The Brain and NF1

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No conflicts of Interest

NF-1

DR. MOODLEY

- Overview
  - **NIH Diagnostic criteria**
  - Revised diagnostic criteria
- Neurologic findings
  - Cognitive disorders
  - UBOs
- Vascular complications
  - Moya moya disease

DR. HARROD

- Tumors in NF-1
  - Overview
  - Management
  - Outcomes
  - Prognosis

Overview of NF1

- Neurofibromatosis is a term for 4 distinct genetic neurocutaneous disorders:
  - NF1
  - NF2
  - Segmental / mosaic NF
  - Schwannomatosis

Overview of NF1 cont'd

AD with great variability of clinical expression and many features show age-dependent penetrance.

Spontaneous mutation rate

- About 50%

Birth incidence of 1 in 3000 – 4000

Currently > 100,000 people in the USA

- More common than DMD or CF.

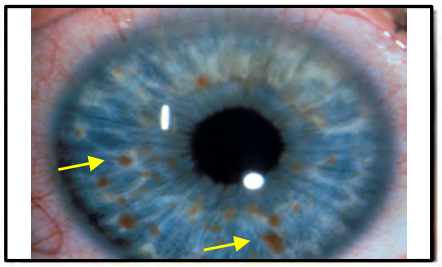
Multisystemic disorder

PNS, CNS, Skin, Bone, Endocrine, G.I. and Vascular system

Clinical Features

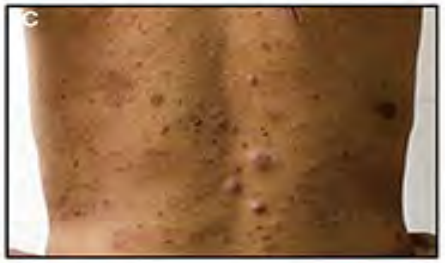
• Cafe-au-lait spots	>95%
• Lisch nodules	>95%
• Neurofibromas	>90%
• Skin fold freckling	85%
• Learning disability	60%
• Family history	46%
• Macrocephaly	45%
• Optic Glioma	20%
• Scoliosis	20%
• Seizures	13%
• Hemihypertrophy	13%
• Vascular disease	9%

