

# 2017 ASG Biannual Meeting Questions and Answers

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*From Chicago (O'Hare Hilton Hotel), 2017-10-29, plus doctors' written responses to submitted questions that were not answered at the meeting.*

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## Causes & Treatments

### **1. Is there gene therapy being researched for amyloidosis?**

MD4- Folks are dreaming about this, but nothing seems imminent.

MD1- A Boston company is trying to use Crisper technology to do gene editing for this.

### **2. Has anyone thought about looking for the problem in the thyroxin or the retin that is being carried with the protein?**

MD1- Yes, this makes sense and should be considered for people with ATTR. Thyroid studies should be done for people with this condition (or any form of congestive heart failure), and vitamin A levels are also reasonable to check. The group at BU is looking at proteins related to retinol (RBP4) in ATTR.

MD2- Very creative, but it's the transporter protein that misfolds, not the cargo. Moreover, thyroxine infrequently occupies the docking site, as it is preferentially transported by thyroid binding globulin.

MD3- Yes, this makes sense and should be considered for people with ATTR. Thyroid studies should be done for people with this condition (or any form of congestive heart failure), and vitamin A levels are also reasonable to check. The group at BU is looking at proteins related to retinol (RBP4) in ATTR.

### **3. Why do we/you need a different treatment for cardiac and nerves if the treatment goes after the ttr in the liver?**

MD1- I think any treatment that silences the TTR gene or stabilizes the protein will work for either condition.

MD2- It's not clear whether one drug can effectively treat heart and nerve ATTR amyloid disease. We need more studies to answer the question. The recently ended phase iii studies will educate us on just that question.

## **Wild Type**

### **4. Because TTR-Wild Type misfolded amyloid is emitted via the liver, has any research ever been done that might link the TTR-Wild Type to any Statin drugs that could/may/no one will admit/ damage the liver?**

MD1- I am not aware of research like this. I will add that alcohol can have similar liver toxicity, but there is not a clear pattern of alcohol use among my patients with ATTRwt.

MD2- While older people frequently take statins, wild type/age related/senile amyloid preceded the advent of statins by decades. Statins did not cause ATTRwt disease.

### **5. Does amyloidosis cause you to have potential orthopedic surgeries or do the implants from orthopedic surgery cause amyloidosis? (Wild Type)**

MD1- Neither is true

MD2- It can, we know that joint cartilage and ligaments can be targets of amyloid (including wtTTR but best reported in dialysis related amyloid (aB2))

MD3- The hypothesis is that TTR amyloid affects the joints causing an increased need for orthopedic procedures in patients with TTR cardiac amyloid. This surgery occurs 5-7 years before the symptoms of cardiac amyloid though this is quite variable. Thus, amyloid contributes to the increased need for orthopedic surgery. The amyloid is not due to the implants.

### **6. Is it unusual to see wild-type pts who have lived over 5 years?**

MD5- Awareness is increasing, so diagnosis is happening earlier, and some pts live an average of 7-8 years (some up to 15). As stabilizing meds come out, this will get longer.

MD3- The diagnosis often probably comes 10 years after symptom onset.

### **7. What is early-onset vs. late onset wild-type?**

MD6- Before vs. after 50.

### **8. Any international countries offering cures for wild-type?**

MD1- We know of none that are real.

## **Epidemiology (origin, types, patterns of occurrence)**

### **9. Ser6 mutation in TTR: How frequent? Pathology? Protective?**

MD1- This is considered a non-pathogenic polymorphism. In other words, our current understanding is that this is a rare change in the TTR gene that doesn't cause trouble. It also doesn't seem helpful.

### **10. Do Africans in Africa also have the common USA African American variant?**

MD3- Yes, they have the Val122Ile mutation.

### **11. My father had amyloid. Did he pass the gene to me?**

MD7- Wild-type is not inherited. There is no gene to pass.

### **12. Is there a list of where different mutations originated?**

MD6- Dr. Benson has a fair bit of information about this.

## Liver Transplants

**13. If liver transplantation provides younger and therefore presumably stable ttr, do blood assays for ttr monomers & dimers no longer reveal their presence? If these are no longer present, why does cardiac amyloidosis tend to progress after liver transplantation? Does this suggest that there is a destabilizing factor (factor x?) present, rather than ATTRwt simply being expressed by simply having an ageing population?**

MD1- Yes, this is possible. Alternatively, once amyloid starts to develop, it's easier for normal TTR to add to it, like crystals that form more easily after an initial deposit.

**14. Is there data 15 or 20 years post liver transplant for V30M survivorship? Is there data about other problems that start to occur 15 years post-transplant?**

MD2- Yes. Progressive amyloid deposits in the eyes and brain.

**15. Got a transplant for non-hodgins lymphoma, then 7 years later got wild-type. Did the transplant cause it?**

MD7- Probably not, but we can't say for sure.

## TTR Medications

**16. What other prescriptions have proven to be beneficial?**

MD1- Something to stop production of the amyloid. Options include diflunisal, new medications not yet approved (tafamidis, patisiran, inotersen – the last 2 are in trials with expanded access for ATTRmut). Non-prescription options include possibly green tea extract (EGCG).

MD2- TTR tetramer stabilizers, amyloid disrupters, or TTR gene silencers manage the disease process.

