Neurofibromatosis

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Neurofibromatosis type 1 (von Recklinghausen’s disease)

Genetics
- AUTOSOMAL DOMINANT inactivation of NF1 gene (17q11.2)
- Penetrance is 100%; expression variable even within families.
- > 300 mutations having been identified
- Gene product (neurofibromin) serves as tumor suppressor - inactivates p21-Ras pathway
- Mutant ras activation -> increased cell proliferation and survival

Epidemiology
- Incidence: 1 in 3000 (2190-7800) - one of most common autosomal dominant genetic disorders in humans!
- Higher in Arab-Israeli subpopulations
- ½ cases appear sporadically (new mutations)
- Mutation rate in NF1 gene (1 case per 10,000 population) is among highest known for any human gene
- Males = females.

Pathology, Clinical Features, Management
- Appear slowly over many years (although genetic change is present at conception):
  Multisystemic involvement is common!

Nerve Sheath Tumors
- Schwannomas (few - thousands) - may affect any organ in body (esp. cutaneous & subcutaneous).
  - Occur in all patients
  - Appear at any time in life (infrequent before puberty).
  - Schwann cells (progenitor cells of neurofibromas) and fibroblasts (plus, perineural cells, endothelial cells, mast cells, pericytes, and other intermediate cell types)
  - Schwann cells in increased number and with reduced association with axons
  - Clinically indolent and benign course - most are asymptomatic.
  - Deep lesions may be detected only through palpation.
  - Number & growth in puberty or pregnancy (large p/e & genital neurofibromas can complicate delivery).
  - Dermal and plexiform variants are characteristic of NF1 (vs. sporadic counterparts)
  - Dermal neurofibromas - well-circumscribed, non-encapsulated benign tumor most often composed of Schwann cells and fibroblast-like cells, with admixture of endothelial cells, lymphocytes, and unusually large numbers of mast cells.
  - Plexiform neurofibromas - almost pathognomonic of NF1
    - Locally invasive and quite deep.
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- extend across length of nerve and involve multiple nerve fascicles or multiple branches of large nerve → sizable ropelike mass of diffusely thickened nervous tissue
- overlying hyperpigmentation or hypertrichosis.
- may cause bony erosion and pain + disfiguring elephantoid overgrowth of skin and subcutaneous tissue + tumors in head or neck region can impair vital functions.
- appear early (plexiform neurofibromas of face and neck rarely appear after age 1 year, and plexiform neurofibromas of other parts of body rarely develop after adolescence).
- present in thoracic region (20% of all patients), abdomen/pelvis (44% of all patients).
- frequently involve nerve roots at multiple levels → extensive compression myelopathy; not amenable to cure (H. multilevel laminectomies* for debulking; loss of neurological function is rare after surgery; regrowth → secondary reoperation)

"progressive kyphosis may require subsequent spinal fusion; most authors, do not advocate fusion at time of initial resection (rather use osteoplastic laminotomy)

- may undergo malignant degeneration (esp. PLEXIFORM NEUROFIBROMAS) to malignant peripheral nerve sheath tumors (MPNSTs) see p. Onc60 >>

- management - careful observation, surgical intervention only for symptomatic cases (no routine spinal imaging because symptoms, not imaging characteristics, ultimately determine surgical management):
  1) spinal cord / intracranial tumors see p. Onc60 >>, p. Onc62 >>
  2) cosmetic indications
  3) compressive neuropathies
  4) painful / irritating neurofibromas - on scalp, along hairline, around waist (where clothes rub).
  5) neurofibromas that press on vital structures (e.g. obstructive uropathy), obstruct vision, or grow rapidly.
  6) plexiform neurofibromas

→ pruritus due to cutaneous neurofibromas → avoid hot showers and baths, DIPHENHYDRAMINE.

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Multiple neurofibromas of spinal roots and brachial plexus in patient with NF1:


Plexiform neurofibroma of right thigh:

Flesh-colored cutaneous neurofibroma:


Large, soft, ill-defined, subcutaneous nodules on right lower back and on right posterior axillary line are plexiform neurofibromas:
EUROFIBROMATOSIS

Von Recklinghausen's disease

Multiple sebaceous neurofibromas
2. SCHWANNOMAS of cranial nerves (CNS in 5% patients), dorsal sensory roots - solitary and sporadic (vs. NF2 - multiple schwannomas).

