Summary at-a-glance:
CNS involvement in ATTRV30M is present from early stages of the disease. CNS manifestations can persist despite use of disease-modifying treatment. Definition of these manifestations, early biomarkers, and new therapeutic targets and strategies are required.

Key terms:
Amyloid, ATTRv amyloidosis, central nervous system, cerebral spinal fluid, oculoleptomeningeal amyloidosis

Introduction
- The most common mutation found in hereditary transthyretin amyloidosis (ATTRv amyloidosis) is V30M (ATTRV30M), which presents as an early-onset, severe, progressive disorder.
- Increasing evidence has shown that pathologic central nervous system (CNS) involvement is present from the early stages of disease; however, symptoms arise as a very late complication.
- The poor prognosis for patients with ATTRV30M prior to the availability of liver transplantation meant that patient survival was not long enough for CNS involvement to be observed.
- CNS and eye transthyretin (TTR) production continues post liver transplant due to TTR production by the choroid plexus and retinal and ciliary pigment epithelium, allowing CNS and ocular manifestations to progress.
- Additionally, there is rare phenotype associated with at least 14 mutations in non-V30M patients called oculoleptomeningeal amyloidosis (OLMA) in which CNS and ocular dysfunction are the first and central manifestations of ATTRv amyloidosis.

Conclusions and implications
- Early diagnosis of disease and increasing availability of treatment will result in CNS involvement affecting more patients.
- Early symptoms and biomarkers of early CNS involvement will need to be identified as CNS deposition can start decades before onset of symptoms.
- New therapeutic targets and CNS penetrability strategies of existing drugs are needed.
Methodology

This review investigated several aspects of CNS involvement in ATTRv amyloidosis*

- Epidemiology
- Clinical presentation
- Pathology and mechanisms of injury
- Treatment and CNS disease
- Imaging and other biomarkers

*Details of review process not provided.
ATTRv amyloidosis, variant transthyretin amyloidosis; CNS, central nervous system.
Epidemiology

• Studies on the prevalence of CNS involvement in ATTRV30M are limited
• A few pathologic studies found leptomeningeal deposition in ATTRV30M patients
  • Disease duration in the studied patients ranged from 3 to 33 years
• In most, if not all, patients with ATTRv amyloidosis, it is likely that CNS amyloid deposition starts in the early stages of disease
• Three independent studies found transient focal neurologic episodes (TFNEs) in 12–31% of post-transplant ATTRV30M patients
• Post-transplant ATTRV30M cohorts have reported cerebrovascular events, such ischemic stroke, occurring in 5–16% and cerebral hemorrhages in 1–5% of patients*

• The OLMA phenotype is much rarer than the ATTRV30M phenotype, and is associated with at least 14 mutations
  • Largely reported in Sweden, China, the United States, and Japan

*These frequencies should be interpreted with caution due to: small sample sizes; uncertainty in stroke diagnosis in patients with transient, occasionally prolonged symptoms that may be TFNEs; and the contraindication for magnetic resonance imaging (MRI) in some of these patients with longstanding disease who have pacemakers. ATTRv amyloidosis, variant transthyretin amyloidosis; ATTRV30M, ATTRv amyloidosis caused by V30M mutation; CNS, central nervous system; MRI, magnetic resonance imaging; OLMA, oculoleptomeningeal amyloidosis; TFNE, transient focal neurologic episode.
Clinical presentation

**ATTRV30M (late-onset CNS involvement)**

- The most reported symptom is occurrence of **TFNEs**
  - “Negative” symptoms, e.g., transient hemi-sensory loss, focal motor deficit, prolonged dysphasia (similar to transient ischemic attacks)
  - ‘Positive’ symptoms, e.g., paraesthesia or non-formed visual hallucinations, including scintillating scotoma, resembling seizures or migraine auras
- TFNEs start on average 14–17 years after onset of disease and increase in frequency over time
- Cerebrovascular events include ischemic stroke, and intracerebral lobar and sub-arachnoid hemorrhages
- Cognitive deficits are another potential effect of CNS amyloid deposition

**OLMA (early-onset CNS involvement)**

- **Heterogeneous** presentation; onset most often reported in 3rd and 5th decades but have also occurred from teenage years to 68 years of age
  - Rare phenotype associated with ≥14 mutations; *most commonly reported cases have the Y69H, D18G, V30G, and Y114C mutations
- Disease can progress rapidly and lead to death within months, or exhibit a longer disease course of up to 33 years
- TFNE occurrence is similar to that seen in ATTRV30M, and cerebrovascular events also occur
- Cognitive decline is usually fluctuating or progressive, but not much is known about its pattern
- Several signs of brainstem or cranial nerve dysfunction have been reported
  - Bilateral progressive hearing loss with 6 different mutations has been described, either isolated or associated with tinnitus, vertigo, and nystagmus

