ATLAS OF NEURORADIOLOGICAL FINDINGS IN NEUROFIBROMATOSIS TYPE 1

Hasan Khosravi, Harvard Medical School Year III
Gillian Lieberman, MD
Agenda

Overview of Neurofibromatosis Type 1 (NF1):
• Pathogenesis
• Diagnosis
• Other Radiological Findings
• Menu of Tests

Neuroradiological Findings
• Case 1: Astrocytoma
• Case 2: Moyamoya Syndrome
• Case 3: Orbital Plexiform Neurofibroma
• Case 4: Spine Plexiform Neurofibroma
Neurofibromatosis Type 1 is an autosomal dominant genetic disorder caused by mutation of \(NF1\), tumor suppressor gene, on chromosome 17.

\(NF1\) gene produces Neurofibromin protein – a GTPase Activating Protein – that negatively regulates Ras pathway.

Mutation of \(NF1\) \(\rightarrow\) reduced functional protein.
Agenda

Overview of Neurofibromatosis Type 1 (NF1):
• Pathogenesis
• Diagnosis
• Other Clinical Findings
• Menu of Tests

Neuroradiological Findings
• Case 1: Astrocytoma
• Case 2: Moyamoya Syndrome
• Case 3: Orbital Plexiform Neurofibroma
• Case 4: Spine Plexiform Neurofibroma
≥2 of the following:

1. ≥6 café-au-lait (flat, uniformly pigmented) macules
2. >2 neurofibromas or 1 plexiform neurofibroma
3. Freckling in the axillary or inguinal areas
4. Optic glioma
5. Two or more iris hamartomas (Lisch nodules)
6. Distinctive bony lesion
   • Thinning of the long bone cortex
   • Sphenoid dysplasia
7. A first-degree relative with NF1
What else should we look for?

- **Intracranial neoplasms**
  - *Astrocytomas*
  - Brainstem gliomas
- **Soft tissue sarcomas**
  - Malignant peripheral nerve sheath tumor
  - Rhabdomyosarcoma
  - Gastrointestinal stromal tumor
  - Glomus Tumor
- **Bone abnormalities**
  - Bone dysplasia
  - Pseudarthrosis
  - Short stature
  - Scoliosis
- **Cognitive deficits and Learning disabilities**
- **Seizures**
- **Macrocephaly**
- **Peripheral neuropathy**
- **Hypertension**
  - From Renovascular Disease or Pheocromocytoma
- **Moyamoya Syndrome**
- Pulmonary artery stenosis, bullous emphysema, and interstitial lung disease
- Arterial dissection
Agenda

Overview of Neurofibromatosis Type 1 (NF1):
• Pathogenesis
• Diagnosis
• Other Clinical Findings
• Menu of Tests

Neuroradiological Findings
• Case 1: Astrocytoma
• Case 2: Moyamoya Syndrome
• Case 3: Orbital Plexiform Neurofibroma
• Case 4: Spine Plexiform Neurofibroma
How can we evaluate for NF1 radiologically?

- **Plain Films:**
  - Bony changes/pain
  - Bony erosions from neurofibromas
  - Scoliosis

- **CT/MRI:**
  - Deep Plexiform Neurofibromas
  - Neoplasms
    - Astrocytoma
    - Optic Glioma

- **Conventional Angiogram:**
  - Moyamoya syndrome
Agenda

Overview of Neurofibromatosis Type 1 (NF1):
• Pathogenesis
• Diagnosis
• Other Clinical Findings
• Menu of Tests

Neuroradiological Findings
• Case 1: Astrocytoma
• Case 2: Moyamoya Syndrome
• Case 3: Orbital Plexiform Neurofibroma
• Case 4: Spine Plexiform Neurofibroma
Our Patient 1: History

CC: 25 year-old female with vertigo for 3 days

HPI:
• Sits down at times and feels world is spinning
• Sensation of lightheadedness when she gets up from a seated position
• ROS: no double vision, tinnitus, facial droop, dysphagia, dysarthria, or change in taste

