Neurofibromatosis

NF type 1 - NF type 2

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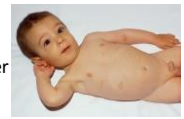
EPNS Training Course March 2015 Budapest

Personal interest

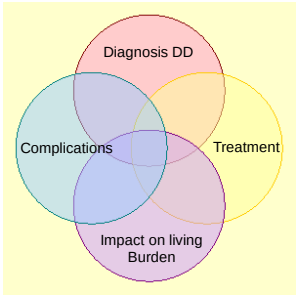
- Prompted by admission of an infant with enteritis «incidental finding» of multiple café-au-lait-spots

  Inform parents? What to tell ?
  (Supervisors decided – Not to tell)



- Literature by Vincent Riccardi – Pioneer
- Meetings with V. Riccardi and others
- Founder of Swiss NF association 1987

INFORMATION



Neurofibromatosis type 1 MIM # 162200

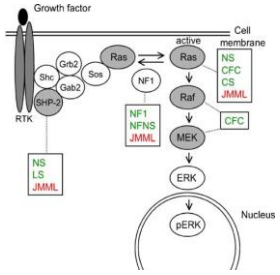
- Prevalence NF 1 ~1:3'000
- Dominant
- ~ 50% new mutations (~80% of paternal origin)
- Full penetrance - no skipping of healthy generation
- Largest (autosomal) gene on chromosome 17q11.2 complex gene
- Complex multi-system disorder

NF 1 gene product „ Neurofibromin „

Main function

- Tumor suppressor or negative growth regulator
- Negative regulator / down-regulator of Ras-MAKP pathway

→ promotion of cellular growth
proliferation
differentiation
leading to tumor formation



Kratz et al, J Mol Med 2007;85:227 (..role of mutant Ras..)

Diagnosis - Diagnostic criteria

- Diagnostic criteria (NIH consensus conference 1987)

- gene at that time not yet known (→identified 1990)
- at present these criteria still used and helpful
- a pathogenic mutation analysis is not (yet) a criterion

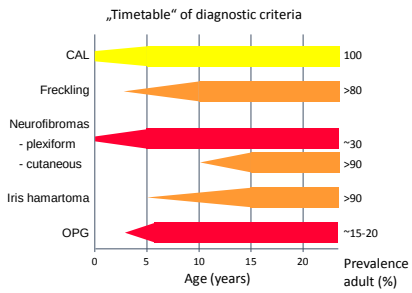
- Formal diagnosis difficult in young age
- Clinical re-evaluation may be required for confirmation

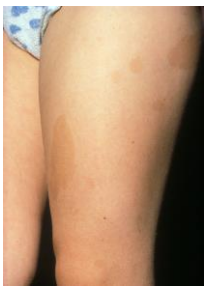
- „Problem“: most patients with SPRED1 mutations fulfil NF 1 critera

NF1 Diagnostic criteria NIH consensus conference 1987

Two or more criteria required for NF1 diagnosis:

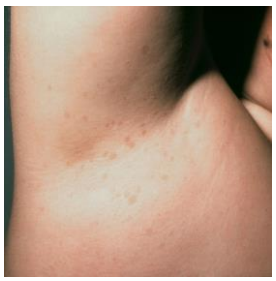
- Six or more café-au-lait spots >5mm in prepubertal, >15 mm in postpubertal individuals
- Two or more neurofibromas of any type or one or more plexiform neurofibromas
- Freckling in axilla or inguinal region
- Tumor of the optic pathway
- Two or more Lisch nodules (iris hamartomas)
- A distinctive osseous lesion such as sphenoid wing dysplasia or thinning of the long bones (with or without pseudarthrosis)
- A first degree relative with NF1 by the above criteria





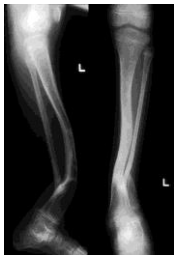
Café-au-lait spots
- Smooth contours
- Regular depth of pigmentation
- Pigmentation varies with exposure to light (summer-winter)

