An Unusual presentation of Neurofibromatosis

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NO FINANCIAL DISCLOSURES



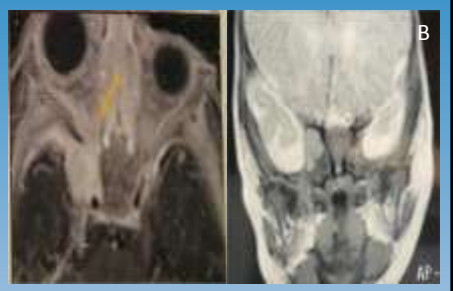
Unilateral **Large corneal diameter**
Large globe
Elevated IOP
corneal opacity
Subtle ptosis
Subtle proptosis

- 7 infants: 4 females
- 3.2 months (2 weeks - 6 m)
- IOP 18.5 (14- 30 mm/Hg)
- CD 14.2 (13- 15 mm)

Initial Imaging :

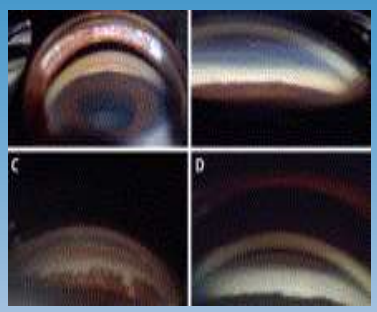
An enlarged globe ±:

- swollen orbital tissue
- engorged orbital veins
- thickened optic nerve sheath
- a “suspicious lesion” in the area of the cavernous sinus



Glaucoma surgery:

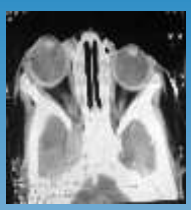
Goniotomy
Trabeculotomy
Trabeculectomy e mitomycin



…… *uncontrolled IOP*

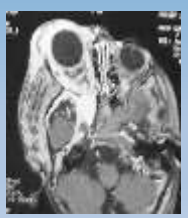
Subsequent Imaging :

1. Defective GWS
2. Neurofibroma at CS
3. Optic nerve glioma
4. Sphenoidal wing meningioma
5. Trigeminal Schwannoma.
6. Hamartomas at basal ganglia (UBO,s)
7. Arachnoid cyst



A right meckel's cave lesion (neurofibroma)

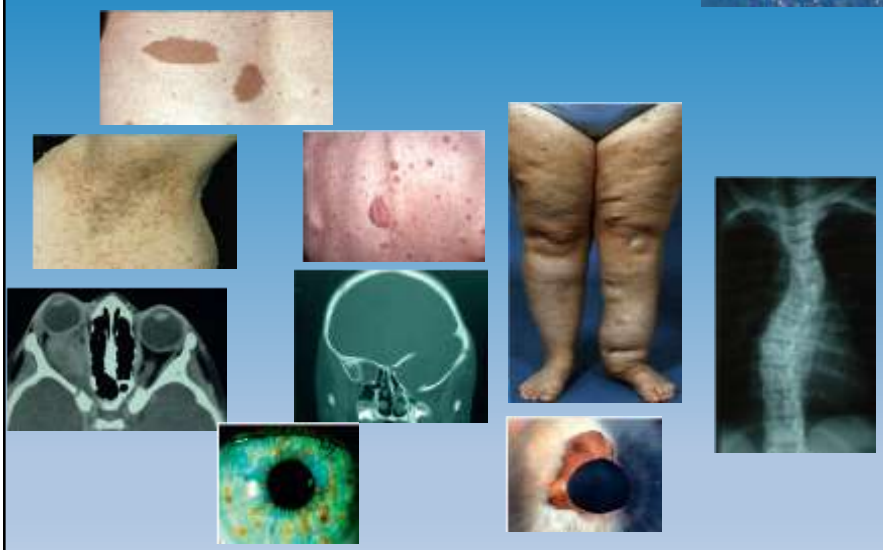
A left paracellar mass most likely a trigeminal neurofibroma, a left temporal subcutaneous neurofibroma, brain hemiatrophy, a left petroclival mass extending to the orbit through the deficient lesser wing of sphenoid.



A Parasellar meningioma with a **Deficient greater wing of sphenoid**

NF-1

- AD 1:3000-4000
- The characteristic lesion is ***benign neurofibroma*** but there is an 8-13 % lifetime risk of developing malignant peripheral nerve sheath tumors .
- Mutations in the NF1 gene (chromosome **17**) codes for ***neurofibromin***, a tumor suppressor
- ***OFNF*** (up to 22 % of cases)
  - involves the face and orbit *(Plexiform neuroma)*
  - earlier in childhood
  - aggressive behaviour



Diagnostic criteria for NF-1 (NIH Consensus Development Conference formulation)

***two or more** of the following :*

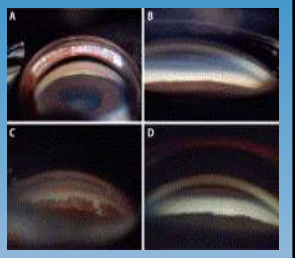
1. **Six or more café-au-lait macules** over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals.
2. **Two or more neurofibromas** of any type *or* **one plexiform** neurofibroma.
3. **Freckling** in the axillary or inguinal region.
4. **Optic glioma**.
5. Two or more **Lisch nodules** (iris hamartomas).
6. A distinctive **osseous lesion** such as **sphenoid dysplasia** or thinning of long bone cortex with or without pseudarthrosis.
7. A **first-degree relative** (parent, sibling, or offspring) with NF-1 by the above criteria.

