Peripheral nerve tumours

Describe the classification of peripheral nerve tumours and their relation ship to NF:

I. Benign tumours

A. Benign nerve sheath tumours

1. Schwannoma: sporadic or part of neurofibromatosis (more in NF2). Schwann cell is the cell of origin. Lobulated tumours with the nerve fibres are splayed around them (basketing). Histologically biphasic tumour with cellular area formed by spindle bipolar cells with nuclear palisading and Verocay body formation (Antoni A) and loose less cellular areas formed by multipolar or spindle cells separated by myxomatous material.. Malignant transformation is very rare< 0.001%. Bilateral acoustic schwannomas is the hall mark of NF2. Stain for S-100. Cellular schwannoma (Hypercellularity, Antoni A areas and mitosis) must be differentiated from MPNST. Stain positive for S-100 and negative for NEA.
2. Neurofibroma: the cells of origin are Schwann cells, fibroblasts and perineuronal cells. Histologically the tumour is composed of spindle cells arranged in bundles within collagen and mucopolysaccharides matrix that makes the tumour soft and even gelatinous. The nerve fibres are within the lesion. Can be sporadic or part of NF1 less commonly NF2. Plexiform neurofibromas are pathognomonic for NF1 and have high potential of malignant degeneration 5-10%. Stain for S-100,NEA (marker of perineural cells)

B. Benign non nerve sheath tumours: involve the adjacent nerves secondarily (Desmoids, myositis ossificans, ganglion cysts, lipomas, myoblastoma, hamangioma, haemangioblastoma etc…)

II. Malignant tumours:

A. Malignant peripheral nerve sheath tumours: Most MPNSTs are sporadic. Malignant changes in Schwannomas are rare <0.001% in sporadic disease and 4% in NF1. Plexiform neurofibroma can undergo malignant changes in 10%. Histologically the tumour is characterised by hypercellularity, pleomorphism, mitosis and necrosis. Cells arranged in fascicles of spindle cells with nuclear atypia, mitosis, necrosis and endothelial proliferation. Heterologous differentiation into muscle, bone, cartilage and epithelium is not uncommon. Immunoreactivity to S-100 is strong. 5 year survival in patients with NF1 is 16-18%, while 5 year survival in patients with sporadic MPNST is around 50%.
B. Malignant tumours of non nerve sheath origin with secondary involvement of peripheral nerve (cancers, lymphomas, other soft tissue sarcomas)

Neurofibromatosis Type I:

- Autosome dominant due to mutations of NF1 gene on the long arm of chromosome 17 (codes for neurofibromin which converts the active form of proto-oncogene ras-

GTP into inactive ras-GDP, hence its tumour suppressor gene properties). Incidence is 1/4000.

- Diagnostic criteria: 2 of the following

1. 6 or more cafe -au-lait spots (>5mm in prepuberty and > 15 mm after puberty). Appear in the first year and increase in size and number with time

2. Axillary and inguinal freckling
3. Lesch nodules (iris hamartomas): Slit lamp in the first decade
4. 2 or more neurofibromas or one or more plexiform neurofibroma: The last has a small risk of malignant transformation

5. Optic pathway gliomas (15%, symptomatic in 7.5%): Pilocystic astrocytomas. The majority require no treatment. Therapy is indicated in case of progressive visual loss or radiological enlargement

6. Bony abnormalities (sphenoid wing dysplasia which may cause sunken or protruding eye globe, thin cortex of long bones with possible pathological fractures and pseudoarthrosis, scoliosis, kyphosis

7. Family history of NF 1

- Other findings :(macrocephaly in 50% "HC 2 standard deviations above the main for age", astrocytomas in other parts of the brain 4% almost always Pilocystic, UBO "high signal intensities on T2 in the brain stem, basal ganglia and cerebellum (not tumours not hamartomas). Vasculopathy (Renal artery stenosis and Moyamoya variants)

- Hypertension: look for pheochromocytoma and renal artery stenosis

Neurofibromatosis Type 2:

- Autosome dominant due to mutation of NF2 gene on the long arm of chromosome 22
- Diagnostic criteria: bilateral vestibular schwannoma or family history of NF2 and unilateral vestibular schwannoma or 2 of the following (meningioma, glioma, schwannoma, neurofibroma and juvenile posterior subcapsular lenticular opacity)

- 25% have other cranial nerve schwannomas (V, III, and lower cranial nerves)
- Meningiomas in 50%. Only symptomatic and enlarging lesions need treatment
- Gliomas (astrocytomas and ependymomas) in 6-33% mostly in the spinal cord.

Phenotypes related to NF:

1. Combination of NF1 and NF2
2. Mosaicism of NF2 (unilateral vestibular schwannoma and unilateral tumours" meningiomas, astrocytomas and so on".