(CAL in DNA repair and ring chromosome syndromes have irregular contour and pigmentation depth)

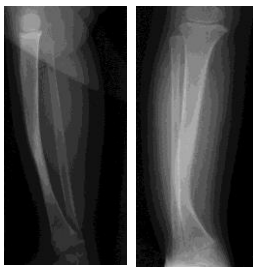


Axillary freckling

8 year old boy

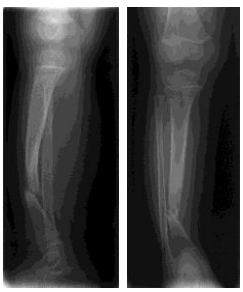


Osseous lesion in NF1 - Tibia



Infant with NF 1
Aged 13 months
Tibial bowing

1st xray



Infant with NF 1
Aged 13 months

2nd xray + 10 days

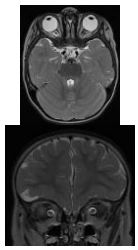
Fracture

Optic pathway gliomas Optic nerve – chiasm - retrochiasmal

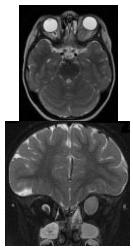
- High prevalence ~15-20%
- Low grade gliomas (pilocytic astrocytomas)
- Not congenital
- Peak ~ „preschool age“
- No newly emerging after puberty
- Majority – no visual impairment
- Minority with impairment – mostly stable (exceptions !)
- (different biological nature of OPG outside NF 1)

→ Routine neuroimaging ??
(„no role“ for initial diagnosis in asymptomatic child)
→ Impact on treatment strategies

NF 1 - OPG are not congenital

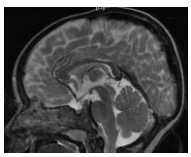


MRI at 15 months - normal

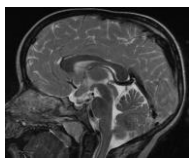


MRI + 2 y. – O N glioma

Neurofibromatosis 1 Chiasmal OPG

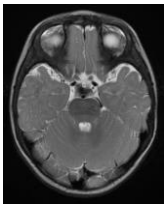


T2w sagittal MRI
Normal anatomy



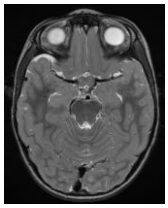
T2w sagittal MRI
Enlarged chiasm

Neurofibromatosis 1



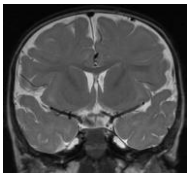
T2w axial MRI
Normal anatomy

Chiasmal OPG



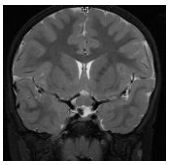
T2w axial MRI
Enlarged chiasm

Neurofibromatosis 1



T2w coronal MRI
Normal anatomy

Chiasmal OPG

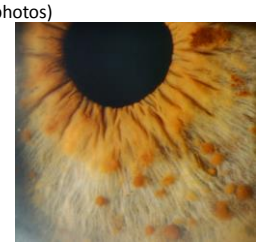


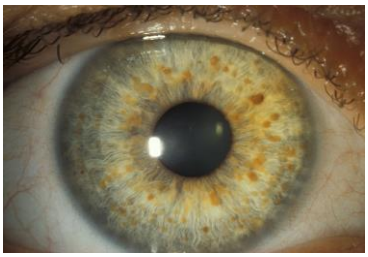
T2w coronal MRI
Enlarged chiasm

Role of ophthalmological examination

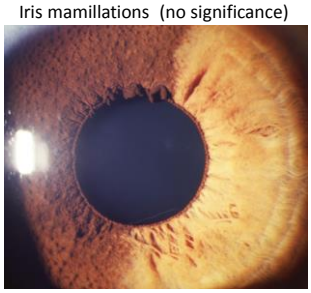
- Evidence for ***visual impairment*** ?
- Iris hamartomas ? (split lamp examination)
  Consider time table !
- Iris hamatomas – DD
  - Iris nevi / crypts
  - Iris mamillations

