Differential Diagnoses of Dementia: Reversible Causes

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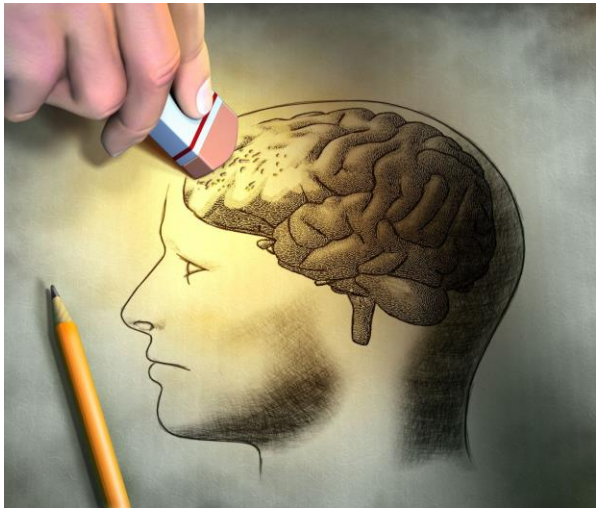


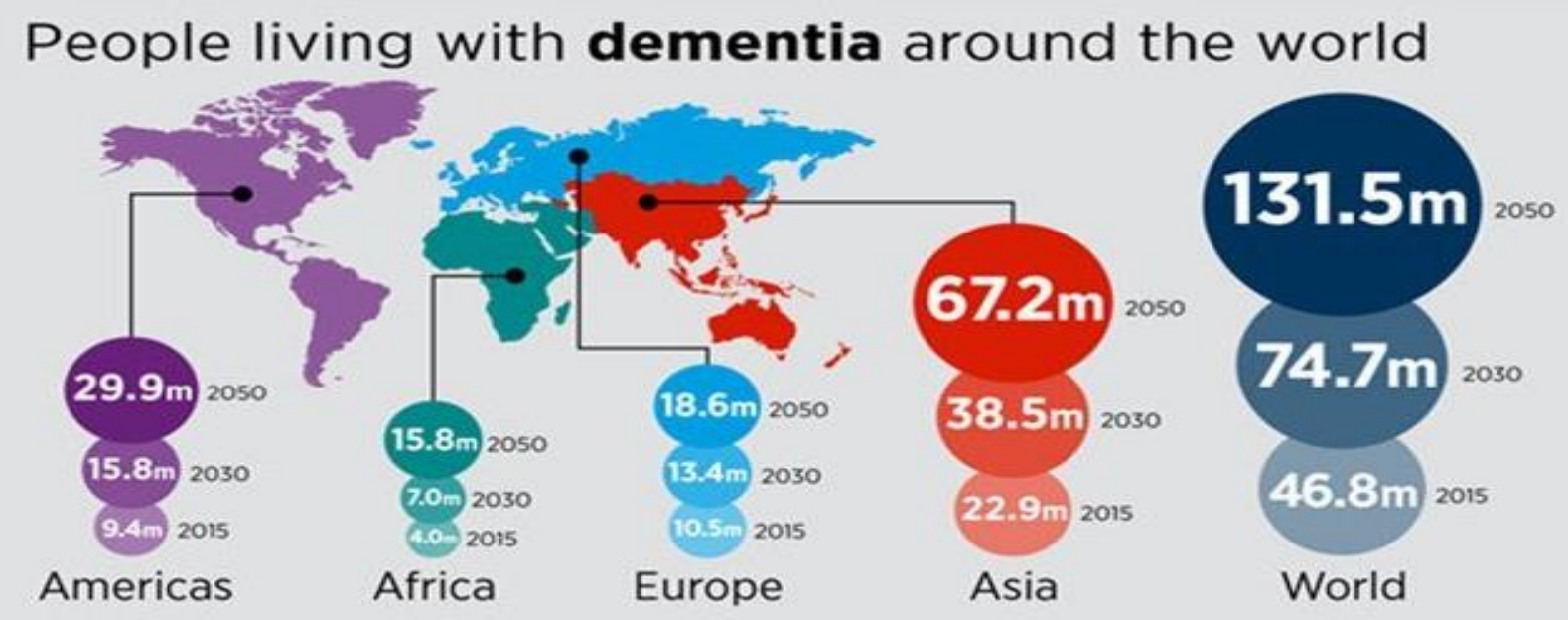
Dementia ....

is a collective name for brain syndromes

Core clinical criteria for dementia … cognitive or behavioral impairment of at least 2 of the following domains:

- Impaired ability to acquire and remember new information **(Memory)**
- Impaired reasoning and handling of complex tasks and poor **judgment**
- Impaired **visuospatial** abilities
- Impaired **language** (i.e., speaking, reading, and writing)
- Changes in **personality, behavior**, or comportment

Prevalence of dementia



Prevalence of dementia around the world, along with forecasts for 2030 and 2050. Source: http://www.worldalzreport2015.org/

Prevalence of dementia

- Currently more than **55 million** people have dementia worldwide, over **60%** of whom live in **low-and middle-income** countries.
- Every year, there are nearly **10 million new** cases.
- **Alzheimer** disease is the most common form of dementia and may contribute to **60–70%** of cases**.**

Prevalence of dementia around the world, along with forecasts for 2030 and 2050. Source: http://www.worldalzreport2015.org/

Confusional State

Acute (hours to days)

Delirium
- Impaired **attention**
- Altered **sensorium**
- **Fluctuations** present
- **Disorientation**
- **Visual** hallucinations
- Abnormal EEG

Acute psychosis
- Attention normal or impaired
- Normal sensorium
- Systematized delusions
- Auditory hallucinations
- Previous episodes
- Normal EEG

Subacute (weeks to months)

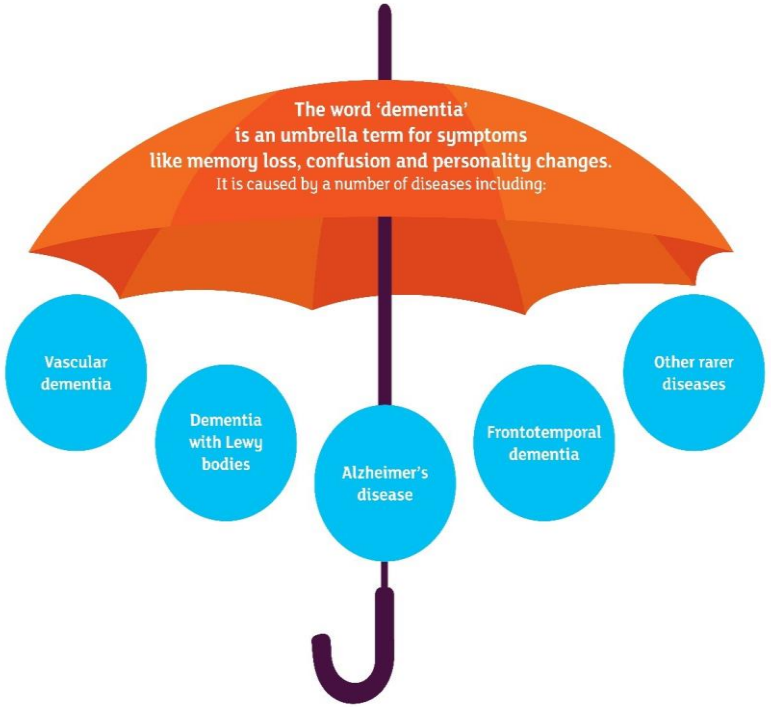
Depression
- Attention normal, may be impaired
- Normal sensorium
- Normal orientation
- **Mood** changes
- No fluctuations
- **Previous** episodes
- Normal EEG