PMH:
• NF 1 diagnosed due to prior
  • Neurofibromas
  • Optic glioma
• ADHD
• Migraine headaches
• Restless Leg Syndrome

Clinical Examination:
• No deficits in sensation or strength
• Normal gait
• No intention tremor, dysdiadochokinesia, or dysmetria
• Negative Dix-Hallpike
# Our Patient 1: Clinical Differential for Vertigo

<table>
<thead>
<tr>
<th>Central:</th>
<th>Peripheral:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Vestibular migraine</td>
<td>• Benign paroxysmal positional vertigo</td>
</tr>
<tr>
<td>• Brainstem ischemia</td>
<td>• Vestibular neuritis</td>
</tr>
<tr>
<td>• Cerebellar infarction and hemorrhage</td>
<td>• Herpes zoster oticus</td>
</tr>
<tr>
<td>• Chiari malformation</td>
<td>• Meniere disease</td>
</tr>
<tr>
<td>• Multiple sclerosis</td>
<td>• Labyrinth concussion</td>
</tr>
<tr>
<td>• Episodic ataxia type 2</td>
<td>• Perilymphatic fistula</td>
</tr>
<tr>
<td></td>
<td>• Semicircular canal dehiscence syndrome</td>
</tr>
<tr>
<td></td>
<td>• Cogan’s syndrome</td>
</tr>
<tr>
<td></td>
<td>• Recurrent vestibulopathy</td>
</tr>
<tr>
<td></td>
<td>• Acoustic Neuroma</td>
</tr>
<tr>
<td></td>
<td>• Amnioglycoside toxicity</td>
</tr>
<tr>
<td></td>
<td>• Otitis Media</td>
</tr>
</tbody>
</table>

How can we evaluate for vertigo radiologically?

1. **CT:**
   - Evaluate osseous component in bony labyrinth, hemorrhage

2. **T2 MRI:**
   - Endolymphatic and perilymphatic spaces

3. **DWI:**
   - Acute Ischemic Changes

4. **Gadolinium MRI:**
   - Neoplastic and Inflammatory lesions
Overview of Computed Tomography (CT)

• An X-ray source rotates around a patient with multiple detectors on the opposite side, forming 2 dimensional image slices
• Radiodensity is measured in Hounsfield Units
• **Key imaging pointers:**
  • Bone is most dense at +1000
  • Acute blood is hyperdense between +55 to +70
  • White matter is less dense than gray matter – parenchyma ranges from +20 to +40
Our Patient 1: Mass on CT

Findings:
- Hyperdense lesion with hypodense center
- Surrounding vasogenic edema
MRI: Patient lies on table with all protons aligning with established magnetic field. Radiofrequency pulses excite hydrogen atoms and their realignment gives off a radio signal that generates tissue contrast.

Key imaging pointers on MRI of the Head:

- **T1:**
  - CSF – dark, White matter – white, Gray matter – gray, Vessels - dark

- **T1 with contrast:**
  - CSF – dark, White matter – white, Gray matter – gray, Vessels – bright
  - Contrast evaluates for blood-brain barrier breakdown

- **T2:**
  - CSF – bright, White matter – gray, Gray matter – white, Vessels – dark
  - Watery, cystic material – bright
Our Patient 1: Mass on T1 MRI

Findings:

- 3.1 x 3.1cm isointense lesion on T1 with heterogenous post-contrast enhancement
Findings:
- Hyperintense lesion
- Broad based with ill-defined borders
- Small cystic internal changes
- Small zone of edema and mass effect effacing adjacent sulci
Differential Diagnosis for Isointense T1 and Hyperintense T2 Lesions:

• Cerebritis
• Glial Tumor
• Nonhemorrhagic Infarction
• Lymphoma
• Meningioma
• Metastasis
• Pituitary Adenoma
Diagnosis: Report from biopsy showed a Grade IV Glioblastoma

Prognosis: For grade IV glioblastomas diagnosed in the US in 1995 to 2008, 1 year and 5 year survival rates were 35 and 5 percent, respectively.

