**بسم الله الرحمن الرحيم**

**هذه عبارة عن سلايدات الدكتور مع بعض النوتات من المحاضرة.**

**Pathology of central nervous system**

**ib8ri**

**Infections of the central nervous system**

* *Meningitis* refers to an inflammatory process of the leptomeninges and CSF within the subarachnoid space.
* *Meningoencephalitis* refers to inflammation of the meninges and brain parenchyma
* *Encephalitis* refers to inflammation of the brain parenchyma.
* Portals of entry of infection into the CNS
	+ *Hematogenous spread*
		- the most common means of entry.
		- ((retrograde venous spread can occur through anastomotic connections between veins of the face and cerebral circulation))
	+ *Direct implantation* *of microorganisms*
		- traumatic or in congenital CNS malformation
	+ *Local extension*
		- occurs secondary to an established infection in a near by organ (air sinus, an infected tooth or middle ear)
	+ Through the *peripheral nervous system* *into the CNS*
		- certain viruses, such as rabies and herpes zoster.

***Meningitis***

An inflammatory process of the leptomeninges and CSF within the subarachnoid space.

***Pyogenic meningitis:***

* Medical emergency
* The causative microorganisms:
	+ **Neonates and infants**: *Escherichia coli*, *Listeria* and the group B streptococci
	+ **Older infants ,children's, adolescents and in young adults:** *Streptococcus pneumoniae* ,*Neisseria meningitidis* (Meningococcal meningitis) and *Haemophilus influenzae* ((immunization against *Haemophilus influenzae* has markedly reduced the incidence of meningitis associated with this organism))
	+ **Elderly , immunecompromised patients & neonates :** listeria monocytogens
	+ *S. aureus* and gram negative rods are common after placement of surgical shunts
* **CSF Findings in spinal tap**
	+ cloudy or frankly purulent CSF
	+ as many as 90,000 neutrophils /mm
	+ a raised protein level
	+ a markedly reduced glucose content
	+ Bacteria may be seen on a Gram stained smear or can be cultured, sometimes a few hours before the neutrophils appear

**Acute meningitis:**

**Clinical Features**

* Systemic signs of infection
* With meningeal irritation signs and neurologic impairment
* Headache, photophobia, irritability, clouding of consciousness and neck stiffness
* Untreated, pyogenic meningitis can be fatal
* Effective antimicrobial agents markedly reduce mortality associated with meningitis

**Complications**

* Phlebitis, that may also lead to venous occlusion and hemorrhagic infarction of the underlying brain
* Leptomeningeal fibrosis and consequent hydrocephalus
* Septicemia with hemorrhagic infarction of the adrenal glands and cutaneous petechiae (known as Waterhouse-Friderichsen syndrome, particularly common with meningococcal and pneumococcal meningitis)
* Focal cerebritis & seizures
* Cerebral abscess
* Cognitive deficit
* Deafness

**Brain abscess**

* May arise from:
	+ Direct implantation of organisms
	+ Local extension from adjacent foci (mastoiditis, paranasal sinusitis)
	+ Hematogenous spread (usually from a primary site in the heart, lungs, distal bones or after tooth extraction)
* Streptococci and staphylococci are the most common organisms identified in non immunosuppressed populations(normal people )\*
* Predisposing conditions:
	+ Acute bacterial endocarditis (usually give multiple microabscesses)
	+ Cyanotic congenital heart disease in which there is a right-to-left shunt

*((السبب : لوكان فيه بالجسم organisms راح تمنع الرئه وصولها للمخ وتسويلها فلتره*

*ولكن مع right-to-left shunt في هذي الحاله ماراح يمر الدم على الرئه ويروح للمخ ))*

* + Loss of pulmonary filtration of organisms ( e.g. chronic pulmonary sepsis, bronchiectasis)
* Most common on cerebral hemispheres
* Morphologically,
	+ it is composed of liquefactive necrosis
	+ The surrounding brain is edematous , congested & contains reactive astrocytes & perivascular inflammatory cells.
* Present clinically with progressive focal neurologic deficits in addition to the general signs of raised intracranial pressure
* The CSF
	+ Contain only scanty cells
	+ ↑ protein
	+ Normal level of glucose
* Complications of Brain abscess:
	+ Herniation
	+ Rupture of abscess into subarachnoid space or ventricle

