DEMENTIA

1. Introduction
2. Epidemiology
3. Causes of dementia
4. Clinical manifestations
5. Diagnostic evaluation
6. Major dementias: Alzheimer disease, vascular dementia, chronic subdural hematoma, normal-pressure hydrocephalus, dementia with Lewy bodies, metabolic causes

1. Introduction

Dementia is the term to describe intellectual and cognitive deterioration of sufficient severity to interfere with normal functioning

Dementia is not a specific disease and can variably affect multiple aspects of cognitive function including memory, orientation, visuospatial perception, abstraction, language and higher executive functions, for example planning ,organizing , and sequencing.

This differs from delirium , which implies an often acute and reversible , global disturbance of mental function. It is characterized by inattention to the immediate environment.

How can we differentiate between Delirium and Dementia?

- Attention is almost always altered in delirium but not dementia
- Increased or decreased motor activity is inherent in delirium but absent in dementia
- Delirium is reversible if the cause is identified but dementia progressively worsen

Dementia Versus Mild Cognitive Impairment

Attempts have been made to better define cognitive changes associated with aging, and varying sets of criteria have produced multiple terms, including such terms as *age-associated memory impairment*, *age-related cognitive change*, and *questionable dementia*, among others. The most widely used term for cognitive change insufficient to meet criteria for dementia is *mild cognitive impairment* or, in the most recent psychiatric lexicon (*DSM-5*), *minor neurocognitive disorder* (see Chapter 50). Criteria for MCI include subjective cognitive complaints and objective cognitive dysfunction but preserved general cognitive function and activities of daily living. Follow-up examinations of individuals with MCI indicate that some, but not all, develop dementia over time.

2. Epidemiology

Dementia is most common in the elderly, but can occur at a younger age, particularly in those with a hereditary predisposition

Approximately 5% of people between the ages of 65 and 70 years have dementia

This increases to more than 45% above age 85 years

Alzheimer disease accounts for 50% to 70% of cases of dementia

Cerebrovascular disease may account for an additional 15% to 20% , and the other causes account for most of the rest

The societal financial burden of dementia is substantial, with recent studies estimating more than 150 billion US Dollars spent in the USA annually on dementia-related cost, a cost similar with those of cancer and heart disease

3. Causes of dementia

* Degenerative: Alzheimer disease, Lewy body dementia,frontotemporal dementia,progressive supranuclear palsy,Parkinson disease,Huntington disease

*Metabolic: hypothyroidism,vitamin B12 deficiency, Wilson disease, hypercalcemia

*Lipid storage diseases and leukodystrophies

*Toxic: drug intoxication, alcohol,arsenic, mercury and lead intoxication

* Infectious: HIV, syphilis,subacute sclerosing panencephalitis(post measles infection)

* Vascular: vascular dementia, vasculitis

* Structural, traumatic, and inflammatory: chronic subdural hematoma, normal pressure hydrocephalus

* Neoplastic and paraneoplastic

* Other: undetermined

* Mixed:(Alzheimer plus vascular)

Primary Neurodegenerative Disorders
Alzheimer disease (AD)
Lewy body disorders
Dementia with Lewy bodies (DLB)
Parkinson disease dementia (PDD)
Frontotemporal dementias (FTD)
Behavioral variant frontotemporal dementia (bvFTD)
Progressive nonfluent aphasia (PNFA)
Frontotemporal dementia with motor neuron disease (FTD-ALS, FTD-MND)
Progressive supranuclear palsy (PSP)
Corticobasal degeneration (CBD)
Huntington disease (HD)
Wilson disease (WD)

Creutzfeldt-Jakob disease (CJD) and other prion diseases
Hippocampal sclerosis
Limbic-predominant age-related TDP-43 encephalopathy (LATE)
Chronic traumatic encephalopathy (CTE)
Others: British familial dementia, HDLS, others
Vascular dementias: multi-infarct dementia, Binswanger disease, CADASIL
Immune-mediated encephalitides: NMDARAE, VGKCAE, others
Demyelinating dementias: multiple sclerosis, adreno- and metachromatic leukodystrophies
Inflammatory dementias: CNS vasculitides, Behçet syndrome, systemic lupus
Infectious dementias: neurosyphilis, neuroborreliosis, HIV dementia, others
Neoplastic dementias: tumors, carcinomatous meningitis, paraneoplastic syndromes
Metabolic or endocrine dementias: B_{12} or rarer vitamin deficiencies, hypothyroidism
Structural dementias: hydrocephalus, brain trauma

4. Clinical manifestations

There is some degree of cognitive slowing that accompanies normal aging

In general, however, most patients with actual dementia have more significant and progressive difficulties, often affecting short-term memory, followed by an indolent deterioration of cognitive function that may involve language, praxis, and personality

Many dementing illnesses manifest characteristic symptoms and clinical findings that are helpful in establishing an etiologic diagnosis

5. Diagnostic evaluation

The initial recognition of dementia is difficult.

Normal aging can mimic its features

Rarely is the patient aware of cognitive deterioration

In most cases the family brings the patient to the doctor months or years after problems have started

Recent research has demonstrated, however, that subjective cognitive decline reported by older adults can be an early indicator of dementia, even in the absence of objective cognitive dysfunction

Thus dementia is the clinical history (including reports by relatives) and the physical examination , especially a very detailed mental status examination

Diagnosis of the cause of dementia consists of matching the major clinical features of the individual patient with the characteristics of known dementing illnesses

Of note, it is important to rule out an underlying depression as the cause of cognitive symptoms, as the associated cognitive abnormalities of depression can mimic dementia

Some tests are to consider in the workup of cognitive dysfunction:

*Hematology screening including ESR

* Vitamin B12 and folate

* Blood calcium

* Liver function tests, including ammonia

* Electrolytes

* Serum urea and creatinine

* Infection workup, including syphilis, HIV, tuberculosis …

* Thyroid function tests

* EEG should not be ordered routinely in a dementia assessment. Its use is justified when the patient has evidence of fluctuations in cognitive status that could be seizures.The EEG may be useful at the initial presentation in patients with suspected Creuzfeldt Jakob disease (CJD)

* CT or MRI Brain: It rules out structural abnormalities such as tumor, subdural hematoma, and hydrocephalus and evaluates cortical atrophy

* Neuropsychological assessment: It is used in the early stages to establish the diagnosis and to use as a comparison tool in the progression of the disease

(Minimental state examination,figure: normal score=30; a score of 20-24=mild dementia; a score of 13-20=moderate dementia and a score less than 12=severe dementia)

* Brain biopsy: It is only indicated in specific cases such as CJD, HIV, CNS vasculitis, and so on, to confirm the diagnosis and find or exclude possible treatable causes

Instructions: Score one point for each correct response within each question or activ