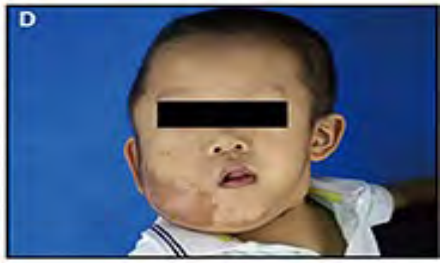
Lisch nodules



CALS

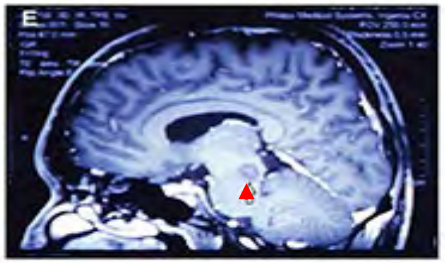
Neurofibromas

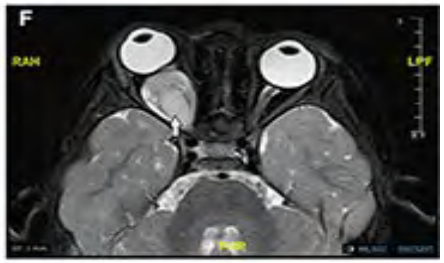




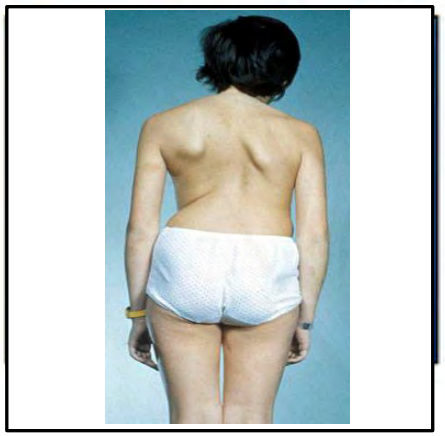
Plexiform neurofibromas

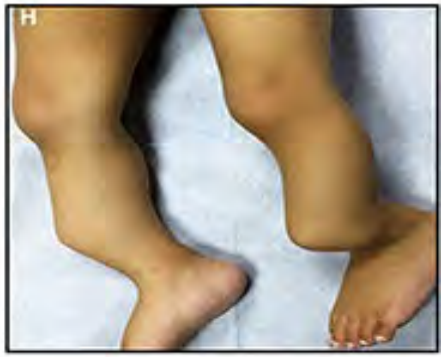
Optic Gliomas





Scoliosis

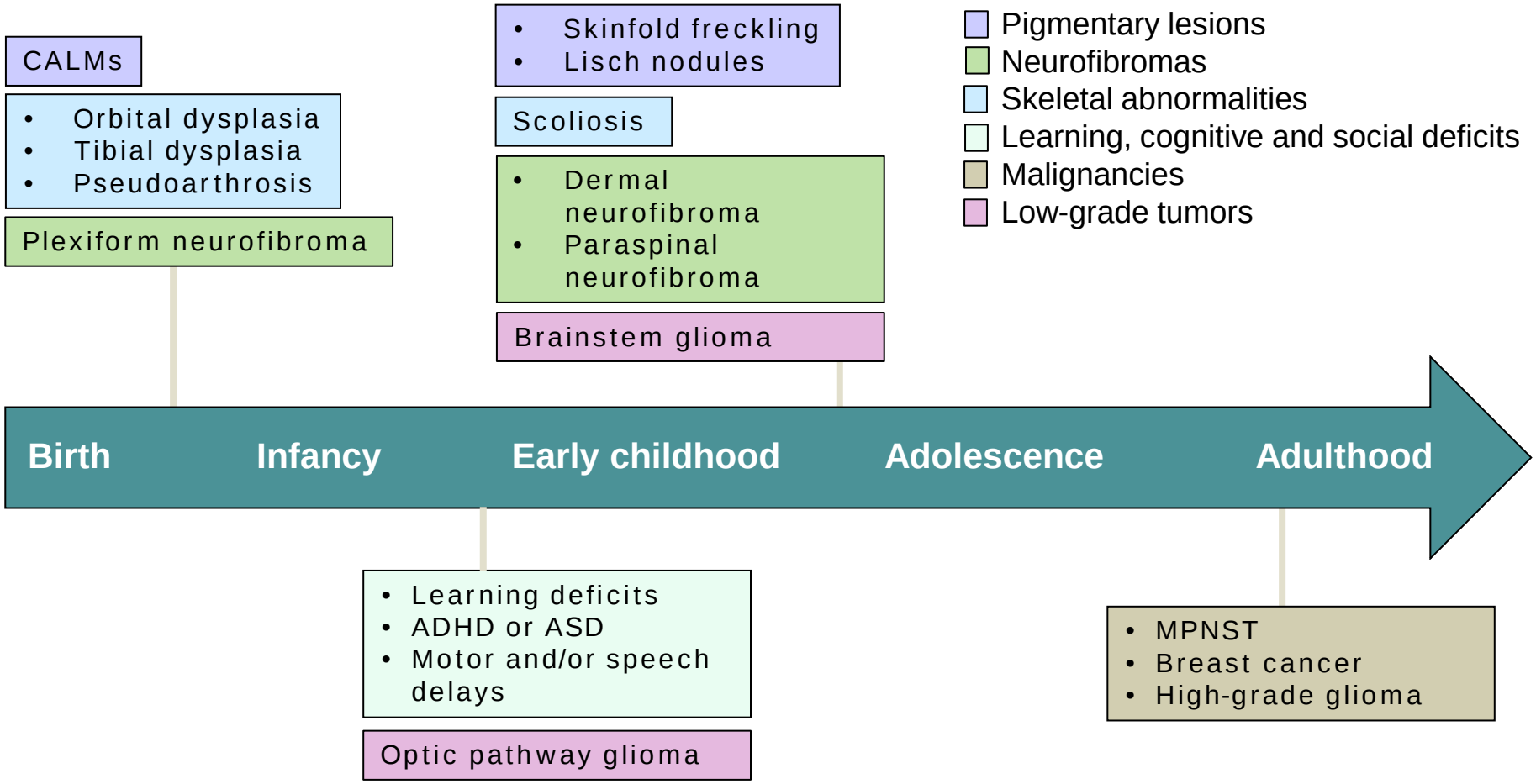




Pseudoarthrosis of the Tibia

Wang W, Wei C-J, Cui X-W, Li Y-H, Gu Y-H, Gu B, Li Q-F and Wang Z-C (2021) Impacts of NF1 Gene Mutations and Genetic Modifiers in Neurofibromatosis Type 1. Front. Neurol. 12:704639.

