CNS pathology
Third year medical students

Dr Heyam Awad

FRCPath

2017

LECTURE 8

Neurodegenerative disorders / part 3

Topics to be covered:

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

Remember :
We said that neurodegenerative disorders are a group of diseases caused by abnormally folded proteins (with one exception), and they might cause dementia, motor dysfunction (..etc) if they accumulate in the cortex, ataxia if they accumulate in they cerebellum, motor dysfunction if they accumulate in the motor neurons ...

Spinocerebellar ataxia

- Ataxia; Greek = lack of order
- = the loss of full control of bodily movements

- التر ّنحات

Spinocerebellar ataxia

- Heterogeneous group of diseases *caused by neurodegenerative diseases .*
- *Although they are heterogeneous group of diseases, they are caused by the same* ***type*** *of mutation which is* trinucleotide repeat expansion mutations *(look at the table –remember Huntington disease)*.

So from the name of the condition, these diseases affect both the ***spinal cord*** *(consequently the peripheral nerves) and* ***the cerebellum****, and they might even reach the cortex leading to dementia.*

*** Not all (CAG) repeat mutations affect Huntington protein*

Disease	repeats	range normal	range mutant
*Huntingon Disease	(CAG)n	11 - 34	36 - 120
*Spinocerebellar ataxia I	(CAG)n	6 - 40	40 – 82
*Machado-Joseph ataxia	(CAG)n	13 - 40	68-69
Friedrich's ataxia	(GAA)n	10 - 21	200 - 900
Myotonic dystrophy	(CTG)n	5 - 30	50 – 2000
Fragile X syndrome	(CGG)n	6 - 50	60-1000

* The (CAG)n is within an exon and produces polyglutamines in the protein product

- Group of diseases that differ in the mutation type, inheritance pattern, age of onset and clinical symptoms.
- Affects 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.

Clinical symptoms 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 *.So the doctor should ask the patient to write and compare it with **his** handwriting from before the onset of symptoms.*
- **Speech and swallowing difficulties** - Speech: slurred, slow, indistinct, abnormal in rhythm. Swallowing: difficulty swallowing or choking (especially with liquids) *that might lead to aspiration and die from aspiration pneumonia*.
- **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, *and nystagmus .*
- **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** *(previously didn't need that much effort).* Patients with ataxia often report needing to "concentrate on" their movements.

We should ask the patient about his occupation because if he is a cook for ex. He might hurt himself because of the fine motor incoordination

***The unstable gait is a late stage complication usually, so to if the person suffers from ataxia before the onset of unstable gait, us should ask him about his gait/posture when getting up the stair or running.*

Symptoms of ataxia

The doctor only mentioned the underlined here…

- **Cognitive and Mood Problems** *(as said before, if the cortex were involved dementia occurs)*
  - 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

Friedreich ataxia

All types spinocerebellar ataxia are rare

- Is a type of spinocerebellar ataxia (*One of the most common of the rares :P)*
- 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

Friedreich ataxia

This disease differs from all the neurodegenerative disease by the fact that in this disease, we are losing a protein compared to abnormal protein accumulation (consequently no inclusions) in all other diseases.

- Gene mutation :Due to GAA repeat expansion.. Coding for frataxin
- Frataxin… important in iron levels especially in the mitochondria
- The repeat mutation causes transcription silencing resulting in decreased frataxin..
- This causes mitochondrial dysfunction, *impaired ATP production, increased incomplete oxidation and* increased oxidative damage

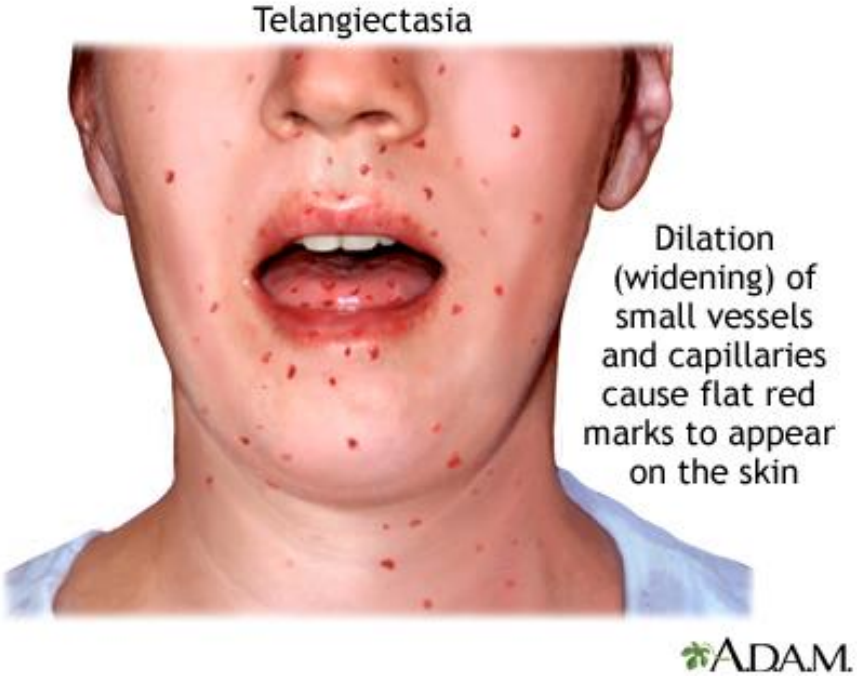
So the mechanism of damage is also different from the other diseases

