Familial Amyloidosis Support Meeting

2011-10-29, Finkel Supply, Wood Dale, IL

Special Guests

Dr. Gertz, Mayo
Dr. Skinner, BU
Dr. Picken, LUMC
Dr. Peter James Dyck, Mayo
Dr. Dan Judge, Johns Hopkins
Dr. Ombrello, NIH
Zeldenrust, Mayo
Dr, Benson, IUPUI
Dr. Hanna, CC
Dr. Gollob
Lisa Ackerman, ISIS
Dr. Denis Keohane, Pfizer (Fold Rx)
Dan Levin, Pfizer (Fold Rx)
Julia Deves, Pfizer (Fold Rx)

Conceptual Framework – Dr. Gertz

In the body, everything that is produced can be recycled and reused. For instance, the oldest red blood cells in the body are 4 months old. After about 4 months, the cell is stripped down, iron recaptured, etc., and the components are re-used. The body breaks things down to constituent parts, and reuses those components to build new cells, etc.

The body produces TTR (a protein) that it later breaks down – imagine it being assembled with ½ inch nuts & bolts, & the body has a ½ inch wrench to use to disassemble it. In Amyloid, a genetic mutation creates a protein (TTR) that, after 40 or 50 or 60 years, begins to be created in a way that cannot be disassembled, suddenly it is made with ¾ inch nuts and bolts, while the body only has ½ inch wrenches to disassemble it.

This aberrant protein is deposited in the nerve, heart, or both.

The heart operates by squeezing & relaxing. It squeezes for about 1/3 second, then 2/3 second relaxing, filling up with blood for the next squeeze. Amyloid differs importantly from usual heart disease seen in the USA, in a way that MD's may miss. In heart disease, arteries get blocked with goop, the heart muscle dies, and the heart can't squeeze as hard. THIS HAS NOTHING TO DO WITH WHAT HAPPENS IN AMYLOID, but is what MD's 1st think of when they see heart problems. In Amyloid, the heart relaxes poorly (vs. the arteries being blocked), BUT THE SYMPTOMS are like those of typical heart disease. In Amyloid, the heart relaxes poorly (has little elasticity). Picture a balloon you fill with water: a healthy heart is a like a balloon that squirts the water out when you take it off the faucet. An amyloid heart is like a balloon made of something like aluminum foil – it won't squeeze the water out very well, after you fill it. Cardiologists measure the fraction of blood (ejection fraction (EF) – 67% is normal). Amyloid – heart fills with less blood, but squeeze is still good, so EF is normal, and MD's see that and think the heart is not the problem. But the amount that is filled is low – maybe 2/3rds of what healthy, elastic hearts fill with, so you have 2/3 of the usual amount of blood circulation. That may be enough for sedentary activities, but when you are active,

Body, under exertion, tells heart to send more blood, but heart can just pump faster, but not more efficiently.
Sx – shortness of breath with exertion.
MD –
Does echocardiogram, sees ejection fraction normal.
Does chest x-ray, heart is not enlarged (usually), so it looks OK to MD.
MD can measure heart wall thickness. Amyloid deposits in heart muscle fibers, so thicker wall is common in Amyloid, but MD thinks of more common cause of thicker wall – high blood pressure (makes wall bigger because hbp makes muscle big, since it makes heart work harder). You say you never had hbp, but MD knows that many people don't know they have had that. So MD does coronary angiography which will be normal and believes heart is fine.
Heart squeeze generate top number of blood pressure. Results from strength of squeeze and volume of blood. So Amyloid can result is slowly decreasing upper blood pressure measure.
Amyloid "short circuits" heart nerves that signal heart beats.
Amyloid – heart failure with preserved systolic function (squeeze is good, but other problems cause poor flow)
Amyloid damages automatic nerves (autonomic nerves), that control basic functions like breathing, bowel & bladder function, blood pressure, etc.
Highest priority for heart is delivering blood to the brain. Body's position affects blood flow to the brain. Higher blood pressure is needed to push blood up to brain if you are standing – autonomic nerves squeeze the arteries to constrict them, to shoot the blood up higher. Amyloid damages these nerves, so when folks stand up, the constriction may be slow, causing light-headedness or fainting (orthostasis).
Bowels – you control swallowing and defecation (intake and release). The rest of bowel function is automatic, including the wave action that moves food through. Damaged automatic nerves may not move the food (it sits for days in stomach or in intestine), or pass it through too fast. Sitting in stomach, food may eventually come up again (vomit), rather than moving on. Food may pass through too fast, before its liquid is removed, coming out as liquid.
Bladder – may not know when bladder is full, or get signal that it is full when it is not.
So blood pressure, bowel, & bladder control can be affected by AM.

