CNS pathology
Third year medical students 2019

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Lecture 5: neurodegenerative diseases part 3:

Ataxias and motor neurone diseases.

ILOS

- 1.understand the pathogenesis, clinical features and histological characteristics of spinocerebellar ataxia
- 2.understand the pathogenesis, clinical features and histological characteristics of ALS
- 3. list metabolic and toxic causes of neurological deficits.
- 4. in depth understanding of vitamin B 12 deficiency and its effect on the brain.

Neurodegenerative disorders / part 3

Topics to be covered:

1. Spinocerebellar ataxia
2. Frederick ataxia
3. Amyotrophic lateral sclerosis
4. Metabolic and toxic effects on the CNS

Spinocerebellar ataxias

- Ataxia; Greek = lack of order
- = the loss of full control of bodily movements, including gait, speech and eye movement.

- التزنّحات

Spinocerebellar ataxias

- This is a heterogeneous group of diseases that differ in the mutation type, inheritance pattern, age of onset and clinical symptoms.
- Affect cerebellar cortex, spinal cord, other brain regions and peripheral nerves
- SO: symptoms are related to the area/s affected and vary from one person to another.All are caused by **trinucleotide repeat expansion mutations.**
- Each type of ataxia is caused by a specific mutation.

Clinical symptoms of spinocerebellar ataxias include:

- Cerebellar ataxia
- sensory ataxia
- Spasticity
- Sensorimotor peripheral neuropathy

Cerebellar ataxia

- Cerebellar ataxia presents with symptoms of an inability to coordinate balance, gait, extremity and eye movements.

Symptoms of Ataxia

- **Gait/Posture abnormalities** - Difficulty maintaining normal upright posture, balance, coordinated walking, and running. Unsteady gait, staggering, tripping, falling, unsteadiness on stairs or maintaining balance on moving platforms, such as escalators or boats.
- **Fine motor incoordination** - Difficulty with handwriting, cutting food, opening jars, buttoning clothes, sewing, typing, playing an instrument or a sport.
- **Speech and swallowing difficulties** - Speech: slurred, slow, indistinct, abnormal in rhythm. Swallowing: difficulty swallowing or choking (especially with liquids).
- **Visual abnormalities** - Blurred vision or double vision. Reading: difficulty moving from word to word. Problems following moving objects or shifting gaze from one object to another.
- **Increased fatigue** - Patients with ataxia due to cerebellar atrophy often experience unexpected fatigue when performing normal activities. The impaired regulation of coordinated movements may lead to increased fatigue **because of the need to expend more effort to perform activities that are no longer coordinated**. Patients with ataxia often report needing to "concentrate on" their movements.

Symptoms of ataxia

- **Cognitive and Mood Problems** - In addition to motor dysfunction, patients with cerebellar degeneration may have cognitive and emotional difficulties.
- The cerebellum plays a role in some forms of thinking.
- Patients with cerebellar atrophy may have impaired recall of newly learned information or difficulty with “executive functions” such as making plans and keeping thoughts in proper sequence.
- Personality and mood disorders, such as increased irritability, anxiety, and depression, are more common in persons with cerebellar degeneration than in control subjects.

Sensory ataxia

- It occurs if there is spinal cord or peripheral nerves' involvement
- Sensory ataxia is distinguished from cerebellar ataxia by the presence of near-normal coordination when the movement is visually observed by the patient, but marked worsening of coordination when the eyes are shut, indicating a positive Romberg's sign.
- Patients complain of loss of balance in the dark, typically when closing their eyes in the shower or removing clothing over the head.

