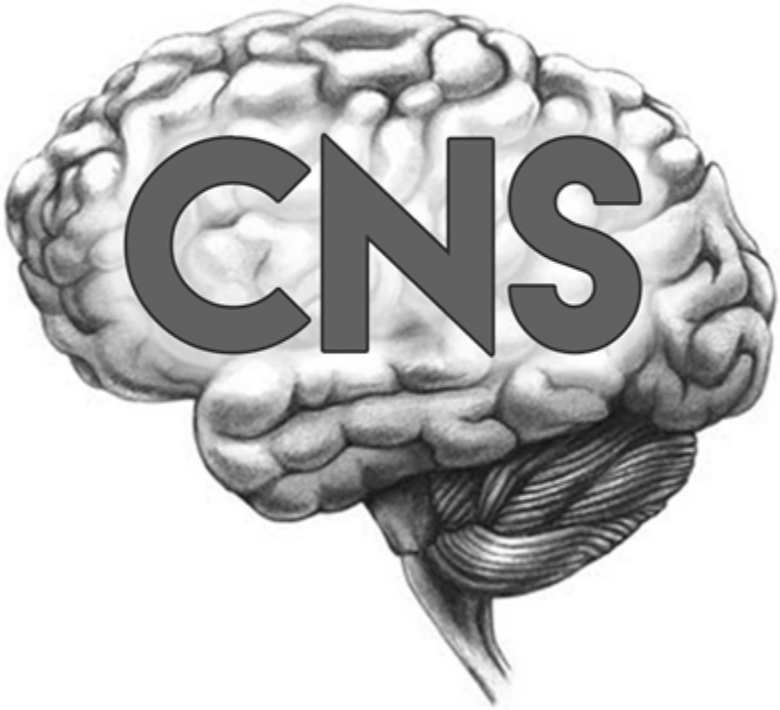

PATHOLOGY

☑ Sheet ○ Slide ○ Handout

Number

11

Subject

CNS tumors 3

Done By

Esra'a Abdo

Corrected by

Correction team

Doctor

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Date: **00/00/2016**

Price:

In the name of Allah we start

CNS tumors

This sheet was written according to the records of section 1 and section 3.

In the previous lectures we started talking about epidemiology, characteristics, and classification of CNS tumors. Also we have talked about the types of gliomas: astrocytomas, oligodendrogliomas, and ependymomas.

Topics of this lecture :

- Embryonal neoplasms : medulloblastoma.
- Meningioma .
- Primary CNS lymphoma and Metastatic tumors.
- Paraneoplastic syndromes.
- Familial tumor syndromes.

Embryonal neoplasms : medulloblastoma

⇨ These are tumors of neuroectodermal origin, the most common type of these tumors: medulloblastoma.

◆ 7 year old child presented with recent ataxia, his mother reported a three months history of headache, vomiting, and lethargy.

- What do you expect ?

- Headache, vomiting, and lethargy → increased intracranial pressure (ICP) which can be due to tumor.
- Ataxia → most likely if the child has a tumor, it will be in the cerebellum.

∞ So the child has symptoms indicate increased ICP then he develops ataxia, thus we can expect that he has a lesion in the cerebellum.

- What are the possible causes of this lesion ?

- Tumor.
- Increased ICP.
- AV malformation.
- Infections.
  - How can we identify this lesion ?
- By imaging studies; using MRI and CT scan.
- After applying these imaging studies, we noticed that there are masses in the cerebellum [figure 1].

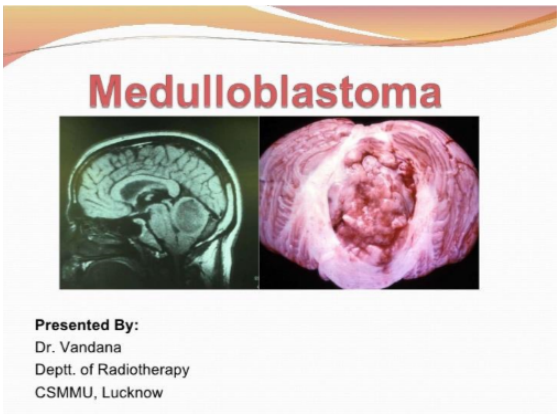


Figure 1 : MRI of the brain presenting medulloblastoma.

