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الفريق العلمي

PATHOLOGY

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بِسْمِ اللَّـهِ الرَّحْمَـٰنِ الرَّحِيمِ

DEGENERATIVE DISEASES & DEMENTIAS

بهاي المحاضرة حنحكي عن الخرف كمقدمة و الاسباب الي ممكن تؤدي اله

و الدكتورفصل عن اربعه من هاي الاسباب , يصنفو من ضمن الdegenerative diseases

بعتذر لكن شرحت فقط لنصف المحاضرة لضيق الوقت

الخرف :

هو عبارة عن شخص واعي لكل ما حواليه بس عنده مشاكل بالذاكرة و ما بقدر يميز الاشياء الي حواليه.

و ينتج هاد الاشي كتابع او نتيجة لامراض عدة.

فهو ليس مرض بحد ذاته و ليس ناتج من الشيخوخه بل هو تابع لمرض معين.

بالتالي اسباب وجود الخرف كتيرة **;**

و هلا حنذكر البعض منهم.

قسمناهم اللى خمس مجموعات :

♦**Dementia** is the **development of memory impairment & other cognitive (recognition) deficits, with preservation of a normal level of consciousness**. It is emerging as one of the most important public health issues in the industrialized world.

There are many causes of dementia (Table 23-3); BUT, regardless of etiology; the **Rule: Dementia is not part of normal aging & always represents a pathologic process.**

Table 23-3

الكلام الاتي تم قرائته من الدكتور : ف الشرح اضافي

Major Causes of Dementia(D)

♦**Primary Neurodegenerative Disorders:**

امراض التنكس العصبي : الي بصير فيهم انحلال في وظائف الجهاز العصبي و يشملو الاتي:

-**Alzheimer** AD,

الزهايمر : ضمور في خلايا المخ يؤدي الى تراجع الذاكرة

-**Huntington** D,

هنتنغتون: موت خلايا عصبية معينة في الدماغ تؤدي الى حركات لا ارادية و اضطرابات عاطفية

-**Motor neuron** D,

العصبون الحركي: تضرر ال motor neuron الي رح يعمل ضعف بالجسم, يزداد مع الوقت

- **Parkinson D**

الشلل الارتعاشي: اضطراب في الجهاز العصبي المركزي الذي يؤثر بالجهاز الحركي

-diffuse Lewy body disease ;

داء اجسام ليوي : بروتينات اسمهم ليوي بتراكمو بالدماغ الي حيؤدي الى مشاكل تبع ذلك

-Pick D & other frontotemporal degenerations,

داء بيك: تراكم pick bodies الي بكون فيهم خيوط بروتينيه يؤدي الى مشاكل في الدماغ

-Progressive supranuclear palsy,

الشلل فوق النووي المرتقي: برضو تراكم بوروتينات ادت لمشاكل

♦**Infections**

-Prion-associated D:

Creutzfeldt-Jakob D, fatal familial insomnia, & others.

-(**AIDS** dementia) :

Human immunodeficiency virus encephalopathy

-Progressive multifocal leukoencephalopathy **(PML)**

(human polzomavirus that affect the oligodendrocyte)

-Miscellaneous forms of viral encephalitis, **Neurosyphilis**, Chronic meningitis

♦**Vascular & Traumatic Diseases**

-**Multi-infarct dementia** & other chronic vascular disorders (common cause)

-Global hypoxic-ischemic brain (injury resulted from severe hypotension, or when circulation stops as in heart block)

-Chronic subdural hematomas

♦**Nutritional & Metabolic Diseases**

-Thiamine deficiency (Wernicke-Korsakoff syndrome),

- Vitamin **B12** deficiency,

-**Niacin** (pellagra) &

-Endocrine diseases.

♦**Miscellaneous** (متفرقه)

-Brain **tumors**,

-Neuronal **storage** diseases,

-**Toxic injury** (including mercuryزئبق, leadرصاص, manganese, bromides)

While the diseases to be discussed in this section are considered as

"degenerative" i.e., reflecting an underlying cellular degeneration of neurons in the brain, …

Not all forms of dementia is degenerative.

