

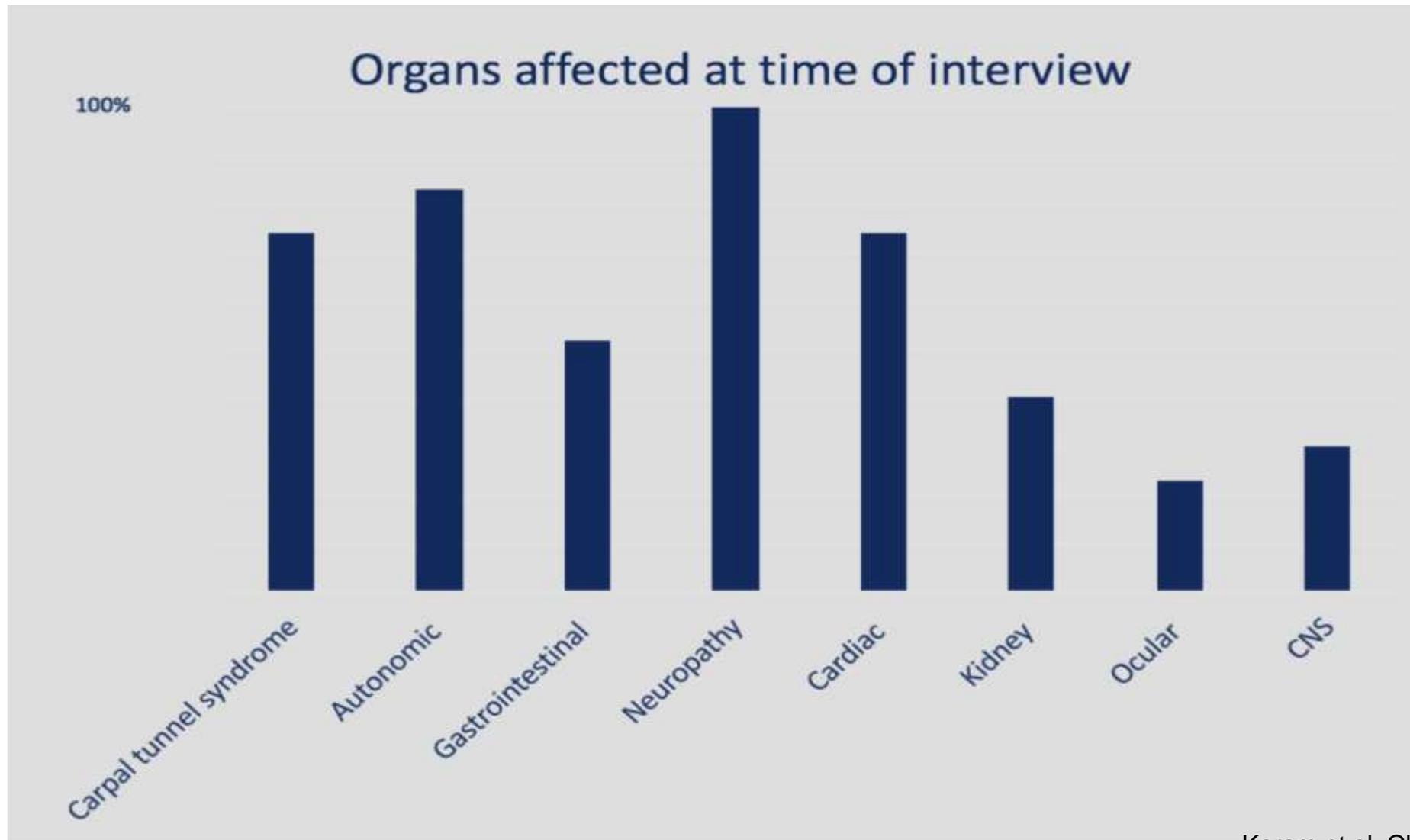
Central Nervous System and Ocular involvement in hATTR

Chafic Karam, MD

Associate Professor of Neurology, Director of the ALS and
Neuromuscular Center and Director of the Neuromuscular Medicine
Fellowship program at the OHSU Brain Institute

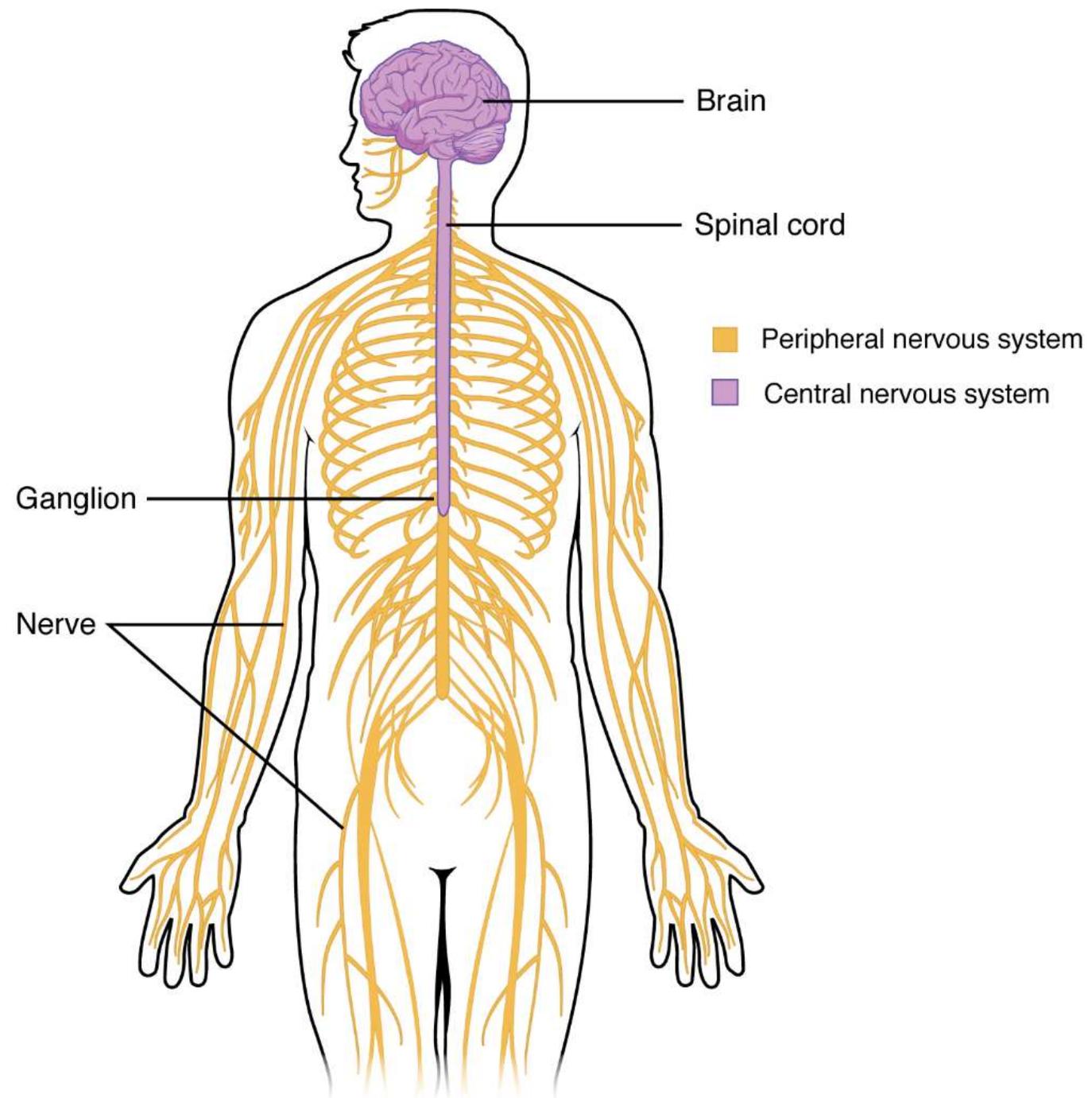


What organs are involved?

