Neurofibromatosis – Swedish perspectives

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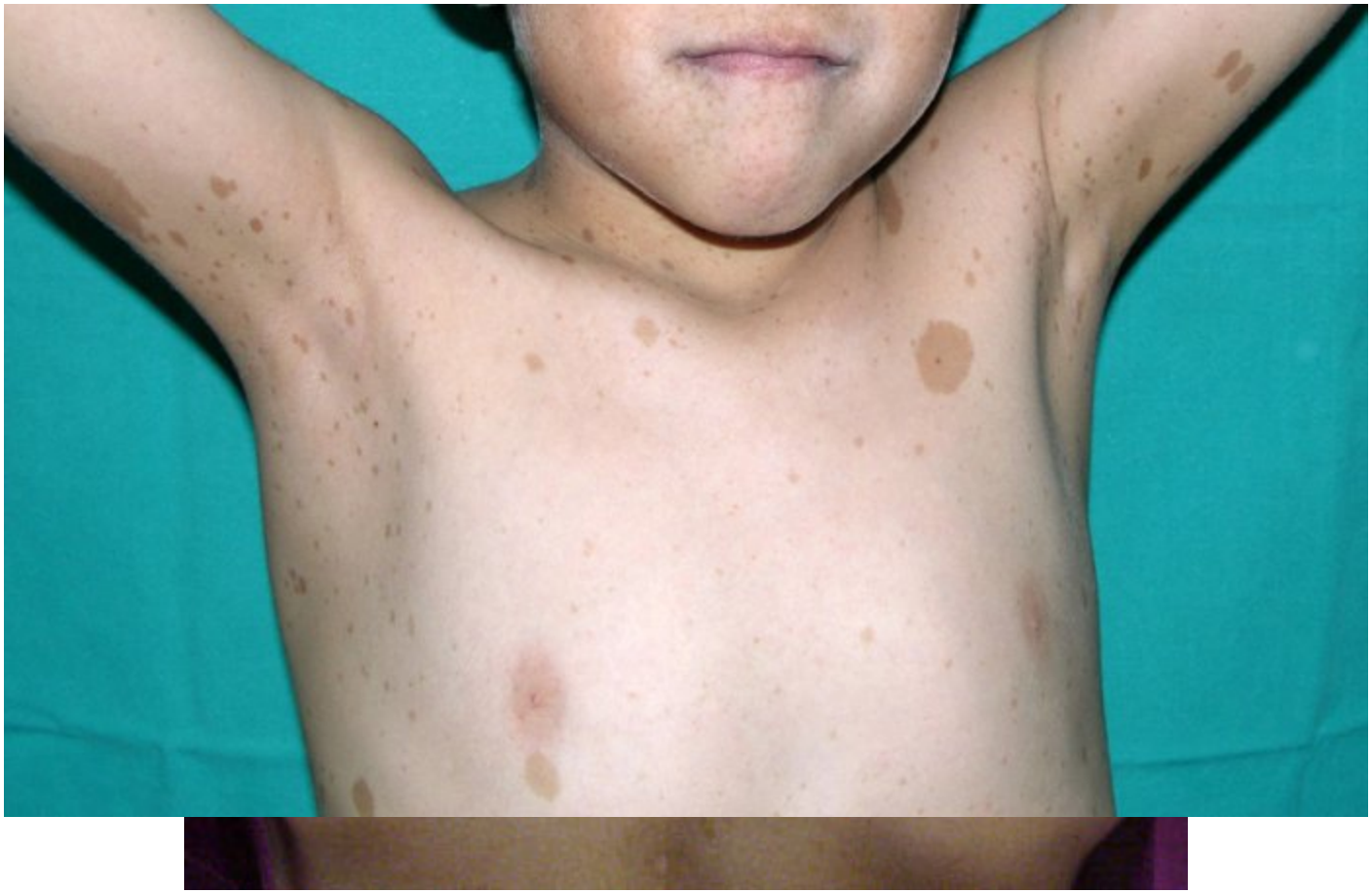
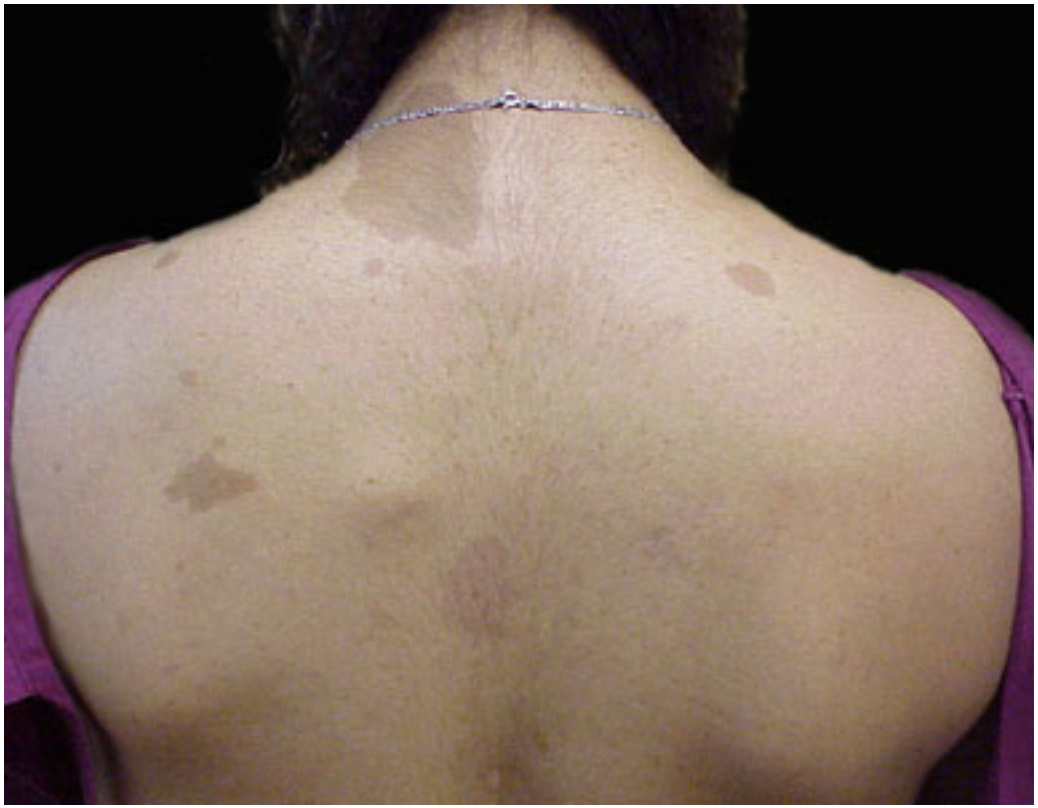


