Hereditary Transthyretin Associated Amyloidosis - a treatable disease

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Disclosures

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- Dr Coelho received support from Pfizer and Alnylam to attend scientific meetings.
- Dr Coelho integrates the speakers bureau of Pfizer.

Objectives of this presentation

- To present the clinical aspects of the neuropathy caused by transthyretin (TTR) associated amyloidosis (also known as Familial Amyloid Polyneuropathy TTR related), with particular emphasis on autonomic symptoms.

- To inform about the disease modifying treatments presently available, to discuss results and indications of liver transplant and the oral drug Tafamidis and to present other drugs under clinical development, with information about clinical trials scheduled to start soon.

- To discuss diagnostic problems to avoid misdiagnosis of this now treatable, severe, and fatal disorder.

Transthyretin associated amyloidosis

- Transthyretin (TTR) associated amyloidosis is a complex disorder due to deposition of TTR (a plasmatic transport protein mainly synthesized in the liver), as extracellular amyloidosis .

- More than a hundred pathogenic mutations have been identified. The presence of a mutation induces instability of the tetrameric structure of the protein and ultimately leads to formation of amyloid deposits, particularly in the heart and peripheral nervous system [1].

- There is no clear genotype-phenotype correlation but we can define three main phenotypes: neuropathy, cardiomyopathy and mixed [2].

- Besides neuropathy and cardiomyopathy, renal disease, carpal tunnel syndrome, vitreous opacities and CNS involvement may coexist in different proportions or may even present as an isolated or predominant manifestation [3].

Genetic epidemiology

§ The disease is present worldwide

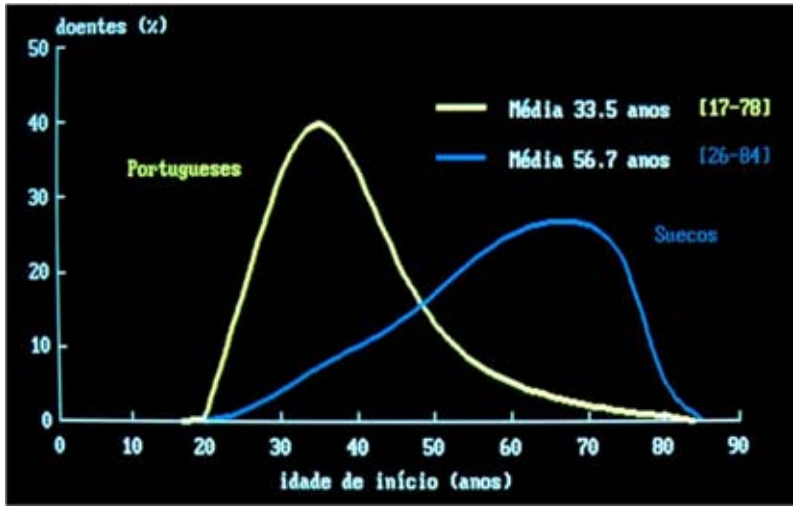
§ Some very large clusters have been identified, mainly related to TTRVal30Met mutation.

§ Variable penetrance of the gene is the rule [4,5].

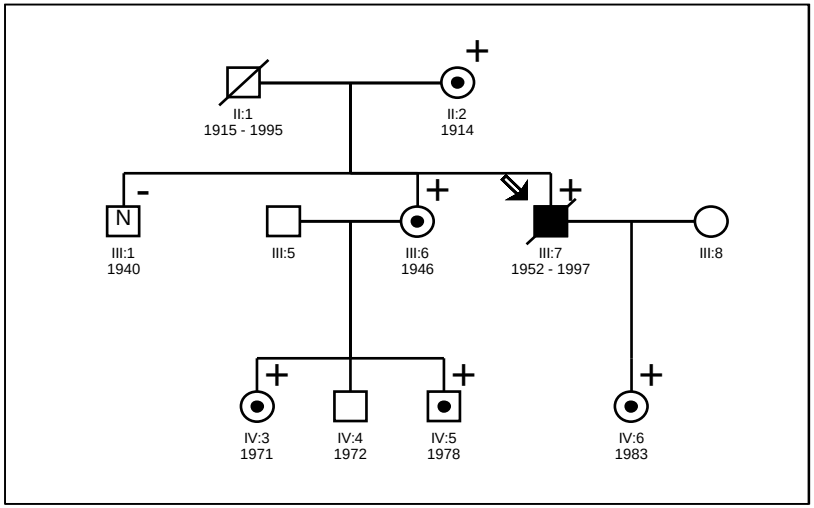
This variability explains:

