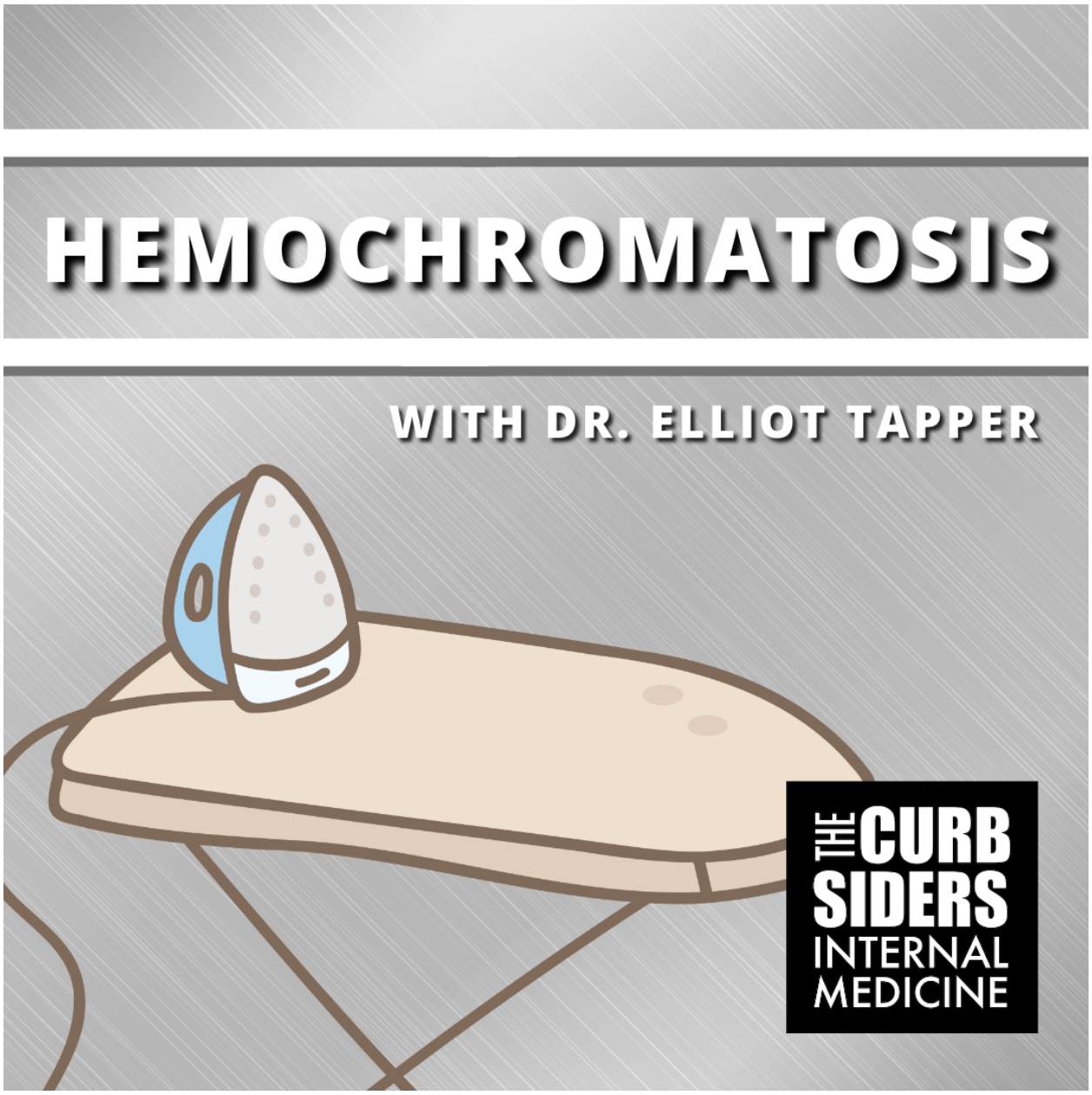
#380 Hemochromatosis with Elliot Tapper



Matt: Paul, I want to tell you a story about [Paul laughs] back when I was in high school, my dad said to me, Matt, I think you have iron deficiency. And I was like, "Shut up dad, you're not a doctor." And then he was like, "Well, Matt, your shirt's wrinkled."