Chronic (months to years)

Dementia
- Attention usually normal
- Normal sensorium
- Impaired **memory**
- **Disorientation**
- EEG- normal or abnormal d/on type & stage

Etiology and Differential Diagnosis

Degenerative disorders	Alzheimer disease,[a] Lewy body dementia spectrum,[a] frontotemporal dementia, Huntington disease, tauopathies, amyotrophic lateral sclerosis (ALS), and prion disorders
Vascular dementias	Multi-infarct,[a] diffuse white matter disease (Binswanger's)[a]
Toxic conditions	Alcoholism,[a] drug/medication intoxication,[a] other toxic disorders
Metabolic disorders	Vitamin deficiencies (B_{12}, B_1, folate, niacin), endocrine disorders (thyroid, adrenal, parathyroid), uremia, hepatic encephalopathy, and cardiopulmonary failure
Infectious dementias	HIV, syphilis, progressive multifocal leukoencephalopathy (PML), and other chronic infections
Traumatic conditions	Chronic traumatic encephalopathy and others
Hydrocephalic syndromes	Normal pressure hydrocephalus
Psychiatric conditions	Depression, conversion disorder, and others
Autoimmune/ inflammatory conditions	Multiple sclerosis, vasculitis, sarcoidosis, and more
Cancer or related mass effects	
[a] among the most common causes of dementia	



Cognitive Impairment & Dementia

Progressive

- Alzheimer's disease (AD)
- Dementia with lewy bodies (DLB)
- Fronto-temporal dementia (FTD)
- Vascular Dementia (VaD)
- Parkinson's disease dementia (PDD)
- Other degenerative dementias

Non-progressive

- Traumatic Brain Injury (TBI)
- Anoxia (e.g., sleep apnea)
- Vascular (e.g., single stroke)

Reversible

- Depression & anxiety
- Multiple medical conditions
- Vitamin deficiencies
- Metabolic problems
- Medication side effects
- Infections/autoimmune
- Normal pressure hydrocephalus
- Tumors

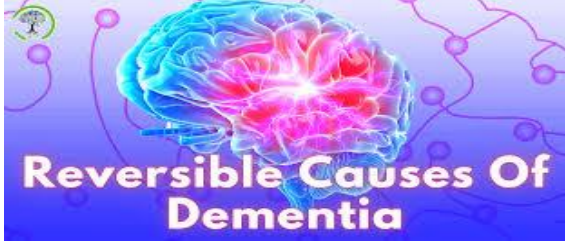
Differences between Progressive and Reversible Dementia

		Progressive Dementia	Reversible Dementia
1.	Definition	Caused by **Degenerative diseases & vascular.** Symptoms of **progressive** dementia **worsen** over time, usually over several years.	Reversible dementias are **caused by other treatable conditions**
2.	**Prevalence**	85% of all dementia	5-15% of all dementias
3.	Causes	Alzheimer's disease, vascular dementia, frontotemporal dementia, mixed dementia, dementia with Lewy bodies	brain infections, brain injuries, or exposure to heavy metals, metabolic, infectious, toxic, autoimmune, paraneoplastic, and psychiatric disorders
4.	**Diagnosis**	History, Cognitive assessment, brain imaging, genetic testing	Identifying & treating underlying cause

Differences between Progressive and reversible Dementia (Cont.)

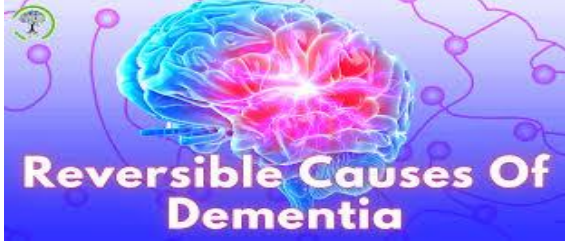
		Progressive Dementia	Reversible Dementia
5.	Reversibility	Irreversible and progressive	potentially reversible
6.	Age	Older	Younger
7.	Treatment	**No cure** but **can improve** symptoms. CEIs, drugs for other conditions & vascular risk factors, life style modifications	Treatment **can often cure** reversible dementias if the brain has not been damaged too much. If **detected and treated early**, these dementias **can be reversed** or their progress halted.

Causes of Reversible Dementia



- **Structural brain lesion**: NPH, subdural hematomas ,brain tumors
- **Alcoholic** Dementia
- **Nutritional Disorders:** B12 deficiency, thiamine deficiency
- **Endocrine Disorders:** hypothyroidism and hyperthyroidism, hypoparathyroidism

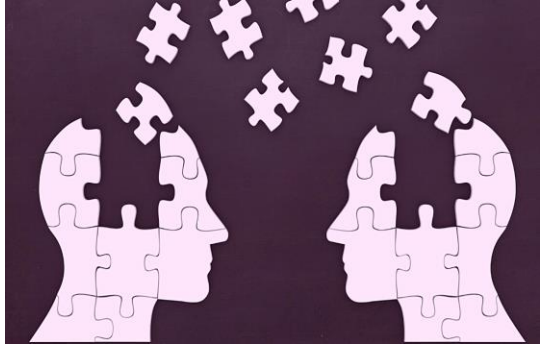
Causes of Reversible Dementia (Cont.)



- **Metabolic Disorders:** Wilson's disease, Electrolyte disturbances and hepatic, renal or pulmonary insufficiency

- **Toxic Conditions:** lead ,mercury, bismuth, aluminum, manganese and arsenic , carbon monoxide

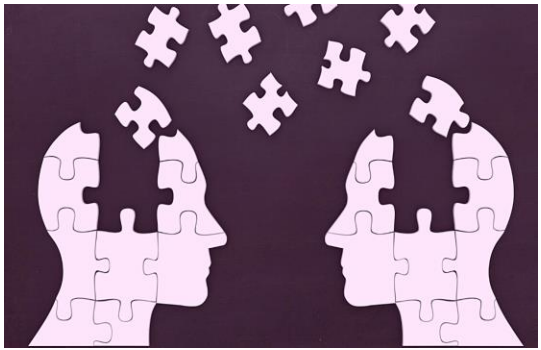
Causes of Reversible Dementia (Cont.)