QUESTIONS

Q: If echocardiogram shows thickness, with normal EF, how does cardiologist recognize AM? A: Doppler. We can tell speed of flow from heart using Doppler principle, and from that can determine the volume of blood. The low volume (rapid speed decrease in "relax" part of heartbeat), narrows possible causes to relatively few disorders, including AM. But that Doppler ultrasound is often not done after normal EF.
Q: How does EF effect priority for receiving a liver? A: Liver transplant prioritization uses EF in its formula, but AM does not affect EF until late in disease. So AM may be inappropriately de-prioritized for liver transplant.
Q: I get cramping when I walk. Is that nerve problems? A: Can be from poorer blood flow, or can be pseudo-claudication (deposits around base of nerve, causing cramping).

Historic Perspective – Dr. Skinner

AM discovered in 1854 by Dr. Virchow
Dr. Andrade from Portugal in 1952 identified TTR in an article (same thing like "an atypical neuropathy)
1967 symposium – only last 1/3 of content was really about FAP
Dr. Andrade analyzed data from 173 cases in Portugal. Observed that "there were no mild cases"
(See slides for timeline of key findings)

Since 1983, more than 100 mutations have been found in the TTR protein (over ½ discovered by Dr. Benson)
TTR = prealbumin = transthyretin
80% of AM is AL AM. 20% is "other"
Within Other:
2% is secondary
2-3% is age-related
10-12% is familial – see slide for more breakdowns, and when various types were discovered.
We have found that within these mutation types, there is more variation (further mutations)
DX: 1st by biopsy, then rule out AL amyloid, the rule out AA (secondary or age related?), then do genetic analysis to determine specific type. Gel can reveal that there is more than one type of TTR (indicating FAP?)
Senile systemic AM (SSA) –Mostly in men, age-related, heart is predominantly the organ involved, usually without multi-system disease. SSA is cause of death in many folks who live past 100.
ATTR = familial Amyloidosis. Over 100 variants. May occur from age 20 to old age, but for each mutation has a typical age of occurrence, with women usually getting the disease a bit later. Most survive 10(7?)-15 yrs. after Sx onset.
A special mutation: V1221. Common in folk of African descent. Occurs late in life, About ¼ to 1/3 of African Americans tested had gene (in Hopkins study). See slide about prevalence, within folk with certain symptoms.
TTR: 127 amino acids in a protein chain, folded up. Mutant TTR folds in unusual way (an unstable way), leading to amyloid deposits. Degree of instability varies with type of FAP.

Treatment

- Liver transplant is only sure treatment for FAP, replacing the factory that manufactures weird TTR with a factory that manufactures normal TTR. Best if transplant is early in disease (although transplant & aftermath have very severe effects on health).
- Several clinical trials are in progress for other treatments

Supportive treatment

Heart

Diuretics, low salt diet, rhythm control (pacemaker)

Peripheral neuropathy

Medications, active exercises, ankle braces, foot care

Autonomic neuropathy: BY & GI

(See slide)

Genetic counseling

Treatment of rare types of FAP

(See slide)

Inheritance

Autosomal dominant inheritance – if you get the gene, you have the disorder, but usually carriers have only one mutant gene (vs. having both genes being mutant)