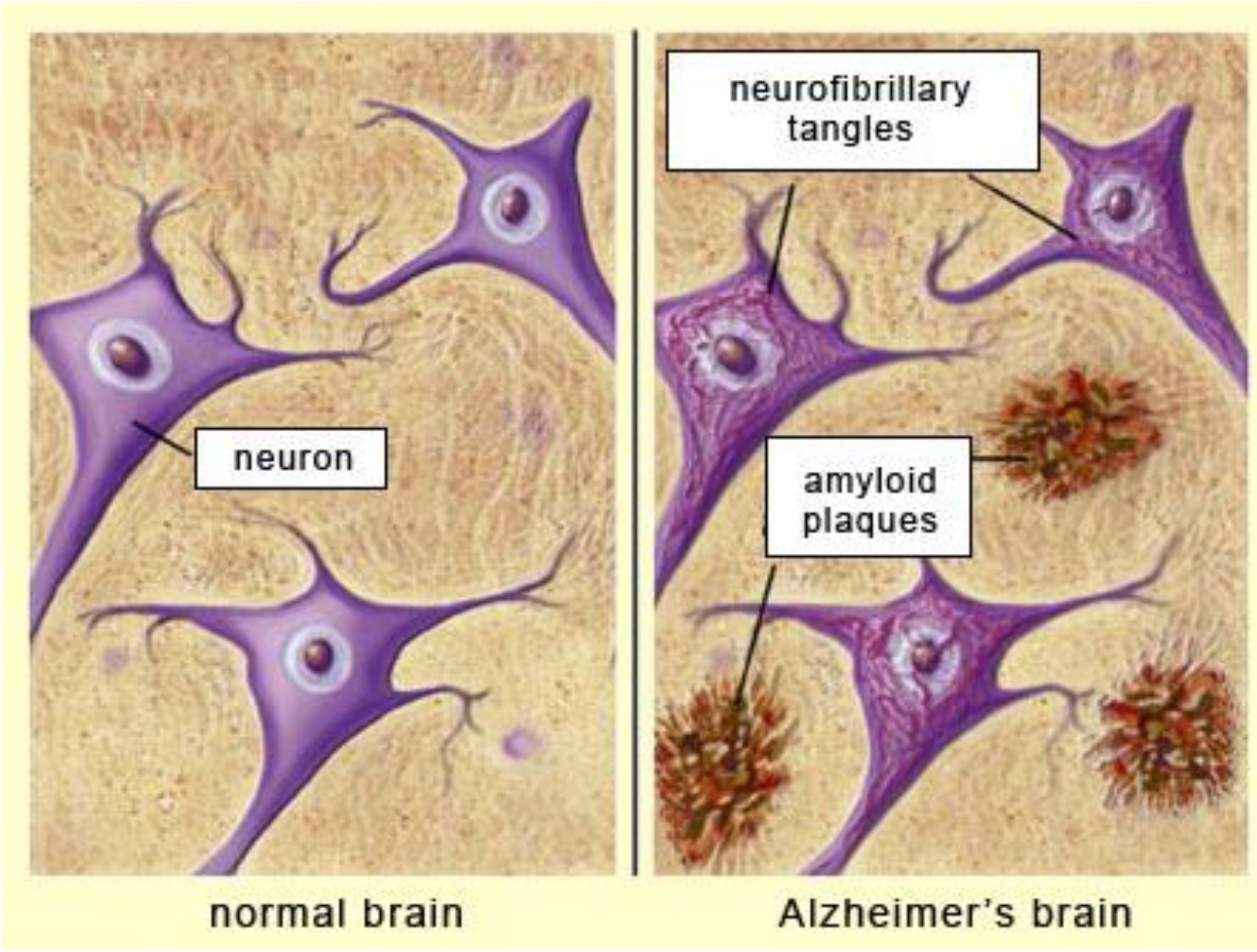
Maximum Score	Patient's Score	Questions
5		"What is the year? Season? Date? Day? Month?"
5		"Where are we now? State? County? Town/city? Hospital? Floo
3		The examiner names three unrelated objects clearly and slowly, the the instructor asks the patient to name all three of them. The patien response is used for scoring. The examiner repeats them until patie learns all of them, if possible.
5		"I would like you to count backward from 100 by sevens." (93, 86, 7 72, 65, ...) Alternative: "Spell WORLD backwards." (D-L-R-O-W)
3		"Earlier I told you the names of three things. Can you tell me what those were?"
2		Show the patient two simple objects, such as a wristwatch and a pe and ask the patient to name them.
1		"Repeat the phrase: 'No ifs, ands, or buts.'"
3		"Take the paper in your right hand, fold it in half, and put it on the fl (The examiner gives the patient a piece of blank paper.)
1		"Please read this and do what it says." (Written instruction is "Close your eyes.")
1		"Make up and write a sentence about anything." (This sentence mu contain a noun and a verb.)
1		"Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.) 
30		TOTAL

6. Major dementias

A) Alzheimer disease (degenerative)

In 1907, Alois Alzheimer , a German clinician and neuropathologist , published the landmark case of a 51-year-old woman with deterioration of her mental state

Her autopsy showed the classic pathology of Alzheimer disease (AD) : neurofibrillary tangles (NFTs) and senile plaques in the cerebral neocortex and hippocampus


neuron
neurofibrillary tangles
amyloid plaques
normal brain
Alzheimer's brain

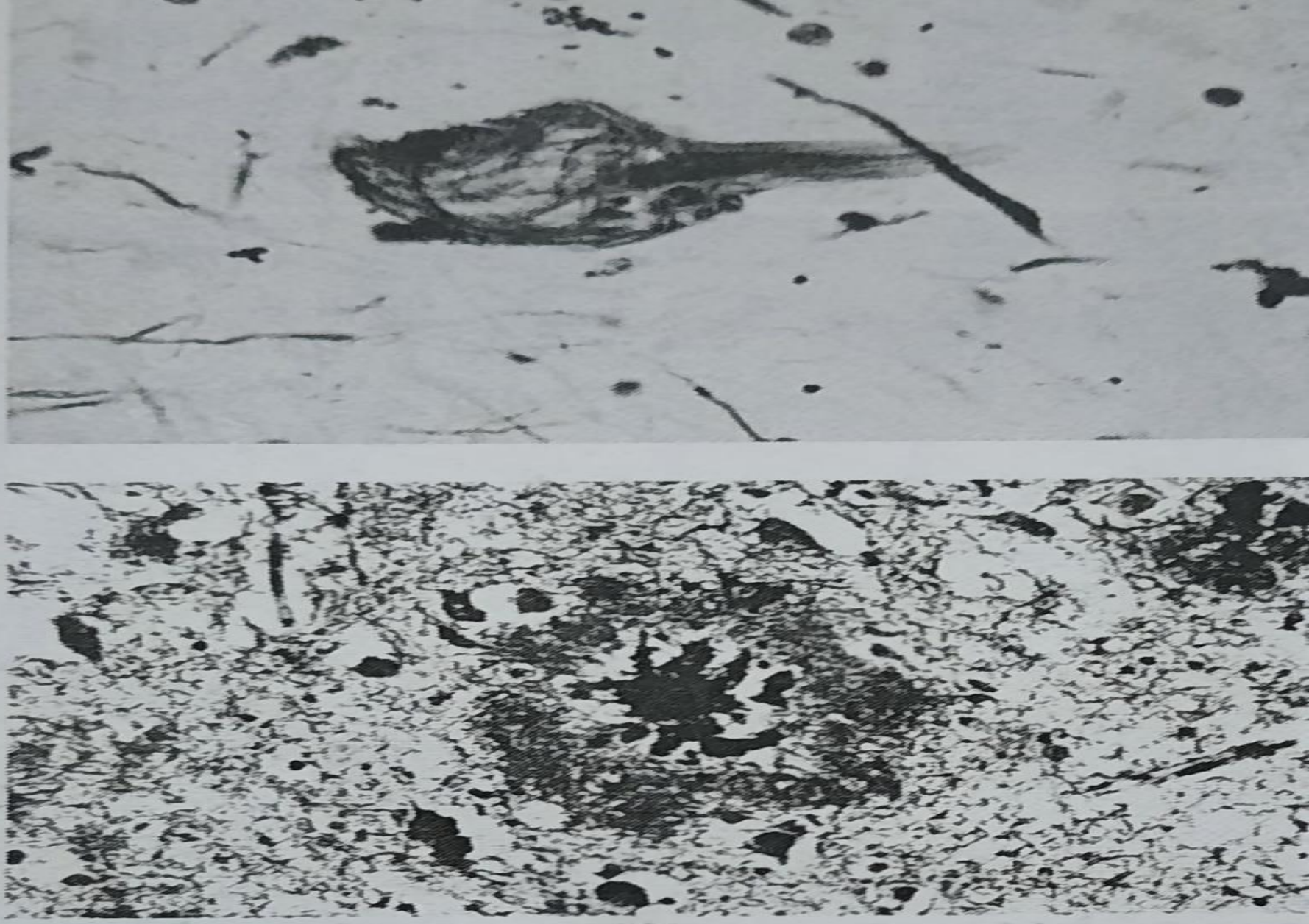
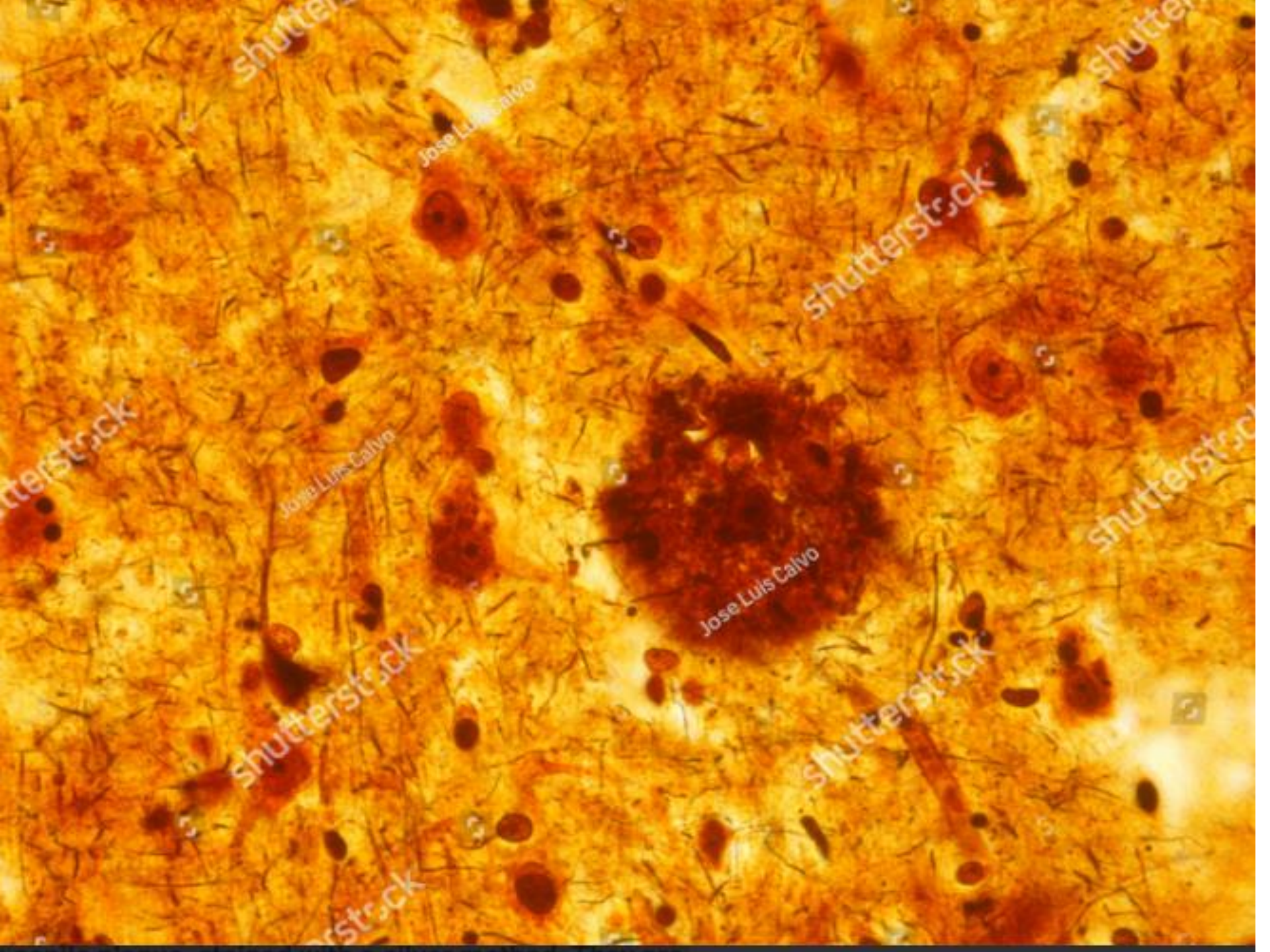