- an age of onset from twenties to nineties
- the frequent diagnosis of “sporadic” patients

Age-of-onset distribution in Sweden and Portugal



A Portuguese family with an *isolated* case



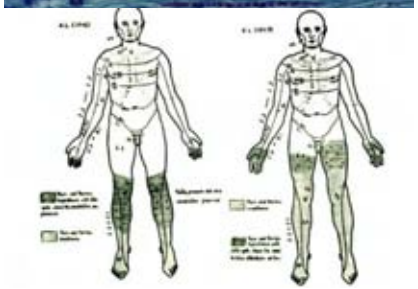
The first description of the disease

"A peculiar form of peripheral neuropathy" [6]

"It is a disease that attacks many members of the same family"

"It begins insidiously in the second or third decade of life"

"Lasting on an average seven to ten years"



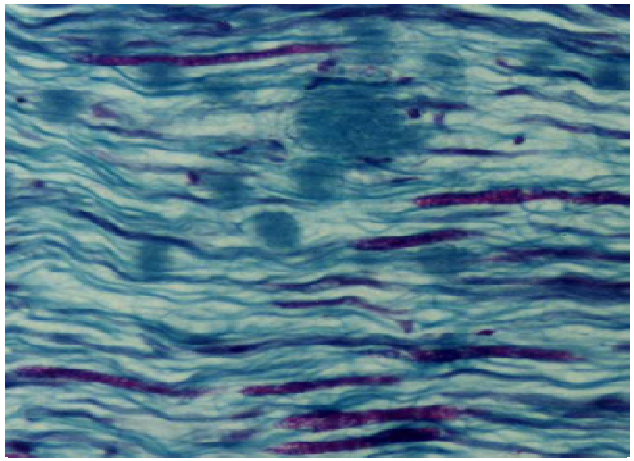
"Generalized atypical amyloidosis, involving especially the peripheral nerves"

"A peculiar form of peripheral neuropathy with lesions in the vegetative system"

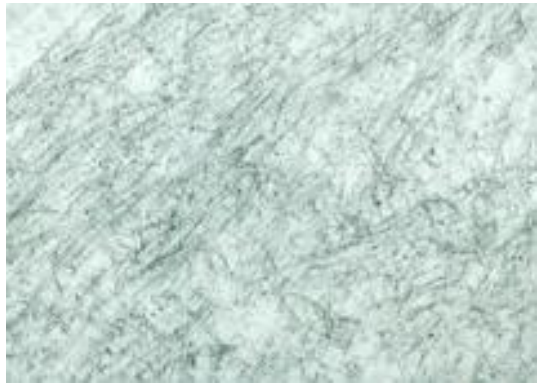
Pathogenesis of nerve lesion

Mechanisms of nerve lesion remain controversial

- Compression?
- Isquemia?
- Toxic effect?



- A toxic effect of amyloid fibrils, the precursor of amyloid substance, have been postulated.



Neuropathy characteristic evolution

- A length dependent, axonal, neuropathy with ascending sensory and motor loss
- Early involvement of unmyelinated and small myelinated nerve fibres
  - autonomic symptoms
  - pseudo-siringomyelic sensory loss with neuralgic pain
- Late involvement of large myelinated fibres
- The severity, the constant progression and the pleomorphism of symptoms are rarely seen in more common neuropathies.

Sensory neuropathy

- Neuralgic pain, dysesthesia and a discomfort in the feet that patients can't describe exactly are frequently the first and sometimes isolated symptoms.
- Loss of pain and temperature sensation associated with loss of vasomotor control is very dangerous. Burns and unexplained wounds are frequent.
- After two or more years sensory ataxia superimposes with motor problems and walking disability.
- Charcot's joints and pressure ulcers are common, either in the feet or more proximal in wheelchair bounded or bedridden patients.

