UNIVERSITATEA DE STAT DE MEDICINĂ ŞI FARMACIE
"NICOLAE TESTEMIŢANU" DIN REPUBLICA MOLDOVA

AUTONOMIC NERVOUS SYSTEM. HEADACHES.

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The Christmas holidays are approaching…

Autonomic nervous system (ANS): history

Visceral nervous system

- Older term (**Used before the 19th century**)
- It referred to the nerves that serve **internal organs (viscera)**.

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Autonomic nervous system

John Newport Langley (1898)

- He proposed this name to emphasize its functional independence.
- He divided the system into three parts: sympathetic, parasympathetic, and enteric.

Objectives

- Anatomical and physiological peculiarities of ANS
- Clinical manifestations of ANS impairment
- Diagnosis of ANS disorders
- Therapeutic approaches

- **The impact of ANS disorders:**

  - quality of life

  - clinical manifestations with varied consequences (e.g., syncope – falls, sudden cardiac death, thermal shock)

  - ANS pathology is underdiagnosed

Structural organization of ANS

The central ANS is hierarchically organized at all levels

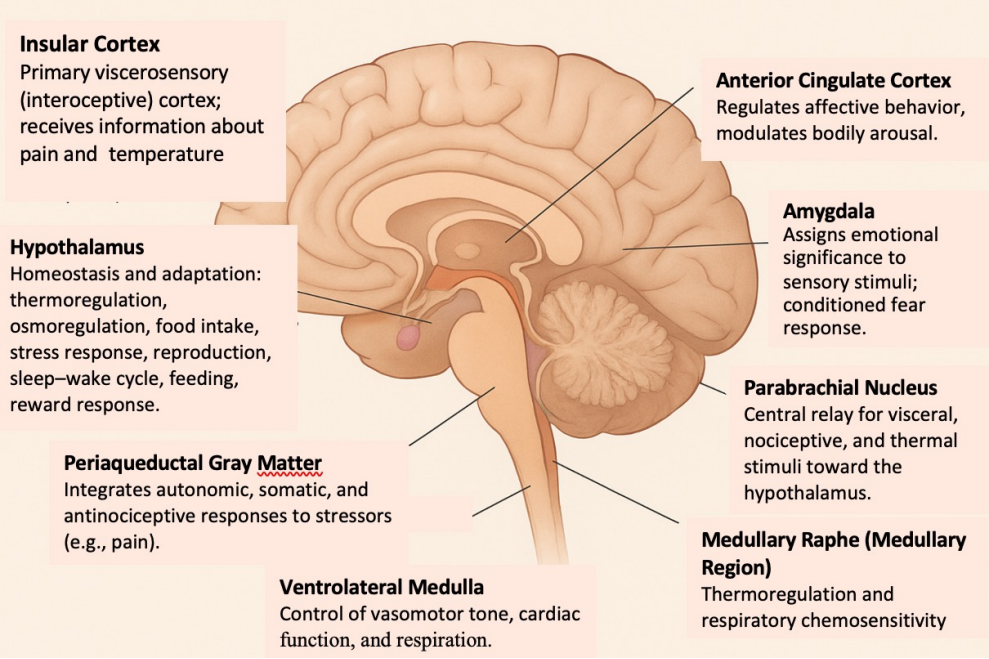


Fig.1. Neural Control Centers of the ANS

Spinal level	Targeted functions
Lower brainstem	Control of circulation, breathing, and urination
Upper brainstem	Pain processing and behavioral state regulation
Hypothalamus	Homeostasis (balance of bodily functions)
Telencephalon + Diencephalon	Stress response and regulation of affective behavior
Anterior limbic circuit	Integrating responses to emotions and behavior

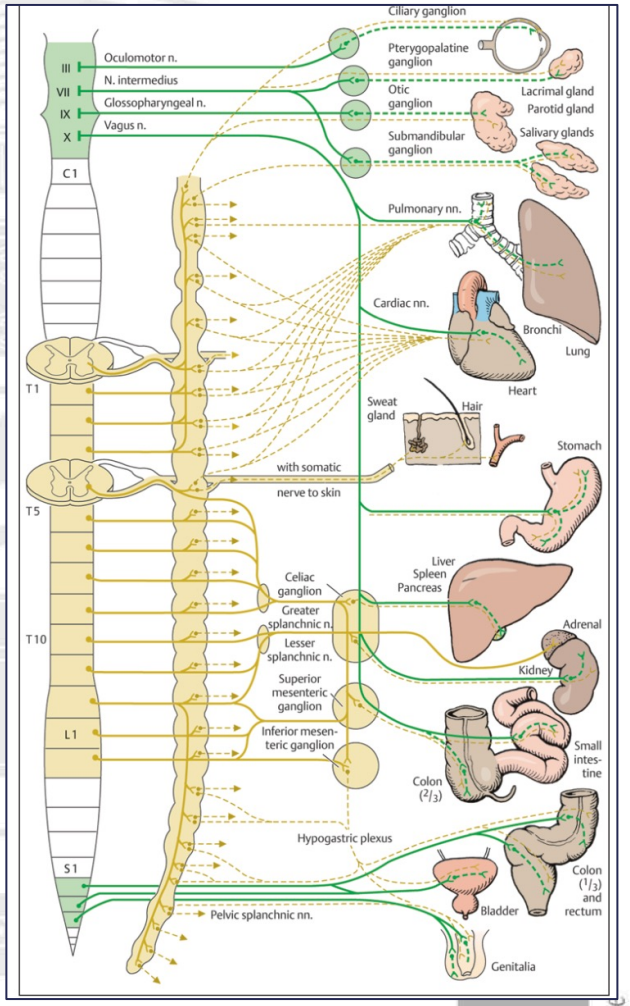


Fig. 2. Sympathetic and parasympathetic ANS

Excitatory mediators: L-glutamate

Inhibitory mediators: acid gamma-aminobutyric(GABA)

Structural organization of ANS

BRAIN

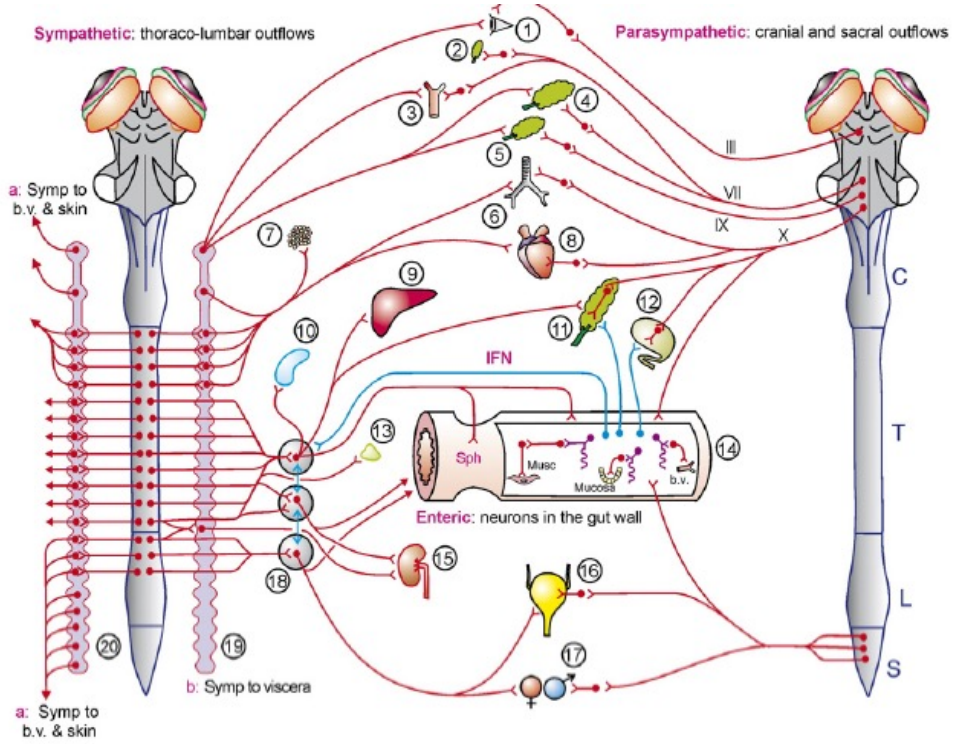
- Limbic System
- Hypothalamus
- Reticular Formation
- Cerebral Cortex

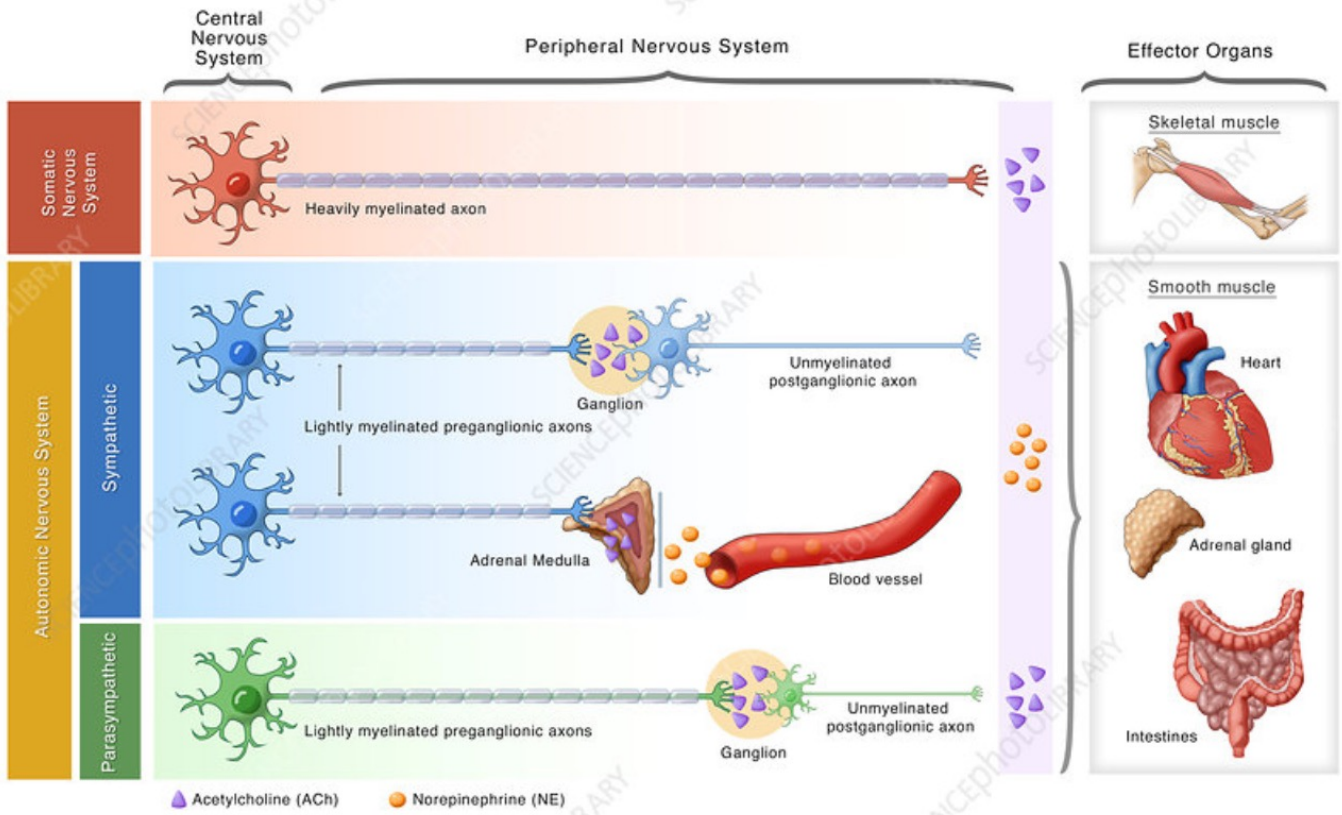
SPINAL CORD

Sympathetic Nervous System

Parasympathetic Nervous System

ANS peculiarities





Hypothalamus

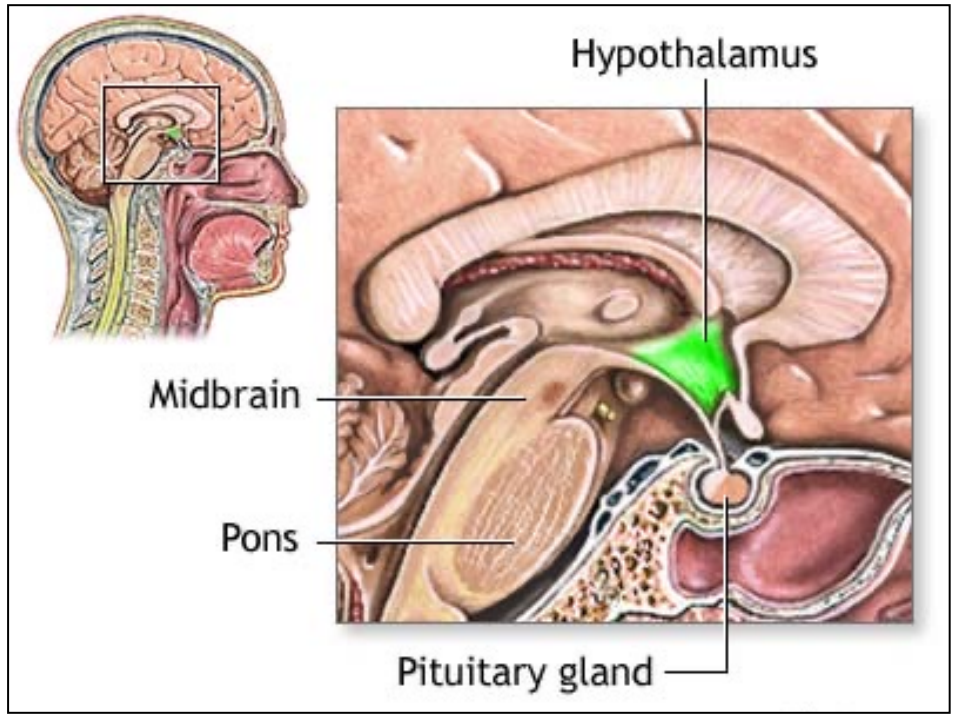


Fig. **Hypothalamus**

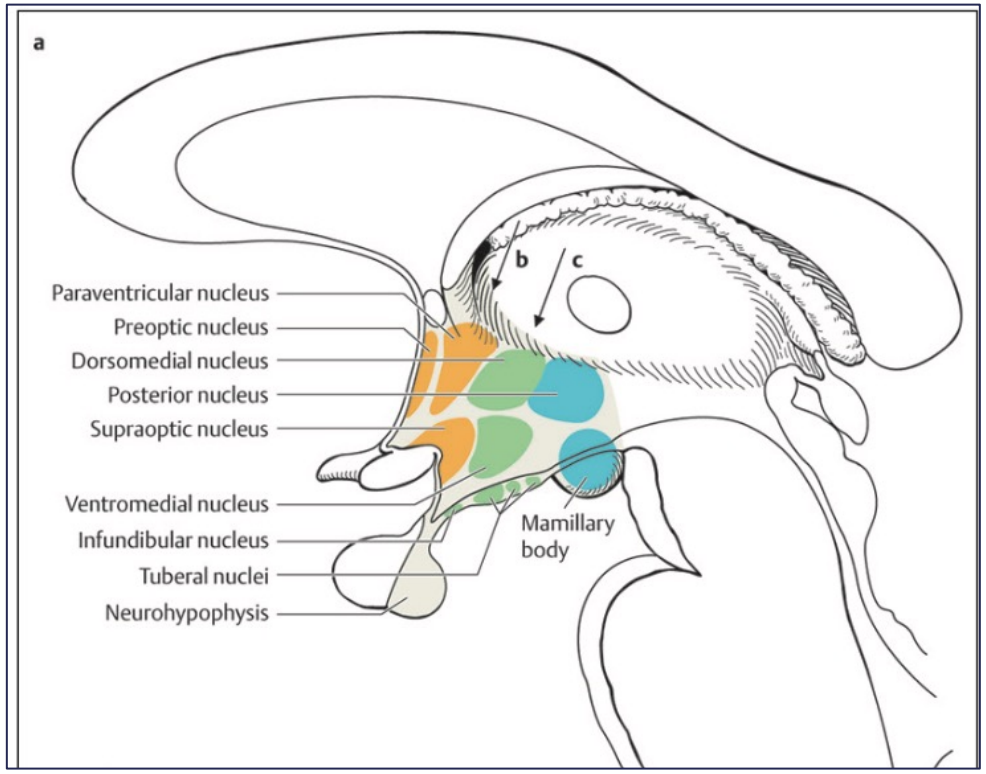
ANS **Endocrine system**

- **Hypothalamus - the highest level of autonomic integration**, under the influence of cortical and limbic structures.
- It ensures **homeostasis, adapts and integrates individual needs**, such as hunger, thirst, sexual function, and sleep.
- **Neurosecretion**

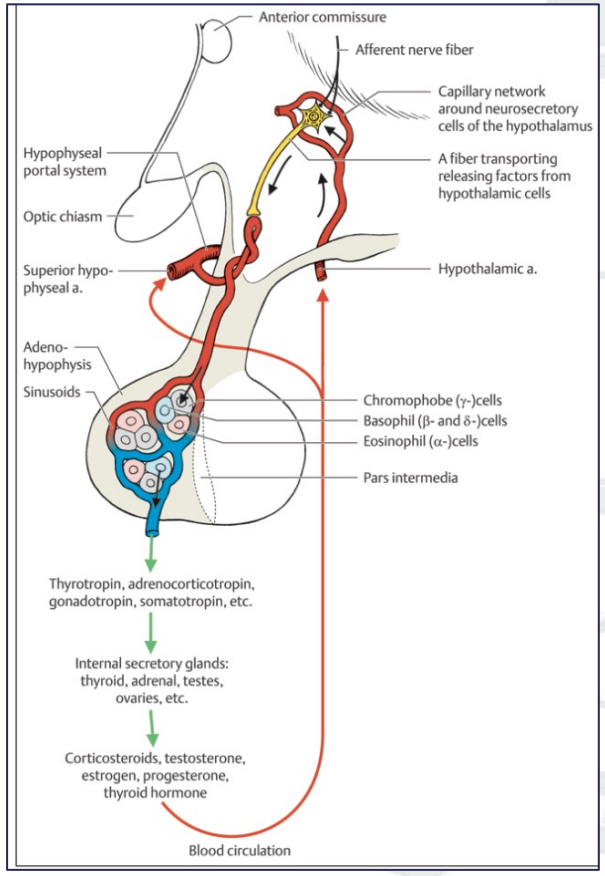
https://medlineplus.gov

Hypothalamus: neurosecretion

Hypothalamus and hypothalamic nuclei

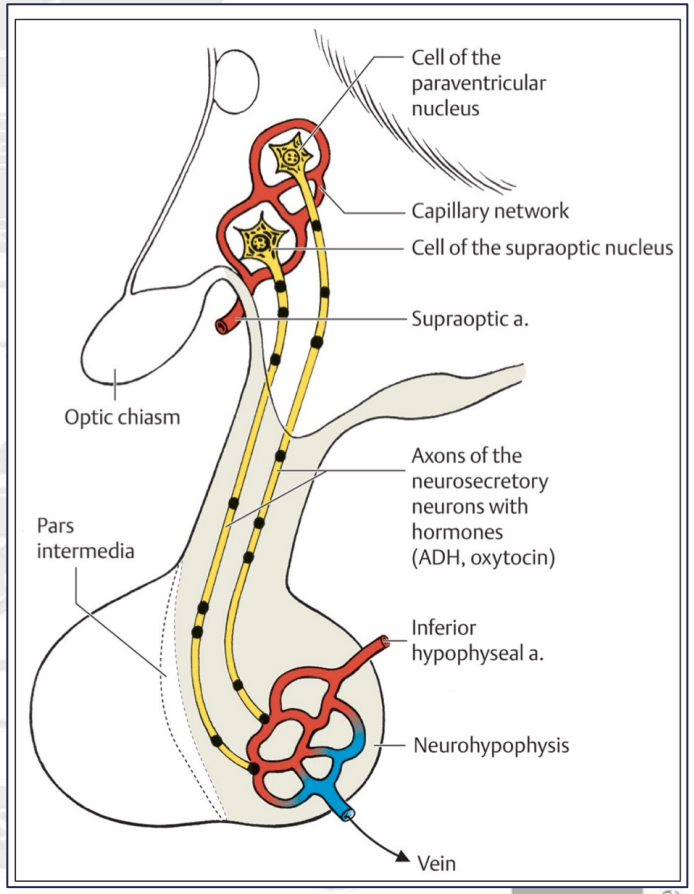


Adenohypophysis



Neurohypophysis

Hormones: Oxytocin, ADH



Baehr M., Frotscher M. Topical Diagnosis in Neurology: Anatomy, Physiology, Signs, Symptoms. 2019, 336 pp.

