NEUROCUTANEOUS SYNDROMES

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CHAPTER CONTENTS

AIMS

This unit aims to outline the diagnosis and management of neurocutaneous syndromes via developing:

- A protocol for assessing the signs of a variety of syndromes
- A framework for making a differential diagnosis of the syndromes
- Management guidelines for the syndromes

LEARNING OBJECTIVES

At the end of these lectures and readings you will be able to:
1. Understand the diversity of presentations of neurocutaneous syndromes
2. Appreciate the complex nature of the aetiology of neurocutaneous syndromes
3. Develop a plan for clinical investigation of these conditions
4. Understand the treatment options that are available

BACKGROUND

This unit examines a group of independent multisystem syndromes, characterized by multiple tumours or tumour-like lesions of which some may be malignant.

The syndromes are sometimes called a 'phakomatosis' from the Greek word phacos meaning spot or lens.

They may arise in disparate organs of the body and present with characteristic ophthalmic features.

The main types of neurocutaneous syndromes are the following:

- Neurofibromatosis type 1 (NF-1; von Recklinghausen's disease) and type 2 (NF-2; central neurofibromatosis)
- Tuberous sclerosis
- Von-Hippel-Lindau (VHL) syndrome
- Sturge-Weber syndrome
- Wyburn-Mason syndrome

Other syndromes include:

- Ataxia telangiectasia
- Incontinentia pigmenti
- Gorlin syndrome (also known as naevoid basal cell carcinoma syndrome)

KEY OCULAR FEATURES

The key ocular features include:

- Characteristic retinal or uveal lesions
- Orbital lesions
- Adnexal lesions

SYSTEMIC FEATURES

- Characteristic cutaneous lesions in several syndromes
- Characteristic CNS lesions in all of the syndromes

NEUROFIBROMATOSIS

Neurofibromatosis is the most common phakomatosis.

It is classified into two distinct forms:

- **NF-1**
  - More common
  - 1 per 3500-4000 persons
- **NF-2**
  - No more than 1 per 40,000–50,000 persons

Males and females are equally affected with no racial predilection for either type.

Many features do not appear until late childhood or early adulthood. Severity varies markedly from patient to patient and, in some cases, the condition may not be identified due to a lack of signs.

The NF-1 gene is localized to chromosome 17q11 whereas the NF-2 gene is localized to chromosome 22q12.

NF-1 gene product – cytoplasmic protein (neurofibromin) – is hypothesized to function as tumour suppressor or negative growth regulator. Neurofibromin normally limits cell growth (via Ras pathway) and its absence or reduced expression can lead to increased cell growth.

NEUROFIBROMATOSIS TYPE 1 (NF-1)

In order to make the diagnosis for NF-1 the patient should have two or more of the following:

- Six or more café-au-lait spots
  - Each spot should be 1.5 cm or larger in post-puberty individuals
  - Each spot should be 0.5 cm or larger in pre-puberty individuals
- Two or more neurofibromas of any type or one or more plexiform neurofibroma
- Freckling in the axilla or groin
- Optic glioma
- Two or more Lisch nodules of the iris
- Distinctive bony lesion (e.g. dysplasia of sphenoid bone, dysplasia of long bones)
- A first-degree relative with NF-1

SIGNS OF NF-1

Signs associated with NF-1 include:

- Intracranial tumours
  - Usually meningiomas, gliomas
- Cutaneous signs
  - Café-au-lait spots
    - Size and number increase during childhood
  - Axillary or inguinal freckling
  - Skin neurofibromas
    - Along course of peripheral or autonomic nerves
    - Discrete/small, nodular, diffuse plexiform
    - Deeply infiltrating
    - Appear at puberty; pedunculated, flabby nodules - neurofibromas or schwannomas
    - Increase numbers during life, often widely distributed
  - Small, soft, skin-coloured to pink polypoid papules that characterize NF1. Exhibit “button-holing”: can be pressed down by light pressure and spring back when released
- Bone dysplasia and remodelling
  - Mild macrocephaly (big head)
  - Craniofacial dysplasia (sphenoid bone)
  - Vertebrae (e.g. scoliosis)
- Eyelid neurofibromas in NF-1
  - Nodular
    - May cause mechanical ptosis
  - Plexiform
    - May be associated with glaucoma
- Skeletal defects in NF-1
  - Facial hemiatrophy
  - Mild head enlargement but this is uncommon
  - Also – scoliosis, short stature, thinning of long bones