The doctor didn't mention anything from this slide.

- 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.

Ataxia Telangiectasia

- Autosomal recessive disorder.
- Starts in early childhood
- Progressive and patients die in the second decade
- Symptoms: ataxia, dyskinesia, telangiectasias in *GI tract, CNS* conjunctiva and skin, immunodeficiency
- Complications: **Infections** are common and *increased risk of malignancies especially* **Lymphoid neoplasms** may occur



Infections are common because of the immunodeficiency, the increased risk of lymphoma is a result of immunodeficiency and the gene mutation itself

genetics

Just read the tragedy below ☹

- Mutation in ATM gene = ataxia mutated gene
- ATM encodes a kinase important for regulating cellular response to double stranded DNA breaks
- Also ATM protein facilitates apoptosis, maintains telomeres and has other actions.

The half-life of P53 protein (in the absence of intracellular stresses) is 30 mins, because it is normally attached MDM2 (مدامته) which decreases the half-life of P53 by signaling it to destruction by ubiquitin proteasome pathway. Now in the presence of stresses, ATM separates the P53 from MDM2, so that the p53 can go and induce repair or apoptosis.
So if the ATM Is mutated, there is nothing to separate the MDM2 from P53, so apoptosis induction is lost and increased risk of mutations.

morphology

- Loss of Purkinjie cells in the cerebellum
- Also there is degeneration of dorsal columns, spinocerebellar tracts, anterior horn cells and peripheral neuropathy.
- There is telangiectasia in the CNS and the skin

This is the last neurodegenerative disorder we'll mention.

Amyotrophic lateral sclerosis

Means a muscle without nutrition (trophy=nutrition, and means nerve supply here)

- 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**. *Initially muscles of Upper and lower limb are affected but with time* difficulty in speaking, swallowing, and eventually breathing occur.

In this disease we have degeneration of upper and lower motor neurons.

Amyotrophic lateral sclerosis (ALS)