Iris hamartomas (Slit lamp photos)





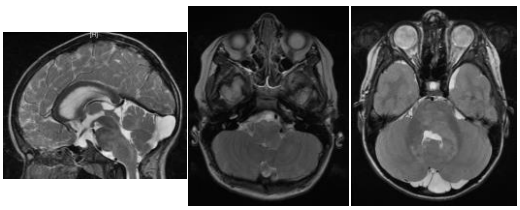
Iris mamillations (no significance)



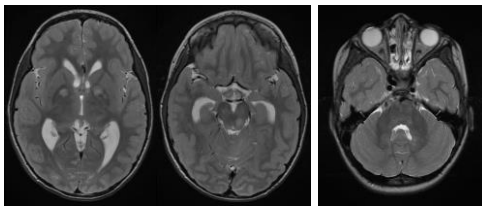
Neuroimaging

- Routine MRI in asymptomatic child – controversial
- Findings in NF 1
  - Optic pathway gliomas
  - Brainstem gliomas (similar „benign nature“)
  - UBO (Unidentified Bright Objects) - T2w hyperintensities
    - Locations: globus pallidus, brainstem, cerebellum
    - Characteristics: not enhancing, not space-occupying
    - Controversial: pathogenesis ? significance ?
    - Documented : *transient* finding ! (≠ hamartoma # tumors)

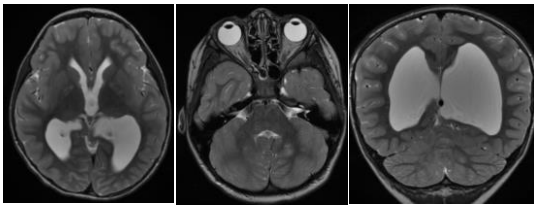
NF1 – asymptomatic brainstem glioma (incidental)



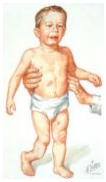
NF 1 UBO‘s in basal ganglia, thalamus, brainstem, cerebellum



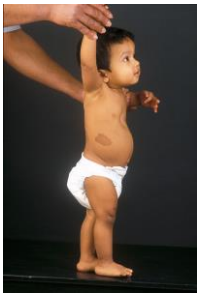
UBOs Basal ganglia (globus pallidus), brainstem, cerebellum



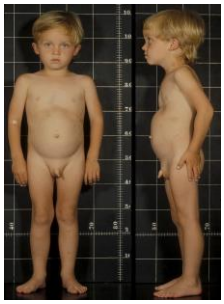
NF 1 in young children
common findings and presentation



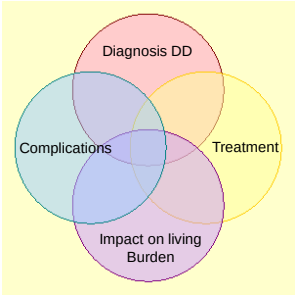
- Macrocephaly (~50%)
- Short stature
  → Growth charts for young children with NF1
  Szudeck,Birch,Friedman
  Am J Med Genet 2000;92:224-7
- Muscular hypotonia
  tendency for protuberant abdomen and funnel chest
- Developmental delay **~ 50%**
  gross motor – fine motor – language – behavior…



Small stature
Macrocephaly
Muscle hypotonia
- funnel chest
- protuberant belly

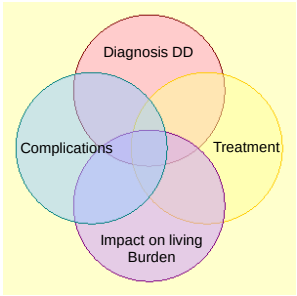


Note
funnel chest
protuberant belly



NF1 Treatment challenges (selection)

- Multiple cutaneous neurofibromas
- Plexiform neurofibromas (spec. face, feet, visceral)
- Dysplastic scoliosis
- Tibial pseudarthrosis
- Optic pathway tumors
- Other brain tumors
- Vascular dysplasias
- Malignancies (spec. MPNST)
- …..