Development of clinical features of NF1



Nature Reviews Disease Primers volume 3, Article number: 17004 (2017)

Clinical diagnostic criteria (NIH 1987)

1. Six or more CALMs equal to or greater than 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in postpubertal patients
2. Two or more neurofibromas of any type or 1 plexiform neurofibroma
3. Freckling in the axillary or inguinal regions (Crowe sign)
4. Optic glioma (OPG)
5. Two or more iris hamartomas (Lisch nodules) (Fig 1)
6. A distinctive osseous lesion, such as sphenoid wing dysplasia or long-bone dysplasia (with associated cortical thickening and medullary canal narrowing), with or without pseudoarthrosis
7. A first-degree relative (parent, sibling, or child) with NF1 according to the aforementioned criteria

Neurologic Findings

1. Progressive

- **CNS tumor**
- **Spinal tumors**
- **Cerebrovascular disorder (MMD)**
- **Hydrocephalus**

2. Static

- **Learning disorder**
- **Neurodevelopmental delay**
- **Behavior disorder**
- **Seizures**
- **Headaches**
- **Macrocephaly**

Mental function and UBOs

About 10% have mental impairment

40 - 50% have ADHD

40- 60% have specific learning disability

High association with ASD (30%)

Etiology: Unknown

UBO

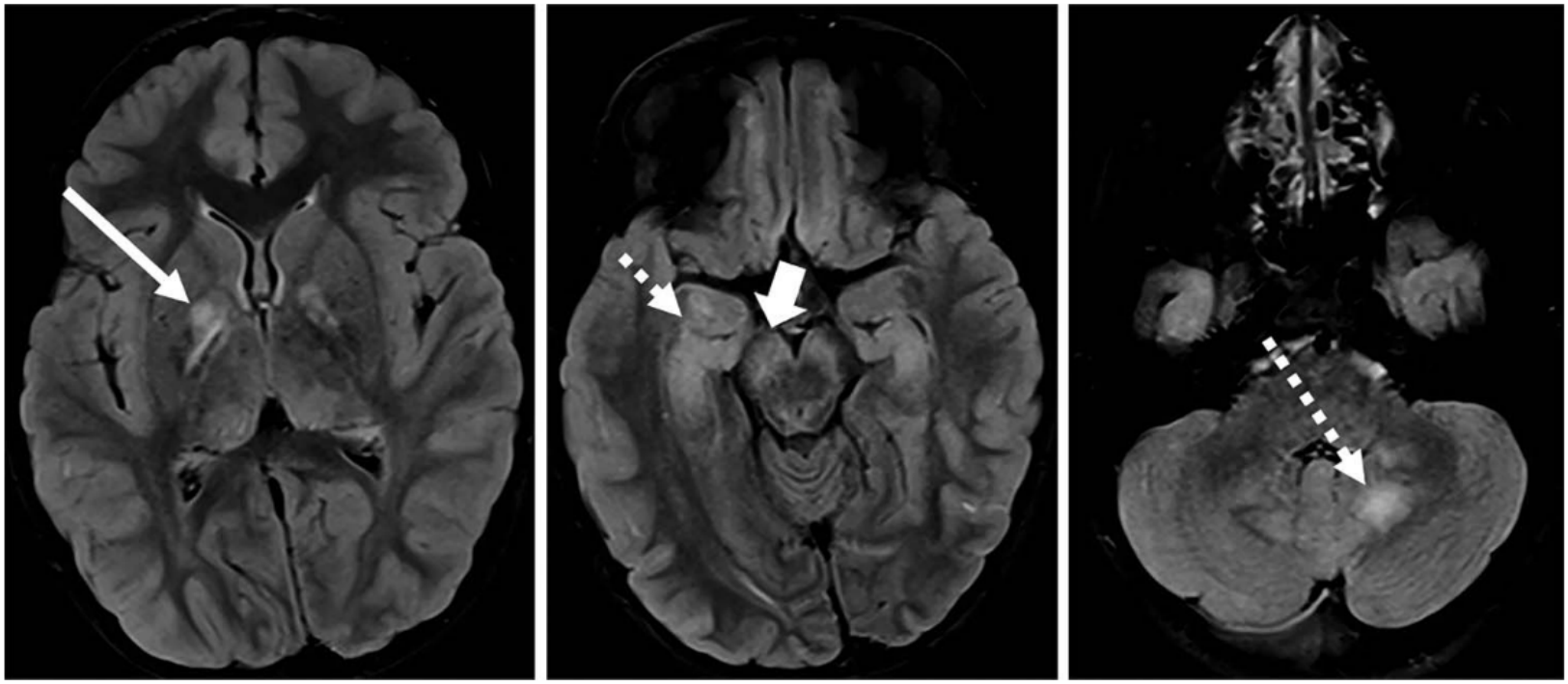
Non-neoplastic UBOs may represent potential biomarkers for cognitive and behavioral dysfunction in NF1. However, different studies haven't found this association.

