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NEUROFIBROMATOSIS

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CASE REPORT

56 year old man with widespread skin neurofibromas since age 19 was referred for investigation after he had visited the SOPD requesting excision of a large neurofibroma.
Family history: Mother (died at age of 72), 48 yr old brother (still alive) and son (died at age 12 from a cerebral tumour) also had neurofibromatosis.
On examination: Extensive skin neurofibromas, axillary freckling and cafe au lait spots. Normotensive.
24-hour urine specimen showed raised metanephrine and normetanephrine concentrations.
Serum calcium, phosphate and calcitonin were normal.
Abdominal CT Scan: 4x4 cm left adrenal mass.
CT and MRI of the brain and a thoracic CT were normal.
Diagnosis: Von Recklinghausen's neurofibromatosis with associated phaeochromocytoma.
Peri-op: Alpha-blocker (phenoxybenzamine) and beta-blocker (propranolol) to maintain a BP 120/70 – 130/80.
Intra-op: BP control achieved with sodium nitroprusside infusion given during intubation and tumour handling.
Surgery: Well circumscribed encapsulated tumour weighing 54g was excised. Histology showed an adrenal gland paraganglioma (phaeochromocytoma) with no evidence of capsular or vascular invasion.
Post-op: Patient made a good recovery.

The above case report by Reynolds et al that appeared in the Lancet in May 2003 highlights a number of aspects of NF that I would like to talk about today, namely, the importance of a thorough history and examination as well as relevant investigations, actively searching for known complications or disease associations (eg phaeochromocytoma) and using all of this to deliver a safe anaesthetic and hopefully avoid a potentially disasterous situation.

In our setting, as in the case report, patients may present either for removal of a "harmless" looking neurofibroma or for procedures completely unrelated to the disease entity itself.

Extra vigilence is required for these patients.

INTRODUCTION

The neurofibromatoses are a group of hereditary diseases that are transmitted in an autosomal dominant fashion. They are characterized by formation of tumors of ectodermal and mesodermal tissues (?endodermal tissue as well) and can therefore involve any organ system.

They belong to the group of neurocutaneous syndromes (Phakomatoses) which includes: tuberous sclerosis, ataxia telangiectasia, Sturge-Weber syndrome, von Hippel-Lindau disease and incontinentia pigmenti. These are disorders of the central nervous system (CNS) that also manifest skin and retinal lesions and most, but not all, have a common ectodermal origin.

Although 8 subtypes of NF have been proposed to date, only two distinct types have been defined: a peripheral and central form. They differ by the predominant localization of the tumors in relation to the peripheral and central nervous systems.

Type 1 / von Recklinghausen disease (affects about 85% of patients)
Type 2 (affects about 10% of patients)

The type 1 form displays predominant peripheral involvement with neurofibromas occurring both along the course of the major peripheral and autonomic nerves and at or near their terminations in the dermis and viscera respectively.

The type 2 form predominantly affects the CNS. Patients display cranial and spinal nerve sheath tumors. The most frequently occurring tumors in this setting are acoustic nerve tumors.

HISTORY

Reports of probable cases of NF have appeared since the 16th century.

1768 - first described by Mark Akenside
1793 - reported by Wilhelm Gottleib Tilesius von Tilenau
1849 - first review of the disease published by Prof Robert W Smith
- suggested that the origin of the tumor was the connective tissue surrounding small nerves
1882 - Friedrich Daniel von Recklinhausen defined the disease as a clinical entity
- proposed that the tumors that characterize the disease arise from nervous tissue

Friedrich von Recklinhausen was born in 1833 in Gutersloh, Westphalia, Germany. He obtained his medical degree in 1855 and 10 years later became professor of pathological anatomy. Aside from his work in NF, he was an expert in embryology and stages of tissue maturation. He also had a deep interest in and was an authority on the pathology of disease of bones (one of the first to describe generalized osteitis fibrosa).

He died in 1910 at the age of 77.

EMBRYOLOGY

All of the major organ systems begin to develop during the embryonic period: weeks 3-8.

