2017 ASG Biannual Meeting Notes

Chicago (O'Hare Hilton Hotel), 2017-10-28

Contents

Agenda

ATTR-HEREDITARYAGENDA

Friday Night Meet and Greet

7:00 to 9:30PM (International Room)

Saturday Meeting (Grand Ballroom)

8:00 - 8:10	Welcome – Muriel
8:10 - 8:20	Why are we here? (Overview) –Gertz
8:20 - 8:30	Nomenclature - (ATTRmt or hATTR) Benson
8:30 - 8:55	TTR Amyloidosis mt and wt - Maurer Q and A - (5 minutes)
8:55 - 9:20	NON ATTR – Fibrin. Apo. Alect2 others – (Where do they come from? Is the liver involved?)- Berk --Q and A - (5 minutes)
9:20 - 9:45	Genetics (who should be tested, when, why, how, who, what about insurance?) - Agre --Q and A – (5 minutes)
9:45 - 10:10	Diagnosis – (Biopsy Fat Pad, Cardiac, Nerve, Scan PYP, other) - Picken- Q and A -- (5 minutes)
10:10-10:35	BREAK- (25 minutes)
10:35 - 11:00	Cardiac – (Heart before and after TTR- why is heart affected, which variants see the most? What happens to the heart) – Grogan Q and A- (5 minutes)
11:00 - 11:25	Neuropathy- (Nerves before and after TTR) – why are nerves affected, which variants see the most? And what can be done, Carpal Tunnel, PN, AN) – Waddington-Cruz Q and A – (5 minutes)
11:25 - 11:50	GI (Gastro-Intestinal) – (When is it the disease, when is it neuropathy, how do we treat? which variants see the most?)- Clarke Q and A- (5 minutes)
11:50 - 12:15	Solid Organ Transplant – (when – which variants do best?) Q and A- (5 minutes)
12:15 - 1:15	LUNCH (One Hour)
1:00 - 1:20	Alnylam Presentation - Pritesh
1:20 - 1:40	Ionis Presentation - Berk
1:40 - 2:00	Pfizer Presentation- Amass
2:00 - 2:20	Prothena Presentation - Wagner
2:20 - 2:40	Non Clinical Trial Treatments (Diflunisal, doxycycline, Green Tea/ EGCG, Anti-Oxidants, Ursidal, Tudca others) – Berk
2:40 - 3:15	Pharma and Non Clinical Trials Treatments- Q and A (all on dais with Gertz as moderator)
3:15 - 3:45	BREAK- (30 minutes)
3:45 - 5:30	Afternoon Breakout Sessions (Rooms to Follow) • Wild Type ATTR- Hanna, Judge, Gertz • Cardiac - (Symptoms, coping, treatments) - Grogan, Ruberg, Maurer, • Nativi • Neuropathy, GI, Caregiving and Coping - (Peripheral and • Autonomic) - OH, GI, CT, etc., Clarke, Waddington-Cruz, Juster-Switlyk, • Waddington Cruz, Sarah Boyd PT, Mayo OT-Sarah Dahlhauser, • Genetic Issues and Non ATTR variants - (When to tell the kids, when should I be tested? How?)- Agre, Brown, Berk, Picken • Clinical Trials - Clinical Trial Reps, Benson, Dispenzieri, and Kelly
6:00 - 7:30pm	DINNER

Sunday

8:30am – Noon	Q and A with doctors facilitated by Dr. Gertz Please turn in on questions to Muriel, Steve, Pat, Paula, Liz, Mike, or Tracey by 8:30 AM Sunday

Welcome – Muriel & Dr. Gertz
Get your flu shot. Immunizations are important.

Nomenclature - Dr. Benson
Three groups use Amyloid Terms

1. Amyloidologists, Amyloid Centers, Researchers "official nomenclature"
2. Medical personnel, Physicians, Nurses, Counselors
3. Patients and Families

Nomenclature Committee
Nomenclature Committee meets biannually
Merrill D. Benson – Indianapolis, IN, USA
Shu-ichi Ikeda – Matsumoto, Japan
Maria J. Saraiva – Porto, Portugal
Per Westermark – Uppsala, Sweden
Jean D. Sipe – Boston, MA, USA
Giampaolo Merlini – Pavia, Italy
Joel N. Buxbaum – La Jolla, CA, USA

Physicians, Nurses, Counselors – use various labels for the disease
- FAP
- FAC – Fam Amy Card..
- ATTRm – Amyloid of transthyreten
- ATTRwt – wild type
- hTTRpn
- HFpEF -

Amyloid protein designation vs. Genetics designation
V30M = V50M – protein designation
I107 V = I 127 V – genetics designation for same thing

Confusing!
Amyloid is a misnomer, but stuck because it was the first label used.
The confusion is most problematic for referring physicians, not familiar with the disease.