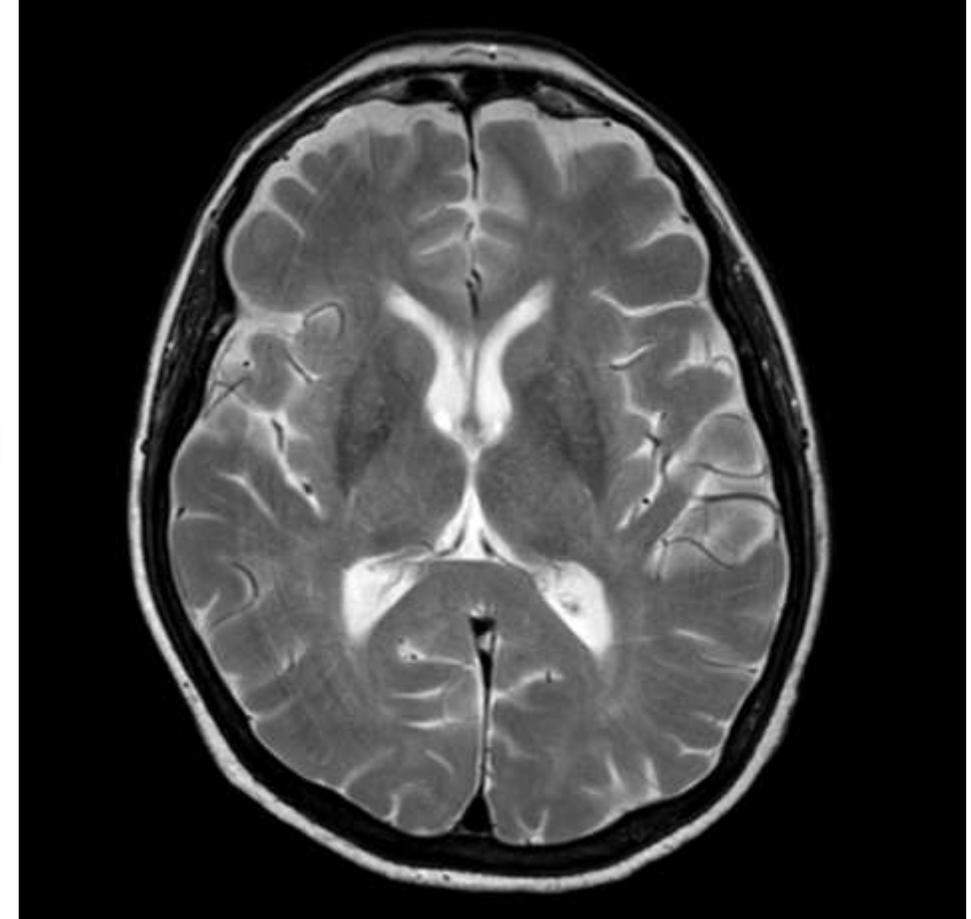


Anatomy

CNS vs PNS

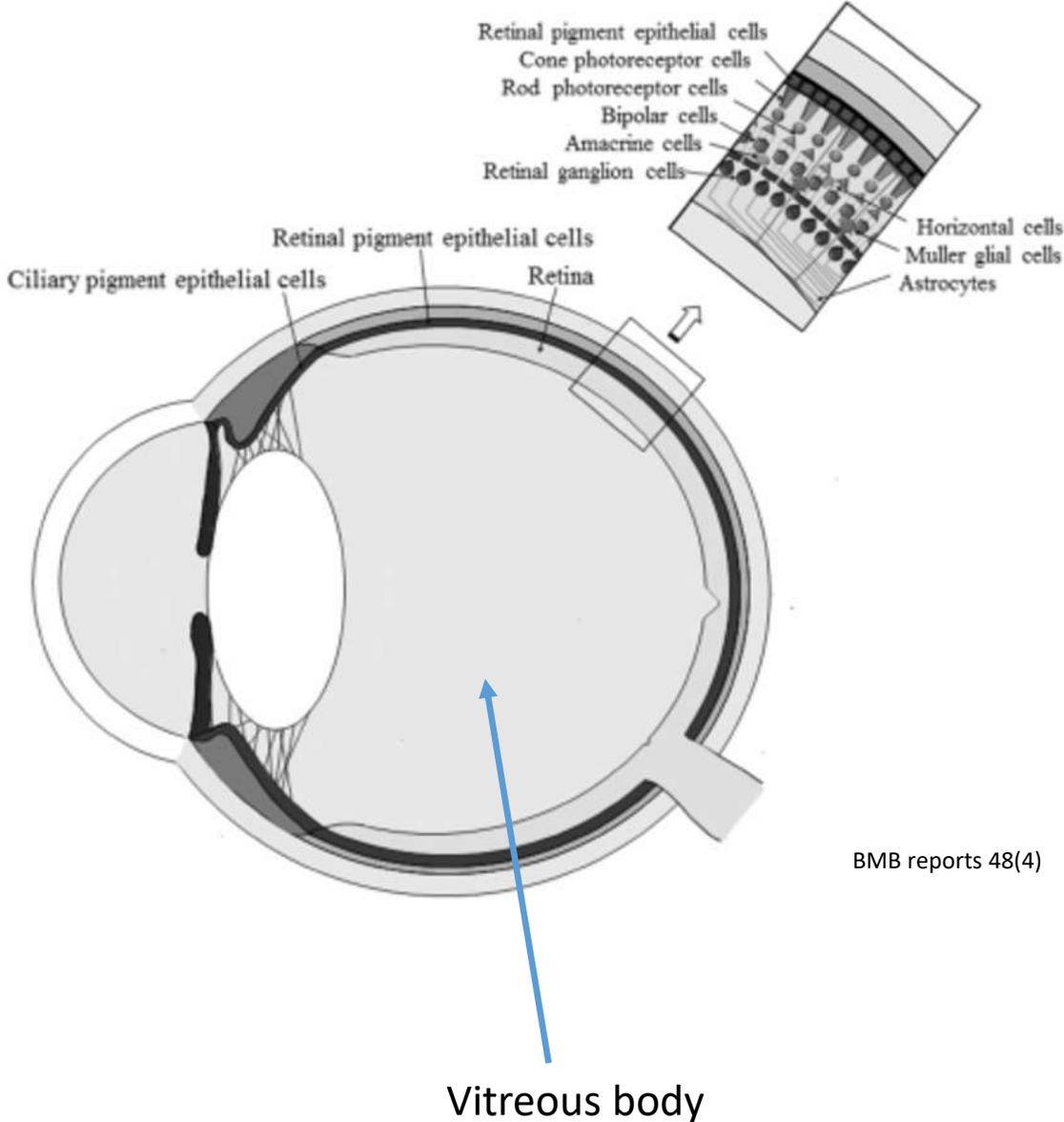
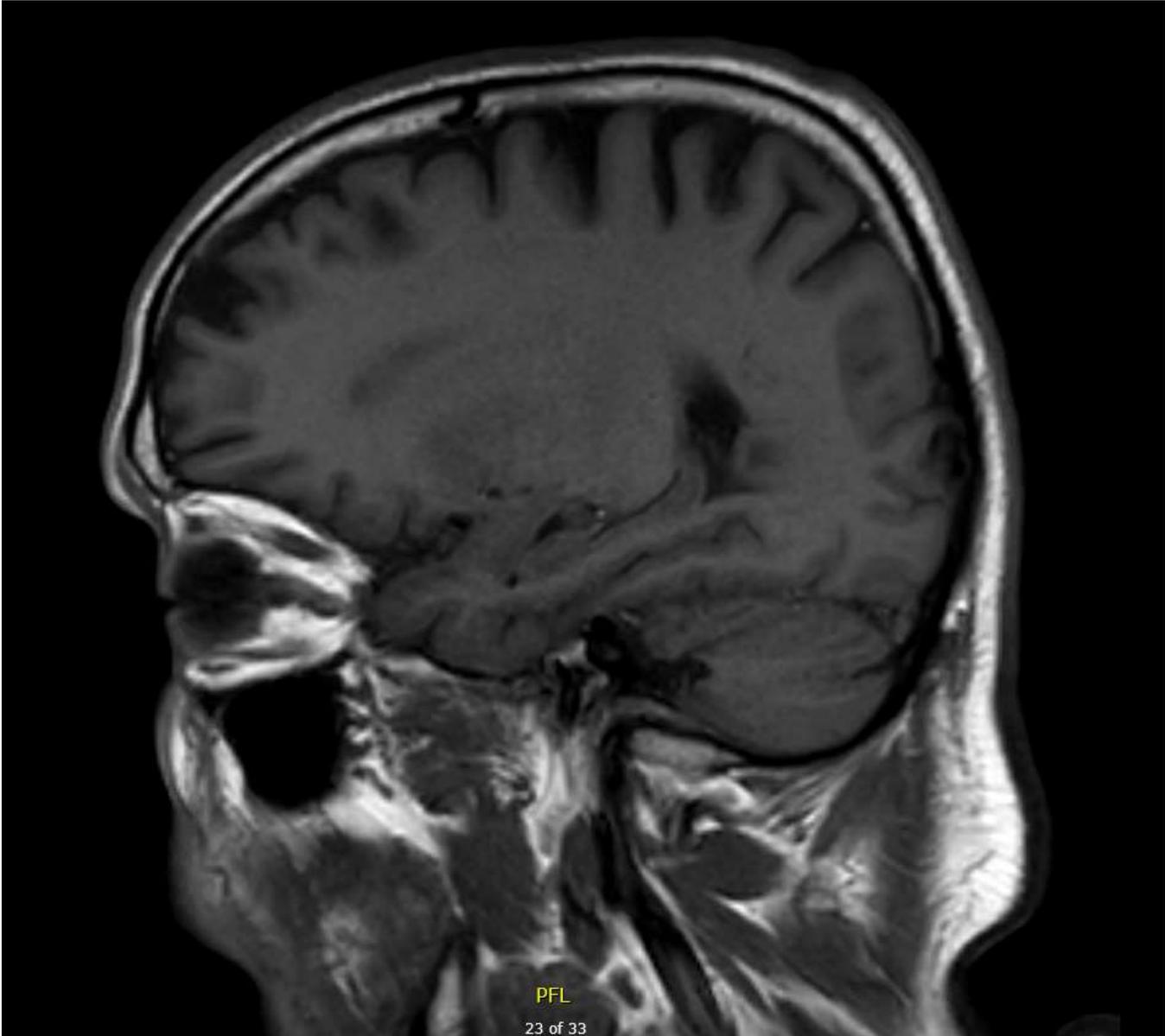