**17. During our research we have come across a prednisone colchicine study for amyloidosis. Would this be beneficial? What about Renal Failure with Colchicine? I have lysosomal amyloidosis?**

MD1- colchicine would be of no value

MD3- These treatments are used to manage the underlying systemic illness that causes AA amyloid. Colchicine needs to be used cautiously in patients with renal dysfunction. Colchicine would not be indicated for lysosomal amyloid nor would prednisone

## Diflunisal

**18. What OTC pain meds can be taken when you are on Diflunisal? I've been told to avoid additional nsaids.**

MD1- Yes, don't use other NSAIDs with diflunisal. Tylenol may be ok, but you should check with your doctors. Low doses of aspirin may also be ok, but again, you should ask your doctors.

MD2- Tylenol, lidocaine patches. At times it may be necessary to hold diflunisal and take another nsaid, e.g., ibuprofen/aleve.

**19. Patients who are taking Diflunisal, should they abstain from taking ibuprofen?**

MD1- Yes both are NSAID's

MD3- Yes, we recommend that patients taking Diflunisal should not take regular ibuprofen. Every once and a while should be OK, but do not take more than 2 or 3 doses in a day.

MD4- Yes. Diflunisal is a prescription-strength nonsteroidal anti-inflammatory drug (NSAID). Even at the low dose that we use for ATTR (250 mg twice daily), this should work like a moderate dose of ibuprofen or naproxen. Higher doses or addition of other medications in this category would increase the risk of kidney problems and other side effects

**20. I am currently taking doxycycline and ursodol for my wild type . Would it be beneficial to start taking Diflunisal? Is so should I stop taking the other drugs?**

MD1- Unknown but is worth a try if no side effects develop

MD3- It may be useful to take all three. However, we have not data in studies demonstrating the efficacy of this approach. Additionally, many of these medications have side effects which can increase when taking multiple medications. The risks and benefits need to be discussed with your provider.

**21. Diflunisal – What side-effects should I be looking for?**

GI irritation – bleeding ulcers, discomfort occur in a small portion of those taking NSAIDS. There are 2 drugs approved to counter these effects: misoprostal (causes diarrhea in ~50% of those taking it and proton-pump inhibitors (7 over the counter ppis: Prilosec, Previcid, Nexium, ... - all are about the same in countering ulcers.). Monitor kidney function, especially in cardiac patients. Try and find the lowest dose that works, to minimize side-effects.

**22. I'm on Diflunisal, ½ tablet twice/day (250 mg/day). Some folks are taking twice that dose. What is the right dose?**

The trial used ½ tablet, twice/day. The study showed little additional amyloid benefit of 500/day vs. 250/day. If you are taking an NSAID for arthritis, maybe the higher dose makes sense, to cover the arthritis.

MD7- Always take it with food.

**23. Will rotiserine help with my eye amyloid?**

No, it won't cross the

**24. Diflunisal or tafamidis?**

MD8- Both agents had similar results in our studies.

MD6- The price may make the difference, for many people.

**25. Why did so many people drop out of the Diflunisal trial?**

MD3- There has been no head-to-head comparison. The tafamidis study was in young people, and Diflunisal was in a much more varied population. Tafamidis may get better with more exploration of the best dose. Tafamidis seemed to have better impact on more severe pts.

**26. Why was there a high drop-out rate in Dr. Berk's Diflunisal study?**

The drug was available in the US outside of the trial. When pts were getting worse, I encouraged them to drop out, and get the medication themselves. About twice as many placebo pts dropped out, compared to the med arm.

**27. Should I start pt on diflunisal?**

MD1- Send pts to neurologist, to better assess whether pt has amyloid-caused neuropathy. Base your medication prescribing on the result.

**28. After liver transplant, should I take Diflunisal?**

MD3- Yes, it may often be appropriate, but be sure to check with your transplant team.

## Other treatments (not medication)

### **29. Is exercise beneficial to cardiac Amyloid condition?**

MD1- Unknown, but maybe.

### **30. Has there been any studies w/mindfulness training, mediation, yoga to slow down the progression of amyloidosis?**

MD1- not to my knowledge

MD2- I think that these modalities can be helpful to manage symptoms such as neuropathic pain but given what we know about the underlying mechanisms of amyloidosis I don't think they can change the rate of progression. With this said, mindfulness can change our outlook and help cope with symptoms.

MD3- Not that I am aware of.

### **31. Is cannabis helpful in amyloid?**

MD7- It has not been studied. Some pts say the oil helps, rubbed on their feet.

MD8- Some pts. smoke marijuana for abdominal pain & nausea. About half of my pts (in San Francisco) have it as their preferred discomfort-reliever.

## Green Tea

### **32. Can we get a Green Tea company to help sponsor the net conference? And a local Bark company also?**

MD1- I'll make some calls but I'm not optimistic.

### **33. Where would you get Green Tea Extract? How much daily? Is EGCG a component of Green Tea? What would we look for in the store?**

MD1- You can get Green Tea Extract (EGCG, epigallocatechin-3-gallate) via Amazon. There is no established dose. EGCG is a component of green tea. In a store, look for EGCG.

MD3- EGCG is the active ingredient in green tea which may slow progression of amyloidosis. The accepted dose of EGCG or green tea extract varies but we recommend 500-700 mg per day.