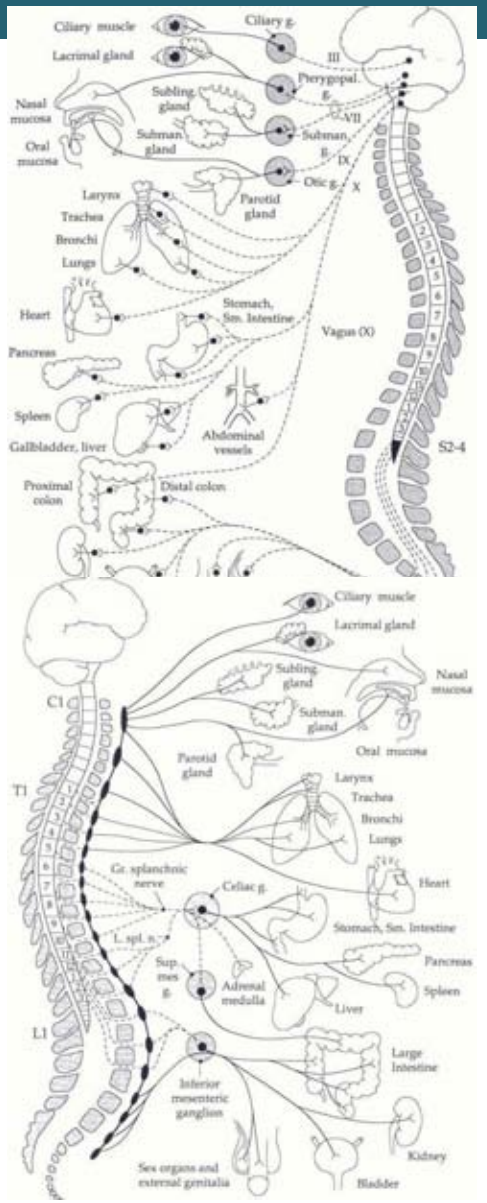
Autonomic neuropathy

Parasympathetic dysfunction

- All systems are early affected and dysfunction progresses constantly

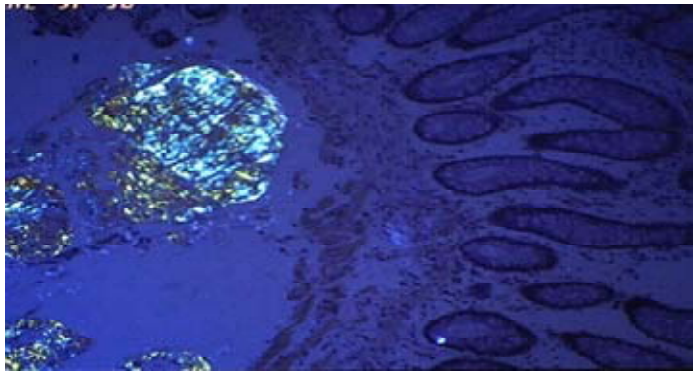
Sympathetic dysfunction

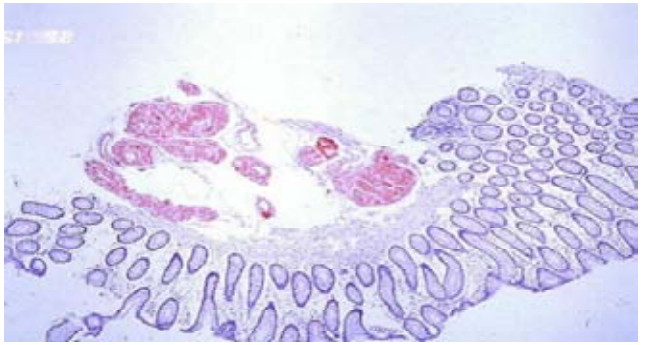
- Also progressive and severe.
- In some systems sympathetic dysfunction appears later than parasympathetic dysfunction.



Digestive and cardiac intrinsic nervous tissue involvement

- Contradictory results about the role of digestive intrinsic plexus lesion have been published.
- Intrinsic cardiac conduction system is known to be severely and early involved.