- **Psychiatric Disorders:** Depression
- **Miscellaneous Causes:** Radiation or dialysis
- **Epileptic Disorders:** Transient epileptic amnesia , associated with symptoms of temporal lobe epilepsy

Causes of Reversible Dementia (Cont.)

- **Autoimmune Encephalopathies:** paraneoplastic disorders, voltage-gated potassium channel antibodies in non-paraneoplastic encephalopathies and NMDA receptor antibodies in paraneoplastic encephalopathies, Hashimoto's encephalopathy
- **Obstructive Sleep Apnea**



Causes of Reversible Dementia (Cont.)

- **Inflammatory Vasculopathies:** Systemic lupus erythematosus, Sjögren's syndrome, Behçet's disease, antiphospholipid syndrome, Primary CNS angiitis, CNS sarcoidosis
- **Vascular Causative Factors:** Dural arteriovenous fistulae (DAVF)

Causes of Reversible Dementia (Cont.)

- **Infections:** cryptococcal meningitis, Lyme disease, Whipple's disease, syphilis and HIV
- **Medications:** Benzodiazepines, antipsychotics, and tricyclic antidepressants, AEDs: topiramate and sodium valproate, Steroid

Diagnosis

The diagnostic approach to dementia requires;

(1) A comprehensive **history**;

(2) A complete **physical and neurologic examination** (cognitive, behavioral, and activities of daily living assessment); and

(3) Laboratory and neuroimaging studies (to rule in or out various systemic and neurologic conditions)

Medical History

Many patients are unable to provide a reliable medical history;

hence, **caregivers become the source**.

- Onset, evolution, and duration of symptoms;
- Precipitating, exacerbating, and relieving factors;
- Comorbid medical conditions;
- Medication intake;

Medical History (Cont.)

- Foreign and domestic travel and associated signs and symptoms;
- Occupation;
- Exposure to neurotoxins and recreational drugs;
- Family history; and previous treatment for sexually transmitted disorders

Physical and Neurological Examinations

- Signs of systemic diseases
- Focal and/or multifocal neurologic deficits
- Uncontrolled hypertension, cardiac rhythm irregularity, valvular heart disease, carotid bruit, and peripheral arterial disease (risk of vascular dementia)
- Temporal tenderness, muscle aches, joint pains, and abnormal pulses (vasculitis)

Physical and Neurological Examinations (Cont.)

- Signs of head trauma
- Parkinsonian signs
- Myoclonic jerks (Creutzfeldt-Jakob disease)
- Cognitive and behavioral tests

Laboratory and Neuroimaging Studies

To exclude potentially treatable and reversible conditions first

- Complete Blood Count
- Erythrocyte Sedimentation rate
- Complete metabolic profile
- Thyroid function studies
- VDRL test, serum B12, folic acid and homocystine levels, urinalysis

Laboratory and Neuroimaging Studies (Cont.)

- CT or MR imaging with and without contrast

- EEG (in patients with possible epilepsy, *Herpes simplex* encephalitis, and Creutzfeldt-Jakob disease)

- CSF studies

Case 1

- 68 year old lady
- Noted by her family as developing **memory problems & deteriorating mobility** for 2-3 years.
- Had a number of episodes of wetting.
- Had been diagnosed with **Alzheimer's disease** and taking treatment.
- No history of meningitis, subarachnoid hemorrhage, or head trauma.
- No specific family history of dementia or hydrocephalus.

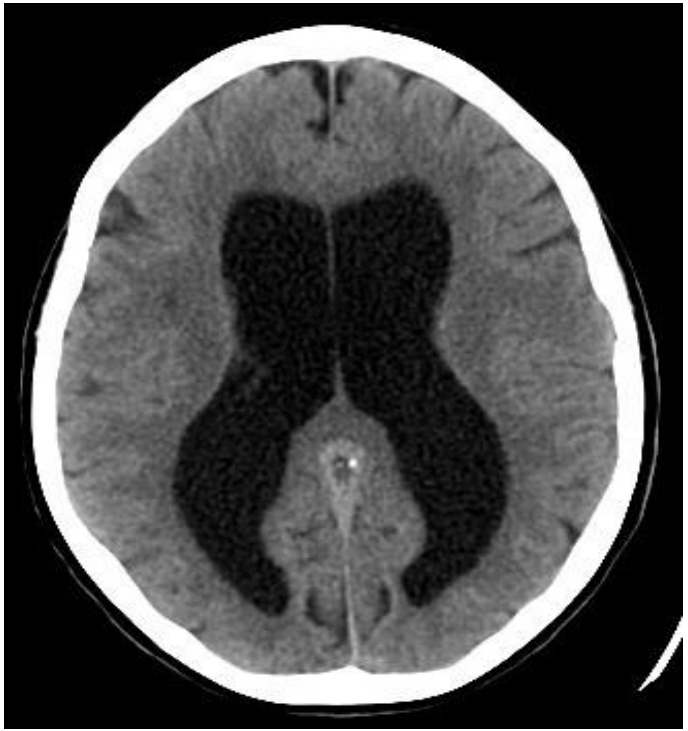
Case 1

Physical Findings

- Vital signs such as blood pressure and heart rate showed no abnormalities.
- MMSE **22/30**
- no neurology deficits.
- Blood tests showed no abnormal thyroid functions nor vitamin deficiencies, and negative infectious screening.

Case 1

- CT showed a possible diagnosis of **Normal Pressure Hydrocephalus.**
- Admitted to hospital and had a **lumbar puncture** after which she felt her memory was improved and she was able to perform better in mobility.
- She was consulted with Neurosurgeon for placement of a VP shunt.



Normal Pressure Hydrocephalus

- A more common treatable form of dementia is NPH

- A syndrome characterized by **gait difficulty**, **urinary incontinence**, **cognitive decline**, and **enlarged ventricles**.

- Gait disturbance is frequently the most prominent sign whereas higher cortical deficits are relatively mild.

Normal Pressure Hydrocephalus

- The most widely used clinical test to assess patients with suspected NPH is a "tap test".

- Lumbar puncture with high volume CSF removed (40-50mls).

