

Amyloidosis Support Groups ATTR/Hereditary Meeting Notes

Chicago, 2019-10-26--27

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03 Diagnosis

Terms

Amyloidosis = Protein folding disorder

TTR = transthyretin: Transports thyroxine (a thyroid hormone) and retinol (vitamin A). Also known as Prealbumin

Over 95% of TTR is produced in the liver. But some is produced by the eye and brain (choroid plexus).

ATTR = amyloid TTR (abnormal TTR, misTTR, the TTR than misfolds)

ATTR production can be caused by one of over 100 genetic mutations (hereditary ATTR (hATTR, ATTRh, ATTRm (m=mutant))), or by age (wild type ATTR, (ATTRwt, wtATTR)).

About 4% of African Americans have hATTR, with the mutation TTR V122I)

Other (non-ATTR) hereditary amyloidosis

See Hereditary systemic amyloidoses in "06 Organ Transplant as therapy" section, below.

General information

Amyloid deposits look white, so they look like starch, which is why it got the name Amyloid.

When the protein is mis-folded, it is sticky - it sticks together, creating insoluble fibrils that resist degradation - but the mis-folded TTR has binding sites for Congo red stain, so we can use Congo red stain to detect it.

The body's protein quality control systems break down proteins. With age, our quality controls become less effective, so older people can get "wild type" amyloidosis, with mis-folded proteins not getting cleared out, and building up, to create problems.

How amyloidosis is usually diagnosed:

1. First, Congo red stain helps detect it
2. Second, laboratory tests determine the type of amyloidosis

Additional tests may support the diagnosis

Differential diagnosis (other diseases that look like Amyloidosis)

Proteinuria/nephritic syndrome in adults may be caused by:

1. Focal and Segmental Glomerular Sclerosis/Minimal change disease
2. Membranous nephropathy
3. Diabetes
4. Amyloidosis

Detecting amyloidosis

Early on, amyloidosis is not easy to detect with Congo red, because there is not as much misfolded protein to detect.

Where do we look, with Congo red? Could do the effected organ, but testing in body fat can be better. Early diagnosis can result in much better outcomes, but is difficult to achieve.

ATTR detection in fat:

Sensitivity is 54-93% = chance of detecting it, if it is there)

Specificity is 93-100% = chance of having a negative test, if you do not have ATTR)

Testing in fat is easy, but a biopsy of heart muscle will be more sensitive (more likely to detect disease, if it is present)

04 - Wild Type

TTR protein becomes unstable with age, and gets stuck in various places in your body, causing problems.

Alternate names for wild type amyloidosis

"Senile Cardiac Amyloidosis" SCA

Senile Systemic Amyloidosis (SSA)

Age-related Cardiac Amyloidosis

Wild type generally hits around age 70, but can hit in the 40s or 50s

How proteins are made (video)

RNA in your body's cells help Amino acids join together to form proteins. The folding creates the "secondary structure", and then folds further to create the "tertiary structure". TTR has 4 proteins, so they fold ever more, forming a "quadrinary structure". The mid-folded TTR protein happens to be folded such that it sticks to other TTR proteins. We don't know yet why it tends to accumulate in certain places, like the heart.

The heart wall gets infiltrated with the mis-folded amyloid, getting thick and stiff, so the heart can't beat as well.

Wild type vs. hereditary ATTR - who gets which?

	ATTRm	ATTRwt
Age (years)	Variable (depends on mutation)	>65
Gender (%M/%F)	50%/50%	95%/5%
Race (To date)	Depend on mutation	Predominately Caucasians
Affected Organs	Nerves, Heart, (Eyes)	Heart

Ejection Fraction Sucks in Cardiac Amyloidosis

Ratio of blood out vs. total blood held in heart - in Amyl, it look fine (Because the heart holds less blood to start - the denominator is small), even though the blood volume ejected is small.

PYP scans can detect amyloid in the heart

Treatment

Restrict Salt! - the mainstay, along with diuretics

Atrial Fib - use a blood thinner, maybe for life

Calcium channel blockers - maybe. For some patients, these can cause more harm than good.

Hypertension - compression stockings and midodrine

AICD / pacer (use of a pacemaker) - More of a role for pacing

New drugs

Tafamidis - FDA approved for Amyloidosis treatment. Expensive.

Diflunisal - Not FDA approved for Amyloidosis treatment. Cheap. Not good for folks with certain conditions (best if there is:

- no recent decompensation
- Good renal function
- Daily diuretic dose < 80 mg Lasix, no metolazone
- ? Use with anticoagulation

Several other medications are approaching approval

05 hATTR - hereditary amyloidosis

Overview of Hereditary Transthyretin Amyloidosis (hATTR)

Frederick L. Ruberg, MD

Amyloidosis Center, Boston University School of Medicine

Alternate names of hATTR

Also called "Variant TTR" or "mutated TTR", familial amyloid polyneuropathy (FAP), familial amyloid cardiomyopathy (FAC) (see later slides)

How the body makes proteins

DNA, made of nucleotides, guides the formation of RNA, which guides the formation of proteins

A series of 3 nucleotides form one of twenty amino acids, which are strung together into proteins.

DNA mutations

Polymorphism - the differences between people

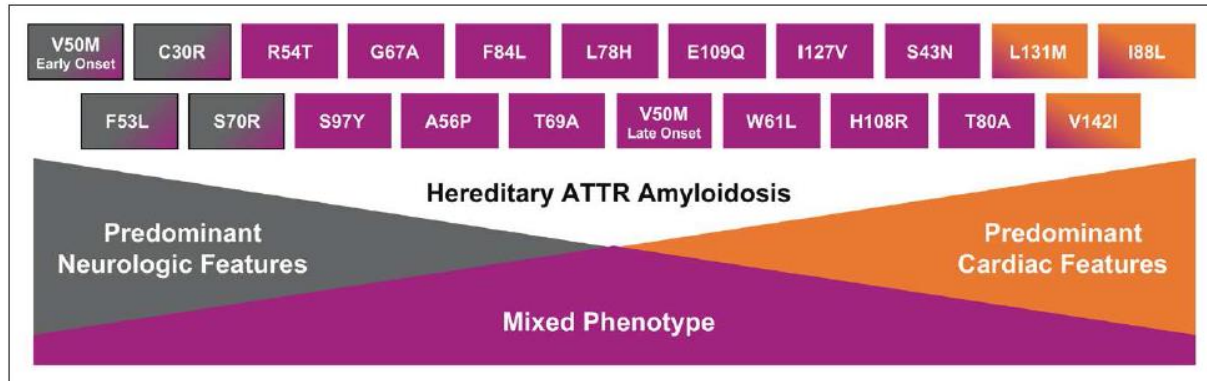
In DNA, polymorphisms can be a change in nucleotides. Sometimes this doesn't matter, but sometimes it changes how the protein that is produced.

TTR is on chromosome 18 (chromosome - a bunch of DNA). If the wrong nucleotide is in a certain place on this, you can have hereditary ATTR (amyloid TTR)

Effects of different types

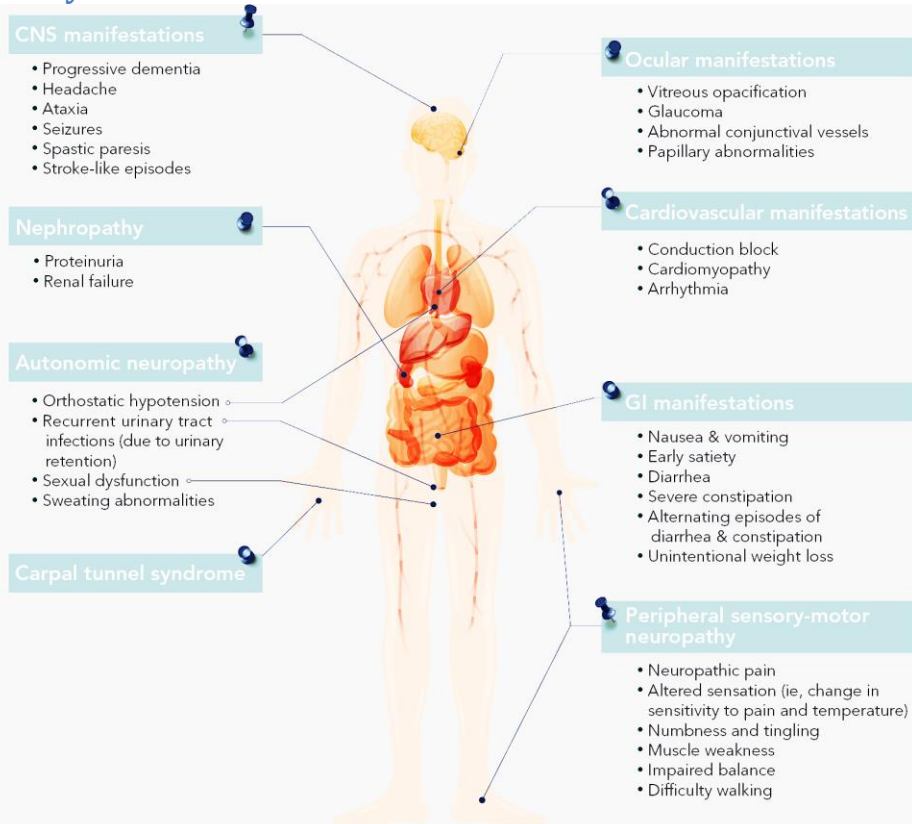
ATTR affects heart and nervous system, in general. But there is a lot of variability.

Different mutations have different sets of symptoms. For instance:



Source: Maurer, *Circulation: Heart Failure* 2019
 Same type may manifest differently in different persons.

Symptoms may include ...



Source: <https://hattramylodosis.co.uk/en-gb/symptoms>

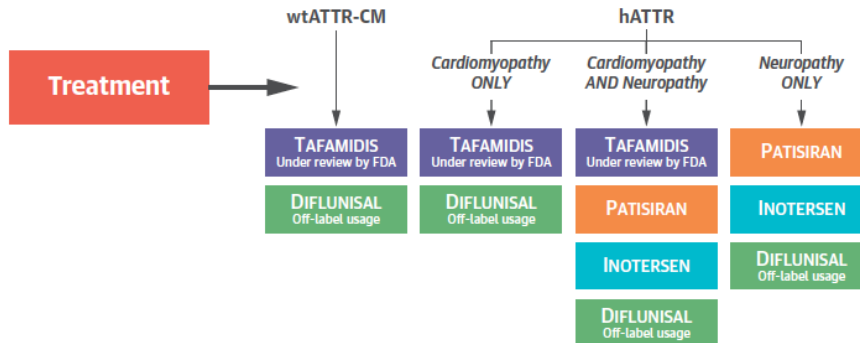
How common is ATTR

- 50,000 worldwide with manifest disease.
- V122i occurs in about 3.5% of African Americans, 150,000 over age 65 at highest risk for hATTR.
- Even at Boston, a top center for ATTR, it goes undetected. We need to keep increasing doctors' awareness.
- Distribution of different types of ATTR varies by country

Type affects treatment

Different types need different treatments

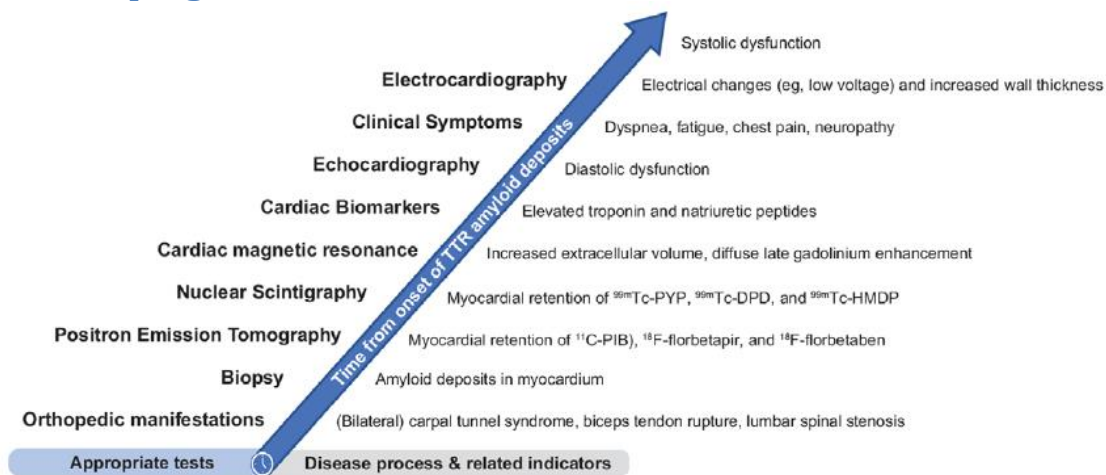
New drugs only approved for hATTR, not wtATTR. So insurance won't pay for them for wtATTR treatment.