- Developmental delay
  in general / in specific areas **~ 50%**
- Attention deficit hyperactivity disorder **~ 40-50 %**
- Learning disabilities **~ >40 %**
  „IQ-shift to the left“
- Impaired social skills and interactions

→Scholastic underachievements

→Problems with peers

→Failures…failures…frustration….

→Parental burden and stress

→Impaired quality of life

→Psychiatric disturbances

→Consequences for
vocational training - professional performance
social contacts – family planning

NF1 Burden

- Somatic complications
- Bening tumors and malignancies
- Aesthetic aspect
- Impairments in schooling, learning, professional life
  Social interaction
  Quality of life

Initial clinical examination

- Skin
- Vision
- Neurological ex. (incl. behavior)
- Skeleton
- Growth / puberty
- Blood pressure
- Developmental aspects
  Cognitive function
  Social network
- (hearing - hearing impairment is **not** a feature of NF 1)
- (epilepsy – prevalence not significantly increased)

Genetic testing

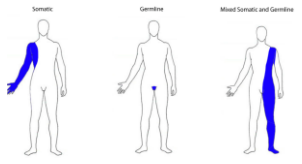
- NF 1 gene very large
- Diagnostic yield (with complementary techniques) <95%
- Poor genotype – phenotype correlation
  (rare exceptions: deletion of entire gene; 3 bp deletion in exon 17)
- Intrafamilial variability !
- Genetic testing not required for diagnosis in majority of patients (if diagnostic criteria are met)
- (Genetic testing does not outweigh lack of clinical experience)

→ Genetic testing of increasing importance

Segmental NF1

- Somatic NF1 mutation (mosaic)
- Cutaneous features of NF1 limited to one or more body segments
- Associated NF1 complications relatively uncommon
- Frequency in larger series ~5%
- Memo: most «segmental hyperpigmentations» # NF1

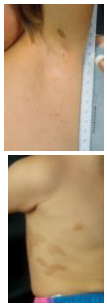
- Mutation may not be found in peripheral lymphcytes
- Mutation may be present in germ line → offspring with full NF1



Mosaicism and Clinical Genetics

NANCY B. SPINNER AND LAURA K. CONLIN

AJMG Part C 2014;166:397



Differential diagnosis (excluding „mosaic NF1)

Conditions potentially mimicking NF 1

- **Legius syndrome** [Eric Legius, Geneticist, Leuven]
- Other overlapping syndromes of Ras-MAPK pathway
  „ Neuro – cardio – facial – cutaneous syndromes“

  Leopard syndrome
  Noonan syndrome
  Costello
  …
- Lentigines syndromes

Legius syndrome MIM # 611431
Neurofibromatosis type 1 - like syndrome

- Families with „mild NF1“, no NF 1 gene mutation
- Mutations identified in **SPRED1** gene on chrom. 15q14
  Brems …*Legius* → Nature Genet 2007;39:1120
- Up to date > 200 patients reported / known
  (limited knowledge about natural history)
- ~ 1-2 % of patients in „NF clinic“ have Legius syndrome
  (Estimated prevalence ~ 1:120'000)
  (GeneReviews [updated 2015 Jan 15])

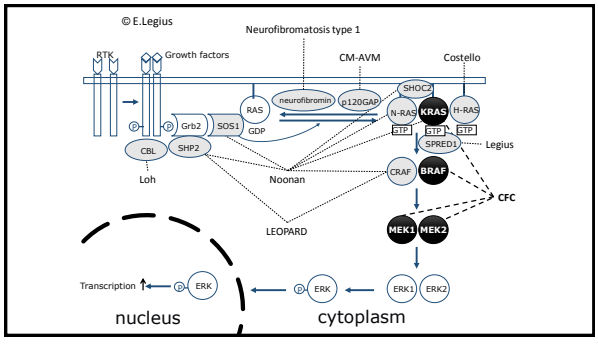
Legius syndrome

Clinical characteristics (reported findings)

- Multiple café au lait spots (consistent)
- Freckling
- Lipomas
- Macrocephaly
- Learning disability / ADHD
- Noonan-like aspect in some individuals

→ → Diagnostic criteria for NF 1 fulfiled in ~ 50% !