القصد انو زي م قلنا الخرف اسبابه عدة , لهيك لا تقتصر اسبابه بال **degenerative ds**

بمعنى مش عشانا بنشرح فيهم صارو هم لحالهم من اسباب الخرف

حنحكي نقطتين بسيطتين عن الامراض الوعائية .

زي ما حكينا قبل شوي ; ف الامراض الوعائية ممكن انها تسببلنا خرف . و عنا مثالين ع ذلك

عنا مرض اسمه vascular (multi-infarct) dementia

هون بييجي عنا المريض و بكون صار و صارلو اكذا سكتة دماغية خلال سنوات

هاي السكته ادت الى تقليل او ايقاف التروية للدماغ الي بالتالي عمللنا infarction

لو هاد ال infarction صار في اكذا مكان بالدماغ (يشمل المادة الرمادية و البيضاء)خاصة المادة البيضاء الي اسمها centrum semiovale,

رح بالاخير يصير عندو خرف نتيجة لذلك.

ان صار و صار عنا قلة تروية في اماكن كتيييرة بالمادة البيضاء الي ادت الى فقدان ال myelin and axons الموجودين فيها

هون المرض رح يصير اسمه binswanger ds

بالتالي اختلفت التسمية على اختلاف المكان الي صار فيو نقصان تروية

Vascular disorders are an important cause of dementia.

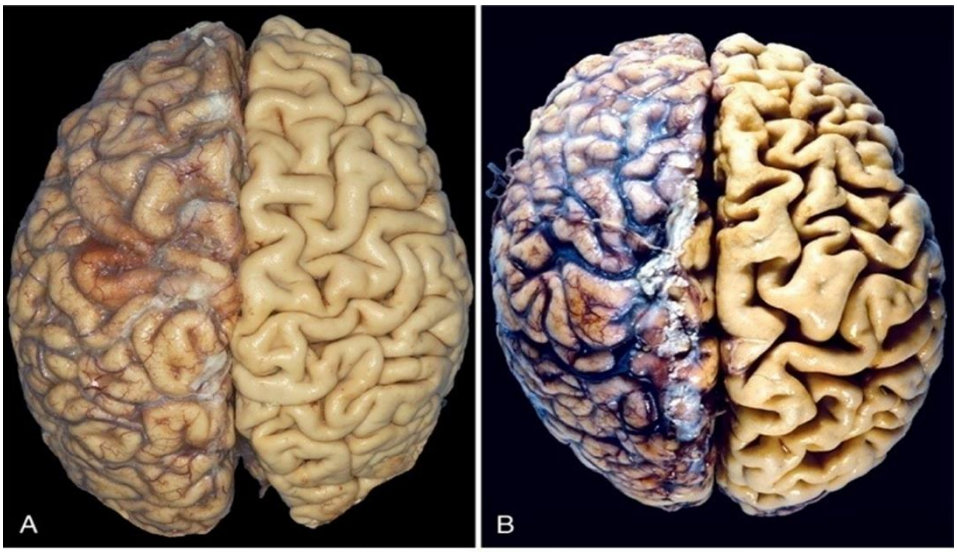
Patients who suffer multiple, bilateral, gray & white matter (centrum semiovale) infarcts during months or years develop dementia, called vascular (multi-infarct) dementia. (common finding)

When the pattern of injury (ischemia) preferentially involves large areas of the subcortical white matter with myelin & axon loss, the disorder is referred to as Binswanger disease (F1-4).

F1-4: **A, Normal** young adult brain.,

B, Atrophy of the brain in an 82 years-old male with atherosclerotic disease. Note that the loss of the brain substance (due to **aging** & **reduced blood supply**) narrows the gyri (تجاويف) & widens the sulci (تشققات) .

This is a vascular cause of dementia = atherosclerosis



Herewith, we will discuss the main causes of dementia, including Alzheimer, Parkinson, & Huntington diseases.