Knowing your type

- 23&me genetic testing looks for a few TTR mutations
- What do we tell children of folks with hATTR symptoms? We don't know whether or when to start therapy for folks with the genetic mutation, but without symptoms.

Disease progression & tests



- See Dr. Maurer et al. paper about progressive testing and treatment: "Expert Consensus Recommendations for The Suspicion And Diagnosis Of Transthyretin Cardiac Amyloidosis" Maurer, Circulation: Heart Failure 2019.
- 1st guidelines for Amyloidosis! From ASNC: how to use imaging testing to detect ATTR

Early signs

Orthopedic manifestations - early sign of ATTR? Tests of tissue removed during carpal tunnel showed about 10% with ATTR, 2 which were hATTR (Sperry, Hanna JACC 2018)

Early signs

- Bilateral carpal tunnel
- Spinal Stenosis
- Spontaneous biceps tendon rupture

Conclusions

- hATTR results from a single base pair change in the TTR gene, that causes a change in the TTR protein resulting in misfolding and amyloid fibril formation
- hATTR is passed down to children in an autosomal dominant manner (50% chance of passage)
- The type of mutation determines the predicted symptoms and organ systems that are affected
- Determination of genotype is critical to selecting treatment
- We must move toward early identification to give treatments the best chance to work

06 Organ Transplant as therapy

Angela Dispenzieri, M.D., Professor of Medicine & of Lab. Medicine, Mayo Clinic

Transplant basics

Used in some ATTR, and other amyloidosis types (AFib, ...)

The liver produces TTR, but is generally not affected by the ATTR.

Hereditary systemic amyloidoses

<u>Fibril name</u>	<u>Mutated precursor Protein</u>	<u>Target Tissues</u>
ATTR	Transthyretin	PNS, ANS, heart, eye, leptomeninges, tenosynovium
AFib	Fibrinogen a-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
Ab2M	b2-microglobulin	Musculoskeletal system

What to do with involved organs

1. Replace the liver - the main source of most of these proteins
2. Replace the affected organs (heart, kidney, ... - but we can't replace nerves or skin)
3. Do both

Liver transplants

Liver ATTR transplants:

- 1st liver transplant for ATTR done in 1990
- 1st domino transplant for ATTR in 1995
- 1st partial liver transplant for ATTR in 1995

Domino transplant

ATTR pt gets new liver, ATTR pt's liver goes to someone else who would not get one otherwise (but it may produce hATTR in the recipient, even within 10 years, so that needs to be considered).

Partial liver transplants

family member gives part of their liver to the person with ATTR.

Does liver transplant cure the disease? Not always

- Symptoms may continue to get worse, even after transplant. Why? It seems like normal TTR may stick to ATTR, if ATTR has already accumulated.
- ValMet30 pts usually DO get better after transplant
- Other types have smaller portion of pts getting better after transplant:
- ATTR wild-type: replacing the liver does not affect things - the problem is in cleaning up TTR is the body, not in what is produced.

10 year survival rate varies by type of ATTR:

Val30Met early onset	85%
Val30Met late onset	45%
Val71Ala (N)	85%
Leu111Met (H)	83%
Leu58His (H/N)	76%
Thr60Ala (H/N) heart & liver	58%
Thr60Ala (H/N) liver Tx only	36%
Ser50Arg	<50% (less than 50%)
Ser77Phe	<50%
Ser77Tyr	<50%
Glu89Gln	<50%
Tyr114Cys	<50%

Note: Quality of life may be poor after a transplant.

When is organ transplant going to help or not?

We don't know for sure. The ATTR type gives us some clue, but there is still uncertainty. Some of the new drugs may help, with or without a liver transplant.

What we know:

- Survival improved with liver transplant in V30M. But would the new drugs help even more?
- Most effective if early. But how early?
- Major benefit in nutrition
- Combined "liver + heart" or "liver + kidney" feasible

What we don't know:

- When is organ transplant futile?
- Which mutations benefit? (most benefit seems to be in early onset V30M, V71M, L111M, L58H)
- If heart involved, need combined heart and liver? And if so, in what order?
- Should transplant patients get new drugs?

Transplants may help some non-ATTR types:

Fibrinogen A (not ATTR) - Liver transplant had some promising data

AApoA-1 (among 16 kidney transplant cases, 10 year graft survival was 77%)

ALys (among 3 kidney transplant cases, all grafts functioning between 0.9 and 6.2 years)

ALECT2 - weak evidence supports kidney transplants

But we need more evidence around these.

Drugs or transplant?

Transplants have waiting lists, can be very debilitating, and have many side effects. We hope that medications will become effective and safe enough that transplants won't be needed.

Morie - had pt that had liver transplant, then gene silences Tx, which seemed to trigger rejection of the transplant.

07 Genetic counseling

Katie Agre, MS, LCGC agre.katie@mayo.edu

Licensed Certified Genetic Counselor

Genetics basics

Change a gene, change a person's characteristic, like eye color. Variation in genes is natural.

Genetic testing helps identify whether ATTR is hereditary or not. That has implications for your blood-line family members (i.e., if yours is hereditary, they likely to be at high risk for ATTR).

Why do genetic testing?

- Confirm whether the amyloidosis in your family is genetic vs. wildtype
- Impacts treatment and eligibility to clinical trials
- Necessary for testing of family members
- Can provide information about what to expect medically

Why talk to a genetic counselor?

- Genetic counselors discuss: many things, but especially how to talk to family members about your condition, support (like ASG), the chance they have it, and a concise, useful package of information (vs. the rabbit-hole of disorganized, confusing information they may find on the internet).
- Genetic counselors prepare you for the various ways your family members may react
 - Your children may or may not want to be tested. That is a personal choice. Just knowing that you have the genetic abnormality affects how folks think
 - Should I change my retirement plans?
 - Does this affect my plans for having kids?
 - Does this point me toward other lifestyle changes?
 - How do I share this information with a partner? A fiancé? Do I talk about it on the 1st date? After our honeymoon?
 - Relatives who are negative may feel something like "survivor's guilt".
- Once you know your gene status, you can't un-know it, so the decision to get tested is personal, and merits being made thoughtfully, after being well-informed.
- Genetic testing can allow for earlier diagnosis, which may have advantages given the availability of treatments.

Who else is at risk?

1st degree relatives (siblings, children, parents) have 50% chance of carrying the gene mutation

Other relatives may also have the mutation

Sharing information about risk?

- Open communication!
- Family letter
- Other resources, like Amyloid Support Group website, <http://amyloidosisupport.org/>
- Identify the family communicator

You know your family best!

Discussing genetic testing with un-tested family members

- Genetic testing is a personal choice
- Think about implication of knowing?
- Make sure your loved ones are informed about risks, benefits, and logistics of testing PRIOR to getting tested,
- Get tools to adapt and share information with family

Things to consider before getting tested

- How will I feel if I am not at risk?
- How will I react if I am positive?
- How will I use this information?
- Am I able to handle the impact of the positive result?
- Is now the right time?
- Insurance implications
- Insurance often covers the cost of the testing
- Genetic Information Non-Discrimination Act (GINDA) protects most individuals from discrimination for:
 - Health Insurance
 - Employability
- GINDA does not apply to:
 - Life Insurance
 - Disability Insurance
 - Long-term Care Insurance

08 The Gut

Dr. Clarke's Dad has wtATTR

Sx per type of GI involvement

Amyloid can affect anywhere in the GI tract

It can affect the outer layer, middle, or inner layer of gut (intestine)

- Inner layer - diarrhea
- Muscles - constipation, small intestine bacterial growth (stuff isn't pushed through fast enough, bad bacteria increases)
- Nerves - Motility coordination decreases - so stuff can move fast or slow, so constipation or diarrhea, nausea.
- Vascular - bleeding

Symptoms per place along the digestive tract affected

Symptoms are linked to area of involvement & are often non-specific

Esophagus

Reflux

Dysphagia

Food impaction

Stomach

Abdominal pain

Nausea
Vomiting
Distention

Small intestine

Diarrhea
Malabsorption
Weight loss
Pseudo-obstruction

Colon

Diarrhea
Constipation
Fecal incontinence

Diagnosing causes of GI problems

Most symptoms of amyloidosis are NOT specific to amyloidosis. Most are very common, and are usually caused by a lot of other diseases, or side-effects of many medications.

Endoscopy, colonoscopy, biopsies - can only detect types that manifest in the inner layer of the intestine.

Imaging - gut thickness, ... Usually reserved for testing if initial tests don't indicate the cause

Motility studies - ... Usually reserved for testing if initial tests don't indicate the cause

Treatment options

Small bowel - usually, a wave of muscle contractions moves material out of the small bowel every 90 minutes. If amyloid hinders that, bacteria can build up, creating gas & other symptoms.

Esophagus

Reflux treatment options

Dietary modification
Antacids
Histamine receptor blockers
Proton pump inhibitors
Endoscopic/surgical options in carefully selected patients

Dysphagia treatment options

Dietary modification
Dilatation
Botox

Stomach

Dietary modification

Prokinetics

Metoclopramide (Reglan)
Erythromycin/azithromycin
Domperidone (not FDA-approved)
Prucalopride

Bethanechol
Pyridostigmine

Agents to help stomach expansion

Herbal therapies (peppermint/caraway)
Bupirone

Neuromodulators

Tricyclics (amitriptyline)
Mirtazapine (Remeron)
Gabapentin (Neurontin)
Gabapentin/pregabalin (Lyrica)

Anti-emetics

Endoscopic options: Botox

Small bowel

Dietary modifications

Prokinetics

Antibiotics (focused on small intestinal bacterial overgrowth)

Octreotide

Steroids

Bile-salt binding agents

Anti-diarrheal

Imodium
Lomotil
Tincture of opium

Parenteral nutrition (rare cases)

Colon

Dietary modifications

Laxatives

Over the counter
Miralax
Senna
Magnesium-based preparations

Prescription

Lubiprostone (Amitiza)
Linaclotide (Linzess)
Plecanatide (Trulance)

Prucalopride (Motegrity)*

Prokinetics

Epidemiology

Studies found less than 45% of ATTR pts with GI symptoms had ATTR detected in GI biopsies. Biopsies often won't reach the affected parts of the GI tract.

Conclusions

- Amyloid can cause symptoms by either direct deposition or nerve involvement
- Only the mucosa can be evaluated by endoscopy so the absence of amyloid on endoscopic biopsy does not exclude amyloid involvement
- Involvement appears to be common (60%) in familial amyloidosis, particularly in neuropathic variants
- Diagnostic options & treatment options exist and can be customized to specific symptoms

09 Registry

What is it?

- A secure, online database
- Patient-reported data about their experience with amyloidosis
- A resource for the entire amyloidosis community
- Created & managed by Amyloidosis Support Groups

Why have a registry?

- Document patterns of disease progression
- Provide data for research
- Link people to clinical trials
- Identify effective self care
- Understand common paths to diagnosis

How is this different from existing registries?

- Patient Supported: Amyloidosis Support Groups operates the registry
- Patient Controlled: patients determine how their data is used
- Includes All Types of Amyloidosis: ATTR, AL, AA, and more
- Designed to Serve Everyone: patients, caregivers, medical professionals, researchers, and pharmaceutical companies

Will my data be private and secure?

- Hosted on the Platform for Engaging Everyone Responsibly (PEER). PEER has hosted over 30 rare disease registries
- Data is secure and encrypted
- Each participant decides who can access his or her data
- All data is “de-identified” and aggregated so the participant remains anonymous
- Participants decide whether to permit contacts from researchers.
- ASG registry managers are certified in Protecting Human Research Participants
- ASG will request that users provide access for specific uses, user can decide

- Registry undergoes annual IRB approval

What can I do to help?

Patients: Sign up! Add your data!

Physicians/ Med Centers: Inform and Promote

Supporting Organizations: Spread the word!

How to sign up

<http://amyloidosisupport.org/registry>

Click Register Now!

Create account, sign in

Take the surveys!

Need Support?

For help or any questions please contact

Paula Schmitt, Patient Registry Manager

registry@amyloidosisupport.org

10 Heart

Heart has millions of muscle cells making it beat. Amyloid gets between the cells, making the heart muscles stiffer.

This leads to extra fluid in lungs.