Figure 18.3 Alzheimer's disease – neuropathological hallmarks. (a) Neurofibrillary tangles, (b) neuritic plaques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Jose Luis Calvo

* Clinical manifestations

“ Doctor, my mother is 75 years old, and over the last 3 years I have noted that she is having more difficulty with her memory. She remembers her marriage 50 years ago, but she does not remember that we were here yesterday. She asks the same questions repeatedly and forgets my answers. She is unable to balance her checkbook , and yesterday she could not find the way home from the store”

This history illustrates the characteristic features of AD

TABLE 12.3 Ten Warning Signs of Alzheimer Disease[a]

1. Memory loss that affects job skills
2. Difficulty performing familiar tasks
3. Problems with language
4. Disorientation to time and place
5. Poor or decreased judgment
6. Problems with abstract thinking
7. Misplacing things
8. Changes in mood or personality
9. Problems with directions or spatial relations
10. Loss of initiative

[a] Adapted from the Alzheimer's Association. 10 early signs and symptoms of Alzheimer's. Alzheimer's Association Web site. https://www.alz.org/alzheimers-dementia/10_signs. Accessed October 15, 2020.

At the beginning of the illness, the examination shows no difficulty with language, reasoning, or performance of normal social and personal behaviours

Only those close to the patient notice small mistakes, suggesting that something is wrong(becoming lost while driving, misplacing objects, the kitchen stove left unattended, missed appointments, loss of social and interpersonal interactions)

Later, the patient has more difficulty with activities of daily life

As the disease progresses, other aspects of cognitive function are lost, including the ability to speak, understand and make decisions

Characteristically, in contrast to patients with vascular dementia, elementary neurologic functions(motor, visual,somatosensory and gait) remain normal until very late in the disease

Psychiatric manifestations are common at this time: personality changes (apathetic or impulsive), aggressive behaviour(physical or verbal), paranoid thoughts and delusions (persecution, things being stolen), sleep disturbances (the word "sundowning" is used to describe worsening psychiatric manifestations during the evening and night), hallucinations(uncommon, and often a side effect of medications) , and depression

The disease course is relentlessly progressive

The average length of time from onset of symptoms until diagnosis is 2 to 3 years, with subsequent nursing home placement after 3 to 6 years

AD patients typically spend 3 years in nursing homes before death

Thus, the total duration of AD is typically 9 to 12 years

* Epidemiology

Recent estimates suggest that more than 2 million people have AD in the USA alone, with nearly 4% of people older than 65 years incapacitated by severe AD

Because of increased life expectancy, the population at risk for AD is the fastest-growing segment of society

Annually, approximately 100000 people die of AD and more than 25 billion US Dollars is spent on the institutional care of patients with AD

* Etiology and risk factors

Many factors are associated with an increased frequency of AD, including age, female sex, cerebrovascular disease, diabetes, and severe head trauma

There are also many putative genetic risk factors

The gene for ApoE4 (on chromosome 19) is associated with both early – and late-onset AD of both sporadic and familial varieties

Early-onset AD has been associated with many different mutations in presenilin genes PSEN1 and PSEN2 on chromosomes 14 and 1, respectively

Adults with Down syndrome have a high risk of AD, in part because of the triplication of the gene for amyloid precursor protein(APP) located on chromosome 21

Another mutation in a gene on chromosome 12 that encodes alpha -2- macroglobulin has been associated with AD

The ApoE4 alleles and the alpha-2-macroglobulin mutation predispose individuals to early onset sporadic AD, and even more to late-onset-AD

* Diagnostic evaluation

With the exception of those patients with identified mutations in known causative genes(APP,PSEN1 and PSEN2), the diagnosis of AD is a clinical one and can only be confirmed with brain biopsy

The diagnosis is suggested by the clinical features and by the insidiously progressive course

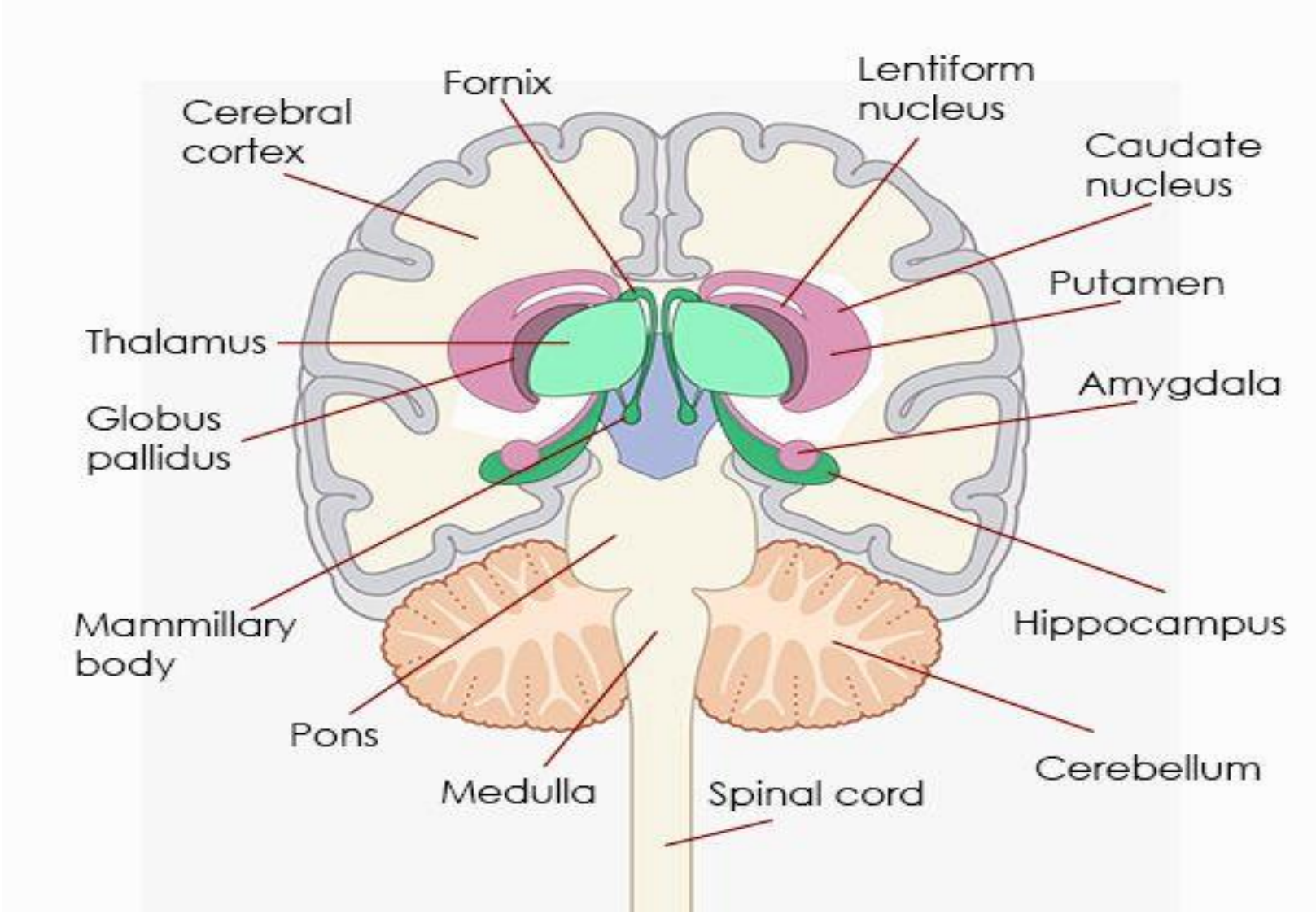
Investigations are designed to exclude other causes of dementia(see previous slides)