This can be bought at any health food site or store. Just pay attention to the caffeine component

MD4- Yes, EGCG (epigallocatechin-3-gallate) is the active ingredient in green tea. It should be available in a pharmacy or health-food/nutrition store without a prescription. Studies for this used 500-700 mg EGCG per day. If the pill also contains caffeine, you should not use it. Remember that there is a higher amount of green tea extract than EGCG because EGCG is a component of green tea.

### **34. Green tea – what dose, how best to take it? Drink? Take extract?**

MD4- In the one study: (German study of ~18 people, 15 completing one year, they used an extract, and found minimal effect). Use 750-1000 mg per day. Beware of the caffeine level in some brands.

## Dealing with healthcare system or insurance

### **35. It seems clear I should be seeing multiple specialists at an amyloidosis center. MY HMO just doesn't have the expertise> How do I convince my HMO (and Medicare) to refer me for multidisciplinary evaluations and treatment? (Val30Met)**

MD1- I recommend persistence, hopefully with the help of your primary doctor.

**36. Amyloid patients can have many medical conditions with different branches of specialists involved in their care. Which of those specialists should be the gatekeeper overseeing care?**

MD1- For TTR it's the cardiology/neurology team

MD3- It depends on what type of amyloidosis you have and where you are seen. Patients with AL may have an oncologist supervising care. Patients with ATTRwt may have a cardiologist, and patients with ATTRm may have a neurologist.

MD4- Traditionally it would be a Primary Care Physician (PCP). But ideally it will be someone who is familiar with amyloid ("amyloidologist" as Muriel Finkel calls many of us). Depending on your location and local availability, you will probably need to choose among the different physicians in your area.

**37. Should I wear an ID badge about having amyloid?**

MD5- I see no downside. Take a copy of your EKG with you, so if you have some event or need a doctor, the doctors can compare to your baseline. It also helps to have a list of your diagnoses and medications and doctors' contact information so we can be called for questions.

## Symptoms, symptom treatments

### Joint replacements

**38. Have there been cohort studies on ATTRwt for the percentage of people with joint replacements? Orthopedic surgeries?**

MD1- Yes, Dr Maurer's group at Columbia is looking at this.

MD2- Not that I am aware.

### Skin issues

**39. Why do red spots, like liver spots appear where excessive scratching has taken place?**

MD1- Probably increased fragility of both the skin and blood vessels in response to amyloid.

**40. Skin itching in wild-type (puritis)**

See a dermatologist. Could be part of neurological impacts.

### Cognition

**41. Do you see any cognitive problems in people that had had TTR amyloid for many years?**

MD1- Some ATTRmut forms can contribute to brain difficulties. However, other conditions should be considered.

MD2- Late disease, Yes.

## Blood pressure

**42. I have mutant TTR. Age 51 male and have always had elevated BP since youth (High 130s-140;s/high 80-90's)..PCP put me on BP meds. Most of my family regardless of weight have had elevated BP...meds have not changed BP much. ...could the ATTRmut be a contributor to the elevated BP?**

MD1- Probably not. My biggest concern is when BP falls with ATTRmut.

**43. Fainting when I stand up**

MD8- I find out about earlier symptoms, observe pt stand from lying down, to understand likely causes. There are many behavioral things you can do to address this – I start with those. [She listed many – I could not keep up.] Blood pressure meds: I start small, several doses per day, but not before bed (you don't want high blood pressure when you are lying down).

MD6- Foods & how hot they are affects blood pressure:

## Urine

**44. I'm a 30-yr-old carrier of the v122i mutation. I have had tricuspid regurgitation, but no amyloid diagnoses. Is amyloid causing the proteinuria in my urine?**

MD4- TTR spillage from amyloid would not usually cause detectable proteinuria. You should get further testing for the cause.

MD5- tricuspid regurgitation – I look for the cause with the following process: ...

MD6- Tricuspid regurgitation is common in many people, with or without amyloid.

MD7- Tricuspid valve replacement is rare. However, amyloidosis in the context of aortic valve replacement is probably more common.

MD8- you may have amyloid, yet have a non-amyloid reason to get a heart valve replacement.

**45. Why am I peeing blood?**

MD2- Blood vessels within bladder ...?????

**46. I self-catheterize to clear my bladder. Is needing to do that common in amyloid (auto-catheterization)?**

MD7- Yes, this is very common.

MD1- Bladder dysfunction is very common in amyloid.

## Heart

**47. Alcohol & cardiac amyloid**

MD6- 1-2 drinks/day is fine, provided the drinks don't interfere with any medications taken. typically 1 drink for a woman and 2 for a man as max but these are not hard and fast rules. ½ bottle of wine may be fine, particularly if there is no high blood pressure or liver problems. Ask your doctor.

**48. Given some set of symptoms (loop recorder for 2 years showed xxxx), should I get a pacemaker?**

MD6- I would do various test, then make changes in blood pressure medication to better understand the symptoms and how they may be controlled. Only after that would I consider if a pacemaker was indicated.

MD7- Wearing a monitor can

MD8- Avoid standing for a long time, especially in the heat (or hot shower). Wear high quality pressure stockings.

**49. Should a defibrillator be put in in advance of a heart event?**

Summary: Very rare that you would need a defibrillator.

MD9- Cardiac amyloid is different than many heart arrhythmia problems. It is unusual for cardiac amyloid pts to have life-threatening arrhythmias. The implanted defibrillators can often cause more harm than good. I generally avoid them (Dr. Maurer & Grogan agree).