Symptoms of autonomic neuropathy

Gastrointestinal

§ Early satiety, nausea and severe vomiting

§ Constipation → Alternating constipation/ diarrhea
→ Diarrhea with loss of sphincter control

Cardiovascular

§ Taquicardia → fixed pulse rate

§ Orthostatic hypotension

Symptoms of autonomic neuropathy (2)

Genito-urinary

- Erectile dysfuction
- Neurogenic bladder: urinary retention $\longrightarrow$ stress incontinence $\longrightarrow$ permanent incontinence

Other

- Loss of vasomotor control
- Loss of distal and excessive proximal sweating
- Dry eye and mouth
- Pupillary malfunciton

Motor Neuropathy

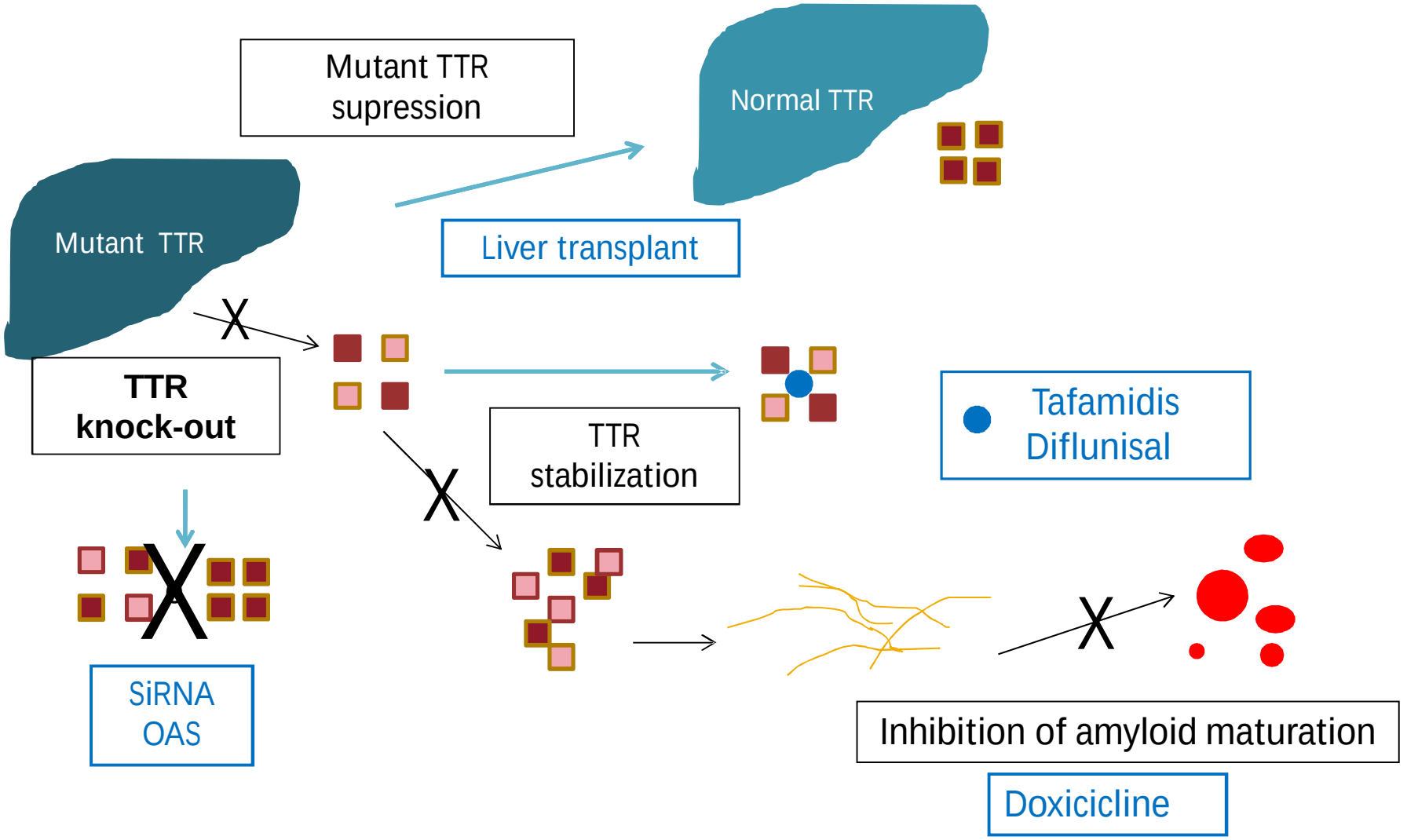
- Motor symptoms appear a few years after onset.
- They start in the lower limbs but atrophy and ascending paralysis ultimately involve all four limbs

When shoud we consider FAP diagnosis?

