"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Review & Questions

437 Biochemistry Team

Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

Neuropsychiatry block

EDITING FILE

1- Biochemistry of Myelin

Types and Structures of Sphingolipids					
Type	**1. Sphingosine**	**2. Ceramide**	**3. Sphingomyelin**	**4. Cerebrosides**	**5. Gangliosides**
Structure	**Long chain, unsaturated amino alcohol**	**= Sphingosine + Fatty acid**	**= Ceramide + phosphorylcholine**	**= ceramide + monosaccharides**	**= Ceramide + Oligosaccharides + NANA**
Example	**-**	**-**	**-**	**Galactocerebroside**	**Gm2**

Myelin Structure and Function	
Structure	**1. It is the membrane around the axon that forms a myelinated nerve fiber.** **2. Myelin is produced by Schwann cells (PNC) and Oligodendrocytes (CNS).** **3. It is composed of 80% lipids and 20% proteins.**
Function	**Nerve insulation: to avoid signal leakage, and to increase velocity of impulse transmission.**

1- Biochemistry of Myelin

Diseases					
	1. Multiple sclerosis	**2. Sphingolipidoses** (lysosomal lipid storage diseases)			
General Information	**It is a neurodegenerative, autoimmune disease.** **Cause : demyelination**	**There is A partial or total missing of a specific lysosomal acid hydrolase leads to accumulation of a sphingolipid.** **It is :** **1. Autosomal recessive disease.** **2. Progressive.** **3. Rare, except in Ashkenazi Jewish.** **4. There is Phenotypic and genotypic variability.**			
Diagnosis	-	**1. Measuring enzyme activity.**	**2. Histological examination.**	**3. DNA Analysis.**	
Examples	-	**1. Tay Sachs disease**	**2. Niemann Pick disease**	**3. Gaucher disease**	**4. Fabry disease**
Lipid accumulated	-	**Gangliosides (Gm2) due to : β-Hexosaminidase (α subunit) deficiency.**	**Sphingomyelin due to : Sphingomyelinase deficiency.**	**Glucocerebrosides due to : β-glucosidase (glucocerebrosidase) deficiency.**	-
Treatment	-	-	-	**1. Replacement therapy.** **2. Bone marrow transplantation.**	-

1- Biochemistry of Myelin

Disease	Tay-sachs	Gaucher	Niemann-pick (A+B)	
Deficient Enzyme	β-Hexosaminidase (α subunit)	**β-glucosidase (glucocerebrosidase)**	**Sphingomyelinase**	
Lipid accumulated	Gangliosides (Gm2)	**glucocerebrosides**	**Sphingomyelin**	
Clinical Features	Blindness. -Cherry-red macula.* -muscular weakness and seizures. -Deficiency of activator protein (Gm2 Activator)	The most common one. - Hepatosplenomegaly - Osteoporosis of long bones. - CNS involvement in rare infantile (in infants) and juvenile (in children) forms. - Enzyme Replacement therapy is usually successful for this disease. Cytoplasm looks like crumbled tissue paper due to accumulation of Galactocerebrosides	Type A : -Enzyme Activity is reduced to 1% and less than normal. -Fatal Disease. -More severe. -Death in early childhood. - Hepatosplenomegaly. -Neurodegenerative course. -*Cherry red macula.	Type B : - Little enzyme act. - Chronic Disease. -Less severe form type A. -Later onset. - Little enzyme act. -Hepatosplenomegaly. -*Cherry red macula.

*Cherry-red macula is: There is an area in the retina that is called macula, it acts as a natural sun-block (it blocks ultraviolet rays that enter and harm the eye), usually it's yellow in color but when it's affected it becomes red under the light. Examples of Sphingolipidoses

2- Vitamin A

- Functions of vitamin A: vision, growth, reproduction, maintenance of epithelial cells.
- In the retina, Vitamin A in the form of retinal binds to a protein called opsin to make rhodopsin and iodopsin.
- When these pigments are exposed to light, bleaching occurs and signals are transmitted to brain through optic nerve.
- Retinal is converted back to its original form to start another cycle.
- Vitamin A deficiency causes diseases: nyctalopia,xerophthalmia, bitot's spots,keratomalacia,complete blindness.
- Vitamin A supplementation may cause toxicity.