UBOs

- **43 to 93% of NF1 patients show UBOs**
  - Focal areas of high signal intensity (the so-called Unidentified Bright Objects (UBOs) on cerebral magnetic resonance).
- **DeBella proposed this finding in the year 2000 as a new diagnostic sign**
  - Affecting primarily basal ganglia, thalami, medial temporal lobes, cerebellar hemispheres, or brainstem: NF1

Neurology: Clinical Practice August 2018 vol. 8 no. 4 283-291
Tadini, G, Legius, E, Brems, H. Multidisciplinary Approach to Neurofibromatosis Type 1, Springer, 2020

Typical UBOs in an NF1 patient



Globus pallidus

Hippocampus/medial temporal lobe

Cerebral peduncles

Neurology: Clinical Practice August 2018 vol. 8 no. 4 283-291

Neurodevelopment

- May have mild motor developmental delay
  - Hypotonia-improves
- Increased speech/language issues, velopharyngeal insufficiency, misarticulation and disfluency .
  - Hearing: usually normal
- About 50% have some type of learning problem
  - Intellectual Disability→ minority (if present, suspect chromosomal microdeletion)
- Social difficulties: common, anxiety and problems with coping
  - Unknown rate of autism, suspected increased susceptibility in NF1 patients
  - Evaluation and management therapists/psychologists

Miller DT, Freedenberg D, Schorry E, et al. AAP Council on Genetics, AAP American College of Medical Genetics and Genomics. Health supervision for children with neurofibromatosis type 1. Pediatrics. 2019;143(5): e20190660

Learning Disability and other cognitive disorders

- About 75% of NF1 children
  - Academic deficiency (maths, reading, etc), motor skill impairment, ADD/ADHD (50%), intellectual disability.
  - 504 accommodation plan/individualized education program

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Seizures and headaches

- Increased susceptibility to develop seizures.
  - Might be due to structural or vascular changes.
- Can occur at any age, usually focal, raise concern for focal CNS lesion
- Headaches: often migraine, more common in NF1
  - Imaging usually not needed, usually controlled with treatment

Miller DT, Freedenberg D, Schorry E, et al. AAP Council on Genetics, AAP American College of Medical Genetics and Genomics. Health supervision for children with neurofibromatosis type 1. Pediatrics. 2019;143(5): e20190660

Indications for Neuroimaging studies in children with NF1

- Focal sensory or motor symptoms
- New onset of seizures
- Headaches that are increasing in frequency or severity
- Signs of increased intracranial pressure (headaches, visual disturbance, increased lethargy)

Miller DT, Freedenberg D, Schorry E, et al. AAP Council on Genetics, AAP American College of Medical Genetics and Genomics. Health supervision for children with neurofibromatosis type 1. Pediatrics. 2019;143(5): e20190660

Indications for Neuroimaging studies in children with NF1

- Stroke-like symptoms
- Decline in visual acuity or visual field abnormalities
- Precocious puberty or accelerated growth
- Head and neck plexiform neurofibromas increasing in size or with new development of pain

Miller DT, Freedenberg D, Schorry E, et al. AAP Council on Genetics, AAP American College of Medical Genetics and Genomics. Health supervision for children with neurofibromatosis type 1. Pediatrics. 2019;143(5): e20190660

Vascular complications

- Vasculopathy: **significant but underrecognized** complication of NF1
  - Up to 20% of NF1 patients may develop hypertension.
- Arterial and venous blood vessels of all sizes.
- Neurofibromin: expressed in endothelial and smooth muscle cells of blood vessels, likely to be involved in the pathogenesis NF1-vasculopathy.