**50. If anti-sap antibody clears cardiac amyloid fibrils, is there any concern that the residual heart muscle will be physically damaged? Does amyloid related atrial fibrillation differ from usual afib...in terms of...origin of electrical activity? Response to cardioversion...initial response, duration of response? Difficulty of performing ablation...Rx; success rate?**

Antibodies look promising, but lots of questions remain regarding safety and efficacy. That's why more clinical trials will be done. AFib is a disorganized pattern of electrical activity in the top chambers of the heart, with or without amyloid. Cardioversion has a poor long-term rate of success for most forms of AFib. I find ablation of AFib to be riskier and less likely to succeed for people with cardiac amyloid.

**51. If anti-sap antibody clears cardiac amyloid fibrils, is there any concern that the residual heart muscle will be physically damaged?**

MD1- Yes its part of the safety monitoring in the trials

MD3- Yes, this is a potential concern

**52. Does amyloid-related atrial fibrillation differ from "usual" afib in terms of origin of electrical activity, response to cardioversions, difficulty of performing ablation RX, success rates?**

MD1- Ablation success is much less and recurrence is very common

MD3- Yes. The chance of maintaining sinus rhythm in the presence of amyloid is less than in other common cardiovascular conditions including the success of an ablation in the long term.

**53. What is the best anti-arithmetic med for patients with both a tendency to runs of v.tach(?) & afib?**

Amiodarone often works, but specific recommendations for treatment cannot be made without more information as part of an appointment with a cardiologist in practice.

**54. Cardiac Amyloidosis is being managed with prescription diuretics, can this work long term?**

MD1- Yes.

MD2- Diuretics manage symptoms of amyloid cardiomyopathy. These drugs will be effective until the heart and/or kidneys are too damaged to respond.

**PYP (Technetium-99m stannous pyrophosphate scanning, also known as myocardial infarct imaging)**

**55. Cost of PYP**

MD3- It is generally not too expensive, and is indicated for amyloid (so insurance should cover it).

**56. Is PYP used in all heart diagnostic testing in amyloid?**

MD9- Yes, in general. First, know whether the amyloid is AL vs. ATTR.

MD6- PYP is not always available everywhere, but soon may be. The organized medical societies are trying to standardize how the test is done and interpreted.

## **Nuerologic**

### **Nuerologic testing, monitoring**

**57. How are trial pts monitored? How should nuero impacts be monitored?**

MD7- Comprehensive sensational exam, nerve conduction, skin response, amplitude of ... (pattern, not just normal/not normal).

MD6- As general practitioner, ask "How are you doing?" (Quality of Life) in your 8-minutes of exam. Pts have insights into their status.

MD8- Do physical exam. How they look, feel, wt change, medication use. Heart blood tests: troponin, BNP/nT-proBNP. Look at combination of pt's self-assessment (feeling better or worse) and clinical measures, to understand complete picture in making a diagnosis. Some serial (repeated) testing is useful, depending on pt situation.

MD9- Some tests are sensitive to what you ate yesterday.

**58. Familial FAP (GAU54) with worsening neuropathy, after heart & liver transplant. What do I do?**

MD8- Could be from many things other than amyloid, including immunosuppressants. Investigate the possible causes, not just amyloid.

MD9- We have seen a fair amount of what looks like amyloid neuropathy 5+ years after a heart transplant. Do PYP scans to see if amyloid is getting into the new heart.

## **Pain, sensation**

**59. I have wild-type TTR cardiac. I am loosing sensation in my feet, with tests showing pre-ganglionic origin. Is this caused by amyloid? Do other wild-type pts have peripheral neuropathy?**

MD7- Not normally. I'd want to know what medications the pt is on. I'd want some biopsies. I'd want the "trigger finger release" results – I do not see that much.

MD8- We recently presented 3 wild-type cases with neuropathy, demonstrated with biopsy.

MD6- I see very few wild-types with severe neuropathy.

MD9- I'd only do a sural –nerve biopsy if it was very useful for the pt, because of the impacts of those biopsies.

MD3- We saw amyloid-caused neuropathy in 2 of 15 wild-type pts with neuropathy. About 4 of 9 heart-transplant wild-type pts later developed neuropathy, maybe because they lived long enough for it to develop.

MD5- A Hopkins doctor is developing a skin biopsy to find amyloid-cause neuropathy.

**60. Do you see ATTRwt patients who complain of loss of taste sensation?**

MD1- I've heard people report this, both with and without ATTR. One possible contribution is zinc deficiency or use of an ACE-inhibitor (ie, Lisinopril), since they bind to zinc. Low zinc levels can cause change in taste. But most of the time, it has nothing to do with low zinc levels.

MD2- Yes. It is a small fiber nerve function, affected by attr in concert with other small nerve injuries.

MD3- Very interesting question, to my knowledge this has not been looked at in TTR. An old AL amyloid study (1996) found that 90% of AL pts had some degree of reduced taste and in 35% this was very severe. I agree that it is likely much more common than we realized and would be a good thing to look into.

**61. I'm wondering if in the late stages of the "Wild Type" Amyloidosis, when there is much pain in the body, (especially the legs) and difficulty breathing on minimal walking exertion, morphine would be helpful for the pain? Would so appreciate your experience and wisdom on this stage of the disease.**

MD1- Yes, morphine would probably be safe and effective for this. It's impossible for me to provide advice on prognosis or stage of disease without more information. These symptoms could be due to something other than amyloid. If only from amyloid, then it seems like an advanced stage. There are good blood tests that can help for prognosis – troponin and proBNP.

