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Solid organ transplant in ATTR and non-ATTR

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Disclosures

Company	Disclosure
Celgene	Research dollars
Millenium	Research dollars
Alnylam	Research dollars
Prothena	Research dollars
Pfizer	Research dollars
Jannsen	Research dollars

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Hereditary systemic amyloidoses

Fibril name	Mutated precursor Protein	Target Tissues
ATTR	Transthyretin	PNS, ANS, heart, eye, leptomeninges, tenosynovium
AFib	Fibrinogen α-chain	Kidney
ALys	Lysozyme	Kidney, primarily
AApoAI	Apolipoprotein A-I	Heart, liver, kidney, PNS, testis, larynx, skin
AApoAII	Apolipoprotein A-II	Kidney
AGel	Gelsolin	PNS, cornea
ACys	Cystatin C	PNS, skin
ABri	Abri-PP	CNS
Aβ2M	β2-microglobulin	Musculoskeletal system

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Strange truths about hereditary amyloidosis

- For most types, the source of the ‘disease driving’ building blocks (mutant proteins) is the liver
- For most types, the disease driving organ (liver) doesn’t ‘appear’ sick

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Transplant Approaches

1. **Remove mutant protein producer**
   - **Liver transplant**
2. **Replace symptomatic organ**
   - **Possible for kidney or heart**
   - **Not possible for nerves or guts**
3. **Do both**
   - **And if both, in what order?**

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ATTR Transplant Trivia

1. First liver transplant for ATTR in 1990
2. First domino liver transplant in 1995
3. Partial liver transplants since 1995
4. ATTR patients do not meet criteria for liver transplant since “normal” liver