Symptoms

- Fatigue
- Shortness of Breath
- Swelling (edema)
- Unable to lie down due to shortness of breath (from fluid in lungs)
- Waking up gasping for air
- Cough, often at night

Heart Rhythm problems (Arrhythmias)

- Bradycardia – heart beats too slow – may need pacemaker
- Tachycardia – heart beats too fast
- Atrial fibrillation – irregular rhythm from upper chambers

Treatment

- Pacemakers
- Medications
- Electrical shock (cardioversion)
- Risk of blood clot – stroke – need blood thinners
- Defibrillator – for arrhythmias from ventricles

Heart Tests to Diagnose Cardiac Amyloid

- Echo – often first suspicion of amyloid. Measure thickness , pumping function, stiffness, valve function, pressure in lungs
- MRI – certain patterns suggest amyloid
- Biopsy – test a tiny piece of tissue taken from Heart (or fat, other organ, if echo suggests amyloidosis)
- For ATTR – PYP scan (bone scan) may sometimes replace biopsy - can detect ATTR
 - If your diagnosis is based on PYP, make sure that AL has been ruled out! If you did not have a biopsy, only PYP – ask your doctor these questions: what are my free light chains, what did the immunofixation of my serum and urine show, is there any monoclonal protein?

Ejection Fraction

Your EF may be fine, but your heart still does not move enough blood! If heart is stiff heart due to amyloid - it can pump fine but does not hold much blood, so it is not pumping as much blood around. The absolute amount of blood your heart is pumping is more important than the percentage. In amyloid, the amount of blood pumped might be okay at rest, but your heart might not be able to keep up with exercise

So ... instead of asking about EF, ask your doctor:

1. What is my cardiac index? Amount of blood pumped per minute for your size
2. What is my stroke volume index? Amount of blood pumped per heart beat for your size

These are available on most echo reports or from heart catheterization, but they need to be carefully measured

Cardiac Amyloid

- Not all about wall thickening. The wall may be thin, but the muscle still may not work well.
- Measuring Heart Wall Thickness is tricky & crude - the same patient may get pretty different measurements on the same day, because the wall thickness varies with small changes in where it is measured.
- Strain means different parts of the heart are beating with different effectiveness.
- There is not a single number that tells how your heart is doing
- You need a cardiologist who really understands amyloid to help you interpret your heart function
- Pictures of the heart (echo, PYP, MRI) are best for diagnosing amyloid and don't help that much with follow up

Blood Tests in Cardiac Amyloid

- Troponin – protein released from heart muscle, usually due to heart attack; often increased in amyloid- but not heart attack
- BNP or NT pro-BNP – another protein from heart, released in response to higher pressure in heart. Varies up to 40% over a week

Treatment of Cardiac Amyloid

- Stop the source of amyloid –new drugs!
- Over time, the body can remove amyloid
- Medication to take amyloid out of heart? Maybe. Studies ongoing
- Diuretics (water pills) - decrease shortness of breath and remove fluid

- Medications used for other type of heart failure often not helpful (beta-blockers, ACE-inhibitors)
- Individualized treatment
- Follow-up for Cardiac Amyloid
- How do you feel?
- How far can you walk?
- How often have you been hospitalized?
- Are you requiring more diuretic?
- What do simple blood tests show? Troponin, NT-BNP (BNP), creatinine

Cardiac Amyloid – What can you do

- Make sure you have the right diagnosis
- Weigh yourself everyday – look out for fluid
- Use compression stockings, if needed
- Limit your salt and fluid
- Exercise – go at your own pace but get moving
- Do some light strength training
- The heart likes to pump to muscle not flab

What should patients and caregivers do?

- Keeping your whole body healthy is crucial
- Eat, Move, Sleep!
- Eat: 5 Fruits/Veggies per day
- Move: At least 10 minutes per day
- Sleep: Eight hours for most

Cardiac Amyloidosis - Summary

- Amyloid - stiff heart - hard to fill
- Heart Failure and Rhythm problems
- Heart function is complex - a single number does not tell you how your heart is doing
- Track your numbers
- Steps and Reps!

11 Nerves and Neuropathy

Janice Wiesman MD, FAAN

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New York University School of Medicine

Adjunct Assistant Professor of Neurology

Boston University School of Medicine

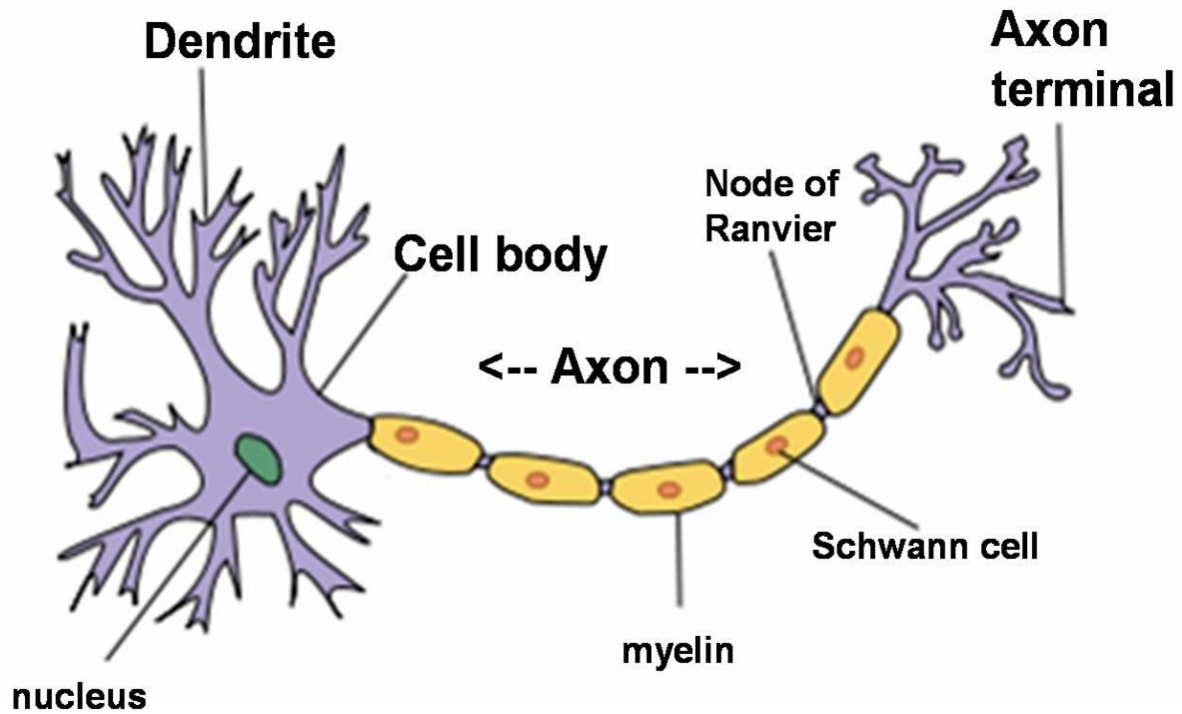
What is a nerve?

- A nerve is a cable-like bundle of axons that runs between the spinal cord and the periphery
- Axons transmit information by an electrical current that runs along the axon like a wire in your home, like electricity running through a wire in your home
- The axons are each surrounded by a fatty coating, called myelin, that acts like insulation on a wire

What is an axon?

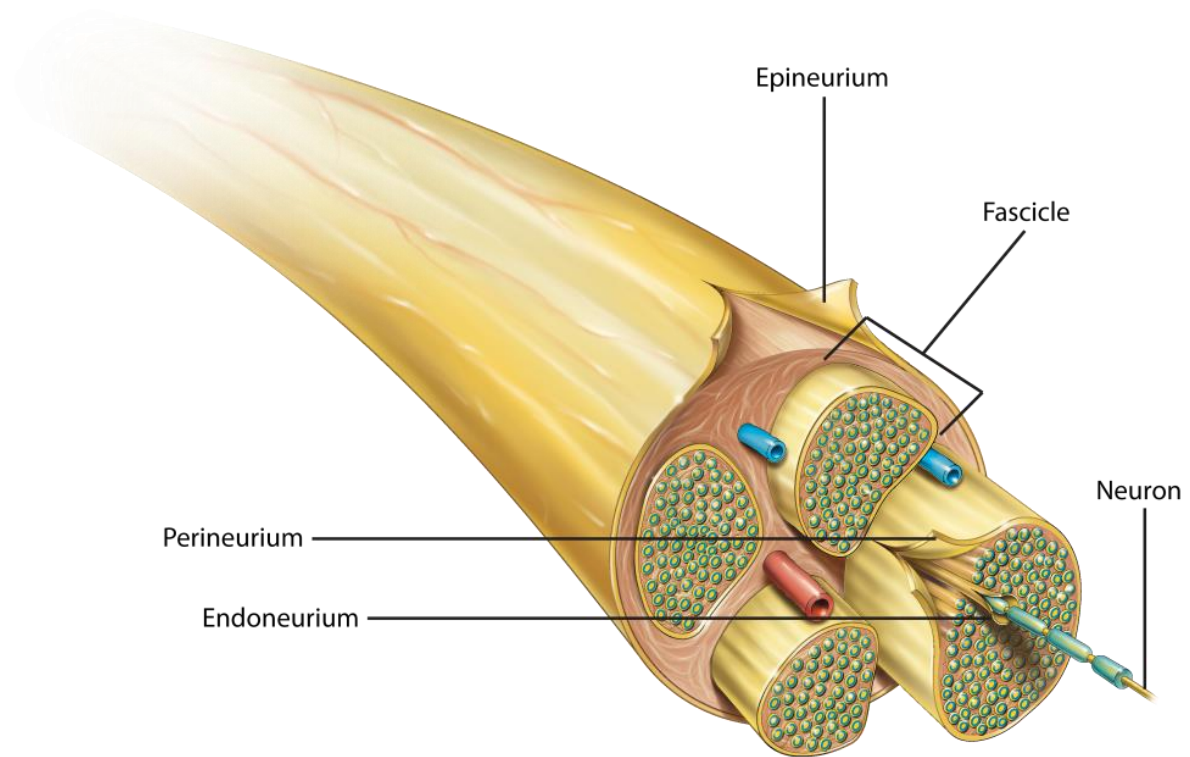
- An axon is the arm-like extension of a nerve cell (neuron)
- Neuron types
 - motor,
 - sensory and
 - autonomic
- The neurons are located in or near the spinal cord

Structure of a neuron



From users.tamuk.edu

Cross Section of a Nerve



Nerve

From www.axogeninc.com

Where do nerves come from?

Nerves come from the brain, through the spine, to spots throughout your body

What do nerves look like?

There are 3 kinds of axons

Motor – information goes out to muscles

Sensory – information comes in from skin, joints, muscles, organs etc.

Autonomic – governs “automatic functions”

Motor Axons

- Motor neurons sit in the spinal cord and send out axons to contact muscle cells
- When the motor neuron fires an electrical impulse, the impulse races down the axon and the end of the axon releases a chemical, called a neurotransmitter, that causes the muscle cell to contract.

Sensory Axons

- Sensory neurons sit just outside the spinal cord and send one long axon out to the skin and organs and one short axon into the spinal cord
- Sensory axons bring information from the skin and organs to the spinal cord and up to the brain so we can feel, hear, taste, smell, see and know where limbs are in space.

Autonomic Axons

The cell bodies that make these axons sit in the spinal cord and brainstem and send out axons that contact

- Salivary glands in the mouth
- Tear glands in the eye
- Muscle in the wall of the stomach and intestine
- Sweat glands in the skin
- Muscle in the wall of blood vessels, including those in the genitals

(Autonomic nerve symptoms often come 1st in amyloidosis)

Different axon types are different sizes

- Autonomic axons are the thinnest
- Sensory axons
 - Thinnest mediate pain and temperature
 - Thickest mediate pressure, vibration and joint position sense
- Motor axons are the thickest with the thickest myelin coat - 60m/sec

Nerve Damage in Amyloidosis

- Can be one nerve, e.g., Carpal tunnel syndrome
- Can be nerve roots as they emerge from the spine: Radiculopathy (“pinched nerve”)
- Can be generalized disorder of nerves, e.g., Polyneuropathy = peripheral neuropathy

Amyloid Polyneuropathy

Axonal, length-dependent, symmetrical, dying-back neuropathy

- Axon itself is damaged by amyloid
 - Compression of axons by amyloid deposits
 - Amyloid compresses blood vessels that supply nerves
 - Metabolic component
- Longest nerves affected first – why?
 - Motor neurons are longest, like 3ft long leg nerve. The same one you were born with. Extremely thin. So a small amount of damage in each inch of nerve can have notable cumulative effect.
- Thinnest axons affected first, thicker axons are affected later
- Symmetrical
- The nerve degenerates from the end, upward

Nerve with amyloid- the amyloid compresses the axons.