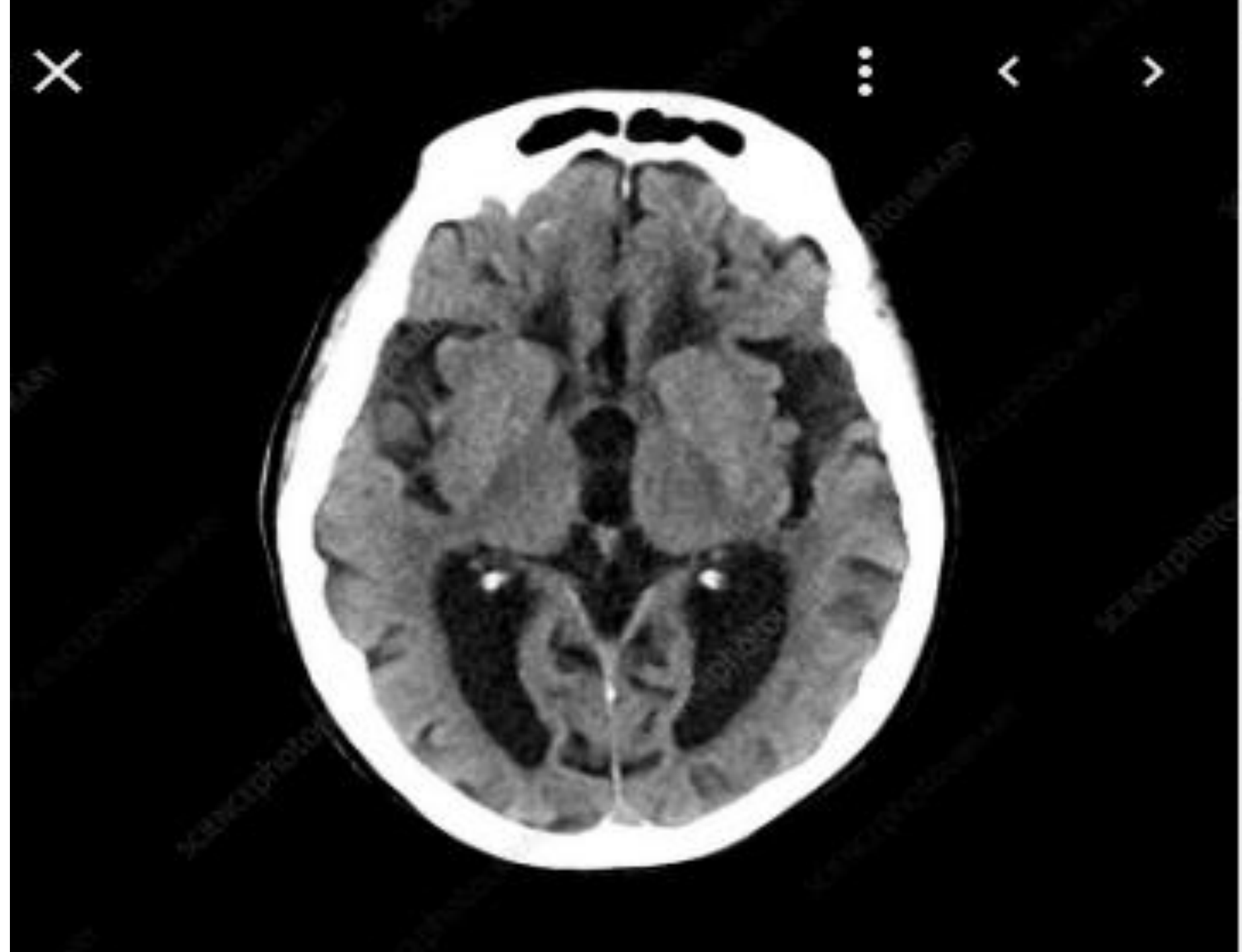
Elevated tau protein and low amyloid-beta-42 levels in the CSF have been suggested as early diagnostic markers for AD

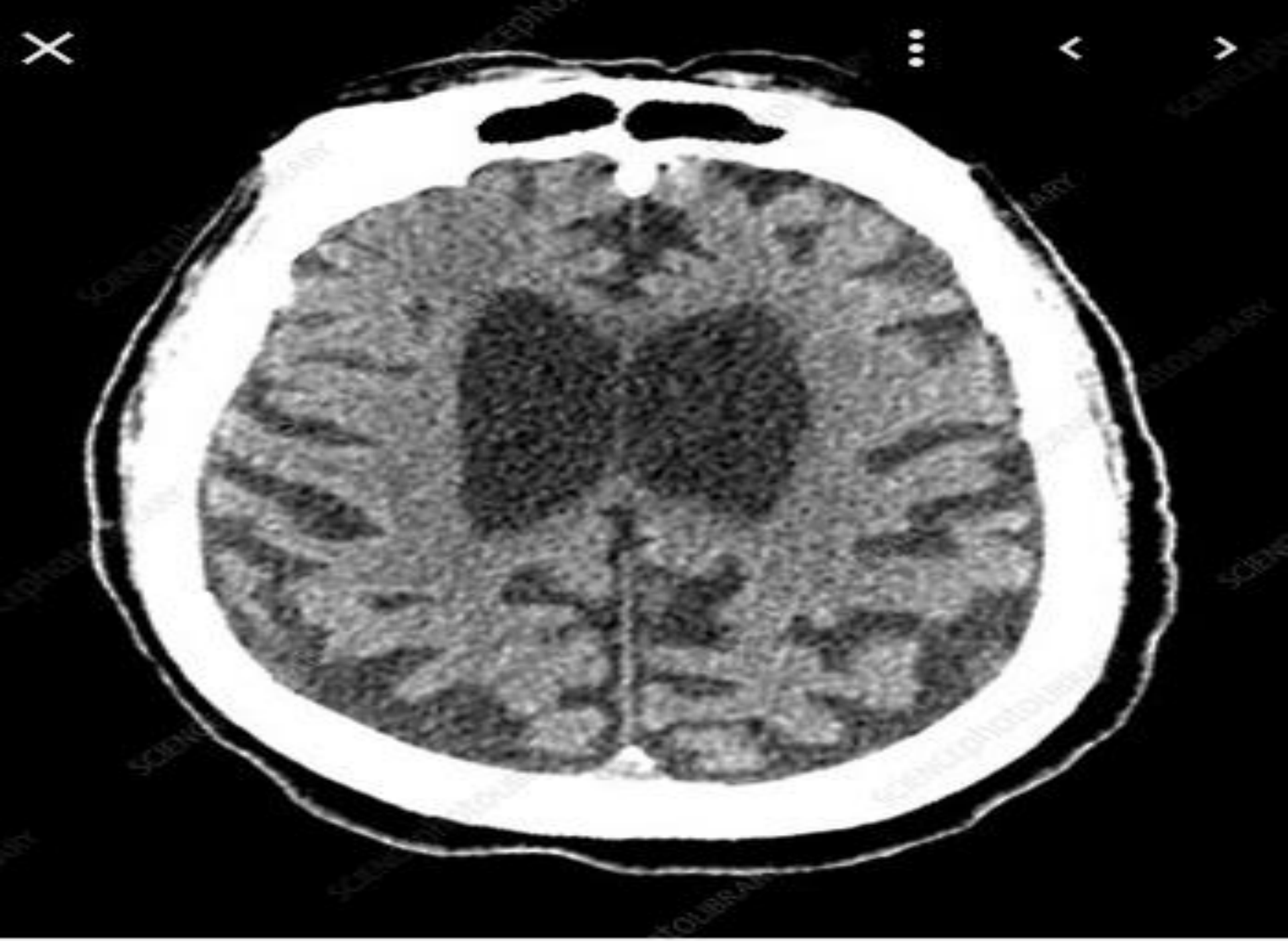
MRI –based volumetric measurements may show reduction of up to 40% in the size of the hippocampus, amygdala and thalamus