What families should know
Know what type you have – is it Wild Type, Transthyretin, (I MISSED THE OTHER ASPECT – GET THEM FROM DR. BENSON) (technically: ATTR, AFIB, AAPOA1, AAPOA2, ALYS, AGEL, ALECT2 – but can we put terms that pts will understand?)
Know you mutation (e.g., VAL30MET)
Know the clinical variations associated with you mutation (how it manifests) – know the likely symptoms, their likely time of onset3

TTR Amyloidosis: Mutant and Wild type

Why do we lump together? (Dr. Maurer)
Columbia University Medical Center

New York Presbyterian Hospital

Transthyretin (TTR) – a protein

Transports protein for thyroxin (T4) and retinol
Has 127 amino acids
There are many, many mutations of this protein (see "The Amino Acid Sequence of Human TTR" slide for amino acids that have been involved in mutations)
Mutations affect various organs
Diverse presentations and natural histories
Genetic and non-genetic mechanisms
You are all unique!!

Wild Type (example)

Typically male
Typically onset over age 65
BUT – exceptions are common (as the audience demonstrated)

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

Why use Phenotypes (classifications)

Phenotypes lump together folk who may have similar causes, manifestations, progression, and effective treatments.
Different mutations to this same protein seem to cause pretty different manifestations.
But there is still a fair amount of variation within phenotypes.
There is much we are still learning.

What is a Phenotype and a Genotype?

Phenotype

From Greek phainein, meaning 'to show', and typos, meaning 'type'
A description of your actual physical characteristics

Genotype

From Greek *genos* 'race, offspring' + *-tupos* 'type
The genetic constitution of an individual

Is it better to lump or split TTR amyloidosis for:

Clinical management?
Understanding mechanism of disease?
Development of treatment?
A "lumper" takes a gestalt view of a definition, and assigns examples broadly, assuming that differences are not as important as signature similarities
A "splitter" takes precise definitions, and creates new categories to classify samples that differ in key ways.

Using phenotypes may simplify answering some questions

Why does one mutation cause a predominately cardiac phenotype while another mutation in a nearby spot in the protein cause of neurologic phenotype?
What other factors affect the clinical manifestations and progression of the condition?

Questions
(Missed 1st 2)

History of Wild Type - Why does a normal protein break up? Is it becoming more common, maybe due to environmental factors?
(Dr. Benson :) In early 1980s, wild type was first described. It is a disease of old age – and lifespan of men in 1940s was 40 to 50, so it did not have a chance to manifest. IT has probably been around for a very long time.

Get shingles immunization shot?
Dr. Gertz: Get it, unless you are on immunospression medication from liver transplant.

Non-ATTR Amyloid (Dr. Berk)
(Mostly) Inherited renal amyloidosis [GET SLIDE – GOOD FOR SHOWING TYPES]
[GET "Deposit Location" SLIDE – add to prior table, add non-medical words to column labels]

Fibrinogen A .. Amyloidosis characteristics
[GET SLIDE – has good info on disease progression]

Fibrinogen A .. Amyloidosis – Kidney or Liver transplant results
[GET SLIDE – has good info on treatment outcomes]
In one of one patients in which it was done, transplant of liver in early stages of kidney damage reversed progression of kidney problems.

AI/II
[GET SLIDE]

Lysozyme Amyloidosis
[GET SLIDE – has good info on disease progression]

Hereditary Renal amyloid
Eliminate the source of the protein if you can, to limit damage.
[GET SLIDE – has some info on transplant treatment outcomes WRITE OUT KT, LKT, LT as Kidney Transplant, …]

Questions

APOA1 – Should I get an early liver transplant?

For Fibrinogen, having the gene does not always mean you'll have the symptoms. APOA1 may be similar – you may want to wait for a good indication that the disease is manifesting in you.
Monitoring serum creatinine levels may provide that early signal.
Dialysis is not good – getting Liver transplant before that degree of damage is wise.

Is anyone looking at gelsolin? Our family's symptoms have not been what is described in literature?

Jeff Kelly is trying to get funding to study it more.
We will talk later about kidney therapies, short of transplant, which may slow progression.

Husband has systemic … Is a kidney transplant worth doing?

Gertz: Kidney transplant may provide some years more of life, based on the data presented in the prior slides.

Most of the transplant outcome data was from UK. Are US outcomes similar?

(Dr. Maurer :) US data sites at different sites, so we do not have good data to compare. But they do good work in the UK, (as do we in the US), so we would expect similar outcomes.