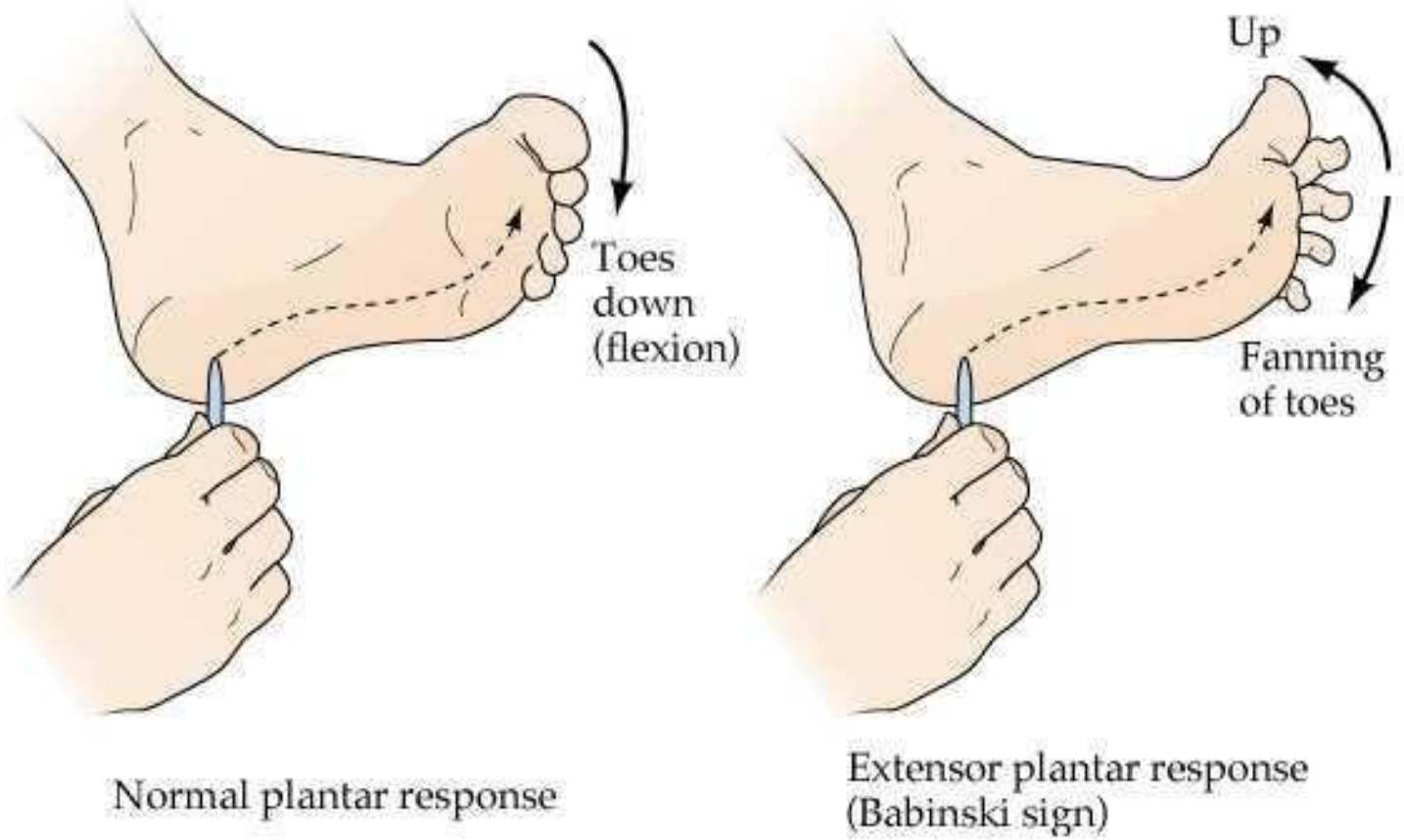
- Results from death of **lower** motor neurons in the spinal cord and brain stem and of **upper** motor neurons in the motor cortex.
- *Characterized by changes in the muscles (see next slide)*

In anatomy we took that the U.M.N lesion occurs in the tracts…
I guess robbins –peace be upon him- is also wrong :P

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 might occur.
- *On average, the patient lives for 2 years*
- Males slightly more than females
- Majority of cases are sporadic
- 5-10% inherited; autosomal dominant
- familial cases: earlier onset but disease progression similar *(similar to most inherited diseases …)*
- 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 and the most common mutation is in SOD1 gene
- 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

morphology

- Grossly: thin grey anterior roots of the spinal cord.

  : motor cortex might become mildly atrophic especially in the severe cases

- Micro: reduction in the number of the anterior horn cells + reactive gliosis *(loss of neurons is always followed by reactive gliosis)*
- Similar micro features seen in motor cranial nerve nuclei except those supplying the extraocular muscle which are spared except in very longstanding survivors

Stephen Hawking

Why did he live till now?
Although good management has to do with it, but experts say that not only good management was the reason, and most likely the reason is that he has a variant of the disease of a very slow progression.

- Born 1942
- Diagnosed with ALS at the age of 21
- Expected to live for 2 years only
- He’s 75 now
- Well known physicist and scientist.. Won Nobel prize
- Married twice and have 3 children.

Euthanasia = mercy killing

CARE NOT KILLING

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.

We need to know when the neurologic problems are caused by toxins or metabolic disturbances because they can be reversed.

Causes :

- 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 syndrome)*.

Wernicke- Korsakoff syndrome

Causes of thiamin def. :

- -Alcoholism *(important cause)*
- -Gastric disorders affecting thiamine absorption: tumors, chronic gastritis
- - Chronic vomiting

morphology

- Foci of hemorrhage and necrosis mainly in mammillary bodies

Vitamin B12 def

- Vit B 12 def causes subacute combined degeneration of the spinal cord
- Combined means that ascending and descending tracts affected
- Symptoms: Ataxia, lower extremity numbness and tingling
- Can progress to lower limb weakness
- Sometimes complete paraplegia can occur and this carries a worse prognosis.

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


Thank
you