Blood brain barrier



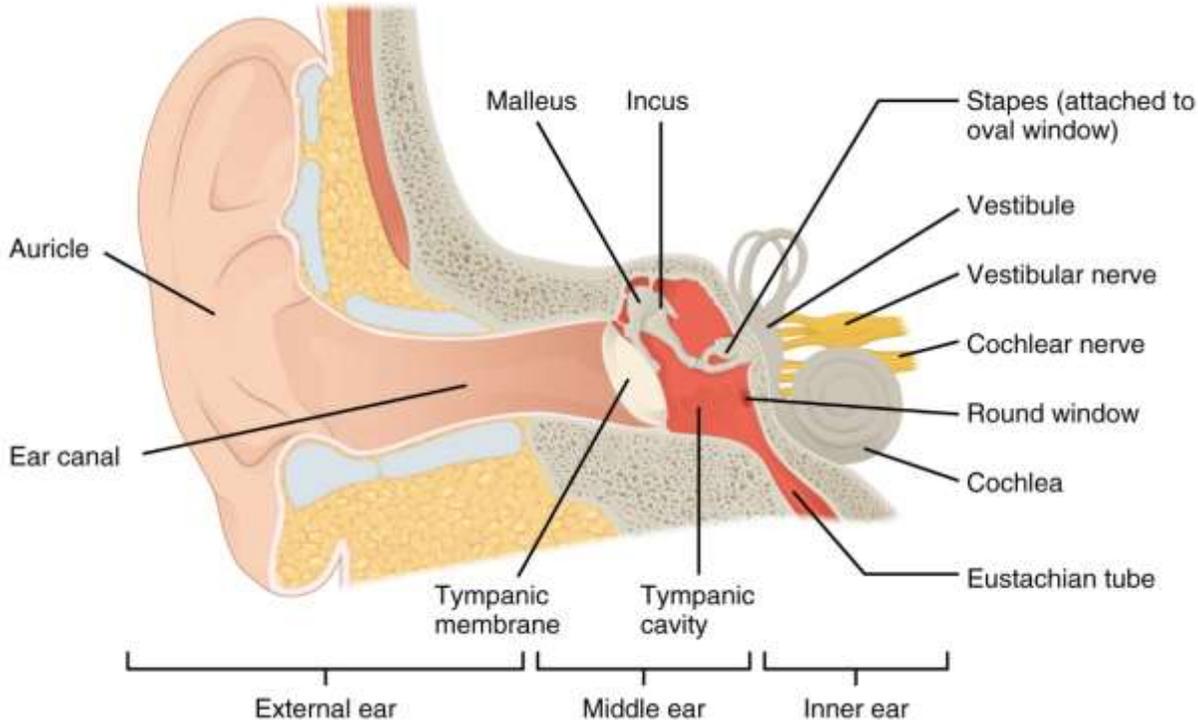
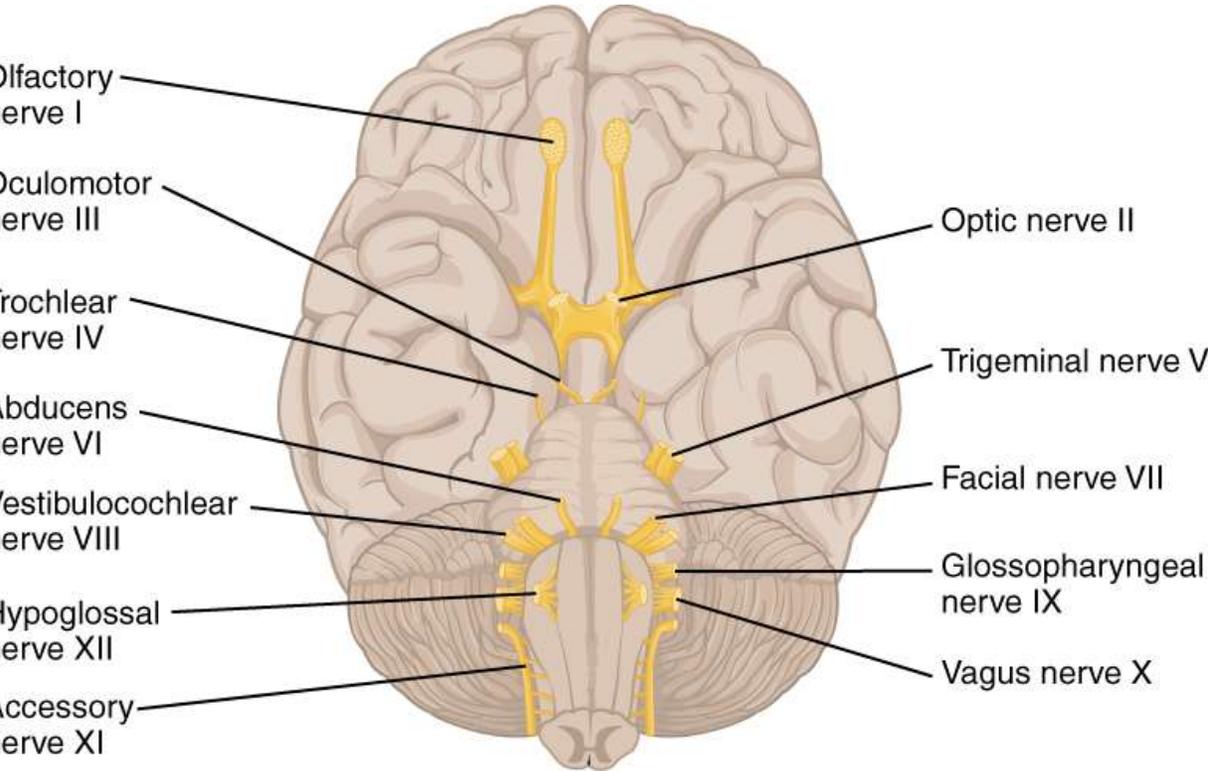
- Small molecules, fat-soluble molecules, and some gases to pass freely
- Larger molecules, such as glucose, can gain entry through transporter proteins

Optic nerve is part of CNS

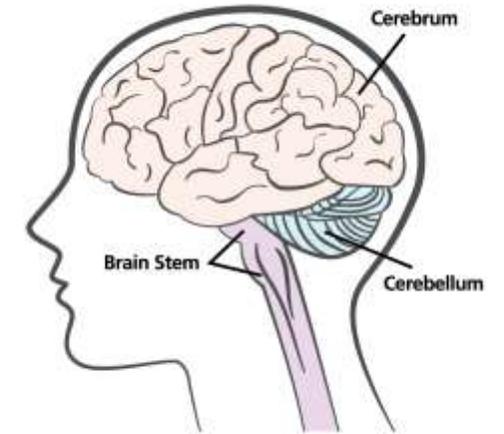
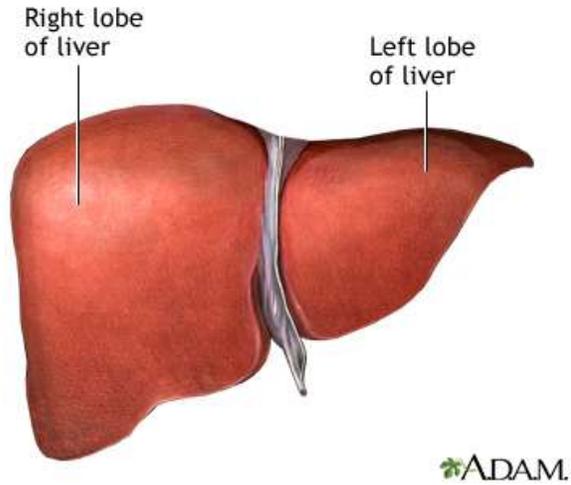


BMB reports 48(4)