Paul: I feel like I don't even really have to be here for these.

[laughter]

Elena: That was the--.

Matt: My delivery is terrible.

[laughter]

Elena: That was it.

[Curbsiders theme]

Matt: Welcome back to the Curbsiders, I'm Dr. Matthew Watto, here with my great friend and America's primary care doctor, Dr. Paul Nelson Williams. How are you doing today, Paul?

Paul: [laughs] I'm great, Matt. Thanks for asking. I felt very sincere. I appreciate that.

Matt: Well, Paul, I'm doing very well because on tonight's show we have a fantastic returning guest, Dr. Elliot Tapper. We're going to be talking about hemochromatosis, a condition which Paul, I thought I was going to diagnose it many times, but I think I have yet to diagnose a case of hereditary hemochromatosis that was convincingly causing any significant disease. But maybe someday, now that I know a little bit more what to look for. Paul, can you tell the audience what is it that we do on this show? And then when you please introduce our wonderful cohost.

Paul: Happy to, on both counts, Matt, we are *the* Internal Medicine Podcast. We use expert interviews to bring you clinical pearls and practice-changing knowledge. As you mentioned, we talked to the amazing Dr. Elliott Tapper, and we are lucky to be joined by Dr. Elena Gibson, producer, cohost, extraordinaire silent for much of this episode due to technical difficulties, but they're with us in the spirit. Elena, how are you?

Elena: I'm lovely. I'm back, returned.

Paul: I agree with both of those.

Elena: [laughs] Yeah, so, happy to be here. We had a great conversation, well, mainly Paul and Matt, but I was listening with Dr. Elliot Tapper. He is a highly educational Twitter hepatologist, if you want to check him out there, who loves caring for people with livers, studying people with livers, and talking about the liver with whomever will listen. So today, that is us. He lives in Michigan, where he has a dream job and spends his free time shuttling his children between activities. He is thrilled to be back on the Curbsiders and we're happy to have him here. Tonight, he teaches us all about hemochromatosis, some good pearls to take away that you'll learn more about include some potential mimics of hemochromatosis and the most common etiologies of elevated ferritin, and those include dysmetabolic iron overload syndrome so that was a new term for us, and then inflammation as well, so, tune in.

Matt: A reminder that this and most episodes will be available for free CME credit for all health professionals through VCU Health at *curbsiders.vcuhealth.org*. Elliot, welcome back to the show. So good to have you back. Your last episode, I don't want to embarrass you too much, but it was one of the all-time top Curbsiders' episodes-

Elena: Yeah.

Matt: -not surprisingly, so welcome back.

Elliot: Privileged to be back.

Matt: Yeah, liver tests, definitely one of the banes of the primary care doctor having abnormal liver tests, so people can go back and listen to that episode. This one's going to build because now we're going to be talking about one of the potential causes here. Let's jump right into a case from Kashlak. Elena, can you start us off?

[music]

Paul: This episode is brought to you by Green Chef. Green Chef is a meal kit company that makes eating well easy with plans to fit every lifestyle. Green Chef has just expanded their menu. Now you can choose from over 30 recipes weekly with an option to mix and match meals from different dietary preferences, all within the same delivery box without changing your plan. So, you can go vegan one day and keto the next, and then just go buck wild and go Mediterranean the next day. The world is your oyster. Oysters not guaranteed. Green Chef is now offering 10-minute lunches as well. For those of us who are attempted by cafeteria pizza, this is a much healthier and more satisfying option. Each week's menu includes two convenient low-prep and nutritious lunch recipes. They're ready in just 10 minutes, no cooking required. Perfect for when you're on the go when you're pressed for time at the office like many of us are.