3. MALIGNANT PERIPHERAL NERVE SHEATH TUMORS (NEUROFIBROSARCOMAS) - not uncommon (lifetime risk 10%).
   • arise from large plexiform neurofibromas or extensive peripheral nerve lesions.
Majority of gliomas in NF1 patients are optic pilocytic astrocytomas!

1. **OPTIC GLIOMA** - most common (12-20%) intracranial tumor (incidence lower in African Americans).
   - usually WHO grade I astrocytomas.
   - occur in 15% patients.
   - may occur at any time* (75% occur in first decade of life).
   - asymmetric, noncorrectable visual loss is most common presenting symptom.
   - less aggressive than optic nerve tumors in general population.
   - bilateral in 4%.
   - affect optic nerve or chiasm, hypotalamus → headache, visual complaints, proptosis, endocrine disturbances (esp. precocious puberty).
   - nonenhancing optic gliomas (60% cases) do not progress!!

   *vs. sporadic cases are seen almost exclusively in children < 7 yrs.

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   - nonenhancing optic gliomas (60% cases) do not progress!!

   - management: much more indolent clinical course than in sporadic cases (may remain static for many years and some may regress) - conservative monitoring until:
     - a) MRI progression / atypical appearance → biopsy
     - b) symptomatic → debulking → adjuvant chemotherapy (VINCRISTEIN and CARBOPLATIN), radiation therapy carries risks of radiation necrosis, cognitive problems, visual loss, secondary malignancy, moyamoya disease.

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2. **BRAINSTEM GLIOMA**
   - indolent course (neurofibromatosis is favorable prognostic indicator for brainstem gliomas):
     - radiographic progression in < 50% of cases and clinical progression in < 20% of cases (irrespective of intervention with surgery, chemotherapy, or radiation therapy)
   - look for synchronous tumors at other CNS locations
   - differentiate from “unidentified bright objects” (UBOs) see below
   - management: serial MRIs → treat only clear progression.

3. **CEREBELLAR GLIOMA**
   - 10% of pediatric cerebellar gliomas are associated with NF1
   - pilocytic astrocytoma > anaplastic astrocytoma, ganglioglioma, pleomorphic xanthoastrocytoma
   - NF1 cerebellar gliomas (vs. sporadic cerebellar gliomas): 1) occur in subependymal white matter of fourth ventricle (vs. vermis or hemispheric location)
2) more malignant phenotype? — radically resect whenever clinically feasible!! (vs. wait-and-see approach for optic or brainstem gliomas); pathologic grade dictates need for further adjuvant therapy

4. MEDULLOBLASTOMAS
5. MENINGIOMA
6. HAMARTOMAS

SPINAL CORD TUMORS
(dumbbell-shaped) — NEUROFIBROMAS, MENINGIOMAS.

ABDOMINAL TUMORS
— neurofibromas, leiomyomas, adenocarcinomas with neuroendocrine function.

- within liver, mesentery, retroperitoneum, GI tract.
- often multiple, germline mutation proximal small bowel.

ABNORMALITIES OF MELANOCYTES

1. Multiple café-au-lait spots (aggregation of neural crest-derived melanoblasts in basal layer of epidermis)

- earliest clinical finding (present in infancy in > 95% patients)
- increase in size and number throughout childhood → tend to fade in adults.
- more common on trunk than on limbs, not found on scalp, face, soles, palms.
- ratio melanocytes : keratinocytes is higher in unaffected skin of NF1 patients and this is more marked in café-au-lait spots.

Several > 1.0 cm café-au-lait spots on upper chest and multiple small macules in axilla (axillary "freckling"); remnants of early, small, pink tan neurofibromata on chest, breasts, and neck.

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2. Axillary or inguinal freckles (Crowe sign) — multiple hyperpigmented 2-3 mm areas - appear during childhood - adulthood — in 2/3 of patients.

- histopathologically indistinguishable from café-au-lait spots.

3. Iris hamartomas (Lisch nodules) — small, elevated pigmented melanocytic hamartomas on surface of iris ("iris nevi")
EUROFIBROMATOSIS

- usually not readily visible without slit lamp
- particularly useful diagnostic criterion - present in > 95% patients aged > 10 yrs; asymptomatic.