**Tuberculosis**

* Chronic meningitis
* The subarachnoid space contains a gelatinous or fibrinous exudate, most often at the base of the brain
* **Tuberculoma** is well-circumscribed intraparenchymal mass
* Rupture of tuberculoma into subarachnoid space results in tuberculus meningitis, & may present as acute or chronic
* A tuberculoma may be up to several centimeters in diameter, causing significant mass effect
* Always occurs after hematogenous dissemination of organism from primary pulmonary infection
* On microscopic examination, there is usually a central core of caseous necrosis surrounded by a typical tuberculous granulomatous reaction

**CSF in TB**

* There is only a moderate increase in cellularity of the CSF (pleiocytosis) made up of mononuclear cells, or a mixture of polymorphonuclear and mononuclear cells
* The protein level is elevated, often strikingly so
* The glucose content typically is moderately reduced or normal

**Fungal infection**

* *Candida albicans, Mucor, Aspergillus fumigatus*, and *Cryptococcus neoformans* are the most common fungi that can cause encephalitis
* *Parenchymal invasion,* usually in the form of granulomas or abscesses, can occur with most of the fungi and often coexists with a meningitis
* *Cryptococcal meningitis and meningoencephalitis*
	+ Observed often in association with AIDS. It can be fulminant and fatal in as little as 2 weeks, or indolent, or it can evolve over months or years

**Toxoplasmosis**

* Causative organisms: Toxoplasma gondii
* The clinical symptoms are subacute, evolving during a 1- or 2-week period, and may be both focal and diffuse
* Ingestion of raw or partly cooked meat, especially pork, lamb, and Ingestion of contaminated cat faeces
* Transplacental transmission --> severe brain injury in neonate (Neonatal hydrocephalus, microcephaly, intracranial calcifications, chorioretinitis, blindness, epilepsy, psychomotor or mental retardation, Rare classic triad - Chorioretinitis, hydrocephalus, cerebral calcifications)
* Most common causes of neurologic symptoms and morbidity in patients with AIDS (40%) -Necrotizing encephalitis-and in immunocompromised Pt.
* Ocular toxoplasmosis (chorioretinitis)

**Viral infections**

* The most common cause of encephalitis
* Almost invariably associated with meningeal inflammation
* General features:
	+ - Perivascular inflammatory infiltrates(mononuclear cells)
		- Microglial nodules \*\*
		- Inclusion bodies

**Herpes simplex encephalitis**

* + HSV type 1 encephalitis causes hemorrhagic necrosis of temporal lobes & orbital frontal areas
	+ Most common in children and young adults
	+ Cowdry type A intranuclear viral inclusion bodies can be found in both neurons and glia

**HIV infection**

* HIV patients are prone of multiple diseases that can affect the CNS, PNS and the skeletal muscle. Infection is just an example.
* Patients affected with HIV encephalitis with dementia referred to as AIDS-dementia complex
* The dementia begins insidiously, with mental slowing, memory loss, and mood disturbances, such as apathy and depression
* Motor abnormalities, ataxia, bladder and bowel incontinence and seizures can also be present

**Morphology, HIV encephalitis**

* On macroscopic examination:
	+ the meninges are clear, and there is some ventricular dilation with sulcal widening but normal cortical thickness
* Microscopically:
	+ a chronic inflammatory reaction with widely distributed infiltrates of microglial nodules, sometimes with associated foci of tissue necrosis and reactive gliosis.
	+ multinucleated giant cell\*\* the hallmark of HIV encephalitis

**Prion diseases**

* A group of neurodegenerative conditions characterized clinically by slowly progressive ataxia and dementia and pathologically by accumulations of fibrillar or insoluble prion proteins, degeneration of neurons, and vacuolization, termed spongiform degeneration
* Lack of infection
* **Group of diseases includes in humans:**