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[music]

Elena: Yeah. Let's do this. All right, so we are seeing a 53-year-old gentleman at Kashlak Memorial. He has a history of diabetes, obesity, and prior alcohol use disorder who was recently hospitalized for abdominal pain. He was ultimately diagnosed with ascites and received a new diagnosis of cirrhosis. During his hospitalization, a workup for the etiology of his cirrhosis included an iron panel to evaluate for hemochromatosis. So, thinking about hemochromatosis as a possible etiology of liver disease, what is hemochromatosis and how common is it?

Elliot: Yeah, it's a great thought because definitely hemochromatosis is on the list of things that we know can cause cirrhosis. In general, hemochromatosis is iron overload and its hereditary hemochromatosis when the person has two copies of a mutated gene that interfere with normal cycle of iron absorption and feedback, typically related to a mutation in hepcidin. Essentially, they have a disorder where they're never telling their body to stop absorbing dietary iron. The iron is absorbed and where does it go? It will go to the liver. It will go to the joints, to the heart, to the pancreas, to the skin. In this world where we have a lot of blood tests, it's very rare to start seeing those classic things that we learned about in medical school like bronze diabetes. Typically, people are going to show up with the most common manifestation of hereditary hemochromatosis, which is liver disease.

Matt: Can you remind people just a little bit about hepcidin why it's important with, I guess, a little bit about iron absorption, it might be useful to just talk briefly about how that happens in the body.

Elliot: Yeah. What we know about iron absorption is that it's happening in the proximal small intestine. It's mainly because of a portal that will open up by way of ferroportin. Now, the thing that controls ferroportin is hepcidin, which is a hepatically synthesized protein. When your bank of iron is completely full, then you have a very strong negative feedback loop that turns that hepcidin activity off.

The difference in hemochromatosis is that there is nothing there to tell it to stop. Now, you had earlier asked a question about how common this is, and I think it's worth explaining that this mutation in hepcidin, the most common one that we are seeing is the C282Y. These mutations are so common that about 1 in 240 Americans carry two copies of this autosomal recessive condition, and it's geographically variable, where actually the greatest density of mutations is in Ireland, where 11% of the population is carrying at least one of these defective genes. But you need two copies to have the genetic condition of hereditary hemochromatosis.

Paul: So, Elliot, for this patient in particular, I feel like we have a lot of things to suspect about underlying liver disease already. Like, we give you a history of underlying diabetes, and this is a patient with obesity, and then even some prior alcohol use added into the mix. I feel like we'd have some fairly good explanations for underlying cirrhosis, I guess, but I do see that we test these patients fairly frequently. I'm wondering should all patients with chronic liver disease be screened for hemochromatosis, even if we have some suspicion that something else might be going on or what should be our general approach in scenarios like this?

Elliot: I'm going to answer this by giving you my approach and show you a little bit about how I think I would differ a little bit from some guidelines. I think typically when you read a liver guideline from America or Europe, they'll say once you've identified somebody with severe liver disease like cirrhosis, you should screen for hemochromatosis. There's a variety of reasons why that's not a good idea in this case. First, this is a hospitalized patient who is ill for some reason, and we know that iron indices are acute phase reactants and we're not going to get the most reliable tests for many patients in the hospital, this is not the right time for this.

Number two is that is just a guideline and it's not based on any hard data. What we do know is that this man is presenting with two things that change the pretest probability of hemochromatosis in incredibly important ways. One, he has obesity and diabetes raising the possibility of metabolic syndrome and NASH and two, he has prior alcohol use disorder, which is a much more common cause of liver disease than hemochromatosis. I tend to want to use what the patient tells me and be guided by the history to have the best use of additional laboratory testing. For people like this who have given me a diagnosis in many ways, I'm not going to reach for ferritins and iron and TIBC in the first pass of my labs.

