Neurophakomatosis:

List the conditions known as neurophakomatosis and demonstrate their clinical findings:

Phacos (Greek): mole or freckle. Neurologic abnormalities combined with skin or retinal pigmented lesions and visceral organ involvement, explained by their common ectodermal (neural crest) origin.

1. Neurofibromatosis type1 and 2. look below
2. Von Hippel-Lindau disease (retinocerebellar angiomatosis).
3. Tuberous sclerosis(Bourneville's disease)
4. Sturge- Weber Syndrome(encephalotrigeminal angiomatosis)
5. Klippel-Trenaunay- Weber syndrome(spinal cutaneous angiomatosis)
6. Ataxia-Telangiectasia (Louis-Bar disease)
7. Rendu-Osler- Weber syndrome (hereditary haemorrhagic telangiectasia) .

I. Neurofibromatosis Type I:

- Autosome dominant due to mutations of NF1 gene on the **long arm of chromosome 17q** (codes for neurofibromin which acts as GTPase and converts the active form of proto-oncogene Ras-GTP (p21) into inactive Ras-GDP, hence its tumour suppressor gene properties). Incidence is 1/4000. It has 100% penetrance and variable expressivity (partially due to mosaicism-the mutation involves only subset of cells)

- 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%)

5. Optic pathway gliomas (15%, symptomatic in 7.5%): Pilocystic astrocytomas .The majority require no treatment. Therapy is indicated in 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 Pilocytic, 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, decreased IQ, dysmorphic features, pheochromocytomas, leukaemia, colonic ganglioneuromas, cerebellar leptomeningeal and astroglial heterotopias.

- Hypertension: look for pheochromocytoma and renal artery stenosis

Neurofibromatosis Type 2:

- NF2 is an autosome dominant due to mutation of NF2 gene on the **long arm of chromosome 22**.This gene codes for a protein called Merlin which links membrane proteins to proteins of cytoskeleton and plays a role in signal conduction. Overexpression of this gene inhibits growth (tumour suppressor gene).

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).Symtoms develop in 2d and 3d decade. The condition should be suspected in patients with acoustic schwannoma younger than 30, in a child with meningioma, multiple CNS tumours (ependymomas, astrocytomas)

- 25% have other cranial nerve schwannomas (V, III, VII 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.

II. **Von Hippel-Lindau disease (retinocerebellar angiomatosis**

- Autosome dominant disease with 80% penetration and variable expressivity due to mutation of VHL gene on **3p chromosome** (codes for VHLp16 and 30 which binds to elongin B and C and inactivates it.

Elongin is necessary for transcription of RNA polymerase II and so acts as tumour suppressor gene. Cells lacking VHLp overrexpress erythropoietin (hence the polycythemia in 25% of patients) and VEGF (hence the vascularity of haemangioblastomas. Incidence is 1: 40000.

- Clinical manifestations:

1. Multiple haemangioblastomas: 100% of patients (younger age 29 years, multiple, supratentorial spinal ad brain stem).
2. Retinal haemangioblastomas: 50%
3. Pheochromocytomas: 35%
4. Liver, pancreas, renal and epididymis cysts
5. Renal cell carcinoma develops in the majority of patients and is the second common cause of death following complications from cerebral haemangioblastoma.

III. **Tuberous sclerosis (Bourneville's disease**):

- Autosomal dominant with 80% penetrance and variable expressivity. 50% due to new mutation
- Incidence 1/10000-1/17000 live births
- Due to mutations of TSC1 and TSC2 genes on **9q a**nd 1**6p** chromosomes. They code for protein Hamartin and Tuberin respectively. These proteins are necessary for differentiation of neurons and have GTPase activity. Overexpression blocks cell growth
- Clinical manifestations:

1. Voght's clinical triad (1.Seizures 2. Mental retardation 3. Adenoma sebaceum (facial angiofibroma) is found in < than 1/3 of patients.
2. Skin lesions include: depigmented skin macules, facial angiofibromas(adenoma sebaceum), subungual angiofibromas of fingers and toes, ash-leaf spots and subependymal fibrosis(shagreen patch)
3. CNS manifestations include: Subependymal giant cell astrocytoma in6% of patients, cortical and subcortical tubers (hamartomas)
4. Visceral manifestations; 50% have cardiac rhabdomyoma, renal angiomyolipoma and hamartomas in the skin, heart, kidneys.

IV. **Sturge- Weber Syndrome (encephalotrigeminal angiomatosis**):

- Congenital vascular malformation affecting the head, face, and brain. The primary process appears to be faulty development of the venous drainage for the cerebral capillary bed. A similar process affects the skin, eye, and the soft-tissues of the head.