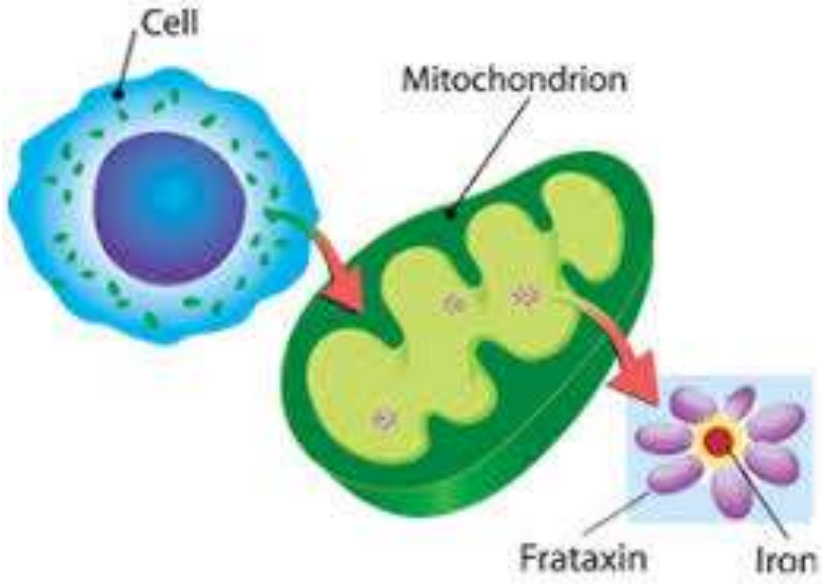
Romberg’s sign

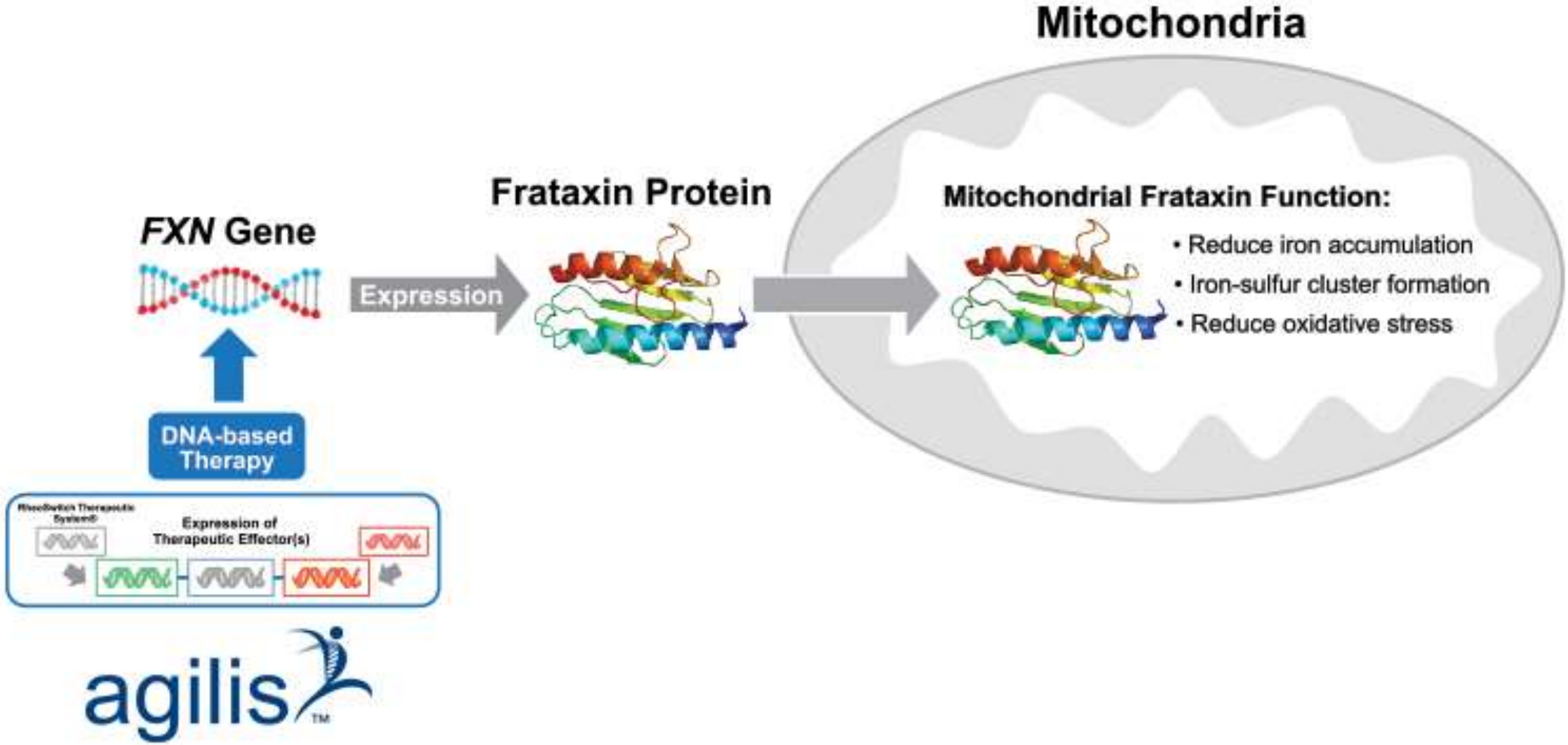
Friedrich ataxia

- Is the most important type of spinocerebellar ataxia
- Autosomal recessive
- Manifests in the first decade of life
- Gait ataxia and hand clumsiness and dysarthria
- **Associated with high incidence of cardiac disease and Diabetes mellitus**