- Assess both **pre- and post-lumbar puncture** with **gait and memory tests.**

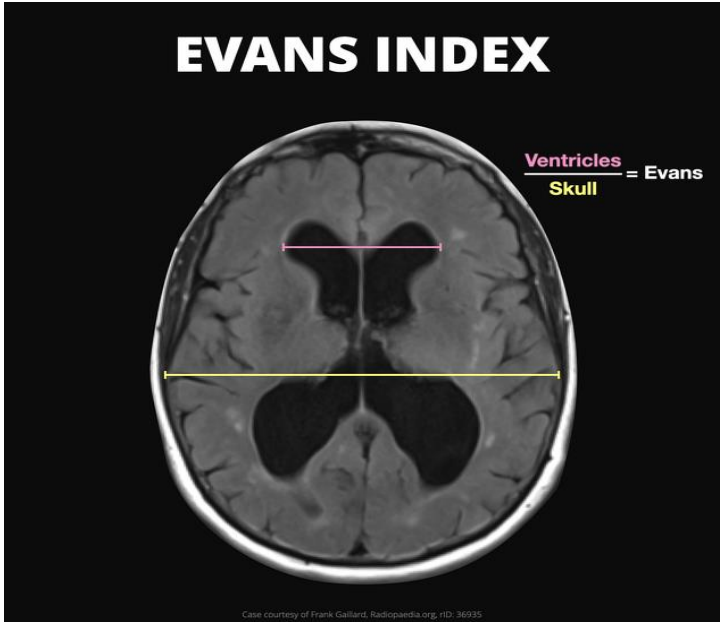
Differentiating NPH from Alzheimer's disease

It was important to differentiate between Alzheimer's dementia and NPH, but in practice this is often difficult.

Evans index

It is useful as a marker of ventricular volume and thus has been proposed as a helpful biomarker in the diagnosis of NPH.

Anteroposterior diameter of **the lateral ventricular** index (cutoff ratio >0.50)



J Magn Reson Imaging. 2009;30(4):708-15.

Case 2

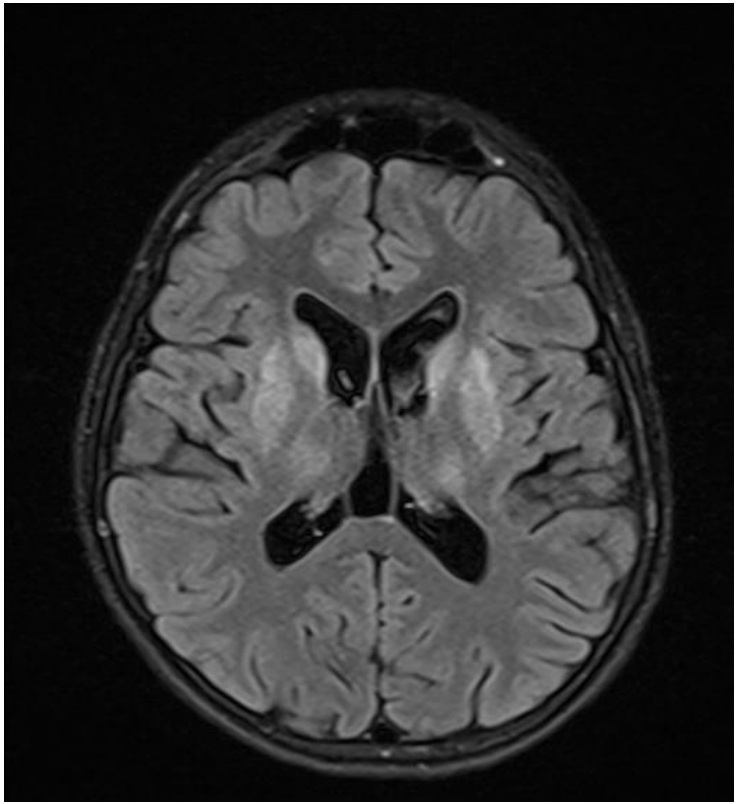
- A 38-year-old nonalcoholic and nonsmoking man
- No medical or psychiatric background
- 6 months h/o **depressive symptoms (apathy, anhedonia)** accompanied by social isolation, fatigability, psychomotor slowing and distal tremor.
- Diagnosed with **reactive depression** and treated with antidepressants and antipsychotics.

Case 2

- Symptoms did not improve and caused significant **extrapyramidal side effects** such as increased psychomotor slowing, hypertonia and tremor.
- Physical and neurological examinations revealed hypomimic face, ataxic march with inability to march in tandem, extrapyramidal axial hypertonia, akinesia and tremor.
- Blood analysis: **ceruloplasmin levels were low** 16.6 (normal >20).

Case 2

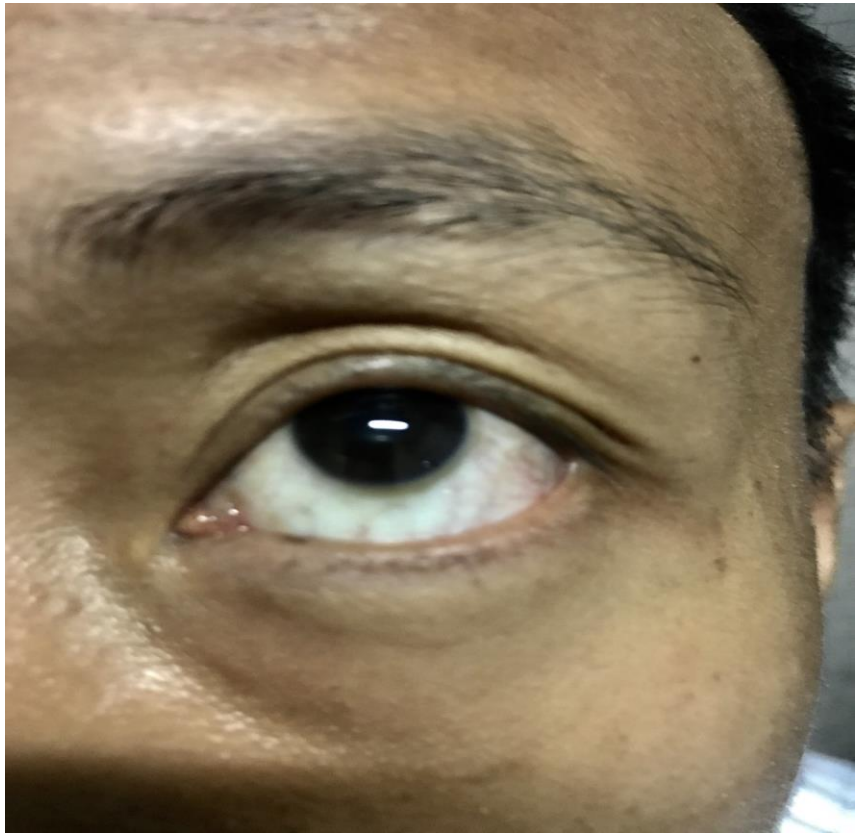
- CT scan showed moderate subcortical & cortical **atrophy.**
- MRI revealed **hyperintensity** on T2 MRI in the **basal ganglia**.