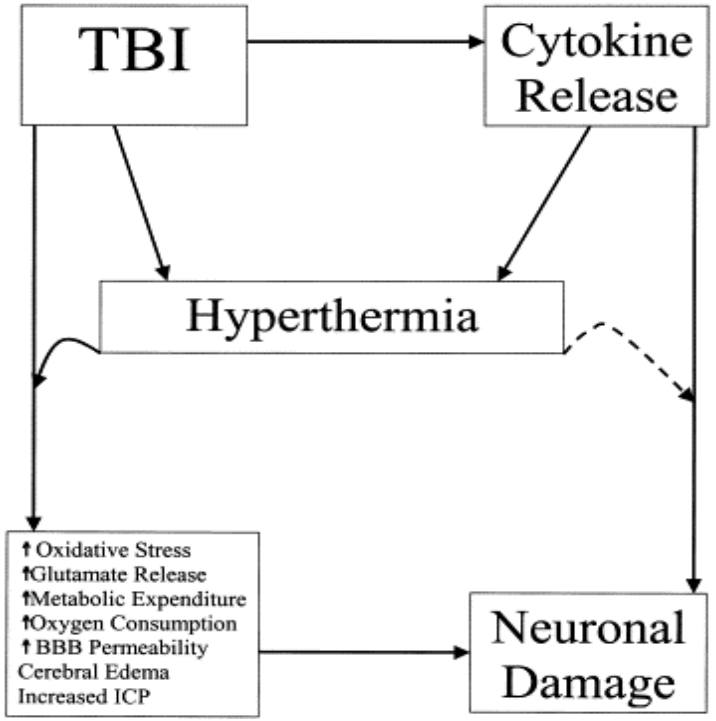
Hypothalamic disorders

Temperature regulation disorders	Dysfunction of the **anterior preoptic region** (e.g., TBI, hemorrhage) – • **central hyperthermia**
	Posterior region disfunction – • **hypothermia or poikilothermia:** e.g., hypothalamic tumors (craniopharyngioma, glioma), Wernicke encephalopathy and hydrocephalus.
Disorders of Fluid Balance	Related to the **supraoptic and paraventricular nuclei:** • **Diabetes insipidus**: characterized by **excessive thirst**, **polyuria**, and **polydipsia;**
Pituitary Hormonal Disorders	• **Pituitary adenoma** (usually benign). • **Panhypopituitarism** (global deficiency of pituitary hormones). • **Hormone-secreting pituitary tumors**, such as: - **Prolactinoma** (hyperprolactinemia). - **Acromegaly** (GH excess). - **Cushing's syndrome** (ACTH excess).

Disorders of body temperature

Dysfunction of the **anterior preoptic region** (e.g., TBI, hemorrhage) –

- **central hyperthermia**



TBI – Traumatic Brain Injury

Posterior region disfunction – eg., hypothalamic tumors (craniopharyngioma, glioma), Wernicke encephalopathy and hydrocephalus

- **hypothermia or poikilothermia**

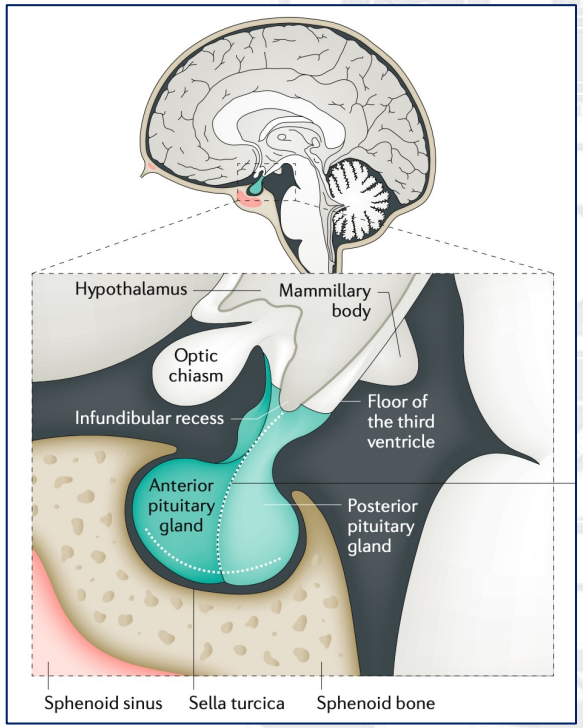


Fig. 1 | Features of craniopharyngioma.

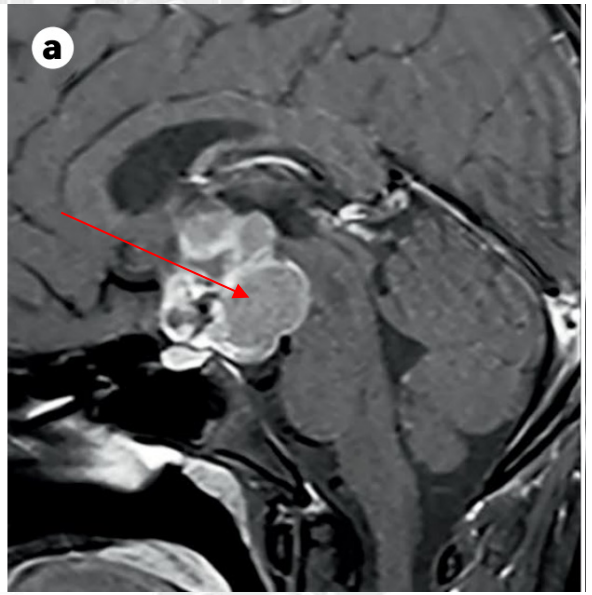
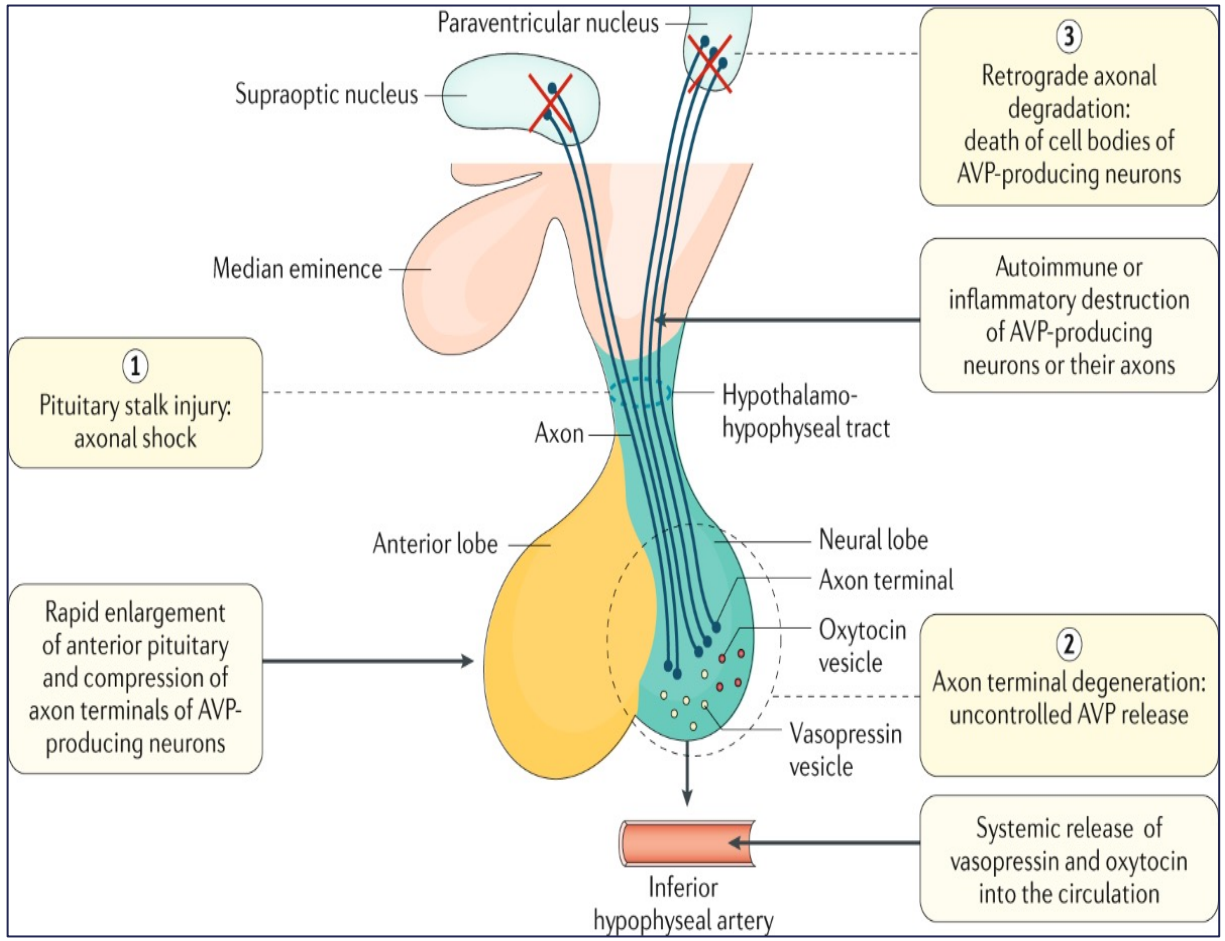
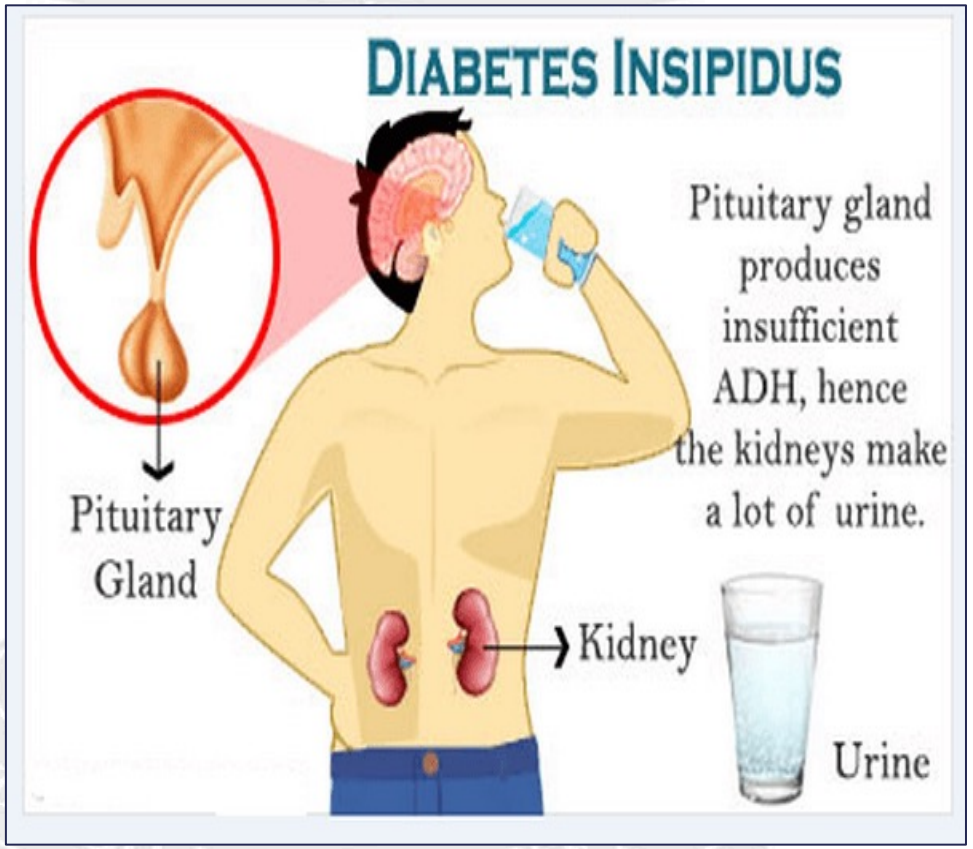


Fig. 2 | MRI of the brain, craniopharyngioma.

Müller, H.L., *et al.* Craniopharyngioma. *Nat Rev Dis Primers* **5**, 75 (2019)

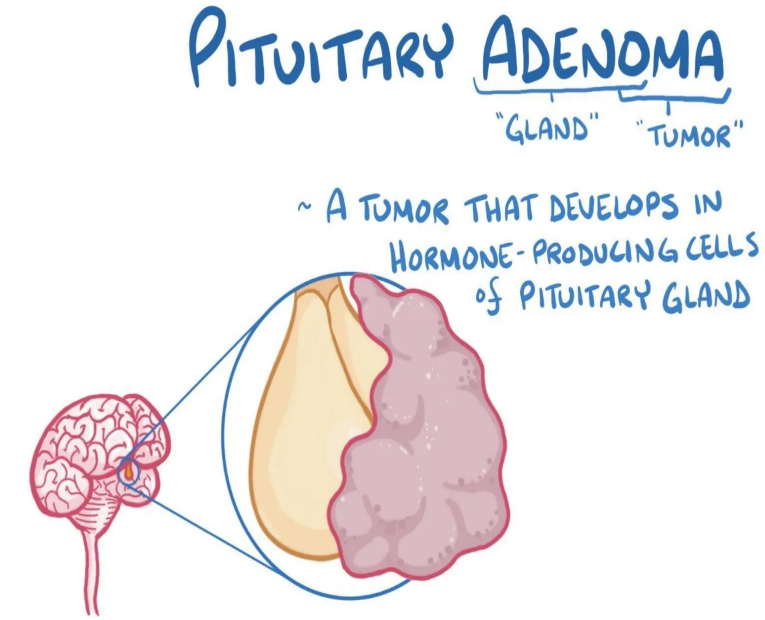
Disorders of Fluid Balance
Diabetes insipidus

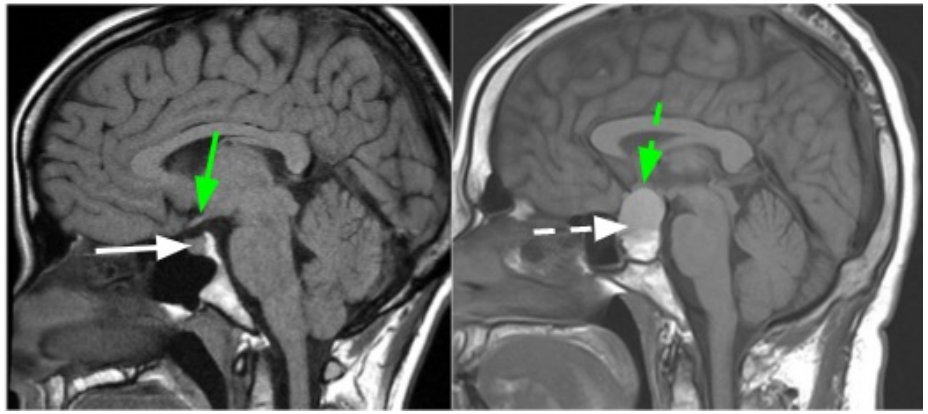




ADH – antidiuretic hormone

Pituitary Hormonal Disorders



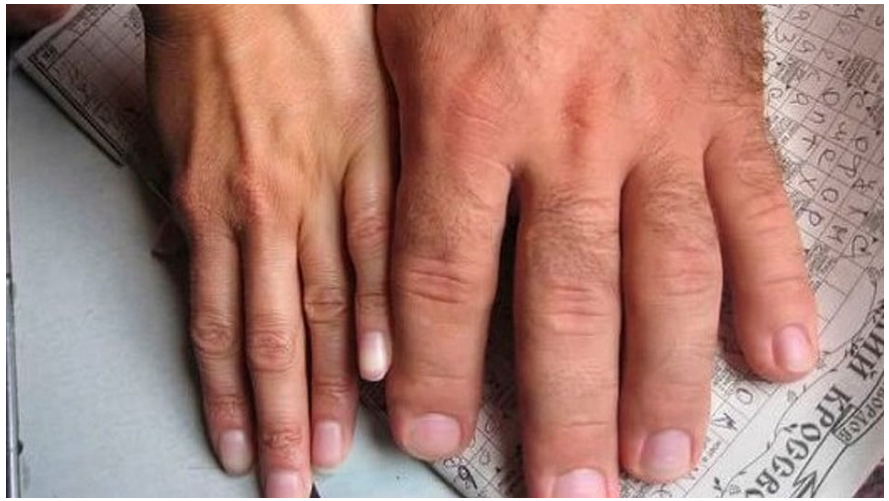


Disorders of Pituitary Gland

Parts involved	Hyperactivity	Hypoactivity
Anterior Pituitary	1. Gigantism 2. Acromegaly 3. Acromegalic gigantism 4. Cushing's disease	1. Dwarfism 2. Acromicria 3. Simmond's disease
Posterior Pituitary	Syndrome of inappropriate hypersecretion of ADH (SIADH)	Diabetes insipidus
Anterior and Posterior Pituitary	.....	Dystrophia adiposogenitalis

Pituitary Hormonal Disorders

Fig. 23-17



Acromegaly

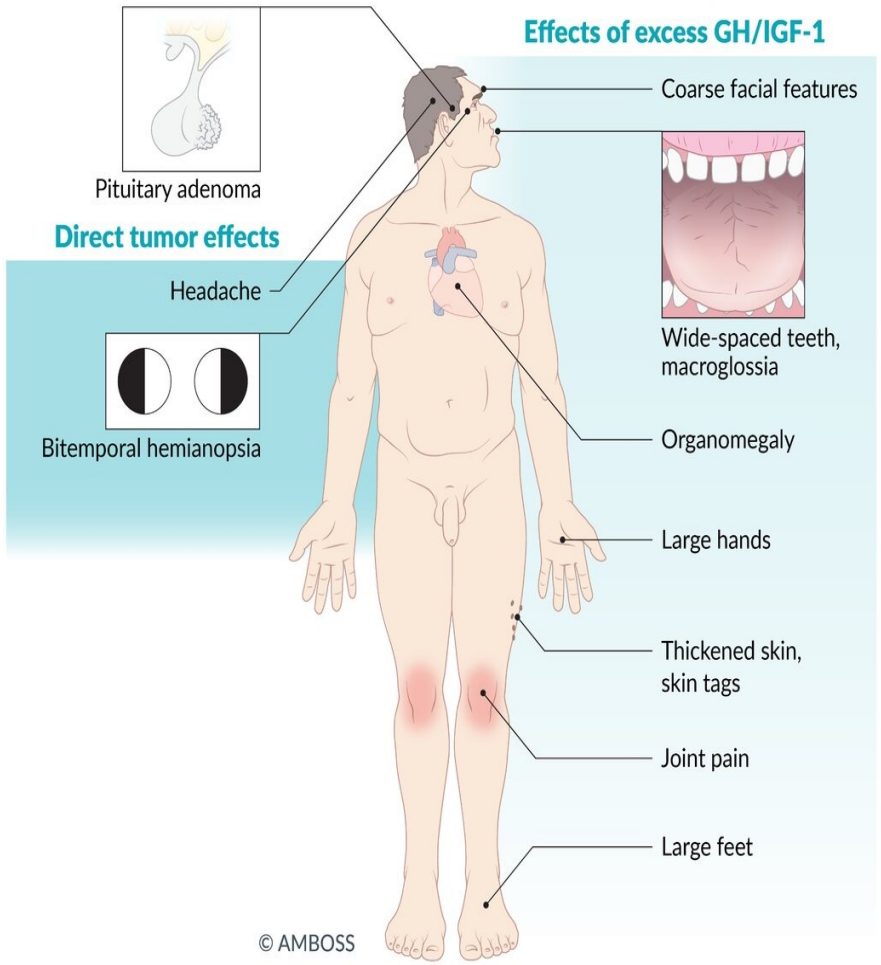
Etiology
Benign pituitary adenoma → excessive GH secretion

Pathophysiology
↑ GH → ↑ IGF-1 → overstimulation of cell growth and proliferation
Other tumor effects:
↓ Secretion of gonadotropins

Diagnostics
↑ Serum IGF-1

Treatment
First-line therapy: transsphenoidal adenomectomy

Complications
Cardiovascular disease (main cause of death), impaired glucose tolerance, carpal tunnel syndrome



Limbic system

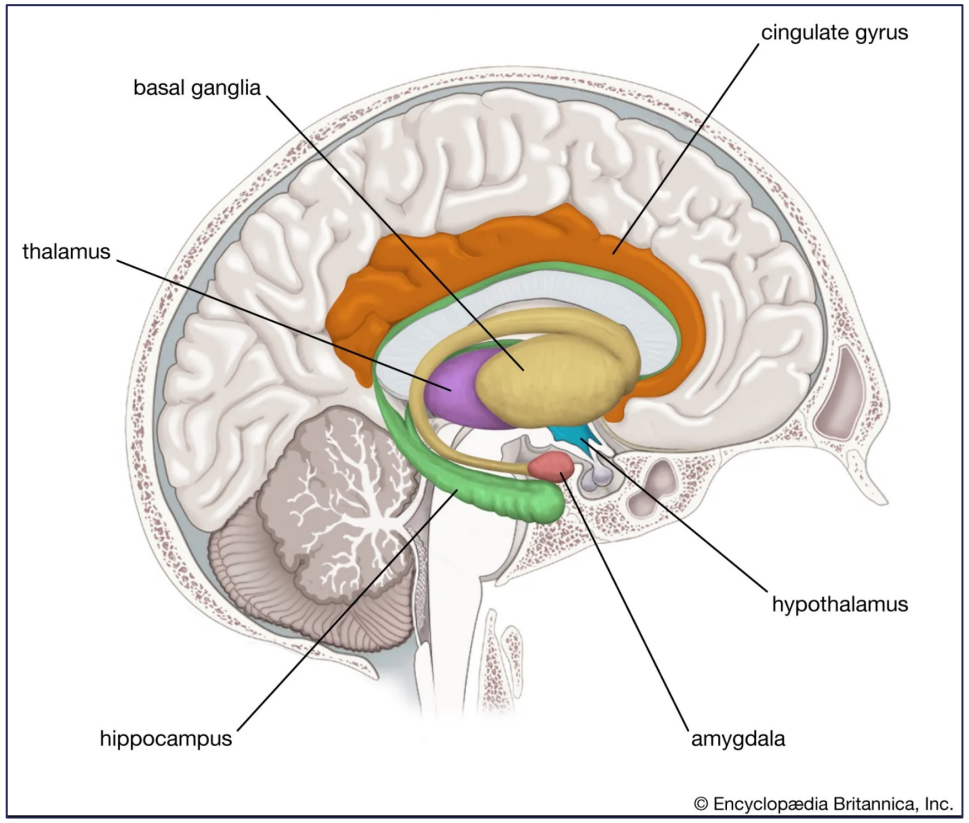


Fig. 1. The limbic system

The term **"limbic"** – derived from the Latin *limbus*, meaning **edge** (coined by Thomas Willis).