OTHER LESIONS

1. Bony abnormalities (may be clinically silent):
   1) Long-bone abnormalities (esp. tibia) may be evident at birth (congenital) - thinning of cortex, bowing, pseudarthrosis (in past, congenital tibial pseudarthrosis led to below-the-knee amputation).

2. Sphenoid bone dysplasia (absence of greater wing of sphenoid bone → pulsating exophthalmos)

3. Kyphoscoliosis (40%), especially severe in young girls.

4. Macrocephaly with normal-sized ventricles (should not cause alarm, unless rapid crossing of ≥ 2 percentiles)

5. Short stature

6. Learning disabilities (+ attention deficit hyperactivity disorder) - in 40% patients (5% patients have mild + moderate mental retardation); association with bright MRI lesions in thalamus!

7. Increased risk of other tumors: rhabdomyosarcomas, juvenile chronic myeloid leukemia, juvenile xanthogranulomas, gastrointestinal stromal tumors (GIST), duodenal carcinoids, C-cell hyperplasia/medullary thyroid carcinomas, pheochromocytomas.

8. GI tract vasculopathy, bleeding, pseudoobstruction, protein-losing enteropathy.

CLINICAL DIAGNOSTIC CRITERIA

Diagnostic Criteria (National Institutes of Health (NIH) Consensus Development Conference Statement) - presence of ≥ 2 criteria:

1. ≥ 6 café-au-lait spots (largest diameter ≥ 5 mm in children < 10 years and ≥ 15 mm in adults)
2. ≥ 2 neurofibromas of any type or one plexiform neurofibroma
3. Axillary or inguinal freckles (Crowe sign)
4. Optic glioma (pilocytic astrocytoma of optic pathway)
5. ≥ 2 axillary freckles (Lisch nodules)
6. Bony dysplasia (sphenoid wing dysplasia/absence, bowing/thinning of long-bone cortex ± pseudarthrosis)
7. First-degree relative (parent, sibling, offspring) with NF1.

N.B. cutaneous manifestations may develop late (younger patients may appear free of NF1 stigmata)

- children of affected parent can be diagnosed within first year of life because diagnosis requires presence of only 1 feature in addition to family history for NF1.
- if at-risk individual reaches age of 10 years without meeting diagnostic criteria for NF1, he or she is unlikely to be affected!

Mean ages of onset for common clinical manifestations (estimated frequencies for each manifestation within NF1 population are given in parentheses):

DIAGNOSIS

Genetic tests (allow prenatal diagnosis):

- linkage analysis
- protein truncation assay (PTA) - low sensitivity (65-70%)
- sequencing of NF1 gene - sensitivity 95%
**EUROFIBROMATOSIS**

**Annual ophthalmologic examinations** - optic nerve pallor, visual acuity changes, visual field defects; slit-lamp examination - Lisch nodules.

**X-ray**
- long bones - intramedullary fibrosis, cortical thinning, pseudoarthrosis.
- bony erosion secondary to adjacent **PLEXIFORM NEUROFIBROMAS**.
- other - unilateral defects in posterior superior wall of orbit, defect in lambdoid with underdevelopment of ipsilateral mastoid, dural ectasia with enlargement of spinal canal and scalloping of posterior portion of vertebral bodies, "twisted ribbon" rib deformities.


**Head MRI / CT** - only for specific indications (if neurological / ophthalmological problems arise);
- some clinicians prefer baseline CT / MRI at time of diagnosis.
- T2-MRI frequently detects **unidentified bright objects (UBOs)** – in cerebellar white matter, dentate nucleus, basal ganglia, periventricular white matter, optic nerve and pathways;
  - isointense on T1.
  - do not enhance, cause no mass effect (do not expand gyri, vs. tubers in tuberous sclerosis).
  - occur in > 50% NF1 patients
- **UBOs** are the most common imaging findings in NF1 patients!
- no apparent predilection for evolving into gliomas*
- UBOs might pose risk for malignant transformation - serial MRI
- resolve as individual gets older (almost never seen at age > 20 years).
- believed to represent **BENIGN HAMARTOMAS** or (more probably) **DEMYELINATIONS**.