Treatment: Right frontal craniotomy with tumor resection

Outcome: Vertigo improved but did not resolve completely
Our Patient 1: Overview of Glioblastoma Findings

1. CT:
   - Hyperdense
   - Irregular hypodense center representing necrosis
   - Mass effect
   - Vasogenic edema around lesion

2. MRI T1:
   - Hypo/isointense mass
   - Central heterogenous signal representing necrosis

3. MRI T1 with Contrast:
   - Variable enhancement with blood-brain barrier breakdown

4. T2/FLAIR:
   - Hyperintense
   - Surrounded by vasogenic edema

5. DWI/ADC
   - Elevated signal due to diffusion restriction

6. PET:
   - FDG accumulation
Agenda

Overview of Neurofibromatosis Type 1 (NF1):
• Pathogenesis
• Diagnosis
• Other Clinical Findings
• Menu of Tests

Neuroradiological Findings
• Case 1: Astrocytoma
• **Case 2: Moyamoya Syndrome**
• Case 3: Orbital Plexiform Neurofibroma
• Case 4: Spine Plexiform Neurofibroma
Patient 2: History

**CC:** 34 year-old female presents for routine follow-up imaging of NF1

**HPI:**
• No new complaints, doing well

**PMH:**
• NF1 with Lisch nodules, café-au-lait spots, and neurofibromas over bilateral upper and lower extremities, trunk, and back. She has bilateral axillary freckling.

**Clinical Examination:**
• Normal neurologic exam
Patient 2: 34-year-old female with history of NF1 presents for follow up

MRI Imaging Results:
• FLAIR/T2 hyperintensities involving periventricular and subcortical white matter on left
• Attenuated Internal Carotid Arteries bilaterally

Follow-up MR Angiogram showed:
• Diminutive distal left M1 segment of Middle Cerebral Artery (MCA)
• M2 branches of MCA were opacified from collateral circulation
• These findings raised suspicion for Moyamoya Syndrome
Patient 2: 34-year-old female with history of NF1 presents for follow up

Need better evaluation of vasculature! Answer: conventional angiography

What is conventional angiography?
- Visualization of vessels after injection of radio-opaque contrast with subsequent fluoroscopy
Our Patient 2: Moyamoya Imaging

Findings:

- Extensive tortuous collateral vascular formation
- Supraclinoid segment of ICA is occluded
- Less collateral filling of ACA and MCA territories
- Classification - Suzuki Stage IV Moyamoya
Our Patient 2: Moyamoya Imaging

Findings:
- Multiple small tortuous collateral vessels
- ICA is stenotic prior to bifurcation
- MCA is not well visualized
- Classification Suzuki Stage III Moyamoya
Moyamoya & NF1 Overview

- Moyamoya: Japanese for “something hazy, like a puff of cigarette smoke”
- Idiopathic stenosis of internal carotid artery and development of collateral vasculature
- Predisposes to ischemic symptoms, transient ischemic attacks, seizure, hemorrhage, headache, or aneurysm development
- Prevalence in NF1 = 0.6%

From getthesmokeout.com

Grading system used to monitor progression of Moyamoya based off conventional angiography:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Narrowing of ICA apex</td>
</tr>
<tr>
<td>II</td>
<td>Initiation of moyamoya collaterals</td>
</tr>
<tr>
<td>III</td>
<td>Progressive ICA stenosis with intensification of moyamoya-associated collaterals</td>
</tr>
<tr>
<td>IV</td>
<td>Development of ECA collaterals</td>
</tr>
<tr>
<td>V</td>
<td>Intensification of ECA collaterals and reduction of moyamoya-associated vessels</td>
</tr>
<tr>
<td>VI</td>
<td>Total occlusion of ICA and disappearance of moyamoya-associated collaterals</td>
</tr>
</tbody>
</table>

Image from NEJM
Goal: Revascularize areas that are not well-perfused by the ICA, preventing future ischemic stroke

Treatment Modalities:

• Medical Therapy:
  1. Antiplatelet agents
  2. Calcium channel blockers especially for headaches

• Surgery:
  1. Direct
     • A branch of the external carotid artery is anastomosed to a cortical artery.
  2. Indirect
     • Placing vascularized tissue, by the external carotid artery, near the brain
     • Examples: Pial synangiosis, encephaloduroarteriosynangiosis, encephalomyoarteriosynangiosis
What is pial synangiosis?