ABSENT Iris hamartomas
Optic pathway gliomas
Cutaneous neurofibromas



Take home messages

- NF 1 is more than a skin disorder
- Complex multisystem disease
- Many individual diagnostic and therapeutic challenges
- Burden in children relates primarily to development, learning, and behavior
- (Burden in adults: plus increased prevalence of psychiatric disorders and malignancies….)

Literature on Development – Learning – Social aspects

Krab L et al. **Helath-related qualitiy of life in children with neurofibromatosis type 1: contribution of demographic factors, disease-related factors, and behavior**. J Pediatr 2009, 154:420-425

Huibregts S et al: **Social information processing in children and adolescents with neurofibromatosis type 1**. Dev Med Child Neurol 2010,52:620-625

Lorenzo et al. **Mental, motor, and language development of toddlers with neurofibromatosis type 1**. J Pediatr 2010,

Krab L et al. **Motor learning in children with neurofibromatosis type 1**. Cerebellum 2011,10:14-21

Mautner VF, Kluwe L, Thakker SD, Leark RA. **Treatment of ADHD in neurofibromatosis type 1**. Dev Med Child Neurol 2002, 44: 164-170

Prinzie P et al. **Personality profiles of children and adolescents with neurofibromatosis type 1**. Amer J Med Genet 2003,118A:1-7

Barton B, North K. **Social skills of children with neurofibromatosis type 1**. Dev Med Child Neurol 2004, 46: 553-563

Johnson H, Wiggs L, Stores G, Husan SM. **Psychological disturbance and sleep disorders in children with neurofibromatosis type 1.** Dev Med Child Neurol 2005, 47: 237-242

Hyman SL, Shores A, North K. **The nature and frequency of cognitive deficits in children with neurofibromatosis type 1**. Neurology 2005, 65: 1037-1044

Oostenbring et al. **Parental reports of health-related qualitiy of life in young children with neurofibromatosis 1: influence of condition specific determinants**. J Pedaitr 2007,151:182-186

Krab L et al. **Impact of neurofibromatosis type 1 on school performance**. J Child Neurol 2008,23:1002-1010

Graf A, Landolt MA, Mori AC, Boltshauser E

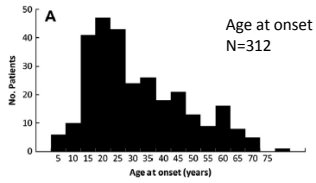
Quality of life and psychological adjustment in children and adolescents with neurofibromatosis type 1.

J Pediatr 2006;149:348-343

NF2

NF2 – general information

- Prevalence ~ 1:40'000
- Genetics
  Dominant
  > 50% de novo (~ 25-30% mocaic, with later onset and milder course)
- Gene locus chromosome 22q12
- Age at onset
  average 18-34 years (range: birth – 70y)
  in large series ~ 20% onset before 16 years (NOT with hearing loss)
  type of mutation affects age of onset
- Diagnostic criteria
  Manchester modification (of NIH consensus)



Age at onset in Japanese series
N=312

Matsuo et al Brain Dev 2014;236:148-152
Characterization of early onset neurofibromatosis type 2

NF2 Diagnostic criteria

TABLE 1. Clinical Diagnostic Criteria for Neurofibromatosis Type 2*

A. Bilateral vestibular schwannomas
B. First-degree family relative with NF2 *and* unilateral vestibular schwannoma *or* any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities†
C. Unilateral vestibular schwannoma *and* any two of: meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities†
D. Multiple meningiomas (two or more) *and* unilateral vestibular schwannoma *or* any two of: glioma, schwannoma, neurofibroma, cataract†

*Data from Baser et al.[10] NF2 may be diagnosed when one of the following is present.
†Any two of two individual tumors or cataract.