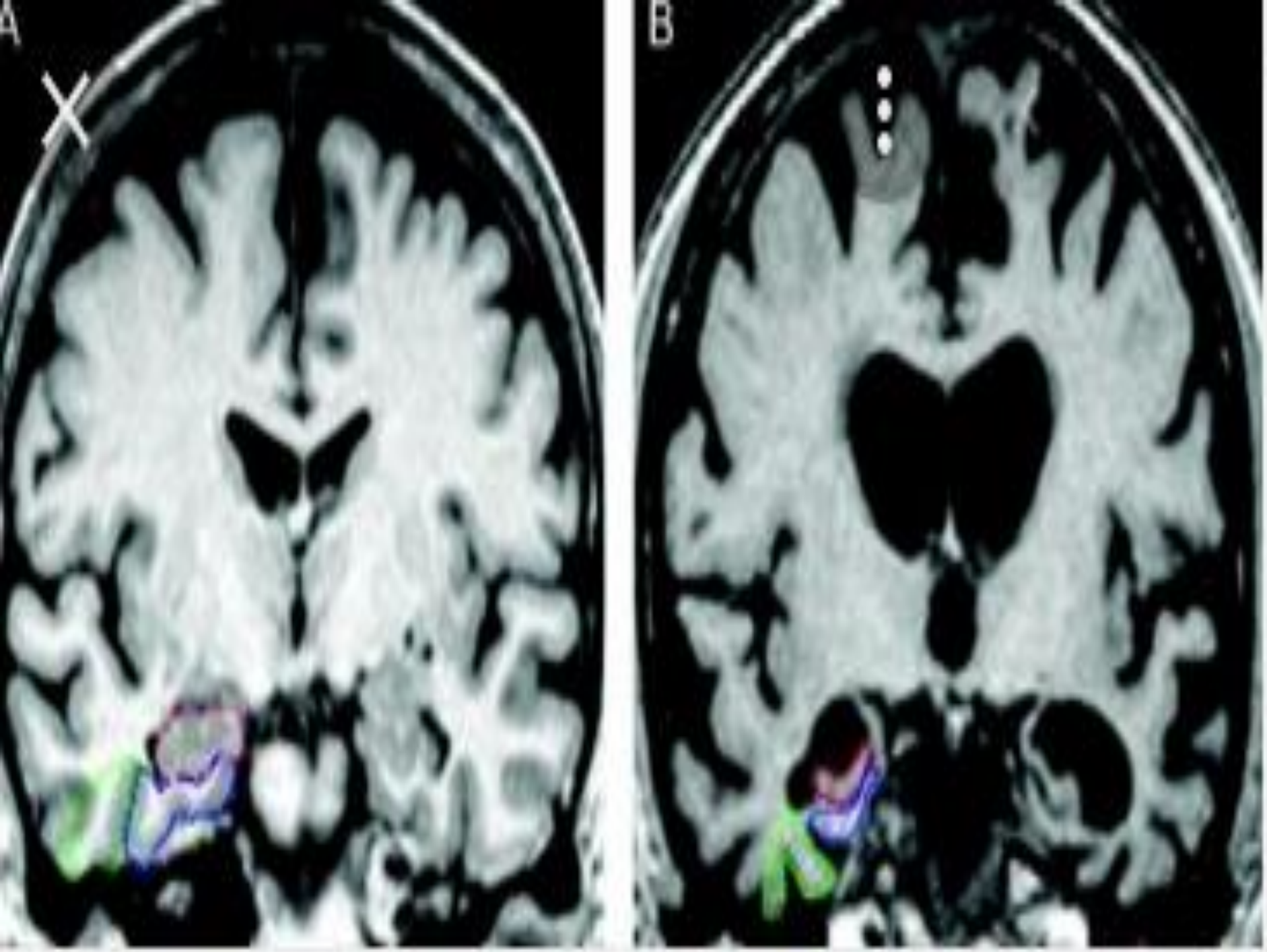
Functional neuroimaging such as positron emission tomography(PET) and single-photon-emission computed tomography (SPECT) used to quantify cerebral metabolism and blood flow may help to differentiate AD from other dementias

In AD, PET and SPECT scans show bilateral temporoparietal hypometabolism, but this is not specific enough to be diagnostic


Fornix
Lentiform nucleus
Cerebral cortex
Caudate nucleus
Putamen
Thalamus
Amygdala
Globus pallidus
Mammillary body
Hippocampus
Pons
Cerebellum
Medulla
Spinal cord



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B

* Pathology

The major pathologic features of AD are brain atrophy, senile plaques and NFTs, associated with a substantial gliosis and loss of neurons in the cerebral cortex

NFTs represent intracellular accumulation of phosphorylated tau protein

Senile plaques are extracellular deposits of amyloid surrounded by dystrophic neurons

How exactly of the known gene mutations associated with AD causes these changes is not established

In the case of APP, mutations are known to cause increased amyloid beta protein production and change the normal structure of the protein, altering its recognition by metabolizing enzymes, therefore leading to a progressive accumulation of the peptide

Other pathophysiologic mechanisms have been proposed, including inflammatory, oxidative,metabolic, nutritional and immune processes

* Treatment

At present there is no satisfactory treatment for patients with AD

Therapy consists of the following:

* Preventing associated symptoms: This includes treatment of depression, agitation, sleep disorders, hallucinations, and delusions
* Preventing or delaying progression: This includes therapy with acetylcholinesterase inhibitors such as donepezil or rivastigmine or galantamine , as well as memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist

* Prophylaxis

Until now,there have been no successful single-drug clinical trials demonstrating decreased dementia incidence

This may be due , in part, to the heterogeneity of the underlying cause of AD, prolonged time course of the illness, and the likely presence of a protracted preclinical disease state

In addition to clinical trials focusing on life-style – related interventions(e.g. physical activity,diet), trials investigating preventative and disease-modifying drugs may one day provide therapeutic options for the aging population (table)

Medication	Mechanism of Action	Comments
Donepezil (Aricept)	Cholinesterase inhibitor	Rare: hepatic toxicity. Common: diarrhea and abdominal cramps.
Rivastigmine (Exelon)	Cholinesterase inhibitor	GI disturbances during dose adjustment. Rare: hepatic toxicity.
Memantine (Namenda)	NMDA receptor antagonist	Dizziness, headache, confusion
Galantamine (Razadyne)	Cholinesterase inhibitor	GI side effects, weight loss

GI, gastrointestinal; NMDA, N

TABLE 12.4 Neurologic Signs and Symptoms Atypical for Alzheimer Disease

Sign or Symptom	Possible Significance
Dominant nonmemory features (eg, language, praxis, visuospatial dysfunction)	Frontotemporal degenerations, posterior cortical atrophy
Prominent behavioral, personality, psychotic symptoms	Frontotemporal degenerations, Lewy body dementia
Early parkinsonism (eg, resting tremor, bradykinesia, cogwheeling)	Lewy body dementia, progressive supranuclear palsy (no rest tremor), corticobasal degeneration, hydrocephalus
Urinary incontinence	Hydrocephalus
REM sleep behavior disorder	Parkinson disease dementia, Lewy body dementia