- Masses in the cerebellum among children can be recognized in Pilocytic astrocytoma which is benign tumor; WHO grade 1 or other tumors such as medulloblastoma (our case in this lecture).
- Then; how can we know the type of tumor that causes this masses, and how can we differentiate between different types?
- -By taking a biopsy.

Pilocytic astrocytoma	Medulloblastoma
- Presence of cysts. - Low cellularity. - Morphology : * bipolar cells with long GFAP positive processes. * Rosenthal fibers. * eosinophilic granular bodies.	- No cysts. - Very high cellularity. - Morphology : *Small round blue cells. * Homer Wright Rosettes; primitive tumor cells around pinkish material known as neuropil.

❖ Medulloblastoma :

- Highly aggressive tumors (WHO IV).
- Neuroendocrine differentiation.
- Highly sensitive to radiotherapy.
  - ⇨ Many tumors in our body, not only in the brain, have this appearance with small round blue cells, all of them are neuroendocrine tumors and very highly aggressive; such as : Small cell carcinoma of the lung (has some similarity to those properties of medulloblastoma).
- Blastoma = primitive undifferentiated cells.
- Histology of medulloblastoma :
  -Highly cellular.
  -Sheets of small round blue cells [figure 2]. They express neuroendocrine markers; then they take a chromogranin synaptophysin stain (a stain for neuroendocrine tumors).

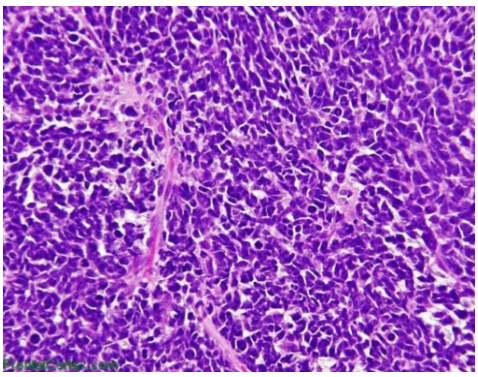


Figure 2 : morphology of medulloblastoma.

Small round blue (basophilic) cells.

-Many mitosis.

-Homer Wright Rosettes [figure 3] = primitive tumor cells surrounding central neuropil (pink material formed by neuronal processes).

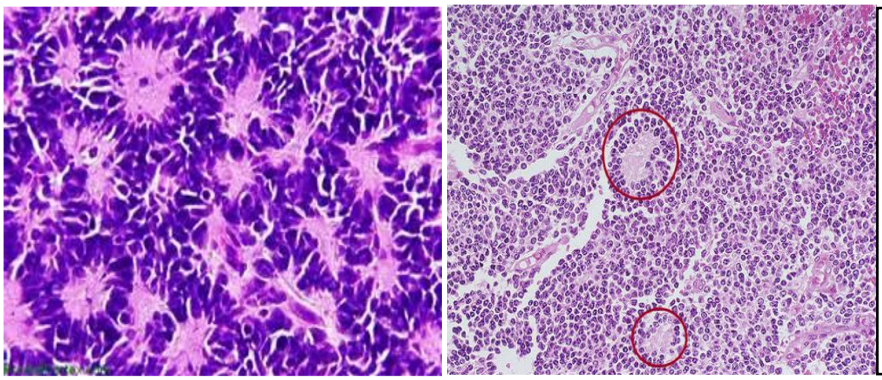


Figure 3 : morphology of medulloblastom.

Homer Wright Rosettes.

⇨ Remember that we can see rosettes also in ependymoma which can be **true rosettes** arise around canals, or **pseudorossetes** arise around blood vessels.

⇨ So, rosettes can be seen in two tumors : Ependymoma. / Medulloblastoma.