Table 1. Manchester diagnostic criteria for NF2 (these include the NIH criteria with additional criteria)

Bilateral vestibular schwannomas or family history of NF2 plus (1) UVS or (2) Any two of: meningioma, glioma, neurofibroma, schwannoma, and posterior subcapsular lenticular opacities
Additional criteria: UVS plus any two of: meningioma, glioma, neurofibroma, schwannoma, and posterior subcapsular opacities
Or
Multiple meningioma (two or more) plus UVS or any two of: glioma, neurofibroma, schwannoma, and cataract

NF2, neurofibromatosis type 2; NIH, National Institutes of Health; UVS, unilateral VS.

From: Evans DG Clin Genet 2012

NF2 associated tumors

- Vestibular schwannomas → compression of cochlear nerve

Other schwannomas

- Meningiomas (in > 50%)
  intracranial – skull base and other site
  intraspinal – intradural
  intraorbital
  Optic nerve sheath meningioma
- Ependymomas – often spinal intramedullary
  often multiple, some asymptomatic
- «No» neurofibromas, «no» gliomas
- 40-50% spinal symptoms

NF2 Ophthalmological findings

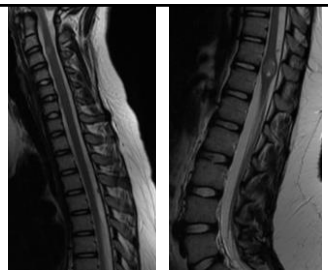
Increased prevalence

- Cataract
- Epiretinal membrane
- Disk glioma
- Retinal hamartoma
- Optic nerve sheath meningiomas

- [no iris hamartomas]

NF2 Presenting symptoms

- In children
  often – spinal tumor / extravestibular cranial nerve /seizure
- Overall
  ca 30% unilateral hearing loss
  Tinnitus
  Bilateral hearing loss
  Balance impairment
  …..



NF 2 Intramedullary lesions level C3 and in Conus
Small meningioma dorsal level thoracic vertebrae 4-5

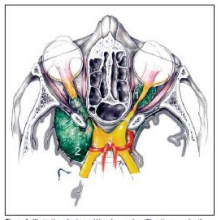
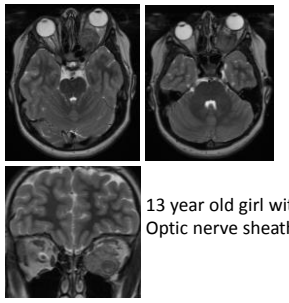


Figure 1. Illustration of primary (1) and secondary (2) optic nerve sheath meningiomas.

Arch Ophthalmol 2006

Boesch MM et al

Optic Nerve Sheath Meningiomas in Patients With Neurofibromatosis Type 2



13 year old girl with NF2
Optic nerve sheath meningoma

NF2 Management

- Complex ! Best in specialized centre
- Mainstay – surgical removal of tumors (timing…)
- VS: difficult to remove to preserve hearing
  high prevalence of postoperative facial nerve palsy
- Optic Nerve Sheath Meningoma
  «don't touch» surgically – high risk for ischemic optic neuropathy

NF2 – when to consider ?

- Vestibular schwannoma
- Unexplained cataract
- Meningoma (overall a rare tumor in children)
- Spinal ependymoma

References

- Plotkin SR et al
  Update from the 2013 international neurofibromatosis conference.
  Am J Med Genet A 2014
- Hirbe AC, Gutmann DH
  Neurofibromatosis type 1: a mutlidisciplinary appraoch to care.
  Lancet Neurol 1014;13:834-43
- Rauen KA et al
  Recent developments in neurofibromatosis and RASopathies: management, diagnosis …
  Amer J med Genet A 2015;167A:1-10