Neurofibromatosis

Definition
Neurofibromatosis is a common familial neoplastic syndrome characterised by autosomal dominant transmission, multiple neural tumours, numerous pigmented skin lesions and pigmented iris hamartomas.

History
Described by von Recklinghausen in 1882 – same year Adams described forward bending test.

Joseph Merrick, the "Elephant Man" may have had neurofibromatosis, or perhaps Proteus syndrome.

Hatzoecher first to describe tibial pseudarthrosis in 1708.

Classification and terminology
NF is classified as:
i. NF type 1 or von Recklinghausen's disease
ii. NF type 2 or acoustic neurofibromatosis

Aetiology
NF 1: 50% of patients have a definite family history consistent with autosomal dominant transmission; the rest appear to be spontaneous mutations. The NF 1 gene is enormous with 350 000 base pairs, which is consistent with the high rate of mutation.

In familial cases the expressivity appears to be variable but the penetrance is 100%.

The NF type 1 gene has been mapped to 17q11.2. This gene encodes a protein called neurofibromin, which down regulates the function of the p21 ras proto-oncogene; the gene therefore belongs to the family of tumour suppressor genes.

The NF type 2 gene has been mapped to chromosome 22 and is also a tumour suppressor gene. The gene encodes a protein called merlin or schwannomin.

NF 2 is also an autosomal dominant disorder

Incidence
NF 1 is relatively common occurring in 1 in 3000 of the population. This makes it one of the most common dominantly inherited genetic disorders.
M=F
White=Black
NF 2 is much less common, occurring in 1 in 40 000.

Pathology of neurofibromas
Grossly: grayish brown, firm rubbery mass.
Microscopically: interlacing strands of elongated cells arranged in a palisading pattern, containing foam cells and pigment.

Clinical features (NF type 1)
Orthopaedic
A. Scoliosis. Found in 10-30%. This can be dystrophic or nondystrophic. Nondystrophic curves can be treated along the lines of idiopathic scoliosis, although they have more of a tendency to be left sided and all need MRI prior to surgery. Some curves that appear initially nondystrophic become dystrophic with further followup
    1. Scoliosis tends to occur in younger patients than normal.
    2. Dystrophic curves:
    3. These are short and angular, involving 5-7 segments, and often to the left
    4. Occur in about 50% of patients
    5. Etiology is unknown
    6. Associated with thinned defective pedicles, widening of interpeduncular distance
    7. Associated with posterior vertebral body scalloping secondary to dural ectasia, which usually occurs at multiple levels
    8. Associated with eccentric unilateral scalloping secondary to a localised dumbbell neurofibroma
    9. Associated with an intrathoracic meningocele where there is protrusion of the dura and arachnoid through a thoracic intervertebral foramen into the extrapleural thoracic cavity. These tend to be unilateral and on the right side
    10. May progress to involve other areas, a process known as modulation.
    11. Kyphoscoliosis
        i. Curves more than 50 degrees usually need anterior and posterior instrumentation and fusion.
    12. Lordoscoliosis
        i. Associated with mitral valve prolapse and decreased pulmonary function
    13. Cervical spine instability

B. Pseudarthrosis of a long bone (particularly the tibia)
    1. Presents initially as either anterolateral bowing or frank fracture
    2. Found in 1-2% of patients with NF 1 (1 in 140 000 without NF1)
    3. Usually evident in the first year of life and may be the first manifestation of NF
C. Scalloping, thinning, twisting of the ribs – pencil ribs. Rib penciling is diagnosed when the rib is smaller in diameter than the midportion of the second rib.
D. Intraosseous cystic lesions – non-ossifying fibromas
E. Erosive defects dues to contiguity of neurofibromas to bone
F. Subperiosteal bone cysts
G. Limb length inequality – e.g. with tibial pseudarthrosis
H. Gigantism of a digit, or entire limb