MD2- Leg pain in attr disease typically signals sensory neuropathy. While wild type disease has associated neuropathy in many patients, typically it is not as severe as hereditary attr nerve damage/pain.

### **Erectile dysfunction**

**62. How common is erectile dysfunction with ATTRwt?**

MD1- Very common, but I don't have a specific percentage.

MD2- Nearly 40% in older men (70-75 years old).

MD3- Erectile dysfunction is, in this setting, thought to be due to an autonomic neuropathy. Given that many patients might not mention it or providers might not ask, there is not a good idea of the prevalence but in my patients who have other autonomic symptoms such as lightheadedness with standing or urinary frequency, it is commonly reported.

**63. In patients with hypotension erectile dysfunction, can they use PDE5 inhibitors i.e. Viagra?**

MD1- can try safely

MD3- I would be very cautious with PDE5 inhibitors in the setting of hypotension and autonomic dysfunction. You can consider a very low dose (like 50 mg sildenafil) but that could precipitate very low BP. Better to see a urologist and consider alternative approaches to ED.

MD4- I do not see a clear concern for this medically

### **Spinal stenosis**

**64. Please explain relationship of spinal stenosis to the wild type?**

MD1- deposits of amyloid in spinal ligaments causing stenosis

MD3- This relationship is just being appreciated. Two reports from Japan and Sweden indicate that the vast majority of subjects who have undergone spinal surgery for lumbar spinal stenosis had TTR amyloidosis on pathologic evaluation on the specimens removed at the time of surgery. In our own experience ~30-40% of patients with ATTRwt cardiac amyloid had previous back surgery for LSS about 5-10 years before they presented with symptoms of cardiac amyloidosis

**65. Can Amyloidosis TTR-Wild Type be the cause of spinal stenosis and sciatic pain?**

MD1- Yes, probably.

MD2- Limited autopsy findings suggest that ATTR deposits and spinal stenosis can co-exist, suggesting ATTR amyloid contributes to narrowing of the spinal canal.

MD3- I agree, I think this is an under acknowledged association and maybe similar to the finding that many patients with carpal tunnel are found to have amyloid in the biopsies. I think the strongest link is between wild-type TTR and spinal stenosis. A paper by Westermarck et Al, (2014 published in Upsala J of Med Sci) investigated whether spinal stenosis was a manifestation of undiagnosed wTTR and found typical amyloid deposits in 21/26 patients who had spinal canal stenosis and 5/15 samples sent for immunohistochemistry were positive for transthyretin. The question is always, is this amyloid deposit causing symptoms. I imagine, in some cases it is.

**66. Patient has Spinal Stenosis diagnosis w/no red congo stains ... does have documented ATTRmt and GI and Carpal Tunnel amyloid ... prognosis and treatment options?**

MD1- Although spinal stenosis may be related to ATTRmut, it might have nothing to do with amyloid. The absence of positive Congo-red staining suggests that the spinal stenosis is caused by something else. You should discuss with your doctors.

MD2- We recognize attr amyloid can deposit in the spinal canal. We do not have remedies for it at this time.

MD3- See question #65, unclear whether patients with amyloidosis have a different prognosis or different outcome with surgery.

**67. Can the pain associated with stenosis be alleviated by surgery (laminectomy or fusion), even though the amyloidosis is still active?**

MD1- It definitely can but the surgery is big because it needs to be multi level

MD2- My general response is in #11 of the last document. I could not find any studies which specifically mentioned whether surgical treatment was as effective in patients with amyloid. This is an area we need more research in.

MD3- It is not known if the response to surgery differs if amyloid is present or not.

**Carpel tunnel**

**68. Carpel tunnel – why do surgeons not notice the amyloid?**

MD4- We are building awareness of the value of doing lab. tests of tissue samples from carpal tunnel, given simple characteristics.

MD7- We need to assure the pathologists who get the samples understand how to test for amyloid.

**Muscle twitches**

**69. Dupitins contractions, trigger finger – is it related to amyloid?**

MD1- There can be many causes. If you get surgery, have a tissue sample be tested.

MD7- we have not seen dupitins contractions or trigger finger with amyloidosis.

### **70. Causes of muscle twitches**

Could be amyloid neuropathy – usually occurring in feet or hands (distal locations). There are many non-amyloid related causes, too.

### **Medication to decrease neuropathy pain**

MD9- Gabapentin (Neurontin) is cheap, does not interact with many meds, and well-tolerated. A more recent update of this med may work if Gabapentin is not tolerated, but cost more. Other possible oral meds: Cymbalta, There are topical agents (creams,): lidocaine, amitriptyline (catalane), caspase-type creams (give a hot feeling on skin), ice-water. Alpha-lactic acid (over the counter pill) has helped some, a little. Gabapentin dose may need to be higher than pts may have gotten from primary care physician (300mg, 3x/day, increasing to 600mg, 3x/day, or more).

MD8- Gabapentin may cause leg swelling, NOT related to heart problems.