- It's not a common tumor, but it's the most common childhood CNS tumor ; **20%** of pediatric brain tumors.
- Most common in children; but it can affect adults.
- Medulloblastoma occurs only in the cerebellum (this might change with the new WHO classification).
- Bad prognosis if it's not treated.

- One of the rare CNS tumors that can metastasize and go outside the CNS because they are very aggressive tumors, they are locally in the brain but also can spread outside it; most commonly they go to the bone then we can do a bone scan to the patient to make sure if there is a metastasis or not; and that's why medulloblastomas are also one of the rare CNS tumors that have M-staging.
  - Very bad and aggressive tumors, but the good thing that there is a treatment; we treat them aggressively by chemotherapy + radiotherapy + surgery.
  - Side effects of using craniospinal radiation :
    -Destroys the cells.
    -Learning\ Mental disabilities; they don't do well in their schools for example.
    - Endocrinopathy; pituitary gland might affected and then they develop hypopituitarism, hypothyroidism, and growth retardation due to the decrease in growth hormone.
    -Increase risk of secondary malignancies including leukemias and lymphomas.
    -Ataxia (we targeting the cerebellum).
    -Vision\ Hearing can be affected.
    - ⇨ These side effects are closely related to dose of radiation therapy and age at diagnosis, the earlier the age,the worse the neurologic toxicity for the developing brain.
      With this aggressive treatment, the 5 year survival reaches 75% but the child might live with disabilities and the older the child, the lower the risk of side effects.
    - ⇨ We try as much as we can to avoid radiotherapy especially in children younger than 3 years; because their brains are still growing and developing.
    - ⇨ To avoid radiotherapies, we have to discover new treatments and this can happen if we know the genetic mutations behind the disease then we can think up of new targeted therapies which are specific to the mutations.

- Genetics :

  There are several mutations (4 mutations actually) but the most important and most common two mutations are :

  - MYC amplification: those with MYC mutation they have a **poor prognosis** (MYC = transcription factor).

  - WNT signaling pathway mutations [figure 4] : better prognosis and there is a targeting therapy without using radiation then the patients can live without the side effects of radiotherapies.

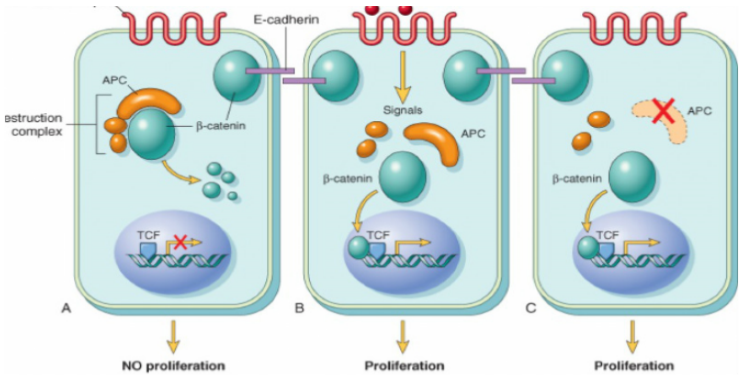


Figure 4 : WNT signaling pathway.

WNT is a soluble small protein act through the beta catenin, as long as there is no stimulation from WNT, the beta catenin is attached to destruction complex that destroys it and then there is no proliferation – the same role as p53 with MDM2–, while if there is a WNT stimulation, the beta catenin will be released from its destruction complex then it becomes free and will translocate to the nucleus to stimulate transcription; so it causes proliferation and possible malignancy .

Then if there is a mutation that will increase the activity of WNT (over activation mutation); beta catenin becomes free, goes to the nucleus, and causes proliferation (medulloblastoma in this case).

* How can we know if there is a WNT mutation or not?

-WNT stain is not available.

-Beta catenin stain [figure 5]:

it's available (found in the UJ hospital), easy, and not expensive.

