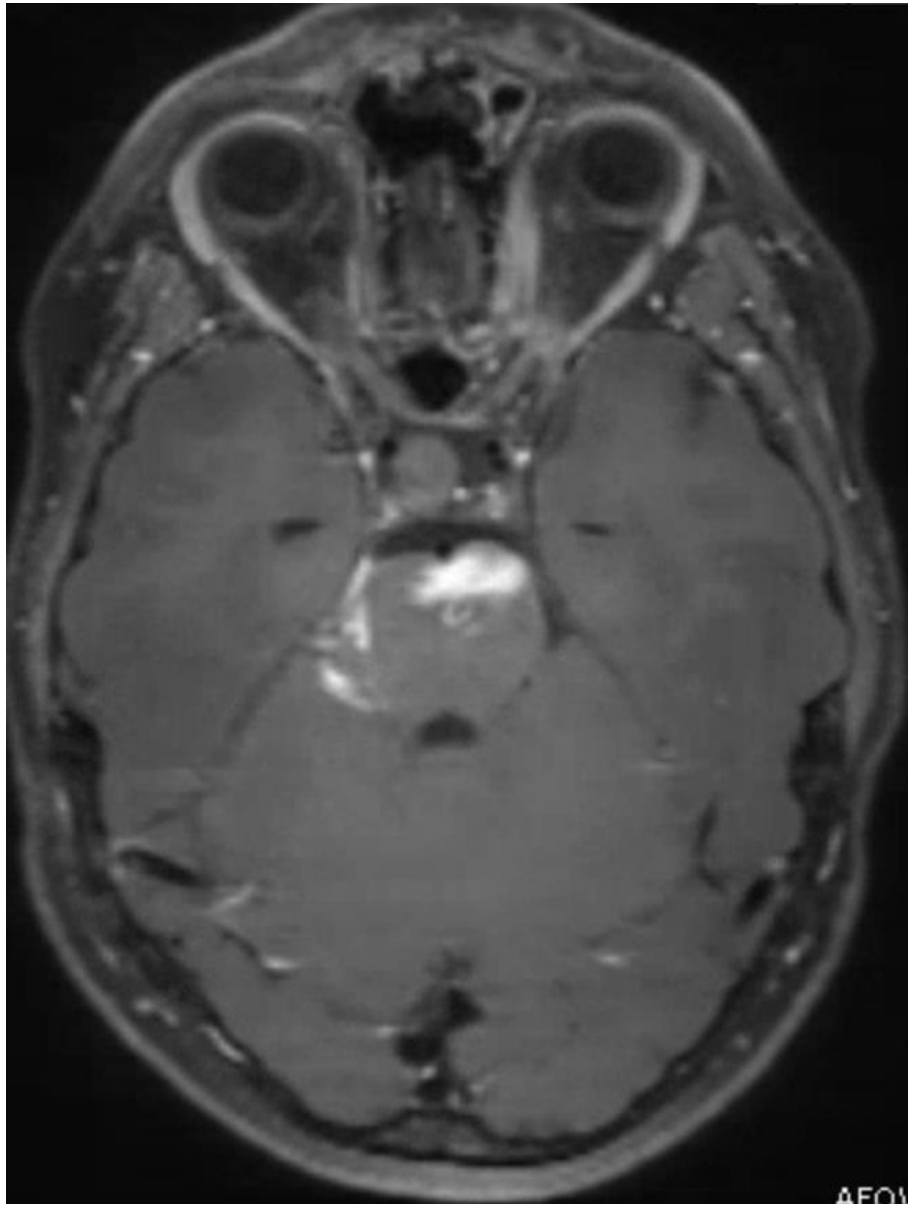




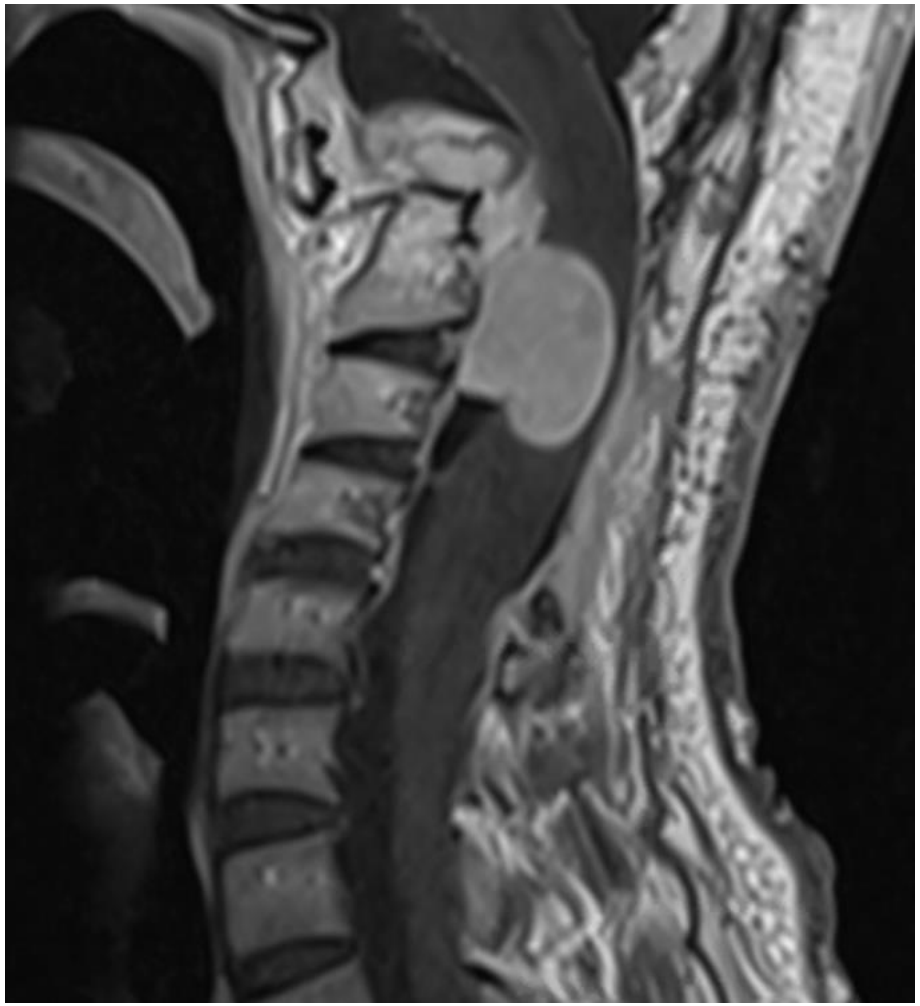
High grade glioma*

- Not progression of OPG/BSG
- Less common, <1% of all NF-1 pts
- occur in adults with NF-1 at younger ages than non NF-1
- Considered “malignant”; no cure
- Prognosis dismal: average survival ~15 months after diagnosis