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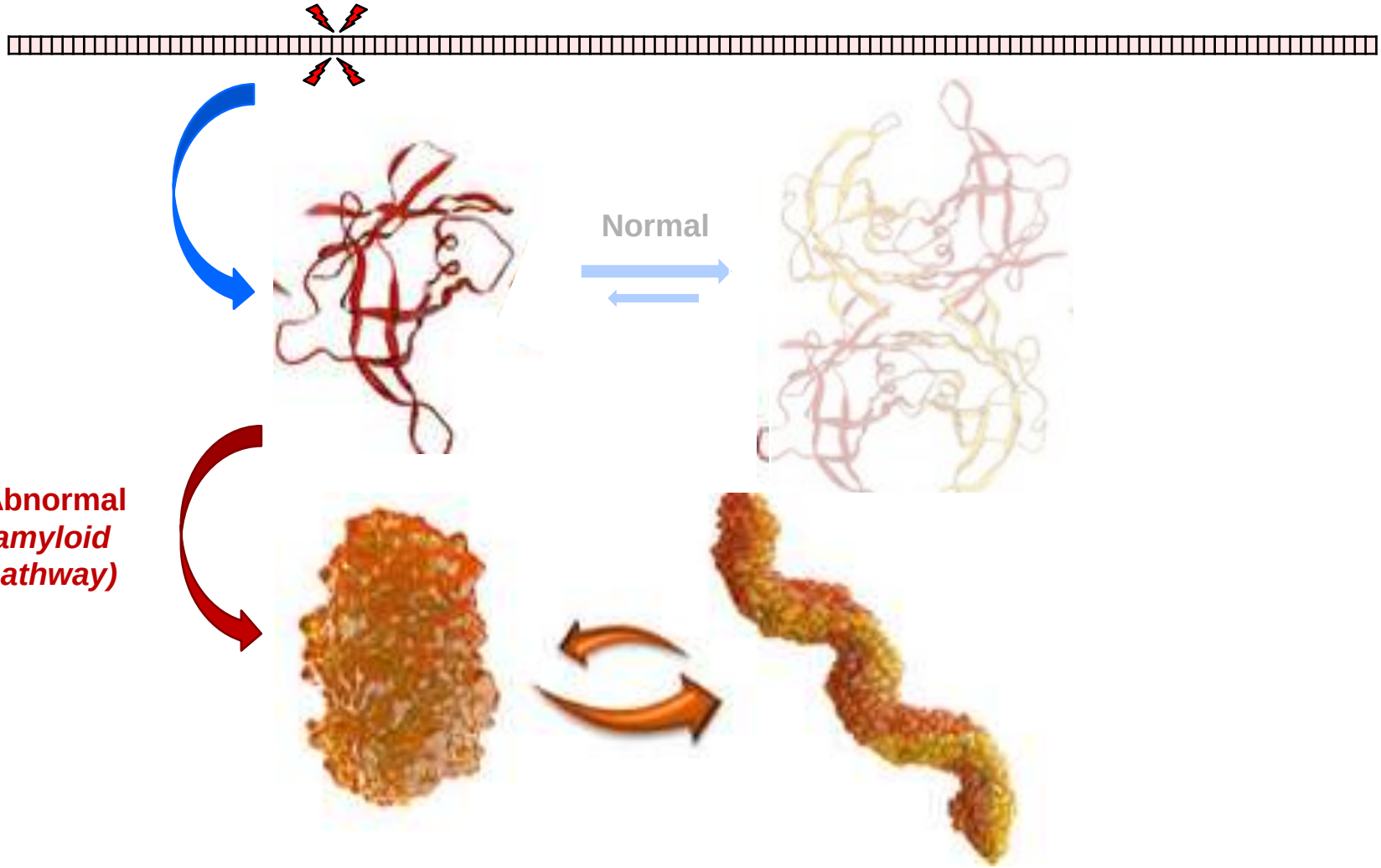
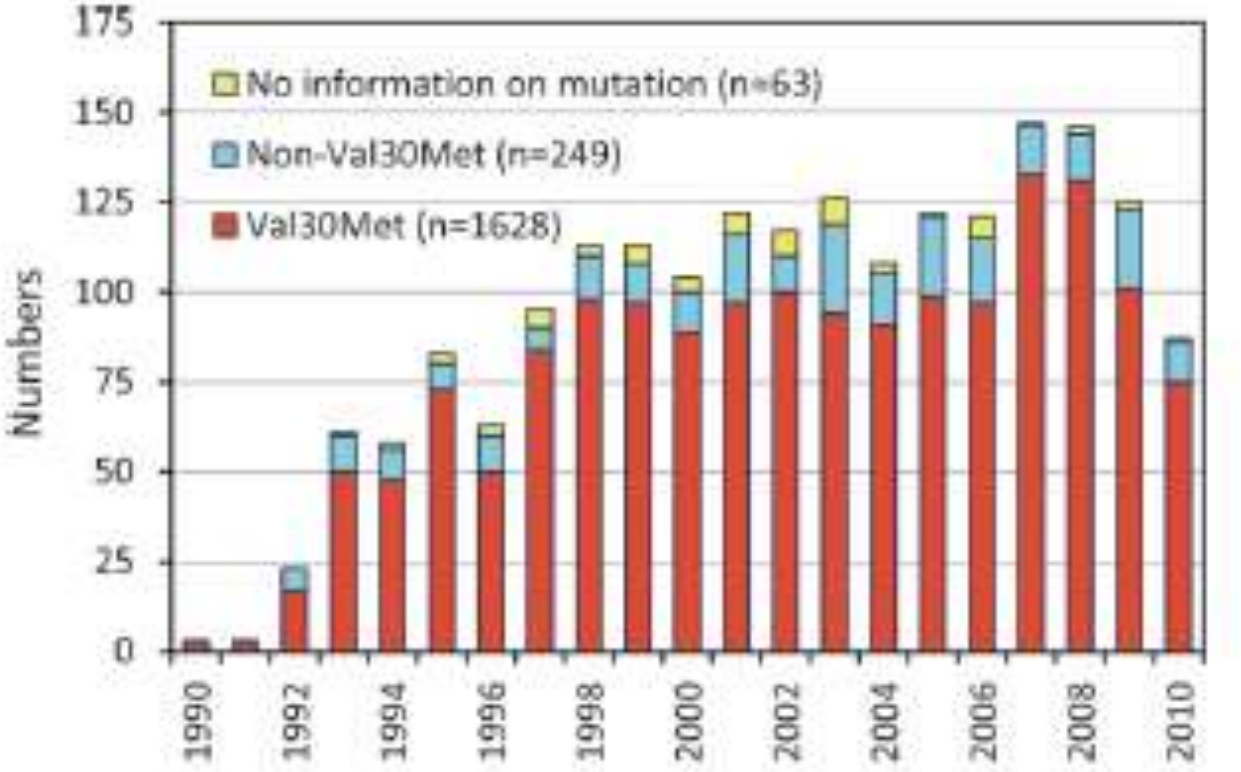
Mutation in protein