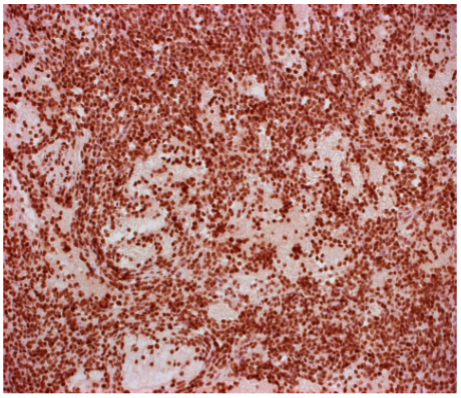


Figure 5 : Beta catenin stain.

If positive then the medulloblastoma has WNT signaling mutation: better prognosis.

If there are beta catenin; all the nuclei will take the stain (brown color) and this reflects the over activity of WNT, then we can know that the patient has a WNT mutation (not a beta catenin mutation) with better prognosis than those with no WNT mutation and we give him a targeted therapy.

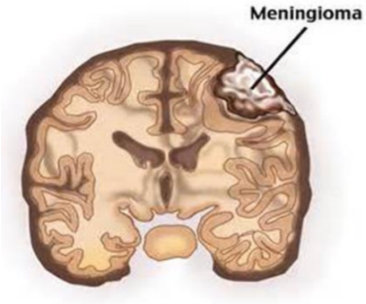
Beta catenin will take the stain in both situations, either if they are free or if they are attached to the complex, and from the position of the brown stain we can know if there is a mutation or not : if the brown color is in the nucleus, this indicates that the beta catenin are in the nucleus and then there is a mutation; while if the brown color is in the cytoplasm then we consider it as negative stain means that the normal beta catenin taking the stain.

Meningioma

- 53 year old woman presented with headache and blurred vision, the doctor reassured her and told her to test her vision, three months later she comes back complaining from seizures.

- What are the possible diagnosis for this case ?

- Can be anything affects the optic tract: tumors, infection, inflammations.
- At first, the doctor thought that the cause of headache is the blurred vision.
- But then when she comes back with seizure, the doctor thought that most likely there is tumor causes compression on the optic nerve and that's why she had that symptoms.
- After doing a CT scan, we find a mass that is not arising from the brain but from the meninges known as meningioma [figure 6].



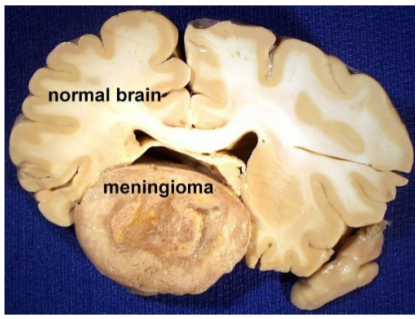


Figure 6 : meningioma.

❖ **Meningioma** [figure 6] :

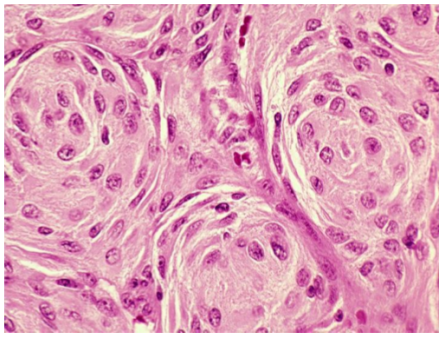
- Doesn't arise from the brain, but it can infiltrate to the brain sometimes.
- Arise from arachnoid meningothelial cells so it has a very good prognosis.
- It's relatively a common tumor.
- Usually occurs in women within 40-50 age groups.
- Histological grades : WHO I, WHO II, and WHO III, there is no WHO IV meningioma.
  They are the counterpart of WHO II, WHO III, and WHO IV in other tumors.
  The less bad one is WHO I and the worst one is WHO III.

- **WHO I: (well differentiated) meningioma** →

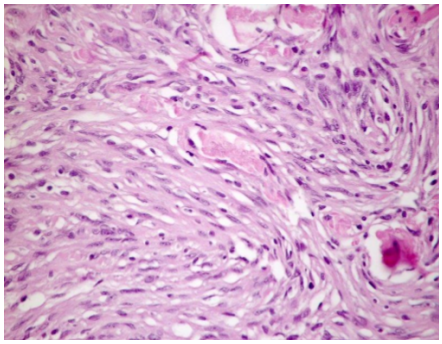
  It's a benign tumor; when it removed everything comes back to normal.