Matt: I like that because we're talking ahead of time where sometimes you see all the iron studies going in a certain direction and you start to think, could this be hemochromatosis? I think you could go down the wrong path if you do that. It's good to know the setting of where we should do that. You're saying someone who's stable in the primary care clinic that would be a totally different mental calculus than the person that's acutely ill and hospitalized.

Elliot: Yeah, definitely. So, if they're acutely ill, I think most people would agree that this isn't the right time to go checking ferritins. Even in the outpatient clinic, it's important to spend the limited time that we have with patients focusing on the most impact that we can have on their lives at that time. While we're diagnosing liver disease, we're talking about the alcohol or the obesity, the diabetes, the metabolic syndrome that is most likely triggering these things. Because bound up in all this discussion is really that there's a differential diagnosis for an elevated ferritin and elevated transferrin saturation, and perhaps we can get to that.

Matt: Yeah, I think let's do it. Let's just say in the hospital, what are you thinking about when you see an elevated ferritin? You can qualify that if you want to put certain cut-offs that make you think in different ways.

Elliot: Okay, so after 10,000, then we're not even thinking about the liver. We're thinking about zebras, we're thinking about severe sepsis, severe inflammation, hemophagocytic lymphohistiocytosis, adult Still's, things that are the stuff of morning report. [Paul laughs] If someone comes in with over 300, 500, that's just a hospitalized patient as far as I can tell.

When you're over 1000 that's still telling me that they have a severe inflammatory condition. I'm still not thinking about hemochromatosis. It's just that in this case if you're several logs above normal, then you're thinking that this person could have a special set of severe illnesses. Just none of them are liver diseases.

Matt: Basically, in the hospital, again, this just tells us a lot of the patients coming in the hospital acutely ill, they're inflamed. Ferritin is an acute phase reactant, so it's going to be up. To add complexity to that, I always think a lot of our hospitalized patients are sick and inflamed, but they're also bleeding. It's like how do you interpret the ferritin? Does it look kind of normal because they're bleeding, but it would be high if they weren't bleeding? all those sorts of things. Anything else you're looking at in the panel, like, in the liver tests or in the CBC when you're considering a diagnosis of hemochromatosis?

Elliot: When considering a diagnosis of hemochromatosis, the two critical indices are one, ferritin, which is going to be elevated and two, transferrin saturation and the cut-off here-- This is based on iron divided by TIBC. Sometimes the lab will give you transferrin saturation, but once you get those numbers, if it's greater than 45%, you start to worry about hemochromatosis. You'll see greater than 50% for men, but if you can only remember one number, let's go with 45%.

When I look at the CBC and the liver enzymes, I'm mainly using this to start calculating in my mind the probability of cirrhosis. Is the AST greater than the ALT? Has the platelet count dropped below 150, below 100, I'm starting to think, is the game afoot in terms of severe liver disease for this patient? It helps me prioritize how important it is to come up with a firm diagnosis for them as well.

Matt: And one other thing I wanted to ask you about, because I hadn't been trained to look at this, I think it was the RBC volume is that what it was that they were talking about above a certain cut-off might tip you in one direction. Do you pay much attention to that?

Elliot: I think that this is one of these things that has stuck around for a while where you will see changes in MCV that were classically associated with hemochromatosis. But red cell indices are neither sensitive nor specific for the kind of thing that we're hunting for, particularly in the outpatient clinic setting.

Matt: Okay, so stick to ferritin and transferrin saturation. When we're looking at the CBC and liver tests, we're just keying in could this person have cirrhosis? I like it. Paul, you look very pensive. I know you have something to say.

Paul: Yeah, I feel kind of at sea here, the opposite to you Watto where it seems like you're always wondering, "Could this be hemochromatosis?" I'm reading through [unintelligible [00:18:09], "Oh God, have I missed hemochromatosis 37,000 times? These indices are often kind of muddled and often so many of our patients have predisposing factors that could be other causes of abnormal liver enzymes and elevated ferritin that kind of stuff. What I'm wondering, I guess is, is there any particular patient or phenotype that is like a Slam Dunk homerun where you think, well, this is what I need to test for hemochromatosis or before you even get labs, is

there something that raises your clinical suspicion for it or is this one of those things that you do for completion's sake?