Symptoms of Polyneuropathy

Sensory Symptoms

- Tingling, numbness, burning, feeling cold, feeling like walking on cotton/something in your shoe
- Feeling off-balance when closing your eyes

- Start in feet, slowly climbs up the legs. When the symptoms are at knee level may have symptoms in the hands
- Often feel worse at night
- Off your feet, no pressure from walking

Why does it feel numb and painful at the same time?

- Different axons mediate different sensations
- Thin axons mediate pain sensation
 - When damaged, they fire at random – brain “feels” it as pain
- Thick axons mediate touch and pressure sensation
 - When damaged, do not transmit information to the brain – so brain does not “feel” touch

Motor Symptoms

- Weakness
 - Starts in feet
 - Weakness in hands
 - Think about carpal tunnel syndrome
- Atrophy of muscle
- Cramps
- Restless legs

Autonomic Symptoms

- Dry eyes and mouth
 - Nerves to the lacrimal and salivary glands are damaged
- Trouble accommodating to bright light
 - Autonomic nerves control constriction of the pupil
- Lightheadedness when standing
 - Autonomic nerves make your blood vessels constrict and your heart rate increase when you stand up
- Skin and nail changes
 - Shiny, dry skin with hair loss
- Diarrhea/constipation
- Erectile dysfunction in both the penis and clitoris
- Decreased vaginal lubrication

Treatment of Polyneuropathy

Questions people ask:

- Is my underlying disease being treated? There are some treatments now.
- Is there treatment to make nerves grow back? Not yet.
- How do I treat symptoms?

Then I (the doctor) ask – Do you want treatment?

- Is it making you crazy?

If I am treated will my nerves grow back?

- Maybe
- Nerves regrow best in people who are young and otherwise healthy
- Nerves grow back slowly: 1 mm a day = 1 inch a month = 1 foot a year

Can I treat the numbness?

- Not much can be done.
- While pain and tingling can be treated, there is no treatment for the numbness
- "Tincture of time" - may get better over time

Symptomatic treatment of sensory symptoms

Without Medication

- Foot rub or warm water foot massage before bed
- Acupuncture (but check with your doctor regarding risk of infection!!!)
- Anodyne light therapy and cold laser
 - Increase blood flow and make feet feel better – expensive
- Use of compression socks - stimulates nerves, can override the random pulses from amyloidosis
- Transcutaneous nerve stimulation
 - May or may not help, can be done at home. Studies disagree on effectiveness, but not it's pretty harmless.
- Percutaneous nerve stimulation
 - Some literature supports this
 - Done in the office

Topical Medication

- Lidoderm cream or patch – topical anesthetic
- Aspirin-like creams (diclofenac)
- Menthol cream (Ex. Ben Gay)
- Capsaicin cream
 - initially increases pain, must be used 2-4 times/day
- Capsaicin patch (Qutenza and generic)

Botulinum toxin injected into the top of the feet in a grid

Medication

- Anti-seizure medications
 - Lyrica (pre-gabalin)
 - Neurontin (gabapentin)
- Antidepressants
 - Cymbalta (duloxetine)
 - "tricyclic antidepressants" like Elavil (amitriptyline) – **not typically used** in amyloid - may compound other symptoms
- Anti-inflammatory
 - Aspirin-like drugs
 - Tylenol
- Long acting narcotics **are usually not appropriate** for the treatment of nerve pain.

What about marijuana?

- There are studies that show benefit of smoked cannabis for pain in diabetic and HIV associated neuropathy
- Fewer studies addressing oral cannabis
- No good data about CBD oil (topical or oral). Some people say it works for them.
- Must take cognitive side effects into account

- Legal in some states, not in others

Treatment of cramps

- No good treatment
- Amazingly, no one really knows why people get muscle cramps
 - Associated with electrolyte abnormalities like salt, calcium and magnesium
- Amazingly, there are not great treatments for muscle cramps
 - Stay well hydrated
 - Stretch muscles for 10 minutes before bed
 - Magnesium supplement (250 mg/day)
 - Check with your doctor first!
 - Bar of soap under sheets?
 - FDA warning against using quinine

Treatment of Restless Legs

- Check iron level and supplement if low
- Stretching the legs before bed
- Warm or cool packs
- Regular exercise
- Cut out caffeine for a few weeks
- Relaxation techniques before bed
- Sleep hygiene
 - Regular bedtime
 - Cool dark room
 - No screens for 2 hour before bed

Medications for Restless Leg Syndrome

- Ropinirole (Requip), rotigotine (Neupro) and pramipexole (Mirapex) are approved by the FDA for RLS. These medicines are also used for Parkinson 's disease
- Gabapentin (Neurontin) and pre-gabalin (Lyrica) may help and have fewer side effects
- Short-acting, Valium-like drugs such as clonazepam (Klonopin) may help but are addictive

Treatment of motor symptoms

- No medication to help with strength
- Physical therapy
- Assistive devices

Treatment of Autonomic Symptoms

- Dry eyes - Artificial tears during the day and lacrilube at night
- Dry mouth - Biotene and Xylimelt products
- Skin changes - Moisturizer
- Low blood pressure
 - Decrease or discontinue high blood pressure medications with your doctor's advice
 - Stay as well hydrated as your heart can handle
 - Sit-up and stand-up slowly
 - Compression stockings – must be thigh high!
 - Medications
 - Midodrine (ProAmatine)

- Fludrocortisone (Florinef)
- Droxidopa (Northera)
- Early satiety
 - Small, low fat meals
 - Metoclopramide (Reglan)
- Diarrhea
 - Lomotil and Imodium are over-the-counter
 - Talk to your doctor
 - Tincture of opium
- Constipation
 - Many OTC laxatives
 - Osmotic (miralax, prunes, bran cereal)
 - Stimulant (Dulcolax)
 - Linzess by prescription
- Erectile dysfunction (men and women)
 - Take it slow
 - Viagra-like medications
 - Require some nerve function to work
 - Other treatments can be discussed with a urologist
- Decreased vaginal lubrication
 - Take it slow
 - Vaginal lotions
 - Estrogen supplements

Things advertised on the Internet

- Private Neuropathy clinics
- Alpha-lipoic acid - Lowers blood sugar
- Neuracel and other pills
 - FDA is forbidden from regulating supplements
- Other crazy contraptions

A word about foot care!!!

If you can't feel your feet you can't feel cuts or sores that can become infected.

- Foot care tips
 - Look between and under your toes every day
 - Wear soft, well-fitting shoes
 - Do not walk barefoot, particularly outside
 - Keep feet soft and well moisturized
 - Have nails filed rather than cut
 - A podiatrist or specialized pedicurist can help
 - Don't cut your own nails!!
- Neuropathy leads to decreased blood flow, and decreased antibiotic delivery, to the feet
- We want you have all 10 toes, all of the time!

Lifestyle changes

- Exercise is good
 - You don't hurt the nerves with exercise
- Sex – yes

- Sleep
 - A good night's sleep makes the next day easier
- Healthy eating

What you can do for healthy nerves

1. CUT DOWN ON ALCOHOL – it is directly toxic to nerves
2. STOP SMOKING – with every puff you cause constriction of the blood vessels that nourish nerves
3. EAT A LOT OF FRUITS AND VEGETABLES, especially dark green leafy vegetables which contain b vitamins (but not if you are taking warfarin)
4. Muscles depend on their nerve supply to stay healthy – USE THEM both

Resources

- Healthy Nerves pamphlet on ASG website
- Boston University Amyloid Treatment and Research Website
 - Podcasts
 - Healthy Nerves pamphlet <http://www.bu.edu/amyloid/resources/patient-resources/>
- New book: *Peripheral Neuropathy: What It Is and What You Can Do To Feel Better*

A word about wtATTR

- With age wtATTR deposits in a variety of tissues
 - Heart (Heart failure with no EF, 13%. aortic stenosis surgery 16%)
 - Ligamentum flavum of the spine (lumbar spine stenosis, 50%)
 - Biceps tendon (rupture)
 - Flexor retinaculum of the wrist (CTS)

12 Nervous system and eyes

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?

Eye and brain produce TTR, like the liver.

They produce it more slowly than the liver, so it takes longer for problems to occur.

The Blood Brain Barrier (BBB) prevents many substances in most of the circulatory system's blood from reaching the eyes and brain, and vice versa.

Transthyretin TTR

Produced by things other than the liver. The eye and brain produce TTR (or ATTR, and the problematic amyloid deposits).

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

Mutations with known risk for 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 - eyes and brain secrete TTR more slowly than liver, so impact is often much later.

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

Potential Ocular complications hATTR

- Pupillary light-near dissociation (Common)
- loss of corneal sensitivity and neurotrophic corneal ulcers (rare)
- anterior capsule opacity of the lens (rare)
- keratoconjunctivitis sicca (Common)
- chronic open-angle glaucoma (rare) → LEADING CAUSE OF BLINDNESS
- vitreous opacities (rare)
- abnormal conjunctival vessels (common)
- optic neuropathy (from ischemia)
- retinal vascular changes

Source: BioMed Research International, vol. 2015, Article ID 282405; BMB reports 48(4)

Certain patients more predisposed: Tir114Cis (100%) and Lys 54 mutations than in patients with variant Val30Met (24%)

Rarely can be first presenting sign

STUDY

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

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

Diagnosis

- 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

- Eyes
 - 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 Blood Brain Barrier)
 - ? Tafamidis
 - ? AG10
 - ? Diflunisal
 - ? Tolcapone
 - ? Resveratrol
 - ? Doxycycline
 - ? TUDCA

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

13 New imaging techniques for diagnosis

Why Image Systemic Amyloidosis?

- Detection of amyloid in the heart, lung, kidney, liver, and spleen (and nerve) using one agent is not currently possible.
- Imaging amyloid can provide more effective and rapid diagnosis.
- The extent of deposition may be of prognostic value and might influence treatment options – and allow physicians to monitor the effect of treatments.
- Currently only one approved method for imaging ATTR in the heart with no agents approved for other forms of amyloidosis.

Imaging ATTR with ^{99m}Tc-PyP

- Images showed darkness in heart of ATTR positive pts

Phase 1 Clinical Trial of 124I-p5+14 PET/CT Imaging of Patients with Systemic Amyloidosis

- Assessing safety, and some efficacy
- Part 1 – Three patients with AL given radioactive p5+14 peptide for initial evaluation of safety. Patients were imaged 7 times over 48 h – COMPLETED.
- Part 2 – Forty patients:
 - 20 AL (6 imaged to date)
 - 10 ATTR (4 imaged, all hereditary)
 - 5 ALect2 (1 imaged)
 - 5 Other (1 recruited)
- Each patient receives a low dose of the peptide and low dose of radioactivity and is imaged at 5 h and 24 h post injection.
- Study is assessing safety and determining whether we can image individual organs that are known or suspected of containing amyloid based on the clinical work-up.
- Patients receive copies of their images as part of the study.

Imaging protocol

Patients visit our Study Physician for a check up

The radioactive drug is prepared at UTMC

The patients come to the Nuclear Medicine Dept

Imaging

- 3D PET/CT Imaging allows us to look at many views of the patient (3D imaging)
- We continue to study the images from all the patients to understand how the peptide works and what it can “see” but the images suggest that it may be possible to see nerve-associated ATTR
- Scans show where the amyloid deposits are, and where they are not. So it indicates which organs are affected.
- Images of patients with only neuropathy symptoms showed obvious deposits in hearts, as well.

ALECT2 amyloidosis

ALECT2 amyloidosis is the third most common form of systemic amyloidosis in the US. Common in people of Mexican descent with most patients in the Southwest US. Amyloid deposits most commonly found in the kidneys, liver, and spleen. Images showed amyloid in those organs.

AL (light chain)

Images showed amyloid where it was expected in those patients.

Future Plans

- The Phase 1 study will continue to recruit for another year (or so) – after which we will extend the study and image as many patients as we can.
- Based on feedback from many of the patients that we have imaged we hope to begin the following studies:
 1. Perform repeat imaging on patients at 12 month intervals so that we can monitor response to therapy.
 2. Recruit TTR mutant carriers who are asymptomatic to see if very early amyloid detection is possible.
 3. Recruit amyloid-free “heathy” subjects.
 4. Increase the availability for imaging of rare forms of amyloidosis.

Future directions

- The Phase 1 study will continue to recruit for another year (or so) – after which we will extend the study and image as many patients as we can.
- We continue to work on understanding the peptide and how the images can be used to benefit patients.
- The specific reactivity of the peptide for amyloid is being further exploited to develop therapeutics designed to enhance the clearance of tissue amyloid.
- The peptide is being developed by a company (Aurora Bio) to make this imaging agent available for widespread use.