Neurofibromatosis - subgroups

- NF type 1 – 1:3000. Gene 17q11.2 .50% new mutations. Very varying expressivity.The protein is neurofibrin 1 .Tumoursuppressor
- NF type 2 – 1:30.000. Gene 22q11-13. Stopgen for merlinprotein
- Legius syndrome – SPRED 1 gene
- Schwannomatosis
- Noonan syndrom ?

Criteria for NF1

- 6 or more CAL spots before 6 years of age, larger than 5 mm before puberty, more than 15 mm after puberty
- 2 or more neurofibroma or 1 plexiform neurofibrom (PNF)
- Freckling in axilla and groins
- 2 or more Lisch noduli (hamartoma of iris)
- Glioma of optical nerve
- Sphenoid dysplasia, pseudarthros in tibia
- Anemic spots
- 1st degree relative with NF
- Pathogenic gene



Diagnosis?

2 or more of the criteria have to be fulfilled.

Lisch noduli and freckles often do not appear the first 4 years. Up till now we would exclude the diagnosis if criteria were less than 2 at the age of 6 years.

Genetic tests now can be made especially to find if the child has Legius syndrom

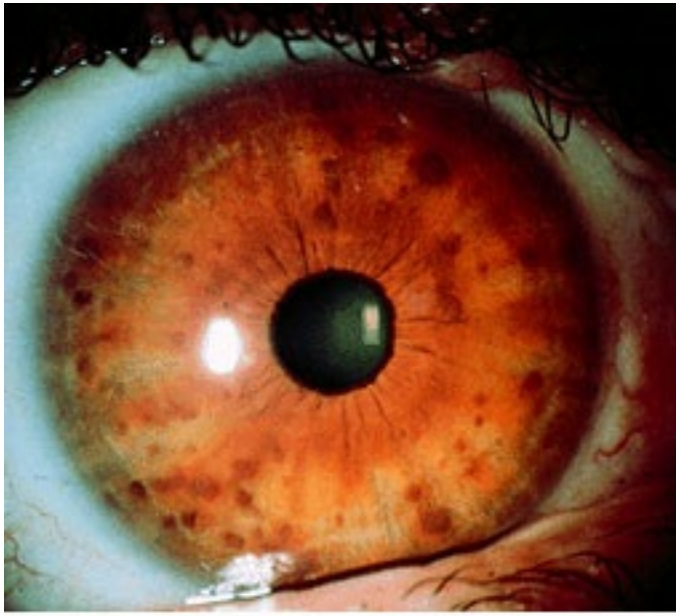
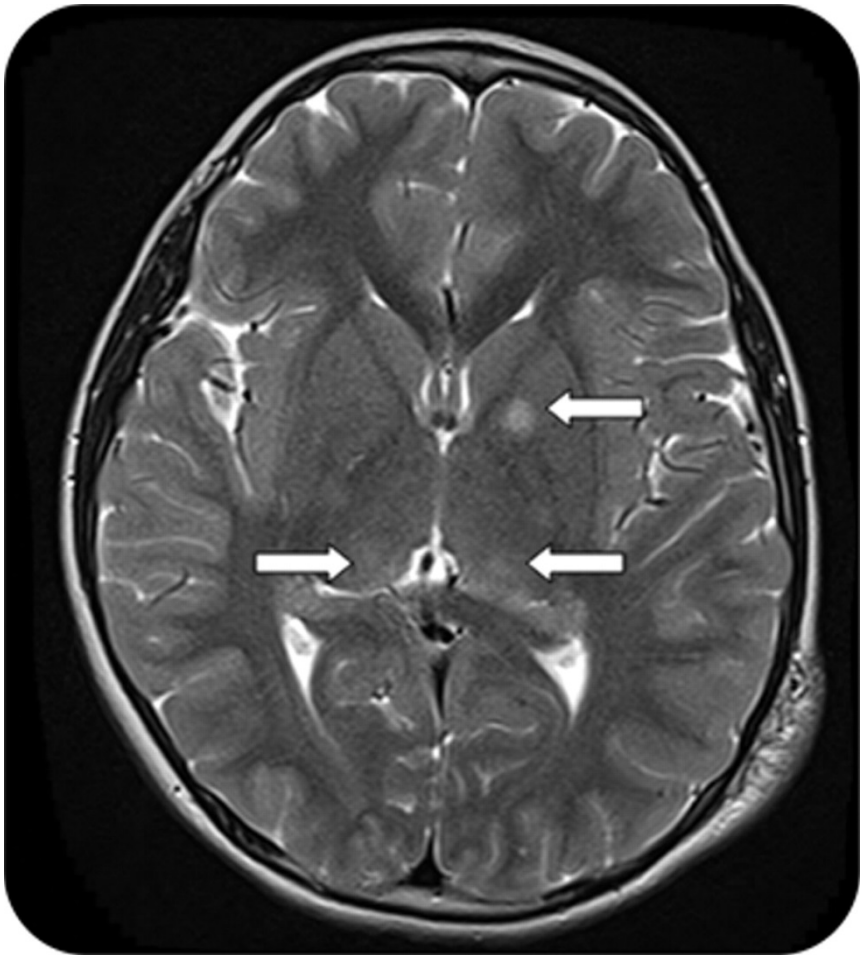


Fig. 3 Iris Lisch nodules.