Elliot: Yes. I am more likely in the first visit to check iron indices in somebody who lacks classic risk factors for what is best described as dysmetabolic iron overload syndrome. People who I know are not drinking, I have biomarkers that prove they're not drinking alcohol to excess. I know that this person doesn't have diabetes or severe metabolic syndrome, but if I have mildly elevated liver enzymes, I'm going to focus on global liver health and lifestyle changes in hopes that I can improve those liver enzymes. I use time to be the greatest arbiter of the diagnosis, where if that person stops drinking or cuts back or if they lose weight and they still do not drop their ALT or do not drop their ferritin, then I start to look into it a little more closely. But I have seen over the course of 6, 12 months, people take ferritins in the low thousands to the low hundreds simply with lifestyle change validating this approach because common things being common, it's much more likely that their elevated ferritin is going to be caused by the dysmetabolic iron overload syndrome.

Matt: Do we understand why that happens? Why the person with chronic liver disease or metabolic syndrome might have elevated ferritin levels? That doesn't quite make sense to me or is it just inflammation? I will accept that one-word answer.

Elliot: Okay, so one in three people with nonalcoholic steatohepatitis, NASH are going to have iron overload. If you stain their liver biopsies, you will find iron there. There're probably two reasons for this in NASH. One is chronic inflammation will influence the way that hepcidin behaves in the liver. Two, inflammation of the hepatocyte is bursting open these cells, spilling their contents into the blood, and among them ferritin. You will see iron and ferritin as a function of liver cell death. Two out of every three people with alcohol-related liver disease will have elevated ferritin. There are at least three reasons there. There's the inflammation, there's the hepatocyte cell death, and then there's the fact that alcohol is itself an influence on hepcidin. It will increase hepcidin activity almost like it's been mutated. So, you can see in people with alcohol use disorder, not only elevated ferritin, but also transferrin saturation. Now, you're not going to see transferrin saturation elevated in every single person with alcohol-related liver disease, but you're going to see it a lot more commonly in people with ALD than those with NASH.

Matt: So, back to our case here, we have this 53-year-old, as we said, diabetes, obesity, she has alcohol use disorder, and we're doing our basic labs on her. So, the iron studies come back. Her ferritin is 1667, her iron level is 170, the TIBC is 203 and that makes a transferrin saturation of 84%. What do you think about these results for this patient? Again, this is a patient who's hospitalized right now for abdominal pain and she's got new ascites and cirrhosis.

Elliot: Well, obviously we've addressed the idea that these labs can be affected in the acute setting. If we come back to the basics about diagnosing hemochromatosis, if you have elevated ferritin, and by that I mean a ferritin greater than 200 for women, 300 for men, and you have this transferrin saturation that's greater than 45%, 50%, then the probability that this person has hemochromatosis is much higher. If I was handed these labs, I would say, "Yeah, hemochromatosis is on the list." But there're two problems. One is that there are things that can influence transferrin saturation like alcohol or genetic hemochromatosis, and then there are things that can influence the ferritin, the acute phase of things. You can have the genetic condition, but it might not be penetrant. So, in people with genetic hemochromatosis, you will always see this elevated transferrin saturation, but you don't necessarily ever develop the iron overload.

Matt: This is probably a good time to mention you had, I guess on Twitter posted, I can't remember how long ago this was, but there was this JAMA Internal Medicine article in 2017 by Dr. Odufalu, and this was a similar case. It was a patient who drank alcohol. They didn't really clarify how much. They had elevated ferritin and transferin saturation. They ended up testing the patient for hemochromatosis. Do you want to talk a little bit about what the pitfall was in that case? Because it kind of relates to what we're getting at here.