- **1878 – Paul Pierre Broca** – *"le grand lobe limbique"*
- **1937 – James Papez** – *"A proposed mechanism of emotion".* **Papez circuit**
- **1952 – Paul D. MacLean** – *"limbic system"*

Limbic system: anatomy and functions

Hippocampus

- short- and long-term memory
- spatial memory
- associative memory

Mammillary bodies

- episodic memory
- thiamine (B1) deficiency
  → Wernicke-Korsakoff syndrome

Amygdala

- emotional processing (fear, anxiety, aggression)
- memory
- decision-making
- Damage → impaired fear conditioning
- Bilateral lesions → Klüver-Bucy syndrome

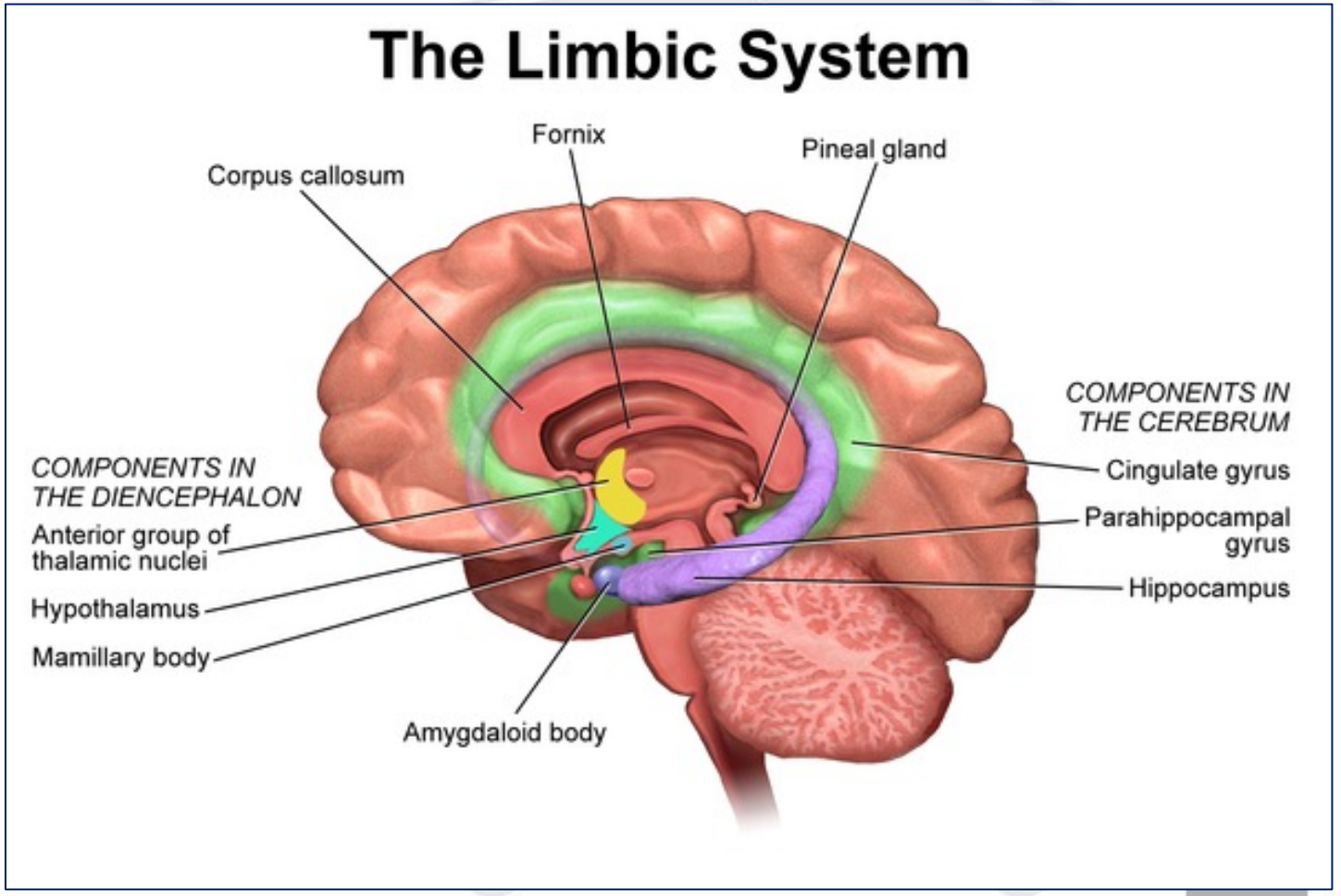
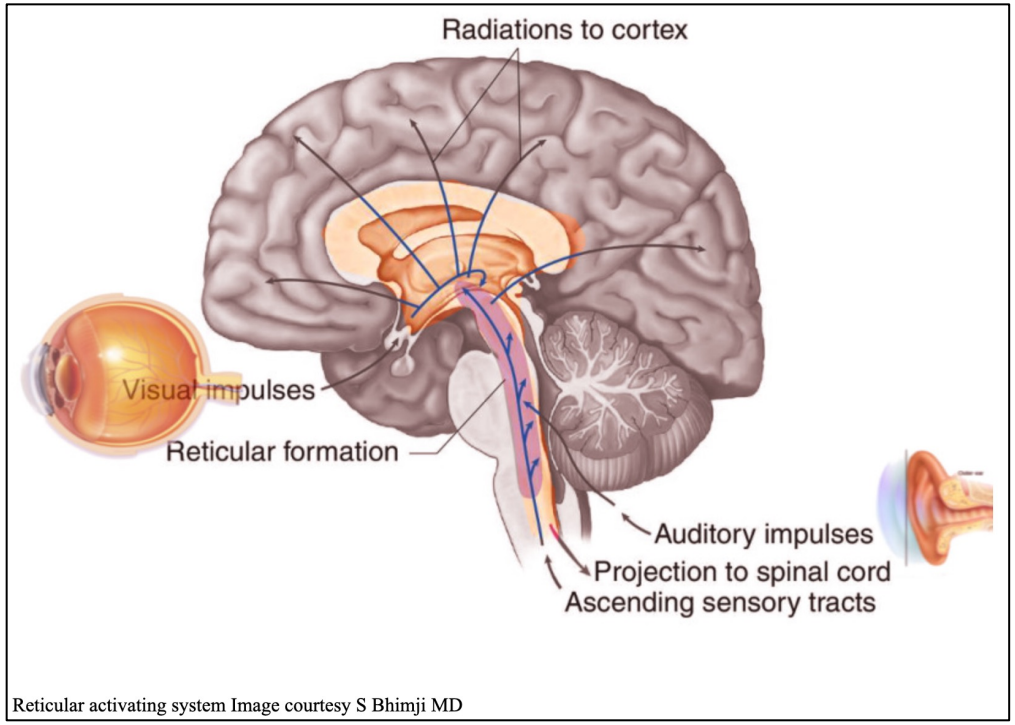


Fig. 1. The limbic system

https://www.physio-pedia.com/Limbic_System

Reticular formation (RF)

RF - complex network of brainstem nuclei and neurons that serve as a **major integration and relay center** for many vital brain systems to **coordinate functions necessary for survival.**



Reticular activating system
Image courtesy S Bhimji MD

Sarah A. Mangold; Joe M. Das, et al, 2023.

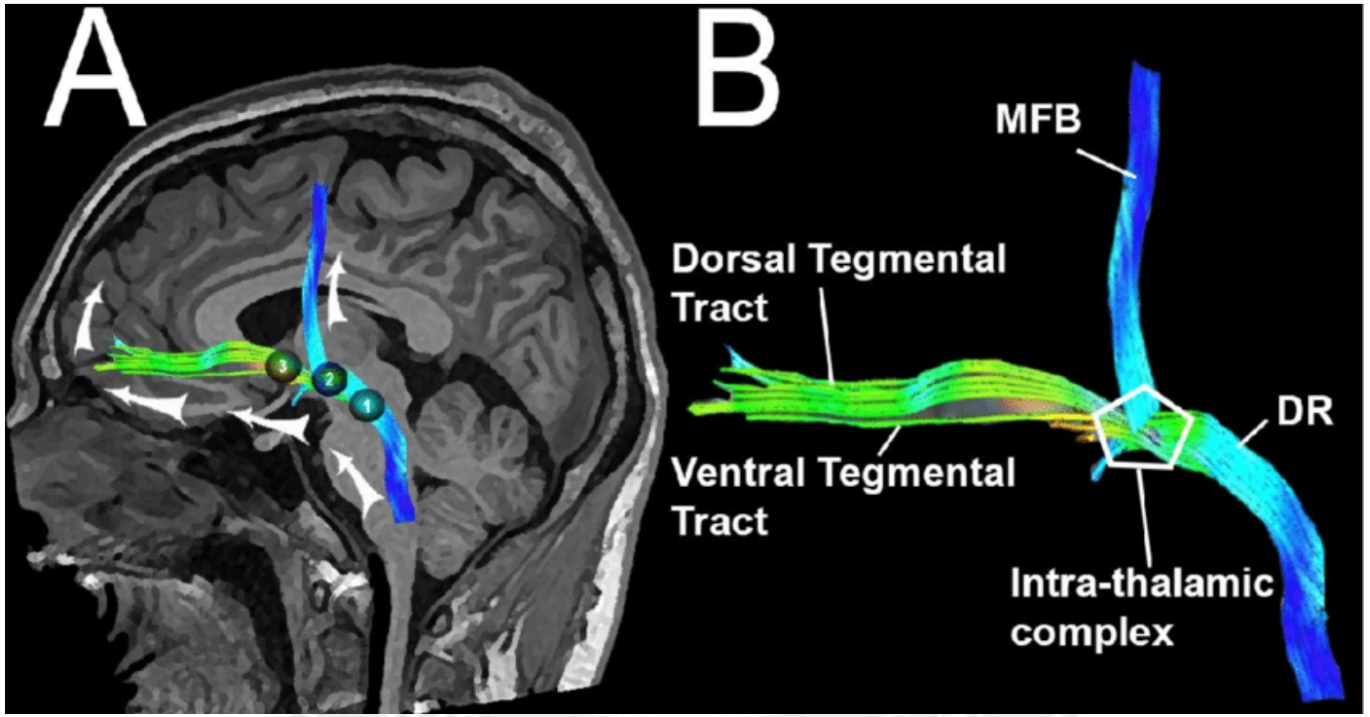
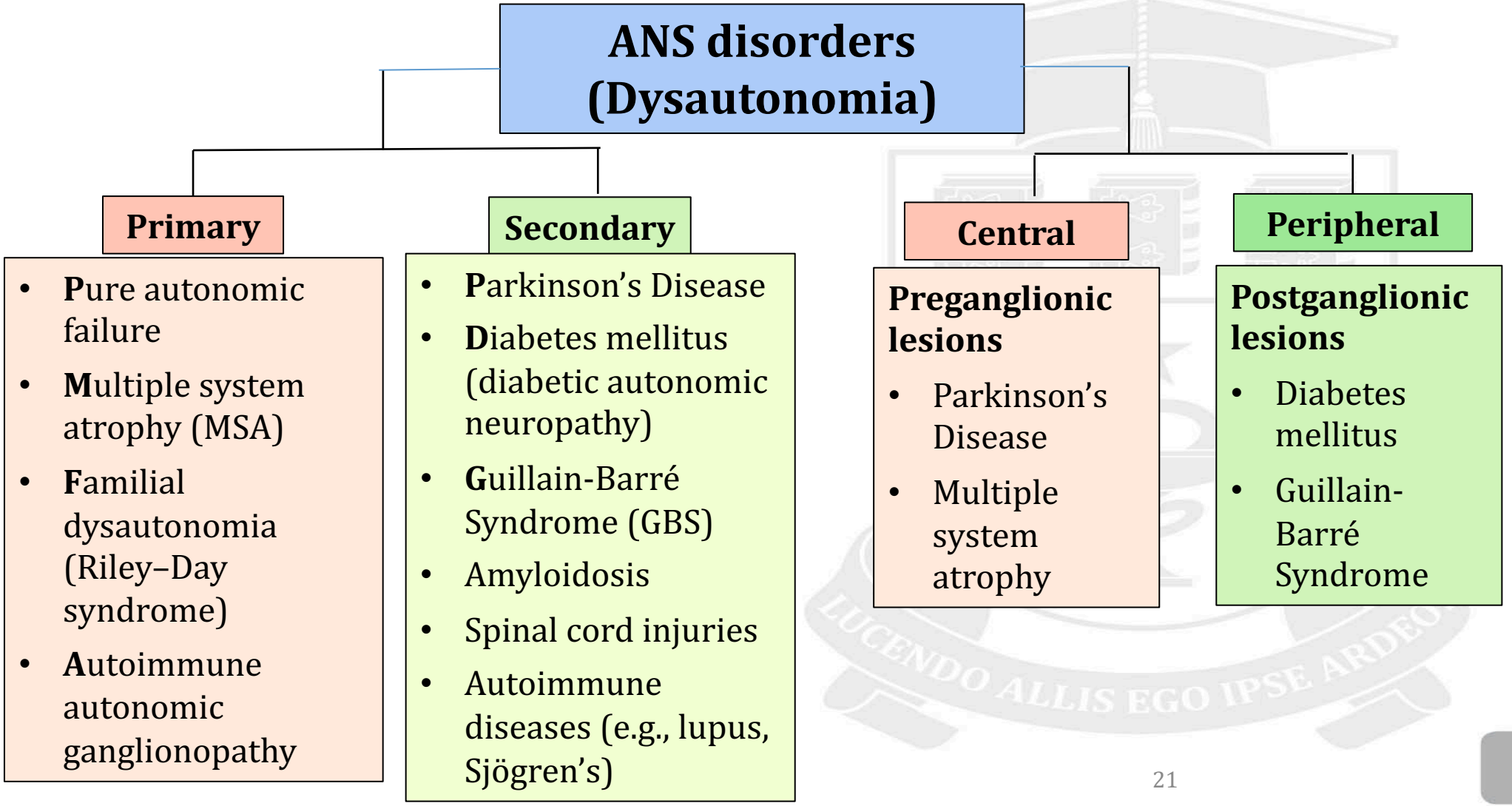


Fig. Schematic illustration of the reconstruction of the ascending reticular activating system (ARAS) fiber tracts with tractography in a normal subject.

Ordóñez-Rubiano EG, et al., 2017

ANS disorders: classification

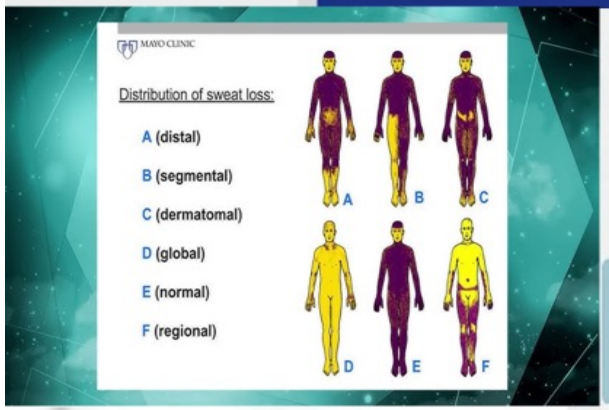


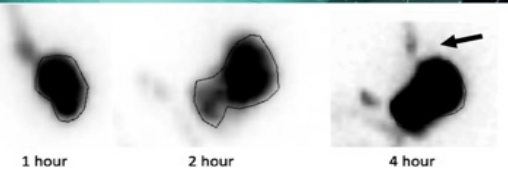
Diagnosis of ANS disorders

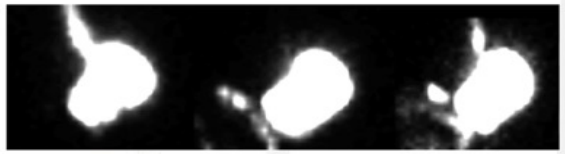
- **Detection and Assessment of the Most Impaired Functions**
  A careful, symptom-guided medical history
- **Objectives of the Clinical Evaluation:**

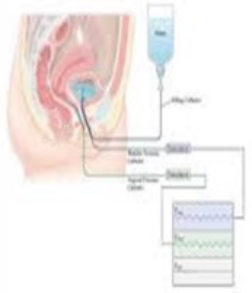
	To identify the presence and distribution of autonomic dysfunction
	To determine patterns of autonomic failure and their association with specific syndromes
	To recognize treatable disorders
	To determine the need for additional investigations (e.g., autonomic laboratory testing)
	To assess progression over time
	To evaluate the impact on the patient

Diagnostic tests



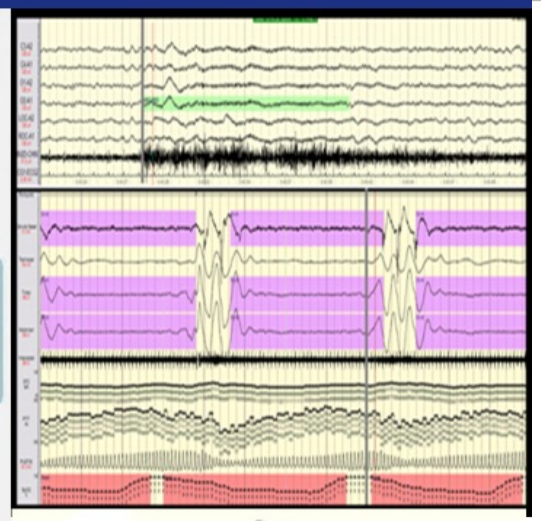


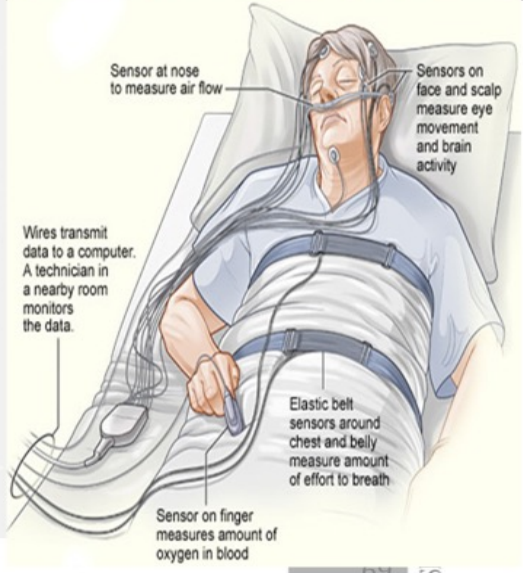




Autonomic Dysfunction: Main Tests / Explanations

Sweating Disorders	Bladder/Sexual Dysfunction	Gastroinstestal Dysfunction	Autonomic Hyperactivity Syndromes	Sleep: Cardiovascular/ Ventilatory
• Thermoregulatory Sweat Test (TST) Gold standard • Quantitative Sudomotor Axon ReflexTest (QSART) • QDIRT / DST/ SIT	• Clinical exam • Lab tests • Questionnaires (IIEF-5, FSFI/SFD) • Urodynamic studies— Gold standard • Penile Doppler + erection test • Electrophysiology	• Videofluoroscopy/ barium swallow • Esophageal manometry • Endoscopy & biopsy • H, pylori testing • Gastric scintigraphy • Colonic transit study • Anorectal manometry • Hydrogen breath test • Labs	• Bedside monitor-ing (HR, BP, O, sat) • Invasive monitoiring (ICU) • ECG **Gold standard** (No single gold standard, relies on careful monitoring + trigger recognition)	• Poiysomnography (PSG/VPSG) • OCST • 24-h off-center BP testing (ABPM) • Cardiovascular reficx tests • 123-I MIBG scintigraphy • Multiple sleep latency test (MSLT

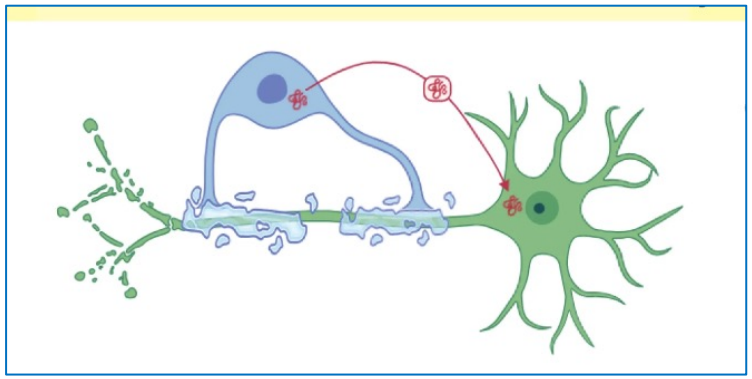




Primary autonomic failure

α-synucleinopathies:

- Multiple system atrophy (MSA)
- Dementia with Lewy bodies
- Pure autonomic failure



Pathological α-synuclein deposition in oligodendrocytes (glial cytoplasmic inclusions)

↓

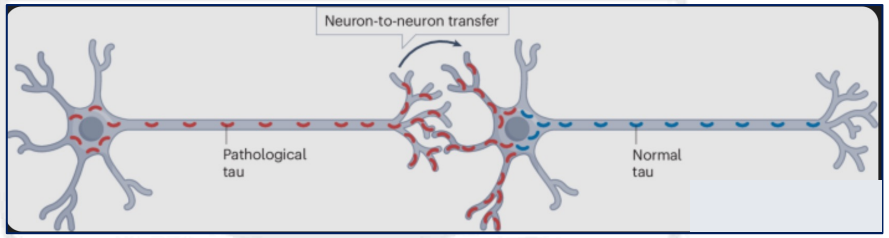
Oligodendrocyte dysfunction → demyelination

↓

Neuronal degeneration and gliosis

τ-pathies:

- Progressive supranuclear palsy (PSP)
- Frontotemporal dementia



- Urgency, incontinence
- Constipation
- Hypo-/anhidrosis
- Orthostatic hypotension

Secondary autonomic failure

Diabetes mellitus

- **Peripheral autonomic neuropathy**: type II DM >1 year, type I DM >2 years
  - hypo- or anhidrosis and vasomotor disorders + sensory disorders in the extremities
- **Autonomic cardiovascular neuropathy** – increased overall mortality and morbidity:
  - resting tachycardia,
  - orthostatic hypotension,
  - reduced exercise tolerance
  - Silent (painless) myocardial ischemia.

