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Neurofibromatosis:

- A phakomatosis (phakomatoses=neurocutaneous disorders involving the ectoderm involving CNS and other tissues like skin). Other phakomatoses:
    - Tuberous sclerosis
    - Von Hippel-Lindau
    - Sturge-Weber Syndrome
    - NF1/NF2
    - *All* of these are very commonly tested!
    - *All of these are relatively common diseases*

Neurofibromatosis type 1 (NF1)

- The most common phakomatosis
    - Hence possibly the most commonly tested
- Autosomal dominant inheritance in many but not all cases (otherwise de novo)
    - NF1 gene on chromosome 17q11.2
    - Tumor suppressor of Ras/MAPK pathway doesn't work correctly
- Random fact: NF1 aka von Recklinghausen disease and "von Recklighausen" has 17 letters—this can help you remember this is 17q
    - In reality are you really going to count letters on your board exam?
- Need 2 or more of
    - At least two neurofibromas or one plexiform neurofibroma
        - Plexiform neurofibroma is a benign peripheral nerve tumor
            - Benign but carries risk of malignant transformation unlike cutaneous neurofibromas
            - Plexiform neurofibromas involve nerves and a nerve plexus but it is overall challenging to distinguish these form other neurofibromas
            - Larger lesions may be excised due to malignancy risk
            - If particularly large fusiform lesion with rapid growth think malignant peripheral nerve sheath tumor
    - Optic nerve glioma
    - >6 café au lait spots in one year
    - Axillary and inguinal (intertriginous) freckles
    - Osseous involvement
        - Sphenoid wing dysplasia
        - Pseudoarthrosis
    - 2+ iris hamartoma (Lisch nodules)
    - First degree relative with NF1
    - CAFÉ SPOT
        - Café au lait spots
        - Axillary/inguinal freckling

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- Fibromas
- Eye hamartomas (Lisch nodules)
- Skeletal abnormalities
- Positive famly history
- Optic nerve Tumors (glioma)

- A few additional points
  - NF1 presents earlier clinically than NF2
  - Has MANY possible associated tumors
    - Malignant peripheral nerve sheath tumors
      - 50% of these arise in patients with NF1
    - Renal angiomyolipoma
    - Many varieties of gliomas
    - Pheochromocytoma, Wilms tumor, many more
  - Neurofibroma involvement may be localized cutaneous or diffuse
    - Know what neurofibromas on a mammogram look like
      - Essentially an aunt minnie on mammography
  - Also involves vascular system
    - Arteriovenous malformations, aneurysms, renal artery stenosis, coarctation of aorta
  - Treatment is surgical resection of tumors with rapid enlargement
  - Supportive therapy

<u>Neurofibromatosis Type 2</u>

- Key point: NOT associated with neurofibromas
  - Hence this was a poor choice of name…
- Also common autosomal dominant inheritance
  - NF2 gene on chromosome 22q12
- CNS predominant disease with
  - Schwannomas (mot common vestibular schwannomas)
  - Meningiomas
  - Intramedullary spinal ependymomas
- MISME acronym
  - Multiple Inherited Schwannomas Meningiomas and Ependymomas
- If you see a meningioma in a child consider NF2
- Bilateral vestibular Schwannomas should be considered to represent NF2 on board examinations

- Here's how I remember this
- NFONE—what is the ONE thing you think of with NF?

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    - The neurofibromas—hence this NF one has the neurofibromas
    - If they show you neurofibromas on a question this is NF1
    - O for Optic nerve glioma or O for orbit
- NFTWO—has two (meaning bilateral) vestibular schwannomas
    - NF22: 22q is NF2
    - NF2 dx in 2nd decade

- Key points to emphasize
    - NF1 17q deletion and NF2 22q deletion
    - NF1 has neurofibromas, NF2 sort of doesn't
    - If you see an optic nerve glioma in a kid think NF1
        - Bilateral optic nerve gliomas regardless of age think NF1
    - If you see aortic coarctation in a kid/teenager think NF1
        - Rib notching (remember 5th to 8th ribs most common with coarctation)
        - NF1 is one of few entities that can have both inferior and superior rib notching with rob notching caused by the neurofibroma and/or collaterals from aortic coarctation
    - Renal artery stenosis in a teenager should make you immediately think NF1
    - NF1 sphenoid dysplasia causes buphthalmos/proptosis or eye on affected side
        - Buphthalmos=enlarged eyeball due to increased intraocular pressure from sphenoid dysplasia (absent orbit)
            - Think NF1 or Sturge Weber syndrome
            - They can show a photo of a child/adult with a bulging, enlarged eye and you should think NF1 or Sturge Weber syndrome
    - NF1 has association with elephantiasis neuromatosa
        - Focal gigantism from diffuse skin thickening/plexiform neurofibromas of an extremity
    - NF1 osseous manifestations include
        - craniofacial dysplasia including sphenoid dysplasia
        - scalloped vertebrae and scoliosis, especially acute cervical kyphosis
            - due to neurofibroma and dural ectasia, most common in lumbar spine
        - pseudoarthroses
        - enlarged spinal neural foramen
    - Schwannoma vs neurofibroma
        - Imaging appearance can overlap
        - Schwannoma is eccentric growth to nerve, can be separated form nerve with surgery
        - Neurofibromas infiltrate the nerve and resection requires nerve sacrifice
        - If a lesion is intracranial this is most likely a schwannoma and you should think NF2

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        - Orbital lesion think NF1
    - In the spinal canal these are both extramedullary intradural lesions
        - Schwannoma, meningioma, neurofibroma, drop metastases
    - If you see an extraspinal lesion below the neck it is most likely a neurofibroma
    - Target sign on MRI favors neurofibroma rather than schwannoma
    - S100 staining is schwannoma, Antoni A/B pattern is schwannoma
  - Lateral thoracic meningocele think NF1
    - Due to enlarged neural foramen with dural and bone insufficiency
    - A pulsion diverticulum due to negative intrathoracic pressure during respiration sucking out meningocele through the enlarged neural foramina
  - Vascular anomalies think NF1
  - Aortic coarctation, renal artery stenosis, aneurysms, AV fistula
- NF1 has the skin and subcutaneous neurofibromas and NF2 has no specific skin findings
- NF1 may have foci of abnormal signal (FASI) in basal ganglia during first decade of life of uncertain etiology but benign—not tumors, this is not seen in NF2

Review:

Skin: NF1 café au lait and NF2 skin tags

Nerves: NF1 neurofibroma and NF2 schwannoma

Gliomas: NF1 astrocytoma and NF2 ependymoma

NF1 kids think pilocytic astrocytoma, adults high grade anaplastic astrocytoma/GBM

Coverings: NF1 meningoceles and dural ectasia and NF2 meningioma

Orbits: NF1 optic nerve glioma and NF2 optic nerve sheath meningioma