14 CRISPR (gene therapy)

CRISPR-Mediated Therapy for Transthyretin Amyloidosis (ATTR)

Mark D. McKee, MD

26 October 2019

Intellia's approach

Intellia is trying to develop therapies to edit the genes that cause hATTR.

The idea - put gene editing tools into the body. The tool would enter cells, and edit the protein, alter the DNA (insert corrected DNA, or knockout the defective portion).

Intellia is trying the knockout approach

The knockout tool finds the problematic portion of gene & cuts it out. The body repairs it - if it gets repaired as it was, it is found a cut out again. Eventually, it gets repaired "incorrectly" (i.e., with different nucleotides), so it stays there. But it probably won't form a good protein, so the no protein at all gets produced.

It may just take one dose, since one dose may change all the problematic genes.

Lipid Nanoparticles (LNPs)

- Large cargo capacity for CRISPR/Cas9
- Transient expression
- Scalable synthetic manufacturing
- Redosing capability
- Low immunogenicity
- Well-tolerated
- Biodegradable
- Adjustable range of tissue tropism

Intellia's LNP delivery system includes a single guide RNA, mRNA encoding S.py Cas9 and a lipid formulation encapsulating these

Editing in vivo requires cargo release, mRNA translation, RNP assembly and Cas9 import into the cell's nucleus

sgRNA: Modification of sgRNA to Improve Potency

- sgRNA chemical modification campaign identified active modification pattern
- Increased potency relative to standard end-modified sgRNA
- Guide-sequence independent

Intellia's CRISPR Development, so far

- In vitro (in a lab dish): Modified LNPs to make more edits per dose
- In live mice: determined what dose achieved a high and durable level of editing
- In live transgenic mice (mice bred to carry human DNA): Demonstrated treatment could decrease amount of a non-amyloid substance in various tissue.
- In live primates: demonstrated >95% decrease in TTR production after treatment

Summary

- TTR LNPs enable >95% knockdown of TTR protein by single-dose editing of TTR across multiple species, including mouse and NHP
- Reduction of circulating levels of TTR sustained for at least 12 months in mice and for 10 months in NHP
- No significant histopathology findings noted
- Rescue of amyloid deposition in multiple tissues seen in humanized mouse model
- Modular platform for LNP-delivered CRISPR/Cas9 gene editing may enable future treatments for multiple genetic diseases

Next steps

- Manufacturing of NTLA-2001 Phase 1 materials
- Submit for FDA approval in mid-2020

15 Lifestyle and equipment aids

Rehabilitation Considerations in Amyloidosis: Practical Help and Assistive Devices

Sarah Boyd, P.T., D.P.T.

Sarah Dahlhauser, O.T., O.T.D.

Signs and Symptoms

Therapy can help with all of these symptoms:

- Cardiac and respiratory issues
- Difficulty swallowing
- Dizziness or feeling faint upon standing
- Fatigue and weakness
- Gastrointestinal issues (diarrhea/constipation)
- Numbness, tingling, and pain in hands or feet
- Skin changes
- Swelling of ankles and legs
- Unsteadiness when walking
- Weight loss

Occupational Therapy vs. Physical Therapy

OT

Help focused on any activity that occupies your time.

Specialists aiming to improve and restore your ability to perform daily activities within the home, hobbies, or job through restorative training or compensatory training using adaptive equipment.

PT

Movement specialists aiming to maintain, improve or restore mobility and prevent disability through specialized interventions addressing strength, flexibility, balance, posture, endurance, and pain.

How can rehabilitation help?

- Safety and mobility assessment
- Adaptive equipment
- Exercise
- Pain management
- Swallow evaluation and recommendations
- Caregiver and family training

What is YOUR goal?

Safety and Mobility Assessment

- Requires an evaluation by neurologic-based physical and/or occupational therapists
 - Periodic re-evaluations are recommended
- If there are safety concerns, the following may occur:
 - Consideration of activity compensation/adaptation - e.g., put a chair in the shower
 - Trial of gait aids
 - Education on falls prevention with home modifications
 - Education on what to do if you fall and how to get up

Mobility Aids – Physical Therapy

- Mild: Canes, walking stick
- Moderate: Walkers of various types, transport chairs
- Severe: Wheelchairs of various types

Lower Body Orthotics

- Certified orthotist will make the brace for you
- Recommended for:
 - Lower body weakness – foot drop, knee buckling, “rolling my ankle”
 - Joint positioning and protection
 - Maximizing walking efficiency
 - Prevent falls
- Various styles and material
 - Off-the-shelf vs. customized
 - Plastic vs. carbon fiber

Adaptive Equipment – Occupational Therapy

- Safety Equipment
 - Shower chair/tub transfer bench
 - Grab bars
 - Toilet safety frame
 - Bed rail
 - Lift chairs
- Lighting
- Daily Activity Aids
 - Button hook (to button shirts)
 - Sock aid (to put on socks)
 - Reacher
 - Rocker knife (much easier to cut foods than with standard knife)
 - Built-up handles (easier to hold)
 - Rubber fingers (easier to grab things - better traction)
 - Dycem (prevent slipping)
 - Multi-Purpose Opener

Equipment Acquisition Process (paying for it, insurance)

- Durable Medical Equipment (DME)
 - To get insurance to pay, get a prescription from your primary care provider or physiatrist
 - Wheelchairs will need consultation with physician and wheelchair/seating specialist (OT or PT)
 - Insurance WILL NOT cover powered scooters if only use for community mobility - they usually just cover mobility in the home
 - Insurance usually covers a new piece of mobility equipment every five years
 - Local medical institutions or rehabilitation centers will be able to direct you to local DME resources (vendors)
 - If you have bracing needs, pursue a local orthotist for brace fabrication
- Adaptive Equipment - not covered by Medicare or most insurance

Day-to-day Strategies

- If feeling dizzy or lightheaded upon standing:
 - Perform leg movements (i.e. bottom squeeze, ankle pumps)
 - Take transitions slowly; pauses
- Simple modifications to implement when eating or drinking:

- Small bites and sips
- Eat slowly
- Chew well
- Chin tuck before swallowing
- Alternate solids and liquids

Connect

- Discuss with your primary care provider or medical team for an evaluation within with Physical and Occupational Therapy
- Get a special request for neurologic-focused rehabilitation
- To find a board-certified therapist: <http://www.abpts.org/FindaSpecialist/> (some PTs are not board certified, but may still be excellent)

Resources

Disclaimer: We do not have any financial interest or relationship with these groups.

- Adaptive Equipment
 - Performance Health: <https://www.performancehealth.com/>
 - North Coast Medical and Rehabilitation Products: <https://www.ncmedical.com/>
- Mobility Aids
 - SpinLife: <https://www.spinlife.com/>

16 Tegsedi

David Hurwitz, Ph.D., Field Medical Director, Akcea Therapeutics

Agenda

- Update on TEGSEDI® safety and efficacy
- Overview of clinical trial study results

How TEGSEDI Works

Hinders the creation of the ATTR protein by obstructing the RNA that creates the ATTR

Pivotal Phase II/III Study (safety & efficacy)

TEGSEDI® was studied in a clinical trial of 172 patients with nerve damage from hereditary ATTR amyloidosis

TEGSEDI was associated with significant improvement in nerve damage compared with placebo

- 36% of TEGSEDI pts improved nerve function, vs. 19% of placebo pts.

Quality of Life improved vs. placebo, too

Summary of OLE Study Results

Starting TEGSEDI® earlier leads to better outcomes on measures of neuropathy progression and neuropathy-related quality of life

Initiation of TEGSEDI in patients previously given placebo resulted in disease improvement versus natural history in neuropathy-related quality of life

TEGSEDI exposure evaluated up to 39 months resulted in continued efficacy

With exposure up to five years, TEGSEDI was not associated with any additional safety concerns

With enhanced monitoring, platelet and renal monitoring have been effective in the OLE study

No new safety signals were identified in the open-label extension study

Connect With Akcea

@akceatx on Twitter

Akcea Therapeutics on LinkedIn

@changeATTR on Twitter

hATTR Change the Course on Facebook

hATTR Change the Course on YouTube

17 ONPATTRO

ONPATTRO® and Vutrisiran for ATTR Amyloidosis

Pushkal Garg, MD

Chief Medical Officer, Alnylam Pharmaceuticals

October 26, 2019

Alnylam

Therapies to break up the RNA the produces specific, problematic proteins

ONPATTRO approvals

U.S.	August 10, 2018	For the treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults
EU	August 27, 2018	For the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adults with stage 1 or stage 2 polyneuropathy
Canada	June 7, 2019	For the treatment of polyneuropathy in adult patients with hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis)
Japan	June 18, 2019	For the treatment of hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy
Switzerland	September 23, 2019	For the treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adults with stage 1 or stage 2 polyneuropathy

Clinically Proven Approach with:

Process for taking ONPATTRO

Intravenous, every 3 weeks

"ONPATTRO is given as a drip into a vein (called an "intravenous infusion"). Reactions to this infusion may happen during treatment with ONPATTRO. Before each infusion you will be given medicines that help to lower the chance of infusion-related reactions."

Safety management

Pts get pre-medication to decrease side effects of the infusion

Take vitamin A supplementation

In development

Subcutaneous injection, once every 3 months

Patient Support Services

Alnylam Patient Access Philosophy

- Help Patients
 - Above all, put patients first
 - Partner with patient advocacy groups, healthcare providers, and payers to support disease awareness, diagnosis, and access efforts
 - Actively listen and respond to all patients seeking support and provide meaningful, practical solutions
- Deliver Value to Payers and Physicians
 - Demonstrate evidence-based value objectively and transparently
 - Establish responsible pricing that reflects value delivered to patients, caregivers, and society
 - Proactively pursue reimbursement through value-based agreements and other innovative approaches
 - Commit to growth through continuous innovations, not arbitrary price increases in the US
- Be Proactive and Accountable
 - Advocate for policies that promote innovation, value communication, and patient access
 - Address and seek solutions to financial barriers to access
 - Act with medical/scientific excellence and integrity
 - Act with urgency to minimize the time it takes to get approved therapies to patients
 - Track and report our efforts to help patients access therapy

Alnylam Act®

Genetic Testing and Counseling Program

- Alnylam Pharmaceuticals is sponsoring no-charge, third-party genetic counseling and testing for individuals who may carry gene mutations known to be associated with hATTR amyloidosis.

Genetic counseling and testing may help to:

- Identify risk of disease for patients and their family members
- Shorten the time to diagnosis and prevent misdiagnoses
- Help patients consider clinical trials
- Provide information about support resources such as patient advocacy organizations

The Bridge

The Bridge® is an Alnylam program that provides resources to help raise awareness of hereditary ATTR (hATTR) amyloidosis and provides education on the condition to patients and their families.

Alnylam Assist®

- A dedicated Case Manager experienced in helping individuals get started on treatment and providing ongoing support
- Assistance with connecting to local resources
- Information about insurance coverage for ONPATTRO® (patisiran)
- Financial support options for eligible individuals
- Educational materials to help you and your family talk to your doctor about hATTR amyloidosis and your treatment

Amylam Patient Education Liaisons

Patient Education Liaisons help raise awareness about hATTR amyloidosis in the community and educate patients and their families. They engage with patients 1:1 to provide education, participate in family meetings, and reach out to community health organizations and advocacy groups.

18 Corino's CRX-1008 (In development - not yet proven for use)

Next Generation Treatment of ATTR: Update on the Clinical Development of CRX-1008

Michael J. Roberts, Ph.D., CEO

What is CRX-1008?

- A novel modified release formulation of tolcapone specifically engineered for ATTR
- Twice daily oral dosing
- Tolcapone, the active drug in CRX-1008, was approved in 1998 as an adjunctive treatment for Parkinson's Disease
 - Inhibitor of catechol-O-methyltransferase (COMT)
 - Current use in Parkinson's Disease is in combination with levodopa to slow its metabolism
 - Fast half-life in circulation after oral dosing
 - Crosses the blood brain barrier

Trying to develop a version that will last longer.

Potential Treatment of All Forms of ATTR

- Potent Kinetic Stabilizer
 - Binds with high affinity to TTR (4X lower IC50 than tafamidis)
 - Lowest negative binding cooperativity of kinetic stabilizers
- Other mechanisms that reduce the instability of TTR tetramer
- Fibril disruptor
- Crosses the blood brain barrier (could affect ocular (eye) and CNS (brain) ATTR, as well as ATTR from the liver)
- Enhance neurotransmitter levels in the CNS

Sekijima Y, Wiseman RL, Matteson J, Hammarström P, Miller SR, Sawkar AR, Balch WE, Kelly JW., The biological and chemical basis for tissue selective amyloid disease, *Cell*. 2005 Apr 8;121(1):73-85.