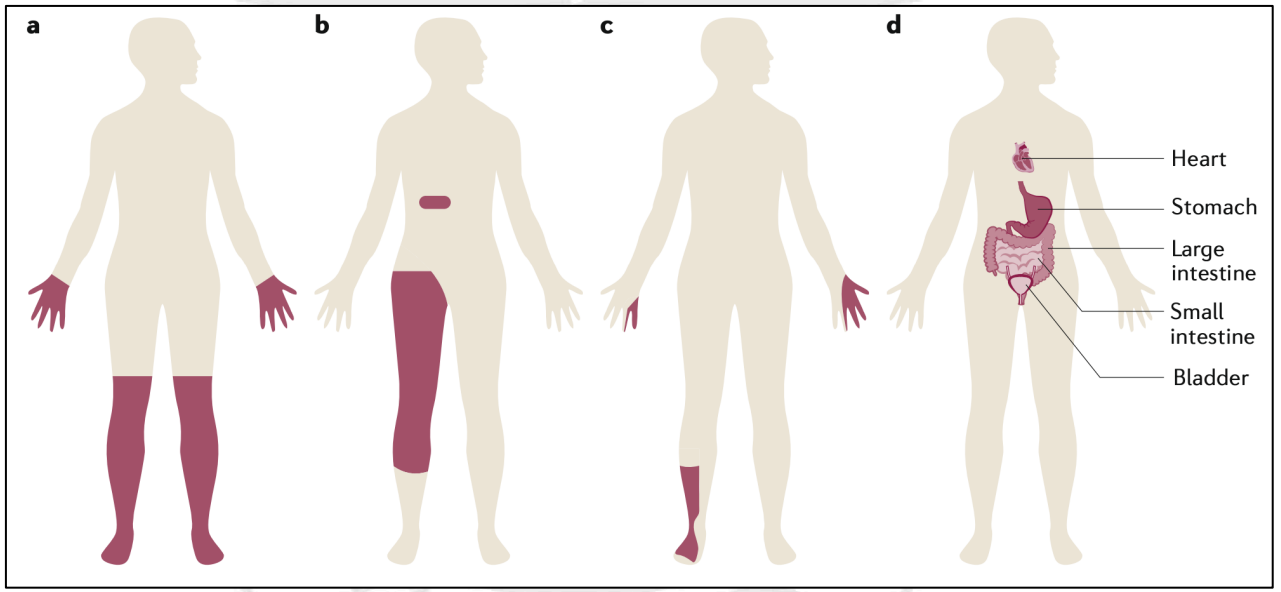


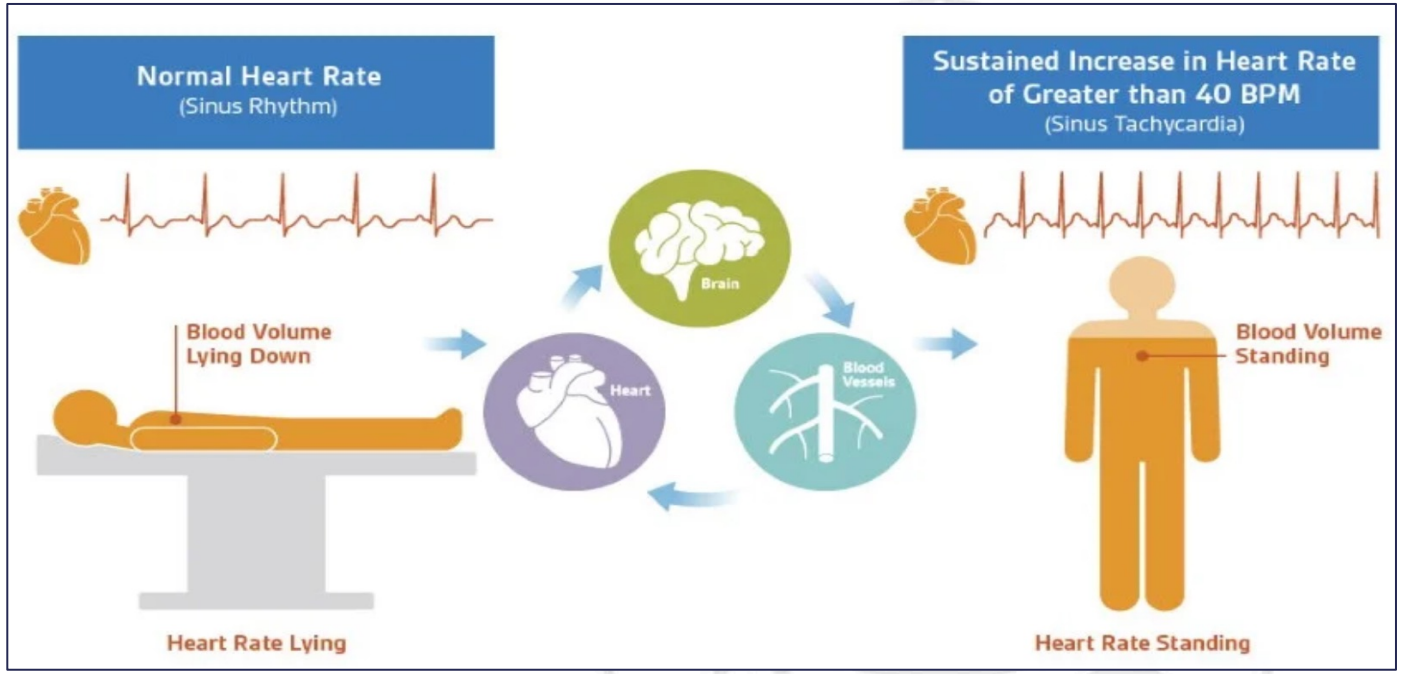
Fig. Diabetic neuropathy patterns

- Cross-sectional study: 162 diabetic patients aged ≥40 years, with a minimum duration of five years of type I and type II DM
- **Prevalence 37.65% silent myocardial infarction** (in literature 20%-40%)

Abdul Manan H, Chishti HR, 2025;Feldman, E. L., *et al.*Diabetic neuropathy.*Nat Rev Dis Primers* **5**, 41 (2019)

Postural orthostatic tachycardia syndrome (POTS)

- **POTS - orthostatic tachycardia in the absence of orthostatic hypotension (HO)**
- **Age** of presentation – between **15 and 50 years**
- F : M – 5 : 1



https://www.luriechildrens.org/

Diagnostic criteria:

on maintaining the orthostatic (standing) position for 10 minutes or during the tilt test:

- **heart rate ⇧ of at least 30 beats per minute or**
- heart rate of 120 beats per minute or more in the absence of HO

POTS: Classification and Mechanisms

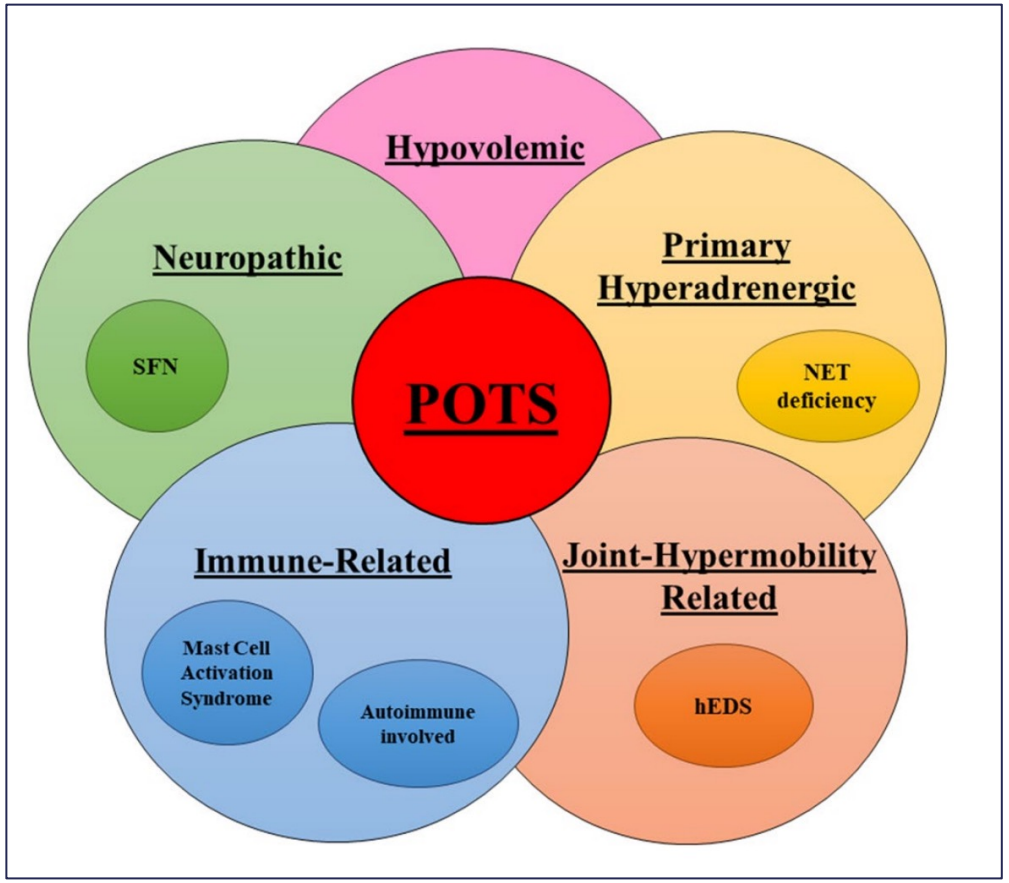
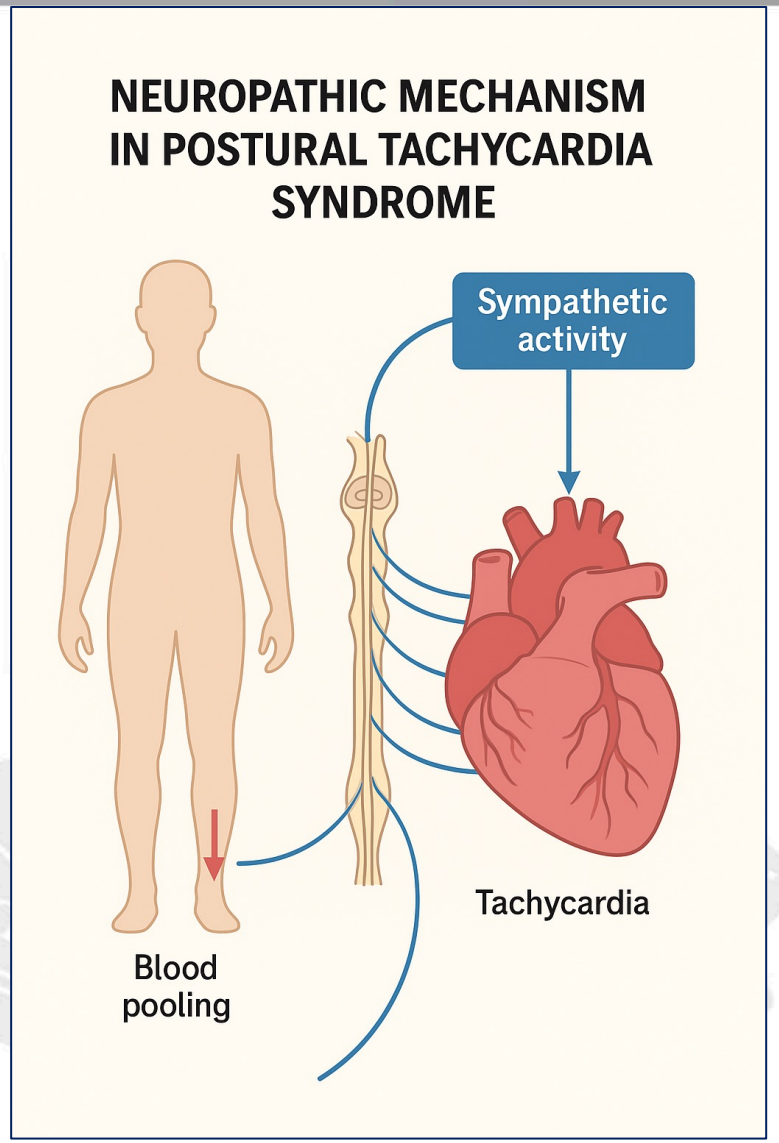
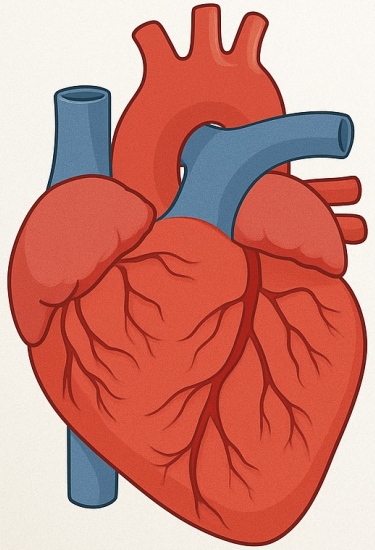


Fig. 1. Subtypes of POTS based on pathophysiology.
Small fiber neuropathy (SFN), norepinephrine transporter (NET), hEDS - Ehlers-Danlos Syndrome, hypermobility type



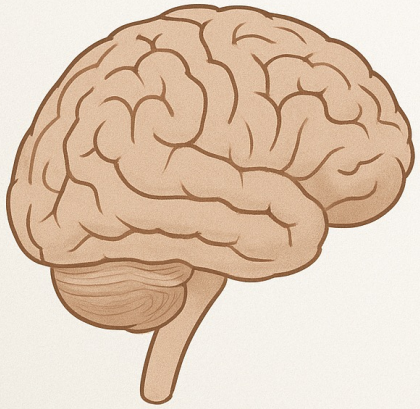
Zadourian, A.,*et al.*Postural Orthostatic Tachycardia Syndrome: Prevalence, Pathophysiology, and Management. *Drugs* **78**, 983–994 (2018)

POTS Clinical manifestations



Cardiac symptoms

- palpitations
- chest discomfort
- dyspnea
- exercise intolerance



Non-cardiac symptoms

- brain fog
- headache
- dizziness
- nausea
- tremors
- weakness
- fatigue

POTS Diagnosis

- **History:**

  - **exacerbating factors:**

dehydration, heat, alcohol, and exercise

  - **triggering factors:**

(e.g., viral infection, trauma, surgery, vaccination)

  - family history;

- **Physical examination**

  - orthostatic/tilt test **BP** and **Heart rate**

  - 12-lead ECG

- **Differential diagnosis:**

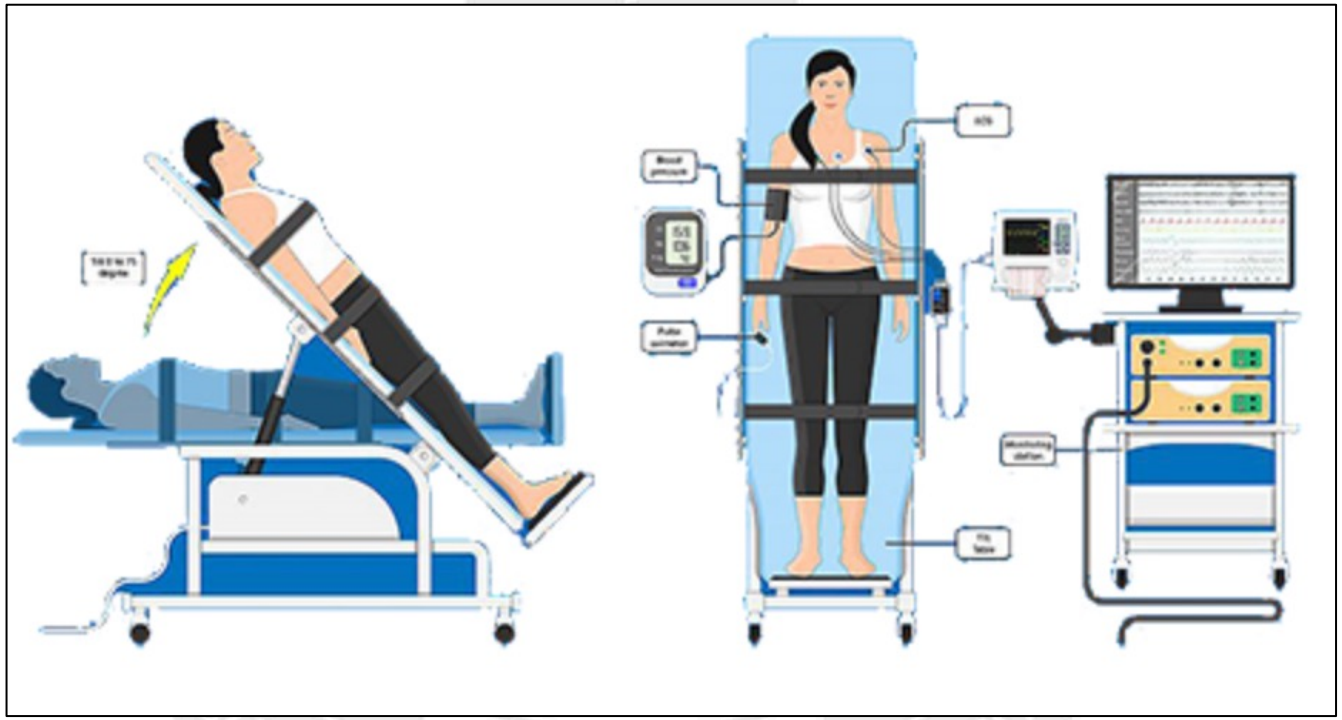
  - general blood test

  - thyroid gland function

  -EchoCG

  -Holter 24 hours MONITORING

  - stress test



Tilt test

POTS treatment

Intervention / Medication	Indicative doses
Avoiding aggravating factors (stimulants, antidepressants, alpha-blockers, CCBs, etc.)	—
Regular physical exercise	≥30 min/day, 4 days/week.
Fluid intake	~3 L/day
Salt intake	~10 g NaCl/day
Raising the head of the bed	>10° during sleep
Garments compression (high-waisted, abdomen + limbs)	—

POTS drug treatment

Drug	Indicative doses
Fludrocortisone	0.1–0.3 mg PO daily
Desmopressin	0.1–0.2 mg PO at need
Saline IV	1–2 L infused occasionally
Propranolol	10–20 mg PO, 4 times/day
Ivabradine	2.5–7.5 mg PO, 2 times/day
Pyridostigmine	30–60 mg PO, 3 times/day
Midodrine	2.5–15 mg PO, every 4 hours, 2–3 times/day
Octreotide	50–100 mcg SC, 3x/day or 10–30 mg IM long-acting
Methyldopa	125–250 mg PO at bed time or 2x/day
Clonidine	0.1–0.2 mg PO, 3 times/day

Orthostatic hypotension (OH): definition

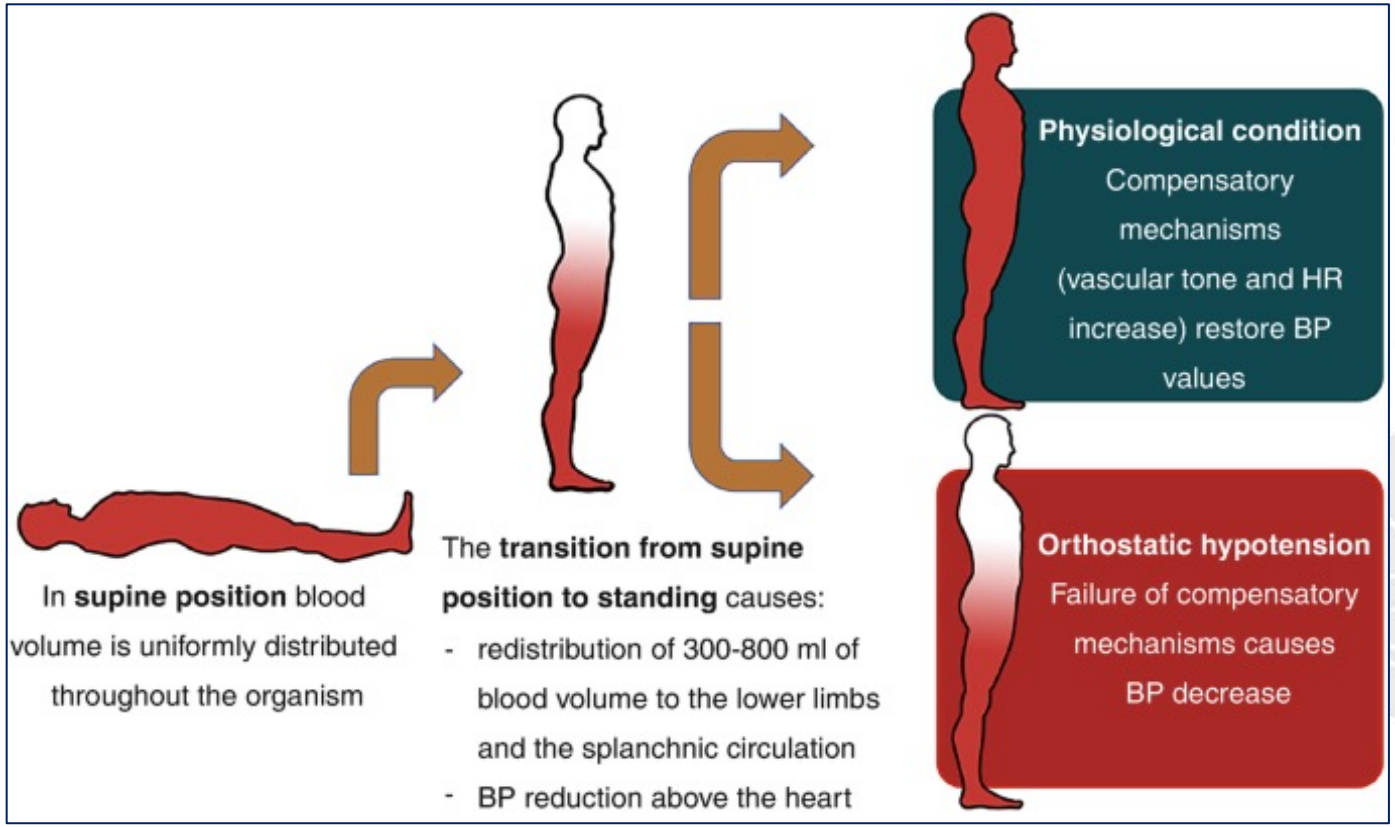
Classical OH:

- sustained reduction of:

systolic BP ≥20 mmHg

diastole BP ≥10 mmHg

- within 3 minutes of active standing or
- on a head-up tilt (HUT) test ≥60°



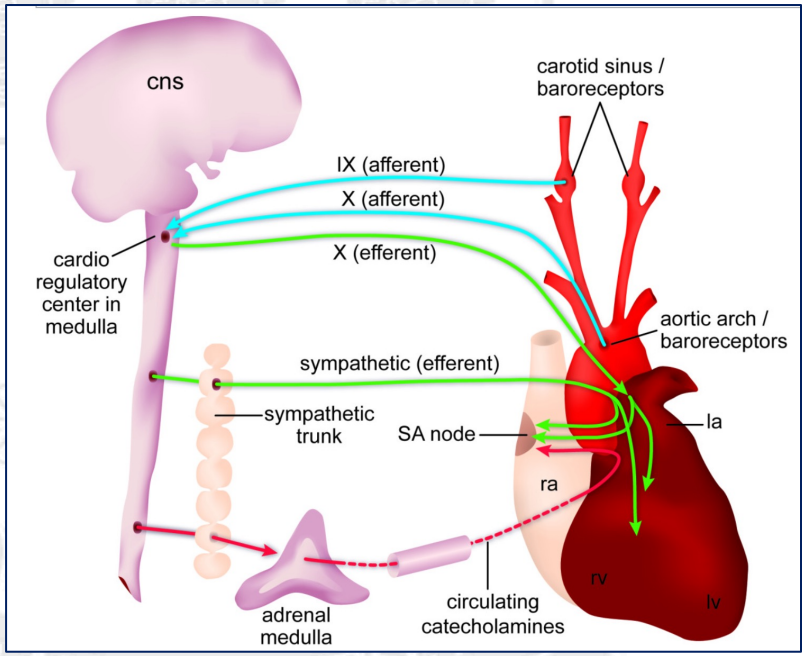


Fig. Diagram of sympathetic and parasympathetic regulation of the baroreceptor reflex.