Alzheimer Disease (AD)

الزهايمر ; اشيع سبب لحدوث الخرف

مرض الزهايمر بصير تدريجيا بشكل متزايد على بطؤ , بحديث ببدا يبين معنا لما تنخفص قدرة المريض على التفكير و التحليل و التخطيط ...(intellectual function↓) و يحدث تغير في السلوك و التصرفات

بعد وقت من حدوثه ممكن يتطور و توصل الى انو المريض بصير عندو تشويش اي بصير عندو صعوبات بالاستقبال و التلقي و بصير عندو فقدان ذاكرة و عدم القدرة على التحدث و هاد بدل انو صار عنا علة شديدة في ال **cortex**

و خلال 5-10 سنوات بتطور الامور ليصير اخرس مقعد غير قابل على الحركة

و بالعادة حالات الوفاة بتصير بسبب حدوث مرض اخر للمريض اثناء معانته مع الزهايمر و هاد ما يسمى بال intercurrent infection

هاد الحكي بصير مع كتيير امراض و بسبب وفيات كتيره كمثال اي اعتلالات في التنفس او مع الكانسر او مع الامراض الغربية بالعموم

♦**AD is the most common cause of dementia in the elderly.**

The disease usually becomes clinically apparent as insidious impairment of higher intellectual function, with alterations in mood & behavior.

Later, progressive disorientation, memory loss, & aphasia indicate severe cortical dysfunction, & over the next 5 to 10 years, the patient becomes profoundly disabled, mute, & immobile.

Death usually occurs from **intercurrent infections.**

تزداد نسبة الاصابة بالزهايمر مع ازدياد العمر

♦**AD** incidence is:

3% (in 65-74 years age group),

و خلال السنوات الجاي يتضاعف الى ست اضعاف عند وصول الى 75 سنه الى 85

19% (75-84 y), &

ثم يتضعاف الى 10-15 مرة عند 85 سنه ف ما فوق

يعني واحد من كل تنين من الي اعمارهم 85 سنه

47% (85 years or more).

♦This ↑ incidence with age has given rise to **major medical, social, & economic problems** in some countries.

في اي مرض يتم التاكيد من التشخيص من خلال ال histological biobsy و هاد بنطبق كمان عالزهايمر

لكن نظرا لصعوبتو شوي و لوجود ما يساعد على التشخيص بشكل اسهل و بدقة في 80-90 بالميه من الحالات زي ال clinical examiation و ال radiological methods الي بتمثل ال MRI , ULTRASOUND , CT Scan

♦Although **pathologic examination** of brain tissue remains necessary for the **definitive diagnosis of AD**, the combination of **clinical** assessment & modern **radiologic methods** allows *accurate* diagnosis in 80% to 90% of cases.

♦Most **AD** cases are sporadic فردية , 5% -10% are familial عائلية .

♦**AD** patients rarely become symptomatic before 50 years of age, but early onset is seen with some of the heritable forms الحالات الوراثية .

ما سبب مرض الزهايمر و الخرف الناتج عنه؟
بحثو لاسباب حدوثو بالناس الي عندهم ياه بالوراثة .
ولقو انو بكل الحالات , بصير في عنا تاركم لبروتين معين يسمى بال amyloid beta .
تراكمه في الخلايا ادى الى تشوها و التدخل بوظائفها الي بالتالي عمللنا الزهايمر.

طيب كيف تم تراكم هاي البروتينات ؟ من وين اجت ؟
بالوضع الطبيعي هاي البروتينات بتكون موجودة لكن يتم التخلص منها بدون اي مشاكل .

ف الي بصير انو يوجد عنا بيبتيات , المخ بدو يتخلص منها
كيف بدو يتخلص منها ؟ بالانزيمات الي اسمهم ال secretase (peptidases)
هدول الانزيمات الهم 3 انواع الالفا و البيتا و الجاما , كل واحد منهم بقص البيبتيد من مكان معين

ف بالوضع الطبيعي كما في الرسمة
الافا secretase رح تشتغل على ال Amyloid B peptide و تاخد جزء منه فقط مع الاشي
الموصول معاه الي اسمو amyloid precursor protein
ف هاد الي الالفا فصلتو رح يكون soluble اي يتم التخلص منه
بالتالي الي تخلصنا منو بالوضع الطبيعي هو ال amyloid precusrer مع جزء من ال AB
peptide بواسطة ال الالفا بيبتيديز
اما ما تبقى من ال AB protein رح يضل بس الالفا حتكمل شغلها عليه بشكل عادي