Elliot: Yeah, it was a great case and a shoutout to JAMA Internal Medicine in the Teachable Moment series. A lot of great stuff in there. What happened here is that by focusing on the stuff that we can diagnose by the orders that we can check off in Epic. We focused on the positive HFE gene mutations that you could find in the blood. Because we had a positive diagnosis from labs, we anchored on the probability that it was the hemochromatosis that was driving the elevated ferritin. When you see that, you'll respond to it by ordering phlebotomy. In this case, the patient actually had elevated ferritin and probably anemia caused by alcohol use disorder, which was hinted at in the history but forgotten when the blood tests came back. They proceeded to get phlebotomies syncopized and then were lost to follow up because of their interactions with the healthcare setting.

The key lesson here is that although hemochromatosis mutations are so common, their actual penetrance is very low. It can be as low as 1 in a 100. About 1 in every 200 people have the copies of the genes, but 1 in every 100 of those people will actually have penetrant disease. Now it could be higher than 1 in 100. So, in some series it's about 14 in a 100 women, 24 in a 100 men. But what we're talking about for penetrants there is that a doctor gave them the ICD-10 code for hemochromatosis. So it could just be that they were responding to it, but in terms of actual iron overload, it's not a guarantee that these genes will result in that. You still have to deal with the common problem of alcohol use disorder, which was missed here.

Matt: Yeah. This case was, I think, particularly because they could have addressed the alcohol use disorder a couple of years sooner. I think the way they eventually figured it out was she eventually presented with cirrhosis, and they realized that the alcohol was causing the high ferritin. Sad case so, hopefully the audience won't miss that now that we're highlighting on this episode and I think we've talked a little bit about some of the mimics of hemochromatosis here. What would be a good way to approach a patient like this? Would you let them kind of cool off for a while, see them back in clinic maybe if they'd stopped drinking. How long would you wait before you would repeat the labs in someone?

Elliot: When you're a hepatologist like me who says things that are little bit against the grain of guidelines, that means that you're on the hook to follow people longitudinally to make sure that you're taking care to follow your diagnoses through. So, this is super common for me. We have a meeting, we talk about a plan, and then depending on how ill they are, the severity of their baseline disease will craft how frequently we have to follow things. But I'll be checking the labs every three to six months. There's no urgency to immediately phlebotomize a patient. If they stop drinking, if they lose weight, their ferritin will come down, phlebotomy or not.

Matt: Paul, any other specific questions about this case? I know we have another one to go to get more into the primary care realm.

Paul: Not about this case in particular. Yeah, I wonder if it's not worth reviewing some of the manifestations. We're focusing on the liver, which is probably the appropriate thing, but in terms, we are talking sort of offline about how often do you see arthritis. I just don't even know what to

do with it. I think I saw the numbers like 24% of patients with the diagnosis have arthritis, but I'm not even sure how much that differs from just the population without so I guess I'm wondering, are there any other characteristics other than the liver dysfunction that you typically see? Or is there a fairly wide spectrum of disease?

Elliot: It's quite complicated because I really do think that the availability of blood testing has changed the presentation of this condition in such a dramatic way that we're now diagnosing it way before it would have been in the days of yore. So, you're never going to see somebody with bronze diabetes and then arthritis is so common. It is definitely more common in people with HFE gene mutations, but I don't know how much more whether that changes things.

I think that you tend to see more in the form of cardiomyopathy, diastolic, CHF, at least in my clinic. I'm not sure how true that association is. If I were to paint a general picture that is roughly accurate, it's basically turbo metabolic syndrome. All of the complications, all of the various comorbidities, just slightly worse in people with hemochromatosis.

Matt: Yeah, I'd buy that because it seems like you could see it everywhere because the manifestations, elevated liver enzymes, arthritis. I was in clinic today, almost everybody had metabolic syndrome that I saw- [laughs]

Elliot: Right. Yeah.