Genetics of ATTR Amyloidosis (Dr. Agre)

Basics

We are made up of millions of cells. Each cell contains our genes (half from you mother, half from your father), which create proteins.
So everyone has 2 versions of the TTR gene (one from you mother, one from your father).
Having one alteration on one of those two genes is enough to cause Amyloidosis.
Genetic testing reveals whether the amyloidosis is hereditary (from your genes) or "wild type" (not hereditary).
Genetic testing reveals the specific mutation, which help us predict the likely disease onset and progression, and what treatments may help.

How to tell loved ones about the diagnosis

Recommends Open communication
Family letter: a good way to clearly communicate the situation, how others can get tested, etc.
Maybe work through the communicator in the family

If I have it, will my kids get it?

If you just have the mutation on one gene (of the pair of TTR genes you have), each child has a 50% chance of getting the mutation from you. Each child's risk is independent of the others.

If I have it, do my relatives have it?

If you just have the mutation on one gene (of the pair of TTR genes you have), each sibling with the same parents (or with the parent with the mutation) has a 50% chance of having the mutation. Each sibling's risk is independent of the others.
Other relatives in that blood line may have similar risks, depending on the path of inheritance of the mutation, through your family tree.

Should I get tested?
Getting tested is a personal choice. It is OK to choose not to be tested.
Recommendation – do not test kids under age 18. Let them decide, when they are adults.

Reasons people decide to get tested
To plan for future – reproduction, life choices
To be more alert to early symptoms, allowing early diagnosis & treatment
To relieve the anxiety of uncertainty

Thing to consider
How will I react if I'm positive?
How will I react if I'm negative?
How will I use the information?
Is now the right time?

Health Insurance impact
The Genetic Information Non-Discrimination Act prohibits the use of genetic test results in setting health insurance rates (or in hiring decisions).

Life & Long Term Care Insurance
Life & Long Term Care insurance companies **are** allowed to use the test results in setting your rates or refusing you insurance.

Testing process
Meet with genetics professional www.findageneticcounselor.com
Submit a blood sample
Wait 2 or 3 weeks for results
If negative (if they do not find the mutation), no further evaluation is needed.
If positive (if they do find that you have the mutation):
- Seek care with physician and medical team with experience in TTR Amyloidosis
- Continue with regular evaluations

Can both parents have a mutation, with different types?
Yes, it is possible. Good practices is to consider either or both parents being carriers.

My siblings got tested in 1988. Should I get tested again, now that testing methods have improved?
(Dr. Benson:) For AL60, the test in 1988 had very good accuracy. Now, the test laboratories test all genes, and do a good job -

I just got tested. Did the lab look for all mutations?
Yes. These days, the labs test for any mutation.

Might a test be negative, if I really do have the mutation?
They would be extremely rare. Panel doctors had not seen any false negatives.

Pathology (Dr. Picken)

Amyloidosis is a protein folding problem.
The normal form of amyloid has a helix form. The problematic form is a "pleated sheet".
The "pleated sheet" form of the problematic amyloid binds to "Congo red" dye.

Diagnosis

Make sure tester test for amyloid!
Under a light microscope, cells may show fibrous areas for many reasons.
For clear diagnosis: Under polarized light, Congo-red stained cells can reveal amyloidosis. It shows up as "apple green" birefringence
So Dr. needs to order Congo-red stain!
Deposits are distributed unevenly, so it may not show up on many samples. The absence of detection does not prove that you don't have it.
Proteinuria often leads to kidney biopsy. Kidney samples tend to be tested very thoroughly. So kidney biopsies may provide a fair portion of amyloid diagnosis, where it was not specifically being investigated.

Good places to sample: often sample body fat

Sensitivity (test detected it if it was there) highly variable 54-93%
Specificity (it was there if the test detected it): 93-100%
Wild-type – fat was 15% sensitive
Hereditary – fat was 50% sensitive

Sensitivity per sample type

Fat aspirate in wild-type (senile) ATTR amyloid cardiomyopathy
Fine et al 2014, 84 patients, sensitivity of 14%
Ikeda et al 2011, sensitivity increased to 73% (8 of 11 patients), deep layer of surgical fat biopsy, patchy distribution

Fine et al, 2014:

biopsy	**all**	**Familial ATTR**	**Wild type senile ATTR**
Fat aspirate	225/106+ 47%	141/94+; **67%**	84/12+; **14%**
Bone marrow	164/60+; 37%	100/41+; 41%	64/19+; 30%
Heart	131/131+; **100%**	42/42+; **100%**	89/89+; **100%**
Sural nerve	54/45+; 83%	54/45+; 83%	0

Coelho et al in FAP:

Labial salivary gland:	89%
Abdominal fat:	50-70%
Nerve biopsy:	75-90%

Fat biopsy is better at detecting hereditary vs. wild-type. Does the same happen with other biopsies, like the heart?