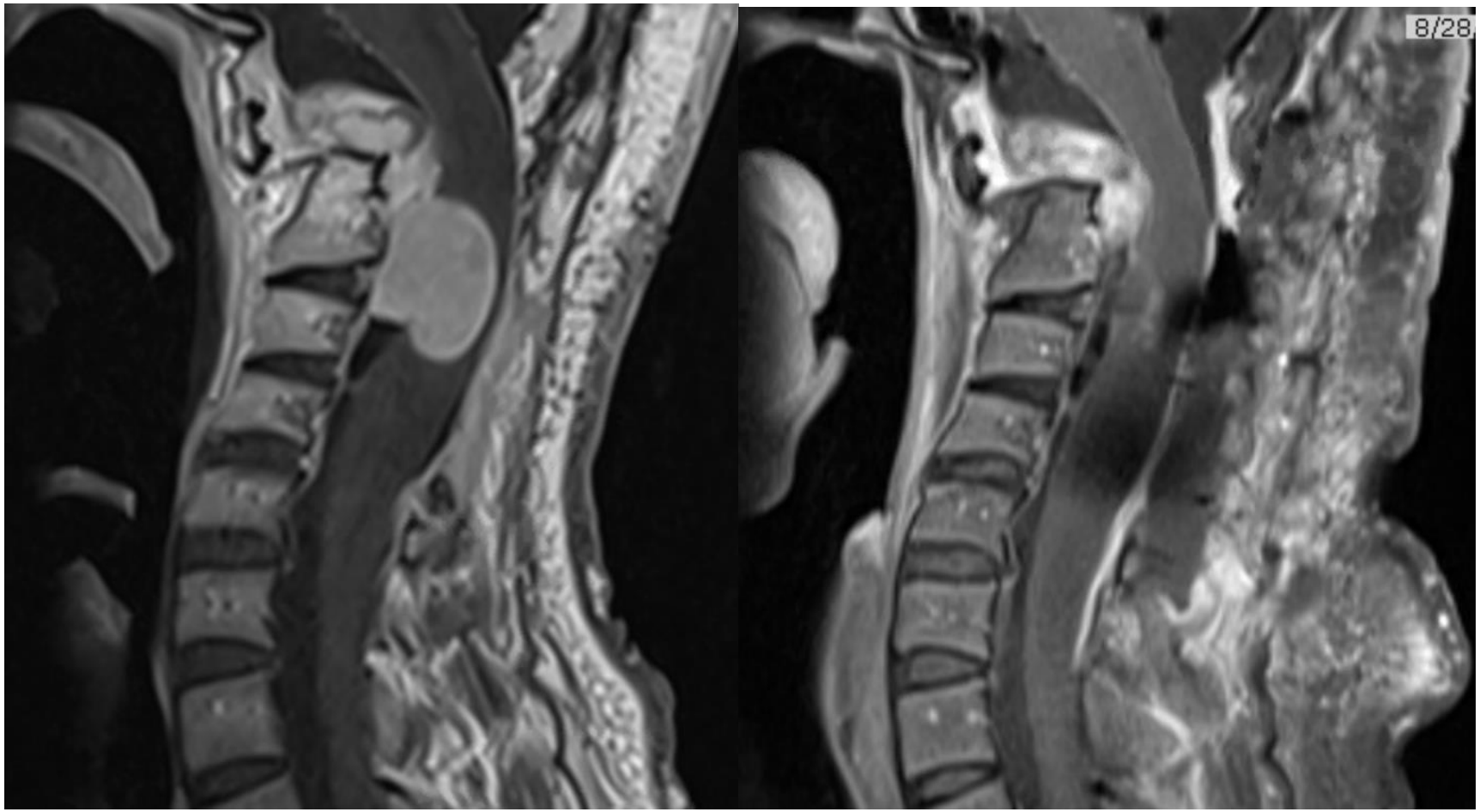
*Campain, et al. CNS Tumors in Neurofibromatosis; J Clin Oncol 2017 Jul 20; 35(21): 2378-2385