اما في وضع الزهايمر
هون الالفا ما بتشتغل بالمرة
و بياخد محلها البيتا سيكريتيز الي رح يفصل ال amyloid precuser اي ال soluble part لحاله
بدون جزء البروتين
و يبقى ال AB protein COMPLETE لم يقسم, الي رح يكون صعب التخلص منه بالتالي رح يتجمع
و يعمللنا amyloid beta aggregates الي رح تتحول الى amyloid fibrils in the cell الي
حتكوون سامة للخلية بالكميات الصغيره , كل ما كترت و كبرت رح تؤدي الى موتها و تعمل لطخة
اسمها neurotic plaque الي بالاخير حيعمملنا زهايمر
فهذا هو سبب موت الخلايا العصبية في الدماغ في مرض الزهايمر

بالتالي نتذكر الاتي

- بالوضع الطبيعي الشغال هو الالفا بيبتيديز الي رح يقصف ال precursor + a fragment of the AB protein
  و المو شغال هو البيتا
- في الوضع المرضي في الزهايمر البيتا هو الشغال و هو رح يقص و يكون pure precursor لحاله و يعمللنا a complete AB protein
- و المو شغال هو الالفا
- فس كلا الحالتين الجاما رح يكون شغال طبيعي

♦Evidence from familial forms of the AD disease indicates that
➔ the **accumulation of a peptide (amyloid β, or Aβ) in the brain initiates a chain of events** that result in the morphologic changes of AD & dementia.
This peptide is derived from a larger membrane protein known as amyloid precursor protein (APP), which is processed in one of two ways **(F 23-28)**

F23-28: **Accumulation of the peptide (β amyloid, or Aβ) in the brain in Alzheimer disease**

معلومة : اي مريض لداوم اذا عاش امتر من 45 سنه رح يصير عندو رهايمر و خرف

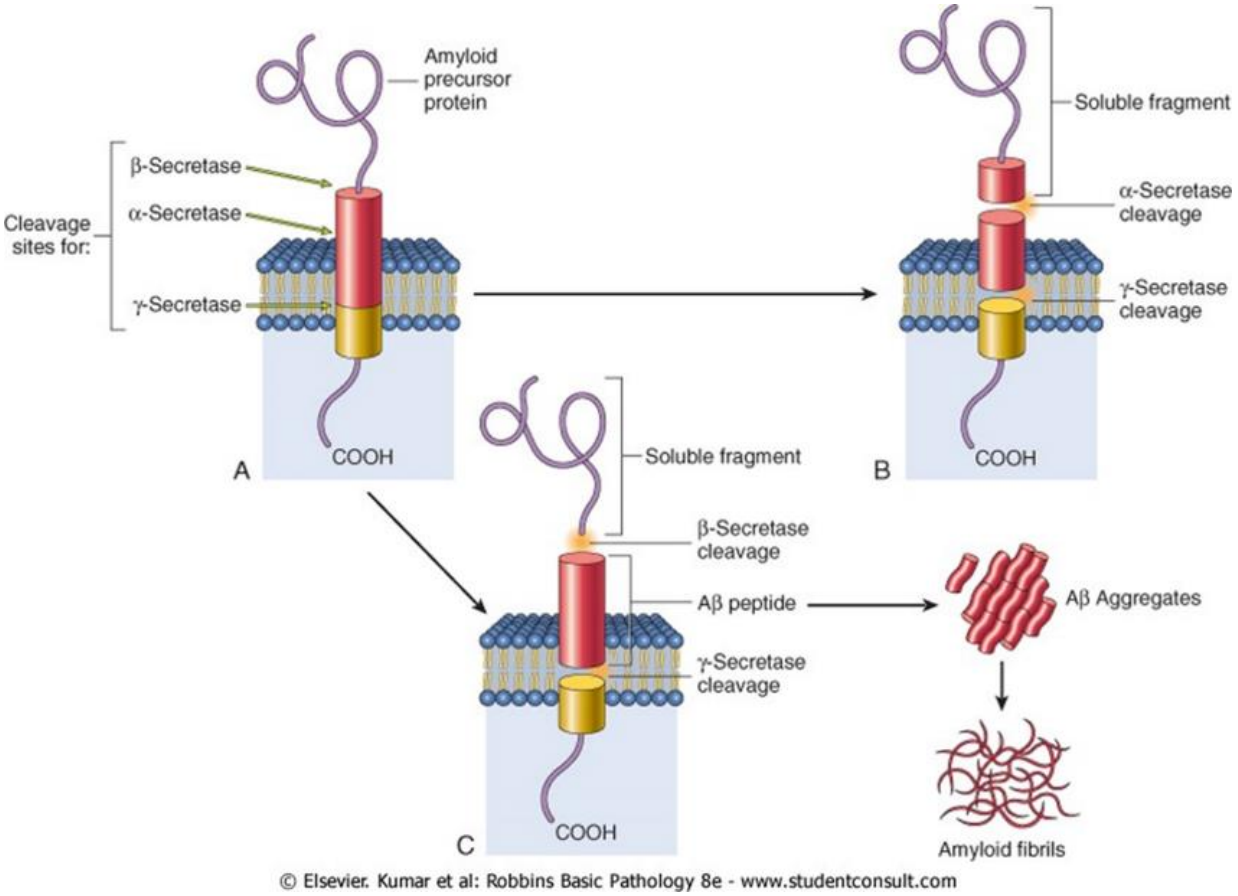
ليه؟ لانو الكروموسوم المصاب بداون 21 يقع فيه جين ال APP