OCULAR SIGNS NF-1

- Lisch nodules (iris hamartomas)
  - Very common
    - Up to approximately 95% of patients have these nodules
  - Visible in the 2nd or 3rd decade of life
  - Translucent or pigmented
  - Small size (< 3 mm diameter)
  - See with slit-lamp examination
- Optic glioma
  - Up to 15% of patients have the glioma

  - Unilateral or bilateral
  - Benign ("Hamartoma-like")
  - True neoplasms
  - Approximately 50% of childhood optic nerve glioma occur in association with NF-1
- Fundus lesions
  - Choroidal naevi
    - Multifocal and bilateral are common
  - Retinal astrocytomas are rare
- Congenital ectropion uveae
  - Uncommon
  - If present there is an association with glaucoma
- Eyelid neurofibromas

GLAUCOMA AND NF-1

Glaucoma can occur in association with NF-1 in paediatric patients. It may also be related to the eyelid neurofibroma pressing on the globe, though it is not very common. If present, is unilateral and congenital.

In children the development of glaucoma may involve the following processes:

1. Infiltration of the anterior chamber angle by neurofibromas
2. Secondary angle closure following neurofibromatous thickening of ciliary body and choroid
3. Ectropion uveae and endothelialisation of the anterior chamber angle
4. Fibrovascularization leading to synechial angle closure and the development of neovascular glaucoma
5. Developmental angle abnormalities e.g. anterior segment dysgenesis

IRIS CYSTS & LUMPS; IRIS & CILIARY BODY TUMOURS (BENIGN & MALIGNANT)

The differential diagnosis includes general iris nodules, other iris pigmentary changes and both benign and malignant tumours of the iris and ciliary body.

The practitioner needs to consider a range of conditions such as:

- Various benign nodules and lumps
  - Associated with syndromic / systemic conditions
  - Koeppe and Bussaca nodules are possible differentials
- Cysts
  - Stromal or epithelial
- Iris
  - Naevi, melanocytoma, melanoma
  - Freckles: smaller than naevi, surface pigment, don’t distort iris
  - Bruschfield spots: pale lesions in peripheral stroma, often in patients with Down’s syndrome
  - Mammillations: tiny villiform lesions, uncommon but seen in patients with congenital ocular melanocytosis, Axenfeld and Peter’s anomaly, unilateral
- Other iris tumours
  - Leiomyoma, haemangioma, metastasis from other sites (typically breast or lung carcinoma)

INTRAOCULAR LESIONS IN NF-1

- Choroidal naevi
  - Common
  - May be multifocal and bilateral
- Retinal astrocytomas
  - Rare
  - Identical to those in tuberous sclerosis

NEUROFIBROMATOSIS TYPE 2 (NF-2)

Individuals with the following clinical features should be considered for a diagnosis of NF-2:

- Bilateral acoustic neuromas (mostly Schwannomas – from Schwann cells around nerves)
  - Hearing loss, tinnitus or imbalance
  - Not to be confused with "schwannomatosis"- a separate disease entity, without vestibular involvement
- First-degree relative with NF-2, unilateral acoustic neuroma plus any two of the following:
  - Meningioma
  - Glioma
  - Schwannoma
  - Early-onset cataract
  - Combined hamartoma of retina / RPE

Ophthalmic features:

- Cataract before the age of 30 (juvenile cataract)
  - Very common
- Fundus lesions
  - Combined RPE/retina hamartoma is commonly observed
  - Perifoveal epiretinal membranes
- Ocular motor problems
  - Seen in approximately 10% of cases
- Other conditions include e.g. optic nerve glioma, optic nerve sheath meningioma

OUTCOME AND COURSE FOR NEUROFIBROMATOSIS

Life expectancy is decreased substantially in patients with NF-1 or NF-2.

Principal causes of early death with NF-1:

- Complications of systemic hypertension
- Expansive growth of benign intracranial neoplasms
- Several types of cancer, including neurofibrosarcoma, other sarcomas, leukemias, and lymphomas, occur with increased frequency in patients with NF-1

Principal cause of early death with NF-2:

- Main cause of early death is expansion of a CNS neoplasm

Unilateral or bilateral blindness occurs in some people affected by NF-1 or NF-2. The effect on vision is usually due to glioma of the optic nerve or chiasm (especially in NF-1) or it is occasionally related to intracranial growth of a vestibular schwannoma (in NF-2).

OPTIC NERVE GLIOMA

An optic nerve glioma is a tumour of the nerve sheath. The condition arises from the nerve, chiasm or optic nerve tract. It is observed in childhood and is a benign, slow growing tumour.

