"Doc... what's wrong with me?"

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Joseph's medical investigations

- Joseph, 46, presents with recent onset of hypertension and a host of health complications. Upon investigation, the following were found:
  - Multiple molluscum fibrosum and hyperpigmented skin lesions, including axillary freckles and multiple *café au lait* lesions (Figure 1)
  - Visual acuity was 20/40 in the right eye and 20/200 in the left eye
  - There is mild anisocoria with a left ptosis
  - On fundoscopy, the discs and margins were within normal bilateral limits
  - Visual fields were intact on confrontation
  - Some facial asymmetry (Figure 2) and slight diminished sensation on the left V2 region
  - Some atrophy and weakness of the left masseter, compared with the right
  - Hearing diminished in the left ear
  - Deep tendon reflexes are 2/2 bilaterally throughout the upper and lower limbs
  - His gait was normal

Joseph's medical history

- Bell's palsy about 20 years ago
- "Blackouts" associated with alcohol consumption; these incidents have stopped since he began abstaining from drinking alcohol
- An overdose on medication due to marital problems
- A recent onset of hypertension
- He has always been overweight
- Five brothers and six sisters, all of whom have died primarily of cardiovascular disease
- He is the only member of his family with cutaneous lesions
- He smokes occasionally

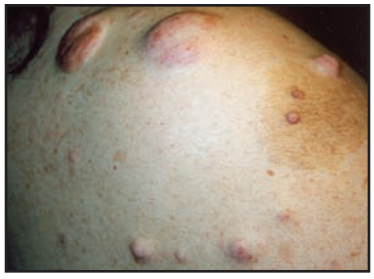

Figure 1. Joseph's right upper back, with multiple hyperpigmented skin tumors and *café au lait* spots.

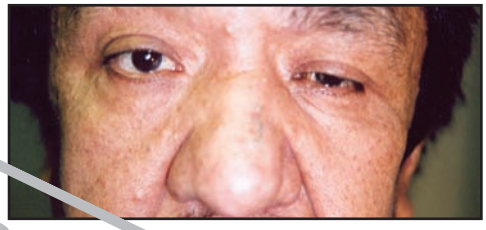

Figure 2. Joseph's face shows noticeable asymmetry and left ptosis.

Clinical investigations

- A CT scan of the orbits, brain and posterior fossa were done and the only abnormality reported was elongation of the anterior posterior access of the left globe. In particular, no optic nerve tumours were found and no other abnormalities of the brain were reported
- Visual-evoked potentials showed normal response in the right eye and complete conduction block in the left eye
- A mild peripheral cochlear nerve delay was reported on the left, on auditory-evoked response testing. The right side was normal
- MRI of the brain was completely normal

What's your diagnosis?

a) Neurofibromatosis type 1 (NF-1)
b) Neurofibromatosis type 2 (NF-2)
c) Tuberous sclerosis

Answer:
Neurofibromatosis type 1 (NF-1)

Case discussion

Joseph has no intracranial manifestations of his neurofibromatosis. This is reassuring especially in view of his history of left fifth, seventh and eighth nerve deficits—the exact cause of which is unclear. The possibility of a peripheral nerve tumour is not excluded. On the other hand, perhaps his Bell's palsy was idiopathic in nature. This would be similar to most other individuals who develop Bell's palsy, with the slightly diminished hearing in the left ear being incidental and unrelated to neurofibromatosis. If he does have fifth nerve motor deficit on the left, this is more difficult to explain and more likely related to neurofibromatosis. However, none of these lesions appear to be progressive at the moment.

It is of interest that he has recently developed hypertension. Hypertension is more common in patients with neurofibromatosis. While it may represent essential hypertension, the possibility of pheochromocytoma, coarctation of the aorta and renal vascular hypertension also needs to be considered, since these etiologies are more common as a cause of hypertension in neurofibromatosis. At this moment, he needs further work-up for these etiologies.

At least eight different clinical phenotypes of neurofibromatosis have been identified and are linked to at least two genetic disorders. Clinical manifestations increase over time.

Diagnosis

About NF

NF is an autosomal dominant disorder that affects the bone, the nervous system, soft tissue and the skin. At least eight different clinical phenotypes of neurofibromatosis have been identified and are linked to at least two genetic disorders. Clinical manifestations increase over time.

Neurologic problems and malignancy development

NF is a neurocutaneous condition that can involve almost any organ system. Thus, the presenting signs and symptoms may vary widely. Two major subtypes exist: NF-1, which is the most common subtype and is referred to as peripheral NF and NF-2, which is referred to as central NF. These descriptions are not especially accurate because NF-1 often has central features. A third variant is known as segmental NF; this term is used to describe disease limited to a single body region. Segmental NF may be related to mosaicism or segmental hyperexpression of the condition. Loss of heterozygosity may

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create the clinical impression of segmental lesions.

Diagnostic criteria

The diagnostic criteria for NF-1 are met if two or more of the following features are present:

- Six or more of the largest *café au lait* macules are > 5 mm in diameter in a prepubertal individual and > 15 mm in diameter in postpubertal individuals
- Two or more neurofibromas of any type or one plexiform neurofibroma
- Freckling in the axillary or inguinal regions
- Optic glioma
- Two or more Lisch nodules (iris hamartomas)
- A distinctive osseous lesion, such as sphenoid dysplasia or thinning of the long bone cortex, with or without pseudoarthrosis
- A first-degree relative with NF-1, according to the above criteria

Diagnostic criteria for NF-2 are met if either of the following conditions are present:

- Bilateral masses of the eighth cranial nerve seen with appropriate imaging techniques (*e.g.*, CT, MRI)
- A first-degree relative with NF-2 and either:
  a) a unilateral mass of the eighth cranial nerve or
  b) two of the following:
  - neurofibroma,
  - meningioma,
  - glioma,
  - schwannoma or
  - juvenile posterior subcapsular opacity.

Treatment

Surgical care

Treatment of neurofibromatosis is predominantly surgical:

- When neurofibromas increase in size or cause pain, malignant transformation should be suspected and excision or biopsy should be performed
- Acoustic neuromas and tumours that cause tinnitus and vertigo should be excised with great caution
- Any signs of epilepsy should be investigated, and responsible tumors should be removed

Consultations

Due to the nature of condition, various specialists should be involved in the treatment of NF:

- Orthopedic physicians should be involved in the management of problems, such as tibial bowing and kyphoscoliosis
- Plastic surgeons may be included in the correction of deformities, especially those of the face
- Psychological or psychiatric assessment may be necessary in monitoring language disorders and learning disabilities
- Considering the autosomal dominant inheritance pattern for neurofibromatosis, genetic counseling should be included in the treatment of all patients affected with this disease. Dx

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