**Source of picture:** Unidentified bright object (UBO) within brain parenchyma:

**Thoracic / abdominal / pelvic CT**
Neurofibromatosis

TREATMENT
- Observation vs. Removal of tumors – see individual tumors.
- Orthopedic care for scoliosis, severe bony defects.

PROGNOSIS
- Many patients are functionally indistinguishable from normal!
- Overall life expectancy is reduced by 15 years – malignancy, hypertension, sequelae of spinal cord lesions.

NEUROFIBROMATOSIS type 2 (s. Central Neurofibromatosis)
- **Relative paucity of cutaneous findings** but **higher incidence of CNS tumors** → worse prognosis (than NF1).

GENETICS
- **Autosomal dominant** mutation (rarely deletion) of NF2 gene (22q12).
- *gene product (MERLIN*) serves as cytoskeletal protein – senses intercellular contact and regulates mitogenic signaling (so functions as tumor suppressor gene).
- *name comes from similarity to cytoskeletal proteins called MOESIN, EZRIN, and RADRIN-like; taking first letters of those words and adding -in (for ending of “protein”)
- type of mutation dictates disease severity
- numerous mutations have been identified – most result in production of truncated protein (Loss of function).
- 99% penetrance by age of 60 yrs

EPIDEMIOLOGY
- **Incidence** of NF-2 is not known (∼ 1 in 25,000 to 40,000 individuals).
- 50% are de novo case in family (new genetic event; high rate of somatic mosaicism ≈ 25% – molecular testing to detect mutation must include tumor tissue).
- males = females.

PATHOLOGY & CLINICAL FEATURES
- **Variable age of onset** (mean 20-22 years; range 2-70 yrs) and severity of symptoms:
  - Paucity of cutaneous features!!!

TUMORS
- Only schwannomas (vs. NF1 – neurofibromas)
- *an histological review, many ‘neurofibromas’ prove to be schwannomas, including plexiform schwannomas misdiagnosed as plexiform neurofibromas
- NF2-associated schwannomas differ from sporadic schwannomas in number of ways:
  1. present at age < 40 (non-NF2 CNS schwannomas typically present at age > 40 yrs).
  2. higher proliferative activity → multiple schwannomatous tumourelets along individual nerves (particularly on spinal roots).
  3. affect any nerve:
     - sensory (incl. spinal dorsal roots), motor (e.g. CN12),
     - may appear multilobular (“cluster of grapes”) on both gross and microscopic examination
  4. cutaneous schwannomas are common (may be plexiform)
- 4% patients develop gliomas (70% are ependymomas; others are diffuse and pilocytic astrocytomas) - 80% are spinal (intramedullary or cauda equina); 10% are in medulla.

Brain tumors:
1. Bilateral retinoblastoma (> 95%) – most common feature!
2. Medulloblastoma – second hallmark of NF2 (50% patients) – difference from sporadic forms:
   - multiple in 40%
   - occur earlier in life
   - higher mitotic index and greater nuclear pleomorphism
3. Ependymoma

1. **Schwannomas** (dumbbell-shaped)
2. **Meningiomas** (often multiple)
3. **Ependymomas** (in most cases, as multiple intramedullary masses)

Numerous schwannomas of the cauda equina in a patient with NF2.

60% incidence of skin tumors (schwannomas, neurofibromas, mixed tumors)

Malignant transformation of benign growths is almost unheard! (vs. NF1)

**Other Lesions**

1. **Posterior subcapsular (juvenile) cataracts** (40-80%) - can predate CNS symptomatology.
   - may progress over time.
   - preservation of vision is paramount in patients for whom hearing will probably be impaired!

2. **Schwannosis** (vs. schwannomatosis) - proliferation of Schwann cells, sometimes with entangled axons, but without frank tumour formation.
   - often found in spinal dorsal root entry zones, sometimes associated with schwannoma of dorsal root, or in perivascular spaces of central spinal cord, where nodules appear more like small traumatic neuromas.
   - less robust, but otherwise identical, schwannosis has been reported in reactive conditions.