Matt: -or drank heavy alcohol. [laughs] I probably could have seen it everywhere today. Let's say this person wasn't going to practice your style and the people get these labs back. They're like TSAT above 45% and the ferritin is 1600. I'm going to just order the gene testing. What gene testing would they look for? You told us a little bit about how you'd interpret it. What specific mutations are there? I know there's some off-brand mutations that's how I'll call them that we might think about as well.

Elliot: Okay, very good question. When you order this test, commercially it will be sent to a lab that will use probes for the C282Y and H36D genes. You'll hear the story about compound heterozygosity where one person will have one of their HFE genes will be mutated C282Y and the other H36D. Those people may tend to ward liver disease, but it's always milder and the data is so much more conflicting. The mutations that really matter is that C282Y. Then if you have a patient who has super high iron, their liver is full of iron, it shines on an MRI. But they don't have these genes and they have a low or normal transferrin saturation, then very rarely those people can have mutations in ferroportin. I have never diagnosed that.

Matt: Okay. So, probably Paul and I won't be diagnosing that [Paul laughs] more than-- [crosstalk]

Paul: [unintelligible [00:31:16] challenged. [crosstalk]

Matt: Maybe once in a career if we're lucky. You mentioned the imaging test, so if this patient Bill that we were talking about, if he was just heterozygous for the C282Y, would you stop there and say, okay, this is probably just your alcohol, the metabolic syndrome, the liver disease. We don't need to do any further testing. We don't need to get an MRI and look for iron in your liver.

Elliot: Well, I love that you brought this up, but let's just say that is where I would stop. Let's just say that he comes back a year because you repeat his labs and the ferritin is worse, the liver enzymes are worse. In this case, I need to try to sort out, does this man actually have iron

overload. In the olden times, we would have to stab him in the liver and then burn the tissue to look for how much iron was there. Nobody wants to have a diagnostic liver biopsy if they can avoid it. Now the noninvasive method is to use an MRI. An MRI will basically have a very hard time seeing the liver because of its paramagnetic properties. Even though iron would mess up the MRI, generally, in this case, we're using it to make the diagnosis. If you have a very bright liver looking for iron, then you have proven that your patient has iron overload.

Elliot: If there is iron in both the liver and the spleen, you know that it's a secondary cause of overload because the iron is being deposited in endothelial cells because of excess transfusions and so forth. Or if there's no iron at all, you know that this person doesn't have deposition of the iron. It's not hemochromatosis, primary, hereditary, or secondary.

Matt: Hemochromatosis, as you said, to start this off as just iron overload, we were talking about the hereditary version. That's the kind that we were talking about with the genetic testing. Even if someone isn't homozygous for hereditary hemochromatosis just from chronic alcohol use, they could potentially build up enough iron that you could see in their liver on an MRI.

Elliot: Yeah, you might be able to. Typically, what you'll see is fine amounts of iron that can be stained on a liver biopsy if you are getting very scientific about it. Severe amounts of iron in the liver, you're typically going to see from hereditary hemochromatosis or other secondary sources of iron overload.

Matt: Okay, so that would be like your transfusion for somebody-- Okay. Yeah. In those states, it's more likely to be pathologic and you would worry about that iron causing liver failure if they didn't have it already. Do people with transfusion-associated hemochromatosis also get, like, arthritis and some of those other complications too? Or is that more with just the hereditary type?

Elliot: I don't know the answer to that, but I assume that they could. The secondary hemochromatosis can mess up a liver just as badly, if not worse than primary hemochromatosis. They can also get significant heart injury. The management is usually more complicated owing to the comorbidities associated with those with the reasons for the iron overload in that setting, but I'm not sure about the whole spectrum of presentations.

Matt: Okay, so I guess to conclude this first case. We decided that this patient didn't have hereditary hemochromatosis. The patient went to see America's primary care doctor, Dr. Paul Williams, [Paul laughs] and we got him treated for alcohol use disorder, stopped drinking, iron levels got better, and the cirrhosis is stabilized. So, as happy of an ending as it could be and then Paul got him listed for transplant too. Didn't you, Paul?