Ghosh, PS, Rothner,D, Emch, T, Friedman, NR, Moodley M. Journal of Child Neurology 28(1) 95-101
Pediatric Neurology 120 (2021) 18e26 Contents

Vascular complications

- **NF1 vasculopathy**
  - Stenosis or occlusion of the vessels →cerebral or visceral infarcts, aneurysms (hemorrhage), or AV fistulae.
  - Most NF1 patients with vasculopathy are asymptomatic
  - Increased mortality has been reported in patients with NF1 and vasculopathy.
  - Characteristic NF1 vascular lesions: in the entire arterial tree, but involvement of the renal arteries with consequent hypertension is most common.
  - Cerebral vascular lesions are patchy in distribution (multiple)

Clinical Characteristics of Children With Neurofibromatosis Type 1–Associated Cerebral Vasculopathy

- Fifteen (4.8%) patients, from 312 (78%) that underwent brain MRI, had cerebral vasculopathy.
  - The mean age at diagnosis of neurofibromatosis type 1 was 4.3+3.5 years (1-12 years)
  - 53.3 % were boys
  - The mean age at the time of diagnosis of their vasculopathy was 11.7 + 7.3 years (2-18 years).
- The indications for neuroimaging were headache (5), seizures (2), brain tumor (1), and screening for intracranial complications (7).
- None of the patients had focal neurologic deficits or complications attributable to their vasculopathy at presentation or at the time of the radiology follow-up.

Journal of Child Neurology 28(1) 95-101

Modalities for evaluation

- AHA, 2008: recommended routine vascular screening with MRA in children with high-risk and relatively common disorders on the management of stroke, known to cause moyamoya syndrome.
- Conventional angiography
  - Gold standard. Highest spatial resolution (small vessels)
  - Risks: 0.7% of stroke
- Magnetic Resonance angiography (MRA)
  - No ionizing radiation. Non invasive
- Computed tomographic angiography (CTA)
  - Use of contrast and high-dose ionizing radiation. Non invasive

Ghosh, PS, Rothner,D, Emch, T, Friedman, NR, Moodley M. Journal of Child Neurology 28(1) 95-101
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Moyamoya disease

- Chronic progressive steno-occlusive arteriopathy of the distal internal carotid artery, and less often, stenosis of the proximal anterior cerebral artery and middle cerebral artery, basilar artery and the posterior cerebral arteries.
  - May involve extracranial carotid and vertebral arteries as well

- Clinical presentation:
  - Transient ischemic attacks (TIAs), strokes, headaches, or cognitive decline.
  - Asymptomatic
  - Clinico-radiologic dissociation: Radiological progression without development of clinical symptoms

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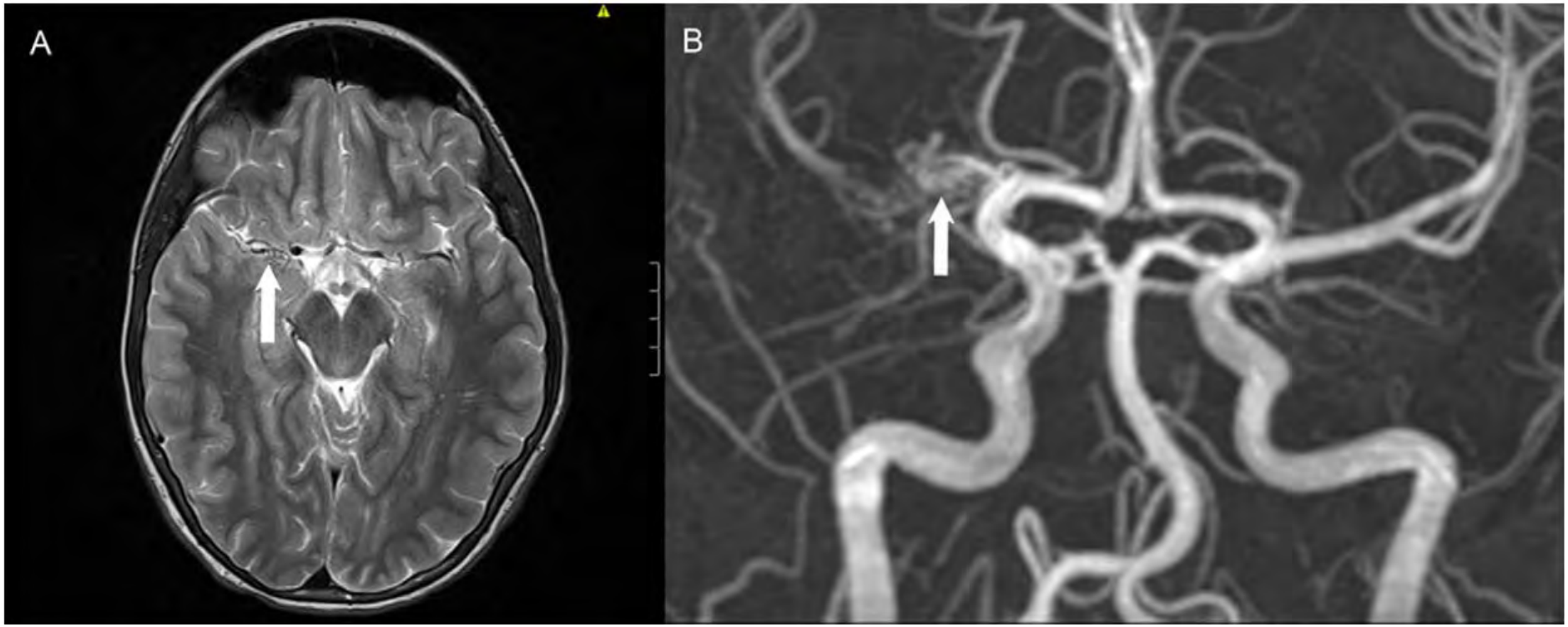