- A small fibre neuropathy with pseudo-syringomielic dissociation and autonomic symptoms.
- An axonal sensory or sensory and motor neuropathy with autonomic symptoms even subtle.
- Neuropathy associated with cardiomyopathy or cardiac rhythm disturbances.
- A severe progressive neuropathy even in the presence of an alternative etiology such as diabetes or alcohol.

Family history is frequently absent

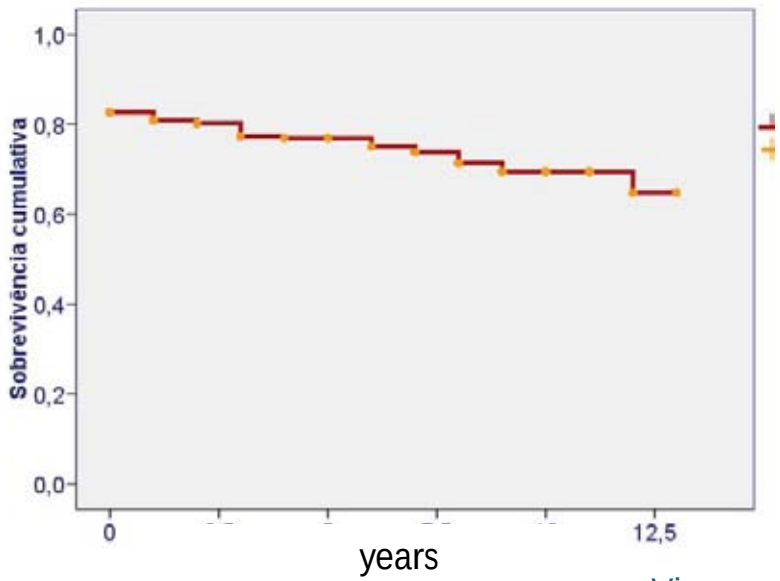
Therapeutic strategies



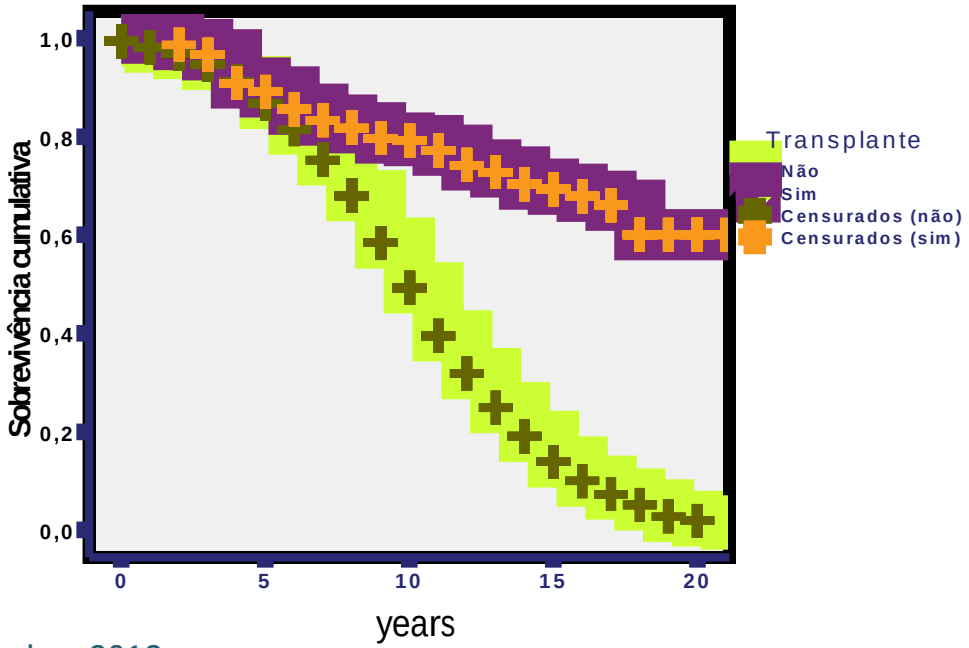
Liver transplant

- Liver transplant (since 1990) has proved to be an effective treatment to prevent the evolution of the disease, if done early in the course of the disease.
- Liver transplantation is associated with significant mortality and morbidity and long term complications but significantly changed the survival of these patients.