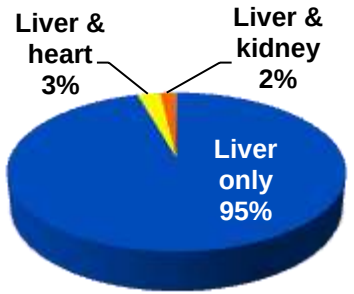
Transthyretin protein *(127 amino acids) stretched out*



Liver Transplantation for Hereditary Transthyretin Amyloidosis: After 20 Years Still the Best Therapeutic Alternative?

1940 patients undergoing 2127 liver transplants





Ericzon, B.G., et al., Transplantation, 2015. 99(9): p. 1847-54.

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10 year Survivorship Post-OLT

focusing on most common variants

- **Val30Met early onset** — **85%**
- **Val30Met late onset** — **45%**
- **Val71Ala (N)** — **85%**
- **L**
- **Leu58His (H/N)** — **76%**
- **Thr60Ala (H/N)** — **36% if liver Tx only**
  58% if heart & liver

Unfortunately, this tells us nothing about quality of life

- **Fewer than 50% alive: Ser50Arg, Ser77Phe, Ser77Tyr, Glu89Gln, Tyr114Cys**

N=nerve; H=heart

Ericzon,, et al., Transplantation, 2015. 99(9): p. 1847-54. Suhr et al Transplantation 2016;100(2):373-381.

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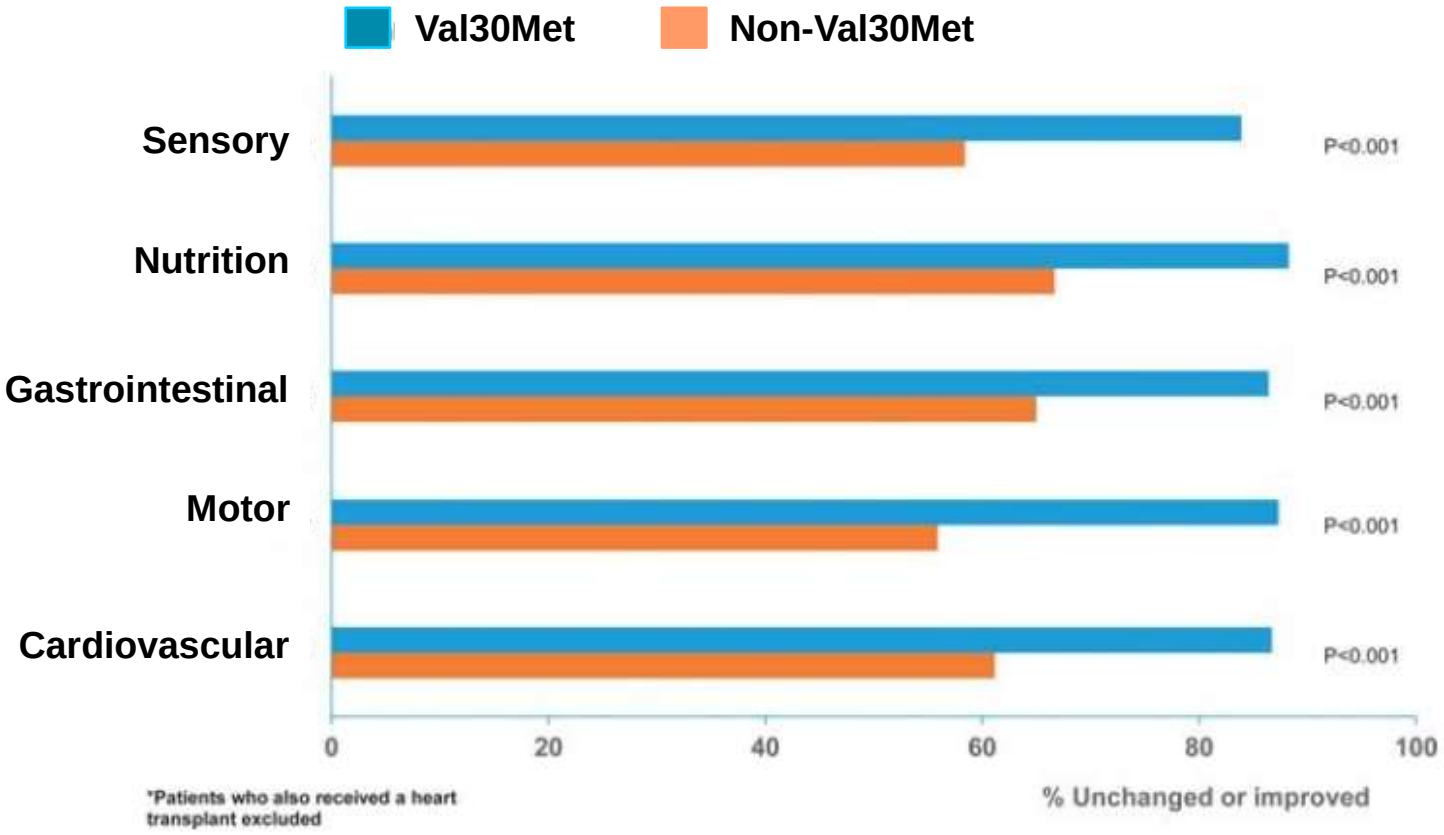
Stabilization of symptoms better in Val30Met Patients than non-Val30Met Patients with Liver Transplantation