Surgeons suture the superior temporal artery to the pia mater to reestablish blood flow as demonstrated on the right.
Our Patient 2: Prognosis and Treatment

• **Prognosis:**
  - Review of 143 patients
    - Incidence of stroke before pial synangiosis: 67%
    - Incidence of stroke perioperatively: 7.7%
    - Incidence of stroke after 1 year follow-up: 3.2%
    - Long-term risk of stroke: 4%

• **Treatment:**
  - No treatment until patient became symptomatic and started experiencing headache and word-finding difficulty.
  - Pial synangiosis was performed.
  - Our patients’ symptoms were resolved, and she has had no seizures or complications.
Our Patient 2: Menu of Tests

1. CT:
   • Hypodensity – stroke

2. MRI:
   • Reduced flow voids in internal, middle, and anterior cerebral arteries with prominent flow voids from collateral vessels

3. FLAIR:
   • Diminished blood flow

4. DWI:
   • Acute infarct, hyperintense

5. Angiography – Definitive Diagnosis:
   • Stenosis of distal intracranial ICA, extensive collaterals at the base of the brain (“puff of smoke”)

Agenda

Overview of Neurofibromatosis Type 1 (NF1):
- Pathogenesis
- Diagnosis
- Other Clinical Findings
- Menu of Tests

Neuroradiological Findings
- Case 1: Astrocytoma
- Case 2: Moyamoya Syndrome
- Case 3: Orbital Plexiform Neurofibroma
- Case 4: Sacral Plexiform Neurofibroma
Our Patient 3: History

**CC:** 39-year-old male with history of NF 1 who presents with large head on examination and blindness in the right eye.

**HPI:**
- He was born with a blind right eye.
- He has had multiple neurofibromas on his neck, chest, and thighs.
- ROS: Occasional vertigo

**PMH:** NF1, renal tumor with hematuria

**Clinical Examination:**
- Visual acuity is normal on left and blind on right.
- Visual field is full on left.
- Optic disk on the left is normal, and the right optic disk is white and atrophic.
- Extraocular movements are intact.
- Pupils react normally to light, both directly and consensually.
Case 3: 39-year-old male with history of NF 1 who presents with large head on examination and blindness in right eye

What are we most concerned about?
Case 3: 39-year-old male with history of NF 1 who presents with large head on examination and blindness in right eye

What are we most concerned about?

Possible Optic Glioma
What is an Optic Glioma?
• Low grade pilocytic astrocytoma

Typical Clinical Presentation:
• Decreased vision
• Proptosis
• Raised intracranial pressure

Menu of Tests for Optic Glioma:
1. CT
   • Enlarged optic nerve
2. T1 with Contrast
   • Hypointense/isointense relative to optic nerve
   • Fusiform enlargement
3. T2 MRI
   • Hyperintense with low signal peripherally

Example Patient with Fusiform Optic Glioma on T2 Axial MRI
Case courtesy of Dr Arthur Daire, Radiopaedia.org
Our Patient 3: Imaging of Orbital Mass

Findings:
- Infiltrating extraconal mass (5.6 x 2.9 cm) in right periorbital area, extending posteriorly to orbital apex
- Hypointense T1 with heterogeneous post contrast enhancement.
- Symmetric bilateral optic nerves
Differential Diagnosis for Extraconal Periorbital Mass on Imaging:

- Neurofibroma
- Bone Neoplasm
- Lymphoma
- Orbital Abcess
- Osteomyelitis
- Pagets
- Trauma
What are plexiform neurofibromas?

- Benign tumor composed of Schwann cells, fibroblasts, perineural cells, and mast cells
- Major cause of morbidity and disfigurement
- Prevalence in NF1 = 50%

Plexiform Neurofibroma
Image from UpToDate
**Diagnosis:** Patient had a plexiform neurofibroma that extended into the right optic canal causing optic neuropathy.