♦ **AD** occurs in all patients with trisomy 21(Down syndrome)where the gene encoding APP is located - who **survive** beyond 45 years.

♦ Accumulation of **Aβ has several effects:**

- Small Aβ aggregates can alter neurotransmission, & can be → **toxic to neurons** & **synaptic endings**.

- Larger Aβ deposits, in the form of plaques, lead to → **neuronal death, eliciting a →local inflammatory response that can result in further cell injury,**



& may cause altered region-to-region communication, through mechanical effects on axons & dendrites.

بالوضع الطبيعي الدماغ يصل وزنه من 1500-1450g

اما في الزهايمر بوصل وزنه الى اقل من كيلو,, اي 33% من وزنه قد فقد

ليه؟

لانو بصير في عنا ضمور في الدماغ الي حيسمح لتشققات الدماغ انها تتوسع في اماكن معينه من ضمنها (و هذا مهم) ال frontal , temporal, pareital lobes

بسبب هذا الدماغ رح يعوض هاد الموضوع ب انه يوسع و يكبر بطينات الدماغ ليضل محافظ عحالو و مالي الجمجمه

و هاي مشكلة!

لانو من ورا هيك برضو كطريقة تعويضية رح يتجمع في البطينات المتوسعه csf الي رح تعمللنا hydrocephalus ex vacuo

هاد صار لانو اماكن تعبئة ال cfs كبرت , من ضمنها بطينات الدماغ

اي هذا ليس بسبب زيادة بال csf ولا بسبب خلل في الامتصاص ولا بسبب الانسدادات

►**GROSSLY,** the brain is small (often less than 1000g) shows a variable degree of **cortical atrophy,** with **widening of the cerebral sulci** in the *frontal, temporal, & parietal lobes* & **compensatory ventricular enlargement.**

♦**AD** is diagnosed histologically by the presence of

- **neuritic plaques** (an *extracellular l*esion);

-& **neurofibrillary tangles** (an *intracellular* lesion) **(F 23-29);**

both of which are **not specific** because they may also be present to a lesser extent in the brains of elderly nondemented individuals

▼The current criteria for a diagnosis of AD are based on a combination of clinical & pathologic feature

♦There is a fairly **constant pattern of progression** of involvement of brain regions:

pathologic changes (specifically plaques, tangles, & the associated neuronal loss & glial reaction) are evident →earliest in the entorhinal cortex,

then → spread through the hippocampal formation & isocortex,

& then →extend into the neocortex.

Silver staining or immunohistochemistry are extremely helpful in assessing the true burden of these changes in a brain.

