Neurofibromatosis

The neurofibromatoses can be distinguished according to type and distribution of hamartomatous lesions. Neurofibromatosis type 1 (NF1) is a common and well known disorder first described by von Recklinghausen in 1849. Neurofibromatosis type 2 (NF2) is a much rarer condition and characterised by the formation of VIIIth cranial nerve vestibular schwannomas.

Neurofibromatosis type I

Epidemiology
- Incidence: 1/2500-1/4000
- Male= Female
- There is considerable phenotypic variability between members of the same family.

Genetics
- Autosomal dominant inheritance
- NF1 is caused my mutations in the *NF1* gene on chromosomes 17q11.2, encoding neurofibromin.
- *NF1* gene mutations are found in ~80% patients fulfilling diagnostic criteria (see below).
- Neurofibromin is a tumour suppressor involved in cell cycle regulation.
- Fifty percent of cases are *de novo* (new mutations).
- Penetrance is 100%

Clinical presentation
Patients with NF1 usually present in childhood with café-au-lait patches or in adulthood with neurofibromas.

Physical Signs
NF1 Diagnostic Criteria [ ]=% of individuals with features

Patients must have 2 or more of the following:
- Café-au-lait patches (6 or more >5mm prepubertal, >15mm in an adult) [>99%]
- Axillary or inguinal freckling [85%]
- Neurofibromas (2 or more cutaneous/ subcutaneous) [>99%]
- Plexiform neurofibromas (1 or more) [30-50%]
- Lisch nodules (benign iris hamartomas see on slit lamp) (2 or more) [95%]
- Optic pathway glioma [15% total, 5% symptomatic]
- Bony dysplasia (Sphenoid wing/ long bone or pseudarthrosis) [2%]
- First degree relative with NF1

Diagnosis
NF1 is a clinical diagnosis made when the criteria (see above) are fulfilled. MRI head/spine only if focal neurological signs or epilepsy.

Genetic testing

Molecular DNA analysis is available for:
- Borderline cases
- Known family mutation
- Pre-natal testing

Complications
- Mild cognitive impairment [30-60%]
- Scoliosis [11%]
- Malignant peripheral nerve sheath tumours [8-13% lifetime risk]
- Cerebral gliomas [2%]
- Raised blood pressure may be due to benign essential hypertension, renal artery stenosis or phaeochromocytoma [2%]

Treatment
- Consider removal of neurofibromas if symptomatic.

Surveillance
- Annual systems review including skin, spine and neurology
- Annual development and ophthalmology assessment in childhood
- Blood pressure

Genetic counselling
- If parent affected, recurrence risk is 50% for each offspring
- If parent unaffected or de novo mutation, recurrence risk is less than 1%
- If parent has segmental NF1 (see box) there is a low recurrence risk.

Neurofibromatosis type 2 (NF2)

Epidemiology
- Incidence: 1/40 000-1/100 000

Genetics
- Autosomal dominant inheritance
- NF2 is caused by mutations in the *NF2* gene on chromosome 22q12.2, encoding merlin, a tumour suppressor
- Fifty percent of patients with NF2 are *de novo* (new mutations)

Clinical presentation
- Typically bilateral vestibular schwannomas, deafness and tinnitus

Physical signs
- Neurological features secondary to CNS tumour
- Deafness
- Cataracts (juvenile)
- CALS: 4% of patients have >3, 0% of patients have >6
- In contrast to NF1, plexiform neurofibromas, axillary freckling and lisch nodules are rare

Diagnosis
- Clinical diagnostic criteria fulfilled

Genetic testing
- Molecular DNA analysis is available

Complications
- CNS tumours and surgical sequelae

Treatment
Surveillance
- First degree relatives should have baseline MRI and annual assessment
- Refer for genetic counselling

Differential Diagnosis of Café-au-lait patches (CALS) (BOX)

- Segmental NF1–typical skin lesions found in only one part of the body due to somatic mutation. Lower recurrence risk.
- Watson syndrome–CALS/ dysmorphic/ pulmonary stenosis
- McCune Albright syndrome
- Proteus syndrome–macrodactyly/ thickened skin/naevi
- NF2
- Recessive mutations in mismatch repair genes associated with CALS, axillary freckling, neuroectodermal tumours, NHL, bowel polyps

Pictures
CALS
Classic neurofibroma
MRI optic glioma
Pseudarthrosis
Lady with phaeo
MRI vestib schwann