**Prognosis:** Optic neuropathy was irreversible.

**Treatment:** Patient had a right anterior orbitotomy with debulking of the right upper eyelid and anterior orbit lesion.

**Outcome:** Plexiform neurofibroma was resected; however, the patient still experiences blindness in right eye.
1. **Plain film:**
   - Widening of neural foramina

2. **CT:**
   - Soft tissue masses of hypodensity due to endoneural myxoid matrix

3. **T1:**
   - Hypointense mass with hyperintense septations from myelinated axons

4. **T2:**
   - Hyperintense due to myxoid matrix with occasional hypointense central focus
Agenda

Overview of Neurofibromatosis Type 1 (NF1):
• Pathogenesis
• Diagnosis
• Other Clinical Findings
• Menu of Tests

Neuroradiological Findings
• Case 1: Astrocytoma
• Case 2: Moyamoya Syndrome
• Case 3: Orbital Plexiform Neurofibroma
• Case 4: Spine Plexiform Neurofibroma
Our Patient 4: History

CC: 31-year-old male with several months of right side lower back pain radiating to his buttock, posterior thigh, and calf

HPI:
- Treating chronic pain with carbamazepine, duloxetine, gabapentin, pregabalin, and topiramate with little results
- ROS: No bowel or bladder incontinence.

PMH:
- NF1 with seizures

Physical Examination:
- Normal gait with full range of motion and some stiffness.
- Straight leg test is negative bilaterally.
- No tenderness to palpation of sacroiliac joint.
- No pain with manipulation of hip.
Our Patient 1: Clinical Differential for Lumbosacral Radiculopathy

- Herniated disc
- Neurofibroma
- Nonradicular back pain
- Spinal stenosis
- Cauda equina syndrome
- Diabetic amyotrophy
- Lumbosacral plexopathy
- Mononeuropathy
Our Patient 4: Enlarged Nerve Roots on T1 MRI

Findings:
- Multiple enhancing masses along exiting spinal nerve roots
- Hypointense on T1 and hyperintense on T2 with central hypointensity.
- Bilateral foraminal masses with extraforaminal extension along anterior sacrum and superficial iliacus
Our Patient 4: Imaging Differential

Differential for Enlarged Nerve Roots:

- Neurofibromas
- Charcot-Marie-Tooth
- Guillain Barré
- Langerhans cell histiocytosis
- Leptomeningeal carcinomatosis
- Leukemia
- Lymphoma
- Neuritis
- Sarcoidosis
- Toxic Neuropathy
Our Patient 4: Diagnosis, Prognosis, and Treatment

**Diagnosis:** Multiple plexiform neurofibromas

**Prognosis:** May transform into malignant peripheral nerve sheath tumors

**Treatment:** Patient referred to pain clinic and physical therapy. Patient was lost to follow up.
Goal: Surgical removal if significantly disfiguring or compressing airway

Limited studies on medical therapies such as chemotherapy

Current clinical trials include:

- Carboplatin
- Imatinib
- Pegylated Interferon
- Sirolimus
- Pirfenidone
- Farnesyl transferase inhibitors
Summary

1. You saw an atlas of neuroradiological findings in NF1 including:
   - Grade IV Glioblastoma
   - Moyamoya syndrome
   - Plexiform Neurofibromas
   - Optic Glioma

2. You looked at three imaging modalities including:
   - CT
   - MRI
   - Conventional Angiography

3. You reviewed anatomy on imaging including:
   - Neuroanatomy
   - Neurovasculature and anatomy of the Internal Carotid Artery
Image Gallery

Index Patient 1: Glioblastoma

Example Image: Optic Glioma

Case Companion 2: Moyamoya Syndrome

Case Companion 3/4: Plexiform Neurofibromas
References


Acknowledgements

Thank you for your teaching, guidance, and support.

   Dr. Ning Lu

   Dr. Gillian Lieberman