Gastrulation is the process that establishes the three definitive germ layers of the embryo (ectoderm, mesoderm and endoderm), thereby forming a trilaminar embryonic disc by day 21 of development. These three layers give rise to all the tissues and organs of the adult.

The ectoderm has 3 parts:
- external ectoderm (surface ectoderm)
- the neural crest
- the neural tube

The latter two make up the neuroectoderm.

The following is a summary of some of the germ layer derivatives:

ECTODERM
- epidermis, hair, nails
- salivary glands and glands of mouth and nasal cavity
- lens and cornea of eye
- epithelial lining of lower anal canal, distal part of male urethra, external auditory meatus

NEURAL CREST
- all neurons within brain and spinal cord
- optic nerve, optic chiasm, optic tract
- astrocytes, oligodendrocytes
- neurohypophysis
- pineal gland

NEUROECTODERM
- ganglia (dorsal root, cranial, autonomic)
- schwann cells
- pia and arachnoid
- chromaffin cells (adrenal medulla)
- c cells of thyroid
- melanocytes

MESODERM
- muscle (smooth, cardiac, skeletal)
- bone and cartilage
- laryngeal cartilages
- connective tissue
- dermis of skin
- dura mater
- endothelium of blood and lymph vessels
- RBCs, WBCs
- kidney
- adrenal cortex

ENDODERM
- epithelial lining of GI tract, trachea, bronchi, lungs, urinary bladder, female urethra, most of male urethra
- thyroid follicular cells
- hepatocytes
- acinar and islet cells of pancreas
- auditory tube, middle ear cavity

GENETICS

NF is autosomal dominant ie if only one parent has NF, his/her children have a 50% chance of developing the condition as well.
Males and females are equally affected.
The severity of the disease can vary from individual to individual (variable expressivity).
As far as genotype (ie genetics of the disease) and phenotype (ie the actual manifestation of the disease) is concerned; NF1 has no clear links between the two with great variability in the severity and specific nature of the symptoms among family members with the disorder. However, with NF2, there is a strong genotype-phenotype correlation and manifestations are similar among family members.

In about 50% of cases, there is no other affected family member and NF occurs through spontaneous random mutation.

NF1:
Due to mutation on long arm of chromosome 17q11.2
This chromosome encodes a protein containing 2818 aminoacids, called neurofibromin. Neurofibromin is a tumor suppressive protein. NF alters or weakens this protein, resulting in rapid, radical growth of cells (the specific nature and type of cells have yet to be identified) all over the body, especially around the nervous system, leading to the development of a wide variety of tumors. When it involves rapid proliferation of schwann cells, neurofibromata eventually form.

NF2:
Due to mutation on long arm of chromosome 22q12.1
This chromosome encodes for a cytoskeletal protein called Merlin/Schwannomin which is also believed to have tumor suppressor properties.

INCIDENCE

NF1:
Birth incidence is 1 in 2500-3300
General population 1 in 5000

NF2:
Birth incidence is 1 in 33 000-40 000
General population 1 in 210 000

PATHOLOGY

NF 1:
Cafe-au-lait spots:
- symmetrical flat areas of skin hyperpigmentation with rounded edges
- vary in size
- brownish colour
- often present at birth and increase in number during the first few years of life
- most prominent over the trunk, axilla (axillary frecking) and pelvis

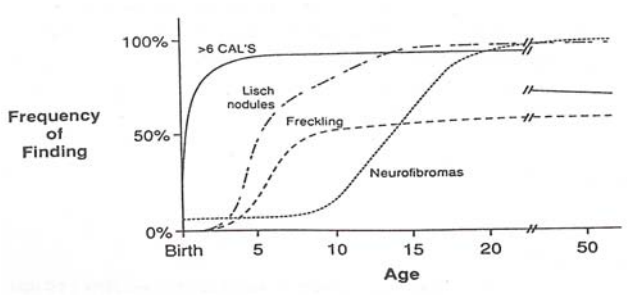
Neurofibromas:
- major feature of NF1
- diffuse tumors in dermal and subcutaneous tissue
- composed of schwann cells, fibroblasts and perineural cells
- clinically and histologically 3 types (based on variability in cellularity as well as in content of collagen and mucosubstances)
  - cutaneous neurofibromas
    - 95% of patients
    - discrete benign tumors
    - found within the dermis
  - nodular neurofibromas
    - arise in peripheral nerves
    - may be found at any site
    - do not infiltrate surrounding tissues
    - paraspinal neurofibromas may reach enormous sizes, giving rise to the classic “dumbbell” tumor
  - plexiform neurofibromas
    - hallmark lesion of NF1
    - 30% of patients
    - affects long portions of the nerve involved
    - can get infiltration of the nerve itself and surrounding tissue
    - can get extensive disfiguration
    - these tumors represent the major cause of morbidity and death