Suhr OB, et al. Transplantation 2016;100(2):373-381.

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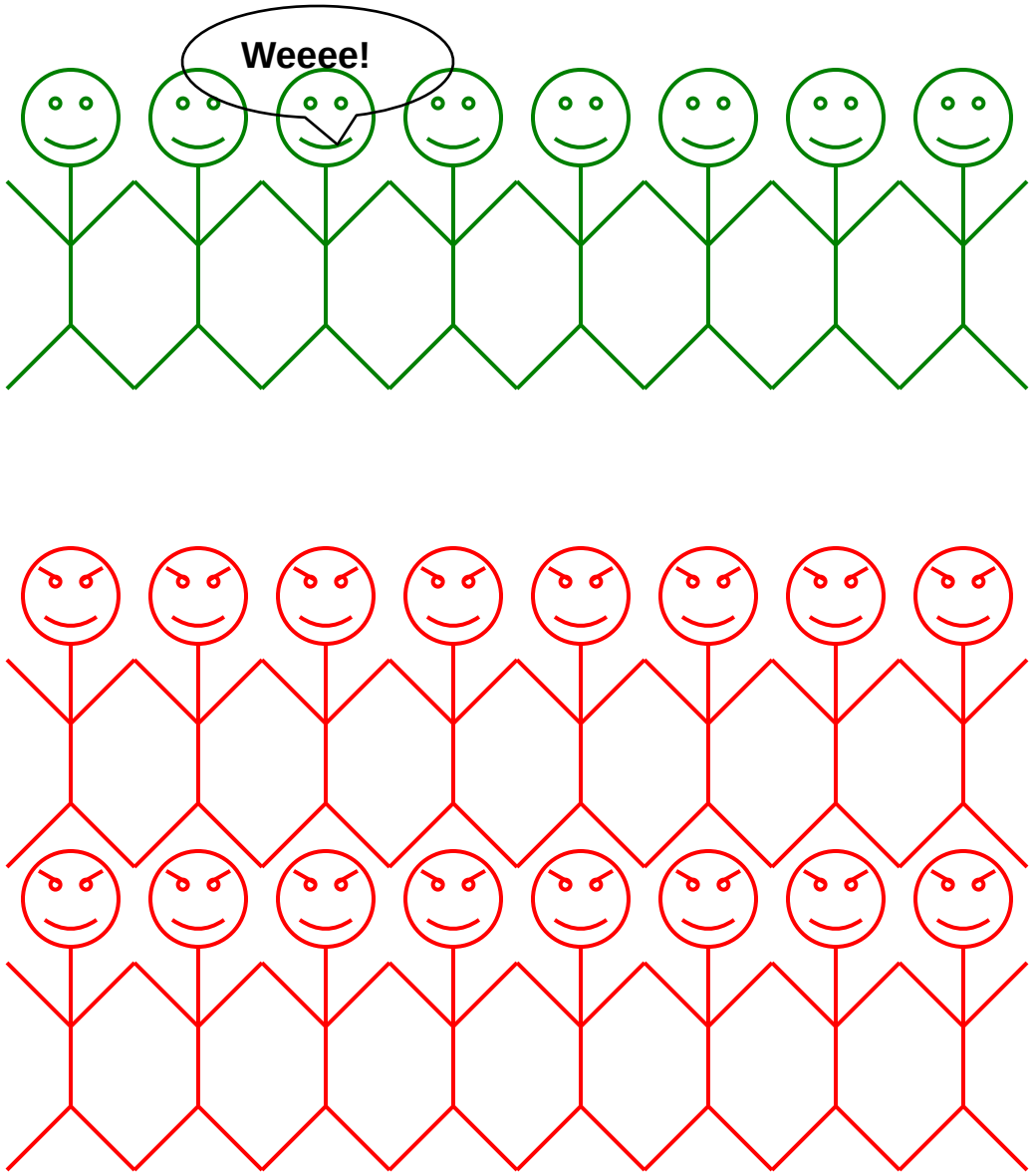
Mechanism of Progression Post Liver Transplantation