Genetic mutation in Friedreich ataxia

- Due to GAA repeat expansion.. Coding for **frataxin**; a protein that regulates cellular iron level especially in the mitochondria.
- The repeat expansion causes **transcriptional silencing** .. This results in **decreased frataxin level.**




Mitochondria
Frataxin Protein
Mitochondrial Frataxin Function:
• Reduce iron accumulation
• Iron-sulfur cluster formation
• Reduce oxidative stress
FXN Gene
Expression
DNA-based Therapy
Expression of Therapeutic Effector(s)
agilis

- Frataxin consists of two α helices and seven β strands .
- It assists iron-sulfer protein synthesis in the electron transport chain to ultimately generate adenosine triphosphate (ATP)
- It also regulates iron transfer in the mitochondria in order provide a proper amount of reactive oxygen species (ROS) to maintain normal processes
- ***Without frataxin, 1. the energy in the mitochondria fails and 2. excess iron causes extra ROS to be created, leading to further cell damage.***

IMPORTANT NOTE

- In Friedrich ataxia, the neuronal damage is ***not*** caused by protein aggregation.
- Although it is considered a neuro-degenerative disease , the mechanism of neuronal damage is **different** from all other neurodegenerative diseases because there is loss of an important protein rather than accumulation.

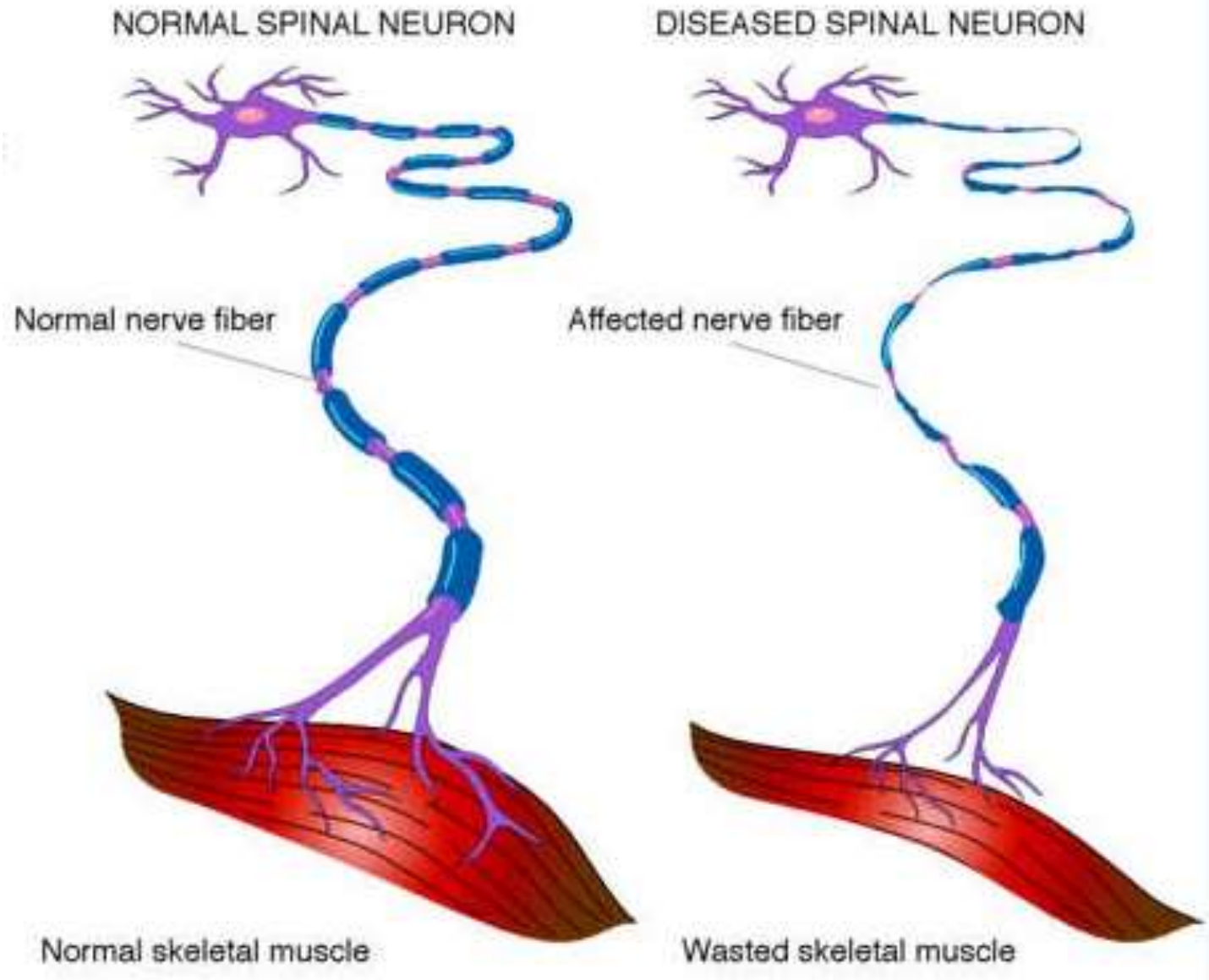
Amyotrophic lateral sclerosis (ALS)