3- Vitamin B6 & B12

Biochemistry437

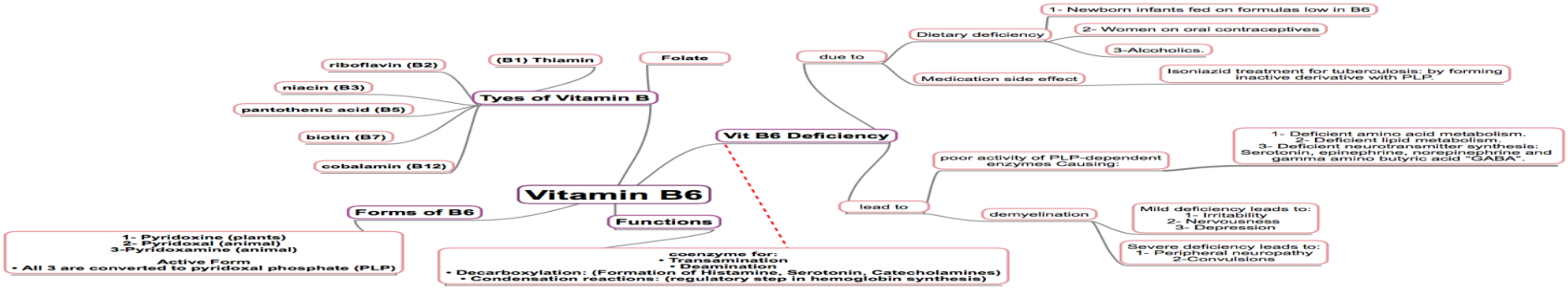
	Vitamin B6	Vitamin B12
Forms	Forms of B6 : •Pyridoxine: From plants. •Pyridoxal: From animal proteins such as eggs and meat. •Pyridoxamine: Same source as pyridoxal. All 3 are converted to pyridoxal phosphate (active form).	Forms of B12 : •Cyanocobalamin •Hydroxycobalamin •Adenosylcobalamin (major storage form in the liver) •Methylcobalamin (mostly found in blood circulation) Three and four are coenzymes for metabolic reactions.
Functions	As coenzyme for: •Transamination. •Deamination. •Decarboxylation. •Condensation reactions.	• Conversion of methylmalonyl-CoA to succinyl-CoA. • Conversion of homocysteine to methionine.
	Deficiency Disorders	**Symptoms**
	•Dietary deficiency : •Newborn infants fed on formulas low in B6. •Women on oral contraceptives. •Alcoholics. •Medication side effect : •Isoniazid treatment for tuberculosis	Neurological : •Paraesthesia (abnormal sensation) of hands and feet. •Reduced perception of vibration and position. •Absence of reflexes. •Unsteady gait and balance (ataxia). Psychiatric : •Confusion and memory loss. •Depression. •Unstable mood.