MRI of brain on T2-weighted image showing loss of flow void signal along the course of the right middle cerebral artery proximal segment being replaced by mesh of vessels (A); corresponding magnetic resonance angiography showing occlusion of middle cerebral artery with moyamoya changes (B)

MRI/MRA

- Disadvantages: Timing, Sedation/anesthesia, Resources and logistics
- Imaging findings: might be subtle and may be overlooked→ **awareness**
  - **Early detection-timely intervention**
  - MRI + MRA = better delineation of intracranial vasculopathy
  - Missed if MRI without MRA.
  - Consider adding MRA to MRI brain (for any indication) in children for early detection of cerebral vasculopathy.

Ghosh, PS, Rothner,D, Emch, T, Friedman, NR, Moodley M. Journal of Child Neurology 28(1) 95-101
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Treatment

- Need for treatment of NF1-vasculopathy guidelines.
- Surgical / medical
  - Revascularization surgery
  - Surgery is associated to several complications, mainly in pediatric population, surgical treatment should be considered carefully
    - Direct revascularization / encephalo-duro-arterio-synangiosis
  - Antiplatelet agents

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What's New in NF1

1. New Clinical Syndromes

2. New Clinical Criteria

3. Clinical Trials and Novel Drug therapies

1. New Clinical Syndromes

- Legius Syndrome
  - Multiple Cafe au lait spots
    - Skin fold freckling
    - Macrocephaly
    - No optic gliomas, neurofibromas or Lisch Nodules
  - Linked to mutations of *SPRED 1* Gene locus 15 q14
  - Routine NF1 gene testing should be implemented especially for sporadic cases viz Patients with no FH of NF1

2. New Clinical Criteria
(recommended changes in red)

1. CALS: 6 or more CALS (bilaterally localized)
2. Axillary and Inguinal Freckling (bilaterally localized)
3. Neurofibromas: 2 or more or 1 PNF
4. Iris Lisch Nodules: 2 or more or 2 or more choroidal abnormalities
5. Optic Pathway glioma