Genetic Information Nondiscrimination Act

2008 – Congress
May 21 2009 – protected from insurance discrimination from genetic test results
xx, 2009 - protected from employment discrimination from genetic test results
See slides for more specifics
THIS DOES NOT PROTECT FROM used of genetic information or protection for determining LIFE INSURANCE
Discrimination penalties capped at $300,000.
Questions
Q: Might GINA be overturned, or can we rely on it? A: GINA is not linked to current health care reforms. GINA is probably here for the very long term.
Q: Do you think anyone will offer tests for xxxxx? A: Test will continue to improve and get faster, but there are not comprehensive FAP protein tests available now (IS THIS WHAT SHE SAID?)
Q: Can environmental factors cause the mutation? A: Environmental factors can affect time of onset, but do not cause the mutations.
Q: Can prealbumin (TTR) be elevated ...? A: Prealbumin is tested for nutrition tests, with low prealbumin indicating nutrition problems. But the level shown has nothing to do with FAP.

FAP Pathology – Dr. Picken, Loyola U. Med. Center

Biopsies are required to make the FAP diagnosis.
Pathologists work in laboratories, looking at tissue samples. (They usually don't work directly with patients).

Pathologist's process for amyloid detection

Pathologist stains a tissue sample. They are often looking for cancers. FAP needs a special stain to be detected, although usual stain can give some indication (revealing areas where there are no cell nuclei). That may get them to use Congo Red stain, which reveals beta-pleated sheets (formed from alpha-helix structures by fibrilogenesis.), indicative of one of several things, including amyloid. After detecting that, pathologist analyzes sample under polarized light.
So, need 1) suspicion (MD asks for amyloid test, or pathologist notices lack of nuclei in routine stain), 2) Congo Red stain (reveals possible amyloid), 3) examination under polarized light (confirms amyloid).
Congo Red under polarized light is the gold standard for detecting amyloid.
Amyloid can be very unevenly distributed within an organ, so lack of detecting it in a biopsy sample does not guarantee that it is not there.
Dr. Picken recommends Congo Red stain be used for all biopsies.
We want to detect amyloid early, when it is not obvious without using Congo Red under polarized light
Best fat biopsy is a small surgical biopsy, not a syringe-extracted biopsy. Surgical biopsy allows multiple slices, allowing more thorough examination.

Technical aspects

Congo Red with polarized light: must have sufficient light to be sensitive to amyloid detection
There are other technical pitfalls. Most pathologists seldom see it.

There are conditions that mimic the amyloid pathology results
Detecting amyloid in 1st person in a family: without a known family history, screening often does not occur.
Q: I had a fat biopsy that was negative for amyloid. Is that conclusive? A: No. Negative diagnosis is never conclusive. Technical challenges and variability leading to lack of in the specific fat sample taken
Q: How do you determine if you have the gene, but it is not active (not producing bad TTR), not present in TTR. A: Answer will come later.
Q: I asked my MD to have the pathologist do a Congo Red under polarized light. The results come back negative, although Dr. Benson found amyloid in a slide. How can I educate our pathology group? A: Get a 2nd opinion (to double-check pathologists result). The issue of educating providers & pathologists is tricky – another session may be organized to address this.

Peripheral Neuropathy Symptoms, Issues, Treatments – Dr. Dyck

Myelinated encapsulated fibers
Sensory fiber classes –

- Large – limb position, ...
- Small – cooling
- Unmyelinated – warming, heat/pain
- (there are more types)

In Amyloid, voltage gain graphs show fewer fibers of all types. Nerves may have only large fibers left, and relatively few of those.
What causes fiber degeneration in amyloidosis?
Could be damage from lack of blood, mechanical displacement (TTR pushing it out of place), Schwann cells embrace unmyelineated fibers. In AM patient tissue, sometimes unmyelineated fibers are gone, with only the schwann cells remaining.
Endpoints or Indicators of whether treatment is working
Neurological exam may provide best endpoint:
Autonomic tests
... tests
.... Tests

Exam

General notes

See the booklet that
Dr's use to go through this exam
This needs a baseline, to separate from everyone's usual pains, etc.
We have good ways to measure neuropathy, and neuropathy is a very good endpoint for assessing amyloid impact.