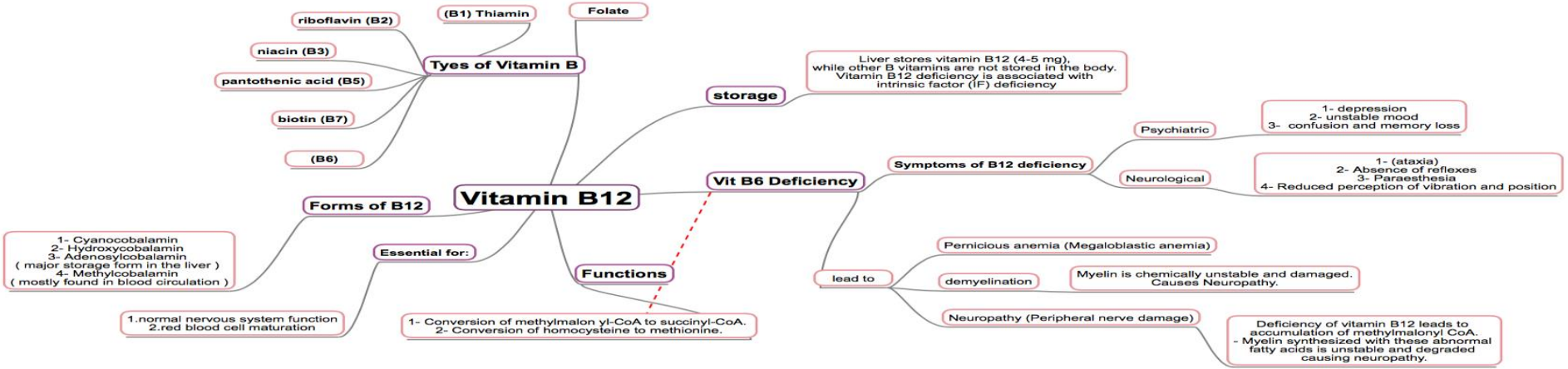
Summary

3- Vitamin B6 & B12

	Vitamin B6	Vitamin B12
Deficiency leads to	• Deficiency leads to poor activity of PLP-dependent enzymes causing: • Deficient amino acid metabolism. • Deficient lipid metabolism. • Deficient neurotransmitter synthesis: Serotonin, epinephrine, norepinephrine and gamma aminobutyric acid (GABA) • PLP is involved in the synthesis of sphingolipids and its deficiency leads to demyelination of nerves and consequent peripheral neuritis : • Mild deficiency leads to: Irritability, Nervousness, and Depression. • Severe deficiency leads to: Peripheral neuropathy and Convulsions.	• Pernicious anemia : • Megaloblastic anemia . • Vitamin B12 deficiency is mainly due to the deficiency of intrinsic factor. • Demyelination : • Myelin sheath of nerves is chemically unstable and damaged. • Neuropathy (Peripheral nerve damage) caused by : • Deficiency of vitamin B12 leads to accumulation of methylmalonyl CoA. • High levels of methylmalonyl CoA are used instead of malonyl CoA for fatty acid synthesis. • Myelin synthesized with these abnormal fatty acids is unstable and degraded causing neuropathy.
General Information	-	Vitamin B12 (Cobalamin) is essential for: •Normal nervous system function. •Red blood cell maturation Liver stores vitamin B12 (4-5 mg) while other B vitamins are not stored in the body. Vitamin B12 deficiency is observed in patients with IF (intrinsic factor) deficiency. B12 Deficiency will leads to folate trap or folate deficiency.

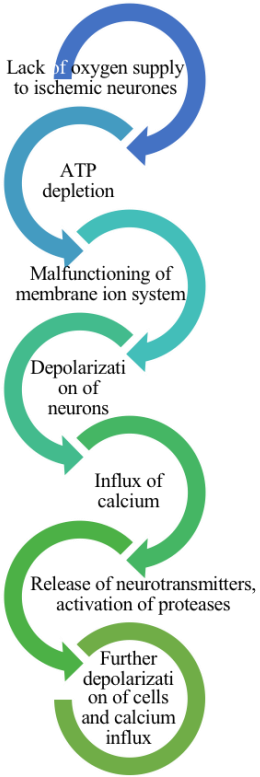
3- Vitamin B6 & B12



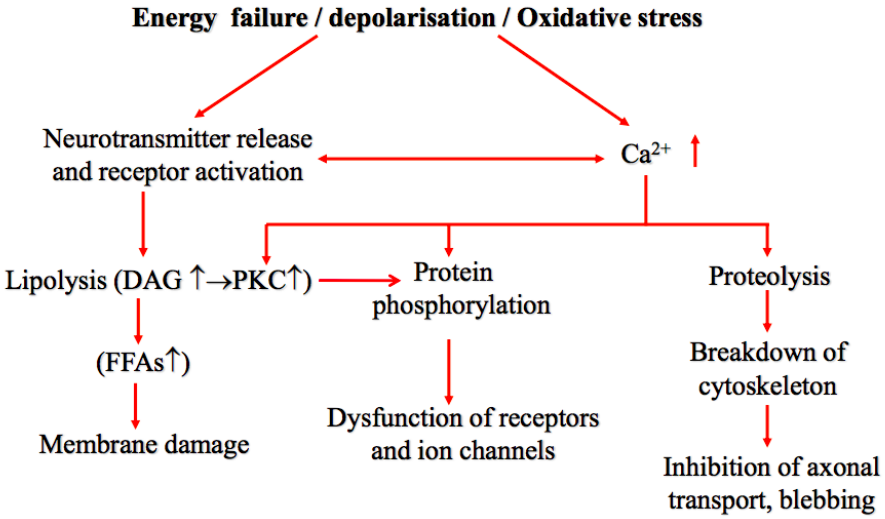


4- Pathogenesis of Cerebral Infarction

Ischemic cascade



Consequences of brain ischemia



4- Pathogenesis of Cerebral Infarction

Stroke	Hemorrhagic	Ischemic
Types	1- Intracerebral 2- Subarachnoid	1- Thrombotic 2- Embolic
Risk Factors	1. Hypertension 2. Smoking 3. Illegal drug use	
	✓ Blood thinning medications like Warfarin	✓ Has much more risk factors, thus it occurs more commonly than the hemorrhagic type.