Read more: pages 3–4 of published paper

ATTRV30M, ATTRv caused by V30M mutation; CNS, central nervous system; OLMA, oculoleptomeningeal amyloidosis; TFNE, transient focal neurologic episode; TTR, transthyretin.
Imaging and other biomarkers

- Both ATTRV30M and β-amyloid cerebral amyloid angiopathy (Aβ-CAA) have identical patterns of vascular amyloid deposition, and insights from Aβ-CAA can aid in understanding the CNS involvement in ATTRV30M

- Imaging and neuropathic evaluation of ATTRV30M patients with rare symptomatic hemorrhages has revealed cerebellar and supratentorial microbleeds in some patients
  - In one case, repeated TFNEs were temporally related to MRI evidence of microbleeds
  - Conversely, brain MRIs of 5 post-transplant patients with TFNEs showed no parenchymal lesions despite presence of substantial amyloid deposition as measured by $^{11}$C-Pittsburgh compound B PET ($^{11}$C-PiB-PET)

- Leptomeningeal thickening and leptomeningeal and spinal root enhancement have been observed through use of contrast in brain MRI

- $^{11}$C-PiB-PET has been shown to detect CNS ATTRv amyloidosis manifestations; a study performing $^{11}$C-PiB-PET in 15 patients with ATTRv amyloidosis displayed positive scans in 11 patients (including all with TFNEs)

- Plasma neurofilament light chain (pNfL) may be a biomarker for ATTRv amyloidosis; one study found that pNfL can differentiate patients with ATTRv amyloidosis from controls, pre-symptomatic from symptomatic patients, and early from late disease stages

11C-PiB-PET, 11C-Pittsburgh compound B PET; Aβ-CAA, β-amyloid cerebral amyloid angiopathy; ATTRv amyloidosis, variant transthyretin amyloidosis; ATTRV30M, ATTRv caused by V30M mutation; CNS, central nervous system; MRI, magnetic resonance imaging; pNfL, plasma neurofilament light chain; TFNE, transient focal neurologic episode.
CNS pathologic findings in ATTRV30M patients

Neuropathology findings from the autopsy study of two patients with ATTRV30M. The images show leptomeningeal and subpial TTR amyloid deposition in the neocortical temporal region, with the characteristic green birefringence under polarized light in the Congo red staining (A and B) and strong immunoreactivity for TTR (C). Massive subpial amyloid deposition is seen in the entorhinal cortex (D) and basal forebrain (E, arrowheads), the later showing severe cerebral amyloid angiopathy with splitting of the vessel wall and a double-barreling appearance (arrow). Subependymal amyloid deposition is noted at the level of the amygdala protruding the ependymal lining into the ventricle (F). Congo red (A and B), TTR immunostaining (C and D), and hematoxylin & eosin (E and F). Scale bars: 500 μm (A–C), 200 (D and E), 100 (F).

Pathologic studies of brains of patients with ATTRv amyloidosis show similar histologic pattern between ATTRV30M and OLMA amyloidosis, with amyloid deposits in the leptomeningeal membranes and vessels, subpial and subependymal locations, without penetrating the cortex and subcortical white matter.
The pathologic findings, symptoms, and potential biomarkers are presented according to available evidence. 

**11C-PiB-PET, 11C-Pittsburgh compound B PET; ATTRV30M, ATTRv caused by V30M mutation; CNS, central nervous system.**

**Pathology in ATTRV30M**

**Manifestations of CNS involvement in ATTRV30M amyloidosis throughout the disease course**

- **Positive 11C-PiB-PET**
- **Cognitive deficit? (late onset cases)**
- **Transient focal neurologic episodes**
- **Stroke?**
- **Subpial deposition**
- **Meningocortical vessels**
- **Leptomeningeal vessels**

**ATTRV30M (late-onset CNS involvement)**

- Early accumulation in the meningeal vessels of the brain cortex and brainstem as early as 3 years after disease onset, mostly in the media of arteries.
- This is followed by deposition in cerebral cortex vessels, then subpial locations (8–13 years disease duration).
- **Heterogeneous distribution** pattern, often associated with astrocytosis.
- Relative higher intake in occipital and cerebellar regions than in Alzheimer's disease.
- Descriptions of amyloid aggregates in the choroid plexus, subependymal parenchyma, cranial nerves including the vagal nerve, and spinal roots and dorsal ganglia.