3. **Meningioangiomatosis** - intracortical lesion - plaque-like proliferation of meningothelial and fibroblast-like cells surrounding small vessels.
   - may be predominantly vascular (resembling vascular malformation) or predominantly meningothelial (sometimes with associated meningioma).
   - occurs both sporadically and in NF2.
   a. **sporadic** - single lesion in young adults or children who present with seizures or persistent headaches.
   b. **NF2-associated** - may be multifocal and is often asymptomatic (diagnosed only at autopsy)

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4. Glial hamartias (s. microhamartomas) – intracortical* circumscribed clusters of cells with medium-to-large atypical nuclei and scant, sometimes stellar, eosinophilic cytoplasm.

- predilection for molecular and deeper cortical layers
- cells stain strongly for S-100 protein, but only focally for GFAP.
- common in and pathognomonic of NF2.
- not associated with mental retardation or astrocytomas.

A and B: Distribution of cerebral microhamartomas in a patient with NF2. These lesions are scattered throughout the cortex and basal ganglia and show strong immunoreactivity for S-100 (B). Reproduced from Wiestler et al. {2410}.

5. Retinal hamartomas, epiretinal membranes - may or may not be visually significant.

6. Sensory motor neuropathies - not related to tumor masses

- mononeuropathies may be presenting symptom in children, while progressive polyneuropathies are more common in adults.
- mostly axonal
- may be secondary to focal nerve compression by tumourlets or onion-bulb-like Schwann cell or perineurial cell proliferations without associated axons

7. Cafe-au-lait spots (1/3 patients)

8. Cerebral calcifications - cerebral and cerebellar cortices, periventricular areas and choroid plexus

CLINICAL DIAGNOSTIC CRITERIA

1991 NATIONAL INSTITUTES OF HEALTH criteria

A Bilateral vestibular schwannomas
B First-degree family relative with NF2 plus:
   a) unilateral vestibular schwannoma
   b) any one of following: meningioma, schwannoma, glioma, neurofibroma, juvenile posterior subcapsular lens opacity

MANCHESTER criteria

A Bilateral vestibular schwannomas
B First-degree family relative with NF2 plus:
   a) unilateral vestibular schwannoma
   b) any two of following: meningioma, schwannoma, glioma, neurofibroma, juvenile posterior subcapsular lens opacity
C Unilateral vestibular schwannoma + any two of following: meningioma, schwannoma, glioma, neurofibroma, juvenile posterior subcapsular lens opacity
D Multiple meningiomas plus:
   a) unilateral vestibular schwannoma
   b) any two of following: meningioma, schwannoma, glioma, neurofibroma, juvenile posterior subcapsular lens opacity

NATIONAL NEUROFIBROMATOSIS FOUNDATION criteria

Confirmed / definite NF2:

A Bilateral vestibular schwannomas
No biopsy is necessary for diagnosis!
B First-degree family relative with NF2 plus:
   a) unilateral vestibular schwannoma at age < 30 yrs
   b) any two of following: meningioma, schwannoma, glioma, juvenile (posterior subcapsular) lens opacity

Presumed / probable NF2:

A Unilateral vestibular schwannoma at age < 30 yrs + at least one of following: meningioma, schwannoma, glioma, juvenile lens opacity
B ≥ 2 meningiomas plus:
   a) unilateral vestibular schwannoma at age < 30 yrs
   b) schwannoma
c) glioma
d) juvenile lens opacity
• patients > 60 years with bilateral CN8 masses are unlikely to have NF2 (NF2 usually presents before age of 40 years).

DIAGNOSIS
Early detection of tumors improves long-term outcome!

Genetic testing
Molecular analysis to detect mutation (if mutation unknown, detection rate only ≈ 65%).
when mutation is known → offer screening for family members* (if mutation unknown, *only after vigorous informed consent process
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prenatal diagnosis is possible! (if mutation is found or linkage analysis is successful in positive family); e.g. in vitro fertilization → preimplantation genetic diagnosis → transfer of unaffected embryos.

Annual eye examinations (start in children).

Annual BAER screening - identification of early hearing loss (latency abnormalities before mass is detectable on MRI).

MRI is preferred technique for monitoring NF2 patients (in addition to annual neurologic exam).

• annual monitoring with head MRIs begin in teens → through late 50s.

• spinal MRI only for symptomatic cases.