KEY

Mutant ATTR fibrils
Made of mutant TTR

Normal ATTR
joining the party

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Heart Transplantation for Hereditary ATTR

- **Trend for a superior overall survival among those receiving heart and liver transplant versus those receiving liver transplant only**

Banerjee D, et al. *Progress in Transplantation*. 2017;27(3):246-250.
Suhr, O, et al. *Transplantation*. 2016;100(2):373-381.

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Heart Transplantation in ATTRwt

Original Clinical Science—General

Outcomes After Cardiac Transplant for Wild Type Transthyretin Amyloidosis

Andrew N. Rosenbaum, MD,[1] Omar F. AbouEzzeddine, MD, CM, MS,[1] Martha Grogan, MD,[1] Angela Dispenzieri, MD,[2,3] Sudhir Kushwaha, MD,[1,3] Alfredo Clavell, MD,[1,3] Richard C. Daly, MD,[4] and Brooks S. Edwards, MD[1,4]

Background. The true prevalence of heart failure due to wild type transthyretin amyloidosis (ATTRwt) is likely underestimated. There is a paucity of data with regard to the management of ATTRwt-related advanced heart failure and the natural history of extracardiac ATTRwt. **Methods.** We conducted a retrospective cohort study of patients undergoing cardiac transplant (HTx) for ATTRwt at a single institution. Comprehensive clinical data, including baseline hemodynamic and echocardiographic characteristics, and posttransplant outcomes, were obtained. **Results.** Seven patients with ATTRwt underwent HTx between 2007 and 2015. All patients were male with a mean age of 66 ± 9. Patients had a reduced ejection fraction (mean, 37 ± 14%) and elevated filling pressures pre-HTx (mean pulmonary capillary wedge pressure 22 ± 7 mm Hg) before HTx. Three-year survival was 100%; 1 patient died of pancreatic cancer 45 months post-HTx (1 death per 30.8 patient-years). Oxygen consumption (Δ +6.8 ± 4.9 mL·kg^{-1}·min^{-1}) and 6-minute walk distances (Δ +189 ± 60 m) improved. Symptomatic gastrointestinal involvement (n = 2) and peripheral nerve involvement (n = 4) by ATTRwt developed late. **Conclusions.** This is the first report of a series of ATTRwt patients receiving HTx in which excellent outcomes are demonstrated. Although cardiac death is averted, systemic manifestations of ATTRwt may develop posttransplantation.

(*Transplantation* 2018;102: 1909–1913)

100% survival at 3 years

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What Does It All Mean?