NF 2 - criteria

- CAL spots appear in a similar way
- Neurinoma of vestibular nerve
- 1st degree relative with NF2
- Pathogenic gene
- Risk of different tumours larger than in NF1; MRI ought to be done after 10 years of age

Symptoms – very variable picture

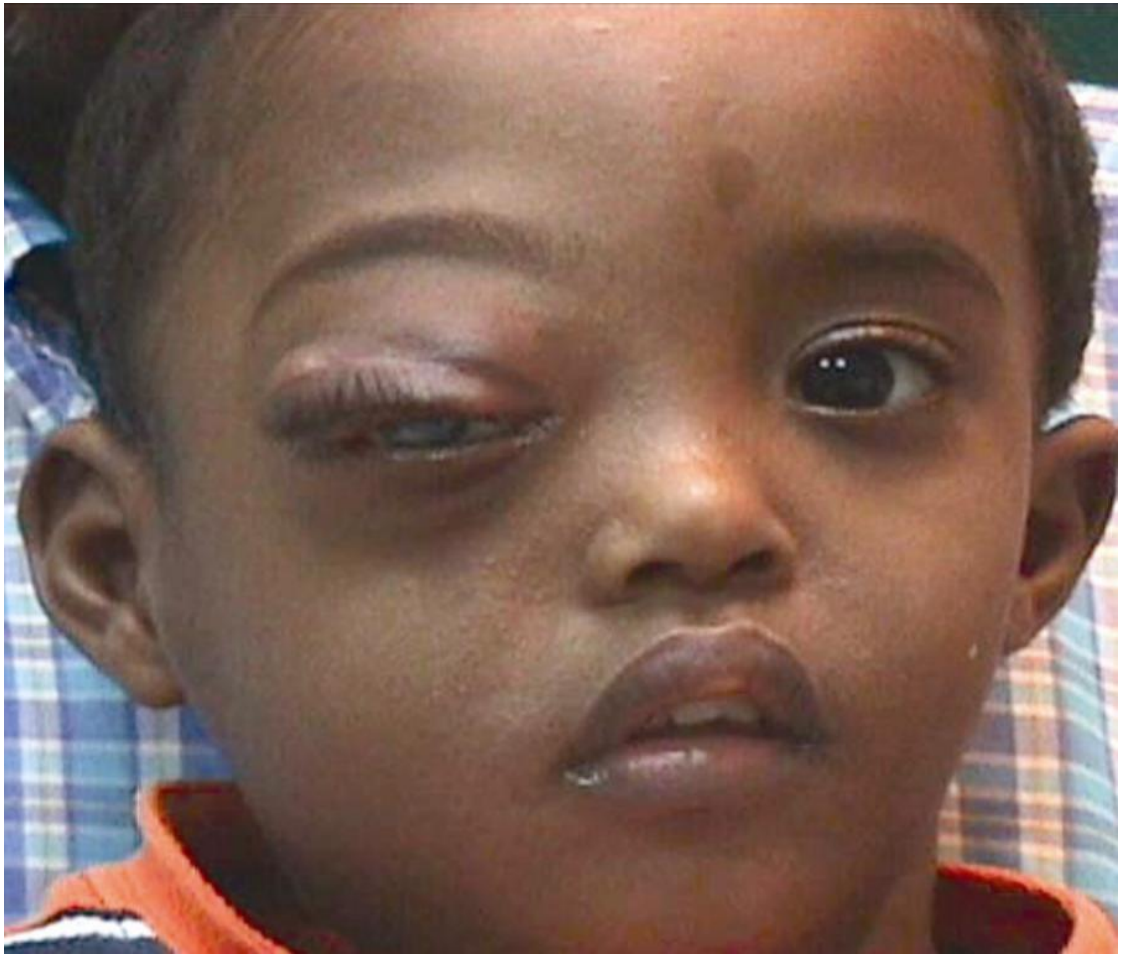
- 50 % have no problems, mostly CAL spots and Lisch noduli
- PNF may emerge at any age and go on growing causing different pressure symptoms
- Optic nerve glioma in 20 %
- Scoliosis 20%
- Less than 5 % have: epilepsy, intracranial tumours, pseudarthrosis,sphenoid dysplasia,stenosis of arteries,phaeochromocytóma,short stature, precoocious puberty

