Transcript: Cardiac Amyloidosis: No Longer Rare and Untreatable

Dr. Malcolm Bell: Welcome to our viewers and listeners to another in our podcast of the interview with the experts. I'm Malcolm Bell your studio host today, and my special guest today is my colleague, Dr. Omar Abou Ezziddine. He's an associate professor of medicine. He's a consultant in the division of cardiovascular, sorry, of the division of circulatory failure. And he has a special interest in infiltrative cardiomyopathies. And in particular, we're gonna be talking about cardiac amyloidosis today. So really looking forward to having you on the show today. Omar thank you for joining us.

Dr. Omar Abou Ezziddine: Thank you, Dr. Bell. Pleasure being with you.

Dr. Malcolm Bell: So cardiac amyloidosis, you know, that disease that we are mimics so many other diseases in terms of, you know, symptoms and signs and, and so often overlooked. Very important for us to be discussing that today. But in particular, I mean our title of our discussion here is cardiac amyloidosis and, and so let's just, you know, focus on the amyloid of the transthyretin protein and maybe because that's really, really, I think where a lot of the advances have been made, you know, in in recent years. And so firstly, could you just tell us, you know, how common that is and what exactly is it and that, how does it fit into that disease spectrum of cardiac amyloidosis?

Dr. Omar Abou Ezziddine: Sure, great question. So as cardiologists, I really, before talking about TTR, it's very important to understand that there is another type of amyloid that impacts the heart, and that's light chain amyloid. And so the two really amyloid subtypes that cardiologists should know very well is light chain amyloid and transthyretin amyloid. And the reason of that I highlight this, is because the clinical presentations and the prognosis and the therapy markedly differs. And so whenever we see a patient that we're suspecting amyloid, the first thing we need to do is to rule out the more malignant of these two, which is the light chain amyloid.

Dr. Malcolm Bell: So this is the al amyloid?

Dr. Omar Abou Ezziddine: Exactly the al amyloid. And, and that is more of a hematologic malignancy, a disparate anemia that is treated with chemotherapy by our hematology colleagues. And, and the importance of early identification is because with each day that it goes unidentified, the patient prognosis gets poorer and poorer. In fact, median survival of light chain amyloids around 18, 12 to 18 months at most, I would say, without therapy. And, and so any talk on amyloid, the first thing that any cardiologist needs to do is make sure that they're not missing the light chain amyloid. And we'll talk more about that later. Now going back to Transthyretin. So Transthyretin is a transporter of thyroxine and retinol. It's a protein that's ubiquitous to us all, but either because of

hereditary reasons or advancing age. There become these, this protein, which is a tetramer, becomes unstable and breaks down into monomers, which then forms these fibro that infiltrate the myocardium among other organs. And cause in the case of the heart, cause diastolic dysfunction, heart failure and, and all the, the subsequent consequences of that. So again, transthyretin wild type, which is the non-variant subtype, and then the variant subtype or the hereditary subtype, depending on which gene it is, you may have a, a a, a spectrum of manifestations from neurologic to cardiac to a combination of the two. As far as prevalence of disease, it depends on which populations we're talking about, particularly when it comes to hereditary type amyloid and what the mutation is. For instance, in the United States, three to 4% of our Afro-Caribbean population are carriers of the Val122ILE mutation, which is predominantly a cardiac cardio, a cardiac manifestation of amyloidosis. In contrast, wild type transthyretin amyloidosis for the longest time was thought to be very rare. But as we, our imaging techniques have, have evolved over time and with increasing interest in therapeutic advances. Now with all these studies, we're starting to recognize that actually the prevalence may vary anywhere from six to around 16% or so of patients, for example, who have heart failure with preserved ef. And when you start looking at various age groups, it can, particularly as our populations are getting older, it impacts anywhere from 15 to 25% of patients over the age of 80, for example. So, so it isn't as rare as we used to once think it is. And we finally have therapies that not only affect survival, but also affect - cardiac hospitalizations and reduce cardiac hospitalizations and improve quality of life. And so for this reason, I think it's very important to recognize this entity of transthyretin amyloid cardiomyopathy.

Dr. Malcolm Bell: Okay. So before we talk about diagnosis and and treatment, so just if, if I'm hearing you right, so the, the TTP, the, is it the wild type that's more common than the hereditary one and but less common than what we would see with AAL amyloid? Is that correct?