♦**Neuritic plaques** are 20 to 200 µm in Ø with microglial cells & reactive astrocytes, consist of a:

Neuritic plaques = amyloid core + Surrounding **dystrophic neurites; i.e.,**

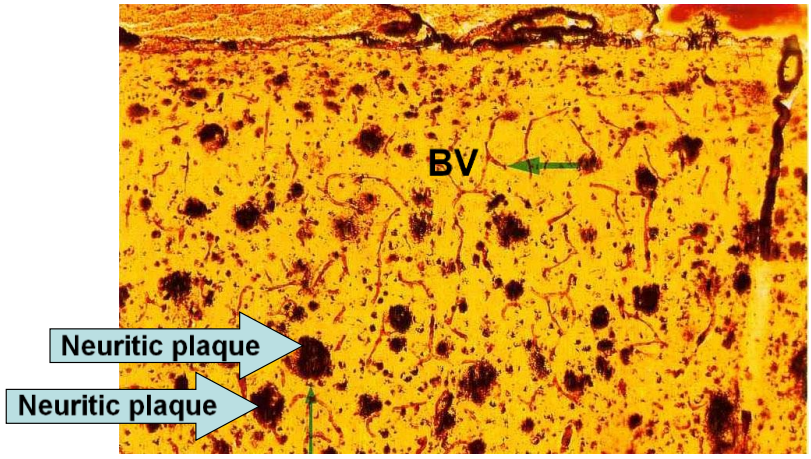
I. Central amyloid core
(contains **accumulation of a peptide (β amyloid, or Aβ,** F 23-29B),

II. Surrounded by **dystrophic neurites (**F23 -29 & ¦ 4.18)
a focal, spherical collections of dilated, tortuous, silver-staining (argyrophilic) neuritic processes present at their periphery.

♦**Neuritic plaques** can be found in the hippocampus & amygdala as well as in the neocortex, although there is usually relative sparing of primary motor & sensory cortices until late in the course of the disease.

♦**<u>Diffuse plaques</u> are Aβ** deposits which can also be found that **<u>lack</u>** any surrounding neuritic reaction

these are typically found in superficial portions of cerebral cortex as well as in basal ganglia & cerebellar cortex & may represent an **early stage of plaque development**



¦ 4.18: **Alzheimer disease: Brain X90.** Biopsy specimen from the cortex of a man of 63 stained by periodic acid silver method.

- The subarachnoid space & cortex surface are at top.
- Many rounded & dark **neuritic plaques** (thin A) consisting of
  (I) Central amyloid core (contains **accumulated β amyloid),**
  (II) Surrounded by **Dystrophic neurites,** spherical collections of extracellular dilated, tortuous, silver-stained (argyrophilic) degenerated neuritic processes

♦**Neurofibrillary tangles;**

Are bundles of paired helical filaments visible as basophilic fibrillary **intracytoplasmic** structures of the neurons, that displace or encircle the nucleus (F23- 29C);

Tangles can remain after neurons die, then becoming a form of extracellular pathology.

They are commonly found in cortical neurons, especially in the entorhinal cortex, as well as in other sites such as pyramidal cells of the hippocampus, the amygdala, the basal forebrain, & the raphe nuclei.

A major component of paired helical filaments is abnormally hyperphosphorylated forms of the protein **tau** (F23-29C).

Tangles are not specific to AD, being found in other degenerative diseases as well

F23-29: **Alzheimer disease.**

A, Neuritic plaque {Bielschowsky stain, arrow} is 20 to 200 µm in Ø, focal spherical collections of dilated, tortuous, silver-staining dystrophic neurites & tangles which are filamentous extracellular inclusions, surrounding a central amyloid core,