Guaraldi, P., et al.(2022). Orthostatic Hypotension. Springer, Cham.; McNeill et al., 2010

Orthostatic hypotension: epidemiological data

- **OH Prevalence:**
  - 5% - in middle-aged adults
  - 20% - in older adults

- **Risk factors:** diabetes mellitus increases the prevalence of OH in all age groups.

- OH → Increased cardiovascular risk, falls and up to 50% relative risk of mortality from any cause

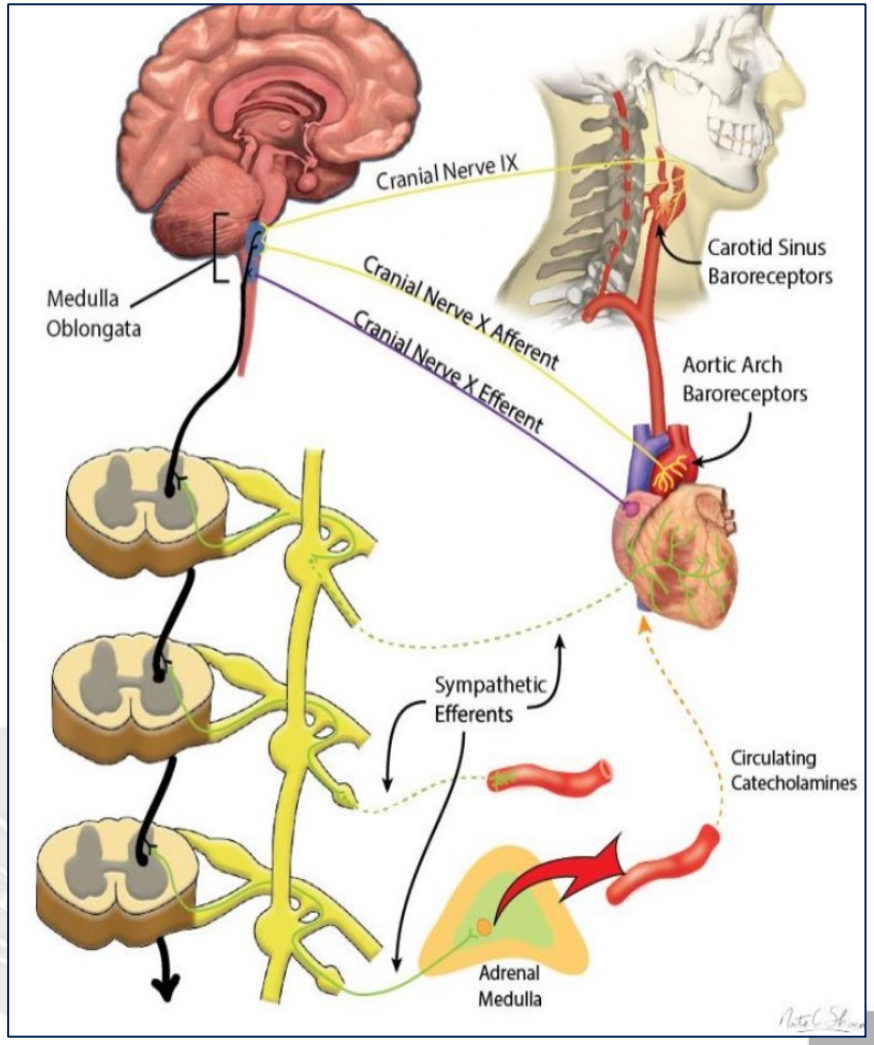


Fig. The baroreceptor mechanism

https://books.byui.edu/

OH Causes

Central causes (CNS damage)

1. Spinal cord diseases:
- Spinal cord injury
- Syringomyelia
- Transverse myelitis

2. Neurodegenerative diseases

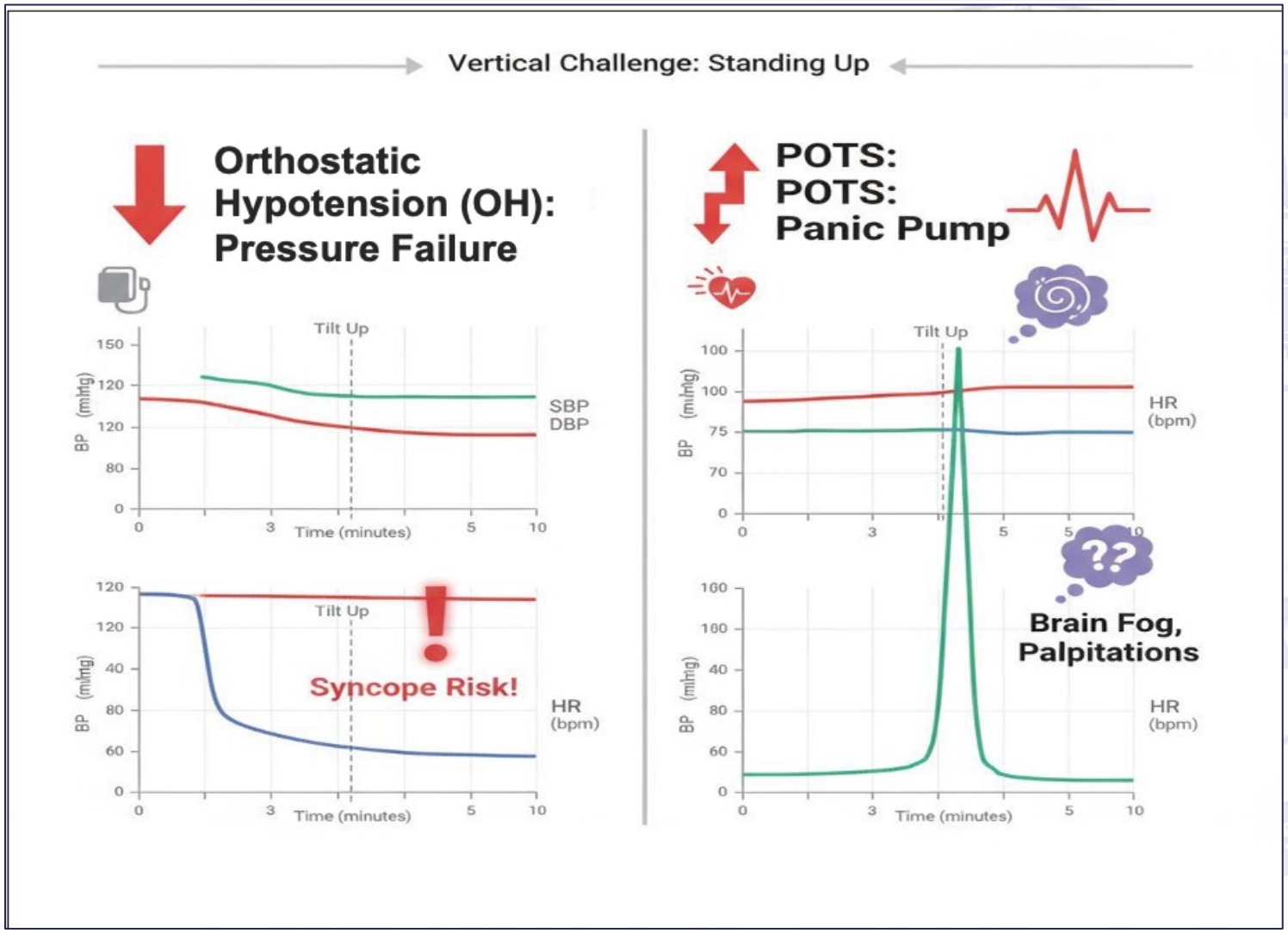
(α-synucleinopathies):
- Parkinson's disease
- Atrophymultisystem
- Dementia with Lewy bodies
- Pure autonomic failure

Peripheral causes (peripheral neuropathies)

1. **Diabetes mellitus**
2. **Acute autoimmune diseases:**
   - Autoimmune autonomic gangliopathies
   - Inflammatory neuropathies
   - Guillain-Barré syndrome
3. **Hereditary neuropathies:**
   - Familial amyloid polyneuropathy
4. **Acquired neuropathies:**
   - Vitamin B12 deficiency
   - Sjögren's syndrome
   - Systemic lupus erythematosus
   - Thyroid diseases
   - HIV infection

https://books.byui.edu/

POTS /OH


Vertical Challenge: Standing Up
Orthostatic Hypotension (OH): Pressure Failure
Tilt Up
BP (mmHg)
SBP
DBP
Time (minutes)
Tilt Up
Syncope Risk!
HR (bpm)
Time (minutes)
POTS: POTS: Panic Pump
Tilt Up
HR (bpm)
Brain Fog, Palpitations
Time (minutes)

Non-pharmacological treatment of OH

	Measures / Medications	Usual doses / Observations
💧	**Increasing water intake**	1.5–2 L/day
🧂	**Increasing salt intake**	6–10 g NaCl/day
🛏️	**Raising the head of the bed**	10–20° (reduces nocturnal diuresis and supine HT)
🦿	**Compression stockings, abdominal belts**	Reduce venous stasis
💪	**Physical countermeasures**	**Crossing legs, Abdominal and leg muscle pumping/contractions**
🚶	**Orthostatic exercises/training**	Progressive standing
🥗	**Diet**	Small, frequent, low-carbohydrate meals; avoiding alcohol
🌞	**Lifestyle**	Avoiding prolonged standing, morning/postprandial activities

💧 + 🧂 + 🛏️ + 🦿 + 💪 + 🚶 + 🥗 + 🌞 = **Hemodynamic stability**

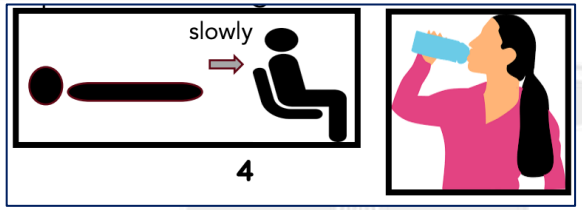
Pharmacological treatment of HO

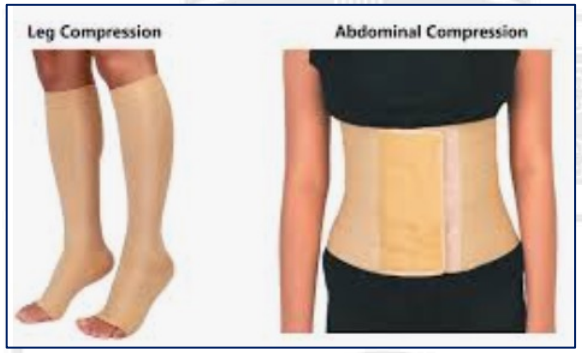
Measures / Medications	Usual doses / Observations
Fludrocortisone	0.1–0.3 mg/day;grow VOLUME plasma and sensitivityto catecholamines
Midodrine	2.5–10 mg x 3 times/day;α1-agonist, increases BP
Ephedrine	25–50 mg x 3 times/day
Pseudoephedrine	30 mg x 4 times/day
Droxidopa (L-DOPS)	100–600 mg x 3 times/day (available in USA/Japan)
Octreotide	12.5–25 µg SC, useful for postprandial hypotension
Pyridostigmine	60 mg x 3 times/day
Other options	Desmopressin, yohimbine, dihydroergotamine, domperidone, atomoxetine, erythropoietin

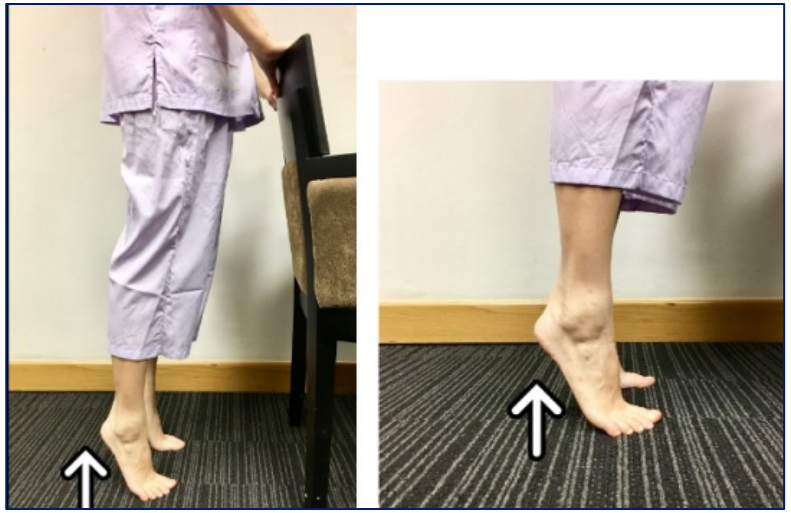
Orthostatic Hypotension treatment algorithm

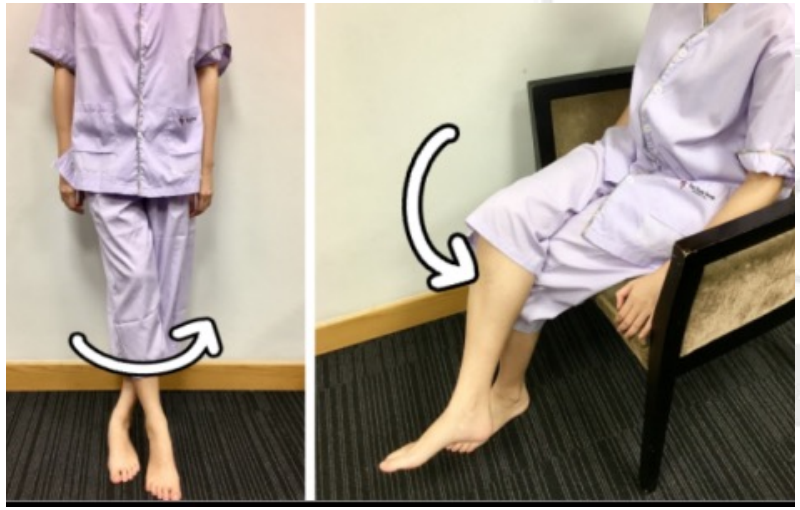
Algorithm:

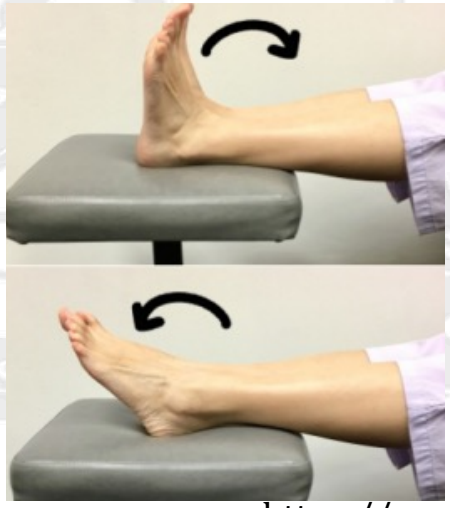
1. **Non-pharmacological measures.**
2. If insufficient →
    - 2.1. Fludrocortisone (first line).
    - 2.2. Midodrine (second line).
3. Special cases → other drugs (octreotide for postprandial HO, pyridostigmine, etc.).











https://www.ttsh.com.sg/

Bladder Autonomic Disorders

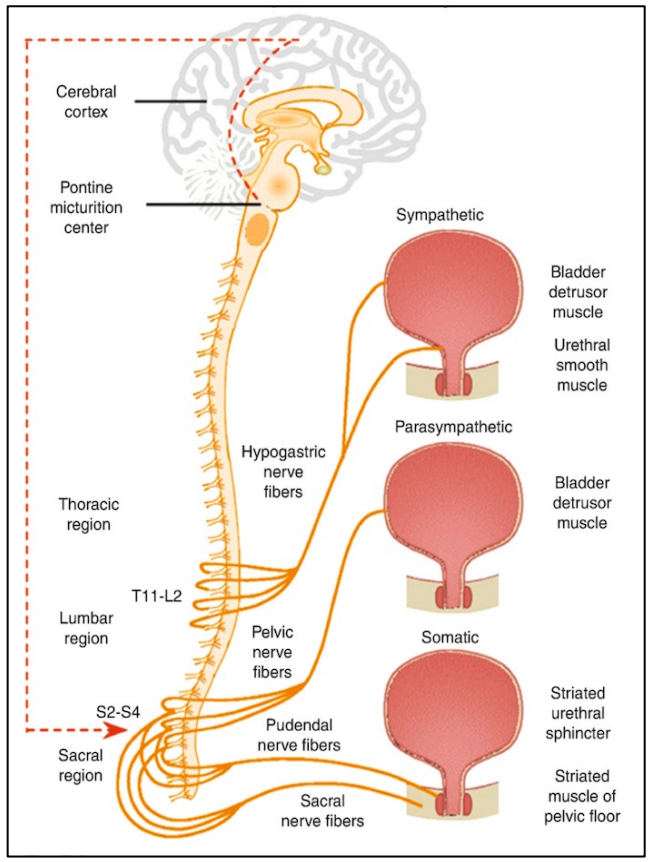


Fig. Central and peripheral control of urination (Hanno P et al. 2014)

Neurogenic dysfunction	Location	Manifestation	Pathologies
Detrusor hyperreflexia	**Above the sacral spinal cord**	Imperative urinary urgency and low residual volume	MS, CVD, Parkinson disease, Spinal cord trauma, TBI
Detrusor–Sphincter Dyssynergia	**Between the sacral spinal cord and the pontine micturition center**	Imperative urinary urgency with incomplete bladder emptying	Cervical myelopathy, MS, Spinal tumors/traumas, Vascular malformations
Detrusor areflexia	**The sacral spinal cord or peripheral nerves**	Reduced need to urinate, inability to initiate micturition	Conus medullaris tumors GBS, spinal tumors Tabes dorsalis Diabetic polineuropathy

MS - multiple sclerosis
CVD – cerebrovascular disease
TBI – spinal cord trauma/traumatic brain injury

Horner's syndrome

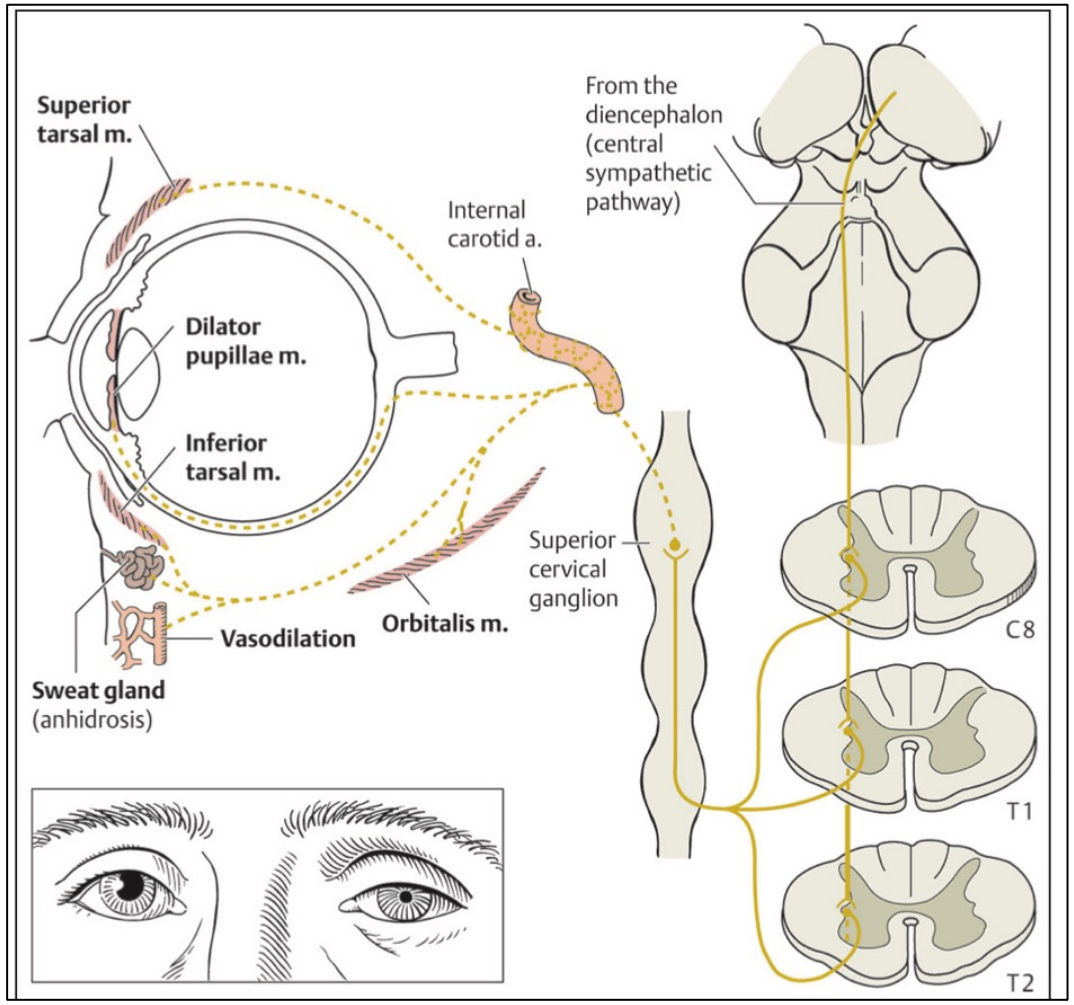


Fig. Sympathetic innervation of the eye and Horner syndrome

Clinical manifestations:

1. **Ptosis** secondary to paralysis of the superior tarsal muscle,
2. **Miosis** (m. dilator of the pupil),
3. **Pseudoenophthalmia,**
4. **Anhidrosis or hypohidrosis**

Causes:

- Cerebral or cervical trauma ,
- Lateral medullary syndrome,
- Stroke, Cerebral hemorrhage,
- Multiple sclerosis,
- Syringomyelia, Acute transverse myelopathy,
- Apical lung tumors,
- Thoracic aortic aneurysms,
- Carotid artery dissection
- Cluster headache

So the Christmas tree becomes a simple picture of the brain: a star that balances, lights that react, and ornaments that store memories and emotions.