Heart biopsy should be very sensitive to either type.
Wild type tends to have amyloid in corpuscle, which is why it shows up more poorly than hereditary, in fat. Corpsicul

Carpel Tunnel surgery – should they always test for amyloid?

(Dr. Picken :) YES. Encourage physician to send samples to pathology, for amyloid and spinal stenosis.
(Dr. Hanna:) In one study, 10 of 96 persons going in for normal carpel tunnel surgery were found to have amyloid deposits. 8/10 TTR, 2/10 were AL.

How can we make the diagnosis earlier?

(Dr. Picken set this as a goal, but I missed any discussion of it.)

Amyloidosis and the Heart (Martha Grogan, MD)

Overview

Amyloid proteins infiltrate heart muscles, getting between cells and making it harder for it to contract and expand – to do it's work.
Heart pumps less blood
Heart function is complex - *a single number* does not tell you how your heart is doing

Symptoms and Signs of Heart Failure

Fatigue
Shortness of Breath
Swelling (edema)
Unable to lie down due to
Shortness of breath
Waking up gasping for air
Cough, often at night
Blood pools in lungs when you lay down, so you start sleeping sitting up.

Heart Rhythm problems that TTR can cause (Arrhythmias)

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

Rhythm problems treatment

Medications
Electrical shock (cardioversion) – if you have amyloid, have them check of a clot first.
Risk of blood clot – stroke – need blood thinners

Heart Tests to Diagnose Cardiac Amyloid

Echo (echocardiogram) – often amyloid is first suspected due to abnormal echo. Measures thickness, pumping function, stiffness, valve function, pressure in lungs
MRI – certain patterns suggest amyloid
Biopsy – Heart, fat, bone marrow kidney
In ATTR – PYP scan can replace biopsy

Technetium PYP (new test)

May replace biopsy in some patients with ATTR if no evidence of AL type amyloid
Heart failure with typical echo/MRI findings of amyloid (thickened heart muscle, abnormal strain)
Always do a genetic test if PYP is positive, to determine if hereditary or wild type.

What is Ejection Fraction?

Ejection fraction: the amount of blood your heart pumps out with each heartbeat, divided by the amount of blood that was in your heart at the start of the heartbeat.
There is no specific "trouble" threshold. Ejection fraction varies a lot. Other factors, like heart size, are important in figuring out if there is a problem.
Normal EF does not mean that heart function is normal, and abnormal EF does not mean that heart function is inadequate. But many doctors do not understand that.

Comment [JG1]: Dr. Grogan deleted this (when "EF" was not in the phrase)

Another test: Myocardial Strain

Used to describe elastic properties of cardiac muscle

Helps us make amyloid diagnosis earlier, but not available in all echo labs
It measures change in length of heart muscle during contraction and relaxation
Negative strain: With contraction, the myocardium is compressed or shortened
Positive strain: Lengthening or relaxation:

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
Trend is more important than one number

Cardiac involvement in TTR manifestations

Varies. We are still learning.

Treatment

We have no proven treatment specifically for the heart involvement in ATTR and other hereditary forms of amyloid.
Track your numbers. No single number tells the story.
Stop the source of amyloid
Over time, the body can remove amyloid
Medication to take amyloid out of heart – in development
Diuretics to decrease shortness of breath and get rid of fluid
Medications used for other type of heart failure often not helpful (beta-blockers, ACE-inhibitors)
TTR pts need individualized treatment

Summary

Heart Function is complex
There is not a single number to follow heart function
No proven therapy specific for hereditary and wild type amyloid *in the heart*
Exciting emerging therapies

Neuropathy. Nerves before and after TTR (Dr. Waddington Cruz)

Progressive axonal loss:

1. Unmylienated fibers
2. Small myelinated fibers
3. Large myelinated fibers

Early detection leads to better treatment outcome
Presentation depends on mutation, age at onset and geographic location
Neuropathy is often the first symptom of TTR

Symptoms

Adapted from: Conceicao et al, First Congress of the European Academy of Neurology (EAN), June 20-23 2015, Berlin, Germany (#P1184):

Ocular Manifestations

- Vitreous opacities
- Glaucoma
- Abnormal conjunctival vessels

- Papillary abnormalities

GI Manifestations
- Nausea & vomiting
- Early satiety
- Diarrhea
- Severe constipation
- Alternating episodes of diarrhea & constipation
- Unintentional weight loss

Carpal Tunnel Syndrome

Autonomic Neuropathy
- Orthostatic hypotension
- Recurrent urinary tract infections (due to urinary retention)
- Sexual dysfunction
- Sweating abnormalities
- Vomiting.
- Diarrhea / Constipation
- Bladder/ Bowel incontinence.
- Massive loss of body weight

Cerebral Amyloid Angiopathy
- Progressive dementia
- Headache
- Ataxia
- Seizure
- Spastic paresis
- Stroke-like episode

