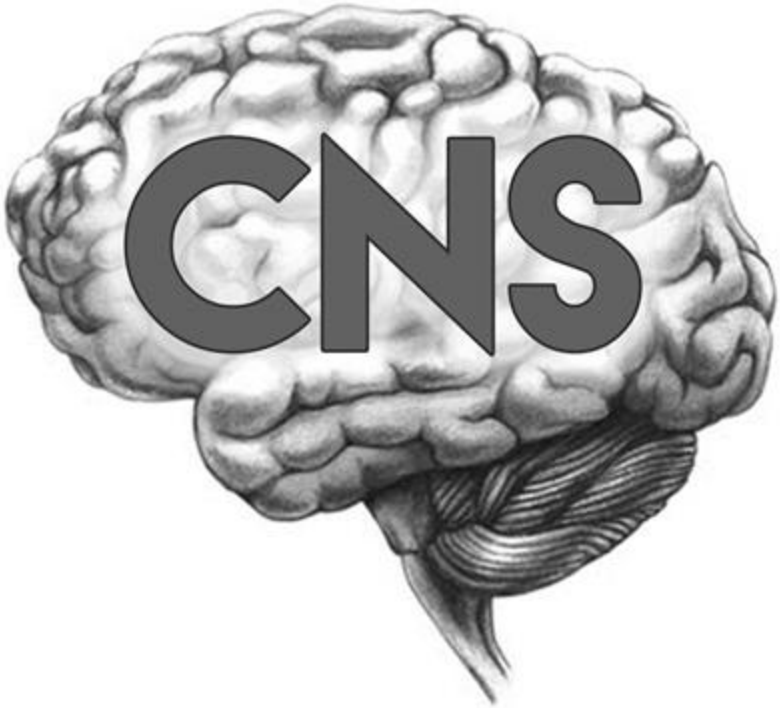

PATHOLOGY

☑ Sheet ○ Slide ○ Handout

Number

8

Subject

Neurodegenerative disorders PT/3

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Date: **7/3/2016**

Price:

- **Remember that**; Neurodegenerative diseases are a group of diseases that are associated with accumulation of abnormal proteins.
  Accumulation of proteins in a particular part of the brain would cause a specific pattern of neuronal dysfunction: Those that affect the **cerebral cortex** result in (dementia); those that affect the **basal ganglia** result in (movement disorders); those that affect the **cerebellum** will result in (ataxia).

❖ Spinocerebellar ataxia

- A heterogeneous group of neurodegenerative diseases that affect the cerebellar cortex, spinal cord, and peripheral nerves and could also affect other brain regions (if they affect the cortex they would cause → dementia).

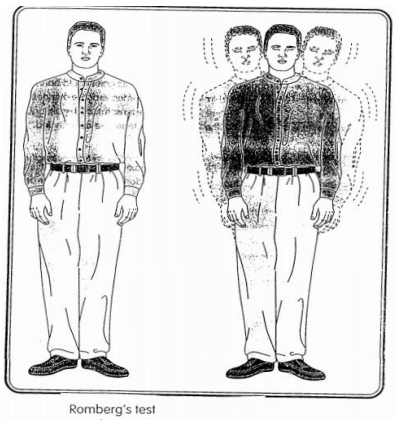
- Ataxia: lack of order
- Caused by → tri-nucleotide repeat expansion mutation (like Huntington) it could be in **CAG** (Huntington), **GAA** (Friedrich's ataxia) or any other tri-nucleotide.

****Clinical findings:**

Degeneration of the cerebellum leads to **(cerebellar ataxia)**

Symptoms of ataxia:

- ✓ **Incoordinated gate**: It might be apparent in the late stages but earlier you might have to ask the patient if they have problems with equilibrium when they go upstairs, or run.
- ✓ **Fine movements** (e.g., writing, typing, opening a jar) they will be incoordinated as well. You should ask your patient about their job "if they use machines it might be dangerous".
- ✓ Incoordination of muscle movement could cause **speech and swallowing difficulties**(dangerous due to the risk of aspiration pneumonia- could cause death-)
- ✓ Extraocular muscles could be affected and that would result in **visual abnormalities** like haziness, nystagmus and blurred vision **(EYE movements)**.
- ✓ **Fatigue** (the need to expend more effort to perform activities that are no longer coordinated), patients need to "concentrate on their movements"
- ✓ **Cognitive and mood problems** → if the cortex was affected



- *Degeneration of spinal cord tracts leads to loss of proprioception;* **(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.