- Results from death of **lower** motor neurons in the spinal cord and brain stem and of **upper** motor neurons in the motor cortex.

Amyotrophic lateral sclerosis

- Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease (MND), is a specific disease that causes the death of neurons which control voluntary muscles.
- Some also use the term "motor neuron disease" for a group of conditions of which ALS is the most common.
- ALS is characterized by stiff muscles, muscle twitching, and gradually worsening weakness due to muscles decreasing in size. This results in difficulty in speaking, swallowing, and eventually breathing.

Amyotrophic Lateral Lclerosis (ALS) pathology



What is ALS?

ALS ASSOCIATION

amyotrophic lateral sclerosis (ALS)

- A progressive, neurodegenerative disease
- 100% fatal

Breaking it down:

"a" means no or negative +
"myo" refers to muscle +
"trophic" means nourishment =
"no muscle nourishment."

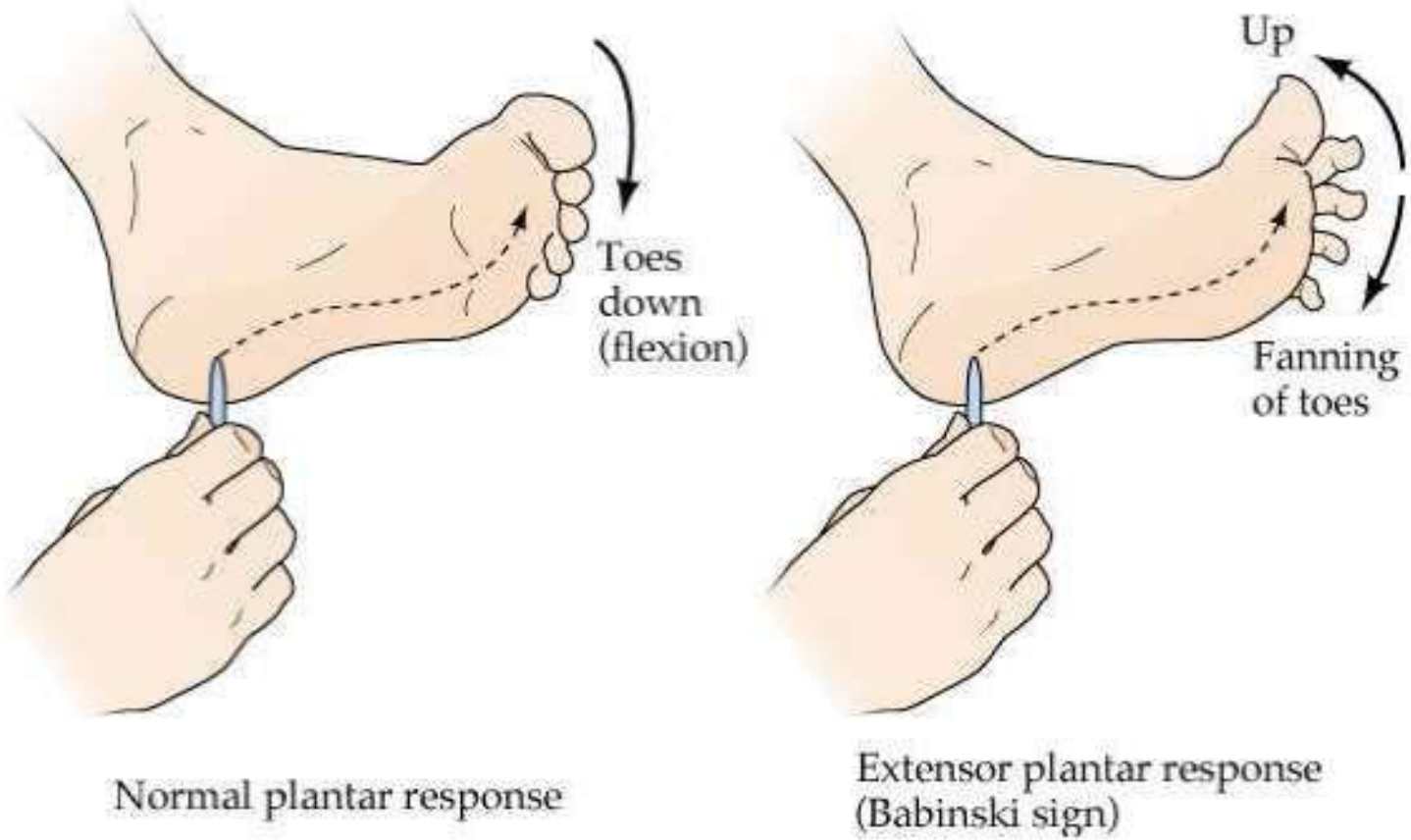
"lateral" is the area in the spine where the brain tells the muscles what to do.

"sclerosis" is hardening: as the disease progresses, the lateral areas harden and the signals stop.

symptoms

- Loss of lower motor neurons results in denervation of muscle , muscle atrophy (amyotrophic)and weakness and fasciculation (a brief, spontaneous contraction affecting a small number of muscle fibers, often causing a flicker of movement under the skin).
- Loss of upper motor neurons results in paresis, hyperreflexia, , spasticity and Babinski sign,
- As a consequence of upper motor neuron loss there is degeneration of corticospinal tracts in lateral portion of spinal cord (lateral sclerosis)

Babinski sign