Dr. Omar Abou Ezziddine: Actually, light chain amyloid is, is not as common now it depends on where you, when you're comparing light chain amyloid, for instance, to wild type TTR, I would argue that light chain amyloid is more rare than, than wild type TTR. But again, it depends on which populations you're looking at. For instance, at our referral center, like here at Mayo, which is a cardiac amyloid under excellence, you know, we get our, our, our prevalence numbers really are very biased that way. And so we do see a lot of light chain amyloid here as well. But in comparison compared to wild type, I would say it's, it's more rare.

Dr. Malcolm Bell: Okay, that's very, very interesting. So let's then just focus on TT R. So in terms of who should we suspect may have this and what would be the diagnostic approach in, in these patients?

Dr. Omar Abou Ezziddine: Sure. So typically the red flags that that that one should think about when they're, you know, considering this diagnosis when it comes to amyloid, there's cardiac manifestations that include heart failure, atrial arrhythmias that are resistant to multiple ablation

procedures. For example, Brady or tachy, tachy arrhythmias and pacemaker dependence. That's the cardiac manifestation of the disease. But in, in combination with that, there's typically, when it comes to TTR, a musculoskeletal involvement as well, particularly wild type involves the carpal tunnel. So you unexplained bilateral carpal tunnel syndrome, spinal stenosis where this amyloid protein infiltrates the ligamentum flava of the spine, the trigger fingers, these are common musculoskeletal if you want presentations. Biceps tendon rupture is another one. And this is because of infiltration of this amyloid protein either into the tendon or the ligaments. Neuropathies either peripheral or autonomic are also common depending again on whether it's wild type or hereditary. Typically neuropathies are more hereditary in nature, but we're increasingly recognizing wild type. So when we see a patient with heart failure who has musculoskeletal, unexplained musculoskeletal presentations like bilateral carpal tunnel syndrome, that's not occupational for instance, or biceps tendon rupture. These are things that should hone us in on the diagnosis. Now I

Dr. Malcolm Bell: Just interrupt you that, so I mean that's, that's really fascinating. And then those are symptoms that, you know, we've all seen from time to time, but you know, putting 'em together that patient with heart failure or some of the symptoms that you've talked about, just remind us, would we typically such symptoms with al amyloid for example

Dr. Omar Abou Ezziddine: Al amyloid is more of a systemic disease that affects multiple organs more so than TTR, including the heart, the kidneys, the nerves. So you end up with more autonomic dysfunction, more GI symptoms, constipation or diarrhea. Peripheral neuropathy is, is common with light chain amyloid gait disturbance could also occur in advanced stages in addition to the cardiac.

Dr. Malcolm Bell: So those symptoms and signs you talked about, you know, carpal tunnel syndrome, spinal stenosis, I mean we may perhaps them should be more suspicious of the patient who might appear perhaps a little bit more healthy than that patient who, who presents with al amyloid and

Dr. Omar Abou Ezziddine: Correct, Correct. Some, some red flags that are specific, more specific to al. I would see say on exam pinch purpura the head and neck, peri, oral orbital, purpura, macroglossia, those are things that are more light chain related.

Dr. Malcolm Bell: Those are the classic things that we were, were taught, you know, many years ago.

Dr. Omar Abou Ezziddine: Medical school. Yeah. But I should mention, and you may take particular interest in this as an interventionist, Dr. Bell, unexplained troponin increases there. I can't tell you the number of of times we have seen patients that come to our clinic that have gone through with

an unexplained quote unquote and STEMI or manca myocardial infarction, you know, without clear coronary disease because there is this phenomenon of myocardial necrosis that occurs because of the infiltration and the toxicity of the light chains in the case of light chain amyloid, that the myocardium actually dies and you do see troponin leaks that are unexplained. So that's another thing to keep well that effect of that protein, you know, deposition that unfolded protein.

Dr. Malcolm Bell: So let's just move to, I I think one of the really exciting areas I think for so many people is, you know, making that diagnosis. I mean maybe, you know, I mean obviously you're gonna be looking at their, you know, cardiac function, I mean echoes things. But in that patient it, it looks as though they may have an infiltrative cardiomyopathy or you are, maybe it's even an early presentation, the specific things that you want to do when you're going to try to make a diagnosis of cardiac amyloidosis and particularly TGR amyloid.