Cardiovascular Manifestations
- Conduction blocks
- Cardiomyopathy
- Arrhythmia

Nephropathy
- Proteinuria
- Renal failure

Peripheral sensory-motor neuropathy
- Typically axonal, fiber-length-dependent, symmetric, and relentlessly progressive in distal to proximal direction

Progression

Time zero
Neurologic symptoms limited to feet & legs, impaired pain & temperature sensation
Sensation of touch is maintained
Unassisted walking

~ 5 years
Motor dysfunction in lower limbs, loss of touch sensation

Mobility maintained, with supports (crutch or walking stick)

~10 years
Pt is bedridden or in wheelchair
Generalized weakness, malnutrition, cachexia, & incontinence
Pain & temperature sensation is lacking, apart from head & neck

Example of progression
Val122Ile, Ancestry: Portuguese / African, residence: Rio de Janeiro, No family history
Carpal Tunnel at 58
Cardiomyopathy at 60
Disautonomia at 64
Dialysis at 65
Cardiac biopsy: amyloid deposition
(4% of African Americans may be carriers of Val122Ile TTR mutation)
THAOS registry has 69 sites, 12 countries, ~3400 pts, mostly Val30Met (~70% of pts)

Questions

Is there a predilection for Amyloid to attach to connective tissues?
It depends on the mutation, age of onset, & geography. Onset can be heart or liver symptoms.
First nerve symptoms are often conduction problems, not …[????]

In Netherlands, asymptomatic pts are getting Diflunisal prescriptions.
It is a risk-benefit decision. Monitor for kidney problems.
If pt is already on an over-the-counter NSAID (non-steroidal anti-inflammatory), the risk difference of switching someone to Diflunisal may be minimal.

GI (Dr. Clark)

Outline
1) Patterns of GI amyloid involvement
2) Symptoms associated with amyloidosis
3) Diagnostic tests at our disposal
4) Treatment options
5) Epidemiology & data regarding variants

General comments
Endoscopic or GI biopsy may not get deep enough tissue to capture the amyloid
Amyloid decreases small intestine contractions -> more bacteria in intestine -> constipation or diarrhea. (normal = ~12 contractions per minute)

Luminal GI Patterns

Mucosal infiltration
Role: site of absorption
Symptoms
Diarrhea
Malabsorption

Diagnosis
Endoscopic biopsy

Muscle infiltration
Role: site of contraction & motility

Symptoms
Decreased motility/stasis
Small intestinal bacterial overgrowth
Diarrhea
Malabsorption
Constipation
Pseudo-obstruction
Nausea/vomiting/abdominal pain

Diagnosis
Imaging studies
Transit studies
Manometry

Neuropathy
Role: coordination of GI motility & neuroendocrine secretion

Symptoms
Dysmotility
Nausea/vomiting/pain
Diarrhea
Constipation
Increased sensation

Diagnosis
Manometry

Vascular
Role: delivery of blood flow to gut

Symptoms
GI Bleeding
Ischemia (pain/diarrhea)

Diagnosis
Endoscopy

Non-luminal GI patterns

Liver involvement
Liver enlargement
Elevated liver tests (alkaline phosphatase)
Clinical manifestations usually mild but a marker of widespread systemic deposition

Cholangitis

Pancreas

Peritonitis

Symptoms
Symptoms are linked to area of involvement & are often non-specific
Many of these symptoms are caused by many other conditions, and are common throughout the population

Esophagus:
Reflux
Dysphagia
Food impaction

Stomach
Abdominal pain
Nausea
Vomiting
Distention

Small intestine
Diarrhea
Malabsorption
Weight loss
Pseudo-obstruction

Colon
Diarrhea
Constipation
Fecal incontinence

Diagnostic tests

Endoscopy & colonoscopy are usually the first tests performed
Allows option to take biopsies for diagnosis
Can also allow treatment
Bleeding control
Dilation
Findings can be nonspecific
Will only pick up mucosal GI involvement
Rectum commonly chosen as yield high (> 75%) and easy to get to
Highest yield in GI tract is in duodenum

Other tests to consider
Imaging studies
CT
MRI
Barium

Motility studies
Scintigraphy

Manometry
Wireless motility capsule
Sitz marker study

Breath tests
"normal" is not well defined yet for breath tests

Treatment options
Treatment should be tailored to symptoms & GI involvement

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
Treatment options

Stomach
Dietary modification
Prokinetics
- Metoclopramide (Reglan)
- Erythromycin/azithromycin
- Domperidone (not FDA-approved)
- Prucalopride (not FDA-approved)
- Bethanechol
- Pyridostigmine

Agents to help stomach expansion
- Herbal therapies (peppermint/caraway)
- Buspirone