Necrosis	Apoptosis
observed early after severe ischemic insults	In more mild insults and with longer survival periods
Involve **calcium-induced calpain-mediated proteolysis** of brain tissue, and **Calpain** includes many proteins; cytoskeletal, membranous, regulatory, and signaling.	

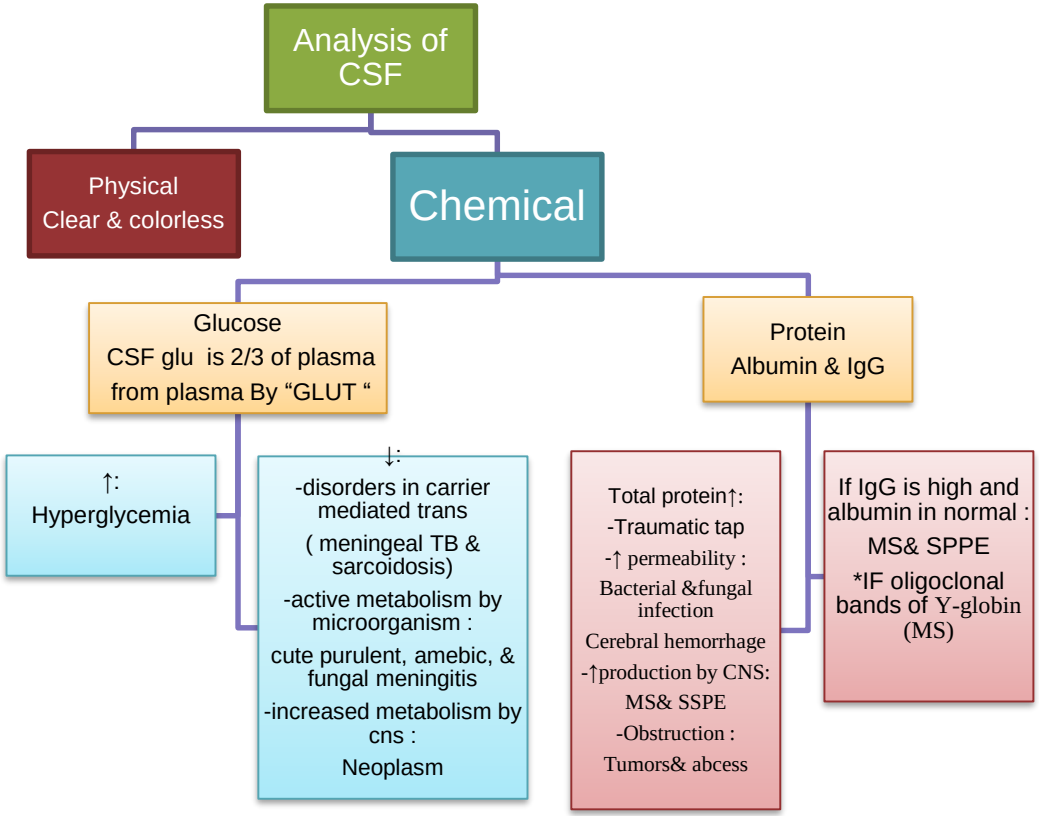
Oxidative stress	ROS & RNS have important functions in the nervous system. - When cells are exposed to amounts of ROS and RNS, and can't fight them with antioxidants, oxidative stress occurs. - The brain is highly susceptible to ROS damage. - ROS has both molecular and cellular damaging effects. - NO has beneficial vascular effects but harmful neural effects.
Metabolic stress	- Ischemia eventually leads to energy depletion mainly due to inhibition of ATP dependent ion pumps which affects the cell membrane. - Influx: Ca^{2+}, Na^{+} Outflux: K^{+} - Increased lactic acid ➤ acidosis ➤increases conversion of O_2^- to H_2O_2.
Neuro-chemical response	- Extracellular NTs are increased: Glutamate - Glycine - GABA - Dopamine - So as intervention we give inhibitors to Ca^{2+}, Glutamate, NO, free radicals, and calpain.
Required Blood tests	- Complete blood count - Prothrombin time, INR, Activated partial thromboplastin time - Thrombin time, Ecarin clotting time - Blood lipids (HDL, LDL) - Cardiac enzymes and troponin