ALS

- Sensation NOT affected.
- Cognitive impairment occurs.
- Males slightly more than females
- Majority of cases are sporadic
- 5-10% inherited; autosomal dominant
- familial cases: earlier onset but disease progression similar

ALS

- Respiratory muscles affected later in the course of the disease resulting in recurrent pulmonary infections which is the usual cause of death

Genetic factors

- Several genetic mutations implicated in the familial cases
- 20% of cases: mutation in superoxide dismutase gene SOD 1 on chromosome 21
- This mutation causes abnormally folded SOD 1 protein
- **The misfolded SOD 1 causes death of neurons**

- **Note: because there are several mutations, there are also several types of misfiled proteins and several types of inclusions.**

Stephen Hawking

- Born 1942
- Diagnosed with ALS at the age of 21
- Expected to live for 2 years only
- Died at the age of 76 last year !!
- Well known physicist and scientist.
- Married twice and have 3 children.

Acquired metabolic and toxic disturbances

-Toxic and metabolic diseases are relatively common causes of neurologic illness

-the brain has a high metabolic demand which makes it vulnerable to nutritional diseases and changes in metabolic stat.

Acquired metabolic and toxic disturbances

- 1. nutritional diseases: thiamin and B12 deficiency
- 2. metabolic disorders: hypoglycemia, hyperglycemia, hepatic encephalopathy
- 3. toxins

Thiamine deficiency

- Thiamine def. causes Wernicke encephalopathy :
- 1. Confusion
- 2. Abnormal eye movements
- 3. Ataxia
- -Treatment: thiamine.. Things go back to normal
- -If thiamine def. untreated: irreversible memory disturbances: Korsakoff syndrome.