1-Creutzfeldt-Jakob disease (CJD),Gerstmann-Sträussler-Scheinker syndrome (GSS)

2- Fatal familial insomnia, bovine spongiform encephalopathy (BSE)" mad cow disease"

* They are all associated with abnormal forms of a specific protein, termed prion protein (PrP)
* **Pathogenesis:**

Unique diseases can be genetic, sporadic or infectious

* + Misfolding or conformational change of the normal prion protein (PrPc) converts it to an insoluble, protease resistant isoform PrPsc.which precipitates as amyloid.(amyloid- rich deposited known as Kuru plaques\*\*)
	+ Loss of function of (PrPc) or toxicity of PrPsc.cause neuronal degeneration and loss by unknown mechanism.
	+ Transmitted via ingestion of infected foodstuffs and via iatrogenic means (e.g. blood transfusion, Instrument ,GH)
* **1-Creutzfeldt-Jakob Disease/Sub acute Spongiform Encephalopathies: (the most common human form)**
	+ A rare but well-characterized disease that have long incubation period and manifests clinically as a rapidly progressive dementia and diffuse atrophy of the brain.
	+ It is primarily sporadic (about 85% of cases) in its occurrence
	+ Familial forms also exist (15% of cases are autosomal dominant)
	+ The disease has a peak incidence in the seventh decade.
	+ There are well-established cases of iatrogenic transmission, notably by corneal transplantation, deep implantation of neural electrodes, and contaminated preparations of human growth hormone
	+ Inflammatory infiltrates are usually absent
	+ The disease is uniformly fatal, with an average duration of only 7 months

**Tumours of the CNS**

* **General concepts:**
	+ Histological distinction between benign and malignant lesions may be more subtle
	+ The anatomic site of the neoplasm can have lethal consequences irrespective of histological classification
	+ The pattern of spread of primary CNS neoplasms differs from that of other tumors:
		- rarely metastasize outside the CNS
		- the subarachnoid space does provide a pathway for spread

**General manifestations**

* Seizures, headaches, vague symptoms
* Focal neurologic deficits related to the anatomic site of involvement
* Rate of growth may correlate with history
* May arise from:
	+ cells of the coverings (meningiomas)
	+ cells intrinsic to the brain (gliomas, neuronal tumors, choroid plexus tumors)
	+ other cell populations within the skull (primary CNS lymphoma, germ-cell tumors)
	+ they may spread from elsewhere in the body (metastases**)**
* **Gliomas:**
	+ ***1-Astrocytomas***
	+ ***2-Oligodendrogliomas***
	+ ***3-Ependymomas***

***1-Astrocytomas:***

((Astrocytoma occur anywhere))

* **A-Fibrillary:**
	+ 4th to 6th decade
	+ Commonly cerebral hemisphere
	+ Variable grades:
		- 1-Diffuse astrocytoma
		- 2-Anaplstic astrocytoma
		- 3-Glioblastoma
* **B-Pilocytic**
	+ Children and young adults
	+ Commonly cerebellum
	+ Relatively benig

**A-Fibrillary Astrocytoma**

* Well differentiated :

1-“diffuse astrocytoma” ( WHO grade II) :

* + Static or progress slowly (mean survival of more than 5 years)
	+ Moderate cellularity
	+ Variable nuclear pleomorphism
* Less differentiated (higher-grade) :
	+ 2-Anaplstiac astrocytoma ( WHO grade III)
		- More cellular
		- Greater nuclear pelomrophism
		- Mitosis
	+ 3-Glioblastoma ( WHO grade IV)
		- With treatment, mean survival of 8-10 months
		- *Necrosis* and/or *vascular or endothelial cell proliferation*

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* + Pseudopalisading necrosis AND/OR
	+ Vascular proliferation

**Genetics**

* In addition to other markers, it became clear that secondary glioblastomas shared *p53* mutations that characterized low-grade gliomas

((secondary glioblastomasعباره عن تطور من low grade الى grade IV ))

* While primary glioblastomas were characterized by amplification of the epidermal growth factor receptor (*EGFR*) gene

(( اما primary glioblastomas فهو يبدأ grade IV على طوول ))