Known Stuff in ATTRv

1. **Survival improved with liver transplant in V30M**
   - ***but what about new drugs?***
2. **Most effective if early**
   - ***but how early?***
3. **Major benefit in nutrition**
4. **Combined liver + heart and liver + kidney feasible**

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What Does It All Mean?
Unknown Stuff in ATTRv

1. **When is organ transplant futile?**
2. **Which mutations benefit?**
   - ***Early onset V30M, V71M, L111M, L58H***
3. **If heart involved, need combined heart and liver?**
   - ***And if so, in what order?***
4. **Should transplant patients get new drugs?**

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Hereditary, systemic amyloidoses

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AApoAII	Apoli	
AGel	Gelso	
ACys	Cystat	
ABri	Abri-PP	CNS
Aβ2M	β2-microglobulin	Musculoskeletal system

Made entirely in the liver

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Fibrinogen A α

- Most common of hereditary renal amyloidoses (Ostertag 1932)
- First mutation described by Dr. Benson, 1993
- Middle age presentation
- If kidney replacement alone, graft fails in 1-7 years with 10-year graft survival of 5% (vs 65%)

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First Report of Liver Transplant without Kidney Transplant for Fibrinogen A alpha chain Renal Amyloidosis

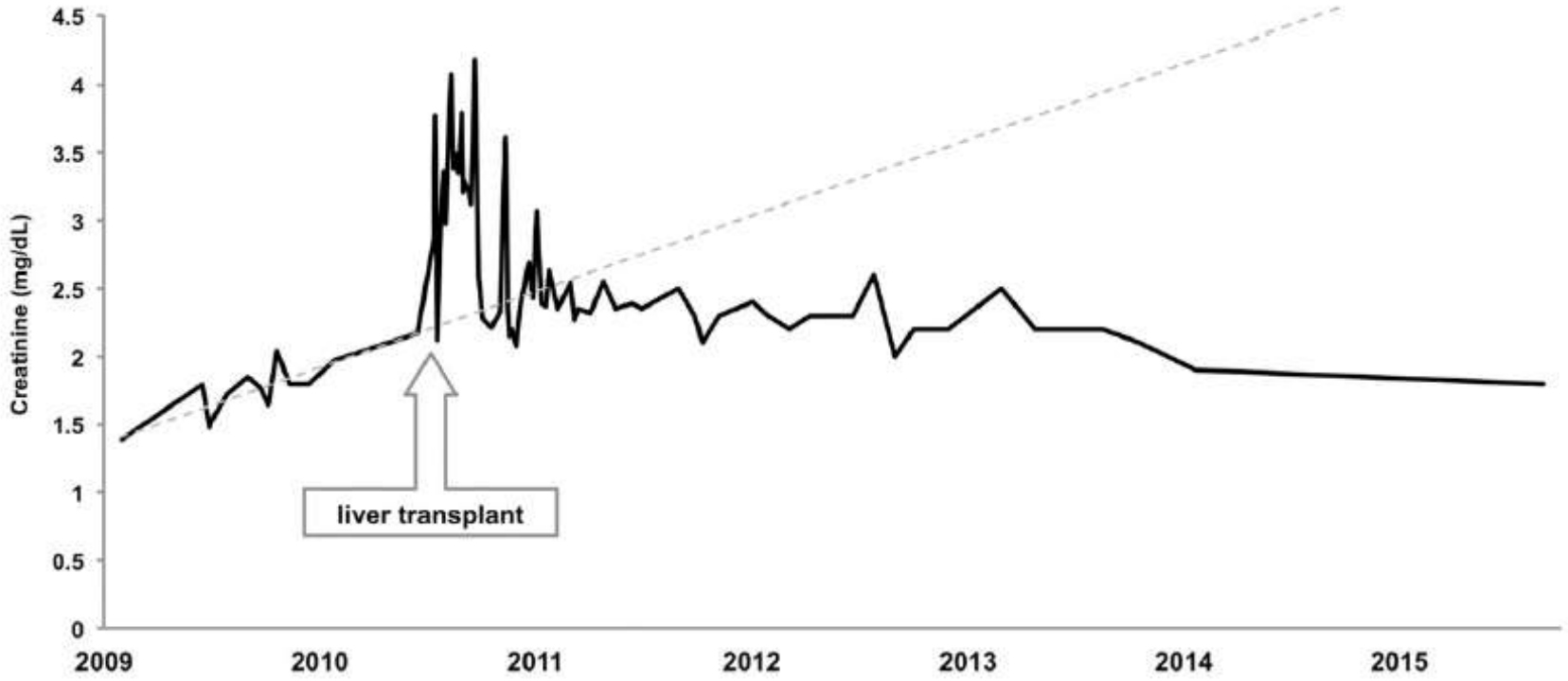

Figure 1. Time course of serum creatinine level in patient with liver transplantation without kidney transplantation.