Headaches

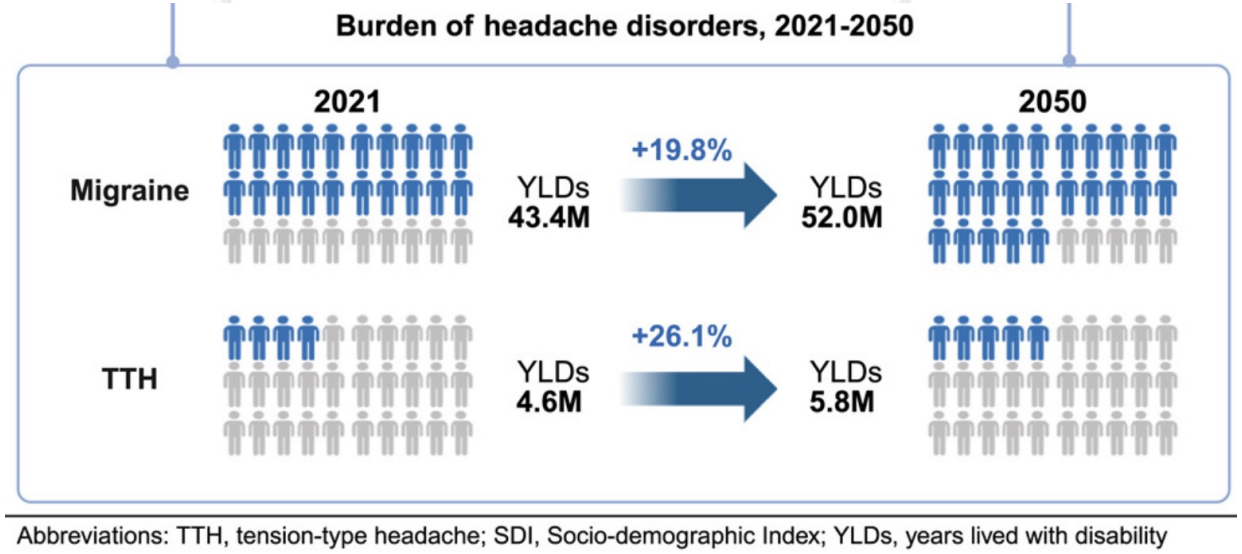
Headache: epidemiological data

Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2021
Institute for Health Metrics and Evaluation

- The **second most common** disease globally,
- Affects ~ **2.8 billion people**
- The **3 leading cause of years lived with disability** (YLD), after low back pain and major depressive disorder.

Migraine and tension-type headache (TTH) – the most common types of headache:

- Migraine - 1.2 billion people;
- TTH - 2.0 billion



GBD 2021 Headache Collaborators Wijeratne et al., Global, regional, and national burden of headache disorders, 1990–2021, with forecasts to 2050: A Global Burden..., Cell Reports Medicine (2025)

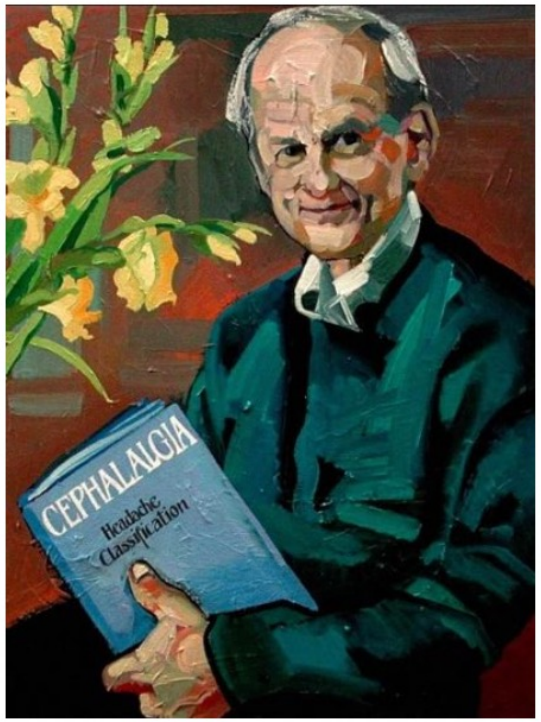
International Classification of Headache Disorders

International Classification of Headache Disorders – developed by the Headache Classification Committee of the International Headache Society (ICHD – 3rd edition, 2018)

https://ichd-3.org/

https://ihs-headache.org/wp-content/uploads/2022/08/ICHD-3-Romanian-rv.pdf

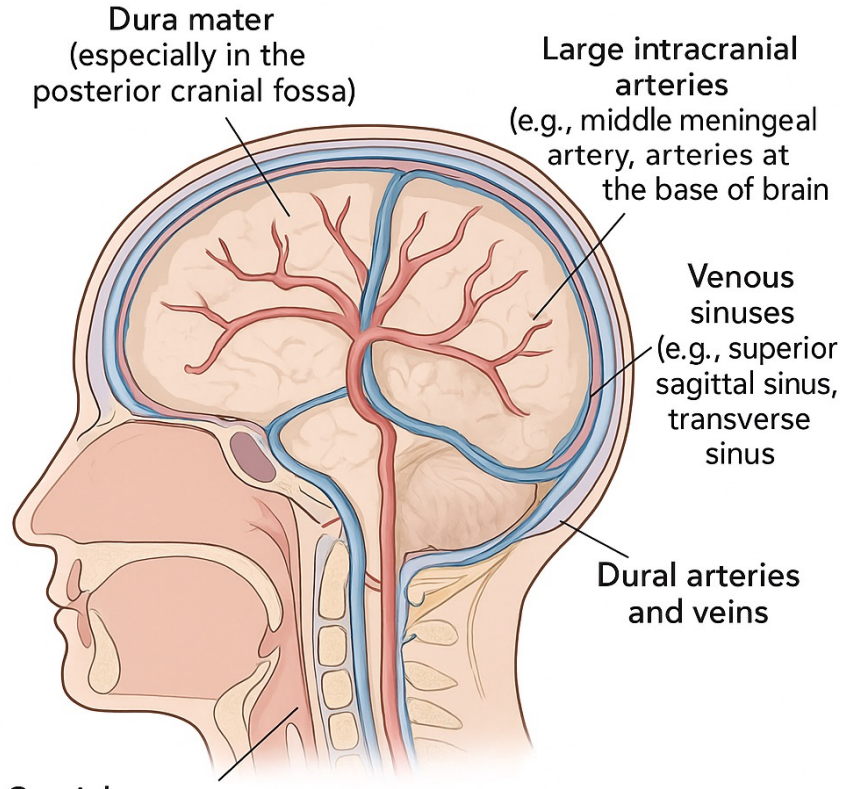
ICHD-I – 1998
ICHD-II – 2004
ICHD-III – 2018



Jes Olesen
Chairman
Headache Classification Committee
International Headache Society

Pain innervation of head and brain structures

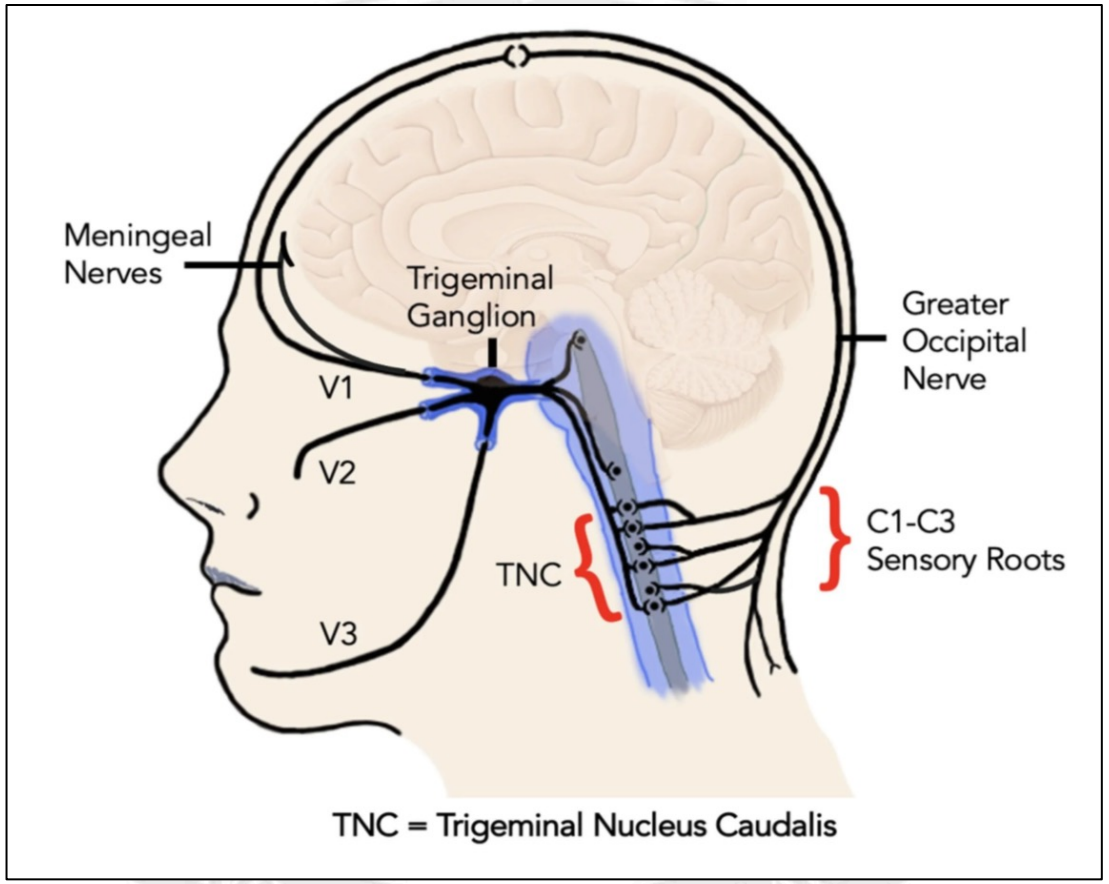
Structures Sensitive for Pain in the Dura Mater and Cranial Cavity



Trigeminal nerve (CN V)
Vagus nerve (CN X)
Glossopharyngeal nerve (CN IX)
Upper cervical spinal nerves (C1-C3)

✓ The brain parenchyma itself is NOT sensitive to pain

✗ The brain parenchyma itself is NOT sensitive



TNC = Trigeminal Nucleus Caudalis

International Classification of Headache Disorders (II)

Part I: The primary headaches

1. Migraine
2. Tension-type headache (TTH)
3. Trigeminal autonomic cephalalgias (TACs)
4. Other primary headache disorders

International Classification of Headache Disorders (III)

Part II: The secondary headaches

5. Headache attributed to **trauma or injury to the head and/or neck**

6. Headache attributed to **cerebral and/or neck vascular disorders**

7. Headache attributed to **non-vascular intracranial disorders**

8. Headache attributed to **substance use or withdrawal**

9. Headache **attributed to infection**

10. Headache attributed **to disorders of homeostasis**

11. Headache or **facial pain attributed to pathology of the skull, neck, eyes, nose, ears, sinuses, teeth, oral cavity or other facial or neck structures**

12. Headache attributed **to psychiatric disorders**

International Classification of Headache Disorders (IV)

Part III: Neuropathies & Facial Pains and other headaches

13. Painful lesions of the cranial nerves and other facial pain

- 13.1 Pain attributed to a lesion or disease of the trigeminal nerve
- 13.2 Pain attributed to a lesion or disease of the glossopharyngeal nerve
- 13.3 Pain attributed to a lesion or disease of nervus intermedius
- 13.4 Occipital neuralgia
- 13.5 Neck-tongue syndrome
- 13.6 Painful optic neurites
- 13.7 Headache attributed to ischaemic ocular motor nerve palsy
- 13.8 Tolosa-Hunt syndrome
- 13.9 Paratrigeminal oculosympathetic (Raeder's) syndrome
- 13.10 Recurrent paiful ophtalmoplegic neuropathy
- 13.11 Burning mouth syndrome (BMS)
- 13.12 Persistent idiopathic facial pain (PIFP)
- 13.13 Central neuropathic pain

14. Other Headache Disorders

Migraine classification

1. Migraine

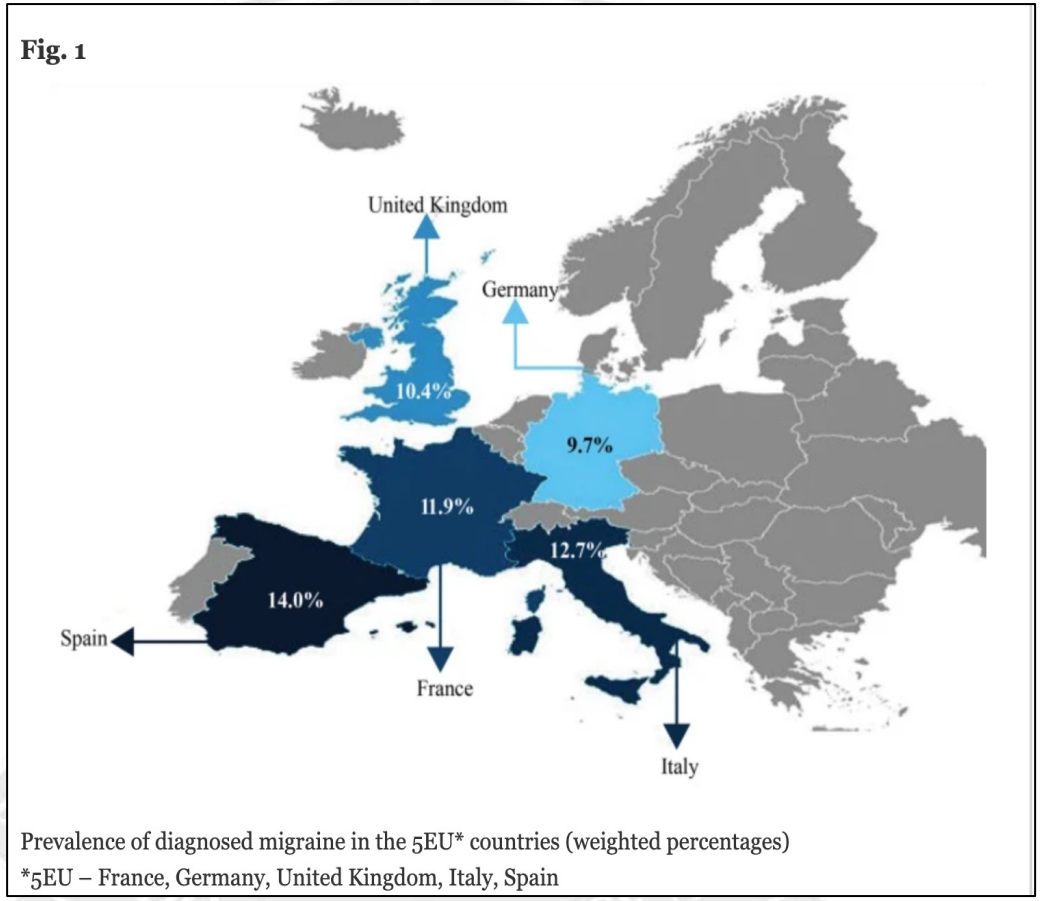
1.1 Migraine **without aura**

1.2 Migraine **with aura**

1.3 **Chronic** migraine

1.4 **Complications** of migraine

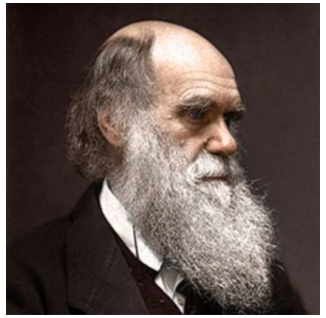
- **Prevalence** – about **11.7%**
- **2 leading cause** of **disability** worldwide and
- 1st among young women (15-49 years)
- **F : M – 2 : 1**



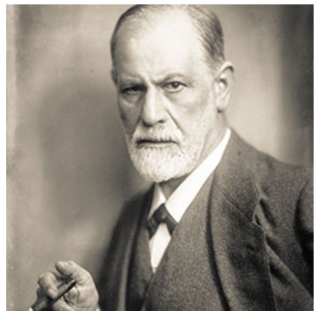
Migraine prevalence in 5 European countries

Coppola, G., *et al.* The epidemiology and unmet need of migraine in five european countries: results from the national health and wellness survey. *BMC Public Health* **25**, 254 (2025).

Famous personalities affected by migraine



Charles Darwin

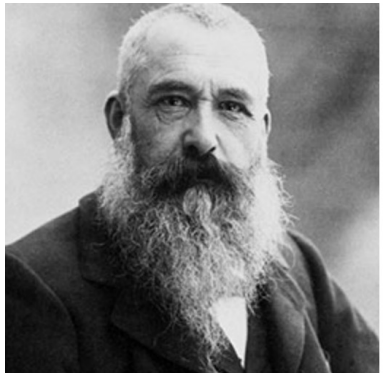


Sigmund Freud

Lewis Carroll

Vincent van Gogh

"The Starry Night", 1889



Claude Monet

„Having a migraine"

Pablo Picasso

„Guernica", 1937

Migraine etiology

- **Genetic factors**
- risk of migraine in affected relatives is 3 times higher
- no specific inheritance pattern has been identified
- Neurological factors
- abnormal brain activity involving nerve pathways, brain chemicals such as serotonin, and blood flow.
- Hormonal/environmental factors

- FHM1 - mutations in the CACNA1A gene (encoding a calcium channel) on chromosome 19;
- FHM2 - mutations in the ATP1A2 gene (encoding K/Na ATPase) on chromosome 1
- FHM3 - mutations in the SCN1A gene (encoding a sodium channel) on chromosome 2

Migraine etiology

Genetic Factors

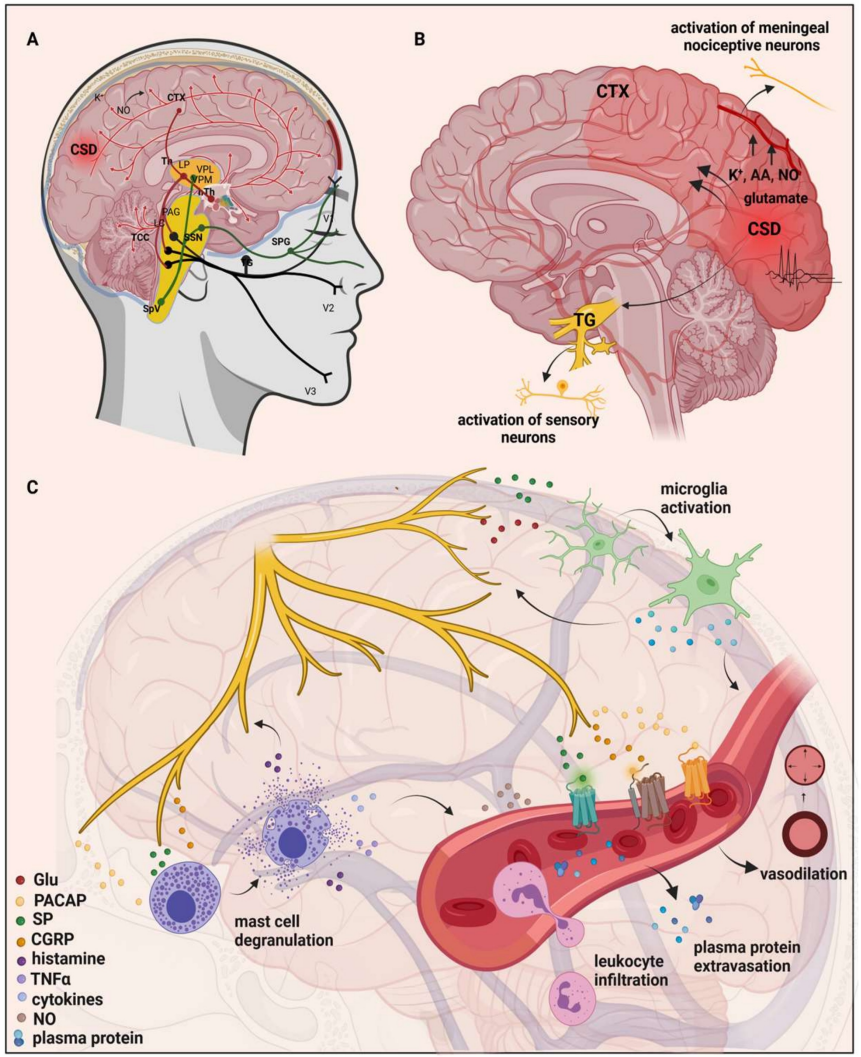
- Risk of migraine is 3 × higher in individuals with affected first-degree relatives
- No specific inheritance pattern has been clearly identified in common migraine forms