2. New Clinical Criteria *cont'd*

6. A distinctive osseous lesion:

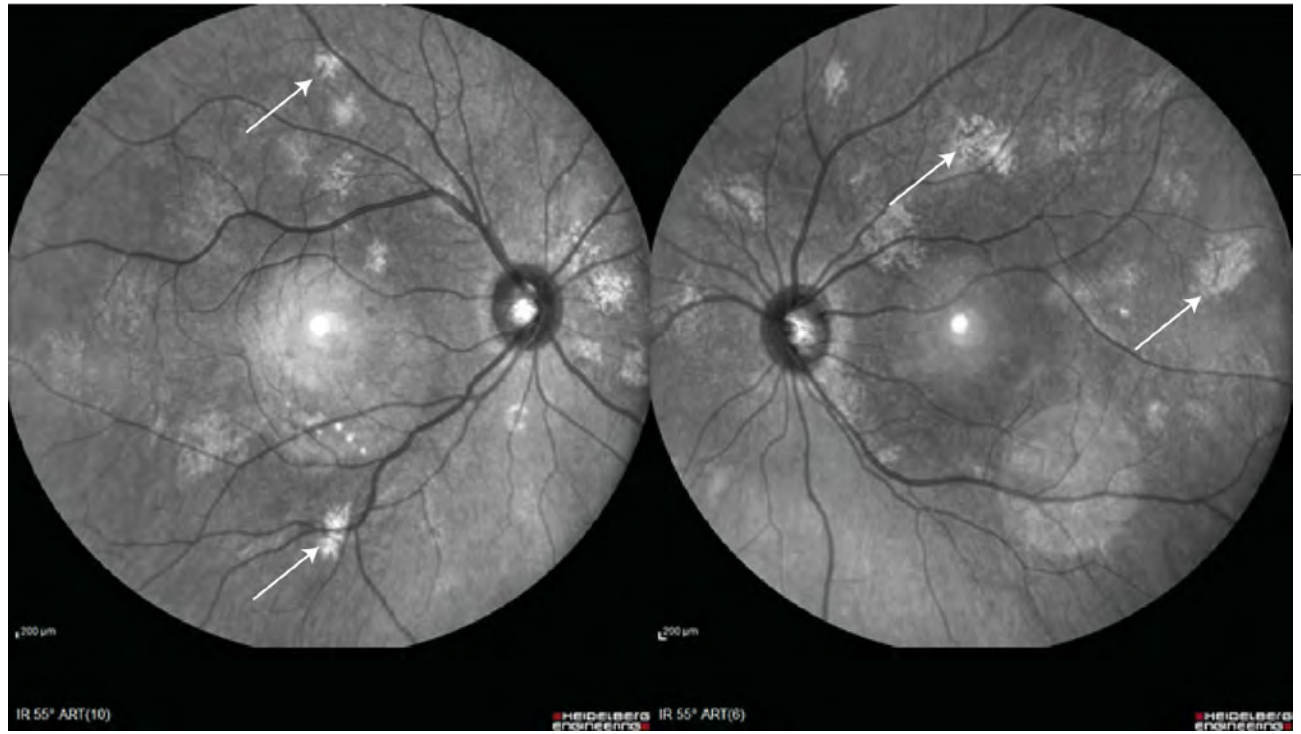
- *Sphenoid wing dysplasia*
- *Anterolateral bowing of the tibia(tibial dysplasia)*
- *Thin long bones, scoliosis*

7. A parent with NF1 by the above criteria

8. A pathogenic NF1 variant (in addition to existing criteria).

* Unilateral freckling and CALS raises concern for mosaic NF1.

Choroidal changes



Lisch nodules are present in over 90% of NF1 adult patients but only 50% in late childhood.

The recently described ophthalmological sign of **Choroidal Nodules** could be diagnostically relevant in the first years of life.

Prevalence of near-infrared reflectance detected choroidal nodules was found to be 71% in pediatric NF1 group, a much higher figure than 43% prevalence of Lisch nodules in the same group of patients

3. Clinical Trials and Novel drug therapies

The *NF1* gene encodes the protein neurofibromin which regulates the RAS signaling pathway that controls cell proliferation acting as a TSG.

Over the last 15 years there has been progress towards identifying effective drug therapies for the Neurofibromatoses via Clinical trials supported by the NIH and the CTF.

- Thalidomide, interferons, pirfenidione
- Rapamycin
- Everolimus
- Selumetinib (MEK inhibitor)
- Other drugs used include; everolimus, V/C -gliomas

Conclusions

- Diagnosis of NF1 is mainly clinical using the NIH Diagnostic Criteria

- Important role for pediatricians in improving outcomes by identifying signs leading to a diagnosis and appropriate tumor surveillance and treatment

- Imaging: indicated when there are symptoms and/or abnormalities during neurological/ophthalmological/endocrinological/orthopedic examinations.
  - More data is needed to determine when to perform surveillance imaging by whole-body or regional MRI

Conclusions

- Vascular problems in NF were thought to be minimal, but now it is known that patients with NF1 have an increased risk of developing vascular complications.

- NF1 is a lifelong condition, and some of the complications are more likely to occur among adults so developing an adult transition program is of utmost importance in the appropriate care of patients with NF1 across the timelines.


RAHMET
OBRIGADO
GRAZIE
HVALA
谢谢
KIITOS
DANKE
TAK
DANK JE
THANK YOU
SHUKRAAN
ευχαριστώ
GRACIAS
BARKA
MERCI
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