The exam

Walk on toes – can't
Walk on Heels – can't
Get up from kneeling – not normal

Various **strength & resistance tests** of head, arms, shoulders, hands, wrists, fingers (could do rest of the muscle groups)
Various **reflex responses**
Sensation tests of foot (would also do these on other points of body) – knowing if you are being touched, "which way is your toe moving – up or down?" "do you feel this buzzing (tuning fork type thing touching foot)?" "pin prick or not?"
Interview questions: All these follow up with questions asking (mild, moderate, or severe?) (same, better, or worse compared to last visit (maybe 4 yrs. ago).

- **weakness** in certain tasks or movements
- **loss of sensation** – sensing pain, heat, …
- **numbness** (asleep or prickly)
- **experience of pain** frequency, severity, location (jabs of pain, burning pain, deep aching pain)
- **autonomic symptoms** nausea, vomiting, feeling of fullness (increased satiety, stomach retention), diarrhea, incontinence, able to have erection

Questions:

Q: Can carpel tunnel progression be an indicator of amyloid? A: Yes. A sample of what is removed in carpel tunnel operation can be very useful for amyloid diagnosis. Progression of symptoms (quantitative sensation, nerve conduction) can help assess amyloid.
Q: Do myelinated fibers grow back? A: All nerves can regenerate. They regenerate better in animals than in man. The speed of regeneration depends on the area affected, the path the nerves take. Peripheral nerves regenerate much better than central nerves. Most important is to preserve nerves vs. trying to regenerate (since regeneration is the harder, longer road).
Q: The exam patient reported decrease in numbness. Is that good?. A: Numbness needs to be defined clearly. … (missed the rest). It is important to distinguish between positive and negative sensation (having abnormal sensations vs. not having normal sensations).
Q: My symptoms include cramps in my thighs. Is that from amyloid neuropathy? A: Maybe. There are many possible causes of cramps.
Q: Can neuropathy result in oversensitivity, rather than loss of sensitivity? A: Yes. Both may be result of loss of nerve function, because nervous systems may "recruit" (overcompensate in responding to signals). This is not typical of amyloid disease.
Q: A question about using one or another pain drug. A: Many people can deal with pain with the simple, less expensive meds (aspirin, etc.) It is important to carefully assess when you have pain, in what situations, and tailor your medication to your needs (vs. keeping a constant dose of the biggest pain killer).

Cardiac Symptoms & Issues – Dr. Judge

Dr. Judge (cardiologist, focus on inherited heart diseases)
Left Ventricle – pumps blood to body, the most important part of the heart.
Heart electrical system –
Cardiomyopathy-
heart failure
Arrhythmia

Amyloid cardiomyopathy –

Heart becomes thick
Affects all portions of the heart
Strength of heart may or may not be normal

TTR cardiomyopathy

Much variation

Other problems that thicken heart

Hypotension (usually not very much thickening)
Aortic stenosis

Heart Failure

Diagnosed based on symptoms

Symptoms

Shortness of breath
Fatigue
Swelling of abdomen ankles
Unable to lie down due to SOB
Wheezing
A lack of appetite
Cough
Awaken at night due to SOB

Arrhythmia

Heart goes too slowly (bradycardia) usually not treated
Heart goes too quickly (tachycardia) (many types, various treatments)
Heart out of rhythm (Atrial fibrillation) – about 5% of those 65+ yrs. old have this. Main problem – can result in blood clotting.

Symptoms

Fainting
Palpitation
Light-headedness
Fatigue
Shortness of breath

Amyloid Detection in heart

Heart biopsy can find amyloid in the heart
Risk: infection, damage to blood vessel
Electrical problems during biopsy (extra heart beats, abnormal beats)
Troponin levels after high with amyloid – it does not necessarily mean you recently had a heart attack, need a stent, etc. (which would be the common interpretation by clinicians) – so remind clinicians about this.