In about 2-16% of patients, nodular and plexiform neurofibromas undergo sarcomatous transformation to form malignant peripheral nerve sheath tumors. This change does not occur until middle or late adult life.

Optic glioma:
- astrocytoma arising from the optic nerve or chiasm
- seen in 15% of patients
- symptomatic in 2-5%
- slow growing
- generally do not undergo malignant change

Lisch nodules:
- benign multiple melanotic hamartomas of the iris
- seen in 95% of patients

The following graph shows the typical time course of appearance of the major clinical features of NF1



Other tumors found in NF1:
- Phaeochromocytoma
- Carcinoid tumors
  - occur commonly
  - carcinoid tumors and neurofibromas have a common neuroendocrine origin
  - tend to occur in duodenum, esp ampulla of Vater
    - present with jaundice or upper GI bleed or obstruction
    - release of vasoactive peptides leading to flushing, diarrhoea, bronchoconstriction and right heart lesions (carciniod syndrome)
  - carcinoid tumors and phaeochromocytoma may co-exist

  - Multiple endocrine neoplasia (MEN) syndrome: It has always been thought that there is an association between NF and MEN syndrome. The two share some similarities:
    - autosomal dominant disorders
    - consists of tumors of endocrine and/or nonendocrine tissues
    - benign or malignant
    - associated with phaeochromocytoma (MEN 2A) and carcinoid tumors (MEN1)

In 1983, Griffiths et al described (in the BMJ) 3 patients who were found to have duodenal carcinoid tumor in association with NF and phaeochromocytoma, and 2 patients with duodenal carcinoid tumor and either NF or phaeochromocytoma. It was suggested that this combination was not a chance association and that the linkage of NF, phaeochromocytoma and duodenal carcinoid tumor should comprise a specific MEN syndrome.

To date, no association has been found between NF and MEN syndrome. The only positive finding was that the carcinoid tumors in these cases were somatostatinomas and the syndrome produced by excess somatostatins consisted of diabetes, diarrhoea, malabsorption and gall stones. Therefore, the literature suggests that in any patient with NF or phaeochromocytoma, who also has diarrhoea, diabetes or cholelithiasis, the possibility of a duodenal carcinoid tumor should be considered.

- Juvenile chronic myeloid leukaemia
- Other tumors of non-neurogenic origin such as thyroid carcinoma and melanoma have been reported, but there has not been enough statistical evidence to regard their occurrence as more than coincidence.

Additional features of NF1:

- macrocephaly
- short stature
- pituitary abnormalities (growth hormone deficiency, precocious puberty)
- learning disabilities
- mental retardation
- epilepsy (esp petit mal seizures in children)
- headaches
- aqeduct stenosis
- hydrocephalus
- deafness (?bony deformity or tumor within the auditory meatus)

The following table shows the major clinical features of NF1 and embryonic origin of tissue:

DISEASE FEATURE	EMBRYONIC ORIGIN
Major disease features: café-au-lait spots neurofibromas Lisch nodules	Neural crest
Major complications: intellectual handicap plexiform neurofibromas orthopedic problems (eg scoliosis) vascular abnormalities	 Neural tube Neural crest Mesoderm Neural crest
Associated tumors optic glioma peripheral nerve malignancy phaeochromocytoma	 Neural tube Neural crest Neural crest

Pathology…NF2:

- Bilateral vestibular schwannomas:
  - defining feature of NF2
  - tumors arising from vestibular branch of VIII cranial nerve
  - present with gradual progressive asymmetrical hearing loss

DIAGNOSIS

NF1: Two or more of the following:
- Six or more cafe-au-lait spots
  - 1.5cm or larger if post-puberty
  - 0.5cm or larger if pre-puberty
- Two or more neurofibromas of any type or one or more plexiform neurofibroma
- Optic glioma
- Two or more Lisch nodules (benign melanotic iris hamartomas)
- A distinctive bony lesion
  - dysplasia of the sphenoid bone
  - dysplasia or thinning of long bone cortex
- A first degree relative (ie parent, sibling, offspring) with NF1 (as diagnosed by using the above criteria)

NF2: The following CONFIRMS the diagnosis of NF2:
- Bilateral vestibular schwannomas OR
- Family history of NF2 (first degree relative) PLUS
  - Unilateral vestibular schwannoma in patient < 30 years old or
  - Any 2 of the following
    - meningioma
    - glioma
    - juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract

PROBABLE diagnosis of NF2 if:
- Unilateral vestibular schwannoma in patient < 30 years old PLUS at least one of the following
  - meningioma
  - glioma
  - schwannoma
  - juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract
- Multiple meningiomas (2 or more) PLUS
  - unilateral vestibular schwannoma in patient < 30 years old OR
  - one of the following
    - glioma
    - schwannoma
    - juvenile posterior subcapsular lenticular opacities/juvenile cortical cataract

Segmental Neurofibromatosis:
- only one body part is affected
- can be seen in NF1 or NF2

ANAESTHETIC CONSIDERATIONS OF NF

Airway

- Neurofibroma of tongue, pharynx or larynx (aryepiglottic folds or arytenoids) may interfere with intubation
- Plexiform neurofibromas occur in the cervical region and large tumors of the parapharyngeal space results in distortion of airway
- Vocal cord palsy secondary to recurrent laryngeal nerve involvement
- Important to look for dysphagia, dysarthria, stridor or change of voice on history
- May require specialist examination with indirect laryngoscopy, CT or MRI
- Macroglossia, macrocephaly, mandibular abnormalities and c-spine involvement. Painless dislocation of cervical vertebrae has been reported in a patient with multiple cervical neurofibroma. Therefore, it is recommended that c-spine x-rays are done if there is a suspicion of cervical vertebral involvement
- Always be prepared for a difficult airway

Respiratory System

- Conducting airways
  - Mediastinal neurofibromas (which originate in posterior mediastinum or spread from the retroperitoneal space or cervical paraspinal areas) cause tracheal and bronchial compression with rapidly progressive symptoms
- Lung parenchyma
  - Intrapulmonary neurofibromas are rare, usually asymptomatic with good prognosis
  - However, they may grow large and result in cough and dyspnoea
  - Association with pulmonary fibrosis resulting in restrictive lung disease. Can lead to pulmonary HPT and right ventricular failure
  - Association with cystic lung disease (large apical cysts)
  - Pneumothorax is rare, but can occur

- Chest wall deformities
  - Scoliosis/kyphosis may compromise lung function. Leads to reduction in lung volume and can result in respiratory failure
  - Neurofibromas and schwannomas can cause erosion of the ribs and can rarely cause a flail chest

Pre-operative CXR, CT thorax and lung function testing is important in these patients

CVS

HPT
- Most common CVS manifestation
- Occurs in 6% of cases
- 70% - essential HPT
- 30% - secondary to renovascular disease (eg renal artery stenosis), aortic coarctation or phaeochromocytoma

Vasculopathy and cardiac pathology
- Micronodular vascular proliferation seen in nervous system and visceral organs. May result in aortic and cerebral aneurysms
- Superior vena caval obstuction from large mediastinal tumors
- Neurofibromas of the heart may cause both hypertrophy and outflow obstruction
- Coronary artery aneurysms may be present

CNS
- Increased incidence of epilepsy, learning disabilities and undiagnosed CNS tumors
- Cerebrovascular disease may co-exist
- Cerebral and spinal neurofibromas are common. May impact on regional anaesthesia

GIT/GUS
- GI tumors present with disordered gut motility, abdominal pain, haematemesis or malena
- GI symptoms may be the first manifestation of NF
- Carcinoid tumors are common
- Neurofibromas within liver, mesentery, jejunum, large bowel, rectum, small bowel leiomyomas
- Retroperitoneal neurofibromas can result in ureteric obstruction and hydronephrosis. Also, bladder outflow obstruction.