  Many histological types:

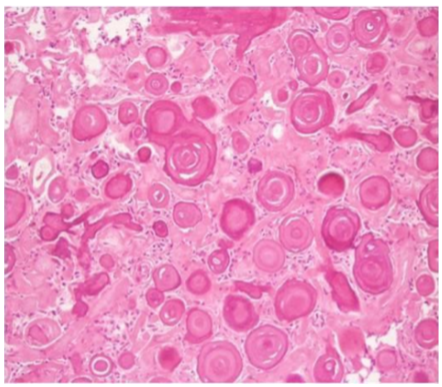
  - Syncytial : whorled clusters without visible cell membranes (دوائر, دوّامات).

  - Fibroblastic: elongated cells and abundant collagen.

  - Transitional: features of both, syncytial and fibroblastic (in between).
  - Psammomatous: numerous psammoma bodies (calcification).

⇨ Psammoma bodies can be recognized in :
-Meningioma.
-Papillary thyroid carcinoma.
-Some ovarian tumors, especially Serous tumors. (we will study them in genitourinary system).

⇨ It's important to know these histological features because if there is a metastatic tumor not known from where it's originate and we recognized the presence of psammoma bodies on the histological picture then we will think of one of these three tumors.

- **WHO II: atypical meningioma** [figure 7]→

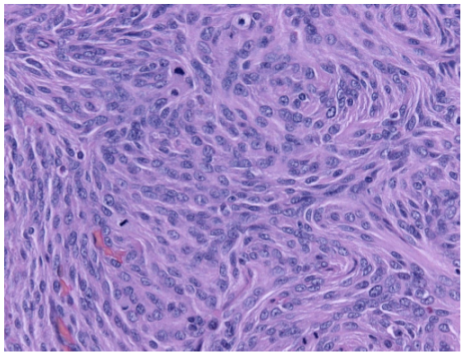


Figure 7 : Atypical meningioma.

Increase in cellularity and mitosis (mitotic activity).

- **WHO III: anaplastic (malignant) meningioma** →
  - Resemble sarcomas.
  - Highly aggressive.

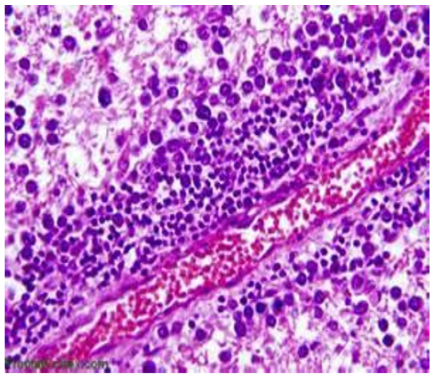
Primary CNS lymphoma and Metastatic tumors.

◆ 65 year old male had a confusion, they thought that it's due to aging, then he comes with headache and vomiting followed by seizures.
Vomiting and headache → increased ICP.
After doing a CT scan, we found multiple masses\ tumors.

- What are the tumors that cause multiple masses in the brain?
  - Differential diagnosis:
    - Lymphoma.
    - Metastatic tumors: if we see multiple masses in any organ of the body, we think of metastasis because the tumors send many cells, each one of them will grow independently and form a mass then we will end up of multiple masses.
      ∞ Thus, multiple masses in the brain can be due to lymphoma or metastatic tumors.
- What can we do to make sure and know which one of them that caused the multiple masses?
  - We take a biopsy.
  - Histologically; if there are small cells arranged around blood vessels then it's a lymphoma.