- *problems with peripheral nerves;*

  (spasticity) &(peripheral involvement "sensorimotor peripheral neuropathy")

Examples of Spinocerebellar ataxias:-

In contrast with all other neurodegenerative diseases, Friedreich ataxia is caused by the absence of a protein rather than accumulation of abnormal proteins.

1. **Friedreich ataxia**

- Autosomal recessive disorder, caused by a GAA tri-nucleotide repeat expansion in the frataxin gene, resulting in transcriptional silencing which results in decrease in Frataxin level
- Disease usually manifests in the first decade of life.
- Associated with cardiac disease and diabetes. (Friedreich has a sweet heart)
- **Symptoms**→Gait ataxia, hand clumsiness and dysarthria.

- Frataxin consist of two α helices and seven β strands, it is a protein that regulates (cellular iron levels especially in the mitochondria).
- It assists iron-sulfur 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

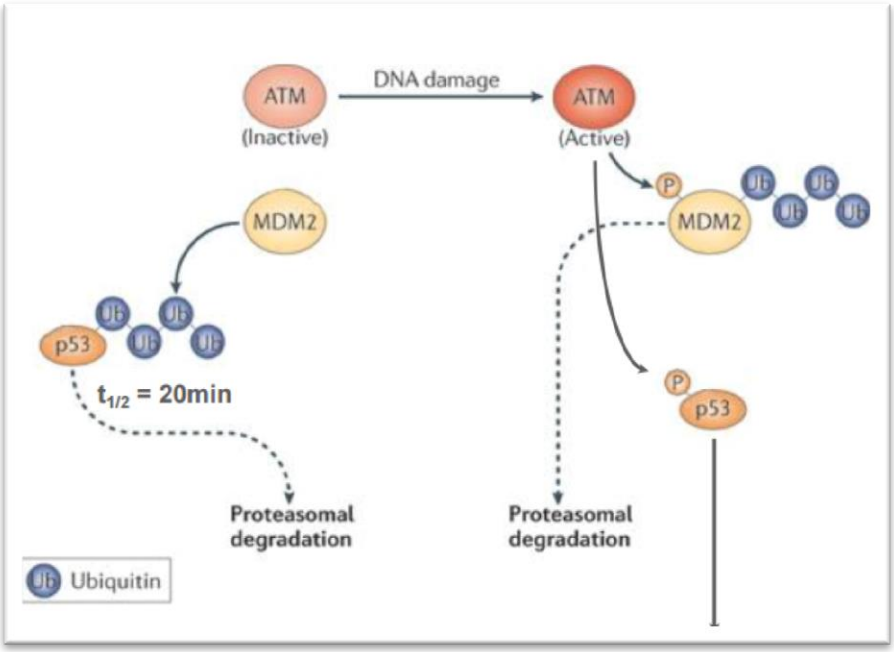
****How does the loss of frataxin cause neurodegeneration?**

- ➢ Decreased frataxin would impair the uptake and storage of iron in the mitochondria that leads to mitochondrial dysfunction and extra ROS due to excess iron → increase oxidative damage to the cell.

2. *Ataxia telangiectasia*

- Autosomal recessive, caused by a mutation in the ATM gene "ataxia mutated gene"
- ATM protein facilitates **apoptosis**, **maintains telomeres** and other actions.
- ATM encodes a kinase important for regulating cellular response to double stranded DNA breaks.
- Starts early in early childhood and **die** in the second decade of life
- **Symptoms**→ataxia, dyskinesia, telangiectasia in conjunctiva and skin, immunodeficiency
- Complications → infections and lymphoid neoplasms ;
  Increased cancers is also the result of the mutation in ATM (see below)
  If ATM is mutated there will be an **evasion of apoptosis**.