**B-Pilocytic Astrocytoma**

* Often cystic, with a mural nodule
* Well circumscribed
* "hairlike“=pilocytic processes that are GFAP positive
* Rosenthal fibers & hyaline granular bodies are often present
* Necrosis and mitoses are typically absent
* ((Pilocytic floor and walls of the third ventricle, the optic nerves, and occasionally the cerebral hemispheres))

**2-Oligodendroglioma**

* The most common genetic findings are loss of heterozygosity for chromosomes 1p and 19q
* Fourth and fifth decades
* Cerebral hemispheres, with a predilection for white matter
* Better prognosis than do patients with astrocytomas (5 to 10 years with Rx)
* Anaplastic form do worse
* In oligodendroglioma tumor cells have round nuclei((egg nuclei)), often with a cytoplasmic halo
* Blood vessels in the background are thin and can form an interlacing pattern
* Classified into:
	+ Oligodendroglioma (WHO grade II)
	+ Anaplastic (malignant) oligodendroglioma (WHO grade III)
	+ There is no grade I and lV

**3-Ependymoma**

* Most often arise next to the ependyma-lined ventricular system, including the central canal of the spinal cord
* The first two decades of life, they typically occur near the fourth ventricle
* In adults, the spinal cord is their most common location
* Tumor cells may form round or elongated structures (rosettes, canals)
* perivascular pseudo-rosettes
* Anaplastic ependymomas show increased cell density, high mitotic rates, necrosis and less evident ependymal differentiation

**Meningioma**

* Predominantly benign tumors of adults
* Origin: meningothelial cell of the arachnoid
* Well demarcated
* Attached to the dura with compression of underlying brain
* Whorled pattern of cell growth and psammoma bodies
* Main subtypes:
	+ Syncytial
	+ Fibroblastic
	+ Transitional
* Also note:
	+ Atypical meningiomas
	+ Anaplastic (malignant) meningiomas

**Medulloblastoma**

* Children and exclusively in the cerebellum لايخدعك الاسم في المكان
* Neuronal and glial markers may be expressed, but the tumor is often largely undifferentiated
* The tumor is highly malignant, and the prognosis for untreated patients is dismal; however, it is exquisitely radiosensitive
* With total excision and radiation, the 5-year survival rate may be as high as 75%
* extremely cellular, with sheets of anaplastic ("small blue") cells

small, with little cytoplasm and hyperchromatic nuclei; mitoses are abundant

**Haemangioblastoma**

* it is benign tumor \*\*ايضا لا يخدعك الاسم في النوع
* Commonly cerebellar tumor
* Aslo the retina and others
* Can occur in association with *Von Hippel-Lindau Disease (cyst in pancreas, liver & kideny and renal cell carcinoma)*
* Highly vascular neoplasm that occurs as a mural nodule associated with a large fluid-filled cyst
* Intervening stromal cells of uncertain histogenesis characterized by vacuolations

**Schwannoma**

* They are often encountered within the cranial vault, in the cerebellopontine angle, where they are attached to the vestibular branch of the eighth nerve (tinnitus and hearing loss)
* Sporadic schwannomas are associated with mutations in the *NF2* gene(( type 2))\*\*
* Bilateral acoustic schwannoma is associated with NF2
* Attached to the nerve but can be separated from it لانه يكون على سطح العصب
* Cellular Antoni A pattern and less cellular Antoni B
* nuclear-free zones of processes that lie between the regions of nuclear palisading are termed Verocay bodies

**Neurofibroma**

* Examples: (*cutaneous neurofibroma*) or in peripheral nerve (*solitary neurofibroma*)
* These arise sporadically or in association with type 1 neurofibroma, rarely malignant
* *plexiform neurofibroma,* mostly arising in individuals with NF1, potential malignancy
* Neurofibromas cannot be separated from nerve trunk (in comparison to shcwannoma) لانه يكون داخل العصب

**Metastatic tumours**

* + About half to three-quarters are primary tumors, and the rest are metastatic
	+ Lung, breast, skin (melanoma), kidney, and gastrointestinal tract are the commonest