3. Autosome dominant multiple schwannomas or and meningiomas in the absence of vestibular schwannomas.

Describe the clinical presentations, epidemiology and natural history of peripheral nerve tumours:

- PN tumours present with soft tissue lump that can be moved from side to side but not along the nerve axis, the lump is not tender. Percussion over the lump may produce Tinel's sign. Patients may have paresthesia in the distribution of the involved nerve and in advanced cases weakness and atrophy of the innervated muscles. The presence of pain or rapid enlargement may indicate malignancy. MRI shows isointense tumour on T1, hyperintense on T2 enhancing with gadolinium. Radiologically it is difficult to differentiate schwannoma from neurofibroma from MPNST. Any patient with PN tumour should be examined for NF stigmata.
- Epidemiology:
- Natural history: Benign nerve sheath tumours are slow growing tumours. Once diagnosed they may remain static or enlarge slowly. Malignant transformation is very rare (Schwannomas <0.001% in sporadic disease and 4% in NF1. Plexiform neurofibroma can undergo malignant changes in 5-10%). Natural history of MNST is poor with 5-year survival of 16-18% in patients with NF1, and 50% in sporadic MPNST.

Discuss the treatment of peripheral nerve sheath tumours:

1. Benign tumours are treated only if they are symptomatic. In patients with NF1 only symptomatic and rapidly growing tumours are resected with intraoperative electrophysiological monitoring.
2. MPNST: treatment options include

A. Wide local resection including surrounding soft tissues (limb sparing) followed by radiotherapy and chemotherapy.
B. Amputation or forequarter resection followed by radiotherapy and chemotherapy (this should be done only in the absence of metastasis). Natural history of MNST is poor with 5-year survival of 16-18% in patients with NF1, and 50% in sporadic MPNST.

Describe the gross and microscopic pathological features of PN tumours:

- Malignant peripheral nerve sheath tumour (MPNST)

Schwannoma

- Macroscopy
  - most commonly arise from peripheral nerves in head & neck, and anterior aspects of extremities
  - cutaneous lesions well described
  - also arise from spinal and cranial nerves

- sensory nerves are preferred site of development
- majority are encapsulated globoid masses
- cut surface reveals a light tan glistening tissue
- may contain bright yellow patches, cyst & haemorrhage

- Microscopy
  - WHO Grade I
  - spindle-shaped neoplastic schwann cells with alternating areas of:
    1. compact, elongated cells with occasional nuclear pallisading (Antoni A pattern)
    2. less cellular, loosely textured, often lipidised areas (Antoni B)
  - schwann cells have abundant, faintly eosinophilic cytoplasm & spindle nuclei
  - commonly found in Antoni A areas are nuclear palisades & Verocay bodies
  - variants:
    a. cellular schwannoma
    b. melanotic schwannoma
    c. plexiform schwannoma
- **Immunohistochemistry**
  - strongly and diffusely express S-100 protein

Neurofibroma

- Macroscopy
  - most commonly a cutaneous nodule
  - less often a circumscribed mass in peripheral nerve or a plexiform enlargement of a major nerve trunk
  - occasionally involve spinal roots
  - almost unknown on cranial nerves
  - cut surface: firm, glistening and grey-tan
  - confined to nerves: fusiform & well circumscribed
  - plexiform: elongate, multinodular lesions
- Microscopy
  - WHO Grade I
  - neoplastic schwann cells, perineurial-like cells, and fibroblasts in matrix of collagen and mucosubstances
  - oval-to-spindle cell nuclei, and smaller than in schwannomas
  - unlike schwannomas, blood vessels generally lack hyalinization
- Immunohistochemistry
  - S-100 staining invariably seen, but % of reactive cells is less than in Schwannomas
  - in contrast to perineurioma, the tumour lacks EMA staining in all but residual perineurium

Perineurioma

- Macroscopy
  - peripheral nerves of extremities primarily affected (cranial nerve lesions rare)
  - segmental, tubular, several-fold enlargement of affected nerve
  - individual nerve fascicles appear course and pale
- Microscopy
  - WHO Grade I
  - neoplastic perineurial cells proliferating throughout the endoneurium, forming:
    - ⇒ concentric layers around nerve fibres
    - ⇒ pseudo-onion bulbs
- Immunohistochemistry
  - vimentin and epithelial membrane antigen (EMA) +'ve

Malignant Peripheral Nerve Sheath Tumour

- Macroscopy
  - 2/3's arise from neurofibroma, often of the plexiform type & in setting of NF1
  - most common sites:
    - buttock & thigh
    - brachial plexus and upper arm
    - paraspinal region
    - cranial MPNSTs v.uncommon
  - globoid or fusiform, pseudoencapsulated, firm-to-hard in consistency
  - cut surface typically cream-grey coloured, with foci of necrosis and haemorrhage
- Microscopy
  - WHO Grade III or IV
  - fibrosarcoma-like fasciculated growth of tightly-packed, hyperchromatic spindle cells with abundant, faintly eosinophilic cytoplasm
  - 75% have necrosis & mitotic activity
  - subtypes:
    - epithelioid MPNST
    - glandular MPNST
    - malignant triton tumour
- Immunohistochemistry
  - in 50-70%, scattered cells express S-100 protein
- Proliferation
  - growth fraction (Ki-67/MIB-1 immunoreactivity) 5-65% (<1% in neurofibromas and schwannomas)