Dr. Omar Abou Ezziddine: So as you mentioned, echo MRI, these are great modalities to look at the myocardium in more detail, but they really don't. And they will give you, you know, they will raise the flag and this patient may have an cardiomyopathy, however it does not really tell you which subtype of amyloid events. And, and this is I think where really there's been a, the, the field has evolved in that now we actually have imaging techniques that after you have ruled out the light chain amyloid process, which should always be the first thing you do, we that is specific for TTR amyloid with a positive predictive value with some of those nuclear studies of a hundred percent after you have ruled out light chain amyloid. And so the first step always needs to be ruling out light chain. And the way we do that is by obtaining serum free light chains and serum and urine monoclonal proteins. And that should be the first part of any algorithm of any patient that you're seeing who has, who you're suspecting amyloid. After you have ruled out light chain amyloid, then you go down the algorithm and proceed with TTR specific if you want testing. And that in the current era we have been very lucky to, to come across this technique which is not a novel technique, it's a basically cardiac scintigraphy using bone radio tracers, technetium pyrophosphate is what we use here. But these are technician based bone radio tracers that are taken up by the myocardium that is infiltrated with TTR. Now caution because you could also have uptake of this blown radiotracer in a myocardium that has al, hence the first step always needs to be ruling out light chain because after you have ruled out light chain the positive predictive value of a positive PYP scan or cardiac sonography is a hundred percent. Which essentially gets rid of the need for for for invasive if you want diagnosis or biopsy

Dr. Malcolm Bell: Or that have too many imaging studies that have that sort of accuracy. That's interesting 'cause you were talking about troponin elevation in some of these patients and I guess we'd have to be a little careful because these were the traces that we used for hotspot, you know, for when we were looking at myocardial infarction your decades ago. Is that, is that correct?

Dr. Omar Abou Ezziddine: Absolutely. Actually you should not do a PYP scan if the patient's had a myocardial infarction within four weeks, within the last four weeks you have to wait four weeks after an MI because as you mentioned, absolutely these were techniques that were used back in the day to identify MI burden.

Dr. Malcolm Bell: So you have a positive scan. And so with a positive scan, I mean is there then a need to do a biopsy to confirm this? And on the flip side, if it's a negative scan, you need to do a biopsy to exclude amyloid.

Dr. Omar Abou Ezziddine: Excellent question. So if you have a positive biopsy and you have done a good job ruling out light chains, so you have no monoclonal proteins and normal free light chains, then a biopsy is not needed. If however, there is an abnormality in monoclonal protein. And this is something we are increasingly starting to see as our populations get older as we age, we do have monoclonal processes that happen. One example is monoclonal myopathies of uncertain significance. So we are starting to see overlap. And in these cases where you have an abnormal monoclonal protein study, unfortunately noninvasive testing is not sufficient and you have to go for the tissue and perform an endo myocardial biopsy. On the flip side, negative studies. So there are false negatives that could occur with PYP imaging. There are some hereditary mutations that form what we call type B fibrosis that don't cause as much myocardial if you want dis disruption. And those patients may have negative PYP scans also the earlier the disease, the higher the likelihood of us missing it. So you must understand that this technique was, was derived and validated in cohorts of patients who had heart failure and clear evidence of amyloid and filtration very little is known about what burden of amyloid is needed to have a positive PYP scan. And so the, the teaching point is always the PYP scan is great, but if it's negative and your index of suspicion is is high still high or if it's equivocal, then you must go for a biopsy. There's other amyloid types that I did not talk about 'cause they're extremely rare that could present like ttr. But then after you biopsy the patient, it turns out it's something like what we call 8.4 or 8.1. These are very rare subtypes of amyloid or AA amyloid, which is a secondary amyloid to systemic inflammatory processes.

Dr. Malcolm Bell: Well we probably better not jump into that rabbit hole.

Dr. Omar Abou Ezziddine: We won't

Dr. Malcolm Bell: It's very, very long. So in the time left to us then, unless there's any, I mean obviously the, the imaging and the biopsy and then the, the exclusion of al amyloid, those seem to be the three critical steps in the diagnostic, you know, workup. But the other really exciting thing of course is the new treatments that we have. And just in the last couple of minutes, I mean maybe you could just let us know what currently we're using, what may be in the pipeline in the future.

Dr. Omar Abou Ezziddine: Sure. When we think about therapy there's, well the first thing I wanna say, there's only one FDA approved agent to date and hopefully more towards the end of the year. But it's a stabilizer of this tetramer called tafamidis and it was studied in the ATTRACT trial and it was found to reduce mortality and hospitalizations by around 30%, which is great. I mean this is a number needed to treat of around seven or eight, which is great for a cardiac drug if you want. It also slowed down the progression of or the deterioration if you want with of quality of life and physical capacities with as measured by six minute walk devs. So tafamidis really has become our go-to agent. It's the only one that's FDA approved for wild type TTR amyloid.