*only after vigorous informed consent process

A. Bilateral acoustic schwannomas (arrows), the diagnostic hallmark of NF2.

B. Multiple meningiomas presenting as contrast-enhanced masses,


Contrast T1-MRI – bilateral internal auditory canal-enhancing masses (CN8 schwannoma) + en plaque meningiomas anterior to brainstem:

Contrast T1-MRI - bilateral internal auditory canal-enhancing masses (CN8 schwannoma) + en plaque meningiomas anterior to brainstem:

Contrast T1-MRI - large enhancing sellar meningioma (black arrows) surrounding both internal carotid arteries; enhancing tissue in ethmoid air cells also represents meningioma extending through ethmoids plain: small, round, enhancing extra-axial mass posterior to tectum (white arrow) – CN4 schwannoma:

Contrast T1-MRI – large left cerebral convexity meningioma with meningeal thickening over falx cerebri + bilateral CN8 schwannomas (arrowheads):

Contrast T1-MRI – bilateral internal auditory canal-enhancing masses (CN8 schwannoma) + en plaque meningiomas anterior to brainstem:

Contrast T1-MRI – enhancement extra-axial meningioma (arrow) anterior to cord; complex enhancing mass (arrowheads) represents conus ependymoma filling spinal canal:

Contrast T1-MRI – large left cerebral convexity meningioma with meningeal thickening over falx cerebri + bilateral CN8 schwannomas (arrowheads):

A. T1-MRI – extraxial mass that extends into widened internal auditory canal, displacing pons (arrows).

B. Contrast T1-MRI – intense enhancement of CN8 schwannoma (white arrow); left CN5 schwannoma - abnormal enhancement (black arrow).
TREATMENT
- see specific tumors p. Onc60 >>, p. Onc62 >>
  • radiotherapy has additional risk!
  N.B. be aware of risk associated with stereotactic radiosurgery for treating benign lesion in patients genetically predisposed to malignancy
  • ERLITZENIB - therapeutic activity for progressive vestibular schwannoma in NF2.
  • if patient lost hearing on one side → consider internal auditory canal decompression for hearing maintenance.

PROGNOSIS
- risk factors for mortality:
  1) care not at tertiary centers
  2) young age at diagnosis
  3) presence of intracranial meningiomas
  4) type of NF2 mutation

SCHWANNOMATOSIS (NEURILEMOMATOSIS)
  - sporadic (sometimes Autosomal Dominant*) disorder - multiple schwannomas (spinal, cutaneous and cranial nerve) without vestibular schwannomas or other manifestations of NF2 or NF1.
  * familial cases represent only 10–15%; gene unknown (different than NF2 but still on chromosome 22)
  • associated with inactivation of NF2 gene in tumors but not in germline.
  • almost as common as neurofibromatosis type 2.

DIAGNOSTIC CRITERIA
Essential is exclusion of NF2 by clinical criteria and by imaging of vestibular nerves (challenging in paediatric patients, as vestibular schwannomas may develop only later in course of NF2)

Definite schwannomatosis
A. ≥ 2 (pathologically proven) schwannomas + lack of vestibular schwannomas on MRI at age > 30 years + no known constitutional NF2 mutation
B. Pathologically proven 1 schwanna + first degree relative with schwannomatosis.

Probable schwannomatosis
A. ≥ 2 (pathologically proven) schwannomas + lack of vestibular schwannomas on MRI at age < 30 years + no known constitutional NF2 mutation
B. Radiographic evidence of 1 schwannoma + first degree relative with schwannomatosis. C. ≥ 2 schwannomas at age > 45 years + no symptoms of cranial nerve VIII dysfunction + no known constitutional NF2 mutation

CLINICAL FEATURES

SCHWANNOMAS
- multiple schwannomas but not in vestibular nerves.
- cutaneous schwannomas may be plexiform.
- tumors have segmental distribution in 30% patients.
- difference from NF2: often severe pain but neurological deficits and polyneuropathy are rare
- histology: prominent myxoid stroma and intraneural growth pattern (sometimes misdiagnosed as neurofibromas)
  Marked myxoid stroma:

MRI (STIR) - multiple, bright, discrete tumors:

OTHER LESIONS
  rare: association with single or multiple meningiomas.
  no extraneural manifestations

BIBLIOGRAPHY for ch. “Phakomatoses" → follow this LINK >>