Neuromodulators
- Tricyclics (amitriptyline)
- Mirtazapine (Remeron)
- Gabapentin/pregabalin (Lyrica)

Anti-emetics
Endoscopic options: Botox

Small bowel
Dietary modifications
Prokinetics
Antibiotics (focused on small intestinal bacterial overgrowth)
Octreotide
Steroids
Anti-diarrheals

- Imodium
- Lomotil
- Tincture of opium

Parenteral nutrition (rare cases)

Colon

Dietary modifications
Laxatives

- Miralax (Over the counter)
- Senna (Over the counter)
- Lubiprostone (Amitiza) (Prescription)
- Linaclotide (Linzess) (Prescription)
- Plecanatide (Trulance) (Prescription)

Prokinetics

Epidemiology

GI involvement in amyloid is reported to be low

2013: 3% (retrospective study of 2334 amyloidosis patients, GI biopsies)
2015: 15% (Korean study of 155 pts with amyloid on biopsy)
2017: 16% symptomatic; 45% of whom had amyloid on biopsies (retrospective study of 583 amyloid patients)

Data regarding variants

Extremely limited
I could find not data on GI manifestations of TTR variants
All GI series published on amyloid are > 80% AL/AA
Weight loss reported to be in 30% range, but multifactorial
Frequent diarrhea/constipation mentioned in TTR articles in other fields (cardiac mostly)

My subjective impression

Perhaps more neuropathy than AL/AA
All distribution patterns seen

Needs a good study

How is amyloid causing reflux and other problems in the stomach?

One factor may be amyloid stiffening the wall of upper stomach may not expand as is normal, leading to reflux. It is probably not an increase in acid – it is probably a more mechanical effect.

What are diet recommendations?

Note that this is from the GI perspective (diet may also be influenced by heart needs, etc.):
Overall: Small portions, low fat is helpful for just about everything.
Reflux: Small portions, low fat, more liquid. Avoid meals within 3 hours before lying down; raise head of bed 2-4 inches
Swallowing issues: chew well, cut up into small pieces
Gastric: more liquid (often helps), Small portion, low fat, more liquid, make lunch bigger (more time before you lay down.
Colon (constipation): more liquid. Fiber may help or hurt (could lead to bloating),
Small bowel (diarrhea): avoid foods that ferment with bacteria (less sugars)

Solid Organ Transplant (Dr. Dispenzieri)

[I DIDN'T HAVE SLIDES, AND MAY HAVE MISSED A LOT.]
Amyloid produced by liver, travels in the blood, and settles in various organs or tissue, depending on the mutation, etc.
If we replace the liver, can we stop the amyloid?
It may not stop all progression of the problems, because normal TTR can bind to deposits of ATTR, if they are already established.

Types of liver transplant

Use part of a living donor's liver
Use a donor's liver after their death
Do a "domino" liver transplant – amyloid pt gets primary donor's lever, and the amyloid liver is transmitted into a pt who will not live long enough to experience the amyloid issues (since they often take 30 years or many more to manifest). About 45% of those getting amyloid liver eventually show symptoms.

Outcomes

Val30Met early-onset has much better post-transplant survival than does late-onset or early- or late-onset ATTR of other mutations (although there is much variation in post-liver-transplant survival among the other mutations) (Data from TAOS registry?)

Unknown Stuff

[GET THE SLIDE]

Was my liver making ATTR since birth, or did it start sometime later?

Some is being made from birth. We do not know if it starts accumulating from birth, or if some trigger starts the accumulation (which is what causes the symptoms). Does an older body get worse at handling poorly formed proteins?

I understand that, in wild-type, the protein is normal coming out of the liver, and then becomes abnormal. Does a liver transplant help, in wild-type?

No, we don't do liver transplants in wild-type, for that reason.

Alnylam Pharmaceuticals (Dr. Gandhi)

Patisiran interferes with the RNA which produces TTR, and so decreases the production of TTR protein, thereby decreasing how much ATTR (misfolded TTR) would be in the body. Alnylam will submit an application to the FDA in late 2017, for approval of patisiran to treat familial ATTR.
Phase 2 clinical trial found use of patisiran led to a TTR production decrease of about an 80%. Their phase 3 study of 225 patients with familial ATTR (57% non-V30M, 56% with cardiac involvement, and a wide range of neuropathy at baseline) found the average change in neuropathy was statistically significantly better for patisiran than placebo. Most adverse events were similar or fewer for patisiran than for placebo, except for "swelling in the arms and legs" and "Infusion-related reactions".

Ionis Pharmaceuticals

Founded to create anti-sense medications

Antisense medications: designed to bind specifically to just one RNA segment, triggering it to be degraded, , thereby decreasing the amount of that protein that is made (inotersen binds to TTR RNA causing it to be degraded and resulting in less TTR protein made by the liver) .
Opening an expanded access program for pts with familial ATTR.