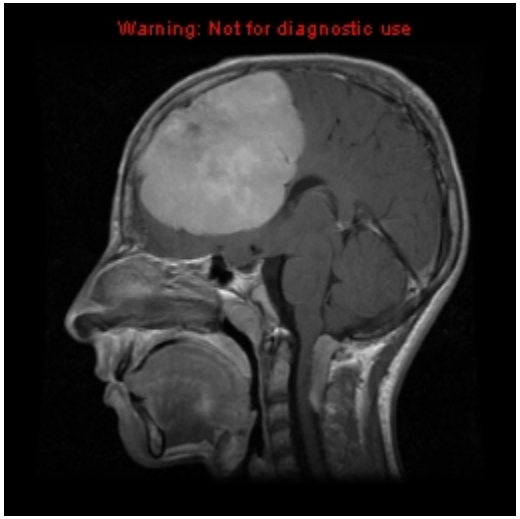
Symptoms - continue

- 5 % have a risk of malignancy during lifetime. Especially in puberty – pain in PNF is a serious sign
- MRI of the brain often shows UBO. They do not cause symptoms but could be a criterium of NF1.Maybe a sign of immature myelinisation, they often disappear!
- Developmental differences exist as for learning abilities and neuropsychiatric signs
- 50 % have slow learning but IQ above 70
- 30% may have autism /ADHD
- Low selfesteem is common

Different symptoms in different ages

- Infants: CAL spots, PNF, vision deviations
- Preschool children:CAL spots,freckles,PNF grows,vision disability,short stature,dysplasia of tibia
- School age: Lisch noduli, scoliosis,learning difficulties,short stature,hypertonia,vision disability – i.e. diminished visual field
- Teenagers: PNF:s go on growing and may malignify, too early or too late puberty,tiredness
- Adults: tiredness, risk of tumours (breast cancer more common), hypertonia