Neurological Factors

- Involve abnormal brain activity affecting:
  - Neural pathways
  - Neurotransmitters (especially serotonin)
  - Cerebral blood flow

Familial Hemiplegic Migraine (FHM) — Genetic Subtypes

Subtype	Gene	Protein / Function	Chromosome
FHM1	*CACNA1A*	Encodes a P/Q-type calum chan	19
FHM2	*ATP1A2*	Encodes a Na^+/K^+ ATPase pump	1
FHM3	*SCN1A*	Encodes a voltage-gated sodium	2



Migraine without aura: diagnostic criteria

A. At least 5 attacks fulfilling **criteria B-D**

B. Headache attacks lasting **4-72 hours** (without treatment or after unsuccessful treatment)

C. Headache has **at least 2 of the following 4 features**:

1. **unilateral** location
2. **pulsatile** quality
3. **moderate or severe** pain intensity
4. **aggravation by routine physical activity** or avoidance of activities (e.g. walking or climbing stairs)

D. **At least one** of the following occurs during the headache:

1. nausea and/or vomiting
2. photophobia and phonophobia

E. Not otherwise specified CITC-3 diagnosis

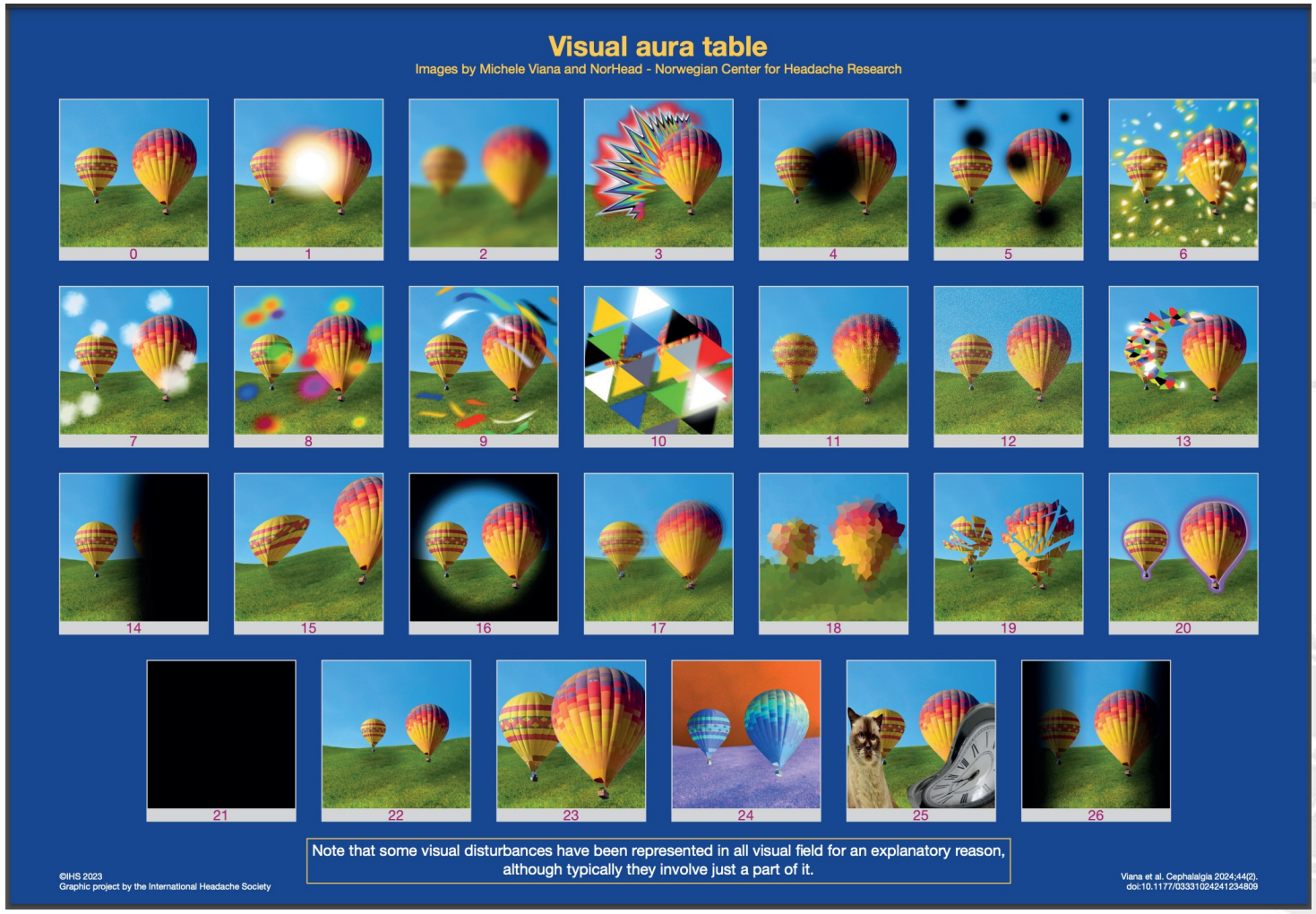
Migraine with aura: (I)

- **Recurrent attacks,** lasting a few minutes, of unilateral, fully reversible neurological symptoms in the visual, sensory, or other focal neurological signs that develop gradually and are usually followed by headache and associated symptoms.

Aura - Latin *aura* ("breeze" or "blow") – derived from the ancient Greek word *aúra* (αὔρα).

- **Focal neurological sign(s):**
  1. visual
  2. sensory
  3. speech and/or language disorder
  4. motor
  5. brainstem
  6. retinal
- **develops gradually** > 5 minutes
- each individual aura symptom **lasts 5-60 minutes**
- aura is accompanied by, or followed **within 60 minutes by, headache**

Migraine with aura: (II)

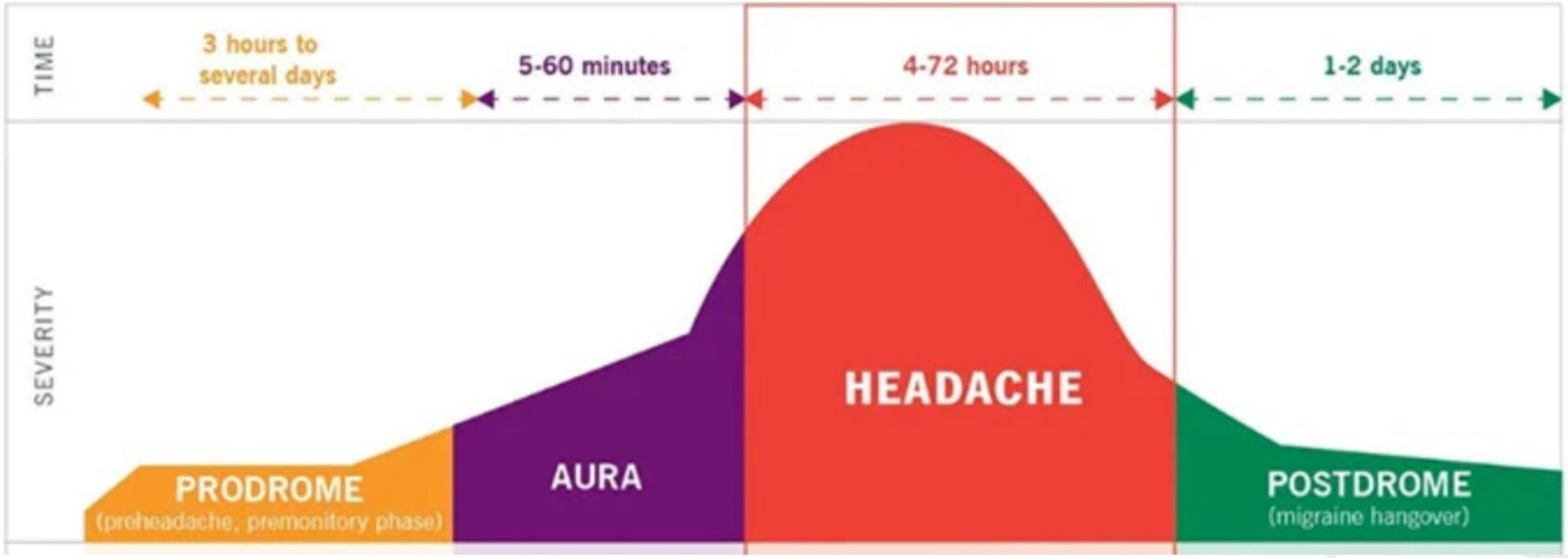


- 30-40% of patients diagnosed with migraine
- Visual aura - in over 90% of patients
- Pathophysiological mechanism –

“Cortical spreading depression”

Viana M, Hougaard A, Tronvik E, et al. Visual migraine aura iconography: A multicentre, cross-sectional study of individuals with migraine with aura. *Cephalalgia*. 2024;44(2).

Phases of migraine



1. **Prodrome –** symptoms lasting hours or 1-2 days
2. **Aura -** 5 - 60 minutes
3. **Migraine attack** - 4 -72 h
4. **Postdrome** - > 48 h

- Fatigue,
- Difficulty concentrating,
- Stiff neck,
- Sensitivity to light and/or sound,
- Nausea,
- Blurred vision,
- Yawning and paleness

- Feeling tired
- Difficulty concentrating
- Stiff neck

https://www.advancedheadachecenter.com/migraines/migraine-stages

Pathophysiological mechanisms

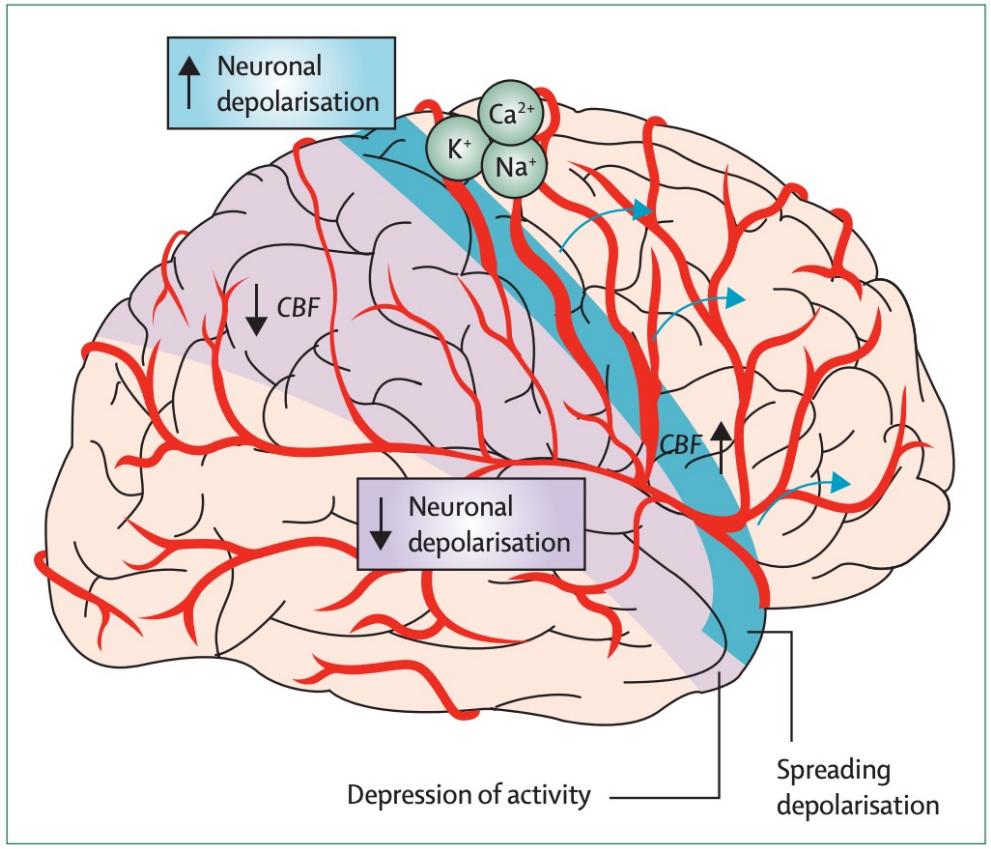


***Figure 1*: Migraine aura is caused by cortical spreading depression**

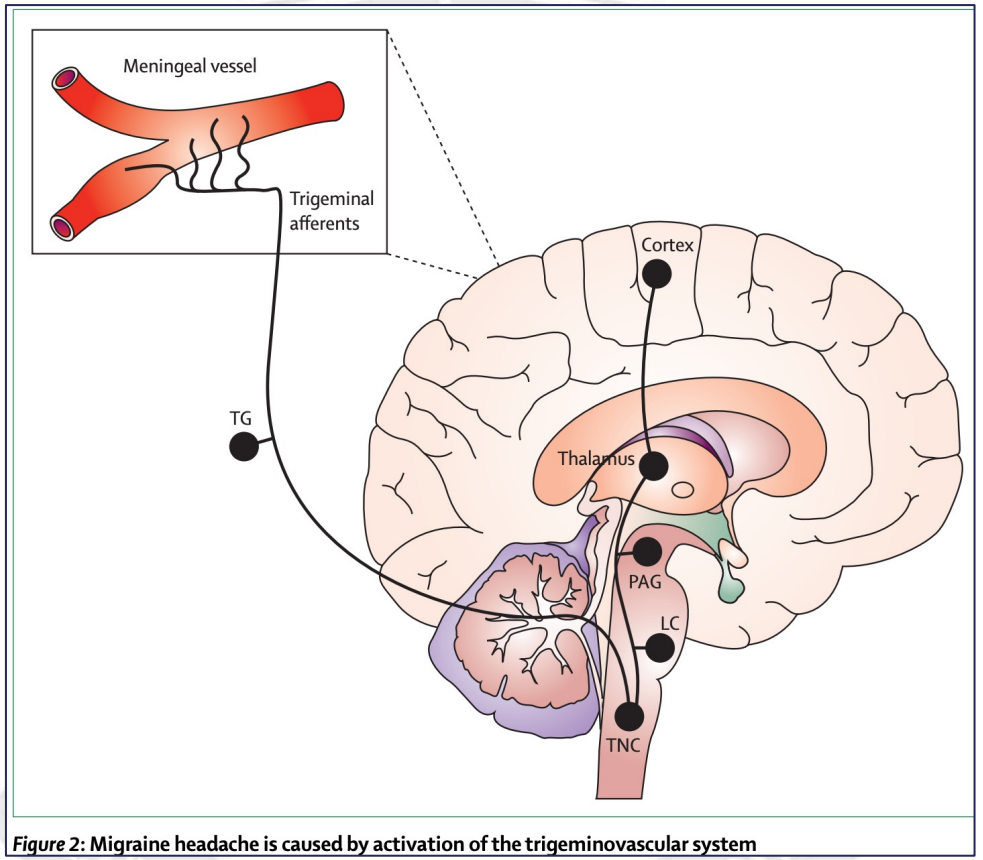
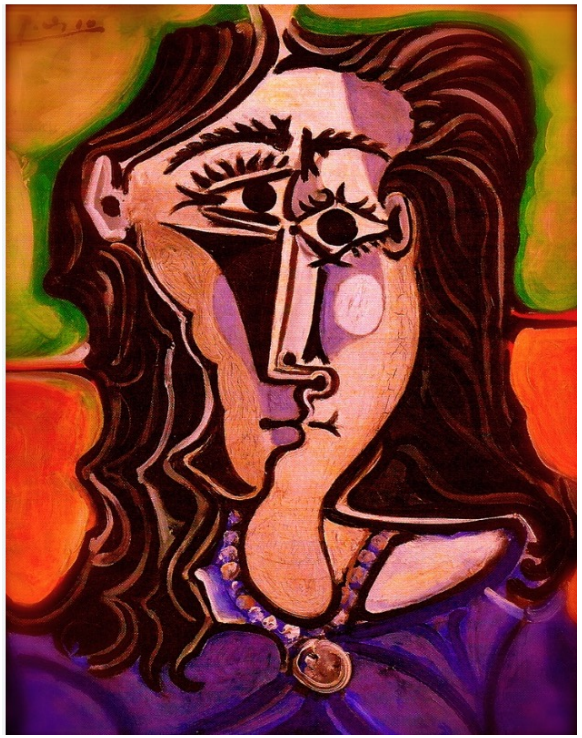


***Figure 2*: Migraine headache is caused by activation of the trigeminovascular system**

Ferrari, Michel D et al. Migraine pathophysiology: lessons from mouse models and human genetics. The Lancet Neurology, Volume 14, Issue 1, 65 – 80, 2015

Migraine treatment



- Abortive therapy – stopping migraine attacks
- Preventive therapy – reducing migraine occurrence (daily administration)

Abortive therapy

- **NSAIDs/ Analgesics**
- **Triptans**
- **Ergot alkaloids**
- **Ditans**
- **Gepants**
- **Antiemetics**

Drug Group / Medication	Pharmacologic Action	Dose
NSAIDs / Analgesics		
Acetylsalicylic acid	COX-1/2 receptor antagonist	500–1000 mg orally
Ibuprofen	COX-1/2 receptor antagonist	400–600 mg orally
Naproxen	COX-1/2 receptor antagonist	250–550 mg orally
Paracetamol (acetaminophen)	Inhibits prostaglandin synthesis	1000 mg orally
Triptans	5-HT receptor agonists	
Sumatriptan	Selective 5-HT1D agonist	5–10 mg orally
Rizatriptan	Non-selective 5-HT1B/1D agonist	50–100 mg orally; nasal spray 10–20 mg; s/c 3–6 mg
Almotriptan, Frovatriptan, Naratriptan, Zolmitriptan, Eletriptan	Non-selective 5-HT1B/1D/1F agonists	Standard oral doses
Ergot Alkaloids		
Ergotamine tartrate	Non-selective 5-HT1D agonist	1 mg orally; suppository 2 mg
Dihydroergotamine	Non-selective 5-HT1B/1DA agonist	Nasal 0.725 mg; IM 0.5–1 mg; IV 0.5–1 mg
Ditans		
Lasmiditan	5-HT1F receptor agonist	50–200 mg orally
Gepants	CGRP receptor antagonists	Standard oral doses
Rimegepant, Ubrogepant, Zavegepant		
Antiemetics Metoclopramide	Dopamine antagonist	10 mg orally

Preventive therapy

Drug group	Pharmacological activity	Dosage
B-blockers • Propranolol	Non-selective beta-1 and beta-2 receptor antagonist	120–240 mg/day
Antidepressants • Amitriptyline • Venlafaxine	Tricyclic antidepressant Serotonin and Noradrenaline reuptake inhibitor	25–150 mg/day 37.5–300 mg/day
Antiepileptic • Topiramate • Valproic acid	Sodium channel blockers/ NMDA receptor antagonist /GABA modulation - GABA transaminase inhibitor	25–200 mg/day 400–2000 mg/day
Ca channel blockers^{2+} • Flunarizine	Ca channel blockers^{2+}	5–10 mg/day
Monoclonal antibodies • Galcanezumab • Fremanezumab • Eptinezumab • Erenumab	It bind and inhibit CGRP **Erenumab is an CLR/RAMP1 antagonist	
• Atogepant	CLR/RAMP1 receptor antagonist	
• **Onabotulinum toxin**	Cleavage SNAP-25 for acetylcholine release inhibition	

2. Tension-type headache (TTH)

2. Tension type headache (TTH)

2.1 **Infrequent episodic** tension-type headache

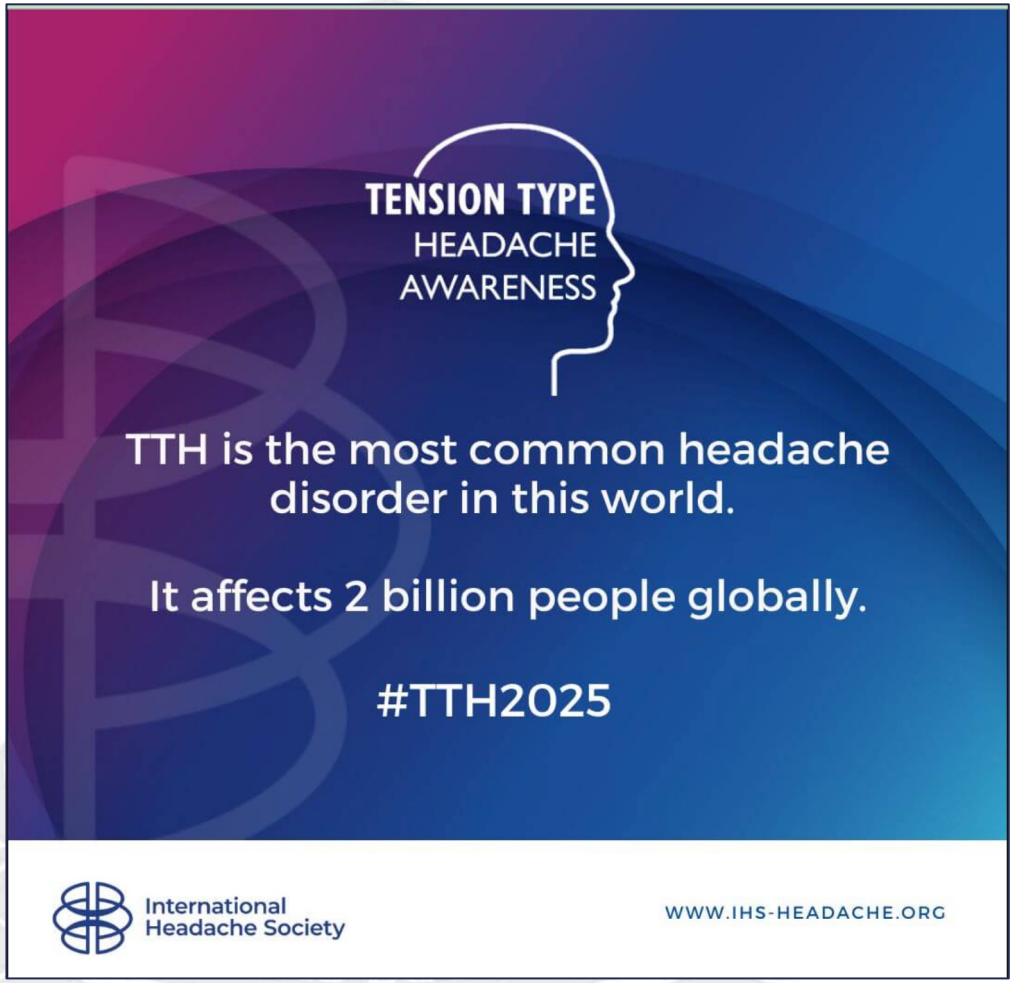
2.2 **Frequent episodic** tension-type headache