Summary

5- Alzheimer's Disease

General Information	• prominent involvement of the cerebral cortex , Its principal clinical manifestation is dementia , Most cases are sporadic. • Becomes symptomatic before 50 years of age but the incidence of disease rises with age. • becomes profoundly disabled, mute and immobile In 5-10 years, At least 5-10% are familial		
Diagnosis	• Combination of clinical assessment and radiologic methods "MRI" • Pathologic examination of brain tissue is necessary for definitive diagnosis • Major microscopic abnormalities include: neuritic plaques , neurofibrillary tangles and amyloid angiopathy		
Microscopic findings	1. Neuritic Plaques	2. Neurofibrillary Tangles	3. Amyloid Angiopathy
	• Spherical : 20-200 mm in diameter. • Contain paired helical filaments and abnormal mitochondria • The amyloid core contains several abnormal proteins • The dominant component of the plaque core is Aβ from (APP) • The two dominant species of Aβ, called Aβ40 and Aβ42	• Bundles of filaments in the cytoplasm of neurons that displace or encircle the nucleus • These filaments mainly contain : 1- Hyperphosphorylated forms of the tau protein 2- A protein that enhances microtubules assembly • There is strong correlation of number of neurofibrillary tangles with degree of dementia than neuritic plaques	• Amyloid proteins build up on the walls of the arteries in the brain • The condition increases the risk of hemorrhagic, stroke and dementia • not specific for Alzheimer's
Genetics of Alzheimer's	1- Mutations in APP gene in Chromosome 21 2- Mutations in γ-secretase (presenilin-1 in Chromosome 14) or (presenilin-2 in Chromosome 1) 3- Apolipoprotein E (ApoE) in Chromosome 19		
Treatment	• Currently, no effective treatment for AD • we can regulate neurotransmitter activity e.g., Enhancing cholinergic function improves AD • Cellular therapies using stem cells offer great promise for the treatment of AD by : 1- Cellular replacement and/or provide environmental enrichment to attenuate neurodegeneration. 2- Neurotrophic support to remaining cells. • Pro-inflammatory responses may be countered through polyphenol(flavonoids) Supplementation of these natural compounds may provide a new therapeutic line of approach to this brain disorder.		

6- CSF



Function of the CSF (Normal blood brain barrier is important for the normal chemistry results of CSF)	**1-Physical support& protection 2-controlled chemical environment .**
Formed by	Choroid plexuses &ventricle cells (500 ML/day)
Mechanism of formation	1-Selective ultrafiltration of plasma 2-Active secretion by epithelial membranes
Excretion (absorption)	arachnoid villi→ venous sinuses →blood stream Excretion volume = production volume
Collection of specimen by	Lumber puncture (L3-L4)
indications	1- CNS infection 2-hemorrhage 3-CNS malignance 4-demylination
Contraindications	1-Bleeding diathesis 2. ↑ intracranial pressure 3. Infection at site of needle

Questions

Q1/ Decreased ceramide level is usually associated with..?

A. Lung disease
B. Liver disease
C. Skin disease
D. Kidney disease

Q2/ Which one of the following is fat soluble vitamin?

A. ascorbic acid.
B. biotin.
C. riboflavin.
D. retinoids.

Q3/ Which of the following is a water soluble non-B-complex vitamin ?

A. Vitamin K
B. Vitamin E
C. Vitamin C
D. Vitamin B1

Q4/ Which of the following cell death mechanisms occurs with more mild insults and with longer survival periods ?

A. Necrosis
B. Phagocytosis
C. Apoptosis
D. None of them

Q5/ Neurofibrillary tangle are composed of:

A. Amyloid beta
B. Tau protein
C. APP

Q6/ Xanthochromia is the presence of what in CSF?

A. urea
B. protein
C. Bacteria
D. hemoglobin breakdown pigments

Q1/ Which substance is higher in CSF?

A. Chloride
B. Calcium
C. potassium
D. Sodium

Q2/ Most of conditions of alzheimer disease are due to:

A. Familial
B. Sporadic
C. MS

Q3/The enzyme that converts superoxide to hydrogen peroxide is ?