***Fix et al. Amyloid*. 2016;23(2):132-133.**

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Transplants for AApoAI and ALys

- **AApoA-I**
  - **14 kidney only**
  - **1 kidney and liver; 1 kidney and heart**
  - **10 year graft survival was 77%**
- **ALys**
  - **3 patients received kidneys**
  - **All 3 grafts functioning between 0.9 and 6.2 years**

Pinney et al. American Journal of Transplantation 2013; 13: 433–441

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ALECT2—Renal Transplant
(short follow-up)

- **5 patients with renal failure and ALECT2**
  - **Biopsy positive in 1 patient at 6 months**
  - **No recurrence in 4 at 20 months**

    Said SM. Kidney Int. 2014;86(2):370-377.
- **5 patients with LECT2 in allografts @ T_0**
  - **FU @ 14, 14, 26 months doing well.**
  - **One died infection at 3 months**
  - **One lost kidney at 84 month due to chronic rejection**

    Mejia-Vilet et al. Am J Kidney Dis. 74(4):563-566.

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AFib, AApoAI, Alys, LECT2: Who and When?

1. **Intriguing concept of OLT before renal failure in AFib**
2. **Hard to be too dogmatic for who and when for these very, very rare types**

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In a perfect word, there would be no liver transplant…

- **…Safe, effective, affordable drugs would help take care of the problem**

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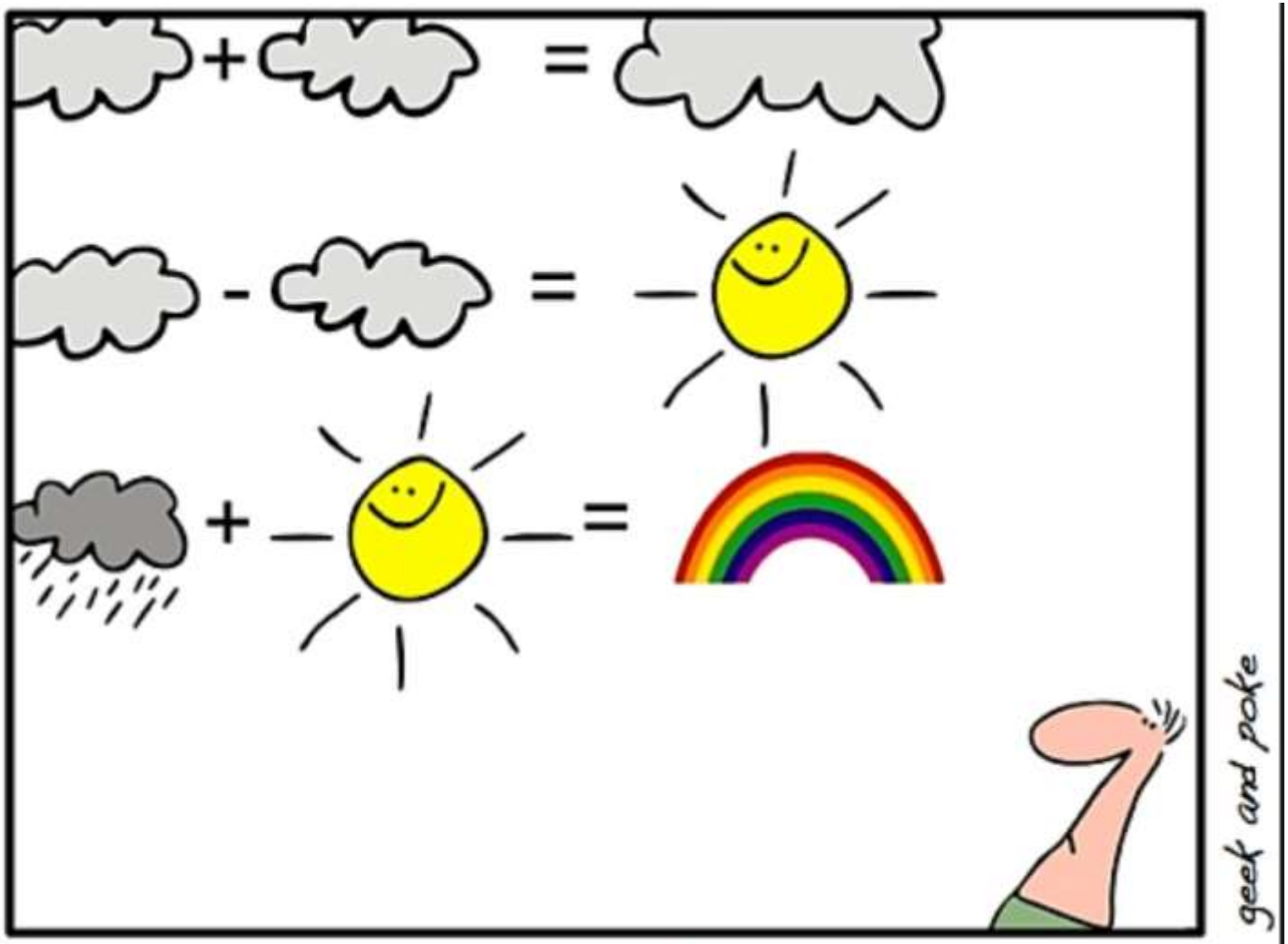
Questions?