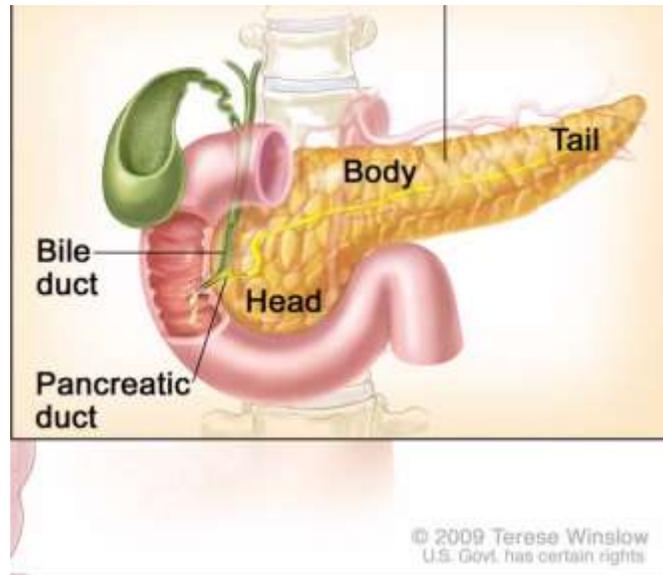
Cochleovestibular nerve part of the PNS



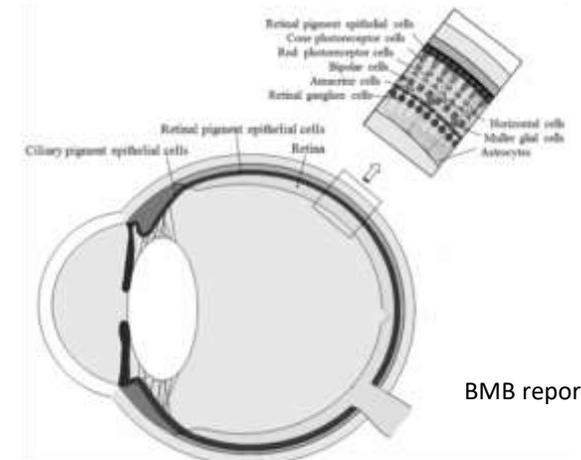
Transthyretin



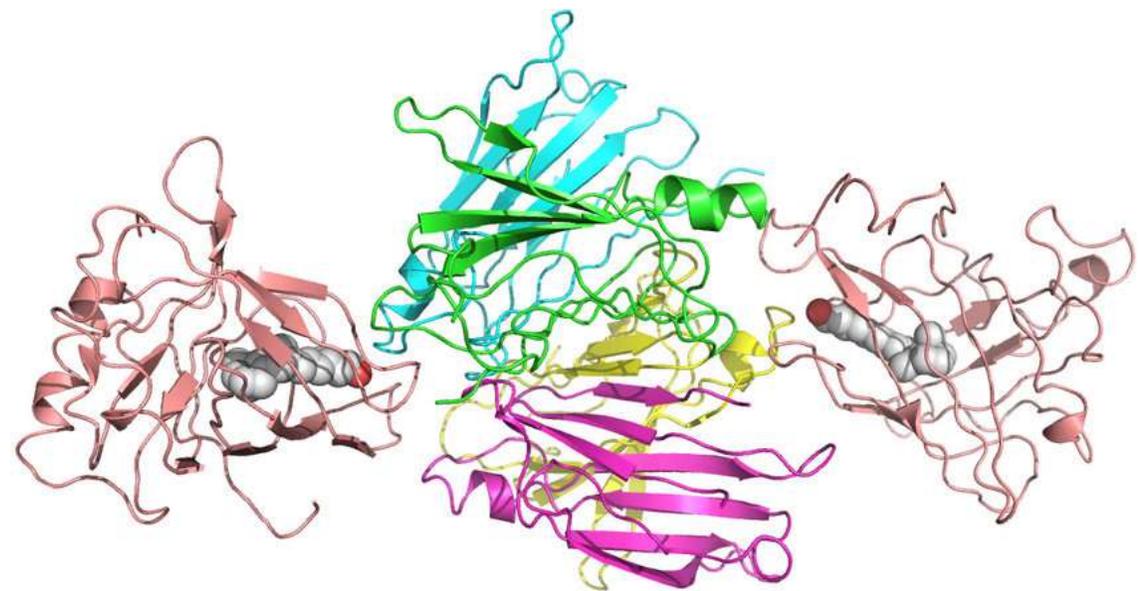
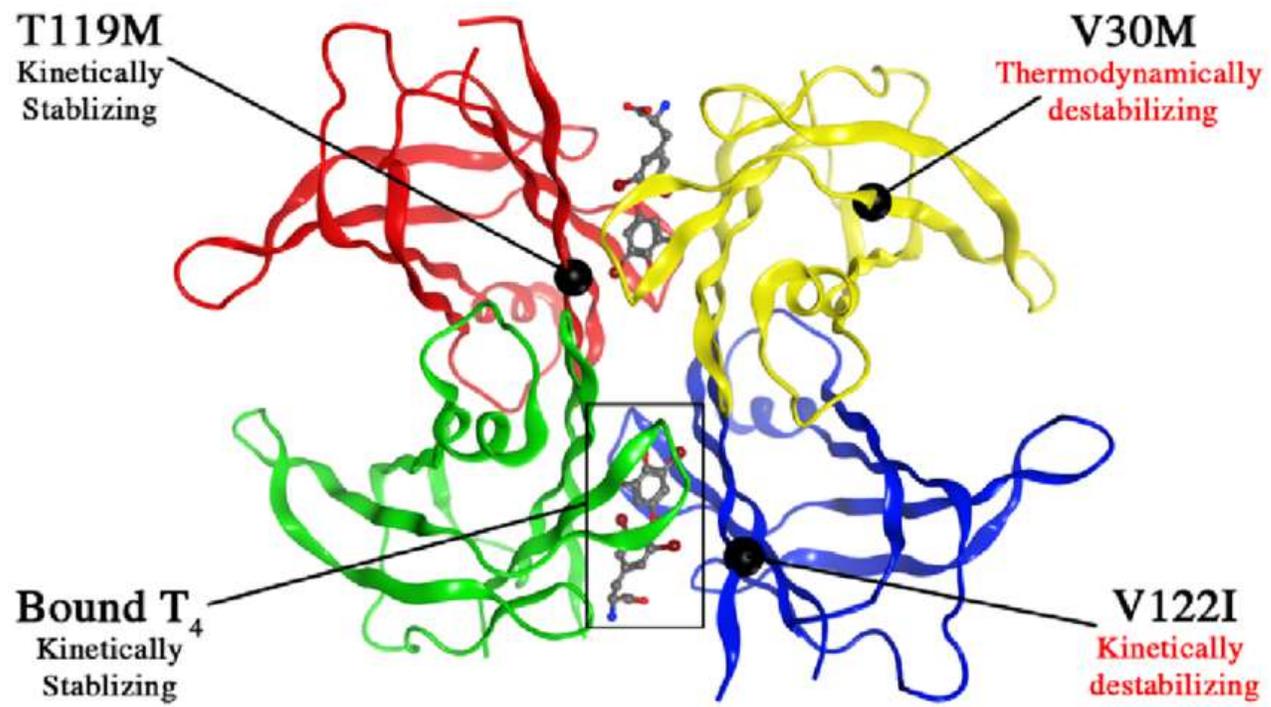
Transthyretin TTR



Local production

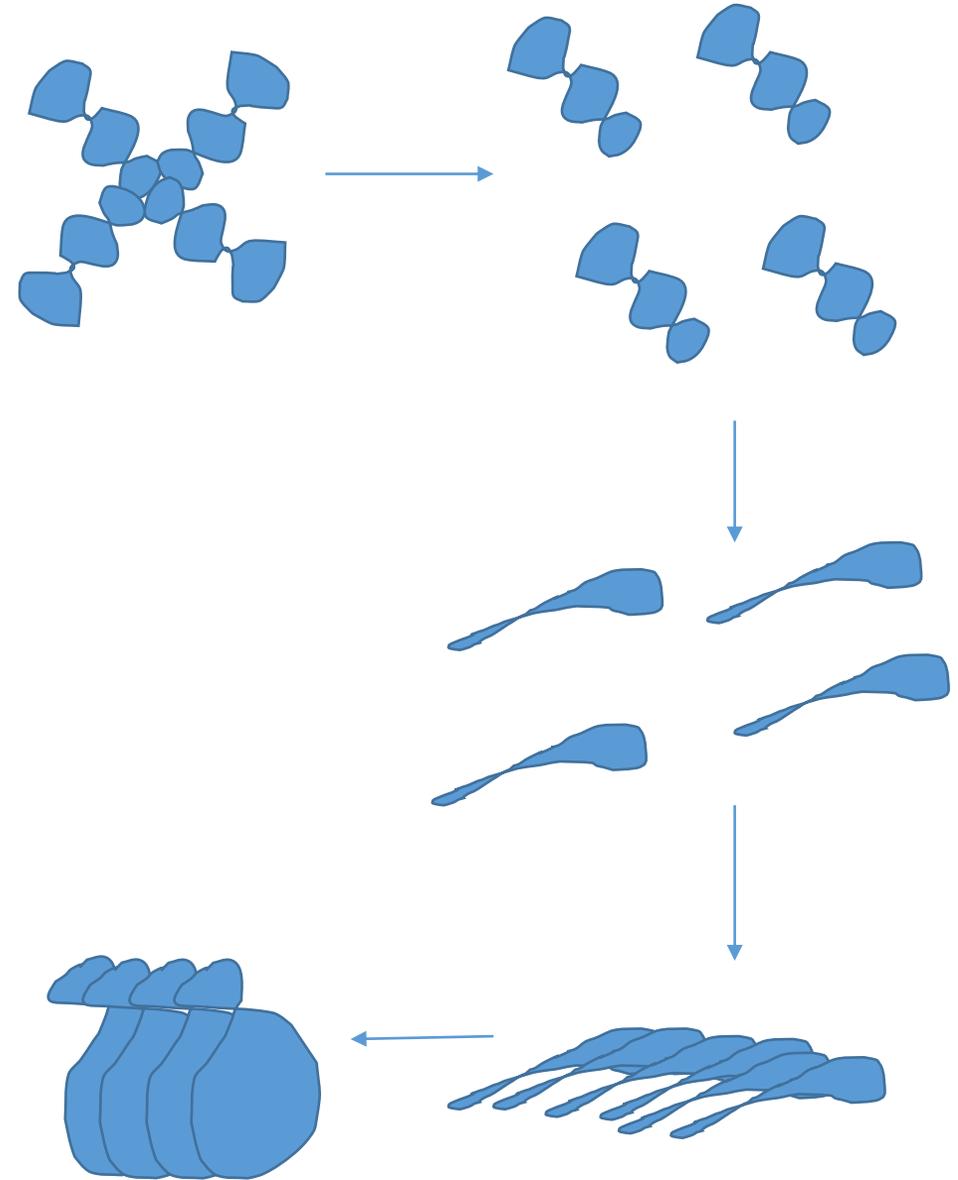


BMB reports 48(4)