MD7- I have used scrambler therapy (small shocks, expensive, sometime effective but sometimes not)

## **GI**

### **71. I may have misunderstood, but I believe that I heard, “getting full quickly is the most common GI symptom and 70% of GI symptoms impacts V30M”. Is this correct?**

MD5- The two most common GI manifestations of familial amyloid are unintentional weight loss & early satiety (which is getting full quickly). V30M seems to have a higher rate of GI issues and according to a THAOS survey, 69.3% of patients with V30M reported GI symptoms, as opposed to 63% in all subjects.

### **72. Can the Amyloidosis be responsible for excessive intestinal gas?**

MD1- Maybe, but there are other causes. Best for Dr Clarke to answer.

MD2- Yes. Slowed motility, small intestine bacterial overgrowth are two circumstance in which it occurs.

MD5- Definitely. Amyloidosis can be associated with altered motility & small intestinal bacterial overgrowth, both of which can lead to relative malabsorption & increased gas production.

### **73. For a wild type patient with weight loss that cannot put on weight, what suggestions do you have? I am on water pills and blood thinners.**

MD1- High fat diet appetite stimulants do not work. If more fat in diet would help food variety will do it

MD3- Consultation with one's clinicians and possibly a nutritionists may be helpful in identifying the cause of weight lost and possible dietary interventions to address this.

### **74. Total parenteral nutrition (TPN - getting all your nutrition via an IV, at night) – when is it indicated?**

MD5- I try to avoid it, but it may be needed if weight loss and nutrition problems indicate. I only consider it at 17 to 18 BMI (when folks are pretty thin). TPN has many negative side-effects, and there are questions about whether the body may get too used to it, so pts may not be able to get off of it. I stop it by 12 weeks. I've only done it in 2 pts.

Most malabsorption issues are in the small bowel, so tubes that skip the throat or stomach (e.g., a J-tube) would usually solve nothing, but may be a bridge to a longer term solution.

MD3- TPN is a bridge to some other treatment, not a solution.

## Diarrhea

### **75. I have occasional diarrhea, constipation, incomplete evacuation, ... Do I have GI neuropathy from amyloid?**

MD5- Could be, but there are many possible causes. Motility studies may help us figure out if it is amyloid, but may not be conclusive. It may just rule-out some other possible causes. Likewise, GI biopsies may show amyloid, but do not rule it out if they do not find it.

MD7- A salivary gland biopsy is very sensitive to this, so you could have that done.

### **76. How to counter diarrhea?**

Diarrhea can have many different causes in Amyloid – intestine bacterial growth, thickening of muscles, GI neuropathy, blood flow changes, medication side-effects, gut motility changes.

Medications: Bacteria: treated with antibiotics ([I missed the med name]). Prokinetics for better motility. Octriatide may be a later therapy, if needed. Imodium or other diarrheal meds are fine to try.

Diet: Maybe try lactose, wheat, or ...-free diet. Increase bulk if "rapid transit" is a problem.

Example: Pt saw GI specialist, diagnosed with celiac disease,

I like tincture of opium (paregoric) (like Imodium, but has some side-effects)

Pt has many explosive accidents – have placed sigmoid ostomy (poop bag), which can re-enable pt to go to social events. (Dr. Clarke: I have only had on pt regret getting an ostomy.)

### **77. Diarrhea 6 times/day – is Diflunisal or doxycycline causing this?**

MD7- Diflunisal usually would not cause diarrhea. Antibiotics sometimes may cause it.

## Onset, diagnosis, testing & monitoring, progression, prognosis

### **78. What does monometry show in small-intestine ...?**

MD7- Sometimes may separate causes (neuropathy vs ?????) . We use it rarely, because it is so invasive, bet rather choose to treat and see.

## Onset, initial identification, treatment before symptom onset

### **79. Is there a path for asymptomatic gene carriers to follow before disease is evident?**

MD1- I recommend echocardiograms, ECGs, and/or nerve conduction studies (depending on the specific mutation) approximately yearly around the age of onset within the family, or when any symptoms develop.

MD2- Serial evaluations at an experienced ATTR amyloid center.

### **80. How can we identify the onset of disease earlier? Is there work going on to help with this?**

MD1- For familial type, I recommend echocardiograms, ECGs, and/or nerve conduction studies (depending on the specific mutation) approximately yearly around the age of onset within the family, or when any symptoms develop. For wild type, better education of health care providers may help.

MD2- Development of a blood assay that identifies when TTR begins to misfold. Scientists are working on developing the assay.

**81. Currently, in the U.S. many general Cardiologists are uninformed in dealing with any form of Amyloidosis, what is being done to get the information to them as a specific group, and do they have the necessary testing equipment to determine what type Amyloid their patient has?**

MD1- The Amyloidosis Support Group's Amyloidosis Awareness booklet helps.

MD2- Diuretics manage symptoms of amyloid cardiomyopathy. These drugs will be effective until the heart and/or kidneys are too damaged to respond.

**82. Does it look the same under a microscope (wild type and mutant attr)?**

MD1- Yes

MD2- Yep.

**83. My father has recently tested positive for Val30Met mutation and is presenting cardio amyloidosis. My grandfather died of amyloidosis that was primarily neuropathic related. I have not been tested. If I were to monitor my symptoms, should I look for cardio or neuropathy symptoms?**

MD1- First get tested then based on the mutation we can tell you about monitoring

MD2- You should be tested rather than just monitor your symptoms that can eventually be neuropathic, cardiac or both.