Dr. Malcolm Bell: Does it provide survival benefit too?

Dr. Omar Abou Ezziddine: Absolutely 30% reduction in mortality. Yep. So it's a very,

Dr. Malcolm Bell: Sorry, earlier I thought you were talking about

Dr. Omar Abou Ezziddine: Very, very effective drug and very no minimal side effects actually was safer than placebo in the trial. And now the other drug that we others a category of drugs that we now also talk about, and these were drugs that are FDA approved if you want for neuropathy polyneuropathy, hereditary polyneuropathy with amyloid. And those drugs are drugs that are gene silencers or RNA if you want RNA interfering agents that actually stop the production of TT R from the liver altogether. And these are FDA approved for patients who have polyneuropathy. They were studied and in a cardiomyopathy patient population, purely cardiomyopathy. And the, although it was a positive trial, the Apollo B trial was a positive trial. It was was a drug called patisiran. The signal of benefit was not of clinical significance, it was statistically significant. And so the FDA did not approve the drugs for this reason. That being said, there is a trial that we are very excited to hear more about at ESC. It's gonna be a late breaking trial that we have heard is markedly positive. That involves one of these RNA an interfering agents called vutrisiran and this is the Helios B trial and there is reportedly a survival and a hospitalization and even the secondary endpoints were there was a significant benefit there. The data is yet to be shown in, in, in full granularity at ESG and we're looking forward to that. There is another category of drugs as well that are under phase two and phase three trials. And these are the monoclonal antibodies against the TTR that are, that are thought to extract TTR from myocardium. And again, these are phase two and three studies that will be reported in entirety until 2025. So we're excited, we're really excited to wait on on those. And lastly, just a plugin for the CRISPR technology even that is gene editing technology. There's a trial that's ongoing and expected to be done in 2028 that that involves this technology where you're completely editing the TTR gene. So very exciting times for therapy. But to summarize, the only FDA approved for TTR amyloid drug is at Tafamidis at this point in time with - which is a sister drug, which we're expecting to be FDA A approved later this year hopefully by the FDA,

Dr. Malcolm Bell: You know, and, and unfortunately I guess there are still some patients that are still gonna need more advanced serious, I mean they're obviously gonna have treatment for their heart failure as well. But my last question then, just, just with a quick response here, obviously in al you know we're talking about chemotherapy stem cell transplant and these types of things, but with TTR amyloid, is there ever a need for cardiac transplantation? And if so, does that require liver transplantation as well? Maybe you could just briefly address that.

Dr. Omar Abou Ezziddine: Yeah, excellent question and thanks for bringing this up. 'cause indeed, if, if we're talking about hereditary TTR amyloid cardiomyopathy, it affects typically younger patients, younger than the age of 70, then absolutely as the heart failure advances, these patients could be candidates for cardiac transplantation. Historically, we have also done liver transplants for these patients. 'cause that's the origin if you want, that's the factory of this protein. In cases where patients are young enough to develop the disease, we think after getting a new heart. Now, I will say, however, in the current era with these novel RNA silencing therapies, I do foresee a future where we would transplant the heart, for example, and initiate some of these patients on RNA silencers. So that forgoes the need or you know, gets rid of the need of, of of liver bi, liver transplantation. So, but obviously this is all hypothetical. I mean we have, there's no clinical trial that's looked at this, but I do foresee a future where, and we are starting to do this in some patients actually who are a bit on the older side of the spectrum who have hereditary amyloid cardiomyopathy, TTR amyloid cardiomyopathy that get a heart transplant, that we are starting them on silencers to tackle their neuropathy as well.

Dr. Malcolm Bell: Omar, it's, it's really been a pleasure having you on the show here. It, it's a complex disease which has like complex treatments but, but same with increasing effectiveness. So thanks so much for sharing your knowledge and expertise and experience with this disease that is you. I think we're beginning to appreciate it's not so rare and it is treatable. So thank you so much for, for your time.

Dr. Omar Abou Ezziddine: You're most welcome Dr. Bell. Thanks for the invitation and always happy to see, see these patients. So if they, anyone ever comes across them and ask questions, please do reach out to us here at Mayo Clinic.

Dr. Malcolm Bell: Okay, well again, I wanna thank our viewers and listeners of joining us and look forward to seeing you in some of our future podcasts.