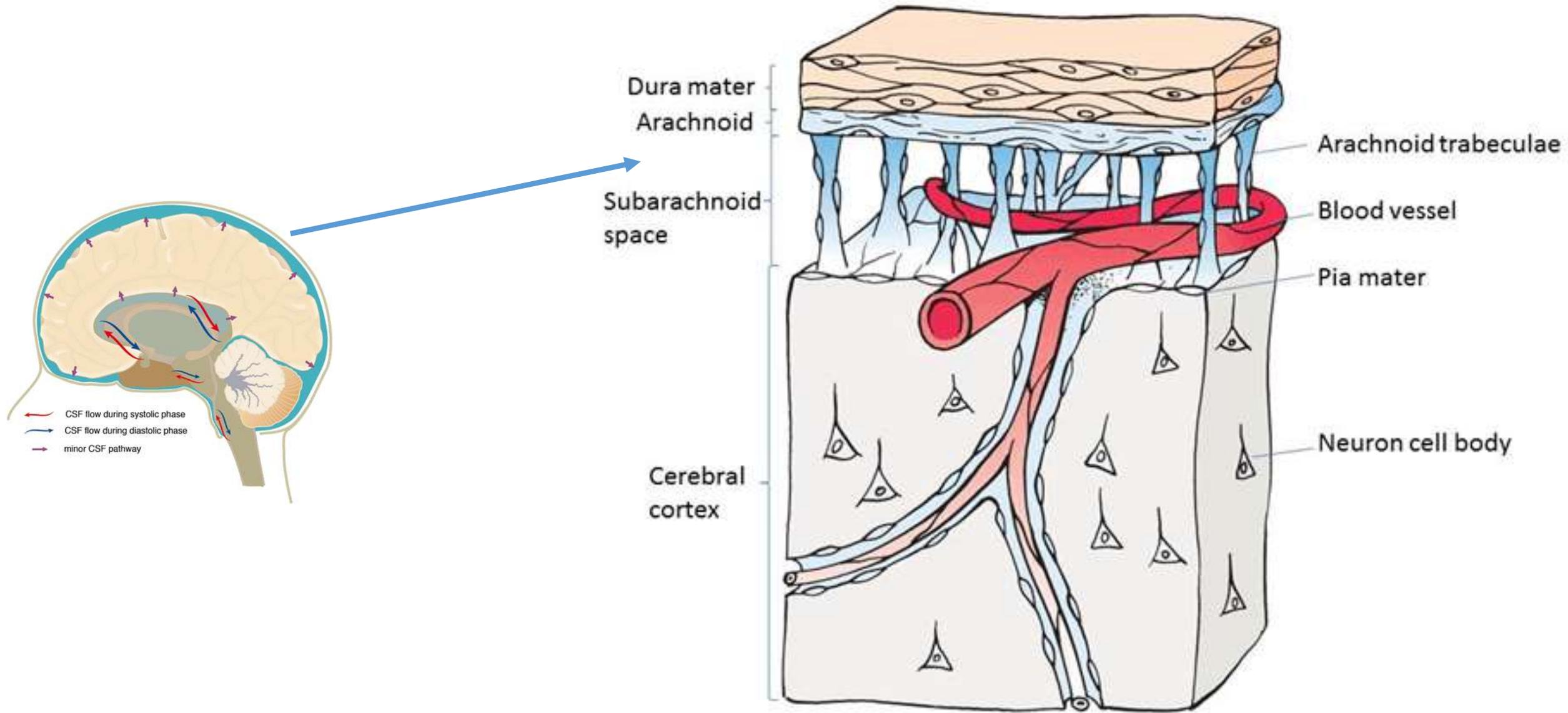


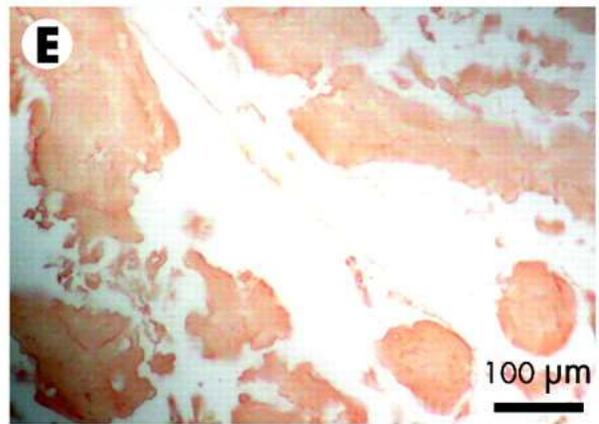
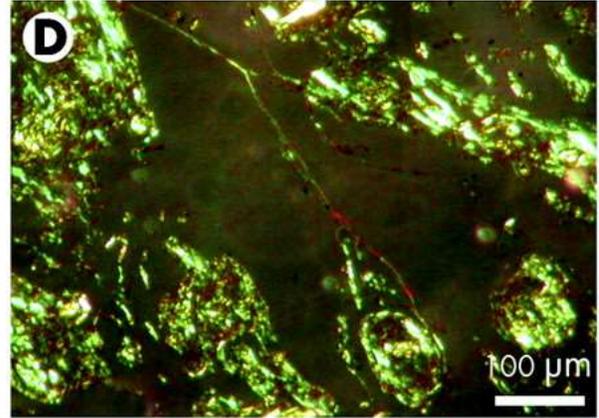
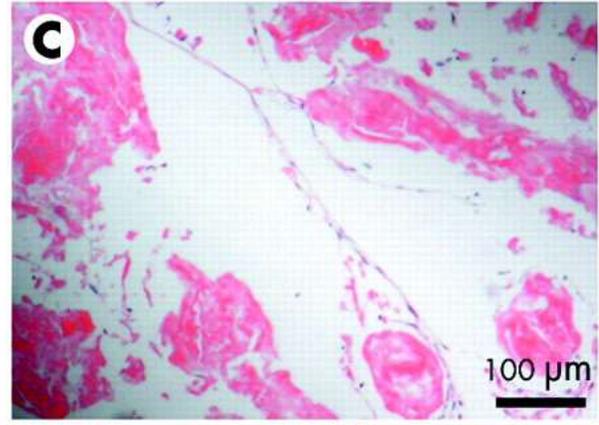
TTR toxicity