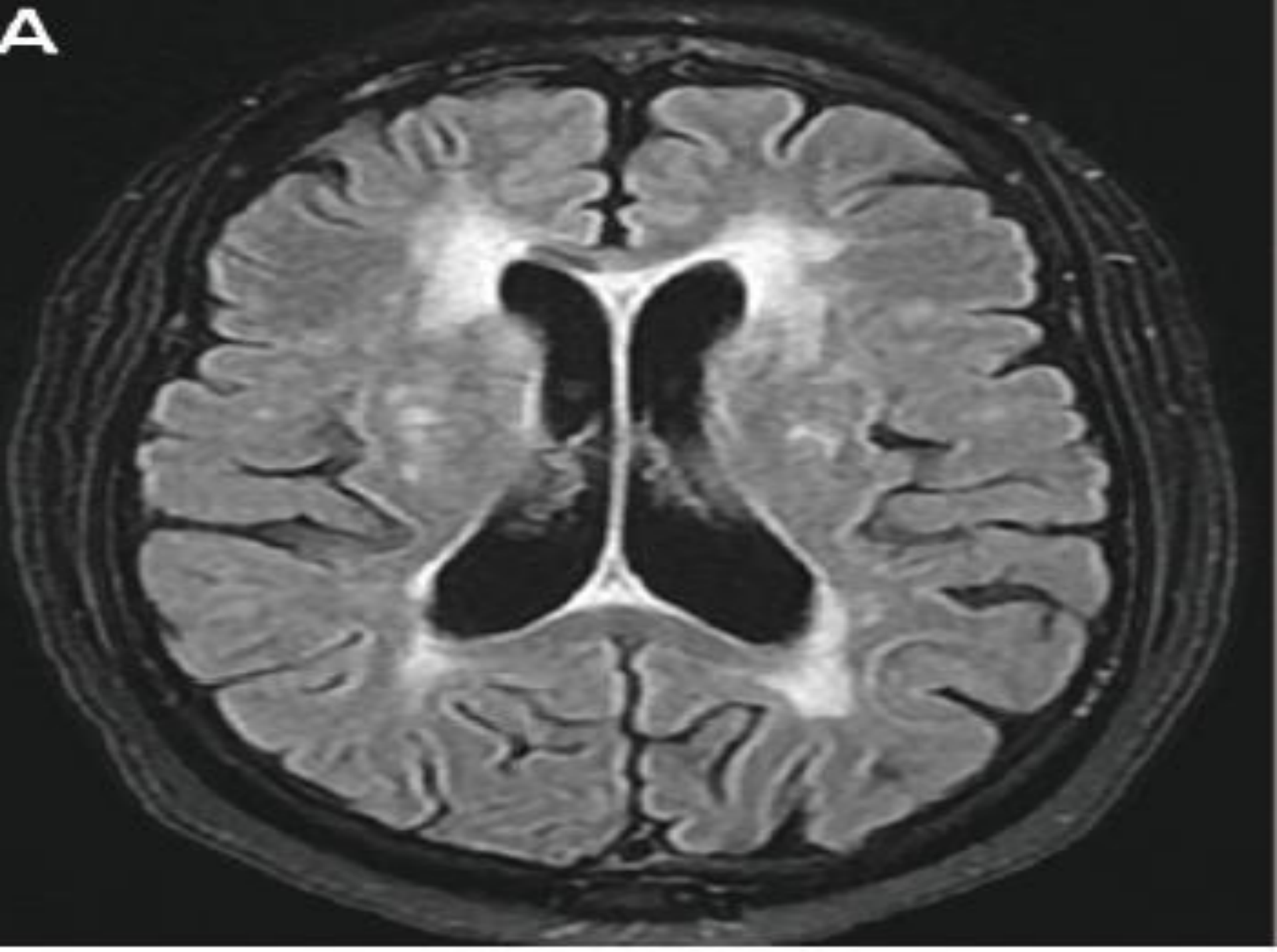
Seizures	Immune-mediated or infectious encephalitides
Myoclonus	Creutzfeldt-Jakob disease
Frequent falls	Progressive supranuclear palsy
Early unexplained gait abnormalities	Lewy body dementia, progressive supranuclear palsy, corticobasal degeneration, hydrocephalus
Early prominence of bulbar/brainstem signs	Progressive supranuclear palsy
Unexplained motor or reflex asymmetries	Vascular dementia, corticobasal degeneration
Unexplained (early) UMN signs (eg, Babinski sign)	Frontotemporal degeneration with motor neuron disease
Unexplained LMN signs (eg, fasciculations)	Frontotemporal degeneration with motor neuron disease

B) Vascular dementia (non-degenerative)

This dementia(previously referred to as multi-infarct dementia) may develop in patients with cerebrovascular disease

There are 2 recognized types: macrovascular related to large infarcts and microvascular , in which the pathophysiologic mechanism of brain injury is subcortical ischemia associated with cerebral small vessel disease (lacunes or deep white matter changes on MRI)

Dementia related to extensive microvascular changes of the white matter is called Binswanger disease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Vascular dementia has the same risk factors as cerebrovascular disease, including hypertension, diabetes, age, embolic sources, and extensive large artery atherosclerosis

It is common for vascular dementia and other diseases (AD, Lewy body disease) to coexist in the same patient

For this reason, it is unclear exactly how commonly dementia can arise from a purely vascular etiology

Clinical manifestations and diagnostic evaluation

The criteria for diagnosis of vascular dementia include presence of dementia and 2 or more of the following: focal neurologic signs on examination; onset that is abrupt, stepwise, or stroke-related; or brain imaging showing multiple strokes, lacunes, or extensive deep white matter changes

Most patients with vascular dementia are hypertensive, diabetic, or both

The diagnosis requires investigation of the cause of stroke

Cardiac and hypercoagulable workups are considered in selected cases

Treatment

The prevention and treatment of vascular dementia are essentially the same as prevention and treatment of stroke.

C) Chronic subdural hematoma (non-degenerative)

This occurs predominantly in the elderly and may follow relatively minor head injury

Indeed, a history of trauma is not always obtainable, perhaps because of the delay(months or even years) before presentation

The typical clinical setting is an elderly patient, predisposed to hematoma formation by cerebral atrophy and hence stretching of veins in the subdural space

Minor head trauma e.g., in the context of alcoholism, may trigger bleeding , especially in a patient who is prone to recurrent hemorrhage because of a coagulation defect

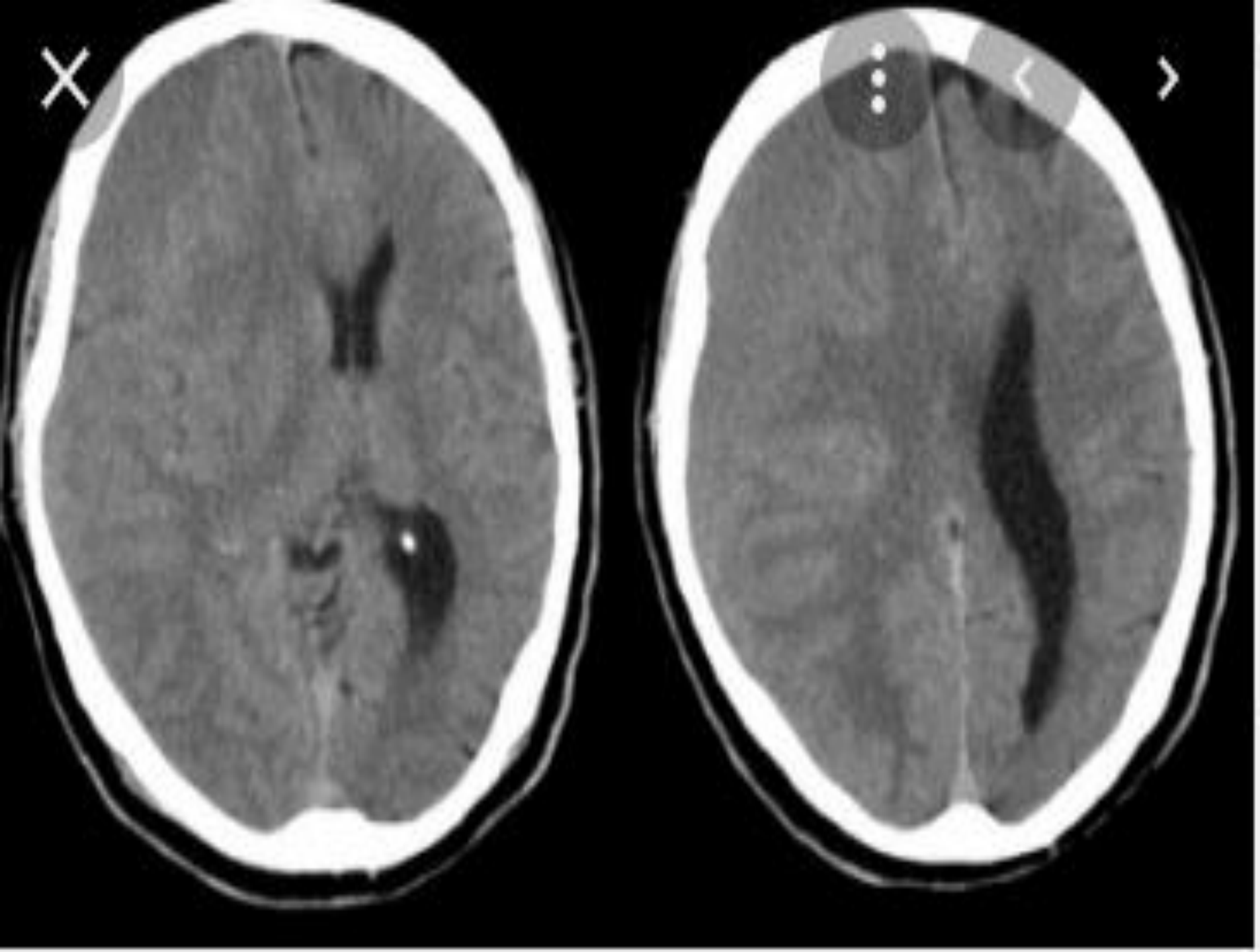
Pathologically, a gradually expanding cavity develops, filled with yellow or brown fluid as a result of breakdown of blood, and is surrounded by a membrane