- Ophthalmology: **Kaiser-Fleischer ring** present

- **Wilson's disease** was diagnosed and started treatment with D-penicillamine 250/6 hours.

- Symptoms improved



Case 3

- A 42-year-old woman presented in the emergency department

- 6-month history of **diffuse headache** of moderate intensity.

- Over a course of 3 months, had gradual onset of **imbalance**, generalized weakness, hypophonia, apathy, dysphagia, constipation and **urinary incontinence**.

- Reported a **change in her personality** over the previous years with frequent episodes of incoherent speech and **memory decline**.
- Her maternal aunt had early-onset cognitive decline and died before the age of 50.
- No history of head trauma or fluid leakage through the ear, the nose or the throat.
- No history of seizures, hallucinations, vomiting, diplopia, blurred vision, agitation, and sensory loss.

- On admission, she was afebrile and bedridden.

- The neurological examination identified a severe apathy with motor impersistence, **marked primitive reflexes** (sucking, palmomental, and Babinski sign), generalized hyperreflexia with bilateral Hoffman sign and ankle clonus but no limb spasticity, an effortful but comprehensible speech, and frequent startles.

- There was no papilledema on the fundoscopy.

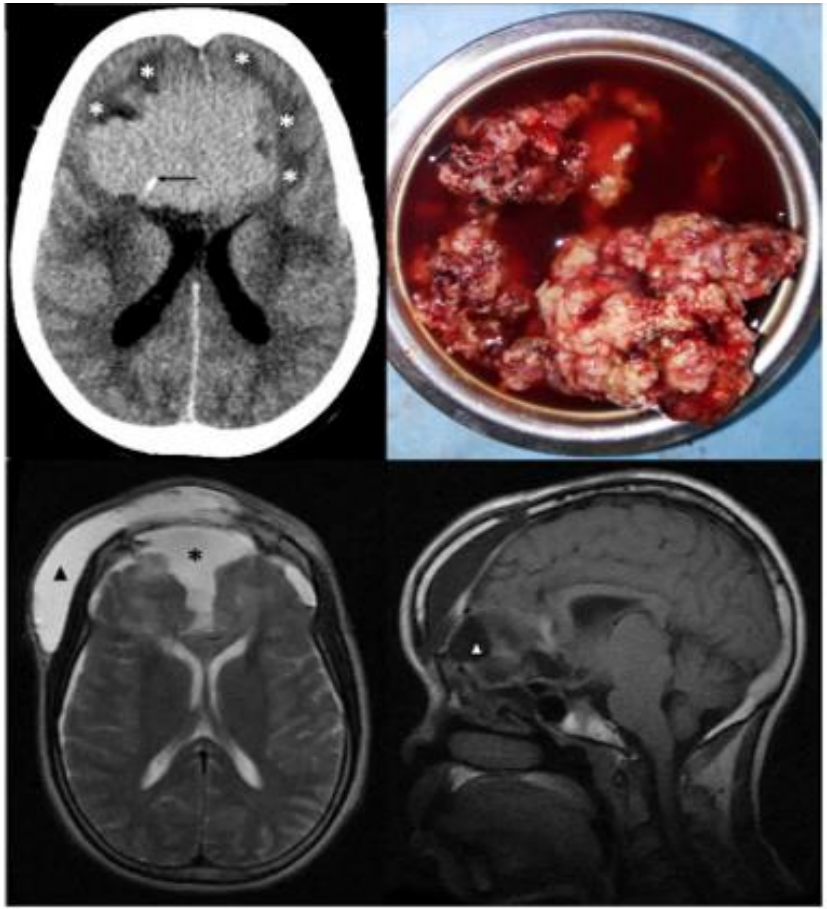
- Because of the severe apathy and somnolence, it was not possible to perform a more precise evaluation of the olfaction, the higher order cerebral functions, and the motor and sensory pathways

- Given the limited resource available, the patient underwent a minimal biological workup.

- The full blood count, the liver and thyroid function tests and the HIV and syphilis screening tests were unremarkable.

- The cerebrospinal fluid analysis revealed a high protein level (1.9 g/L) with normal cell count, microscopy and culture.
- The kidney function could not be assessed for technical reasons
- A brain computed tomography (CT) scan without contrast (unknown creatinine level) revealed
- A **large irregular paramedian subfrontal extraaxial mass**, slightly hyperdense with some calcifications and a local mass effect, with effacement of frontal sulci

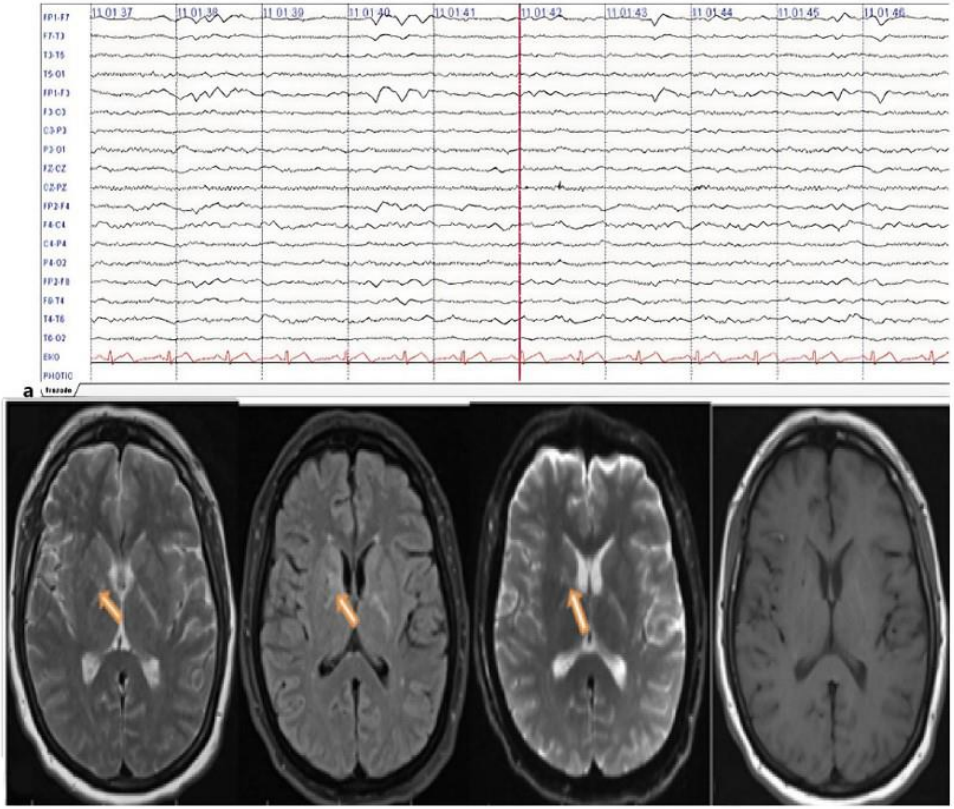
- **Olfactory groove meningioma**.
- After surgery → significant improvement of her symptoms.
- The histological examination a grade I meningothelial meningioma.
- The post-operative MRI complete resection of the tumour and the re-expansion of the frontal lobes
- The post-operative follow-up **asymptomatic** and independent 6 weeks after the surgery