MD3- Cardiac symptoms may be shortness of breath, ankle swelling, palpitations, dizziness, or passing out. Nerve symptoms may be numbness/tingling in hands feet, pain in hands/feet, diarrhea, nausea/vomiting, dizziness

MD4- Both. In the USA, most people who have Val30Met ATTR have later onset than in Portugal or Brazil. I recommend that people have a baseline echocardiogram and nerve conduction study, if possible. Then future testing can be compared to those tests. The timing for the baseline and subsequent testing would depend on your age.

**84. I have the mutation, but no symptoms. What should I do?**

MD5- Go to a center of excellence, for good monitoring. You no longer need a positive biopsy to be accepted as a pt at one of these centers.

**85. Is it still true that an individual follows the parents disease process? if dad dies at 68 I will too. Is it worse if you are a son or daughter and inherited the disease from mom or dad?**

MD1- This is very inconsistent and one should not believe that 68 is some firm ceiling because supportive care is so much better and there is therapy

MD3- Outcomes in individual patients are difficult if not impossible to predict. There is some evidence that earlier disease onset called penetrance does occur in some genetic disease with successive generations which is called "anticipation".

**86. What is a mosaic parent in ATTR MT? Would the salivary gland biopsy be more accurate and less invasive than the nerve, skin or fat biopsy?**

MD1- ATTRmut genetic mosaicism refers to people who have an alteration of the TTR gene occurring after conception. As early embryonic cells divide, they become different parts of the body. The main issue that influences ATTR is production of the mutant protein by the liver. Manifestations in different parts of the body will depend on the amount of abnormal protein produced by the liver. I generally don't recommend salivary gland biopsies.

**87. ALA with no symptoms, age 55, father died at age 60, what kind of tests should I have?**

MD6- Recommend going to an experienced center, and being seen by experienced neurologist. If there is heart disease associated with the mutation, we recommend technetium pyrophosphate (PYP) test to determine heart involvement, as well as echo, ECG, heart blood tests and exam.

MD3- Go to an amyloid expert, a center of excellence. Most general practitioners will have very little or no direct experience with amyloid.

What criteria do you require to diagnose neuropathy?

MD9- Simple tests can be done, but are often negative despite the presence of amyloid.

MD7- Nuerologic testing early to get a baseline, to be able to track progression, can be very useful.

**88. Do genetic testing like "23 & me" check for amyloid?**

"23 & me" does not use a method that would detect the gene. There are

**89. What kind of testing do I need to be sure of wild-type TTR?**

MD1- Genetic testing (to rule out hereditary, mass-spec may not be enough), ...

**90. Is there a reason not to use salivary biopsy?**

MD1- I use it a lot. Pretty high years, hurts more than fat biopsy. Needs expertise to do it right.

**Monitoring your kidney**

**91. Thr60Ala Question: Kidney involvement-seems like it happen less than w/other mutations. Are we sure it is not just asymptomatic and not being tested? Although heart and peripheral neuropathies are taking center stage, can we consider using kidney tests with this mutation?**

MD1- Kidney involvement is not common in Thr60Ala, but the amyloid centers routinely test for it.

MD3- Kidney involvement is not seen in ATTRm T60A amyloidosis or ATTRm amyloidosis in general.

MD4- Yes ATTRmut usually involves the kidneys in later stages, and symptoms or abnormal lab testing typically occurs later.

**92. monitoring kidney function - creatinine**

We monitor creatinine in pts often, especially to adjunct diuretics.

Creatinine changes for various reasons, and sometimes increases are effects of treatments that are making other important improvements

**Monitoring your heart**

**93. How do you recommend talking with your doctor or cardiologist about what test should they be consistently running to monitor conditons of heart impacted by ATTR? Is there a protocol you would recommend?**

MD1- Ask their monitoring plans with Echo & biomarkers

MD3- I would direct the doctor to any of the recent review articles by the cardiologists at the meeting or refer to the following website: <http://www.arci.org/academy/>

MD4- Regarding cardiac amyloid, the best markers that we have now are blood tests (NTproBNP and troponin). You should be able to ask your doctor to send those tests, then to review the published papers (mostly from Mayo) regarding the prognostic implications of those results.

**94. How often should an echo-cardiogram be done?**

Summary: Echo-cardiograms don't need to be done much, unless there are specific clinical measures. Adjusting water pills (diarrhetics) does involve a fair amount of clinical monitoring of various types.

MD3- Maybe once every few years, if that. If something is being changed that would impact the echo, maybe more often.

MD9- We only do these when clinically indicated, such as for a pt who is getting worse. About diuretics – these require a lot of individual adjustment, based on

MD8- I do EKGs often, to look for early signs of amyloid heart problems. (Dr. Grogan: Yes, if the pt does not have a pace-maker)

MD7- Atrial fibrillation occurs in many wild-type pts. Blood thinners are necessary to prevent stroke or other embolic event.

**Progression, prognosis**

**95. How long will I live?**

MD6- Doctors can only guess.

MD7- Know that most studies use median years of survival, so half live longer, and half live less. And you can't necessarily generalize from a study, which reflects a population of patients, to an individual patient.

**96. Information for disease progression rates for wild-type? Can we diagnose aggressive vs non-aggressive?**

MD5- I look at how the pt is feeling, and their need for diuretics. Isabel is trying to get placebo arm information from clinical trials, to get a natural history.