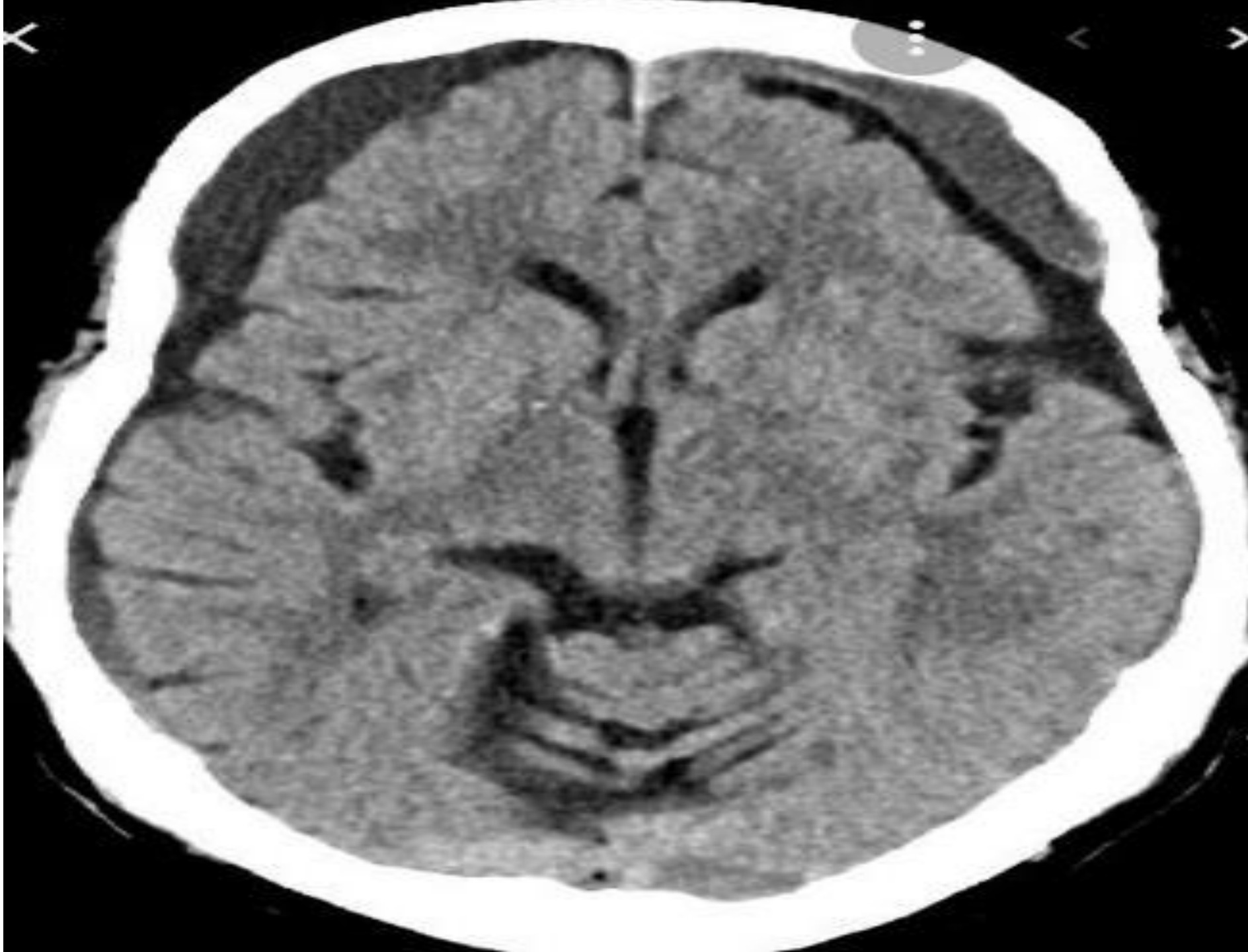
The mechanism of enlargement of the hematoma with time was originally thought to involve protein degradation and hence increasing osmotic pressure within the cavity, but recurrent bleeding is now judged the more important pathogenetic factor

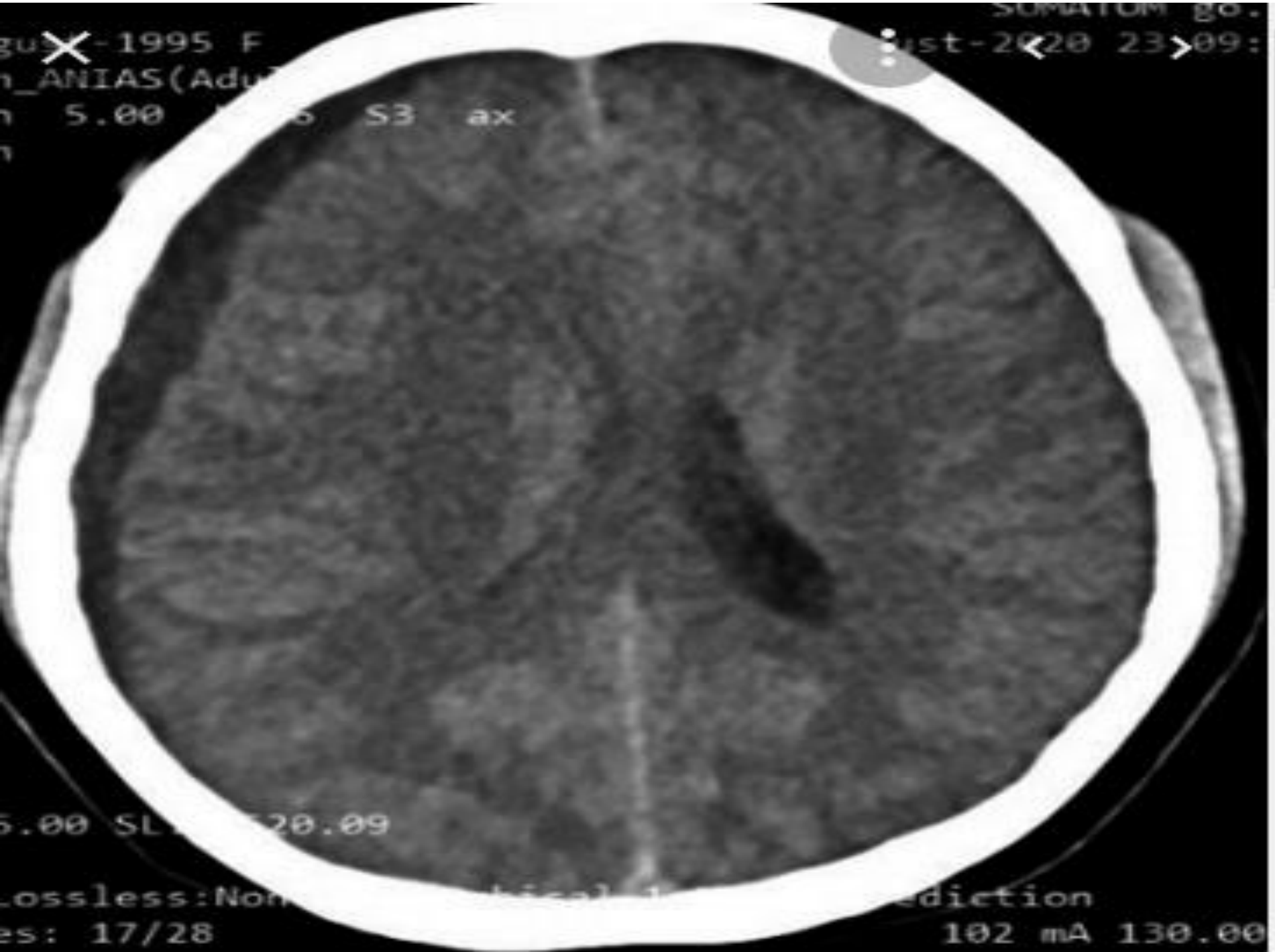
The expanding hematoma exerts mass effect with shift of midline structures(unless bilateral subdural hematomas are present)