Wernicke- Korsakoff

Causes of thiamin def. :

- -Alcoholism
- -Gastric disorders affecting thiamine absorption: tumors, chronic gastritis
- - Chronic vomiting

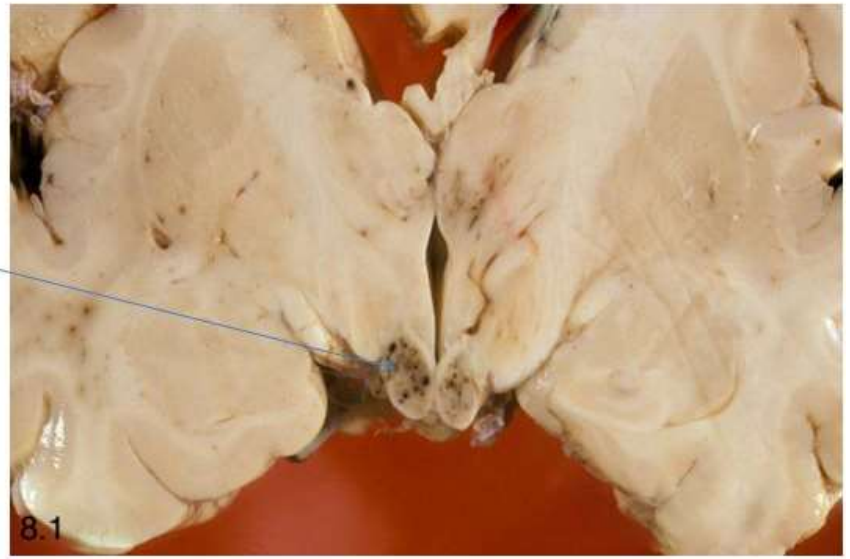
morphology of Wernicke Korsakoff

- Foci of haemorrhage and necrosis mainly in mammillary bodies

Morphology

Hemorrhage and necrosis in **mammillary bodies**

Lesions in medial dorsal nucleus of **thalamus** correlate with **memory disturbance** in Korsakoff syndrome