MD4- We do not lump all wild-types together. Some get diagnosed very early, some do not. Different treatments may be best for folks with different symptoms.

[But what is the typical progression, not from diagnoses, but of the symptoms, from the onset of symptoms?]

**Studies**

**Getting into a study, expanded access trials**

**97. Pt with wild-type, carpal tunnel with peripheral neuropathy – can I get into a current trial?**

MD8- No.

**98. Why do different centers require different tests for patients getting on the same expanded access program?**

MD1- I don't know. The protocol for both expanded access trials should be clear on these issues.

MD2- Assessments of neuropathy, heart and kidney functions are required. However, the protocol does not give specifics for the evaluation, leaving it up to the amyloid center to decide.

**99. I want to join an expanded access trial. How do I, and what are the ongoing logistics?**

Alnylam: We have 50 slots open for this intravenous shot given every 3 weeks in doctor's office, talk to your physician. Generally, you need documented hereditary amyloid mutation with documented neuropathy. Pts with heart involvement over NY association level 2 are excluded (i.e., can't have shortness of breath with minimal exertion, like just moving around the house). Being on tafamidis is OK, but not being on Diflunisal. Liver transplants are not allowed. We have amended the protocol to allow for 150 pts (representing an increase of 100 over the initial protocol). Additionally, we do not require discontinuation of Diflunisal in the US EAP or of Tafamidis or Diflunisal in the EU Compassionate Use Program (CUP).

Ionis: The criteria are not yet final. The number of patients is not yet determined – probably more than 50. Need to be gene positive and have neuropathy. Inotersen is a self-administered once/week sub-cutaneous injection at home. .) Cardiomyopathy will not be a disqualifying condition as long as you also have hereditary polyneuropathy, but other protocol requirements must be met in order to qualify. Liver transplants allowed but other protocol requirements must be met in order to qualify. Diflunisal is allowed. 3-Monthly visits to a study site will be required toward the start for each patient and then patients will transition to quarterly visits.

## How studies operate

**100. Why is there many times a 2 year waiting period if someone wants to change from one trial to another? I would think positive or negative outcomes would be helpful information for the drug companies.**

MD1- Trials take 3-4 years to complete

MD3- Companies want to make sure that any changes you experience in your symptoms or testing is related to the drug you are taking, and not some lingering effect of prior treatment or combination of treatments. Different trials have different waiting periods to assure this.

MD4- This is probably to discern side effects from the prior study medication vs. the new study medication. But not all studies require such a long interval

**101. Is there any serum testing for the blood levels of ttr in the wild type patient to be used as test for efficacy of drug testing? Normal TTR protein vs folded protein.**

MD1- TTR levels can be done but have no monitoring value

MD3- Not that is clinically available currently.

**102. Do trails always let you continue on the medication after the trial?**

MD3- find out up front. It will be part of the consent.

MD2- In the trails we have done, participants have been given continued access. But for how long is not well defined. When the drug becomes available on the market,

## Future studies

**103. *I've read that Amyloidosis TTR-Wild Type is often under-diagnosed, therefor is it currently getting the (research) attention it deserves?***

MD1- No. Hopefully you will add your voice to advocate with NIH, CDC, and Congress to increase funding for this condition.

MD2- Cardiologists are getting better at identifying patients with ATTR amyloid cardiomyopathy.

**104. *When will we see Alnylam and Ionis' drugs on the Wild type Population?***

MD1- Trials will open in 2018

**105. *Tell me about your future spinal stenosis & wild-type study***

MD8- Many pts who have had spinal stenosis back surgery show wild-type TTR.

**106. *What are the current lobbying efforts to increase number of pts in clinical trials?***

Isabel: I don't know of any. In myamyloidosispathfinder.com, you can inter your disease history, so pharma companies can see if you fit in a trial.

## Details about past studies

**107. *What was the cause of death for the pts who died in the Endeavor trial?***

We do not know. It may be available in the Paris meeting.

**108. *Did tafamidis trials involve non-V30M pts?***

The original trial was just V30M patients, but extension, open-label trials without placebo control, have other mutations.

**109. *Is there a maximum NT & ????? score allowed for the ... extended access study?***

No.

## Other

**110. *Muriel, how are these meetings funded? Pharma? Doctors? Wealthy Donors?***

All of the above, and not so wealthy donors as well. Our doctors donate their time and knowledge. Alnylam, Ionis, Pfizer and Prothena have been very supportive of the amyloidosis community they serve financially and otherwise. We honestly have very few (if any) "wealthy donors". Our donors are made up of people, just like many of us who make donations to charities at the end of the year for their tax write offs, or are especially grateful when something happens and share the gratitude in the form of a check, or sometimes make a donation in lieu of flowers in memory of a lost loved one.

**111. *Advice on talking to family about genetic testing***

Start with what it means for you.

Leave a lot of space for questions

Have folks consider if they are ready to get tested, think through how they would react to positive or negative results. Dr. Agre encourages that each person make their own decision, and to wait until they are 18 years old to make their decision about if or when to be tested. You don't have to wait until you have symptoms to get the genetic testing.

Is finding out your child's gene status for your benefit, or for their benefit. There is no intervention for the very young.

Use resources from the ASG website, so family members

**112. Will the slides be available?**

Muriel will make things available on the website.

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