Case 4

- A previously healthy 49-year-old woman
- **Working memory loss**, disorientation, inappropriate behavior, structured visual hallucinations, and **myoclonic seizures**, which progressively increased to epileptic encephalopathy.
- Infectious and neoplastic causes were ruled out.
- EEG for 12 h continuous attenuation with no good sleep patterns and fast activity overlapping bilateral frontal intermittent slowing complex (extreme **delta brushes** [EDBs])

- 12 h of EEG with LFF at 1 Hz & HFF at 70 Hz.
- Evidence **bilateral frontal intermittent slowing complex**.
- **Hyperintense lesions** on T2&Fluid attenuated inversion recovery (FLAIR) MRI image compromised the basal ganglia right side with restricted diffusion, no lesion enhancing.



- An immunological cause confirmed by doing a brain MRI → showing an inflammatory process, as hyperintense lesions in T2 over the suitable **basal nuclei** with restricted diffusion images.

- had a normal CSF but a positive CBA **serologic NMDA-R antibody test.**

- **Anti-NMDAR encephalitis**

- Administered 1 g **methylprednisolone** pulses for 5 days with slight improvement.

- Treated with **plasmapheresis** for five sessions and subsequently **azathioprine** 50 mg twice a day.

- Currently, she has no seizures and showed **significant improvement in cognitive domains.**

Case 5

- A 54-year-old obese female who was diagnosed with **clinical dementia**
- On a complicated regimen of **psychiatric medications** for underlying depression and panic disorder.
- Noted increased **deterioration in executive function & gradual memory impairment** starting in early 2020.

Case 5

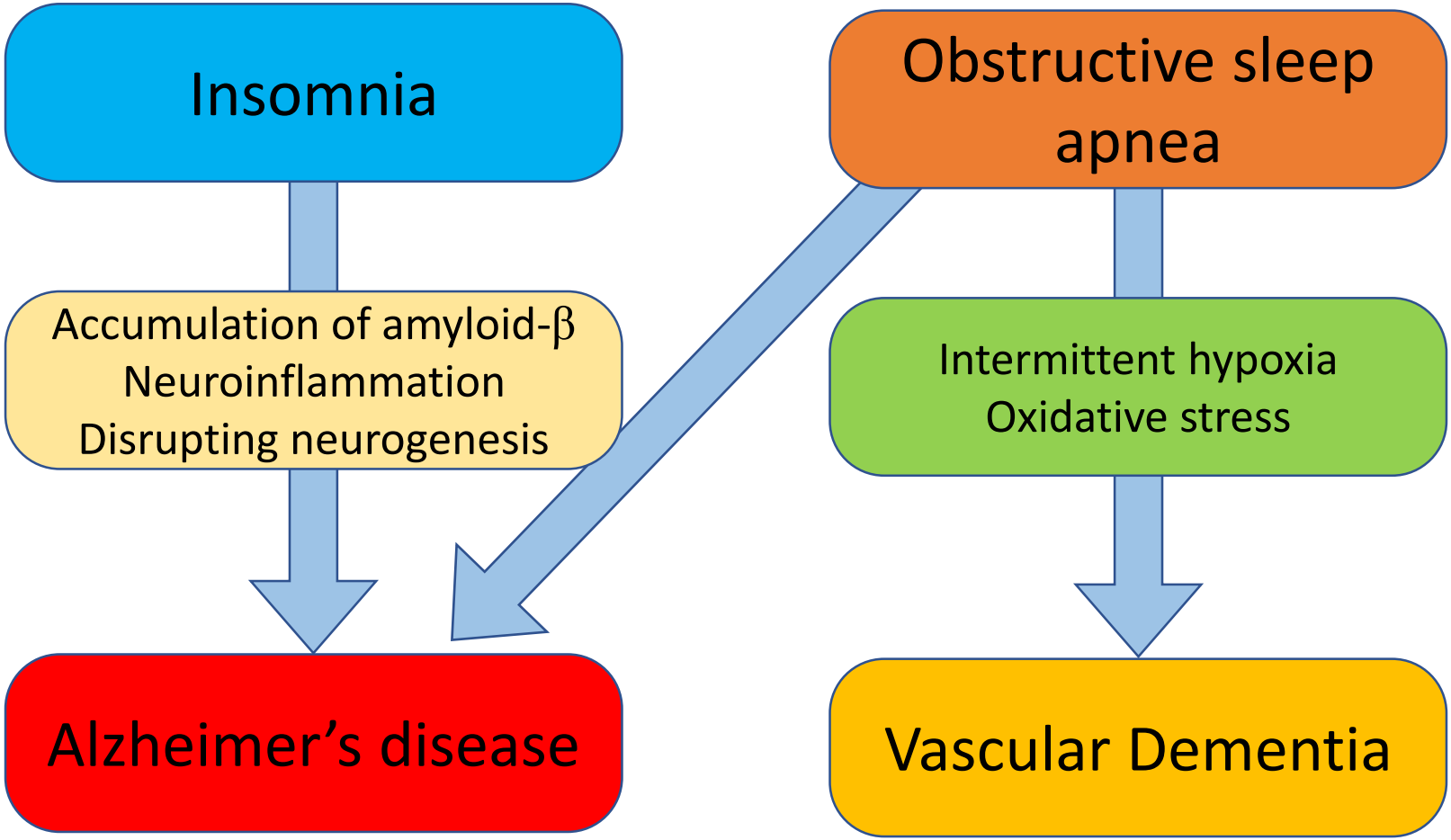
- Neuroimaging → prominent neurodegeneration & other brain pathology were not observed.
- OPD follow-up → **severe obstructive sleep apnea** (OSA) was confirmed
- Based on the diagnostic results, a clinical impression was made for **reversible dementia due to psychiatric drugs and OSA**.

- During hospitalization for 10 days, the patient's regimen of psychiatric medications with anticholinergic effects was changed, and long-acting benzodiazepines reduced.

- Underwent continuous positive airway pressure titration to ameliorate OSA.