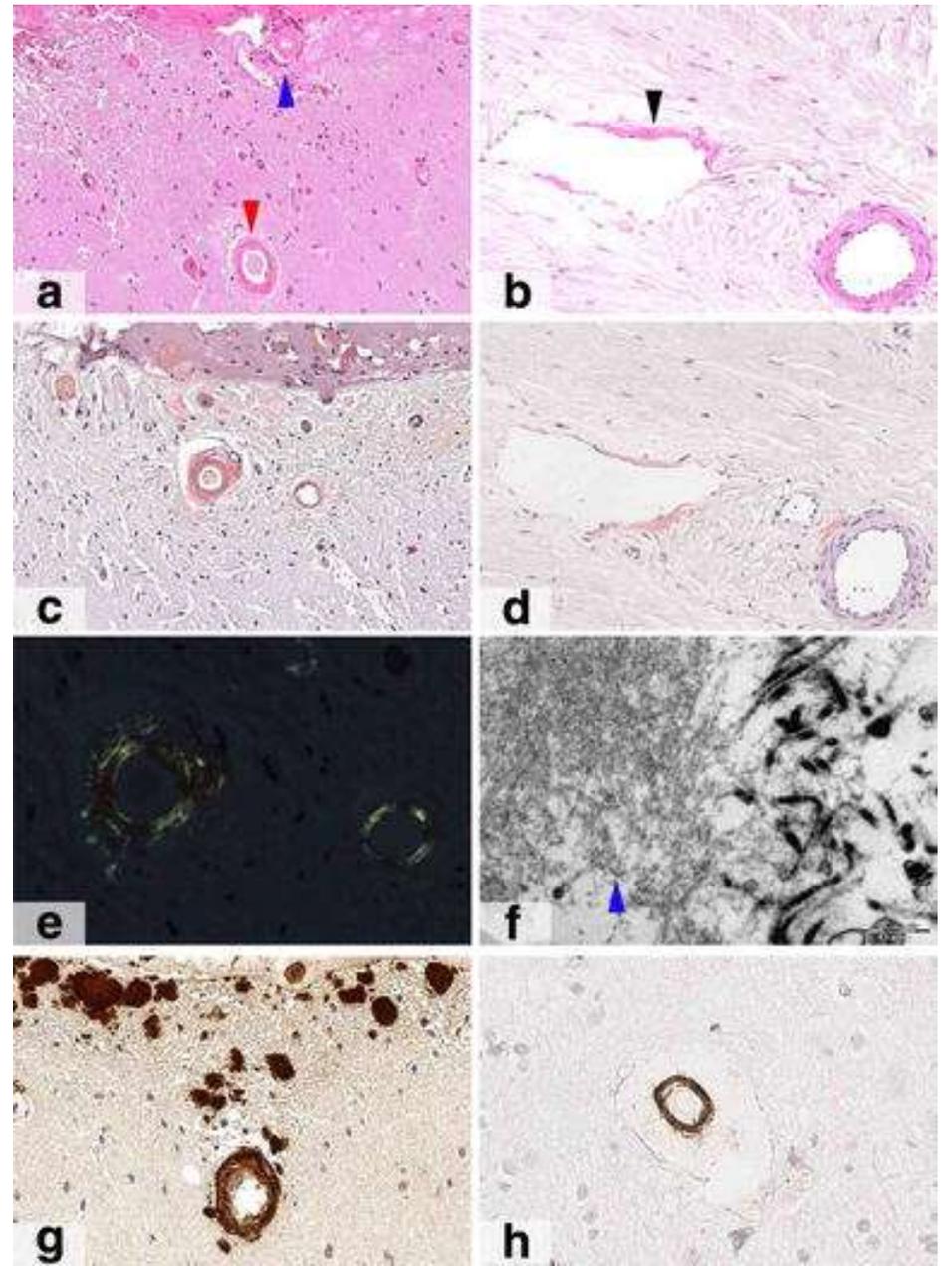
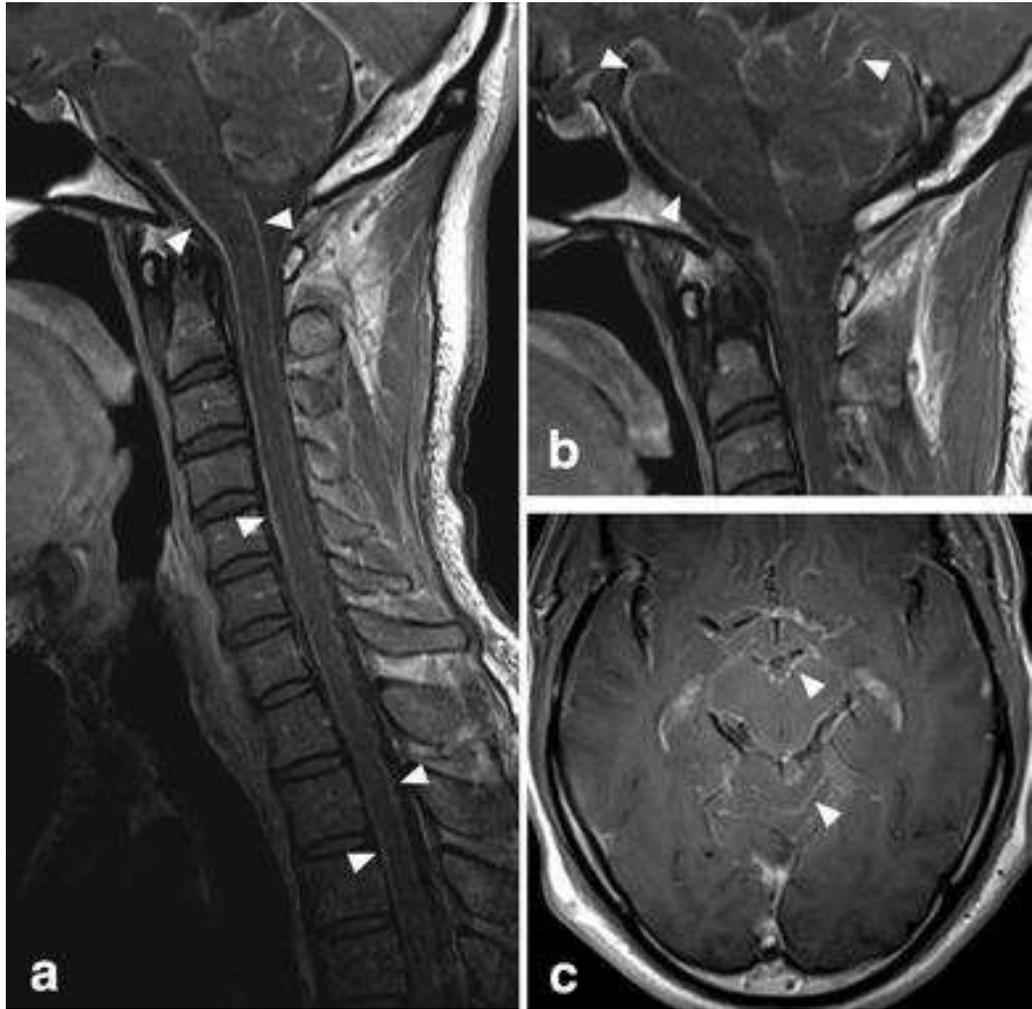
- Variant TTR (genetic mutation) causes dissociation of tetramer and release of monomers
- The monomers misfold (which itself is toxic)
- The monomers and oligomers aggregate and eventually form amyloid fibrils



CNS involvement







CNS TTR symptoms

- Episodes of confusion, psychosis
- Fatigue
- Weakness
- Headache (severe migraine like- SAH)
- Transient or focal neurological events (FNE)
- Seizures
- Cognitive issues, dementia (superficial siderosis)
- Ataxia, unsteadiness (superficial siderosis)
- Hearing loss (superficial siderosis)
- Vision loss
- Stroke (cerebral amyloid angiopathy)
- Incontinence
- Hydrocephalus

Potential CNS TTR complications

- Mutations reported: A18G, A36P, A25T, G53A, L12P, P64S, Ser44, L58A, T114C, T49P, T69H, V30G, V30M
- Rarely can occur without peripheral neuropathy (A18G)
- In general late manifestation of the disease >10 years (usually in slow progressive disease)
- Or in patients treated with liver transplant

RESEARCH PAPER

CNS involvement in V30M transthyretin amyloidosis: clinical, neuropathological and biochemical findings

Luís F Maia,^{1,2,3} Rui Magalhães,⁴ Joel Freitas,² Ricardo Taipa,⁵ Manuel Melo Pires,⁵ Hugo Osório,⁶ Daniel Dias,⁷ Helena Pessequeiro,⁸ Manuel Correia,² Teresa Coelho^{1,9}

MC and TC shared last coauthorship.

For numbered affiliations see end of article.

Correspondence to

Dr Luís F Maia, Serviço de Neurologia, Hospital de Santo António—CHP, Largo Prof. Abel Salazar, Porto 4099-001, Portugal; luis.lf.maia@gmail.com

Received 13 March 2014
Revised 11 July 2014
Accepted 16 July 2014
Published Online First
4 August 2014

ABSTRACT

Objectives Since liver transplant (LT) was introduced to treat patients with familial amyloid polyneuropathy carrying the V30M mutation (ATTR-V30M), ocular and cardiac complications have developed. Long-term central nervous system (CNS) involvement was not investigated. Our goals were to: (1) identify and characterise focal neurological episodes (FNEs) due to CNS dysfunction in ATTR-V30M patients; (2) characterise neuropathological features and temporal profile of CNS transthyretin amyloidosis.

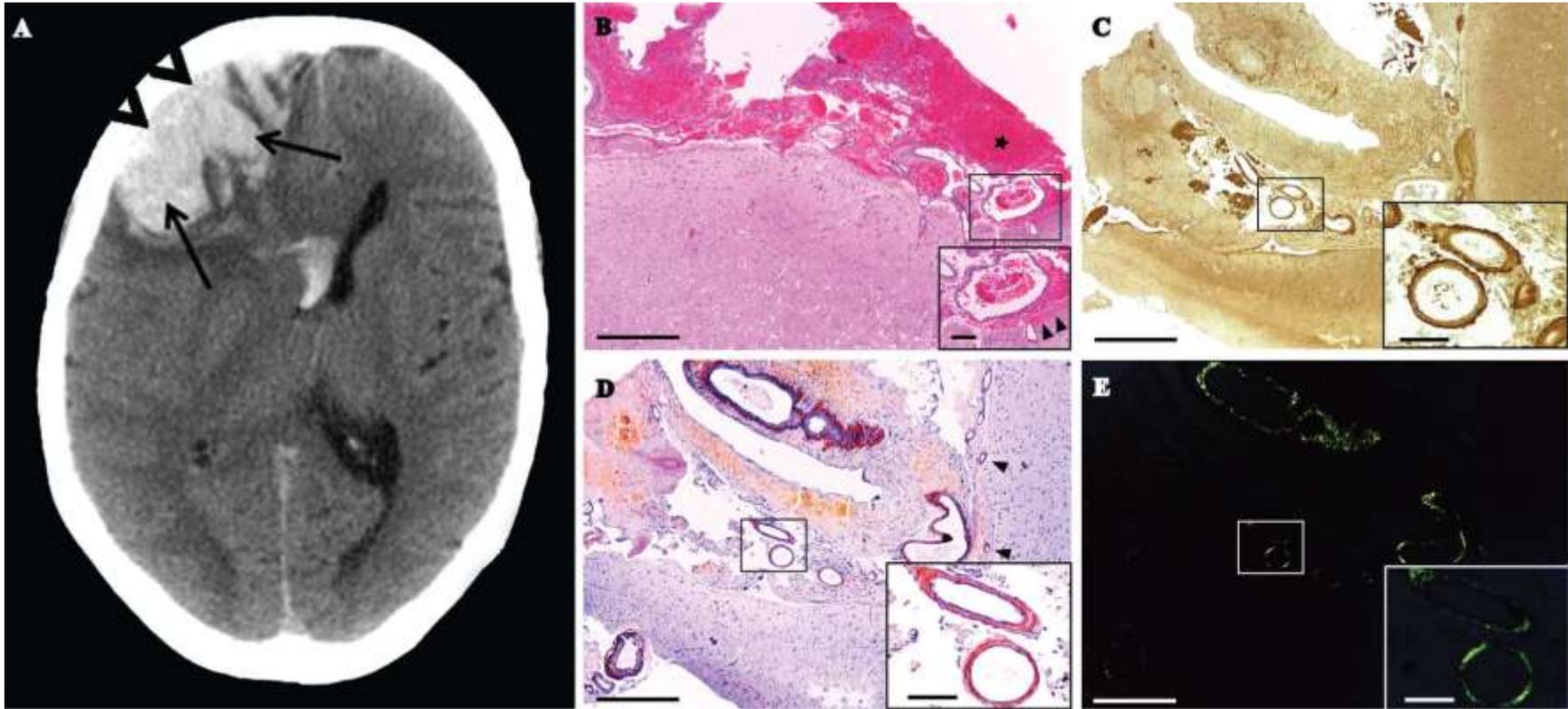
Methods We monitored the presence and type of FNEs in 87 consecutive ATTR-V30M and 35 non-ATTR LT patients. FNEs were investigated with CT scan, EEG and extensive neurovascular workup. MRI studies were not performed because all patients had cardiac pacemakers as part of the LT protocol. We characterised transthyretin amyloid deposition in the brains of seven ATTR-V30M patients, dead 3–13 years after polyneuropathy onset.