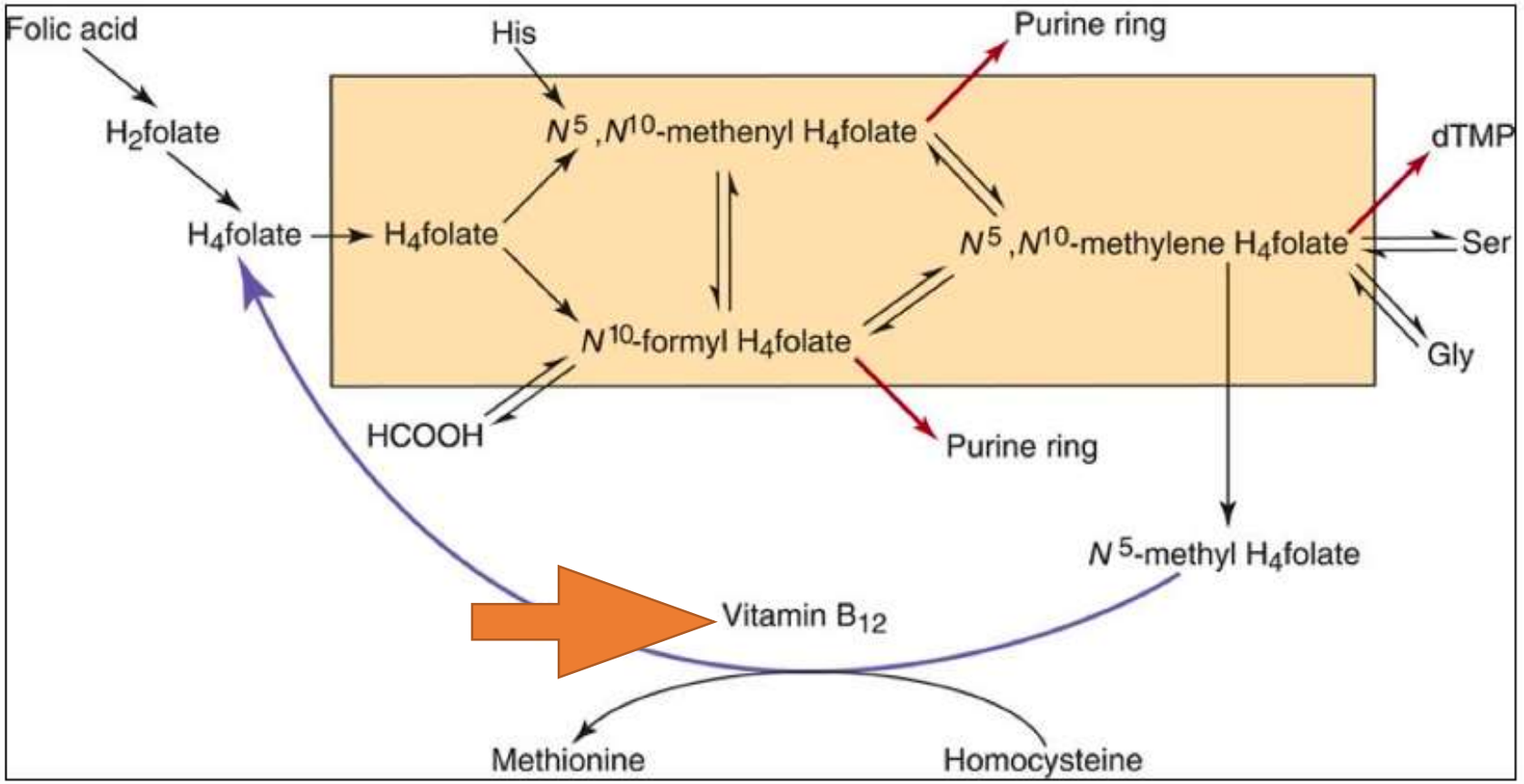


Vitamin B12 and its effects the nervous system

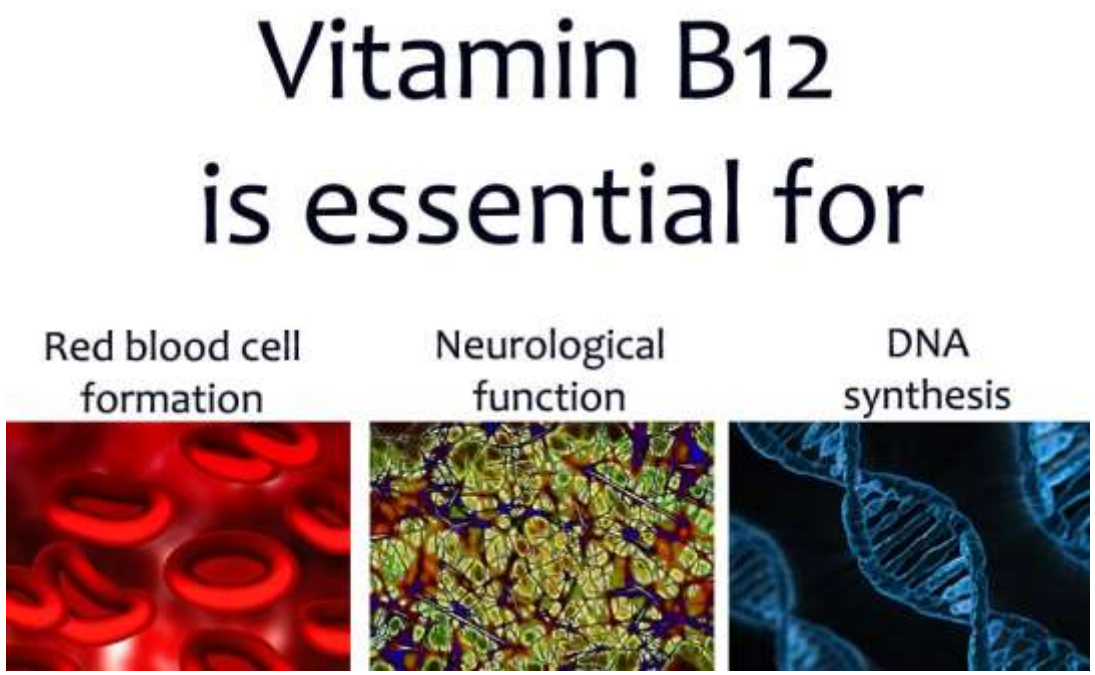
VIT B 12

- **Vitamin B_{12} (Cobalamin)** acts a co-enzyme in methylation and rearrangement reactions which are needed in one carbon metabolism.
- one carbon metabolism: group of reactions that involve transfer of one-carbon groups
- these one carbon reactions are important in amino acid and nucleotide synthesis
- Because vit B12 is important for these reactions, its deficiency affects nucleotide (RNA and DNA) as well as amino acid (neurotransmitter) synthesis… so neurological symptoms develop.