NF1 and Glaucoma

- It has been reported in 1/300 NF1 patients.
- In 23-50 % of cases with orbital-facial NF1
- Rare at birth and early childhood
- Refractory glaucoma

……very poor prognosis

Mechanism of Glaucoma



- Gonioscopy:
  - Anterior iris insertion
  - Increased pigmentation
  - Long iris processes
  - Fibrovascularization and synechiae
- UBM:
  - Thick CB (mechanical angle closure)
- Enucleated eyes:
  - Endothelialization of the angle
  - Overexpression of the Ras -MAPK genes

Defective greater wing of sphenoid……sphenoidal dysplasia

- Uncommon manifestation….. yet 1 of 6 distinctive features of NF1
- Pulsating proptosis
- NOT present in earlier imaging < 6 m
- Appeared in nearly all cases later on!!!!!
- *Three case reports*: Harkens and Dolan1990 , Macfarlane et a l1995, Haijun et al 2015

Congenital or Acquired???

- Congenital mesodermal maldevelopment/ defective ossification *(Hunt and Pugh)*

  …….. Why is it always unilateral?

- Vascular theory of Mcfarlane……. Abnormal increased circulation resulting in local expansion of SOF and progressive prolapse of the adjacent temporal lobe
- Erosion by neurofibromatosis tissues
- Small congenital malformation that became more prominent over time …….. like growing fracture of the skull in infants

???? Lisch nodules / ectropion uveae

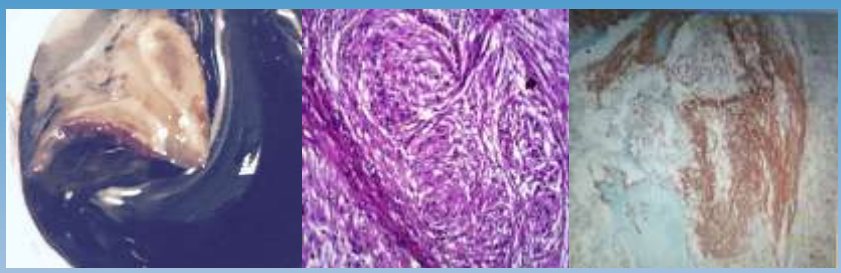
- Characteristic signs of NF1
- > 6 years

Nichols JC et al, Characteristics of lisch nodules in patients with neurofibromatosis type 1. J Pediatr Ophthalmol Strabismus, 2003;40:293-6.

Prognosis……..

- 2 cases: multiple surgeries, IOP under control with medication, useful vision
- 1 case underwent a gamma-knife excision for a huge sphenoidal meningioma….optic atrophy …….enucleation before 4 y
- 2 cases had enucleation for a blind painful eye following repetitive surgeries elsewhere(5,7 y)
- 1 child died due to CNS complications after a brain tumor surgery (2y)
- 1 case had hemophthalmos following trauma (3.5 y)

Histopathology



Of seven cases……

1 dead & 4 enucleations!!

Red Flags

1. *Keep a high index of suspicion towards any case of unilateral congenital glaucoma with the slightest doubt of ptosis or proptosis*

1. *Timely Informed imaging request for diagnosis confirmation as well as early detection of associated intracranial lesions…… LOOK for any abnormality in the region of the cavernous sinus*

1. *Earlier aggressive management of Glaucoma in view of this sinister prognosis*

MEK Trial

Somatic inactivation of NF1 gene that encodes the tumor suppressor protein " neurofibromin" (Ras-GTPase inactivating protein)

↓

elevated level of activated Ras

↓

activation of Ras-mitogen-activated protein Kinase(MAPK)-MEK signalling

↓ ← MEK Inhibitors

↑cellular proliferation

MEK1/2 Inhibitors under trial :

- *Trametinib*
- *Debrafenib*
- *Cobimetinib*
- *Vemurafenib*
- *Binimetinib*
- *Encorafenib* …… *Selumetinib*

- ***Phase I trial (Sept 2011 to Feb 2014)***

  - Selumetinib induced partial response in 71 % of 24 children (3-18 y) with inoperable advanced plexiform neurofibromas.
  - Selumetinib was administered orally twice daily 20-30 mg/ m^2
  - No recurrence or disease progression observed to date.

- ***Phase II SPRINT trial: presented 2018 ASCO annual meeting:***

  - Selumetinib induced partial response in 72 % of 50 pediatric patients (2-18 y) with inoperable plexiform neurofibromas enrolled in the study and stability of condition in another 24%
  - Selumetinib was given 25 mg / m^2 twice daily orally continuously in 28 -day cycles (patients received a median of 19.5 cycles)
  - Improvement were seen in both function and patient's reported perspectives of pain, motor function and quality of life.
  - The most common adverse effect was gastrointestinal disturbances, rash, paronychia and asymptomatic elevated creatine phosphokinase.

The FDA in February 2018 has granted this drug:

- ***Breakthrough therapy designation*** for treatment of Pediatric patients ≥ 3 y with progressive symptomatic plexiform neurofibromas.
- ***Orphan drug designation*** for treatment of NF1 (also European Medicines Agency, August 2018)

Thank You