Treatments

HF meds – many not be helpful for amyloid.
Current standards are blood thinners to prevent strokes (clotting), and preventing heart from going too fast (vs. trying to force a very regular rhythm). Blood thinners include Coumadin, aspirin, & newer meds.
Pacemakers – can kick in to slow heart (shocks heart, feels like a punch to the chest). Use in amyloid is not well examined. There are important pros & cons about using these.
Natural remedies – soy & curry in massive amounts (beyond what is realistically possible to consume) may decrease poor protein folding.
Vitamins – vitamin E – evidence not clear, but some studies indicate it may be harmful, not helpful.
Other remedies – most lack evidence. Beware – we don't know if they will harm, rather than help.
Heart transplant – may help, but many negative health consequences.
Heart pump ("left ventricular assist device") – Study in severe cases, helped 1 yr. survival, but not 2 yr. survival.
Continuous flow Heart pump ("left ventricular assist device") – show better 2 yr. survival that pulse heart pumps. Cons: need continuous power, infections, other complications.
Portable devices that assist both ventricles are being developed.
Artificial hearts are being developed.

Summary

Currently, diuretics are the main, effective treatment for amyloid cardiac symptoms.

NIH news – Dr. Ombrello

Dr. Ombrello, auto-inflammatory disease specialist
Bad folding may occur after prolonged inflammation (inflammation triggers TTR production)
AA amyloidosis – median survival of 133 months (~11 yrs.)
AA amyloidosis can be caused by infections (tuberculosis, malaria, leprosy HIV, chronic osteomyelitis) or autoimmune disease (rheumatoid arthritis, ankylosing spondylitis, systemic juvenile idiopathic arthritis)

Inherited auto inflammatory disease

Familial Mediterranean Fever

Need both mom and dad contributing gene for symptoms to be expressed.
Causes episodes of ~72 hours, with fever, abdominal pain, chest pain, arthritis. Episodes may occur sporadically, with intervals of a week, several years, or whatever.
Treated with daily Colchicine use (decreases severity of flares, decreases AA amyloidosis risk from 49% to 2%).
Daily injections with anakinra have been effective in preventing ...(some symptom)

Tumor Necrosis Factor Receptor Associated Periodic Syndrome

Fevers lasting 3 days to weeks, abdominal pain, periorbital edema, rashes, joint pain.
A pt. got a kidney transplant, got kidney transplant, developed amyloid in new kidney.
Pts do not respond to colchicines.
Steroids help, but have nasty side-effects.
Anakinro decreases symptom duration
Etanercept helps with symptoms & AA amyloidosis

Cryopyrin Associated Periodic Fever Syndromes

Familial Cold Auto inflammatory syndrome, Muckle-Wells syndrome, ...
Fever, rash, arthritis
May manifest as severe arthritis is children (?)
Flares can be caused by cold temperatures.
I01 ("eye-oh-one") blockers are extremely effective in stopping the amyloid progression.

Kiacta trial

Trial of Eprodisate Disodium
70 sites worldwide
Subjects must have ...
Theory – may help decrease deposit of bad TTR (not affecting it's production).

TTR & Organ Transplants - Dr. Zeldenrust

Extra points

You have to have a fair amount of amyloid in the body before we are likely to detect it.
If you have the gene, you still may not get the disease ("penetrance is not 100%).

Why a liver transplant?

The liver is the main source of the TTR, because we have no other cure.
Liver makes the majority of circulating TTR.
Transplant is NOT done in asymptomatic gene carriers. You must 1st show that you have the atypical TTR.
http://www.fapwtr.org/ "Familial Amyloidotic Polyneuropathy World Transplant Registry and Domino Liver Transplant Registry"- transplant registry – tracking 1800 transplants, with volunteer reporting. 120 transplants/yr. 2/3rd of tracked folk are from Portugal, France, & Sweden.
The removed liver can be given to someone else ("domino transplants"), so getting on transplant list may be easier than for other folks who need transplant.

Outcomes

3% mortality (over what period? Is this just immediate mortality, from the surgery?)
Liver transplant improves survival in V30M.
Most effective if done early. Early diagnosis is key.
Major benefit is better nutrition after the transplant.
Multi-organ transplants (liver & heart, liver & kidney) are feasible, and can have good outcomes.

Outcomes predictors:

Modified Body Mass Index (mBMI) (nutritional status) (best not to be malnourished)
Disease duration – best if less than 7 yrs. from onset to transplant (maybe – there is some counter evidence from Sweden)
Mutation – V30M mutation outcomes are better than non-V30M
Autonomic neuropathy – more severe is associated with poorer outcomes.