- **Morphology**: loss of Purkinje cells in the cerebellum.
  Also there is degeneration of dorsal columns, spinocerebellar tracts, anterior horn cells and peripheral neuropathy.
- We see telangiectasia in skin, viscera and CNS



(JUST READ)
In non-stressed, healthy cells, p53 has a short half-life (20 minutes) because of its association with MDM2, a protein that targets p53 for destruction
(MaDaMto gets p53 to hell). If ATM (ataxia telangiectasia mutated) is activated by DNA damage, p53 is released from MDM2 and that increases its half-life and enhances its ability to drive the transcription of target genes to work through specific pathways to induce apoptosis or repair, etc

Motor neuron disease

motor neurons can be affected by degenerative diseases through accumulation of abnormal proteins

❖ ***Amyotrophic lateral sclerosis***

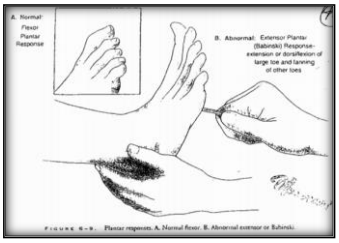
A → without myo → muscle trophy → nutrition

- ALS is a degenerative disease which causes the death of neurons that control voluntary muscles.
- 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: stiff muscles, muscle twitching, and gradually worsening weakness due to muscles decreasing in size. This results in difficulty in speaking, swallowing, and eventually breathing.

- **Symptoms**:

✓ ***Lower motor neuron signs***: denervation of muscles will cause weakness, muscle atrophy "amyotrophic", twitching and fasciculation, flaccidity, impaired reflexes and negative Babinski sign.

✓ ***Upper motor neuron signs***: paresis, Hyperreflexia, spasticity and positive Babinski sign, degeneration of corticospinal tracts in lateral portion of spinal cord (lateral sclerosis)



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

> Disease usually begins with distal extremity weakness (upper and lower limbs) but it progress to involve speaking, swallowing and eventually involves respiratory muscles – Respiratory failure is the most common cause of death.(expected after approximately 2 years of diagnosis)

- **Sensation is usually NOT affected** but **cognitive impairment** <u>**could occur**</u>
- Males slightly more than females**.**
- Most cases are **sporadic**, 5 to 10% inherited (autosomal dominant)
  Familial cases: earlier onset but disease progression is similar to sporadic.

- Several genetic mutations have been implicated in the familial cases:
  - ✓ (20% of cases)→ mutations in superoxide dismutase gene, ***SOD-1***on chromosome 21
  - ✓ These mutations causes abnormally folded SOD-1 protein → causing death of neurons.
- **Morphology**:

  Grossly→Thinning of anterior roots of spinal cord

  → motor cortex might become mildly atrophic (especially in severe cases).

  Microscopically: loss of anterior horn cells + reactive gliosis

  (reactive gliosis accompanies any type of neuronal loss)

> Similar micro features seen in motor cranial nerve nuclei except those supplying the Extraocular muscle which are spared except in very long standing survivors

OFF TOPIC: -

ALS Association
Fighting Lou Gehrig's Disease

Scientists discovered a new ALS gene, NEK1, known to be among the most common genetic contributors of the disease. This important finding is a direct result of your outpouring of supporting during 2014's ALS Ice Bucket Challenge.

Stephen Hawking

- 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

❖ ***Acquired metabolic and toxic disturbances***

This is important because metabolic and toxic problems can be reversed

1) Nutritional deficiencies

A) Thiamine deficiency can affect the brain resulting in:

Wernicke- Korsakoff syndrome

Wernicke encephalopathy presents with ataxia, confusion and abnormal eye movement. **Treatment** with thiamine → can reverse these deficits. If the acute stages go untreated, they are followed by irreversible memory disturbances then be called → **Korsakoff syndrome**.

****characterized by** → foci of hemorrhage and necrosis particularly in the mammillary bodies.

Causes of thiamine deficiency:
- Alcoholism {most common).
- Gastric disorders→ affecting thiamine absorption: tumors & chronic gastritis.
- Chronic vomiting.

B) Vitamin B12 deficiency may lead to*:*
Subacute combined degeneration *of the spinal cord*;
(combined=both ascending and descending tracts of the spinal cord are affected).
Symptoms → ataxia, Lower extremities numbness and tingling and sometimes progress to complete paraplegia "paralysis of both legs" a worse prognosis.

2) Metabolic disorders:

A)Hypoglycemia → effect similar to global hypoxia,
hippocampal neurons and Purkinje cells first affected**.**

B) Hyperglycemia→ketoacidosis or hyperosmolar coma, confusion then coma.

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

(recall: hyponatremia should also be corrected gradually to avoid central pontine myelinolysis "locked-in syndrome")

C) Hepatic encephalopathy results in coma due to increased ammonia, inflammation and hyponatremia.

3) Toxic disorders: Alcohol, ionizing radiation, pesticides and carbon monoxide all could affect the brain

THE END ♥