Clinically, patients may present solely with dementia but there may also be fluctuations in conscious level, epilepsy, signs of raised intracranial pressure and focal neurological deficits

The diagnosis ,is usually apparent on CT Brain scan, though difficulties may arise early in the course of the condition , when the hematoma is isodense with brain tissue, particularly if bilateral lesions are present and hence there is no midline shift



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Treatment is surgical evacuation of the hematoma through burr holes , often with dramatic benefit

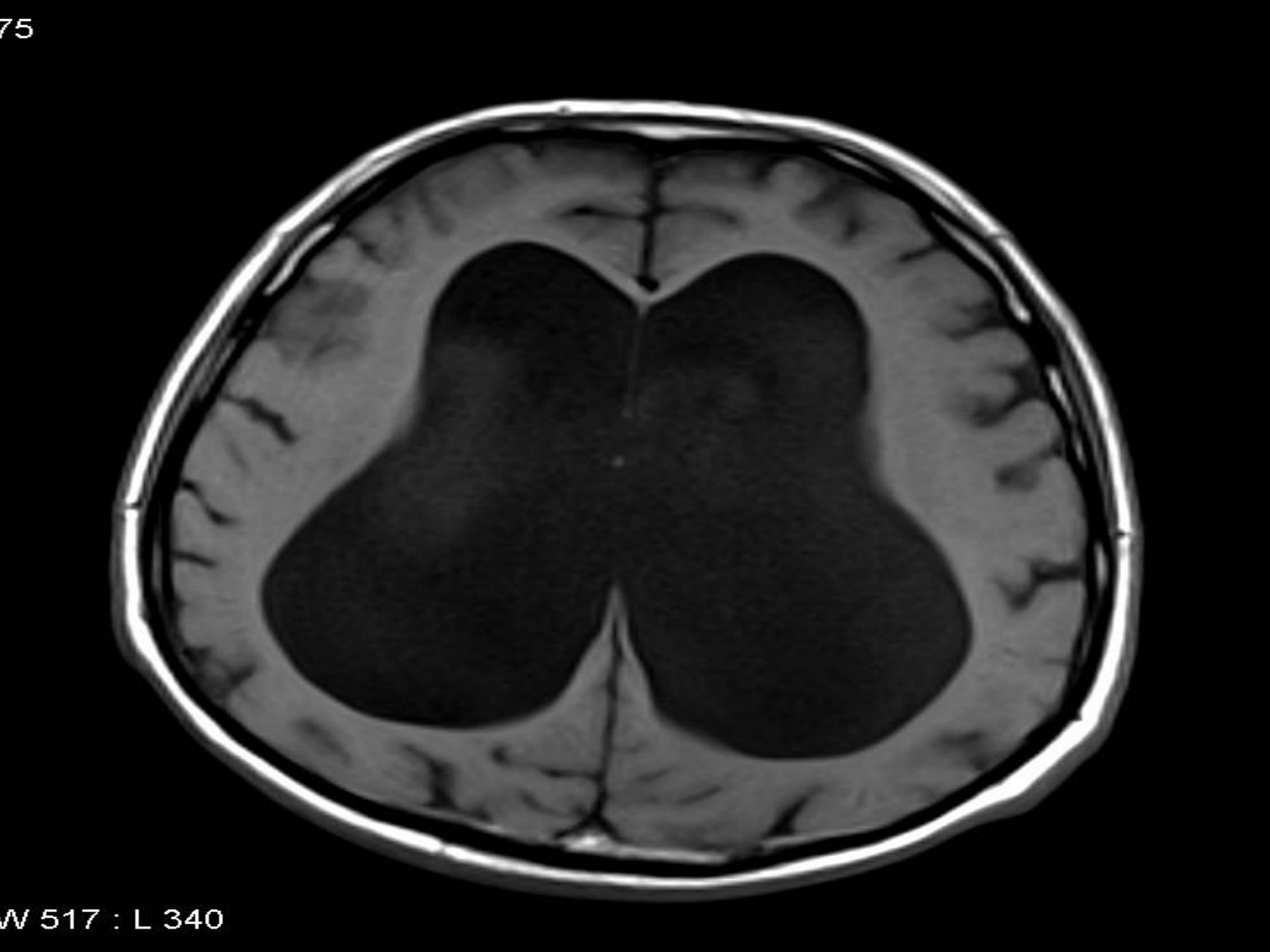
D) Normal-pressure hydrocephalus(non-degenerative)

This is suggested by the classical clinical triad described by Hakim and Adams:

- Dementia
- Gait disturbance
- and early urinary incontinence

Gross ventricular enlargement without cortical atrophy is seen on CT Brain scan and lumbar puncture reveals normal CSF pressure

The pathogenesis of the condition is obscure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Though a single reading of CSF pressure at lumbar puncture is likely to be normal, continuous intracranial pressure monitoring over 1-2 days, may reveal waves of raised pressure

Results of surgical treatment by ventriculoperitoneal shunting are variable

E) Dementia with Lewy bodies (LBD) (degenerative)

Friedrich Lewy first described the cytoplasmic inclusions found in the substantia nigra in Parkinson disease (PD) in 1912, but it was not until 1961 that these later-named "Lewy bodies" were noted in the cortex of patients with dementia

LBD is now thought to be the 2nd leading cause of dementia (rather than vascular dementia)

The clinical picture of LBD is that of a parkinsonian dementia syndrome;it is considered to be a spectrum of PD dementia

* Clinical manifetations

LBD patients typically present with early progressive cognitive decline, frequently beginning after age 55

Visual hallucinations, often manifesting as small children or animals, tend to be a prominent feature

Unlike in AD , cognitive domains such as attention and visuospatial skills are typically affected earlier than memory difficulties

The extrapyramidal symptoms can also be slightly different in that rest tremor is less common, and signs are often symmetric

Bradykinesia and gait impairment are more common than rest tremor

Marked fluctuations of alertness, delusions, and an extraordinary sensitivity to neuroleptics (i.e. marked worsening with drugs like haloperidol) are also key features of LBD

* Diagnostic evaluation

The pathologic hallmark of this disease is the Lewy body, an eosinophilic intracellular inclusion of the protein alpha synuclein

In LBD and PD, widespread limbic and cortical Lewy bodies are found, to the point that it can be difficult , based on autopsy, to distinguish pathologically from which clinical syndrome a patient suffered

Other pathologic abnormalities of AD-type can be present, including varying degrees of AD-type abnormalities such as NFTs and amyloid plaques

* Treatment

Management of LBD can be complex, because treatment of the parkinsonian syndrome may worsen neuropsychiatric dysfunction and treatment of the neuropsychiatric disorder may exacerbate the parkinsonian syndrome

Low dose of atypical neuroleptics such as risperidone and quetiapine have been used to treat behavioural symptoms

F) Metabolic causes of dementia(non-degenerative)

Vitamin B12 deficiency may present as a progressive dementing illness

Usually, however , there are may other neurologic features and signs on physical examination, including dysfunction of the spinal cord (subacute combined degeneration) and peripheral nervous system, such that the diagnosis becomes evident even prior to the development of dementia

The most common neurologic symptoms are those of neuropathy (paresthesias in hands and feet, sensory ataxia, visual loss, orthostatic hypotension) and memory loss

Other systemic manifestations include anemia and a sore tongue

Appropriate replacement of vitamin B12 should suffice in the treatment

Other metabolic causes of dementia are **hypothyroidism, Wilson disease, hypercalcemia , and Addison disease**

TABLE 12.6 Dementias Categorized by Protein Pathologies

β-Amyloidopathy	AD
α-Synucleinopathy	Lewy body disorders (DLB), PDD
Tauopathy	Frontotemporal dementia: Pick disease, PSP, CBD (Note that AD has secondary tau pathology.)
TDP-43 proteinopathy	Frontotemporal dementia (FTD-U), ALS with dementia
Prionopathy	Creutzfeldt-Jakob disease, sporadic/familial fatal insomnia, GSS, vCJD