V30M outcomes

40% have neuropathy improvement
80% improve nutrition (mBMI)
50% continue having worsening cardiac problems
Eye deposits progress

Non-V30M outcomes

(based on small number (108) of pts. for any one mutation)
Neuropathy improvement
GI symptoms improve in most
Eye & brain can worsen due to local production of TTR (i.e., production of TTR by retina & brain lining).
Many continue having worsening cardiac problems
Pace of TTR deposition in heart can increase after transplant
Cardiac deposits develop in those with no heart involvement at transplant.
New deposits contain normal TTR made by transplanted liver (i.e., normal TTR may accrue on deposits that were established by abnormal TTR)

Unknown

When is transplant futile?
Which mutations benefit?
If heart has symptoms, should it be transplanted as well?
Does transplanting the liver halt, slow, reverse, or accelerate the amyloid production?

What about transplanting other organs?

Heart

Outcomes similar to heart transplants done for other reasons
Controversy about whether best to do both (liver & heart) at same time, or do them sequentially
Some centers say you should got both transplanted, or neither, but not just one.

Kidney

Kidney involvement rare at Mayo.
... (see slide)

Summary

ATTR is a clear indication for liver transplant
Early & accurate diagnosis is critical
Possibility of doing "domino transplants" (reusing the removed liver) shortens the wait time. Recipient can develop amyloid symptoms if they survive a decade after the transplant.
Those seeking multiple organ transplants have longer wait time.

Questions

Q: I had eye symptoms before my transplant. I've had many eye surgeries. Did you say TTR may still be produced by my retina? A: Yes.
Q: Can there be retina transplants? A: No, not for the part or retina that produces TTR.

Q: ... A: Eye symptoms are vitreous opacities (amyloid blocks light transmitted through the fluid in your eye). Eye doctors know how to treat it, even if they do not know it is caused by amyloid.
Q: Is any research going on looking at vitreous amyloid (i.e., in eye fluid)? A: I don't know of anyone looking into that.
Q: Is domino donor issues worked out in US, in a way that could be shared with Canada, to ease the deliberation there? A: Not sure how this is calculated into the Meld(sp?) score, but it does affect lists in US. The process is a bit nebulous.
Q: What experiences have you had with Isoleucine 122 mutation? A: We have little experience with such patients. This has symptoms that are focused on the heart, and may be appropriate for just a heart transplant (not liver). The patients are usually older (age 65+), so getting prioritized for a transplant may be more difficult.
Q: Should I wait for a combination transplant (liver & heart), or just get the liver? A: A liver transplant before evidence of heart involvement is indicated if there is amyloid elsewhere. But the heart would not be transplanted then.

Non-TTR & Organ Transplants - Dr. Benson

Chapter 15 of Dr. Gertz's book has more information about non-TTR familial amyloidosis.
Non-TTR are hard to diagnose
Non-TTR treatment is challenging
See slides for table of many mutations, and their dominant symptoms.
See slides for manifestations of various symptoms in patients and in tissue samples.
Amyloid deposits can fill the filter components of kidneys, making them pretty ineffective.
You can't tell one type of amyloid from another – they all look the same. It takes a lot of diagnosis acumen to determine the differences.

Treatment

Apo AI: liver transplant, affected organ transplant (kidney, heart)
Fibrinogen A-alpha: liver transplant (curative), maybe with affected organ transplant
Lysozyme: Affected organ transplant (kidney, liver)
Apa AII: Affected organ transplant (kidney)
Gelsolin – Affected organ transplant (cornea)
Cystatin C: avoid fever (maybe) (take aspirin each day?)

