The Fabry Exchange: Optimizing Diagnosis and Treatment Initiation

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Disclaimer

Disclosures

I am one of the cardiologists in the crowd, so I will be addressing cardiac involvement in patients with Fabry disease.

What can we do to accelerate early diagnosis in our daily clinical practice to support timely initiation of treatment?

I think one of the obvious questions dealing with patients and family members and looking at the larger population is, of course, tests that we can look at/use to detect early diagnosis, because this is where the evidence is strongest, at least for the cardiac involvement that ERT makes a difference, so sort of homing in on what you can use to make the diagnosis early, so that enzyme replacement therapy, and now other types of therapy, can be started early.

Type of Biomarkers

I think biomarkers here are key and the term biomarkers here is used broadly, so it includes any kind of measurement that reflects the disease and it can be a diagnosis, a diagnostic biomarker, prognostic biomarker or a biomarker that reflects pathophysiology and maybe, down the road, tailoring our therapies as we have more and more therapies for Fabry disease.

The three major types of biomarkers that we use in patients with Fabry disease are imaging, of course, very critical for the cardiac imaging and I will show you cardiac MRI is the preferred methodology here; of course, genetic testing and, as you heard from Alberto, how that is being used and some of the challenges with it. Of course, in women the diagnosis is made by genetic testing thereby a chemical assessment is not adequate because it is, of course the X-linked gene and the genetic testing there is important, but it does raise the issues of things like polymorphism and gene variance and so on, which I think is something not only for Fabry disease but for all genetic disease, we need to certainly have addressed, as molecular medicine and genetic testing becomes more common. Of course, biochemical assessment, plasma, urine analysis, lyso-Gb3, is a very important biomarker, of course the

classic alpha-galactosidase A activity is important, and BNP, which we do use for the cardiac assessment, very specific for cardiac involvement but not very sensitive.

Improved Long-Term Effects of ERT in Patients With Fabry Cardiomyopathy

Here are some of the key studies that are really documented, the importance of starting ERT early, at least from a cardiac perspective.

Two classic papers here from Frank Weidemann's group in *Circulation* in 2004 and in 2009. He showed that if enzyme replacement therapy is started early you actually have a very nice impact in preserving strain rate, and his follow-up paper showed very nicely that you can actually reduce hypertrophy but also preserve exercise capacity, so both functional and structural measurement shows that early enzyme replacement therapy here is important.

More recent data from the Registry shows very nicely that patients – part of this includes a natural history component – and what they show here is patients who did not go on enzyme replacement therapy clearly had more progressive hypertrophy, and patients that did go on enzyme replacement therapy did have a stabilisation, at least, and in a younger cohort almost a reduction in hypertrophy. Again, it is a Registry cohort, so things are not very well controlled, but a number of patients, you can see there, treated males is 115, untreated males 48, so a pretty good number for a Registry, again, supporting that enzyme replacement therapy should be used early in these patients.

Diagnostic Dilemmas – How to approach individuals with an uncertain diagnosis of Fabry disease

Moving on to some of the diagnostic dilemmas and how we can approach this.

Myocardial Tissue Characterization With Non-Contrast MRI T1 Mapping

Again, from a cardiac perspective probably the biggest impact in the field in the last decade, in terms of cardiac assessment, is the cardiac MRI and T1 mapping, so this is an important parameter. There are two aspects here, so the late gadolinium enhancement, this is with gadolinium contrast, so this reflects fibrosis and you can see – I can show you on the slide here – that white marking there in the left ventricle – I will point on this screen here – that is the right ventricle, that is the left ventricle, and that inferior lateral wall, that white appearance, that is fibrosis and you see that, that is gadolinium accumulating in the myocardium and that showed up with fibrosis. This is important because with a non-contrast, this is without gadolinium, which is practically important in this patient population because of the prevalence of renal dysfunction and gadolinium is contraindicated in patients with moderate-to-severe renal dysfunction, you want to stay away from this fibrosis region and, in fact, what you want to do is measure the septum, so stay away from the fibrosis region and measurement, a non-contrast measurement should be made in the septum anterior wall, so

that is important. This is an intrinsic property of the myocardium, it is the longitudinal relaxation time and longer T1 values are associated with fibrosis, this is without gadolinium, so they are more prolonged fibrosis, whether you use the MOLLI technique or the SASHA technique you get the same results.

Native Myocardial T1 Mapping in Fabry Disease

This is our data, so very impressive and we compared our cohort with a cohort with the same degree of hypertrophy, from a non-Fabry etiology, and we could show that the T1 mapping here completely separates non-Fabry-mediated hypertrophy from Fabry-mediated hypertrophy. Again, we image our patients in this region, the septum, we stayed away from the inferior wall, and you can see the blue here are the lower values and that clearly separated out the controls, the hypertrophic controls from the Fabry cohort. Again, very importantly, it is independent of the degree of hypertrophy and independent of gender, so that is particularly important for women where, unlike in the kidney world, women are actually fairly well affected by Fabry disease in the heart, so even though it is an X-linked disease we do see about one-third of our patients in our clinic are actually women compared to two-thirds that are men. Heart disease, at least in women, is quite prevalent and we believe this T1 is associated with accumulation of glycosphingolipids in the myocardium and it is probably what is reducing that relaxation time of the T1 mapping.