**Versus OLMA (early-onset CNS involvement)**

- Severe amyloid deposits in the leptomeninges of the cerebral surfaces, spinal canal, and up to the proximal spinal nerve roots.
- Exceptionally rare case reports in patients with the Y114C mutation describe amyloid deposits in the brain parenchyma and cervical spinal cord.

Read more: pages 5–6 of published paper.
Mechanisms of injury – hypotheses

- Endothelial damage has been seen in the peripheral nervous system of patients with ATTRV30M where microvascular disease is observed even in the absence of nearby amyloid deposits, implicating mechanisms other than mechanical.

- A disturbance of CNS clearing mechanisms may be an effect of the distortion of superficial vessels and blood–brain barrier (BBB) malfunctioning.

- Potentially, TTR may be secreted into the cerebrospinal fluid (CSF) and follow its clearing pathways into systemic circulation:
  - This would include transfer through arachnoid villi to the cerebral venous system and through dural lymphatics along cranial nerves.

- Clearance may be undermined by a large amount of amyloid deposition in the sub-arachnoid space and surrounding cranial nerves.

- Theoretically, amyloid angiopathy may distort glymphatic pathway channels, obstructing TTR clearance and increasing its concentration in the CNS.

ATTRV30M, ATTR caused by V30M mutation; BBB, blood brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; TTR, transthyretin.

Read more:
page 6 of published paper
Treatment in ATTRV30M amyloidosis

Liver transplant

- Plasma TTR levels decrease dramatically following liver transplant
- Limited reports of CSF TTR levels have found that variant TTR levels either remained unchanged or reduced by up to 50%
- No comparisons of CNS involvement have been made between liver-transplanted and non-transplanted individuals, but therapeutic effect is unlikely

TTR stabilizers

- In a study of longstanding ATTRV30M patients, tafamidis in the CSF was found at 1.5% of the plasma concentration
  - All patients had CNS symptoms, suggesting that at this concentration, tafamidis did not prevent CNS disease progression; eye pathology also developed
- Tolcapone is a TTR stabilizer in plasma that can cross the BBB
  - In vitro studies have shown tolcapone to stabilize A25T, V30G, and Y11AC variants but it is not known if this effect would be reproducible in the T4-rich CSF
Treatment in ATTRV30M amyloidosis cont.

**Gene silencing therapies**

- Antisense nucleotides and small interfering RNAs (siRNAs) are designed for preferential uptake by the liver and do not cross the BBB; however, there may be potential for intrathecal administration.

- An animal study found that parenterally administered antisense nucleotides had no effect on choroid plexus TTR production, but when delivered intraventricularly, this resulted in a significant CSF TTR concentration reduction.

- Additionally, another study in mice that were parenterally administered siRNAs found that the mice did not display lower TTR levels in the CSF, but did have reduced non-fibrillary TTR deposits in the meninges and meningeal vessels.

**Anti-amyloid therapies**

- Serum amyloid P component (SAP) contributes to aggregate stability and is a promising therapeutic target.

- A Phase 1 trial tested an amyloid P component depletant (CPHCP or miridesap) followed by a single dose of anti-amyloid P antibody (dezamizumab), and found non toxic and effective reduction of systemic amyloid deposition in different amyloid types.

- SAP in the CSF is also susceptible to clearance by miridesap; a transgenic mouse model showed depleted systemic levels of SAP and clearance of brain Aβ-amyloid aggregates.
Conclusions and implications

**Discussion points**

- As the majority of patients withATTRv amyloidosis have the V30M mutation, CNS involvement has severe clinical implications.

- Early diagnosis and availability of treatment will result in CNS involvement affecting more patients as this manifestation becomes apparent later in the disease course.

- The clinical course and the manifestations of CNS involvement need to be defined systematically.

- The effect of disease-modifying therapies in CNS manifestations requires clarification.

**Implications**

- CNS amyloid deposition starts decades before the onset of symptoms, and so early symptoms and biomarkers of early CNS involvement need to be identified urgently.

- New therapeutic targets and the development of CNS penetrability strategies of existing drugs are required for the management of patients with ATTRv amyloidosis with CNS involvement.

- The mechanisms and therapeutic targets of CNS involvement in patients with ATTRV30M may provide insights into the treatment of OLMA patients.

**Links to further useful papers/materials:**

Glossary

- **Transient focal neurologic episodes**: episodes of transient, often stereotyped, focal CNS dysfunction with complete recovery; also known as amyloid spells