Questions

Q: Information about (some specific type) A: mostly heart involvement.
Q: How much amyloid is needed to cause symptoms? A: In the heart: normal = 350 grams. Amyloid = 650 to 1000 grams, at death. Say that occurs at 10 yrs. – maybe 30 to 60 per year (~10% plus increase in heart weight each year). Liver may produce a lot of amyloid, but only a small portion may get deposited.
Q: When does amyloid build-up start? At birth? A: Biopsies of relatives ages 28-35 showed no amyloid, but age 40-50 all had amyloid. So it probably does not start at birth. It may start when you get gray hair or brown spots on your skin – i.e., when your body starts to change. Younger bodies may be able to handle the abnormal proteins well, getting rid of them. (So it isn't that the nuts and bolts become ¾ inch, but that you've always had some ¾ inch nuts & bolts, and you just loose the ¾ inch wrench when you get older.
Q: What is the speed of progression? A: Within a family, progression & onset seems to be consistent.
Q: Identical twins – If one doesn't have it when the other does, will that twin get it? A: Yes, both identical twins will usually get it, even if onset time differ.

In US, the most common are ALA60, ... ().

Breakout Workshop – ALA60 – Dr. Benson

Dr. Benson brought a genealogy from Karl Rogers, which ties many of the ALA60 folk together.
Transthyretin booklet has a genealogy showing the 1st person in which ALA60 was identified.
Stiff blood vessels don't expand & contract to give enough blood to the heart, when you are exerting yourself. (not just inelastic heart, but inelastic blood vessels).
The Met30 patients are different at the molecular level. What works for them may be very different than what works for the ALA60s.
Dr. Benson has never found a TTR mutation in a Native American, and few in Asians. Almost all are in folks of European decent.

Symptoms:

Q: is there a usual progression of symptoms? A: Typical is carpel tunnel (followed by surgery). 5-6 years later they have some heart symptoms – fainting, shortness of breath, ... Then 2 years later they get the amyloid diagnosis. Many doctors won't test, even if you let them know of the family history.
The youngest person Dr. Benson has seen with ALA60 with symptoms was age 42. He died, probably of heart problem (fatal arrhythmia), a year later.
Most typical symptom: cardiomyopathy occurs 1st, and is prominent. But there are exceptions.
Some autonomic & GI involvement, often later in illness (after cardiomyopathy) - Bowel dysfunction, weigh loss
Dry cough can be indicator of cardiomyopathy
Women tend to get symptoms about 6 to 8 years later than men.
A baseline echo is good to have, to measure heart wall, to allow early detection.

Treatment

Heart transplant doesn't help much.
Liver transplant – may or may not help. English specialist saw many folk get much worse in heart symptoms after liver transplant. Maybe the transplant was causal, or maybe it was just normal disease progression.
Neuropathy does tend to worsen even after liver transplants.

Questions

Q: Are there medications to control bowel symptoms? A: Bowel is complicated. Stomach grinds stuff. Colon removes moisture. Both functions can be obstructed. Reglan (metoclopramide) helps empty the stomach. Fiber may help decrease the diarrhea. Tincture of opium (paregoric) slows the bowel. Imodium & the like sometime help.
Q: Is this like diabetic gastroporesis, where a gut pacemaker may help? A: I don't know. I'm not familiar with those.
Q: Is liver transplant questionable if you get an early diagnosis? A: You may do much better, but we don't know for sure. Liver transplant works well for the Met30 patients, but they are different at the molecular level from the ALA60s. What works for them may be very different than what works for the ALA60s.
Q: Is there something that family might do (food, ...) that may aggravate or accelerate symptoms? A: Not that we know about.

Q: So I'm hearing, "There's not a medication to stop this disease right now. Liver transplant benefit is unclear. So there aren't great options." A: Yes, we don't have options that, definitively, will help. But we are working on it, although Dr. Benson does not expect to see a cure in his lifetime.
Q: Before amyloid is found, what biopsies should I get, at what frequencies (given that I have the gene)? A: Get heart baseline at onset of carpel tunnel. And get a pyrophosphate scan. Getting biopsies before then is probably not worth doing before then.
Q: Will exercise help my outcomes? A: Loss of muscle is due to nerve damage. It is good to be as active as you can manage to maintain muscle.
Q: What can we, a roomful of ALA60 folk, do to help? A: Raise a bunch of money to fund research.

Clinical Trials

Alnylam - Dr. Gollob

Diflunisal – Dr. Berk

Formatted

ISIS - Lisa Ackerman

Pfizer (Fold Rx) – Dr. Denis Keohane, Dan Levin, Julia Deves

END OF DOCUMENT