Spinal tumors

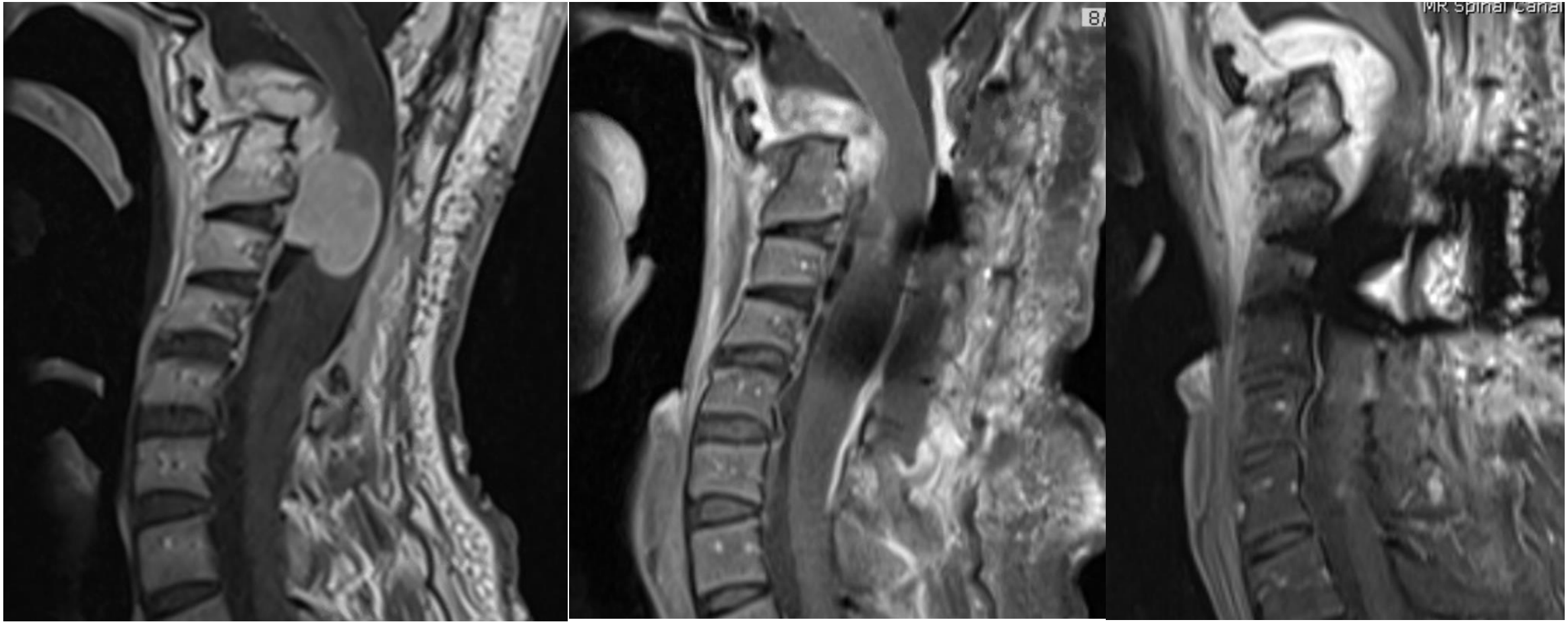
- Rare: generally case reports
- Extensive debilitation
- Usually present with spinal cord compression
- Surgery: often first step in treatment



Spinal tumors – Plexiform NF extending INTO spinal cord



Conversion to MPNST



Brain Tumors in NF-1

- Young children (<5yo) → Optic pathway gliomas
- Mid childhood → Low grade gliomas (typically brainstem)
- Early Adulthood → increased incidence of high grade glioma

- Peripheral nerve tumor conversion to MPNST (Malignant Peripheral Nerve Sheath Tumors)

CNS tumors in NF-1 patients - Treatment

- Complete resection = 90% overall survival at 10 years
  - No need for chemotherapy or radiation therapy
  - Rare due to location
- Radiation is effective therapy, but too risky for routine use
  - Side effects (acute)
    - Possible need for central line, anesthesia, headaches, fatigue
  - Late effects
    - second malignancies
    - vasculopathies
    - Neurocognitive effects
- Thus CHEMOTHERAPY (Medical therapy) is mainstay of treatment

CNS tumors in NF-1 patients - Treatment

- CHEMOTHERAPY (Medical therapy) is mainstay of treatment
  - Historical: Vincristine/Carboplatin (or Vinblastine)
  - Current: Research trials at time of diagnosis testing historical against MEK inhibitors
  - Other possibilities:
    - mTOR inhibitors (Everolimus, Serolimus)
    - Bevacizumab (Avastin) - ? Temporary response?
    - Temozolomide (alkylating agent risk- 2nd malignancies)

CNS tumors in NF-1 patients - Outcomes

- Low grade gliomas (EFS = 60-70%; OS = 90-100%)[1]
  - OPG (~67% occur here)
    - Goal to preserve vision
  - Brainstem glioma (~15-20%)
  - Other CNS tumors (~10-15%)
    - OS = 90% with resection, without chemo/radiation
- High grade gliomas (adult, rare)
- Spinal tumors (debilitating, rare)

1. Jones, et al; Pediatric low-grade gliomas: next biologically driven steps; Neuro Oncol. 2018 Jan; 20(2): 160-173.

Thank you for your time
Questions?