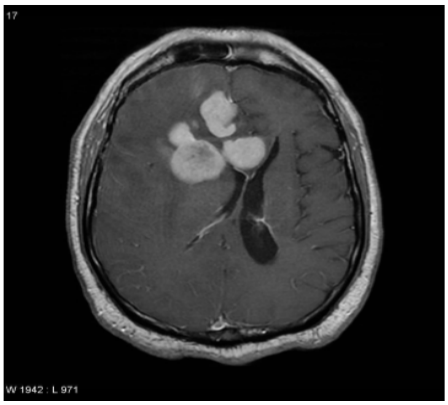
❖ **<u>Lymphoma</u>** →

- The characteristic picture of lymphoma in the brain :Tumor cells are closed to the blood vessels.



➔ Note arrangement around blood vessels.

- Usually <u>multiple</u> nodules within the brain parenchyma.



- Occurs in the elderly.
- Aggressive disease with poor prognosis.
- The most common lymphoma in the brain is diffuse large B-cell lymphoma that is usually related to EBV (Epstein – Barr virus).
- Can be developed in immunocompetent and immunocompromised people. The most common brain tumor in immunocompromised people is primary CNS lymphoma (diffuse large B-cell lymphoma).
- Treated by chemotherapy, which is given intrathecally, and some types are given intravenously.
- In general; lymphomas are highly respond to chemotherapy, however; the response of primary brain lymphoma to chemotherapy is less sensitive than the peripheral lymphoma and that's why their prognosis is worse.
- Lymphoma in the brain usually doesn't go outside and lymphoma in the periphery (lymph nodes and other organs) doesn't go to the brain. They act as two different diseases; if they present in the same person we know that both of them are primary tumors.

❖ **<u>Metastatic tumors</u>** →

- Can be multiple masses (tumors send cells and each one of them can form a mass).
- ¼ to ½ of intracranial tumors.
- Most common primary sites: lung, breast, melanoma, kidney and GIT.

Paraneoplastic syndromes

- CNS and peripheral nerves can be affected in disseminated cancer as part of the paraneoplastic syndromes.
- These include several manifestations including dementia, ataxia, sensory neuropathy and psychosis.

➔ Meaning that if we know that the patient has a disseminated cancer (stomach cancer for example) and then he comes with CNS signs and symptoms, these symptoms not necessarily indicate that the patient has metastasis to the brain, it could be due to metastasis or due to the involvement of CNS in a paraneoplastic syndrome.

- Paraneoplastic syndrome : symptoms that can't be explained by the primary site of the tumor, metastasis, nor endogenous hormone secretions.

Familial tumor syndromes

- Usually the brain is affected by certain familial conditions known as familial tumor syndromes, this means that the person has an inherited syndrome which makes him more susceptible to develop tumors such as brain tumors.
- Inherited syndromes (they are inherited as autosomal dominant; one mutation is enough to have the phenotype).
- Mutations in several tumor suppressor genes.
- Associated with increased risk of certain types of cancer.
- We are going to talk about two syndromes : **Tuberous sclerosis** and **von Hippel Lindou**. → (both are inherited (AD) and both have a mutation in tumor suppressor genes).

A. <u>Tuberous sclerosis</u> →

- It's a mutation in tumor suppressor genes.
- Syndrome inherited as autosomal dominant (AD).
- They cause **<u>hamartomas</u>** and benign neoplasms in brain and other sites.

  Hamartomas = It is composed of tissue elements normally found at that site, but they are growing in a disorganized manner.

  It was considered as a congenital anomaly not a neoplasm, but nowadays we think that it's neoplastic because there is certain translocation.

  For example:

  -Hamartomas in the lung : normally, the lung has alveoli and cartilage arranged in certain way, but in case of hamartoma they become disorganized.

  - Hamartomas in the brain : mixture of glial and neuronal elements, but they are not arranged as a normal architecture.

- CNS tumors: **cortical tubers** and **subependymal hamartomas** (they are benign conditions).