- Clinical manifestations:

1. Unilateral facial capillary haemangioma (port-wine stain) in the distribution of the first and second divisions of the trigeminal nerve.
2. Ipsilateral parieto-occipital leptomeningeal venous angiomatosis. After birth, there is progressive atrophy of the affected hemisphere(s) Patients present with seizures or spastic hemiparesis within the first 2 years of life. The disease is usually unilateral, but bilateral cases can occur
3. Cortical atrophy with calcification and cystic degeneration under the area of angiomatosis
4. Angiomas may involve the eye and be associated with glaucoma

V. **Klippel-Trenaunay- Weber syndrome (spinal cutaneous angiomatosis):**

- Possible autosomal dominant with incomplete penetrance
- Skin haemangiomas in dermatomal distribution associated with spinal cord haemangiomas in the same dermatomal distribution.
- Osseous or muscular hypertrophy of the involved limb.

VI. **Rendu-Osler- Weber syndrome (hereditary haemorrhagic telangiectasia):**

- Autosomal dominant characterised by fibrovascular dysplasia leading to the development of telangiectasias, arterio-venous malformations and aneurysms of the skin, mucous membranes and CNS
- Clinical presentations: Epistaxis, gastrointestinal , genitourinary and subarachnoid haemorrhage
- Can present with brain abscess secondary to septic emboli from the lung(arteriovenous malformation)

VII. **Ataxia telangiectasia:**

- Autosome recessive
- Clinical presentations :p

1. Progressive ataxia due to degeneration of Purkinje cells. Starts early in life
2. Multiple cutaneous telangiectasias starting from the age of 3 years
3. Intellectual impairment

4. Humoral and cellular immunodeficiencies and predisposition to malignant disease, especially lymphoma and leukaemia

Death usually in the second decade due to infection or neoplasia

Discuss the genetic testing and prenatal diagnosis of neurophakomatosis:

1. **Neurofibromatosis**: Genetic testing is available for families with documented cases of NF1 and NF2. Genetic analysis can be used to confirm clinical diagnosis if the disease is a result of familial inheritance. New (spontaneous) mutations cannot be confirmed genetically. Prenatal diagnosis of familial NF1 or NF2 is also possible utilizing amniocentesis or chorionic villus sampling procedures
2. **VHL syndrome**: Molecular genetic testing is indicated for all individuals known to have or suspected of having VHL syndrome. Since the detection rate for VHL gene mutations is nearly 100%, molecular testing may also be used to evaluate individuals with a single VHL-associated tumour and a negative family history of the disease. For individuals with manifestations of VHL syndrome who do not meet strict diagnostic criteria and who do not have a detectable VHL germline mutation, somatic mosaicism for a de novo VHL disease-causing mutation should be considered. In some instances, molecular genetic testing of the offspring of such individuals reveals a VHL mutation. VHL syndrome should be suspected if patient is diagnosed with **haemangioblastoma at age < 30 years, multiple haemangioblastomas and extracerebellar location and family history of VHL syndrome.** Prenatal diagnosis for pregnancies at 50% risk is possible by analysis of DNA extracted from fetal cells obtained by **amniocentesis,** usually performed at about **15-18 weeks'** gestation, or **chorionic villus sampling (CVS), at about 10-12 weeks' gestation**. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.
3. **Tuberous sclerosis**: There are three primary uses for this DNA testing: confirmation of diagnosis made on clinical grounds, carrier testing for other at-risk family members and prenatal diagnosis. It is possible to identify approximately 80% of the mutations in samples that are submitted for testing. In the other 20% of the cases, the mutation is considered a hard to find mutation or a new mutation (a mutation on a new spot in the gene) not yet known to cause TSC.

Discuss the indications for intervention in treatment of fibromas in patients with NF:

There is no cure for NF1 or NF2. Present treatments are aimed at controlling the symptoms of the disease. For NF1

1. Surgery can remove painful or disfiguring tumours; however, there

is a chance that the tumours may grow back and in greater numbers, according to NINDS.

2. In the rare instances when tumours become malignant (rapid growth, become painful) (3 to 5 percent of all cases), treatment may include surgery, radiation, or chemotherapy.
3. Scoliosis or tibial pseudoarthrosis.

For NF2 surgery or stereotactic radiosurgery are used to

4. Treat vestibular schwannomas with the aim of preserving hearing or delaying hearing loss, relieving mass effect
5. Remove symptomatic meningiomas which tend to be multiple with tendency to reoccur

The average life span in NF2 is only 40 years