Gliomas comprise approximately 70% of all ON sheath tumours.

- About 30% of patients with optic nerve glioma have NF-1
  - If bilateral it is diagnostic for NF-1
  - Present in 15% of NF-1 cases
- Presents with proptosis, visual loss, optic atrophy
- Neoplasm of astrocytes, affects primarily children (mean age, 8 years).
- No gender predilection exists

- Optic nerve alone affected in 28% of cases
    - 72% involve the optic chiasm and, of these, 43% involve the chiasm and midbrain
- Neurofibromatosis lesions may be bilateral

Signs:

- Association with NF-1 is common
- Presents end of first decade with gradual visual loss
- Gradually progressive proptosis
- Optic atrophy
- Oedema and exophthalmos

Symptoms:

- Slow loss of vision
- After an initial decrease, vision remains stable in 80% of patients
- Hypothalamic signs may be seen in 22% of cases

Treatment

- Observation only if there is no growth, good vision and good cosmesis
- Radiotherapy required if there is intracranial extension
- Excision: poor vision and poor cosmesis

Management

- Stable vision and no tumour growth only requires observation
- Progressive visual loss and tumour growth on scan indicates that surgery is required

Surgery

- Lateral orbitotomy versus craniotomy

TUBEROUS SCLEROSIS (BOURNVILLE'S DISEASE)

Tuberous sclerosis (TS) is a rare multisystem genetic disease that causes non-malignant tubers to grow in the brain and in other vital organs such as kidneys, heart, eyes, lungs and skin.

This is an autosomal dominant disease (genes involved TSC1 and TSC2),

Hamartomas occur in multiple organs from all primary germ cell layers. Approximately 60% of the cases are sporadic.

Cutaneous signs

- Confetti skin lesions; café-au-lait spots
- Skin thickening, fibrous plaques
- Hypopigmented spots (macules) on skin

Neurological signs

- Astrocytic nodules
- Hamartomas
- Giant-cell astrocytoma
- Visceral tumours

Ocular Signs

- Fundus astrocytomas
- Patchy iris hypopigmentation
- Atypical iris colobomas
- Retinal hamartomas in 50% of patients

VON HIPPEL-LINDAU (VHL) SYNDROME

Clinical hallmarks of von Hippel-Lindau disease are the development of retinal and central nervous system (CNS) hemangioblastomas (blood vessel tumours), pheochromocytomas (neuroendocrine tumours), multiple cysts in the pancreas and kidneys, and an increased risk for malignant transformation of renal cysts into carcinoma.

This is an autosomal dominant (AD) condition with mutation of chromosome 3p25-p24.

CNS haemangioblastoma (cerebellum, spinal cord, medulla, pons) affects approximately 25% of patients with retinal tumours.

- Phaeochromocytoma (adrenal gland, rare)
- Catecholamine-secreting tumours
- Renal cell carcinoma, pancreatic islet cell carcinoma
- Cysts (kidneys, ovaries, testes, lungs, liver, pancreas)
- Polycythaemia (excess RBCs)

Refer for:

- Retinal assessment
    - Retinal capillary haemangioma
        - Vision-threatening tumour in 50% of patients
        - May be multiple and bilateral
        - Associated dilatation and tortuosity of feeder vessels
- Systemic and neurological examination
- Regular physical
- Ophthalmoscopy
- Renal ultrasound, etc.

It is important to screen any relatives given the AD inheritance pattern of the disease.

STURGE-WEBER SYNDROME

This is a congenital, sporadic phakomatosis that involves the face, eyes and leptomeninges. A vascular hamartoma is the main feature of the syndrome.

Signs

- Facial naevus flammeus (i.e. a port-wine stain)
    - Extends over area of the trigeminal nerve branche(s)
    - Congenital, does not blanch with pressure
- Parietal or occipital leptomeningeal haemangioma
    - CT scan is required
    - Complications include seizures and visual field hemianopia

Ocular signs:

- Increased risk of ipsilateral glaucoma if along ophthalmic and maxillary division of the 5th cranial nerve
- Episcleral haemangioma
- Iris heterochromia
- Diffuse choroidal haemangioma
    - Typically affects patients with Sturge-Weber syndrome
    - Can be easily missed
        - Compare with normal fellow eye
    - Diffuse thickening that is most marked at the posterior pole

Ocular features:

- Buphthalmos in approximately 60% of cases
- May be associated with episcleral haemangioma