Neurofibromatosis

NF type 1 - NF type 2

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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
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 criteria

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 Chiasmal OPG

T2w axial MRI Normal anatomy
T2w axial MRI Enlarged chiasm

Neurofibromatosis 1 Chiasmal OPG

T2w coronal MRI Normal anatomy
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
• 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
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)

Note:
- Funnel chest
- Protuberant belly
• 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
- Benign 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 lymphocytes
• Mutation may be present in germ line → offspring with full NF1

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
  ...
• Lentigiones 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 fulfilled in ~ 50% !  
ABSENT  Iris hamartomas  
Optic pathway gliomas  
Cutaneous neurofibromas

© E. Legius  
Neurofibromatosis type 1  
Growth factors  
CM-AVM  
Costello

Transcription  
Cytoplasm  
Nucleus

© E. Legius
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


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


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 – general information

- Prevalence ~ 1:40'000
- Genetics Dominant
  > 50% de novo (~ 25-30% mosaic, 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. 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
3) Multiple meningiomas (two or more) plus UVS or any two of glioma, neurofibroma, schwannoma, and cataract

NF2: neurofibromatosis type 2; NIH, National Institute of Health; UVS, unilateral VI.

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

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

- Hirbe AC, Gutmann DH
  Neurofibromatosis type 1: a multidisciplinary approach 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