2.3 **Chronic** tension-type headache

2.4 **Probable** tension-type headache

In function of headache frequency :

- **Infrequent episodic** TTH **(<1 day per month**)
- **Frequent episodic TTH (1-14 days per month)**
- **Chronic TTH (≥15days on month)**



https://ihs-headache.org/

TTH: Diagnostic criteria

A. At least **10 headache episodes** that meet criteria **B-D**

B. Last from **30 minutes to 7 days**

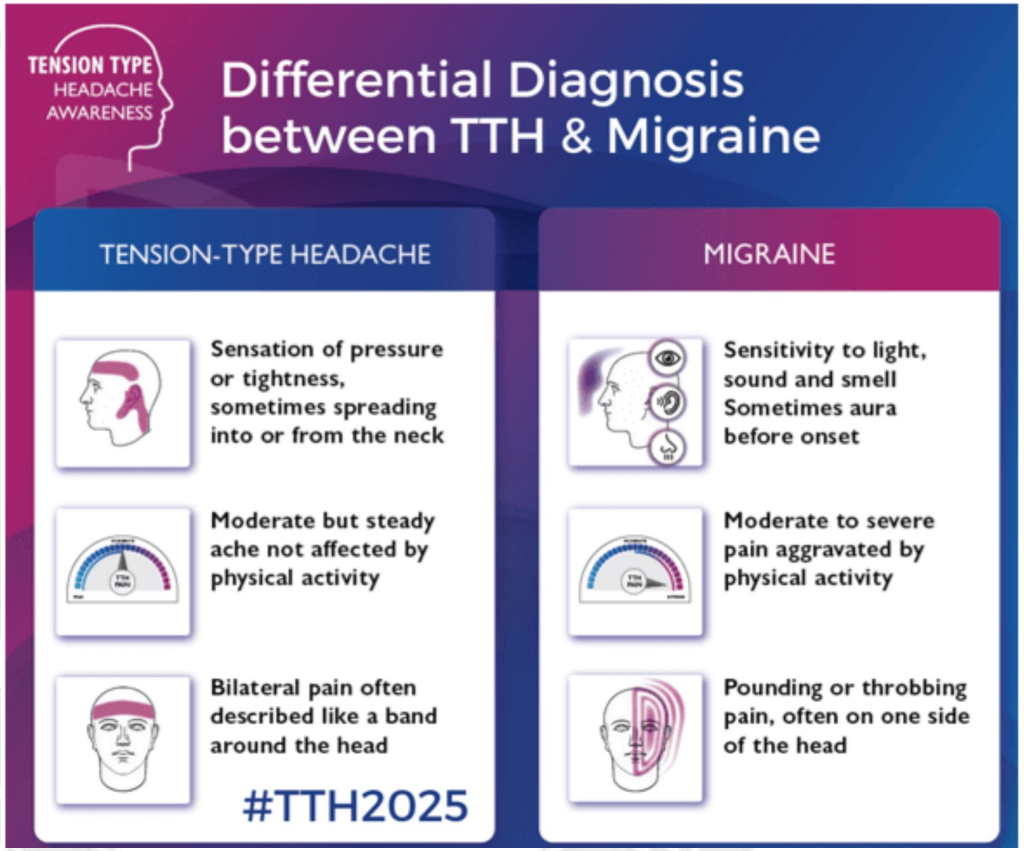
C. At least **two of the following** four features:

1. bilateral location
2. pressing or tightening (non-pulsating) quality
3. mild or moderate intensity
4. not aggravated by routine physical activities such as walking or climbing stairs

D. **Both** of the following:

1. no nausea or vomiting
2. no more than one of photophobia or phonophobia

E. Not better accounted for by another ICHD-3 diagnosis



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TTH: Pathophysiological mechanisms

- **Peripheral mechanisms: episodic TTH**

Sustained pericranial muscle tension

↓

Peripheral nociceptors sensitization

- **Central mechanisms: chronic TTH**

Sensitization of 2nd order neurons of the V nerve and Dorsal horns at C3-C4

↓

Supraspinal neurons sensitization

↓

Alteration of pain processing mechanisms

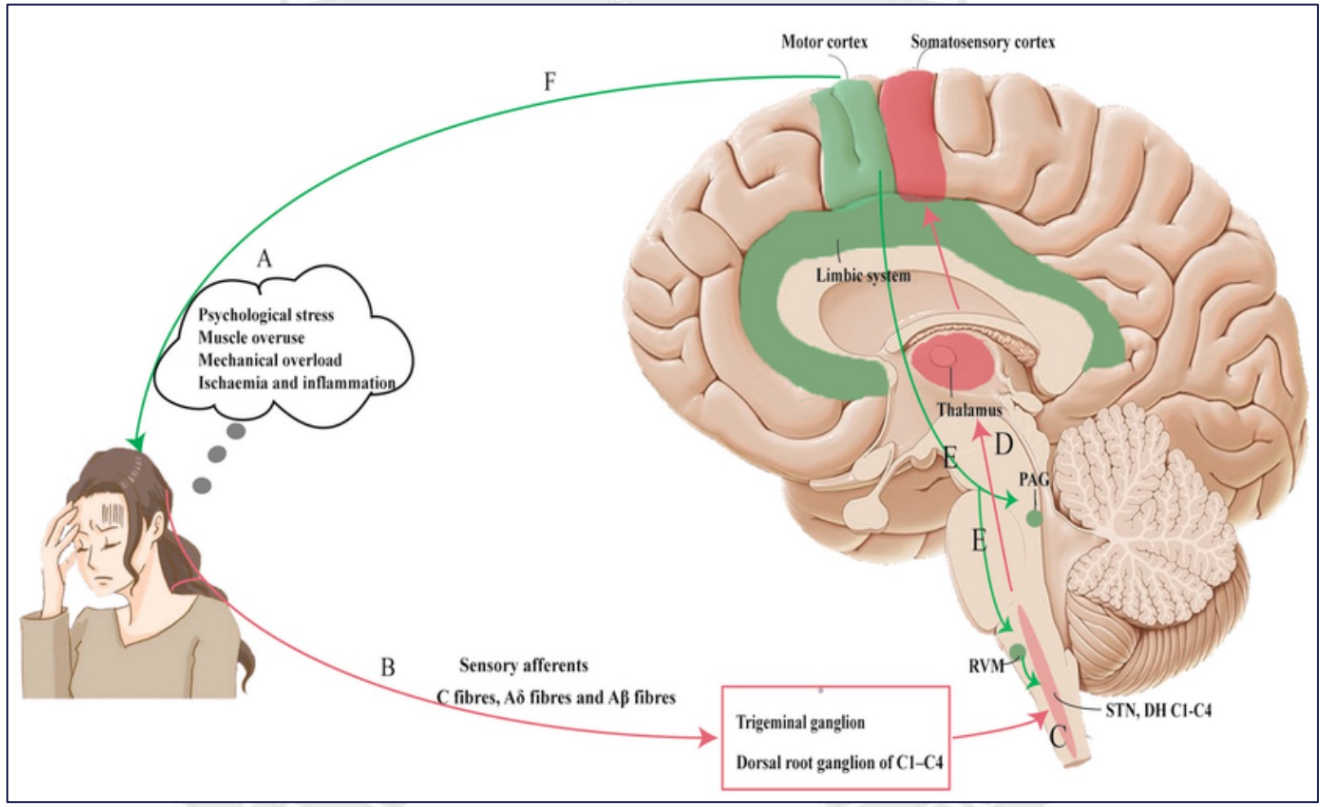


Fig. 1 Pathophysiological model of TTH

Guo-jing Fu, liu-ding Wang et al. (2024) 28:439–451

Central mechanisms in TTH

- **CNS dysfunction**
  - Impaired central pain processing: ***anterior cingulate cortex, insula, and prefrontal cortex***
  - Central sensitization
- **Role of neurotransmitters and mediators**
  - Involvement **of nitric oxide (NO)**
  - **CGRP:** possible role in the progression/remission of chronic TTC
- **Factors favoring central sensitization**
  - Chronic stress
  - Insufficient sleep
  - Poor post-effort relaxation
  - Self-perceived poor general health

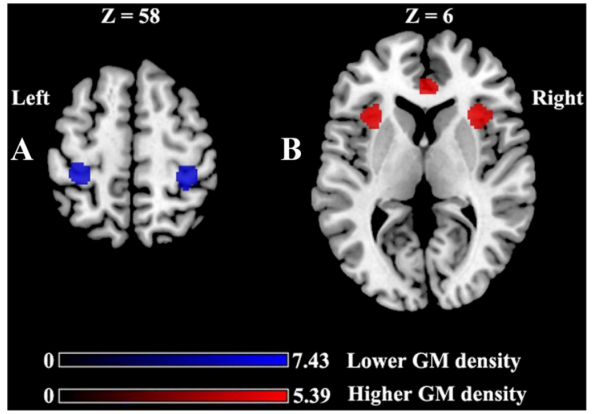


Fig. 1 a: lower GM density in the bilateral primary somatosensory cortex, **b**: higher GM density in the bilateral anterior cingulate cortex and anterior insula

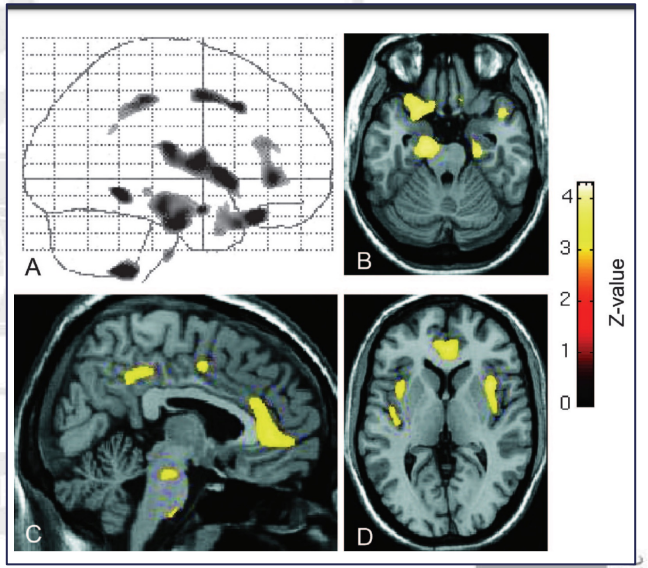


Fig. T1-weighted brain MRI, voxel-based morphometric investigation.

Chen et al., 2016. Schmidt-WilckeT, 2005

TTH treatment

- **Pharmacological**
- **Non-pharmacological**

- **Purpose:**
  - pain relief
  - restoration of function
  - improving the quality of life

- **Comorbidities:**
  - anxiety
  - depression
  - sleep disorders
  - neck pain or other painful conditions

https://ihs-headache.org/

TTH treatment

Infrequent episodic CTT

- access level:

Paracetamol	1000 mg
Acetaminophen	
Ibuprofen	200–800 mg
Acetylsalicylic acid	500-1000mg
Caffeine comb.	65-200mg

- lifestyle change:

sleep hygiene

realignment techniques (meditation, yoga)

diaphragmatic breathing

hydration

-physical therapy:massage

- **Frequent/chronic episodic CTT**

(10 -14/month /> 15/month)

-prophylactic drug treatment

- behavioral interventions

- non-invasive physical therapy (massage, physiotherapy, ultrasound, electrical stimulation)

- multimodal treatment

Prophylactic therapy for frequent episodic/ chronic TTH

Substance	Daily dose	Recommendation level
First-choice drug		
• **Amitriptyline**	30–75 mg	A
Second-choice drugs		
• **Mirtazapine**	30 mg	B
• **Venlafaxine**	150 mg	B
Third-choice drugs		
• **Clomipramine**	75–150 mg	B
• **Maprotiline**	75 mg	B
• **Mianserin**	30–60 mg	B

Bendtsen, L., et al. (2010), EFNS guideline on the treatment of tension-type headache – Report of an EFNS task force. European Journal of Neurology, 17: 1318-1325.

Trigeminal autonomic headaches

3. **Trigeminal autonomic cephalalgia (TAC)**

- 3.1 Cluster headache
- 3.2 Paroxysmal hemicrania
- 3.3 Short-lasting unilateral neuralgiform headache attacks
- 3.4 Continuous hemicrania
- 3.5 Probable trigeminal autonomic headache

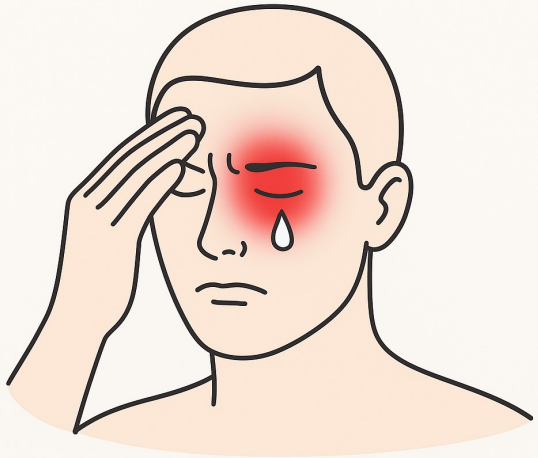
Cluster headache – prevalence 0.1% of studied populations

Cluster Headache: diagnostic criteria:

1. At least **five attacks** fulfilling criteria B-D
2. **Severe or very severe unilateral orbital**, supraorbital and/or temporal pain lasting **15-180 minutes** (when untreated)[1]
3. Either or both of the following:
   1. **at least one of the following symptoms** or signs, ipsilateral to the headache:
      - **conjunctival injection and/or lacrimation**
      - **nasal congestion and/or rhinorrhoea**
      - **eyelid oedema**
      - **forehead and facial sweating**
      - **miosis and/or ptosis**

      parasympathetic activation

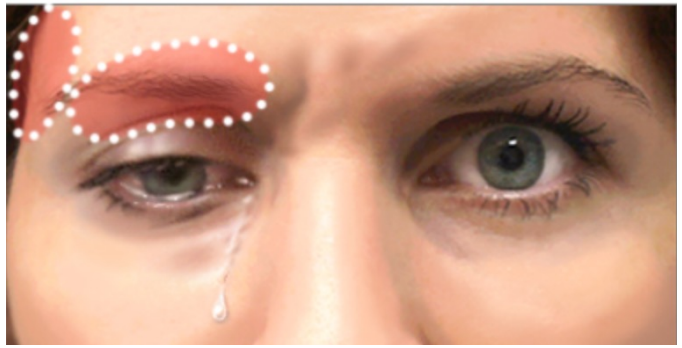
      sympathetic activation
   2. a sense of **restlessness or agitation**
4. Occurring with a frequency between **one every other day and 8 per day**[2]
5. Not better accounted for by another ICHD-3 diagnosis.

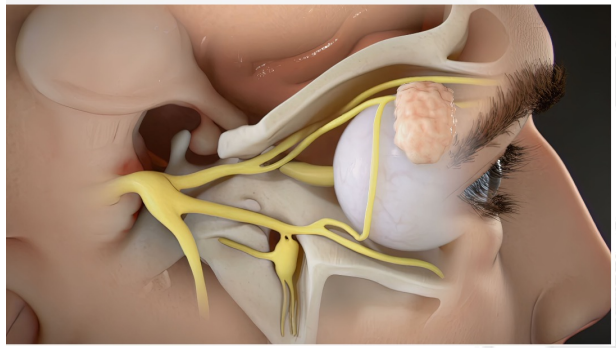


CLUSTER HEADACHE

ICHD 3. Cephalalgia 2018; 38: 1–211. © 2018 International Headache Society

Cluster Headache particularities





- Attacks occur in **series lasting weeks or months**
- They are separated by **periods of remission** that usually last months or years
- About **10-15%** of patients have **chronic cluster headaches**, without periods of remission
- Attacks can **be triggered by alcohol, histamine, or nitroglycerin**
- **Agitated during the attack**
- Follows the **circadian and circadian pattern** of attacks

49 year old patient with CC (ICHD)
Tattoo illustrating symptoms during an attack

Catherine F. Slattery, et al. Picturing the torment of cluster headache. Neurology. October 20, 2015
https://medlineplus.gov/ency/article/000786.htm.https://www.ghostproductions.com/image/cluster-headaches-real life

Cluster Headache Treatment

Acute treatment

- **O_2 inhalation 100% 12 L/min** for 20 min. (75% response after 15 minutes)
- **Triptans:**

  (Sumatriptan, Zolmitriptan)
- **Dihydroergotamine**
- **Lidocaine 4%–10% - 1ml** –nasal instillation in ipsilateral nostril

Prophylactic treatment

- **Verapamil –**80 mg x 3-4 times/day

ECG mandatory until treatment

- **Prednisone** 60-100 mg 5 days
- **Lithium carbonate** 600–1500 mg
- **Topiramate** 100 mg/day
- **Melatonin** 10 mg
- **Galcanezumab**

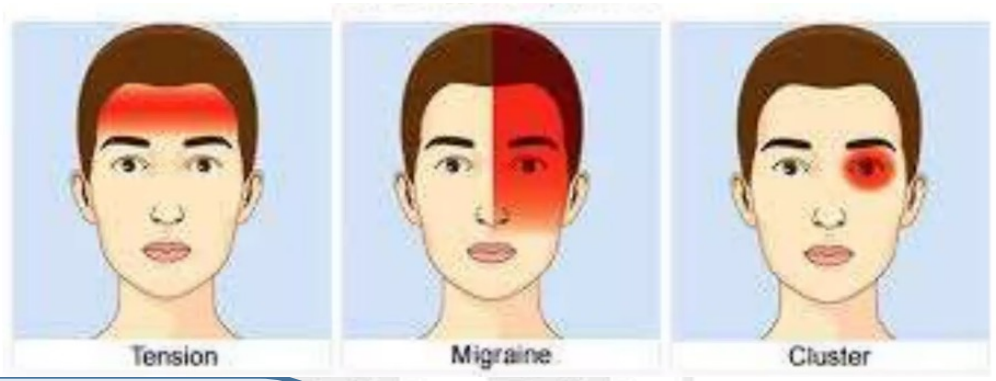
Invasive and non-invasive procedures

- Non-invasive vagus nerve stimulation
- Infiltration of the greater occipital nerve
- Stimulation of the greater occipital nerve and sphenopalatine ganglion

Diagnosis of primary headaches
Patient history

The diagnosis of PRIMARY HEADACHES is clinical!

No imaging is necessary if there are no alarm signs!



Patient History

- **Pain Characteristics**
  - **Location:** Uni- or bilateral? Frontal/ occipital/ diffuse? Eyeball?
  - **Quality:** Pulsating/Pressing/ Drilling/ Sharp/ Stinging?
  - **Intensity:** Mild, moderate or severe? Impact on daily activities
  - **Duration:** How long does each headache episode last? (hours, days)
  - **Pattern:** Continuous or intermittent?
  - **Frequency of attacks**

Diagnosis of primary headaches
Patient history

Associated symptoms:

- Nausea and/or vomiting
- Photophobia (sensitivity to light)
- Phonophobia (sensitivity to noise)
- Visual disturbances or aura (description of specific symptoms)
- Other sensory changes (numbness, tingling)
- Aggravating and relieving factors

Headache triggers:

- Stress or emotional factors
- Environmental factors (weather changes, smells, perfumes, chemicals, smoke)
- Food or drink (in the past 24 hours)
- Skipping meals
- Physical activity
- Sexual activity

Diagnosis of primary headaches
Patient history

- **What worsens the headache?**
  - Movement or physical exertion
  - Coughing, straining, Valsalva maneuver
  - Changes in position
- **What relieves the headache?**
  - Rest/sleep
  - Medications (effectiveness, duration of effect)
  - Non-pharmacological measures
- **Onset and timing of occurrence**
  - When did the first headache episodes begin?
  - How did they start? (gradual vs. sudden)
  - Frequency of headaches (episodic vs. chronic)
  - Time of day when they usually occur
  - Does the headache appear during sleep?

Byanne Russian
www.gettyimages.com/

Headache *"Red Flags"* signs

✅	**Systemic symptoms, including fever** **NB! Meningites**
✅	History of neoplasm
✅	Neurological deficit or dysfunction (decreased level of consciousness, focal disorders)
✅	**Abrupt onset ("thunderclap headache")** **NB! SAH**
✅	Age > 50 years at onset
✅	Recent change in headache pattern
✅	**Positional headache (worsened/improved by position)**
✅	Triggered by coughing, sneezing or physical exertion
✅	**Papillary edema** **NB! ICH**
✅	Progressive or atypical headache
✅	Pregnancy or puerperium
✅	**Headache with ocular pain + autonomic symptoms**
✅	Post-traumatic onset of headache
✅	Immune pathology (e.g. HIV, immunosuppression)
✅	Analgesic abuse or new medication associated with onset

Thank you!

Growth mindset on human head and brain, importance of emotional development and inner balance

Maria Stavreva
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