Inotersen Phase 3 trial - Dr. Berk

Included d Stage 1 & 2 disease
Included about equal number of V30M vs. other mutations
About 60% had used either tafamidis or diflunisal before starting the trial. The stabilizer medications were not allowed during the trial
1 placebo pt per 2 active drug pts
Inotersen given as subcutaneous injection which pt can do at home

Safety issues

platelet count reduction (3 severe drops, one death),
renal events (5 pts had kidney function decline that caused them to discontinue the study, 1 of whom was placebo)

Outcomes

Quality of Life: inotersen group's avg. QoL-DN score improvement was 11.7 points better than the placebo group's, $p < 0.001$. Analysis of subgroups found statistically significant QOL improvements among: V30M, non-V30M, Stage 1, Stage 2, and those with no previous treatment with stabilizers.
Neuropathy Score: inotersen group's avg. mNIS+7 score improvement was 19.8 points better than the placebo group's, $p<0.0001$. Analysis of subgroups found statistically significant neuropathy improvements among: V30M, non-V30M, Stage 1, Stage2, previous treatment with stabilizers and no previous treatment with stabilizers

Tafamidis (Pfizer) (Dr. Amass)

Tafamidis binds to TTR, stabilizing it (preventing it from folding into the ATTR which leads to amyloid deposits)
Approved in 41 countries in Europe, Latin America and Asia to delay neurologic progression in TTR-FAP.
Taken as a once-daily pill.
Top-line results of Phase 3 TTR cardiomyopathy study of Wild Type and Hereditary/Mutant subjects will be released ~June 2018. A publication describing the design and rationale of the ATTR-ACT Phase 3 study in TTR-CM was just published.

Long-term TTR-FAP study B3461023

Just published results of open-label extension of 2 prior studies (Study B3461023, a long-term open-label extension for participants of studies Fx-005, Fx-006 and Fx1A-201). The results assess safety and efficacy, following participants for up to 5.5 years.

Efficacy (neuropathy)

Using a composite measure of peripheral neuropathy, the NIS-LL, the tafamidis-tafamidis group (n/48) had smaller rise in neuropathy than did placebo-tafamidis group (n=46), but the difference was not statistically significant.
When patients who had been on placebo in the initial study were switched to tafamidis for the open-label extension study (B3461023), the progression of their neuropathy slowed (statistically

significant), becoming almost identical to the rate of progression among follow-up study patients who had been on tafamidis in the initial study.

Safety

After up to 5.5 years long term treatment on tafamidis, no new safety signals observed, other than what was found in previous trials. No deaths directly related to tafamidis treatment. From the study: "Twenty-three (24.7%) patients experienced at least one treatment-related AE, with headache, oedema peripheral and urinary tract infection (n = 2 [2.2%] each) most frequently reported."

PRX004 (Prothena) (Dr. Zago)

In pre-phase 1 stage of development.
(Prothena also has NEOD001 for AL, now in phase 3 trials.)
PRX004 is designed to break-down & remove ATTR deposits.
Studies so far are in animals.
PRX004 binds to ATTR, then body's immune system microphages attack the PRX004-covered ATTR.
Studies indicate PRX004 binds to ATTR, and not normal TTR.
Studies would include hereditary & wild type.

Non Clinical Trial Treatments (Dr. Berk)

Neurodegenerative Diseases

- Alzheimer's disease (AD)
- Parkinson's disease (PD)
- Amyotrophic Lateral Sclerosis (ALS)
- Multiple Sclerosis (MS)

Mechanisms of these disease

- Inflammation/oxidative stress
- Cell death

Polyphenolic Nutraseuticals

Flavonoids

Vegetables, fruits, grains, bark, stems, teas, wine

Effects on AD pathology

Limit oxidative injury
Inhibit Ab fibril/aggregation, destabilize formed Ab
Inhibit killer cell activation
Increase cell survival signaling

Curcumin (active spice of Tumeric)

Epigallocatechin gallate (EGCG)

Resveratrol

Curcumin

Natural polyphenol (diarylheptanoid)
Inhibits Ab aggregation/breaks up Ab fibrils
Blocks toxicity of Ab fragments on brain cells
Competes T4 binding to TTR
Promotes clearance of TTR aggregates
Inhibits steps of ATTR fibril formation
Crosses blood brain barrier
Works in the simple TTR in mice, but human TTR is much more complex

Resveratrol

Damaged grapevines, pines, peanuts
Stabilizes TTR tetramer conformation (T4 pocket)
Promotes aggregation of potentially toxic TTR monomers

Comment:

Insufficient data in humans
Poor bioavailability (you can eat it, but you'll poop it out)
Effective dose undefined

EGCG

Inhibits neurodegeneration in ALS
Protects rat brain neurons from Ab toxicity
Activates cell survival (PI3K/Akt) pathway
Stabilizes TTR tetramers; Different mechanism than **Diflunisal**
Inhibits ATTR amyloid fibril formation
Promotes breakdown of amyloid deposits

- Early amyloid aggregates
- Mature/fixed amyloid deposits

Study - ATTR

14 ATTR cardiomyopathy patients
EGCG 500-700 mg/day x 12 months
Findings:

- Echo: no change in LV wall thickness
- Cardiac MRI: 12.5% decrease LV mass

Study - AL

59 pts with AL amyloid cardiomyopathy
Decreased thickness of wall of heart – a good thing.