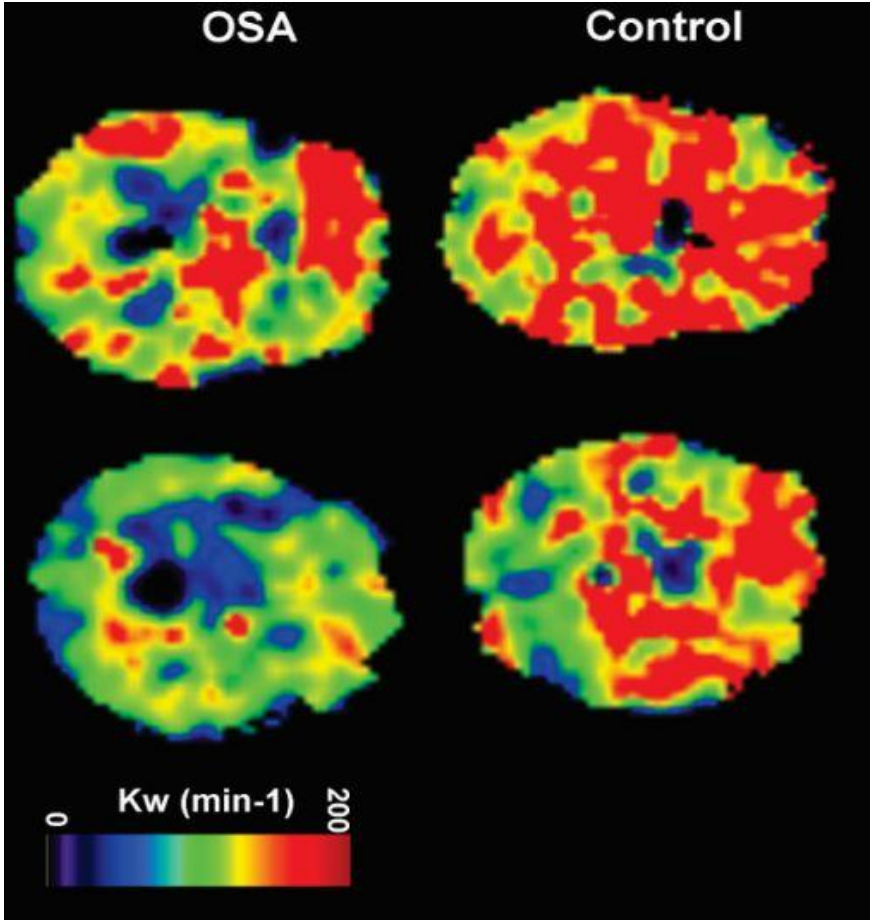
- Reported subjective cognitive improvement and a comprehensive neuropsychiatric test performed at discharge later showed a normal range in all cognitive domains, patient's activity of daily living evaluated at OPD after discharge.

- **Recovered to normal cognition** in only 11 days through appropriate intervention.

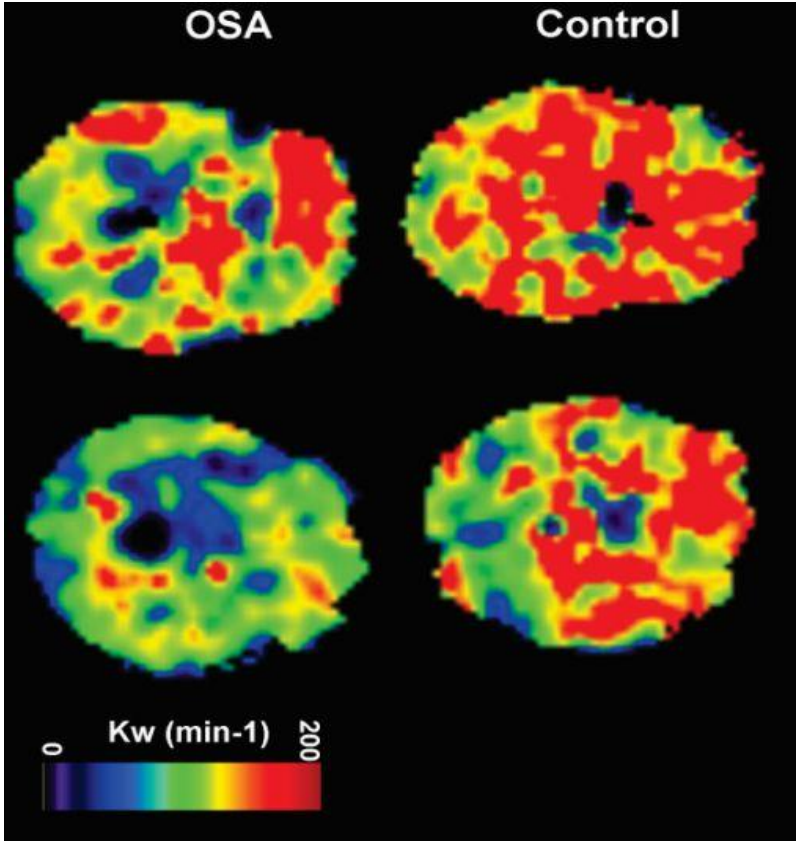

Insomnia
Obstructive sleep apnea
Accumulation of amyloid-β
Neuroinflammation
Disrupting neurogenesis
Intermittent hypoxia
Oxidative stress
Alzheimer's disease
Vascular Dementia

- Blood–brain barrier with compromised function (blue) in a brain with obstructive sleep apnea and in a healthy brain (reds and yellows).

- The blood–brain barrier limits harmful bacteria, infections and chemicals from reaching the brain



- BBB becomes **more permeable** in obstructive sleep apnea, a **breakdown** that could contribute to brain injury & potentially enhancing or accelerating **the damage**.



Case 6

- A 29-year-old woman
- **Progressive cognitive impairment** over a period of 9 months.
- Premorbidly well-adjusted
- Initial signs of the condition included decreased interaction, withdrawn behavior, apathy, and **executive dysfunction**.

- Impaired **judgment** while cooking, loss of **attention** during conversations or while speaking, and perseverating behavior like repeatedly folding clothes, followed by **episodic memory impairment**.

- As symptoms progressed over the next 6 months

- Required increased assistance & encouragement to complete ADL

- Speech output gradually reduced to single words

- No prior history of language difficulty, getting lost in familiar or unfamiliar places, hallucinations, delusions, hemineglect, apraxia, or urine and bowel incontinence

- **A history of veganism**

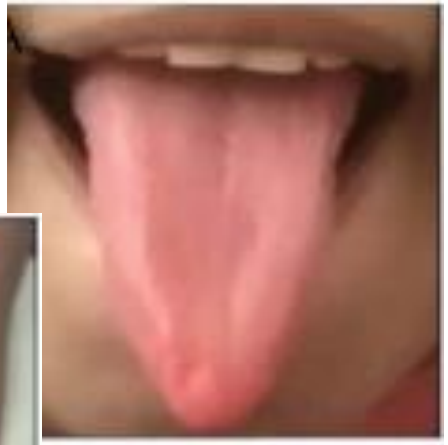
- Amenorrhea for 5 months.