kidney, heart and gastrointestinal tract, leading to organ specific dysfunction.^{1–5} Additionally, TTR can deposit in the central nervous system (CNS) of these patients in a meningeal-vascular location.⁶ Still, clinically relevant presentations such as cerebral haemorrhage, communicating hydrocephalus and myelopathy, are rarely reported in ATTR-V30M patients.^{7–8} In patients carrying other TTR mutations associated with prominent CNS TTR deposition (eg, L12P; D18G; T49P), dementia, ataxia, brain haemorrhages and focal neurological episodes (FNEs) are often described.^{9–11}

In 1990, liver transplant (LT) was introduced for the treatment of ATTR-V30M patients as a way to eradicate mutant TTR (mut-TTR) from the blood plasma. This resulted in improved survival and slower disease progression compared with non-transplanted patients.^{12–13} Since then, over 1000 ATTR-V30M patients have had LT worldwide with a

CNS complications after Liver Transplant

- 87 patients with V30M who underwent liver transplant
- 31% had Focal neurological events (FNE) (stroke, migraine, seizure)
- FNEs occurred on average 14.6 years after disease onset



Ocular Involvement

pupillary light-near dissociation
(Common)

vitreous opacities
(rare)

loss of corneal sensitivity and neurotrophic corneal ulcers
(rare)

abnormal conjunctival vessels
(common)

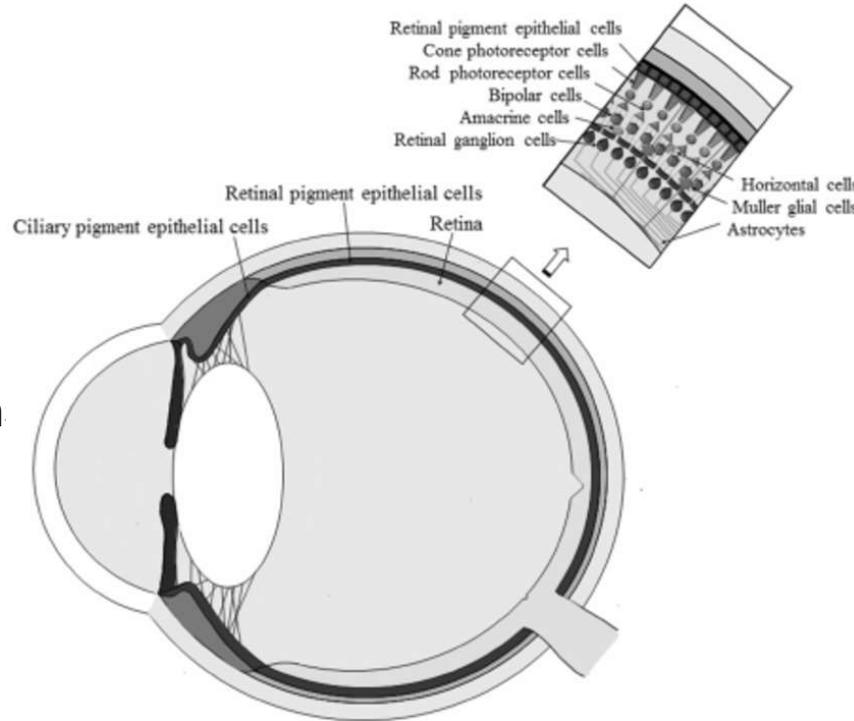
anterior capsule opacity of the lens
(rare)

optic neuropathy (from ischemia)

keratoconjunctivitis sicca
(Common)

retinal vascular changes

chronic open-angle glaucoma
(rare) → LEADING CAUSE OF BLINDNESS



Potential Ocular complications hATTR

- Certain patients more predisposed: Tir114Cis (100%) and Lys 54 mutations than in patients with variant Val30Met (24%)
- Rarely can be first presenting sign



Amyloid

The Journal of Protein Folding Disorders



ISSN: 1350-6129 (Print) 1744-2818 (Online) Journal homepage: <https://www.tandfonline.com/loi/iamy20>

Ophthalmological manifestations in hereditary transthyretin (ATTR V30M) carriers: a review of 513 cases

João Melo Beirão, Jorge Malheiro, Carolina Lemos, Idalina Beirão, Paulo Costa & Paulo Torres

To cite this article: João Melo Beirão, Jorge Malheiro, Carolina Lemos, Idalina Beirão, Paulo Costa & Paulo Torres (2015) Ophthalmological manifestations in hereditary transthyretin (ATTR V30M) carriers: a review of 513 cases, *Amyloid*, 22:2, 117-122, DOI: [10.3109/13506129.2015.1015678](https://doi.org/10.3109/13506129.2015.1015678)

To link to this article: <https://doi.org/10.3109/13506129.2015.1015678>

477 patients (343 had been liver transplanted)

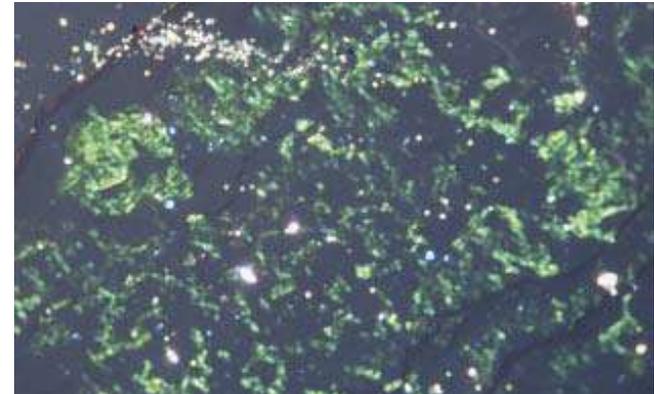
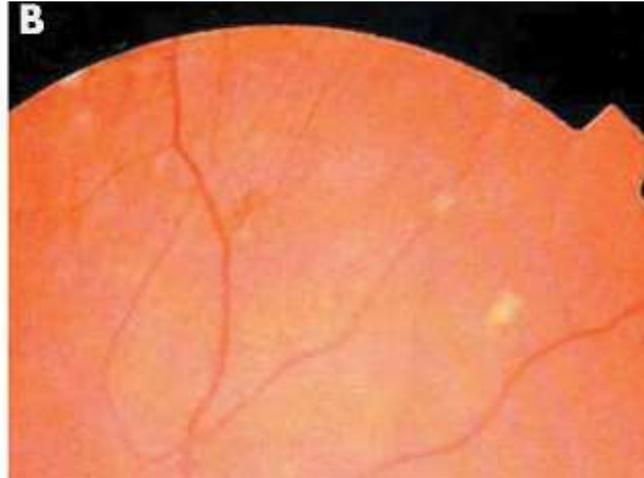
- 80% had dry eyes
- 39% had amyloid deposition on the iris
- 33% amyloid deposition on the anterior capsule of the lens
- 28% scalloped iris
- 20% glaucoma
- 17% vitreous opacities



Figure 2: Multiple indentations of the pupillary edge and amyloid deposits in a 43-year-old patient with FAP 1, submitted to liver transplantation about 9 years ago [4].

Vitreous opacities

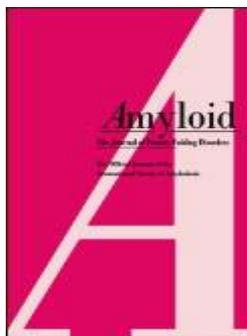
- Complicates between 5 and 35% of hATTR patients
- Can manifest as floaters and visual loss



Hearing Involvement

Potential Hearing Complication in hATTR

- Conductive hearing loss due to amyloid infiltration of the middle ear
- Sensorineural hearing loss due to cochlear and/or neural infiltration
- Can have both



Amyloid
The Journal of Protein Folding Disorders



ISSN: 1350-6129 (Print) 1744-2818 (Online) Journal homepage: <https://www.tandfonline.com/loi/iamy20>

Association between hearing loss and hereditary ATTR amyloidosis

Sophie Bartier, Diane Bodez, Mounira Kharoubi, Aziz Guellich, Florence Canouï-Poitrine, Véronique Chatelin, André Coste, Thibaud Damy & Emilie Béquignon

To cite this article: Sophie Bartier, Diane Bodez, Mounira Kharoubi, Aziz Guellich, Florence Canouï-Poitrine, Véronique Chatelin, André Coste, Thibaud Damy & Emilie Béquignon (2019): Association between hearing loss and hereditary ATTR amyloidosis, *Amyloid*, DOI: [10.1080/13506129.2019.1663814](https://doi.org/10.1080/13506129.2019.1663814)

To link to this article: <https://doi.org/10.1080/13506129.2019.1663814>

Table 2B. Presence and type of hearing loss according to TTR mutations ($n = 19$ patients).