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Brain Microbleeds 12 Years after Orthotopic Liver Transplantation in Val30Met Amyloidosis

Fabrizio Salvi, MD, PhD,* Francesca Pastorelli, MD, PhD,* Rosaria Plasmati, MD,* Cristina Morelli, MD,† Claudio Rapezzi, MD,‡ Andrea Bianchi, MD,§ and Mario Mascalchi, MD, PhD§

Unexplained focal neurologic episodes (FNEs) can occur in patients with transthyretin-related familial amyloidotic polyneuropathy (TTR-FAP) after orthotopic liver transplantation (OLT). A patient with Val30Met FAP underwent OLT at age 34 years. Twelve years after transplantation, she presented with recurrent FNEs lasting from 10 minutes to 8 hours each, with nonuniform deficitary clinical features and variably associated with headache. Magnetic resonance imaging showed multiple brain microbleeds and diffuse contrast enhancement of the craniospinal leptomeninges consistent with amyloid deposits. Our observation suggests that microbleeds associated with meningovascular amyloidosis can underlie FNEs in TTR-FAP. Moreover, it confirms that OLT does not halt progression of leptomeningeal and vascular amyloid deposition due to TTR production in the choroid plexuses. Such a progression might compromise the good long-term prognosis of patients with TTR-FAP due to increased risk of intracranial hemorrhages. Pharmacologic therapies targeting brain TTR production may modify this scenario. **Key Words:** Cerebrovascular amyloidosis—magnetic resonance imaging—microbleeds—TTR-amyloidosis.

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Series of V30M patients

Table 1. Clinical data of patients included in the study, pre and post-OLT.

n = 54	Pre-OLT	Post-OLT
Neuropathy worsening		37 (71%)
Nephropathy	8 (15%)	18 (35%)
Cardiopathy (any)	14 (26.4%)	32 (61.5%)
Arrhythmias	5 (9.4%)	20 (38.5%)
HF	1 (1.9%)	5 (9.6%)
AVB	5 (9.4%)	18 (35.3%)
Maximum wall thickness	10.08 ± 2.15mm	13.1 ± 4.75mm
Diastolic dysfunction	6 (13.3%)	16 (53.3%)
LVEF	61 ± 3.6%	59 ± 6.7%

Ripoll-Vera, T., et al. (2019). Amyloid 26(sup1): 18-19.