One carbon metabolism: note that fit B12 is essential for such reactions.



- B 12 is also important for synthesis and maintenance of myelin.. we will talk about myelin diseases in the next lecture.



Vitamin B12 def results in

- Subacute combined degeneration.
- Peripheral neuropathy
- Psychological problems
- Dementia-like symptoms

Subacute combined degeneration

-Subacute combined degeneration : demyelination of the **dorsal and lateral** spinal cord causing progressive degeneration
-Initially, the myelin sheath is damaged, followed by the degeneration of the axons (nerves).
-The initial symptom: tingling sensation and numbness felt on both sides, as well as clumsy movements.
-Other symptoms include weakness, visual problems, cognitive disturbances, abnormal reflexes, and bladder and erectile dysfunctions.
-Early treatment of this condition with vitamin B12 supplementation gives good results. A delay in treatment can result in an incomplete recovery of lost functions.

Peripheral neuropathy

-transmission of nerve signals between the spinal cord and different parts of the body is disrupted. T
-he problem may be due to direct damage caused to the nerves or demyelination that leads to axonal damage.
-The symptoms are tingling sensations, pain, and numbness. Depending on the type of nerve affected, there can be a loss of sensation or muscle mass and activity.
-This condition also needs early treatment to limit damage and obtain effective results

Psychiatric problems due to B 12 def

-Symptoms: Delusions, hallucinations, cognitive changes (like memory decline), depression, and dementia.
-probably caused by deranged production of neurotransmitters

Dementia

Vitamin B12 deficiency can lead to brain atrophy.

Various studies have shown that cobalamin deficiency is more common in patients with Alzheimer's disease, Parkinson's disease, and various conditions causing dementia. But a causal relationship between vitamin B12 deficiency and these diseases remains inconclusive.

Effect of B 12 def in infancy

-Vitamin B12 and folate deficiencies in fetal and early life cause poor brain development and cognitive functions

-Folate and vitamin B12 play very important roles in brain development, especially during the fetal and first 2 years of life. Furthermore, these vitamins are essential till puberty as myelination that starts during fetal life continues untill puberty.

-Pregnant women with folate and B12 deficiency need supplements to prevent the development of these neurological complications.

Metabolic disorders

- 1. **Hypoglycaemia**: effect similar to global hypoxia…hippocampal neurones and Purkinje cells first affected.
- **2.Hyperglycaemia:** ketoacidosis or hyperosmolar coma: confusion then coma

Note: hyperglycemia must be corrected gradually because rapid correction can produce severe cerebral edema.

- **3.Hepatic encephalopathy**: decreased consciousness and coma due to increased ammonia, inflammation and hyponatremia

Toxic disorders

- Alcohol
- Ionizing radiation
- Pesticides
- Carbon monoxide
- And many other toxic agents can affect the brain function

- So: if you have a patient with neurological symptoms, take detailed history and exclude all reversible treatable causes before labelling the patient with a chronic neurological diseases.

Summary 1/2

- Spinocerebellar ataxias are a group of inherited disorders that result in abnormal uncoordinated movement.
- They are caused by trinucleotide repeat mutations.
- Friedrich ataxia is the most common form, it is caused by trite-eat mutation in GAA that causes transcriptional silencing in **frataxin**; a protein that regulates cellular iron level especially in the mitochondria.
- Without frataxin, the energy in the mitochondria fails and excess iron causes extra ROS to be created, leading to further cell damage.
- ALS results from degeneration of upper ad lower motor neurones resulting in muscle weakness. SOD mutation is the most common one.

Summary 2/2

- Metabolic disorders and toxic substances can cause neurological deficit which cane reversible.
- Wernicke- Korsakoff is caused by Thiamin deficiency. It is characterised by : confusion, ataxia and abnormal eye movement. Alcoholism is the most common cause and patients have haemorrhage within the mammillary bodies.
- B 12 is important for production of neurotransmitters and myelin synthesis. The most important complication of its deficiency is subacute combined degeneration.


Thank
you