Martins da Silva A, Cavaco S, Fernandes J, Samões R, Alves C, Cardoso M, Kelly JW, Monteiro C, Coelho T., Age-dependent cognitive dysfunction in untreated hereditary transthyretin amyloidosis, *J Neurol*. 2018 Feb;265(2):299-307

Proof of Concept Clinical Studies in ATTR

Stabilization:plasma - completed

Stabilization:CSF/plasma - data analysis ongoing

Stabilization:CSF/plasma - data analysis ongoing

CRX-1008 Demonstrates Near Complete TTR Stabilization

- 17 participants
- Near complete stabilization at 2 hours after single dose
- <50% of maximal effect at 8 hours
- No effect detectable after 24 hours

- Maximum stabilization occurs at a CRX-1008 plasma concentration of 2.7 µg/ml (9.9 nM) after a single dose (50% at 0.5 µg/ml (1.8 nM))

See: Gamez J, Salvadó M, Reig N, Suñé P, Casasnovas C, Rojas-Garcia R, Insa R., Transthyretin stabilization activity of the catechol-O-methyltransferase inhibitor tolcapone (SOM0226) in hereditary ATTR amyloidosis patients and asymptomatic carriers: proof-of-concept study., *Amyloid*. 2019 Jun;26(2):74-84.

See: Gamez J, Salvadó M, Reig N, Suñé P, Casasnovas C, Rojas-Garcia R, Insa R., Transthyretin stabilization activity of the catechol-O-methyltransferase inhibitor tolcapone (SOM0226) in hereditary ATTR amyloidosis patients and asymptomatic carriers: proof-of-concept study., *Amyloid*. 2019 Jun;26(2):74-84.

19 Eidos's AG10 (In development - not yet proven for use)

Eidos & AG10 Clinical Update

Jonathan Fox, MD, PhD, FACC, Eidos Chief Medical Officer

AG10

The medication, AG10, is designed to stabilize the ATTR protein, to prevent the mis-folding that leads to the amyloid deposits.

Note: AG10 is an investigational drug. Its safety and efficacy have not been fully evaluated, and it has not been approved by any regulatory authority.

AG10 clinical program overview

4 phase 1 studies (safety studies, healthy adults)

2 phase 2 studies (safety & dosing, adults with ATTR)

1 phase 3 study is planned: 12 & 30 month endpoints

Two-part trial design includes 12-month and 30-month endpoints

6-Minute Walk Test is a clinically meaningful, treatment-responsive endpoint in ATTR-CM

ATTRibute-CM is a global, multi-center registrational Phase 3 study

ADD MORE HERE

20 Ionis AKCEA-TTR-L (In development - not yet proven for use)

Morie Gertz, MD, Consultant, Mayo Clinic, Minnesota

AKCEA-TTR-LRx an Antisense Therapeutic in Development for All Forms of ATTR

AKCEA-TTR-LRx - how it works

Obstructs creation of TTR protein by RNA

"An Antisense Approach to Treat all forms of TTR-related Amyloid Diseases"

Binds to the template of TTR Protein (mRNA)

Binds to wild-type (normal) TTR mRNA and all known mutations

Results in degradation of TTR mRNA and lowering of TTR protein production

Phase 1 Study Design in Healthy Volunteers

- Looked for dose-dependent Reductions in TTR Levels in Healthy Volunteers
 - Primary Objective: Evaluate the safety and tolerability in healthy volunteers with ATTR

- Secondary and Exploratory Objectives: Evaluate the pharmacokinetics and pharmacodynamics in healthy volunteers and patients with ATTR

Summary Phase 1 Results in Healthy Volunteers

- TTR reductions maintained between monthly doses
- Maximum mean reductions of 86% and 94%, from baseline two weeks after the 4th dose of 45 and 90 mg, respectively
- No Safety Issue Identified

Anticipated Profile

- High Potency: $\geq 90\%$ reduction in TTR levels at low doses
- Convenience: Once monthly low volume self-administered SC injection
- Improved safety & tolerability profile: No unusual monitoring (including platelets/renal)
- Combination with stabilizers not contraindicated

ATTR-CM Phase 3 Study Design for Cardiomyopathy

For Patients with Hereditary and Wild type Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR-CM)
~750 patients with cardiomyopathy
Tafamidis (Vyndaqel/Vyndamax) can be taken during the trial
Open Label Extension planned

ATTR-PN Phase 3 Study Design for Polyneuropathy

Compares AKCEA-TTR-L to Inotersen/tegsedi.

Adults with hATTR-PN meeting all 3 of the following criteria:

Stage 1 or Stage 2 (neuropathy?)

Documented TTR genetic mutation

Symptoms and signs consistent with polyneuropathy (NIS ≥ 10 and ≤ 130)

- No Placebo in this trial

- Tafamidis (Vyndaqel/Vyndamax) or Diflunisal (Dolobid) not allowed during the trial

- Inotersen arm crosses over to AKCEA-TTR-LRx after Week 35

21 Prothena's PRX004 (In development - not yet proven for use)

Dr. Ferenc Martényi

Vice President, Head of Clinical Development

October 25, 2019

PRX004

Designed to find and break down ATTR proteins and amyloid deposits (the aggregates of the mis-folded protein, which are the direct causes of amyloidosis symptoms). PRX004 binds to the protein, and attracts the body's natural macrophages, which attack and break down the proteins that have PRX004 attached.

- Targets non-native structures of TTR (misTTR) associated with pathology that forms amyloid fibrils
- Designed to deplete soluble and clear insoluble aggregates and prevent amyloid formation
- Potential to impact both wild type and hereditary forms of the disease

Preclinical studies show that the normal function of TTR is spared (i.e., PRX004 does not bind with regular TTR, but rather just with ATTR).

Shown to have binded to deposits in heart, nerve, and GI tract tissue. It did not bind to those sites in tissue from healthy adults.

MisTTR Assay Study (recruiting participants)

- Study goal: To detect and quantify non-native forms of TTR found in blood plasma from patients with ATTR amyloidosis
- <https://trials.sanguinebio.com/hATTR-amyloidosis-research-1/>

Phase 1 Multiple Ascending Dose Study Design

- up to 36 patients, NCT03336580
- Primary Objectives:
 - Evaluate safety, tolerability, PK and PD (misTTR assay)
 - Determine MTD or RP2D(s)
- Secondary Objective: Evaluate immunogenicity
- Exploratory Objective: Characterize the preliminary efficacy of PRX004 in subjects with hATTR-PN (with/without hATTR-CM)

22 Alternative Therapies for ATTR

Neurodegenerative Disease

Oxidative Injury causes cell death, and consequently neurodegenerative disease

Polyphenolic Nutraceuticals (things we eat)

- Flavonoids: Vegetables, fruits, grains, bark , stems, teas, wine
- Effects on AD pathology
 - Limit oxidative injury
 - Inhibit A β fibril/aggregation, destabilize formed A β
 - Inhibit killer cell activation
 - Increase cell survival signaling
- Curcumin (active spice of Turmeric)
- Resveratrol (grapes/wine)
- Epigallocatechin gallate (EGCG)

Phytochemical (herbal medicines)

- Epigallocatechin-3-galate
- Curcumin
- Quercetin
- Resveratrol
- Limonoid
- Coptis chinensis - berberines

Curcumin

- Natural polyphenol (diarylheptanoid)
- Inhibits A β aggregation/breaks up A β fibrils
- Blocks toxicity of A β fragments on brain cells
- Competes T4 binding to TTR
- Promotes clearance of TTR aggregates

- Inhibits steps of ATTR fibril formation
- Penetrates blood brain barrier – extent unclear
- Poor bioavailability limits use

Curcumin in mice decreases ATTR, but we DON'T see this decrease in humans

Resveratrol

- Damaged grapevines, pines, peanuts
- Stabilizes TTR tetramer conformation (T4 pocket) - to decrease the problematic folding
- Promotes aggregation of potentially toxic TTR monomers
- In mouse models, inhibits A β aggregation, disrupts plaques
- Attenuates oxidative damage of A β aggregates in neuronal cell culture and brains (hippocampus) of AD patients
- Poor bioavailability
- Effective dose undefined
- CNS penetration appears limited
- Inconclusive data from human clinical trials

See Bourgault S et al. Biochem Biophys Res Comm. 2011; 410(4):707

See Gomes B et al. Oxid Med Cell Longev. 2018

Role of Resveratrol in AD

See Gomes B et al. Oxid Med Cell Longev. 2018

EGCG

- Inhibits neurodegeneration in ALS/AD
- Protects rat brain neurons from A β toxicity
- Low dose inhibits inflammatory pathways
 - IL1, TNF, TGF
- Activates cell survival (PI3K/Akt) pathway
- Stabilizes TTR tetramers
 - Different mechanism than diflunisal
- Inhibits ATTR amyloid fibril formation
- Promotes breakdown of amyloid deposits
 - Non-toxic aggregates

EGCG data

See: Kristen AV et al. Clin Res Cardiol 2012; 101(10):805

See: Mereles D et al. Clin Res Cardiol 2010; 99:483

ATTR

- 14 ATTR cardiomyopathy patients, no controls
- EGCG 500-700 mg/day x 12 months
- Findings
 - Echo: no change in LV wall thickness
 - Cardiac MRI: 12.5% decrease LV mass

AL

- 59 patients with AL amyloid cardiomyopathy
- EGCG 600-800 mg/day + AL amyloid treatments

- Findings
 - 11 patients -- > 2 mm septal wall decrease
 - 6 months (range, 3-10)

EGCG for ATTR Cardiomyopathy

No difference seen in survival. Controls started worse off in several measures. Heart thickness appeared to improve in EGCG group, but related results were not encouraging.

- Retrospective study of ATTR CM patients
- Tuscan Regional Amyloid Center, Florence Italy
- 30 pts (+) EGCG 675 mg/day > 9 months;
- 35 pts (-) EGCG
- Median follow up 691 days
- 5 deaths (+) EGCG; 8 deaths (-) EGCG
- Survival estimates 60+15% v. 61+12%, p=0.276

EGCG CM Comments

- The follow-up time may have been too short - even tafamidis at 30 months showed no improvement.
- Retrospective design not as persuasive as a randomized trial
- No stabilizer study (diflunisal, doxycycline, tafamidis) with cardiac remodeling at 12 mos.
- Tafamidis at 30 mos.: no echo improvements
- TTR gene silencer cardiomyopathy subgroup
- ~30% wall thickness, LV contractility, NTproBNP

Diflunisal

- Slows disease - does not stop disease. Inhibits progression, does not stop it.
- Quality of life showed improvement vs baseline, and very large improvement vs placebo.
- Conclusions
- Diflunisal inhibits neurologic progression and preserves quality of life in patients with ATTR-FAP
 - Effective across gender, mutations, and severity of disease at entry
 - Cost effective – if no kidney, heart, GI issues
 - \$0.75/day in Chicago today

Doxycycline

See: Berk JL et al. ISA 2016

- 44% of people discontinued, due to sensitivity to sun (would blister, not just get sunburn)
- 56% completed the study
- The jury is still out about the value of Doxycycline for amyloid treatment

23 Insurance & financial assistance

Monica Fawzy Bryant, Cancer right attorney, Triage Cancer

See <https://trriagecancer.org/>

See slides for useful tables and other information.

Resources

When diagnosed with a major disease, go to <http://CancerFinances.org> to understand important financial considerations.

Financial Toxicity

Diseases can damage your finances, especially as treatment makes them more chronic (vs. deadly)

Contributors to Financial Toxicity

- Health insurance status
 - Inadequate coverage, ...
- Employment changes
 - When no work or not
 - Accommodations
- Life changes

Insurance Terms

In-Network vs. Out-of-Network

Allowed Amount or Contracted Amount

Pre-authorization

Prior authorization

We don't get lists of what needs preauthorization

Insurance companies may decide you needed pre-authorization for something you thought did not need it

Out-of-pocket maximum

Usually (per ACA) it is: deductible + co-payments + co-insurance

Usually only applies to services from in-network provider.

Premium – monthly payment. The cost to Have Health Insurance.

Costs When You Use Your Health Insurance

Deductible – each year (fixed \$ amount)

Co-Payment – each time you get care (fixed \$ amount)

Co-Insurance or Cost-Share – each time you get care (%)

Out-of-Pocket Maximum* = deductible + co-payments + co-insurance [* Usually only for in-network services]

Types of plans

- Fee-for-service
- Managed care
 - HMO - You have to see your primary care provider first
 - EPO - Large network, no out-of-network coverage (you'd pay 100% for out-of-network)
 - PPO - large network, some out-of-network providers, most expensive

ACA/Affordable Care Act/Obamacare

Required that most Americans to have health insurance

Set standards and rules that health insurance had to follow

Requires that insurance companies continue paying for routine care for clinical trial participants.