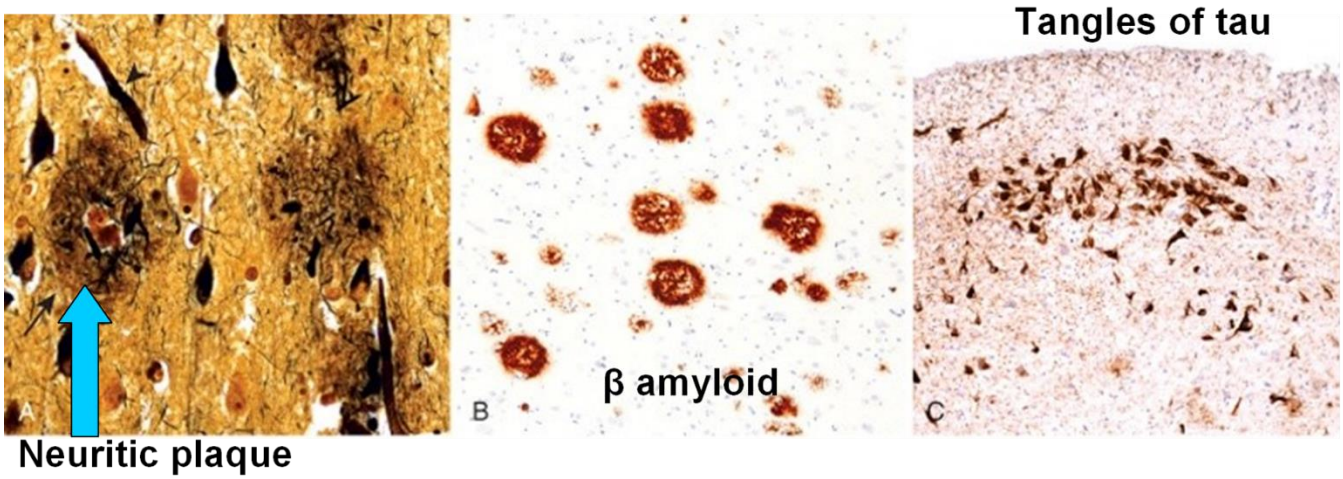
B, Immunohistochemistry against **Aβ (β amyloid)** shows that the **Aβ** peptide is present in the core of the neuritic plaques & in the surrounding region.

C, Immuno stain for **tau** protein showing neurons containing **tangles**).

Frontotemporal Dementia

♦**Is** another **major** category of disease that results in dementia, some of these dementias are caused by <u>mutations in the gene encoding **tau,**</u> the protein found in tangles

They shares clinical features **(progressive language deterioration & personality changes**) corresponding to degeneration & <u>atrophy</u> of temporal & frontal lobes. **These symptoms often occur before memory disturbance, &** this difference in



presentation can assist in their separation from cases of AD on clinical grounds.

►**GROSSLY,** the basic finding is **frontal & temporal lobes atrophy.** Different subgroups characterized by specific inclusions, which in some consist of **abnormal** accumulations of **tau.**

Parkinsonism

♦Is a clinical syndrome characterized by diminished facial expression

<u>-(masked facies),</u>

<u>-</u>stooped (<u>bended) posture</u>,

- <u>slowness of voluntary movement</u>,

- <u>festinating gait</u> (progressively shortened, accelerated steps),

-rigidity,

-& a "pill- rolling" **tremor.**

♦This **syndrome** of motor disturbance is seen in a number of conditions that share **damage to dopaminergic neurons of the substantia nigra** or to their projection to the striatum,

Including:

- **post-encephalitic Parkinsonism** (associated with the influenza pandemic),

-multiple system atrophy,

-progressive supranuclear palsy,

- corticobasal degeneration,

- & some cases of HD.

♦**Parkinsonism can be induced** by drugs that affect these neurons, particularly **dopamine antagonists & toxins**;

one toxin, **MPTP,** has now become an important tool in **animal models** to develop & test new therapies.

Idiopathic Parkinson disease

Is the most common neurodegenerative disease associated with Parkinsonism. Its ▼ **Diagnosis** is made in patients with progressive Parkinsonism in the **absence of a toxic or other known underlying etiology & if they show clinical response to l-dihydroxyphenylalanine (l-DOPA) treatment.**

♦Most Parkinson disease cases are sporadic;

♦However, there are both autosomal dominant & recessive forms of the Parkinson disease.

♦Genetic analysis has identified specific causal mutations, e.g.;

α-synuclein mutations cause autosomal dominant Parkinson disease, as can gene duplications & triplications.