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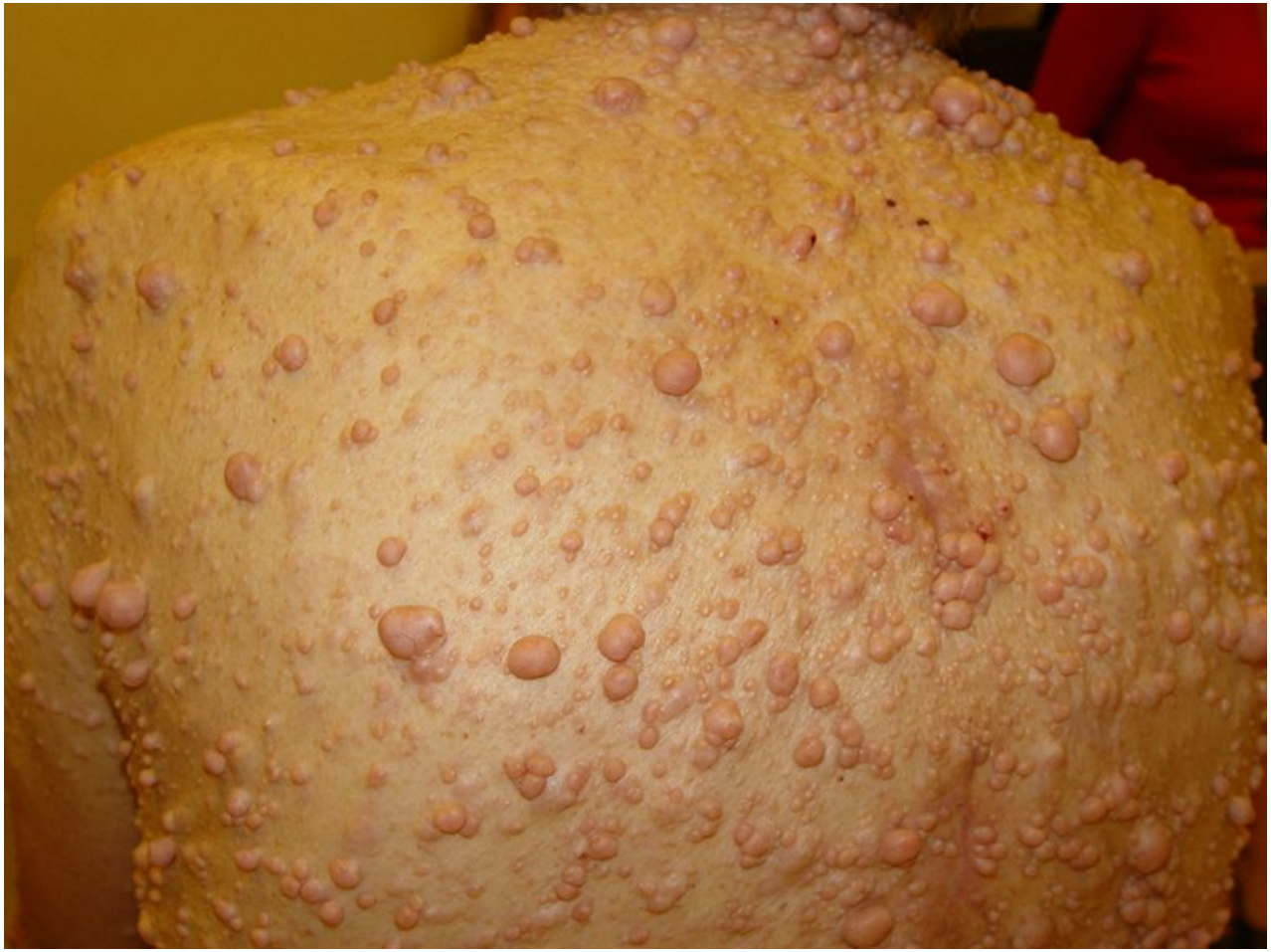