❖ **<u>cortical tubers</u>** [figure 8]→

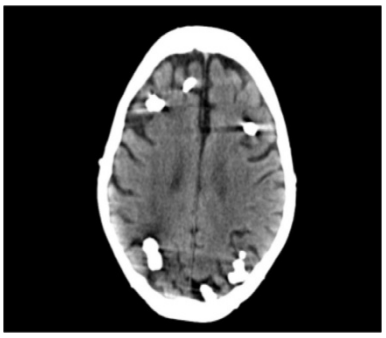


Figure 8: tuberous sclerosis.

Brain masses look like potato.

- Cortical tubers: look like potatoes (درنات تنمو تحت الأرض); Tuber: thickened underground part of a stem.
- It's named tuberous because it's form masses in the brain that look like potato.
- Cause **seizures**.

❖ **subependymal hamartomas** →

- Can cause **hydrocephalus**.

❖ **Tuberous sclerosis/Extra-cerebral lesions** →

It's a syndrome; so it will affect brain and other organs and causes hamartomas everywhere :

- **Renal angiomyolipoma** : angio = blood vessels, myo = muscles, lipoma = fat → They are the normal components of the lung but here they are disorganized and arranged haphazardly.
- **Retinal glial hamartomas**.
- **Pulmonary lymphangiomatosis** : lymphatics are part of pulmonary; so it can be considered as a form of hamartomas.
- **Cardiac rhabdomyoma**.
- **Cysts in liver, kidney , and pancreas.**
- **Skin lesions:** angiofibroma, hypopigmented areas, thickened patches**.** → These features are very important because they can be observed and seen on the patient. The patient comes with thickened patches everywhere and hypopigmented areas of skin; if we see this appearance then we think that this patient might has tuberous sclerosis.
  *Sclerosis = thickened patches of the skin.

Choristoma vs Hamartoma →

Choristoma : A mass of histologically normal cells with normal architectures present in an abnormal location; for example; normal pancreatic tissue present in the stomach (outside the pancreas).

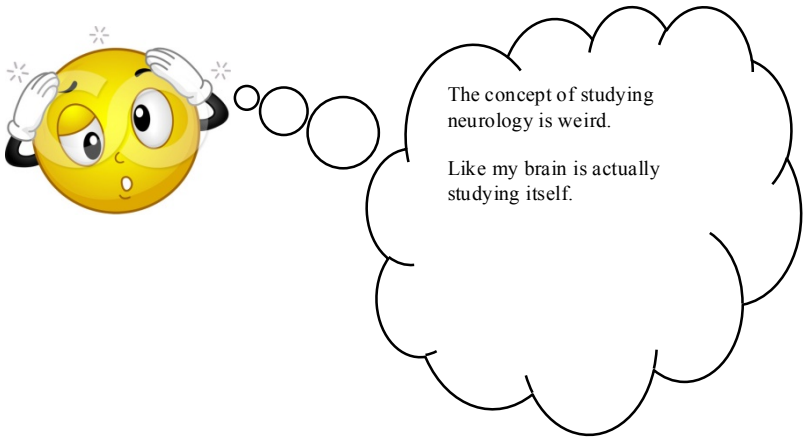
It's a congenital anomaly not a neoplasm.

Hamartoma : It's composed of tissue elements normally found at that site, but which are growing in a disorganized mass.

B. <u>Von Hippel Lindau</u> →

- Inherited as autosomal dominant (AD).
- Mutation in Von Hippel Lindau (VHL) tumor supressor gene.
- It causes **hemangioblastomas** mainly in cerebellar hemispheres, retina.

  Hemangioblastomas : hemangio = related to blood vessels, blastomas = primitive cells.
- Cysts in pancreas, liver, and kidney.
- A big problem about von hippel lindau that <u>it's Increase risk of renal cell carcinoma</u>; while in tuberous sclerosis they all considered as a benign conditions.
- A mutation in VHL tumor suppressor gene will result in development of vascular tumors; because this gene is related to angiogenesis and hypoxia-inducible factors (HIFs); if it mutated there will be an over activation of hypoxia-inducible factors (HIFs) and this will lead to development of vascular tumors.



~~~ The end of CNS tumors ~~~

~~ The end of pathology lectures ~~

~ All the best ~

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