A. NADPH oxidase
B. Superoxide dismutase
C. Catalase
D. Glutathione peroxidase

Q4/ Vit B12 is mainly stored in liver in the form of ?

A. Adenosyl cobalamin
B. Methylcobalamin
C. Cyanocobalamin
D. Phylloquinone

Q5/ Vitamin A is stored in the liver and adipose tissue in the form of ?

A. all trans retinol
B. retinyl palmitate(retinyl Easter)
C. retinoic acid
D. none of them

Q6/ Which of the following is the combination of ceramide and monosaccharides?

A. Sphingomyelin
B. Cerebrosides
C. Gangliosides
D. Sphingosine

Q1/ In SPHINGOLIPIDOSES the defective function leading to accumulation of substrate in organ is the.. ?

A. Synthase
B. Degradation
C. Transformation
D. Storage

Q2/ Excessive carotenoids intake lead to skin discoloration in what color?

A. yellow
B. orange
C. blue
D. red

Q3/ Formation of histamine is a..... reaction ?

A- Condensation Reaction
B- Decarboxylation reaction
C- Transamination Reaction
D- Deamination reaction

Q4/ ROS & RNS are mainly generated by ?

A. Microglia and astrocytes
B. Oligodendrocytes
C. Schwann cells
D. Myelin sheath

Q5/ Alzheimer disease usually associated with which condition?

A. Spina bifida
B. Down syndrome
C. MS

Q6/ Protein is normal in:

A. viral meningitis
B. Multiple Sclerosis
C. bacterial meningitis
D. tuberculous meningitis

Q1/ Complete the table :-

Parameter		Condition		
	Normal	Bacterial Meningitis (pyogenic)	Tuberculous Meningitis	Viral Meningitis
Appearance				
Predominant cell	---			
Cell count/mm3				
Bacteria/virus	---			
Protein				
Glucose				
Chlorides				

Parameter	Condition		
	Bacterial Meningitis (pyogenic)	Tuberculous Meningitis	Viral Meningitis
Appearance	Often turbid	Often fibrin web	Usually clear
Predominant cell	Polymorphs	Mononuclear (lymphocytes)	Mononuclear (lymphocytes)
Cell count/mm3	90 - 1000+	10 - 1000	50 - 1000
Bacteria/virus	+ve smear & culture	Often none in smear	negative smear or culture
Protein (0.15 - 0.45 g/L)	> 1.5 (↑ ↑)	1-5 (↑ ↑)	<1 (Normal)
Glucose (2.8 - 4.2 mmol/L)	<1/2 plasma (↓ ↓)	<1/2 plasma (↓ ↓)	>1/2 plasma (Normal or slightly ↓)
Chlorides (115 - 130 mmol/L)	↓ ↓	↓ ↓	Normal or ↓

Q2/ Name the microscopic findings in AD and give a brief description about them ?

	1. Neuritic Plaques	2. Neurofibrillary Tangles	3. Amyloid Angiopathy
Microscopic findings	• Spherical : 20-200 mm in diameter. • Contain paired helical filaments and abnormal mitochondria • The amyloid core contains several abnormal proteins • The dominant component of the plaque core is Aβ from (APP) • The two dominant species of Aβ, called Aβ40 and Aβ42	• Bundles of filaments in the cytoplasm of neurons that displace or encircle the nucleus • These filaments mainly contain : 1- Hyperphosphorylated forms of the tau protein 2- A protein that enhances microtubules assembly • There is strong correlation of number of neurofibrillary tangles with degree of dementia than neuritic plaques	• Amyloid proteins build up on the walls of the arteries in the brain • The condition increases the risk of hemorrhagic, stroke and dementia • not specific for Alzheimer's

Q3/ How can NO have beneficial and harmful effect ?

- NO produced by endothelial NOS (eNOS) improving vascular dilation and perfusion (i.e **beneficial**)
- In contrast, NO production by neuronal NOS (nNOS) or by the inducible form of NOS (iNOS) has **detrimental** (harmful) effects

Q4/ What are the vitamins? What are their functions? And how do we classify them?

- **They are, Non-caloric Essential Organic compounds present in small quantities in different types of food and are required in very small amounts**.