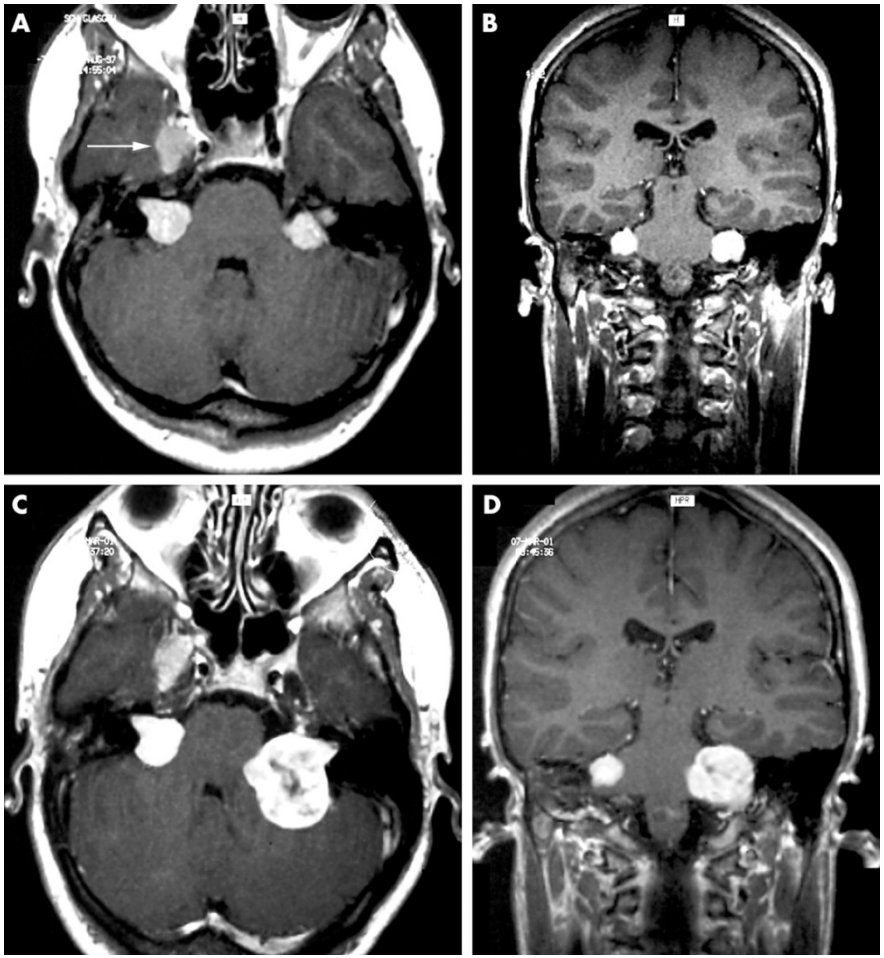
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Treatments