Diflunisal

2',4'-difluorophenyl salicylate derivative
Non-Steroid Anti-Inflammatory Drug (NSAID)
High serum concentrations and low toxicity
Significantly neuropathy progress than diabetes (??), using NIS+7

May be sufficient treatment for a minority of pts, but not for most.

Diflunisal inhibits neurologic progression and preserves quality of life in patients with ATTR-FAP
Effective across gender, mutations, and severity of disease at entry
Provides a rare example of repurposing old drugs for new indications

Doxycycline/TUDCA

Doxycycline 100 BID/TUDCA 250 mg TID x 12 m
20 Subjects (17 ATTRm, 2 ATTRwt, 1 Domino LT)
Some early indications that there may be slight benefit. It might help stabilize disease.

Tolcapone

Tolcapone inhibits Wild Type & V122I ATTR

AG10

New TTR Tetramer Stabilizer
Binds T2 docking site
More selective binding of T4 than Tafamidis or Diflunisal
No identified toxicities
Potentially more mg potent than other
TTR protein stabilizers

Other

Several more agents are in progress. It's amazing how many there are, compared to what we had 10 years ago.

Expanded Access Programs

What are they?

An EAP is an expanded access program, which is a program that provides access of an investigational drug outside of a clinical trial for people with serious or life-threatening conditions who were not able to participate in the clinical trials

When will they be available?

Alnylam – when we get approval from FDA of what we submitted. We will be filing the EAP amendment with each site starting next week
Ionis – we will submit application to FDA soon and will be posted on ClinicalTrials.gov in the coming weeks.

Will pts need to pay transport costs, etc.?

Both - We don't know. The medication will be free. The medication is being provided to the site at no cost. There are additional costs that are associated with the administration that may not be coved by your insurance. Each patient must discuss these costs with their treating physician before enrolling to the program.

May statins help promote creation of ATTR?

Dr. Nativi-Nicolau: We have no data to suggest that statins will increase ATTR creation.

How long can someone stay on Diflunisal?
Dr. Berk: As long as renal function is not adversely affected (like fluid retention, swelling, wt gain, or kidney function), pt may continue. We should consider Diflunisal as a potentially valuable compliment to take along with other treatments.
Dr Hanna: We used to avoid giving Diflunisal to heart patients, now we give it with caution, and most tolerate it well, with individual adjustments.

What medications can patienst who have had liver transplants take?
Dr. Waddington Cruz: It is individual.
Dr. Gertz: In the US, such prescribing would be off-label, as would prescribing for wild-type, for some of these medications.
Dr: Nativi-Nicolau: A lot will depend on what the insurance companies will pay for, including around off-label use.
Dr. Ruberg: EGCG is very safe, so use may be relatively liberal. Decisions about off-label use of other substances should be made in consideration with their safety profile.
Dr. Maurer: The next hurdle will be around getting access to medications after they are approved; getting insurance coverage.

Should my gene-carrying, asymptomatic, biopsy-negative, 35-yr-old daughter take these meds?
Dr. Judge: When meds. are prescribed for folks who don't need them, all you get are side-effects (i.e., only harm). Prescribing needs to be based on data.
(Pfizer Dr): As more treatments become available, we may see combination therapies.
Dr. Gertz: Ignoring the cost of multiple meds, because many of these medication hit different aspects of the ATTR development, so combinations may make sense.

Questions

What happens to the encapsulated amyloid (with patisiran)?
The body slowly breaks them down.

Who is eligible for expanded access programs?
See "**Error! Reference source not found.**" question from Sunday, far below.

When is G-SK trial coming to the US?
It is being planned, we don't know the date.

Fast-tracking and compassionate care: when does the pharma company apply to FDA for this?
Compassionate use: Pt's physician makes application directly to FDA, with coordination with the company.
Accelerated approval: If a biomarker is shown to be a good proxy for the clinical outcome.
Fast track: An arrangement between FDA & pharma company to have more interaction, to speed the processing of the application.

Sunday Q & A
See the document, "2017 ASG Biannual Meeting - Questions and answers.docx"