♦Even in cases of Parkinson disease not caused by mutations in this gene, the **diagnostic feature of the disease-the Lewy body-is an inclusion containing α-synuclein.** This is a widely expressed neuronal protein that is involved in synaptic transmission & other cellular processes.

♦**The presence of α-synuclein in the Lewy bodies** has suggested that defective degradation of the protein in the proteasome might play a role.

►**Grossly,** typically there is **pallor of the substantia nigra (F23-30A & B) & locus ceruleus**.

♦H, there is (1) loss of the pigmented, catecholaminergic neurons in these regions with gliosis;

& (2) **Lewy bodies (F23 30C**) may be found in some of the remaining neurons.

♦**Lewy bodies** are **single or multiple, round or elongated, eosinophilic intracytoplasmic inclusions that often have a dense core surrounded by a pale halo**.

♦Ultrastructurally, Lewy bodies are composed of fine filaments, densely packed in the core but loose at the rim. These filaments are **composed of α-synuclein,** along with other proteins including **neurofilament & ubiquitin.**

Lewy bodies may also be found in the cholinergic cells of the basal nucleus of Meynert, & in other brain-stem nuclei.

♦The presence of **Lewy bodies** in limbic & neocortical structures is associated with cognitive impairment-the disorder recognized as **[Dementia with Lewy bodies]**.

F23-30: **Parkinson disease.**

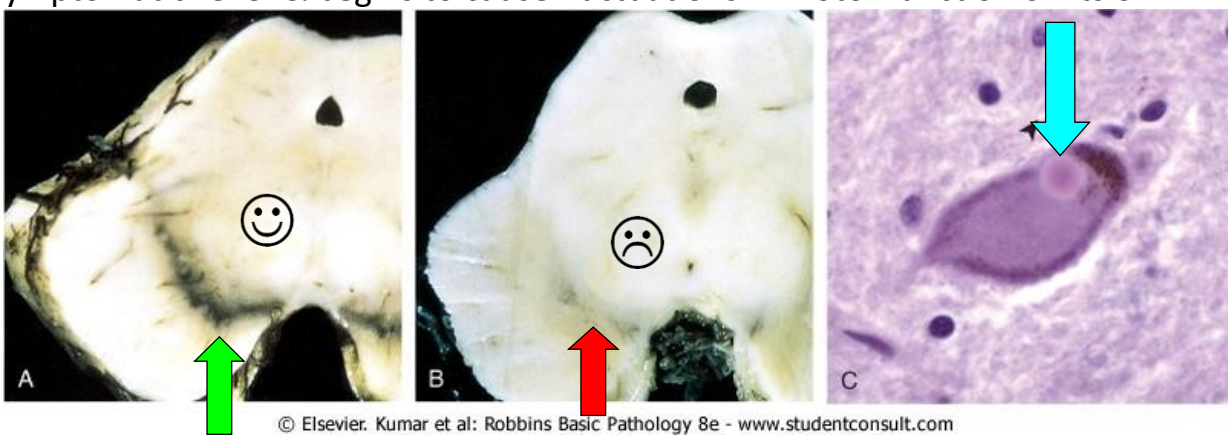
A, J Normal substantia nigra.

B, L Depigmented substantia nigra in idiopathic Parkinson disease.

C, Lewy body (arrow) in a neuron from the substantia nigra stains pink. An eosinophilic, round intracytoplasmic inclusion having dense core surrounded by a pale halo.

Clinically, **l-DOPA therapy is often extremely effective in symptomatic treatment,** but it does not significantly alter the progressive nature of the disease.

Over time, l-DOPA becomes less effective at providing the patient with symptomatic relief & begins to cause fluctuations in motor function on its own.



▼The disease usually progresses over 10 to 15 years, with eventual severe motor slowing to the point of **near immobility**.

1- N Death is usually the result of **intercurrent infection** or
2- **trauma from frequent falls caused by postural instability**

♦About **10% to 15%** of Parkinson patients develop **dementia**, with the incidence ↑ with advancing age. While many affected individuals also have pathologic

evidence of AD, the **dementia in other Parkinson disease patients is attributed to widely disseminated Lewy bodies in the cerebral cortex**