- Short stature – GH treatment
- Puberty deviations – maybe hormone treatment
- Ophtalmologist – to follow the visionfield
- Otolaryngologist (more NF2) - maybe surgery
- Dermatologist – Laser treatment
- Plastic surgeon- removal of PNF
- Glioma of optical nerve may be operated
- Malignancy may treated
- BUT – most difficult are the growing PNF:s – there is not yet any treatment that can stop them growing.Research is however intense !

Guidelines for follow up

- 0-6 years of age:
  - clinical follow up every 6th month with medical history and check up of eyes
  - if symptoms appear depending from where: x-ray of sceleton, EEG, MRI of brain,referral to orthopedian surgery,maybe oncologist
  - if delay of development neuropsychological assessement espec. before school start

If diagnostic difficulties clinically a NF1-mutation analysis should be done

Guidelines continued

- 7 – 18 years of age:
  - clinical assessment every year, as for the eyes up to the age of 12 years
  - special note shoud be given to scoliosis,high blood pressure,growth,behavoiur change, learning disability, PNF growth – malignancy? precocius or delayed puberty

  Psychological support may be needed

  After 18 years of age regular follow up is needed.

The doctor who follows patients with NF could be a general pediatrician or a general practitioner with knowledge about NF!

What about our/my perspectives?

- In Sweden the general knowledge about NF is low. Few clinics – Stockholm, Lund and Gothenburg – have shown interest
- We do have a patient´s association,trying to have contact with the stronger ones in Denmark and Norway
- In Holland and Belgium there are special clinics for children with NF as in Great Britain
- Finland has a good centre in Helsinki and Åbo started by a dermatologist!
- Denmark also has a centre for children and adults from a genetic basis

Perspectives continued..

- Almost every year there are European meetings but very few Swedes join.We had a conference in Gothenburg 2005,which gave us some possibilities to continue contact with the European and American specialists
- At the latest conference in Barcelona in September 2014 we decided to build Scandinavian networks
- Most research is done in the USA,in Great Britain and in Belgium
- In 2010 we hade a teamconference in the Swedish Riksstämma for doctors.

Perspectives continued..

- In Sweden it has become possible with more advanced genetic tests – could be of good help
- However, the diagnosis is not easy and you need a team of specialists : pediatrician,neurologist,dermatologist,ophtal-mogist,ENT-specialist,orthopedic surgeon,neurosurgeon,plastic surgeon,endocrinologist,oncologist,geneticist,psychologist,social worker,special teacher...

Last perspectives

- NF is not considered a rare disorder since the prevalence/incidence is too high
- But those with complications could be counted rare
- In Sweden most persons with NF can not get habilitation according to the rules
- There are guidelines written,also to be looked over now and then
- In Gothenburg we now have got the possibility to try and start a team under the umbrella of rare disorders ! A real challenge !