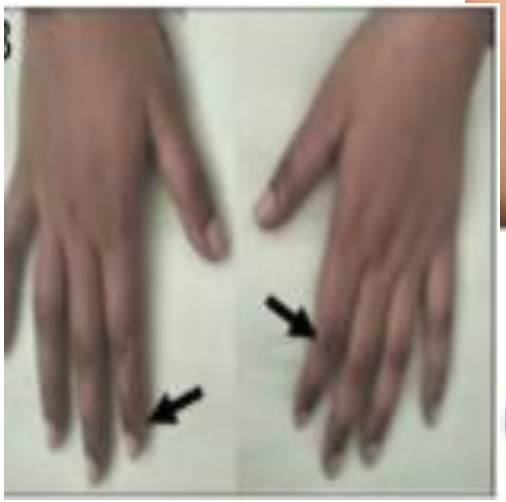
Examination

- Reddish, smooth tongue and hyperpigmentation of knuckles

- (MMSE) score of **19/30** with impairment of attention, calculation, **recent memory**, and orientation components.

- Impaired verbal fluency, recall, 3D construction, **clock drawing test (CDT), and calculation**.





- Motor perseveration
- Predominant **frontal and temporal lobe dysfunction**.
- Fundi and cranial nerves were normal
- **Involuntary movements** (+) in the form of upward twitching of eyebrows, cervical dystonia with anterior & lateral flexion associated with choreoathetoid movements of upper limbs—primarily on the left side.
- Hypotonia of limbs with brisk deep tendon reflexes and extensor planters bilaterally.

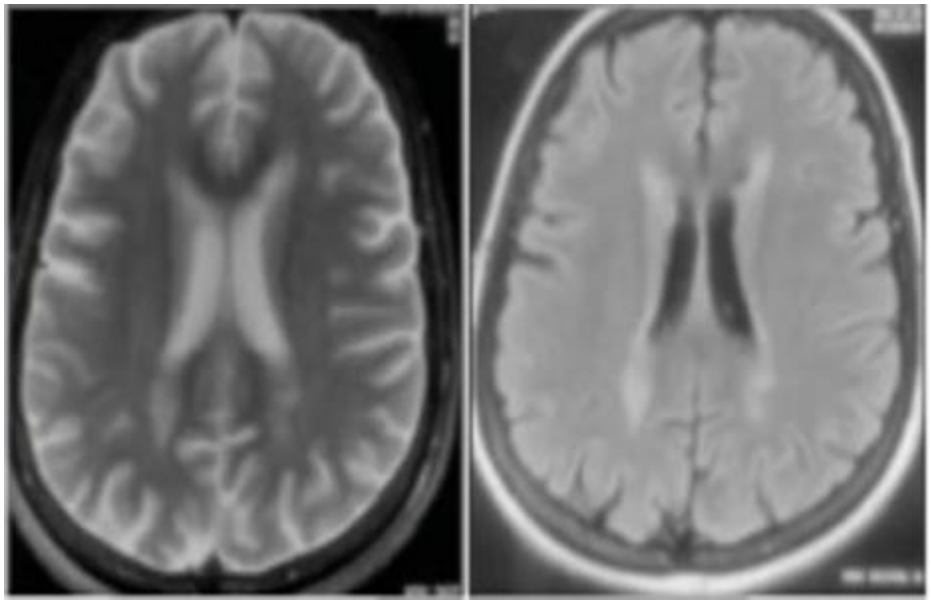
Laboratory results

- Hemoglobin 11.9 g/dL,
- White blood cell count 5.1 K/µL,
- Mean corpuscular volume 114.6 fL,
- Peripheral smear macrocytic hypochromic blood picture,
- Erythrocyte sedimentation rate 36 mm/h.
- **Serum vitamin B12 of 140 pg/mL (211–911 pg/mL) was low**
- **High serum homocysteine** (173.5; 25.80(3.1–19.9 ng/mL).
- Methylmalonic acid and other vitamin levels – not available yet

- Thyroid, hepatic, and renal function tests, serum electrolytes, ammonia, and lactate → normal.
- Antinuclear antibody profile revealed SSA 2+ positive
- nRNP-Sm, Sm, Ro-52, SS-B, Scl-70, SSc, PMScl 100, Jo-1, CENP B, SSc, PBC, PCNA, dsDNA, nucleosomes, histones, ribosomal P protein, AMA M2 → (-)
- Infectious workup (CSF analysis, HIV, venereal disease research laboratory) & autoimmune encephalitis panel (NMDA, voltagegated potassium channel, LGI1, Caspr2, anti-TPO)→(-)

- Ultrasound of the abdomen and pelvis was normal.
- Nerve conduction studies were normal.
- Upper gastrointestinal endoscopy showed normal appearance of mucosa and gastric mucosal biopsy showed **mild chronic inflammation and focal atrophy.**

- Brain MRI showed bilateral T2-weighted and fluidattenuated inversion recovery **periventricular hyperintensities**



Neurology(AAN) . August 10, 2021 ; 97(6): 643-646

- Treated as **reversible dementia due to B12 deficiency**. Received a B-complex multivitamin injection with vitamin B12 1000 µL/d daily for 1 week, then once a week, and then monthly

- Started to improve at 4th day of therapy, speech & CDT were better.

- At 1 month follow up, subjective improvement of 70%. able to cook with good judgment, take care of her child, and the perseverating behavior and chorea athetoid movements disappeared.

- Her menstrual cycles resumed, MMSE improved to 29/30 (1 lost in calculation)
- After 2 months, MMSE was 30/30, vitamin B12 >2000 pg/mL, and homocysteine 17.7 µmol/L.
- After 2 years, construction ability showed normal state.

Conclusion

- Identifying treatable causes of dementia is important as **it can be cured completely** with treatment of the **underlying etiology**.
- Numerous potentially reversible conditions may be associated with or even present with cognitive impairment and dementia.
- Some are rare, yet treatable (e.g., Wilson's disease)

Conclusion

- Other conditions are more common, but may only occasionally present with dementia in the absence of other neurological symptoms (e.g., space-occupying lesions).

- some are **very common** and should be looked for in all patients with dementia (e.g., depression, vitamin deficiency).

- Most reversible conditions are easily identified by a careful history, physical examination, psychiatric evaluation, brain CT or MRI, and routine laboratory tests.

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Thank You!