ACA challenged as being unconstitutional

There are rulings and appeals that could result in the ACA being ruled as being unconstitutional.

Medicare

Complex

Medicare has 4 parts (part A, B, C, & D).

Part A has copays

Part B has a premium, deductible, and cost share, with no out-of-pocket maximum

Part C - sold privately, cant cost over \$435/year.

Part D - sold privately, pays for prescription drugs

Medigap

How do I cover the gap between the out-of-pocket maximum?

Supplemental plans (Medigap, Medicare Advantage), classified A-Z.

60% of insurance appeals are decided in favor of the client.

Break-out - Insurance

I live in a small town. My plan does not cover Mayo Clinic. I'm on ONPATTRO (ONPATTRO - \$25,000 every 3 weeks.). If we switch plans, what questions should I ask?

1. What is the network of providers
2. What is the RX coverage?
3. What are the costs (premium, deductible, out-of-pocket, ...)?

ACA marketplace plans must follow the ACA calculation of out-of-pocket costs.

The ACA allows us to get formulary (covered drug list) before we sign up for a plan.

The provider lists that plans provides are often out of date - so verify with the provider if they are covered, if it is important to you. Be sure to ask about the specific plan "... silver", not just "do you take Obamacare".

I have Medicare A & B already. I am shopping for extra coverage during open enrollment. Do I need to check whether a provider will take my Medicare card?

You need to check with the provider. If a provider accepts Medicare, then they take Medicare A and B. But providers may take some specific Medicare C or D plans, but not others. Similarly, providers may take some specific Medicare Advantage plans, but not others.

Medicare is not useful for health care outside of the US. Nor are most US health insurance plans.

On Medicare.gov you can shop for Medicare Part D (drugs), Medicare Advantage, or Medicare Advantage and Medigap.

On Medicare.gov you can input the name of a drug, and where you get it, and it will show plans that may cover it. This does NOT yet have all the drugs. If the drug is not on the website list, then you can call each plan, the pharmaceutical company that makes the drug,

What puts you into and out of the "doughnut hole"?

You go in because of . You come out because of .

As of next year, there is no "doughnut hole". Once your drug costs

How often can a plan change which providers are in or out?

AS often as they want.

Then how do I assure that I'm getting in-network care?

Get prior authorization, or call and ask.

DO NOT assume that a referral automatically makes something in-network.

What about "surprise medical bills", where one provider on a team is not in network?

Some states have laws that prevent this, but many do not.

Tafamidis coverage - How do I assure that coverage continues when I re-enroll in January? What approach is most stable?

It depends. It depend on where you live and the laws there, coverage decisions by plans,

I'm 65, and I've got insurance for me and my husband through my employer. Should I switch to Medicare?

Why would you consider coming off your employer plan? -Medicare is usually more expensive.

Many people keep their employer plan until they retire, then switch during a special window that occurs as their employer plan ends.

Some people sign on to Medicare plans that include providers that are not in their employer plans. Their employer plan may then cover same costs that Medicare does not cover.

I like my Medigap plan F plan. But I can't figure out what drug plan to get.

Medigap Plan F & C cover the most things, but will not be available next year.

Drug formularies are in tiers: tier 1 = generics, tier 2 = on formulary, etc. Use the internet to look at State Health Insurance Assistance Program (SHIP programs: unbiased sources of information) find them on the Medicare.gov site. So understand what drug is covered at what tier.

I'm wondering whether to try to get Medicaid coverage.

Medicaid covers a pretty narrow group of persons. In most states, you have to have very few assests (like no more than \$2000 in the bank), or have certain disabilities. In Medicaid expansion states, your income needs to be under 138% of the federal poverty level. In other states, in must be even lower. Medicaid coverage is generally pretty good. You'd need to check with your state about whether the amyloid drug you want will be covered.

The marketplace website, healthcare.gov , will point you to Medicaid, if it looks like you qualify, based on how you answer questions on that site.

Medicaid qualification is based on household income, not individual income.

Is ACA bronze or silver plans good options for us?

Usually, no. Gold or Platinum plans are usually financially best for folks with serious illness.

I'm 68, on my wife's employer's Blue Cross/Blue Shield via Cobra. And I'm on Medicare. We lose that in February. My wife could extend Cobra out of our own pocket, at that point.

If you weren't already on Medicare, you would have to pay a penalty.

Buy Medigap now, because 1) now you can get plans F & C, which won't be available to you next year, and 2) If you get in now, when you have insurance, you might avoid the pre-existing condition waiting period.

Dropping Cobra does NOT trigger a period when you can go into the open marketplace - you'd have to wait until the next open enrollment (around the end of each calendar year).

When do I need to enroll in Medicare, to not pay a penalty?

Initial enrollment for Medicare is 7 months - 3 months before you birthday month, that month, and 3 months after. You can also sign up right after you end employer insurance (but NOT retiree plan).

(continued) ... Can I still get Tegsedi (a Part D drug), after I'm off BC/BS?

Look at Part D plans. You might want to start that now, and have double coverage for a few months, for the sake of having continues Tegsedi coverage after March. Also look at Medigap coverage.

How do I keep a Medigap plan that picks up my Medicare deductibles?

Medigap C & F are not available as of next year for NEW enrollees. If you already have it, you can keep it forever (as long as you keep renewing it). So get it now, if you can, and you have expensive drugs.

How do we get coverage for expensive drugs if we are on private insurance?

Talk to the drug company. They have some programs that can cover much of the costs. But it can be very expensive.

My husband was in a clinical trial for an effective drug. Why can't my husband use the pharma company's patient assistance plan to keep getting the drug?

There are rules that restrict how pharma companies can help people on Medicare, versus how they assist people on private insurance.

Talk to your elected officials. Let them know how the Medicare rules are affecting you.

Can I avoid going onto Medicare, so that I can still use a pharmaceutical company's patient assistance plan?

No, you can't avoid going on Medicare Part A & B if you qualify (if you have worked, and become age 65).

Are most bankruptcies due to medical debt?

In a study shortly before the ACA started, 60% of bankruptcies involved medical debt. 75% of those were for people who had health insurance.

I want to switch health insurers. Can the new plan refuse me or charge me more because of pre-existing condition?

HIPAA requires that if you have had coverage for at least 60 days, the insurer cannot deny you coverage or charge you more due to a pre-existing position.

What are insured versus self-insured plans?

If the employer uses a "funded" or "insured" plan, the employer and employee pay an insurer, who takes on the risk and pays for care.

Self-funded (self-insured) plans are where the employer pays directly for its employees' health care (although the information about who had what charges is kept from the employer).

How can Medicare turn down coverage for an FDA covered, in-hospital treatment?

That denial decision should probably be appealed, through the Medicare appeal process. Infusions are covered by Medicare Part B (medical treatments).

I take Tafimidis. I'm on Medicare. My 2ndary insurer denied Tafimidis coverage. How can that happen?

Part D plans can choose to cover a medication or not. Part D is sold and administered by private companies; they vary a lot. Consider switching to another Part D plan during open enrollment.

I have coverage under my spouse. If she dies, can I get coverage via the ACA marketplace?

Yes, you would have a period when you could sign up without penalty.

My husband is retired, getting coverage under a state plan, and has not paid into social security. Can he get Medicare at age 65?

Yes, but he would have to pay a premium to get Medicare part A.

Could he get Medicare coverage without paying a part A premium, because I qualify?

No, whether you pay Medicare Part A premiums just depend on your own work history.

Q & A

1. Hearing loss: My MD recommended an MRI to see if my hearing loss is due to amyloidosis. But there is no treatment for the hearing loss, so should I get the MRI?

Amyloid of any kind can have focal deposits. Having it in both ears would be strange. If it is just loss in one ear, it could be amyloid.

Leptomeningeal amyloid might have hearing loss. No other hearing loss is known to be associated with amyloidosis.

I am asymptomatic carrier of ATTR. Should I take diflunisal

You don't want any end-organ damage. We'd like to start therapy when the TTR mis-folding begins. But we can't tell when that is.

When pre-albumin levels drop, it may indicate that TTR mis-folding has begun, but it is a very imperfect marker. If it goes down and you start getting tingles, you might consider starting diflunisal.

There are some counter-indications. Keep your doctor involved in the decision.

For some mutations, like C1S114, TTR levels may be low almost from birth.

Diflunisal has some risks. If you take it, have your kidney function followed, and monitor stomach irritation. Taking it closer to age of onset might be best.

Some centers wait for 1st signs of amyloidosis before starting pts on amyloidosis.

It is probably the only drug you could use now before symptom onset.

Some centers follow blood serum levels of TTR. We are still learning about what changes in TTR may indicate - under various conditions, increases or decreases may be good or bad.

Stabilizer drugs increase the TTR level, silencer drugs decrease the TTR level.

Jeff Kelley is developing tests that may allow better understanding of the TTR stability, which may help in the future in informing decisions about when to start therapies, and the effectiveness of therapies.

If I'm on a silencer and a stabilizer drug, how can my doctor make sense of my TTR level?

Silencers usually take TTR levels to very low levels, and would overcome the TTR increase that a stabilizer might bring.

Is wild-type TTR truly "wild", or are there un-discovered gene mutations that may cause it?

We have not discovered all the mutations. We discover now ones all the time. But most pts who have wild-type probably do not have ATTR because of a mutation.

We still have a lot to understand about the causes of wild-type.

An analysis of 11 persons with wild-type, looking for genes that interact with TTR revealed no notable mutations.

One theory: Wild-type may have to do with a change in tissue that attracts proteins (to form amyloid), making the cause not so much "bad protein" as it is "bad tissue".

What is penetrance?

Penetrance = likelihood of getting the disease, given that you have the gene

If you have the gene, will its effects "penetrate" to cause the disease.

We know that some portion of gene carriers never develop the disease.

We are still

Is there a genetic pre-disposition for wild-type?

We do not know. We have not seen a notably higher incidence among families, but we don't know for sure.

Can you have wild type and hereditary ATTR?

Yes, it has happened.

We do not know if one causes a pre-disposition for the other.

I've been taking a gene silencer for 2 years. My neurological symptoms are getting worse. I'm also on diflunisal. Should I try something else?

Diflunisal is good, but gene silencers are much more effective - in a class beyond diflunisal.

Gene silencers may not stop all TTR.

Many people take gene silencers but still don't do very well. You can consider adding another stabilizer drug.

The longer you have had the disease before you start the silencer drug, the less effective it may be in fixing your manifestations. Some damage may be beyond repair.

In studies, improvement from silencers was best in people who were in early stages of disease. Folk with later stage never got as healthy as folks who started treatment in early stages.

A 15-18 month delay in starting gene silencer may cause un-repairable loss. Treatment should probably start as soon as symptoms start.

Can someone be on two gene silencers?

Maybe. There is no obvious counter-indication.

With both silencers, there are indications of improvement (thinning) of the walls of the heart, over time. The body may heal itself, to some extent.

In AL amyloid, when the problematic light chains are stopped, the body does heal.
The degree of recovery depends on where you start (better if you were in better shape when you start).
The improvement may be small.

What is the consensus about what is triggering the genes to start producing the mis-folding genes?

We don't know.
Inflammation may be a trigger.

What is the microbiom?

The microbiom is the collection of bacteria in your gut. Different collections affect weight gain, depression, and other things. We are at
We are in the infancy of understanding the microbiom. There is a lot of research going on, much of it very exciting.

Can I change my microbiom with diet or lifestyle?

Yes. Diet, travel, and antibiotics affect it.
A plant-based diet and fermented foods seem to foster better microbioms.
We still have a lot to learn.

What are the stages of cardiac ATTR?

There are several models. Some look at kidney function, some look at troponin.
Staging it done at diagnoses.
Folks want to know if they are getting better. We can't measure that through staging especially well(?).
New York Heart Association staging has 4 levels. Level 1 is best, 4 is worst. It looks at several markers, and the more you have, the higher your stage.
There is a classification based on your gate speed (how far you walk in a 6 minutes).
Some measures used max oxygen consumption.

Many amyloid friends have severe cramping.