	Val122Ile $n = 7$	Val30Met $n = 6$	Other mutation $n = 6$
Number of patients			
No hearing loss	1	0	1
Hearing loss	6	6	5
Type of hearing loss			
Unilateral Hearing Loss	0	2	0
Bilateral Hearing loss	6	4	5
Sensorineural Hearing loss	3	6	2
Mixed Hearing loss	2	0	3
Conductive Hearing Loss	1	0	0

“Other mutation” regroups: Gly47Ala, Ile68Leu, Thr60Ala, Ile107Val, Ser77Tyr and Arg21Gln.

Investigations

Investigations

- Brain MRI can show Leptomeningeal enhancement, stroke, bleeding or evidence of prior bleeding (hemosiderin deposits)
- CT scan in case brain MRI cannot be done
- EEG for seizures
- Audiometry can demonstrate hearing loss
- Eye examination

Management

Local treatment

- Dry eyes: Eye drops, topical cyclosporine
- Vitrectomy if floaters are severe
- Glaucoma: topical treatment, surgery (trabeculectomy with mitomycin C)
- Laser for retinal angiopathy

- Hearing loss: hearing aids

- Blood pressure control to reduce risk of stroke and bleeding

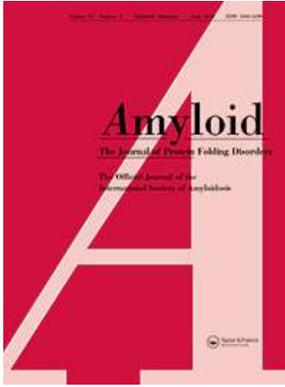
Systemic Treatment

Unlikely to be helpful

- Liver transplant
- Systemic RNA knock down (unless ASO given in the ventricular system)
- ?Abs

Possibly helpful (penetrates the BBB)

- ? Tafamidis
- ? AG10
- ? Diflunisal
- ? Tolcapone
- ? Resveratrol
- ? Doxycycline
- ? TUDCA



Amyloid

The Journal of Protein Folding Disorders

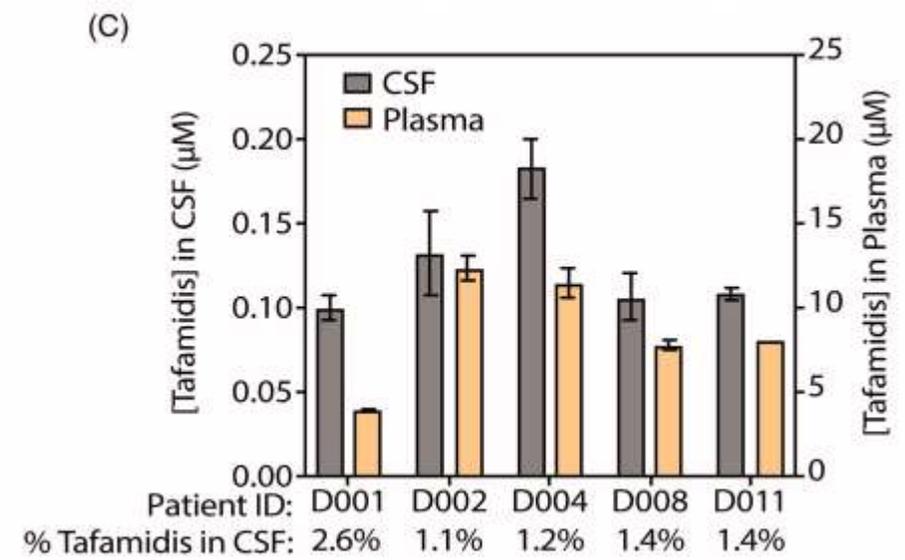
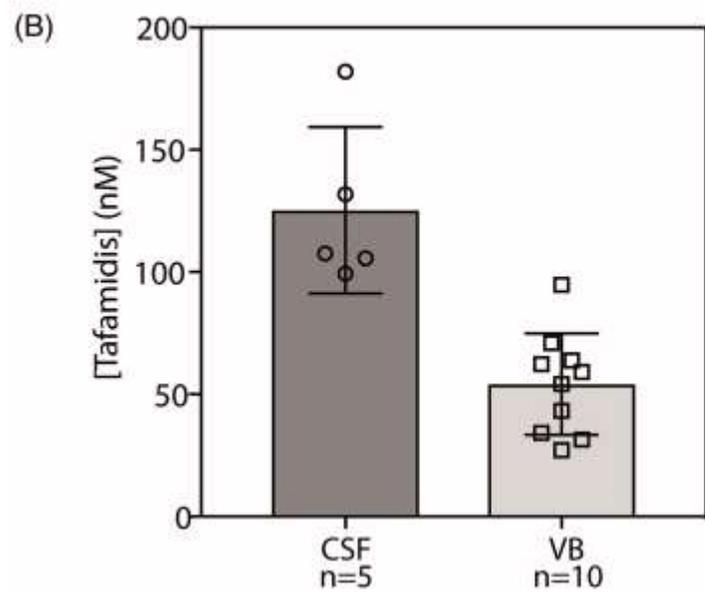
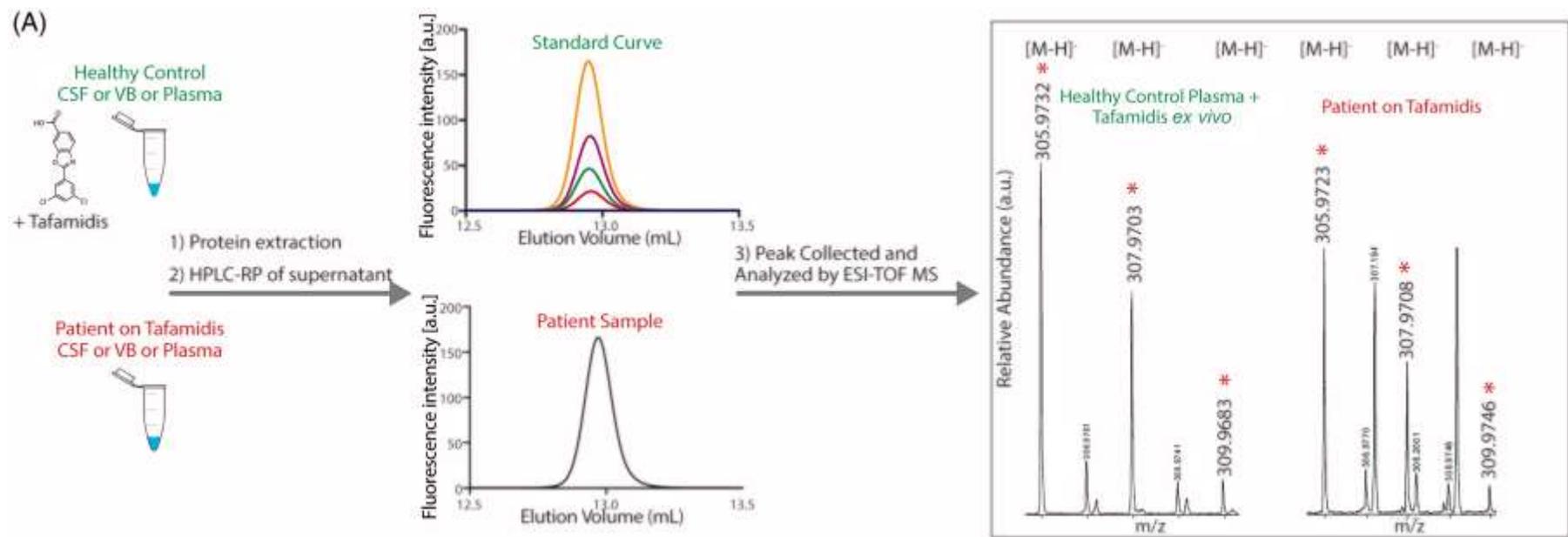
ISSN: 1350-6129 (Print) 1744-2818 (Online) Journal homepage: <https://www.tandfonline.com/loi/iamy20>

Cerebrospinal fluid and vitreous body exposure to orally administered tafamidis in hereditary ATTRV30M (p.TTRV50M) amyloidosis patients

Cecilia Monteiro, Ana Martins da Silva, Natália Ferreira, Jaleh Mesgarzadeh, Marta Novais, Teresa Coelho & Jeffery W. Kelly

To cite this article: Cecilia Monteiro, Ana Martins da Silva, Natália Ferreira, Jaleh Mesgarzadeh, Marta Novais, Teresa Coelho & Jeffery W. Kelly (2018) Cerebrospinal fluid and vitreous body exposure to orally administered tafamidis in hereditary ATTRV30M (p.TTRV50M) amyloidosis patients, *Amyloid*, 25:2, 120-128, DOI: [10.1080/13506129.2018.1479249](https://doi.org/10.1080/13506129.2018.1479249)

To link to this article: <https://doi.org/10.1080/13506129.2018.1479249>



Summary

- CNS complications are rare
- Certain TTR mutations have a higher risk of CNS complications
- Patients with longer disease, or with liver transplant are at a higher risk of developing CNS complications
- Special investigation are necessary to detect whether CNS is involved
- Several of the stabilizers may penetrate CSF and affect course of CNS involvement in hATTR amyloidosis

Thank you!