Pharmacology
- Controversy surrounding sensitivity to neuromuscular blocking agents
- Both increased and decreased sensitivity has been reported
- The recommendation is to always use a nerve stimulator to monitor neuromuscular activity in patients with NF

SPECIAL CONSIDERATIONS IN PREGNANCY

- Associated with an increase in the number and size of neurofibromas

- ?potential for rapid increase in size of CNS tumors

- Problems in pregnancy:
  - Associated with high rate of spontaneous abortion and stillbirth
  - Pre-term labour in about 30% of patients
  - Documented evidence of difficult/obstucted labour because of uterine or vaginal neurofibroma
  - Hypertension is common in pregnant patients with NF1
  - Phaeochromocytoma and renal artery stenosis may present during pregnancy. Phaeochromocytoma may mimic pregnancy induced HPT
  - Vascular abnormalities also occur and involve vessels of any calibre and may be either aneurysms or stenosis, with HPT being the most common consequence. Therefore, it has been suggested that HPT always be investigated thoroughly and CT angiogram done to diagnose aneurysms

- Instrumental delivery is usually done to avoid expulsive efforts that may lead to rupture of an aneurysm. Therefore, these patients usually present for anaesthesia.

- Anaesthetic considerations:
  - These patients should be identified, assessed and investigated early, before the onset of labour
  - A thorough neurological examination is essential
  - Detailed informed consent must always be taken before proceeding with any form of anaesthesia or regional analgesia
  - If problems are anticipated with regional analgesia, alternate methods of pain relief can be considered eg entonox, systemic opiates
  - Mild disease: treat as for patients without NF

- Extensive disease: General vs Regional Anaesthesia
  - Regional techniques may be preferred esp if airway problems are suspected. However, regional anaesthesia may be technically difficult if patient has spinal neurofibromas or scoliosis.
  - Spinal neurofibromas have been seen in 40% of patients who have asymptomatic NF. Most arise laterally at the intervertebral foramen and are at risk of pucture from an epidural needle if they

extend towards the midline.

- It is recommended that CT/MRI of brain and spinal cord is done preferably late in pregnancy (as the tumors may increase significantly during pregnancy)
- Raised intracranial pressure must also be excluded before attempting regional anaesthesia
- With general anaesthesia, care must be taken to blunt the intubation response to prevent any increase in blood pressure (esp if aneurysms are present or suspected)

NEUROFIBROMATOSIS IN THE NEWS

Huang Chuncai: the elephant man

- born in china in 1976
- at 1 month, parents noticed that his head was distorted
- at 4 years, he developed his first sarcoma (on the face) by 31 years, the tumor was 57cm long, 97cm in circumference, weighed 23kg and had completely distorted his face. He had also lost almost all hearing and capability of speech.
- in July 2007, he underwent surgery at the Fuda Hospital in China and 15kg of tumor was removed
- in January 2008, he underwent a second operation and another 4.5kg of tumor was successfully removed

Pascal Coler

- face disfigured by NF at the age of 6
- in March 2007, he had the first successful full face transplant done by Prof Lantieri and his team of doctors in France
- the surgery lasted 16 hours and involved replacing Mr Coler's face with that of a dead donor

TAKE HOME MESSAGE

- Be aware of the clinical features of NF
- Patients may present for minor procedures – don't be fooled into thinking that the anaesthetic is minor too
- Keep in mind the association with phaeochromocytoma and carciniod tumors
- Potential difficult airway, therefore one needs to plan ahead
- Regional analgesia/anaesthesia may be a problem
- Important to investigate appropriately eg CT scan/MRI
- Special considerations in pregnancy

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