Extraskeletal

A. Neurofibromas
    1. Arise in or are attached to nerve trunks anywhere in the skin including palms and soles, as well as any internal nerve
    2. Composed of Schwann cells, fibroblasts, endothelial cells and glandular elements
    3. Acoustic neuromas when present are unilateral in contrast to the bilateral lesions of NF 2
    4. Fibroma molluscum are small lesions up to 5cm in size that are the most common cutaneous manifestation of the disease. They are also known as neurofibromas. They tend to appear more extensively after puberty and pregnancy.
    5. Plexiform neurofibromas are huge multilobar pendulous masses 20 cm or more in greatest diameter containing numerous thickened, tortuous nerves with pigmentation of the overlying skin. These can cause striking enlargement of the limb or affected body part. If they approach or cross the midline it is likely they arise from the spinal canal and will be aggressive
    6. The neurofibromas of NF 1 become malignant in about 3% of cases, becoming a neurofibrosarcoma
    7. Malignant change is most common in deeper neurofibromas as opposed to superficial lesions
B. Cutaneous pigmentation
    1. Occurs in more than 90% of patients.
    2. Most commonly occurs as café au lait macules, with generally smooth borders – coast of California (as opposed to the irregular borders of the lesions of McCune-Albright syndrome – coast of Maine)
        i. They are usually round to oval with their long borders paralleling the underlying cutaneous nerve
        ii. Often found in areas not exposed to the sun
        iii. More than 6 spots greater than 15mm in size in adults, and more than 6 spots greater than 5mm in children consistent with a diagnosis of NF
        iv. Note that 15% of the population will have one or two café-au-lait spots as a normal variant, and 1% of the population has more than 2
        v. Café-au-lait spots tend to increase in number, size and pigmentation up until the 3rd decade
C. Verrucous hyperplasia
    1. A condition with tremendous overgrowth of the skin, with thickening and a velvety soft papillary quality.
    2. The skin tends to develop cracks and become infected, producing a foul smell.
D. Axillary and inguinal freckles (Crowe sign)
    1. This is the second most common sign to appear in children after café-au-lait spots. Found in 81% by age 6.
E. Lisch nodules (pigmented iris hamartomas)
    1. Present in more than 94% of patients greater than six years old
F. Tumour predilection
    1. Pts with NF 1 have a 200-400% increased risk of developing other tumours especially:
        i. Meningiomas
        ii. Optic gliomas
        iii. Pheochromocytomas
G. Intelligence
    1. Although patients may have normal intelligence there is definitely an overall tend towards lower intelligence

H. Renal artery stenosis resulting in hypertension
I. Intramural gastrointestinal lesions resulting in GIT obstruction
J. Pulsating exophthalmos due to temporal lobe herniation through a deficient posterior wall of the orbit
K. Optic gliomas

Children with NF have a higher rate of Wilm's tumour and rhabdomyosarcoma.

Diagnosis of NF 1
The Consensus Development Conference on Neurofibromatosis in 1987 concluded that diagnosis could be based on the presence of 2 or more of the following 7 criteria:

1. More than 6 café –au-lait spots, at least 15mm diameter in adults and 5mm in children
2. Two or more neurofibromas of any type or one plexiform neurofibroma
3. Freckling in the axillae or inguinal regions (Crowe sign)
4. Optic glioma
5. Two or more Lisch nodules (iris hamartomas)
6. A distinctive bone lesion, such as sphenoid dysplasia or thinning of the cortex of a long bone, with or without pseudarthrosis
7. A first degree relative with NF 1 by the above criteria

Imaging of neurofibromas
Neurofibromas are usually isointense on T1 weighted scans and of increased signal on T2 weighted scans.

Differential diagnosis
1. McCune-Albright syndrome
2. Leopard syndrome

Management
1. Scoliosis
   a. Instrumentation is advisable for lesser curves than in idiopathic scoliosis if the scoliosis is dystrophic in nature
   b. Figures of >20 degrees with curve progression are an indication for posterior fusion
   c. Dystrophic curves greater than 50 degrees should be treated with anterior and posterior fusion
   d. Non-dystrophic curves are treated on their merits
2. Congenital tibial dysplasia
   a. Surgical treatment is not particularly successful and prefracture bracing is preferred

   Surgical options include:
   b. Maintenance of alignment with Sofield rods
   c. Excision and autografting of defect with external fixation
   d. Excision and vascularised fibular grafting
   e. Excision and bone transport
   f. Amputation

Clinical manifestations in NF 2
Bilateral acoustic neurofibromas are invariably present
Skin tumours may or may not be present
Café au lait spots are present
Lisch nodules are <u>not</u> present