To do this, this is actually available in all Siemens magnets, so my colleague, Richard Thompson, who is a physicist, wrote the protocol and anyone who has a Siemens magnet can have this protocol downloaded onto the system and you can do this for free, but it has to be the Siemens system and it takes about 5 minutes to do, so it really doesn't prolong your imaging time. It is important that you have a good relationship with the radiologists and the radiology department, because they are the ones often who are running the tests, so if they don't understand what is going on and they don't buy into this then they are not likely to do the right tests, so in your local hospital, local centers, you do need to have that relationship with the imaging radiology department.

Cardiovascular T1 Mapping as a Potential Disease-Specific Biomarker

Again, identical data from James Moon's group, these were published within a few months of each other, showing, again, that Fabry disease is associated with reduced septal T1, and then in four other cases of hypertrophic cardiomyopathy these T1 values are all elevated, especially when you have fibrosis, like things like amyloidosis, so these values are clearly separated and if you look at this line, here, 940 ms, this clearly separated the Fabry's cohort from every other disease. It is sensitive and it is specific, so that makes it an ideal diagnostic test to be used in patients with Fabry disease.

Diagnostic Dilemmas – Attenuated and Late-Onset Phenotypes "Patients in Waiting"

OK, so moving on to my third and final component, so this you have screening, so this probably could take half a day discussion, but a very important concept, of course, not only for Fabry disease but all types of genetic disorders.

Genetic Screening for Fabry Disease in the Clinical Setting

Here is a fabulous paper published in *JACC* in 2016 in which they did a 10-year study, prospective, multidisciplinary study, looking at a range of techniques screening patients over 2,000 probands, they were able to identify 37 carriers of the *GLA* mutations and followed with cascade screening, which revealed an additional 60 affected family members, so very, very/relatively high pickup rate. You can see the sub-specialities in which these were detected, of course we believe the heart being the most important organ, so you are looking at 1–2% detection rate in these subspecialty clinics. The older numbers, at least from hypertrophic cardiomyopathy, were 4% and 10%, this is the older Italian and English study, but those are, clearly, higher but I think the number to go with is 1–2%, so that is a significant pickup rate. Very importantly, two-thirds of these patients had cardiac involvement, so it is very important that the cardiologists, not only the nephrologists, are aware of this, so patients with isolated hypertrophic cardiomyopathy really need to consider Fabry disease and, of course, the kidneys are involved and, of course, the nervous system including ophthalmological findings.

Identifying Fabry Disease in Patients With Hypertrophic Cardiomyopathy

Then, finally, to bring this home is a very important study, we have talked about the old study from Italy and England and then a recent study, 6 months ago, from Iceland, with, I am glad to see, these folks here, you guys probably know these names, Christine Seidman, who discovered the first genetic cause for hypertrophic cardiomyopathy, that is the beta myosin heavy chain mutation, she is from Harvard, a coauthor in this paper where they actually looked at a cohort of patients that they were convinced were hypertrophic cardiomyopathy, that they were following for several decades, they identified eight individuals with Fabry disease in two different families. These patients were being followed for several decades, clearly not treated with enzyme replacement therapy and these were the mutations, one classic and one cardiac variant. Even in more recent cohorts these patients are there, they are, obviously, unfortunately misdiagnosed and they have, of course, missed an important therapeutic intervention.

What is important to know is that the Fabry gene is involved, is included in the genetic testing for hypertrophic cardiomyopathy, so this is from the Blueprint Panel, so it is included as part of the genetic testing for hypertrophic cardiomyopathy, but it may or not cover all of

the variants or things like copy number variants and deletion, it may not be able to detect those.

Patient case

Just leading into what David is going to get into, so this is a patient of mine, from my clinic that I have been seeing, so one of my sicker Fabry patients and I know most of you haven't seen a coronary angiogram, so I will keep playing this and I will come back to it. This is a 57-year old man affected by Fabry disease, he has been a semiprofessional hockey player, had to give up his hockey and has been on enzyme replacement therapy now for over two decades, but, very importantly, predominantly cardiac involvement, very stable renal function, no albuminuria and very stable GFR, but very progressive heart disease despite enzyme replacement therapy, very good blood pressure control, ACE inhibitor, statin therapy and he has progressed, not only has he progressed with LVH, his mass index number is 145 – 7 years ago it was 121. His ejection fraction though, so that is the pumping function of the heart, has dropped and that is a very ominous sign in patients with infiltrative hypertrophic cardiomyopathy, so this guy is not doing well, his ejection fraction has dropped from a relatively preserved value to a value of 49%, he is now in permanent atrial fibrillation, he has had multiple chest pain syndromes with positive troponins, he has had tachy–brady syndrome, so in addition to the AFib, he now requires a dual chamber pacemaker.

What that angiogram is showing you is an under-recognized aspect of Fabry disease and that is the coronary involvement, so the blood vessel involvement. As you can see here, see how slow this blood flow is through the coronaries, so this is at a blood pressure of 100 mmHg, that blood should be – that contrast should be just whipping through those coronaries, so he has a very slow reflow, but you cannot pick up any major blockages here in that major coronary artery, so he does not have the classic coronary artery disease where you have major blockages in which you can put a stent or apply a bypass graft to correct the defect. What he has is, of course, microvascular angina and his microvasculature are severely affected and, as you can see, the peripheral runoff here is very, very slow, so this is why he is having chest pain syndromes and positive low-grade troponin, so he is having microinfarcts in his heart, so probably explains the drop in ejection fraction.

This is a patient who is on enzyme replacement therapy, risk factors that are well treated, what else can we do for this patient? We have a number of patients like this that are progressing, despite being on enzyme replacement therapy, so we need to do more for our patients.

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