Cramps are neuropathy. See Dr. Weisman's final slides.
The nerves fire over and over, triggering cramps.
Having low electrolytes can cause cramping.
Quinine used to be used as treatment, but FDA stopped that due to bleeding side-effects.
We have no good pill now. The main treatment is lifestyle changes.
Stretching before going to bed may help.
Patients on diuretics often get cramps. Doctor may look a electrolytes to understand the cause.
Some patients swear by yellow mustard. Some patients swear by magnesium spray.
Just by smelling pickle juice, my cramps subside.
Some folks use oral capsasin, marketed as "hot shot". Some folks just swish it in their mouth then spit it out, for cramp relief - it makes my mouth hot.
I pinch my upper lip, and it helps.
The sensory system and the motor system are linked, so these things that create a strong sensory signal can relieve a motor problem.
Is the progression of ATTR linear?
Neurologic problem progression is not linear. The problems may increase very slowly at first. There may be a period of rapid increase in problems, followed by a plateau.

If you have 100 axons, and lose 10, you only lost 10%, so it may be a small effect. If you have 20, and lose 10, then you have lost 50%, so the degree of change may be much more notable. There may be linear changes in physical things that cause non-linear increases in symptoms.

When should my kids start getting treatment?

When they have symptoms that can be attributed to amyloidosis, they should start treatment. When they have symptoms, we make sure that those are not caused by things other than amyloidosis. Have non-symptomatic carriers seen at an amyloid center, to get counseling and monitoring. If they get carpal-tunnel syndrome, make sure they get a biopsy to see if it was caused by amyloid. A full assessment can reveal neuropathy that the patient did not notice. It can even be enough to indicate that treatment should begin. Trigger finger is another early symptom.

If I get carpal-tunnel syndrome and have no other symptoms, should I get a gene silencer?

If the carpal-tunnel was caused by amyloid, you might consider getting a gene silencer. It is debatable.

Bi-lateral carpal-tunnel, no neuropathy - do you start a gene silencer? Diflunisal?

Consensus: Silencer, no (needs neuropathy for insurance coverage, anyway). Diflunisal, yes.

Should drug trials include a greater variety of patients (like including wild-type as well as hereditary)?

The drug companies try to keep their trials as quick and simple as possible. They just get one chance at approval. So they design trials for very specific endpoints, with specific patient groups. The lack of variety is due to these incentives.

When to start treatment (Dad has lysozyme)? My children have had symptoms. Genetic counselors say not to test, because there is no treatment.

Knowledge is power - suppose you test and find that your kids do not have the gene - that would change your actions. Insurance will not pay for the testing. But there is a strong argument that they should - consider appealing.

I had carpal-tunnel twice, with surgery twice. Duperkins contractor too - could that be caused by amyloid?

It could be related.

Whenever a surgeon removes tissue, have them test it for amyloid. You may have to be assertive about this.

Carpal-tunnel does often return even for folks without amyloid.

Markers

A-fib, trigger finger, stenosis, carpal tunnel.

What are you doing to educate clinicians to do the right investigations to look for amyloid.

In our institution, we implemented a protocol to test all carpal-tunnel procedure tissue, and have found a number of ATTR cases. We presented at a hand surgeon conference, and got a lot of interest. We should do more.

The pharma companies are doing a lot to try to raise awareness.

How to manage disabling diarrhea

Tincture of opium. (Doctors need to work hard to write that prescription because of opiate problems).

Which diuretics should I use?

Most effective diuretics are loop diuretics. Which depends on other symptoms and conditions, including heart conditions.

I often add Spiro lactone.

We monitor weight, and adjust oral diuretic. If patients don't respond well to that, we may add injectable

What is PYP & SAP scan?

SAP scan is not used in the US, or very relevant to us.

PYP is a whole-body scan. It often is used to reveal amyloid deposits in the heart.

Patients with normal function can have amyloid penetration revealed through a pyp scan.

Can I skip the pre-infusion treatment?

Petiseran is covered by a coat of fat. It can induce an allergic reaction. The pre-infusion treatment is designed to decrease the chance of that.

If you go through 3 infusions and have no reaction, you can drop the dexamethasone dose. After 3 more with no reaction, you can drop it more.

You will be on this treatment for years, so pre-meds may be important in avoiding long-term impacts.

Cardiologist keeps changing medication doses to try to get them working well: carvedalol (beta-blocker)

Carvedalol protects the heart in cases of It is a beta-blocker. Likewise sotalol, ...

Many ATTR pts do not tolerate beta-blockers, and they are usually not indicated.

There are exceptions, when beta-blockers might be appropriate. But cardiologist should not use the common, non-amyloidosis guidelines for treating amyloid patients.

Treatment guidelines need to have

An untested relative is on beta-blockers and is not doing well. How should they be treated?

If you don't feel right on a medicine, there is something wrong.

Mom & aunt had hATTR. All kids were tested in 2000. We all were negative. I have symptoms - should I get re-tested?

It is unlikely that the tests were wrong, but it is OK to get re-tested.

There are some changes in testing since 2000.

If they were testing for a specific gene, the original test is very likely to be correct about the absence of that gene.

I have hereditary ATTR . I am on diflunisal. Would I be better to begin commercial therapy, or join a clinical trial?

In a clinical trial you might get placebo, so consider that risk.

Should strain mapping be used in long term therapy?

Strain is good for detection, but we don't know how to use it well for monitoring.

All strain is not the same. Results can vary between the software used in the testing office. You can't reliably compare measures between offices.

Annual echocardiograms?

Experts vary from doing it every 6 months to every few years, for folks who have no documented heart problems. Once a year is OK.

The experts are developing consensus recommendations about heart monitoring.

I look at ..., then biomarkers, then echocardiograms. The imaging is not the primary measure I use for assessing heart.

Do quality of life measures consider whether someone is working?

There are several measurement tools. Some do consider employment.

Tegsedi trial data collection included Norfolk Quality of Life and SF-36 scales.

What is a p value? What does it measure? How is it calculated?

P is the probability that something is linked, for instance that taking a drug decreases some symptom. If it is less than 0.05, the result is considered to show that there is correlation.

Is this penny true, or is it weighted to fall more often on one side than the other? If I toss it twice, and it is heads both times, would you say it is weighted? No. If I toss it 25 times, and it is heads every times, would you say it is weighted? Probably. If I toss it once, there is a 50% chance of it being heads. Twice being heads, 25%. 3 times, 12.5%. 4 times, 6.75%. 5 times, about 3.5%. In medical science, we have agreed that once the probability drops below 5%, then we'll act as though it is true.

Do you have results from Jeff Kelley's blood test to detect and track TTR in the blood more precisely?

Not yet

Is there rationale for combining Tafamidis & diflunisal? Should we add a silencer?

No, Tafamidis & diflunisal are very similar, act similarly, so taking both probably won't bring more benefit. Adding a silencer - we are testing that in a clinical trial now.

It makes theoretical sense to add a silencer to Tafamidis or diflunisal. You'd probably use diflunisal, because insurance may not cover both a silencer and Tafamidis.

Silencers won't usually stop all TTR production, so adding a stabilizer is reasonable.

Do monitor for side-effects

Diflunisal is tolerated well by many people. It is not for patients with significant heart failure, significant kidney dysfunction, or significant bleeding issues.

What is the best age to be tested for a mutation, if you are asymptomatic, if a family member has a mutation?

It depends on the mutation. Consider testing 10 years before the symptoms tend to occur.

There are life insurance, disability, and other implications. Understand them.

Get genetic counseling beforehand.

Some genetic counselors say it is inappropriate to test before age 21, the age of consent.

Is there a diet to help control diarrhea?

If bloating is not an issue, consider eating a lot of fiber.

About 1/3rd of people bloat if they eat a lot of fiber.

Avoid food that causes gas or mal-absorption.

Try diets for 2 weeks, see if it makes a difference. Slowly re-add food that you'd like to put back into your diet.

There is not much evidence around pro-biotics, but little evidence of harm.

How often do wild-type ATTR have peripheral neuropathy, not just cardiac?

wtATTR impacts the body well beyond the heart. Peripheral neuropathy is not common, but does occur.

As patients get transplants and live longer, neuropathies are seen.

If a pt has carpal-tunnel and a positive PYP scan, should they start therapy?

Silencers are not approved for just cardiac yet. A trial about that is in progress.

Start them on Tafimidis (or diflunisal).

What are the long term risks of silencers?

We are not sure yet. There are theories, but folks are pretty unsure.

Should I take extra vitamin A if I am on a silencer?

In the silencer trials, everyone is required to take vitamin A supplements, since TTR transports vitamin A in the body. Silencers take measurable vitamin A levels to undetectable levels.

Don't take more vitamin A than prescribed. Vitamin A is stored in body, not excreted, and can cause pressure in the brain.

No vision problems were detected in the trials. (Vitamin A helps in vision.)

See recommended daily allowance.

How to treat APO1?

APO1 is very rare. Patients get kidney problems, or cardiac and skin (falling?) (one or the other, not both). We have no treatments yet. The gene silencing therapies are being considered for treatment. It is produced in the GI tract as well as the liver.

There are healthy living things to do - don't smoke or vape, eat well, ...

Doxycycline may be used, but there is not good evidence for it, so you need to be ready to stop it if there are side effects.

The evidence for it is very theoretical and tenuous. It may help, so if it does not hurt, it might be OK, but if it starts to hurt, stop.

If you have APA1, get to an amyloidosis center. It is complex.

Is drinking alcohol OK?

Alcohol in moderation is OK.

Heart patients should limit themselves to one drink per day.

Alcohol is a direct neurotoxin. To decrease nerve impact, have just half a glass per day.

GI impact is not a concern, at low levels of drinking.

Should I check my blood pressure daily, if I don't have symptoms?

No. But, per doctor instructions, check it often if you have problems, or are changing therapy.

A home monitor may provide truer measures of blood pressure that you get in an office.

Should folks look for amyloid if polyps removed during a colonoscopy?

No, not as routine practice. But yes if you have a mutation, or are otherwise at high risk of amyloid.

I had an echocardiogram. Will they tell me if I have amyloidosis?

Many echo cardiographers do not interpret results as indicating amyloid, for lack of awareness or knowledge.

The changes indicating amyloid can be subtle.

Echocardiograms are not especially sensitive.

Echocardiogram interpretation vary from person to person

What are mis-rates with Congo red?

Using too much stain can result in false positive.

Collagen can be mistaken for amyloid, by less experienced testers.

Mass spectrometry can be used to confirm a positive result.

Electron microscopy can be used to confirm a negative.

How is thyroid affected by silencers?

TTR is a 3rd line carrier of thyroid. The body has other means for transporting it. We don't expect a thyroid impact from silencers.

Should I get physical therapy to deal with my weakness?

It is great. It can help with many things.

It won't make your nerves grow back.

Gait training is great. Your doctor may need to prescribe it specifically.

What blood pressure is too low? 90/60?

If you are not dizzy, and it causes no symptoms, that blood pressure can be fine.

I have wild-type. I get good blood oxygen level results. Why do they test that?

Is aerobic activity OK?

Exercise is great.

If you have fluid in your lungs, the blood oxygen reading may be low. But you may have heart problems but good blood oxygen levels.

Cardiac rehab is great for determining how much exercise you can do.

Exercise is great. Ramping up is wise, to see what you can tolerate.

Recommended place for genetic testing: 23&me, lab, drug-company sponsored service?

Lab with counseling is a good option.

23 & me is just looking for 3 mutations, and provides no counseling.

Will doctors keep measuring quality of life after drug trials end?

It is not usually used in practice.

Does neuropathy spread throughout the body?

Yes. See Dr. Wiesman's presentation about how it tends to progress.

Can a person with a pacemaker have a PYP?

Yes

How does amyloidosis cause death?

It may be an arrhythmia, or congestive heart failure.

Nuero symptoms can cause malnourishment, increasing risk of infection, which can be deadly.

Amyloidosis may lead to kidney damage, then kidney failure.

How to test for autonomic neuropathy?

Tilt-table tests

Sweat testing

Gastric ... (eat eggs & toast, then do scans to see its digestion).

Can I donate blood while I'm taking a gene silencer?

No

Is trigger finger often a first symptom (vs carpel tunnel)?

The tissue that causes carpel-tunnel also causes trigger finger. It is hard to get tissue from a trigger finger surgery, to test for amyloid - the procedure does not get much tissue.

Trigger finger is often a first symptom, as is carpel tunnel.

Will my back pain from spinal stenosis come back after surgery?

Maybe. Surgery may be effective. If it is effective, it sometimes is not a permanent fix.

Is Viagra safe if you have cardio-myopathy?

Yes

Is PYP just for diagnosis, or also for monitoring?

Right now, it is just for diagnosis. Maybe we will eventually learn how it might be used for monitoring.

Thank you, doctors. You have changed our lives. There is a sense of hope that we did not have 8 years ago.

END OF DOCUMENT