- **They help in various biochemical processes in cell. Most of them act as coenzymes.They are important for growth and maintaining good health.**

- Vitamins are classified based on their solubility into :-
  - Water soluble
  - Fat soluble

Q5/ What are the functions of vitamin A ?

A)Vision

B)Gene Transcription

C)Immune Function

D)Embryonic development and reproduction

E)Bone metabolism

F)Skin health and antioxidant activity

Q6/ Deficiency of Vitamin B6 leads to ?

- ❑ poor activity of PLP-dependent enzymes causing:
  - ➢ Deficient amino acid metabolism.
  - ➢ Deficient lipid metabolism.
  - ➢ Deficient neurotransmitter synthesis: Serotonin, epinephrine, norepinephrine and gamma aminobutyric acid (GABA)

- ❑ PLP is involved in the synthesis of sphingolipids and its deficiency leads to demyelination of nerves and consequent peripheral neuritis :
  - ➢ Mild deficiency leads to: Irritability, Nervousness, and Depression.
  - ➢ Severe deficiency leads to: Peripheral neuropathy and Convulsions.

Q7/ Deficiency of Vitamin B12 leads to ?

- ○ Pernicious anemia :
- ○ Megaloblastic anemia .
- ○ Vitamin B12 deficiency is mainly due to the deficiency of intrinsic factor.

- ○ Demyelination : Myelin sheath of nerves is chemically unstable and damaged.

- ○ Neuropathy (Peripheral nerve damage) caused by deficiency of vitamin B12 leads to accumulation of methylmalonyl CoA.
- ○ High levels of methylmalonyl CoA are used instead of malonyl CoA for fatty acid synthesis.
- ○ Myelin synthesized with these abnormal fatty acids is unstable and degraded causing neuropathy.

Q8/ How do we diagnose Sphingolipidoses?

- Measure enzyme activity:
- Cultured fibroblasts or peripheral leukocytes.
- Cultured amniocytes or chorionic villi (prenatal)[1].
- Histologic examination.
- DNA analysis[2].

Q9/ How do we treat Gaucher disease ?

By :

1. Replacement Therapy (e.g. recombinant human enzyme).
2. Bone marrow transplantation.

Q10/ What are the vascular effects of ROS ? And what are the molecular effects ?

❑ Vascular :-

- Altered vascular tone and cerebral blood flow
- Increased platelet aggregability
- Increased endothelial cell permeability

❑ Molecular :-

- DNA damage
- Lipid peroxidation of unsaturated fatty acids
- Protein denaturation
- Inactivation of enzymes
- Cell signaling effects (eg. release of Ca2+ from intracellular stores)
- Cytoskeletal damage
- Chemotaxis

Q11/ How does VB12 cause neuropathy?

- **Neuropathy (Peripheral nerve damage) caused by deficiency of vitamin B12 leads to accumulation of methylmalonyl CoA.**
- **High levels of methylmalonyl CoA are used instead of malonyl CoA for fatty acid synthesis.**
- **Myelin synthesized with these abnormal fatty acids is unstable and degraded causing neuropathy.**

- **Q12/what is happen in case of Folate trap?**

- **Homocysteine re-methylation reaction is the only pathway where N_5-methyl TH4 can be returned back to tetrahydrofolate pool.**

Hence folate is trapped as " N_5-methyltetrahydrofolate (folate trap) "
This leads to folate deficiency and deficiency of other TH4 derivatives (N_5 -N_{10} methylene TH4 and N10 formyl TH4) required for purine and pyrimidine synthesis.
TH4: Tetrahydrofolate.

Q13/what's the difference between traumatic tap and xanthochromia?

Traumatic tap
Bright red color
RBCS in decreasing number as the fluid is sampled
Not a hemorrhage , rupture of a blood vessel during specimen collection → blood in the CSF (contaminated CSF).
CSF sample in the beginning RBCs are found (red) as a result of rupturing the blood vessel, then as the needle gets deeper it's not found (white).

Xanthochromia
(hemoglobin breakdown pigments) = RBCs lysis & metabolism previously occurred (at least 2 hr earlier)
Real hemorrhage due to trauma or any other causes
Blood in the CSF , rupture of RBCs (like a bruise) [heme degrades-biliverdin (green)- bilirubin(yellow)].

Good Luck !

Team Leaders :-

معاذ الحمود – رهام الحلبي

Made By :-

عبدالله العنقري