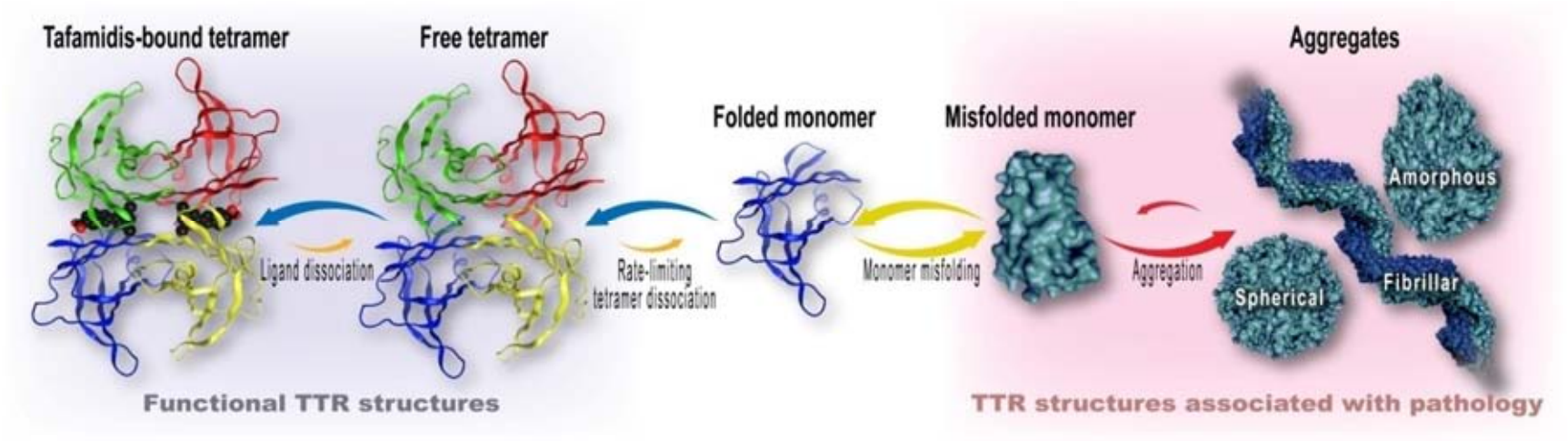
Survival of FAP pts
after liver transplant



Non-transplanted vs
transplanted pts survival



Tafamidis: mechanism of action



Cedido por J Kelly, TSRI

Tafamidis binds selectively to thyroxine binding sites, stabilizes the tetramer and prevents its dissociation into monomers and further formation of amyloid .

Tafamidis / Vyndaqel® EU indication

- Tafamidis is indicated for the treatment of transthyretin amyloidosis in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment

- Recommended dosage: 20 mg capsule once daily

- Treatment should be initiated by and remain under the supervision of a physician knowledgeable in the management of patients with transthyretin amyloid polyneuropathy

Other drugs under clinical development

- Diflunisal, another TTR stabilizer
  - A phase 3 double blind clinical trial with Diflunisal in Val30Met and non Val30Met FAP patients was closed recently and results are expected soon

- Drugs that knock-out TTR (wild and mutant)
  - Phase 3 clinical trials with a antisense oligonucleotide (ISIS) and a siRNA (Alnylam) are planned for the second half of this year
  - Promising results were shown at phase 1-2 trials

Conclusions

FAP is more common than previously thought

- It is present all over the world
- It is certainly underdiagnosed
- The variable penetrance with extreme differences in the age of onset and lack of family history and the variable clinical expression are common causes of delayed or missed diagnosis.

We can´t miss the diagnosis of a treatable disease

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