Paul: I mean, sure, why wouldn't I?

Matt: [laughs] All right, let's go on to the second case. Paul, would you do the honors?

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Paul: Sure. We're moving on to Francesca, who is a 51-year-old female with a history of celiac disease who's presenting for her annual visit. She was recently tested for hemochromatosis due to a positive family history in her brother and was found to have a C282Y homozygosity and I'm sorry if I said those numbers in a weird way, but that's what we're stuck with. Her labs are notable for a ferritin of 278, a TSAT of 59%, and a hemoglobin of 15.1. I guess the follow-up question is we're in a different territory now. How is this case markedly different and what are the potential complications here as opposed-- let's just stop right there. What are the potential complications we might be on the lookout for?

Elliot: Yeah. This is a person who now is starting to fit the bill of someone where if these were the only numbers that I got, I would be worried about genetic and partially at least penetrant hemochromatosis. She has a ferritin greater than 200. She's also coming at me as a woman with a history of a disease that is associated with iron deficiency. I have a feeling that she has-- this ferritin has fought against great odds.

[laughter]

Elliot: I'm a little bit nervous already. But the ferritin, although it can be diagnostic of hemochromatosis, it's typically the case that when it is less than a 1000, there's a higher likelihood that they have not developed cirrhosis. Back when we were trying to be very sparing with whom we would biopsy, we would actually wait until the ferritin was greater than a 1000 before deciding to biopsy to rule out cirrhosis. It is true that if you present with hemochromatosis and ferritin of a 1000, you're much more likely to have underlying cirrhosis. My gut sense is that this is somebody who is about to get diagnosed with hemochromatosis, but we're going to have a much more laid-back discussion about it.

Matt: What would your spiel be like for this patient? How would you explain it and what she might expect going forward if we're to find that?

Elliot: Yeah, the first thing I would do is start drawing out the cascade from hepcidin to ferroportin and the [crosstalk].

[laughter]

Matt: There you go.

Elliot: But at the end of the day, I think this person would be able to understand that their body is very hungry for iron and that it's dumping it in the liver. That when you start to dump extra toxins into the liver, it has the capacity to cause inflammation, which I liken to something like burning your skin. If you burn your skin, it can cause damage. The redness or inflammation will eventually go away and can be left with a scar, and that same process can be occurring in the liver. The two main objectives that I have in clinic today are to talk about, one, how I can reduce the odds that she'll develop inflammation or scar formation and two, be able to tell her, perhaps even today how much scar tissue she has in her liver so that she can know about her overall liver health and the need to do other things, like screening for liver cancer and so forth.

Matt: What testing might you order as a follow-up to this? because we have these baseline labs from Paul. Paul is referring her over to you because he had the same gestalt.

Paul: Exactly how it would go down. Yes, this feels great.

[laughter]

Elliot: This is a good set of labs. If I was seeing somebody like this and I didn't know their liver enzymes, I would go get their liver enzymes. If I had their liver enzymes and they were elevated, I would ask about alcohol. I would consider checking a phosphatidylethanol or PEth level, which is a test that has really revolutionized my practice. I always tell people that I am going to be looking for a biomarker that tells me how much alcohol that they've been consuming over the last three weeks. I don't try to do this as a gotcha and anyone who walks into my clinic who hasn't been checked for hep C or hep B is going to. But that's just to round things out. Beyond that diagnostic part, the prognostic information that I'll get, you can get in clinic by calculating something like the FIB-4, which is based on the platelets, the AST and the ALT.

But in my clinic, I'll be using FibroScan, which has functionally replaced liver biopsy in this setting. I don't need a liver biopsy to tell me if there's iron. In this person, I've got HFE gene mutations and a positive transferrin saturation and elevated ferritin, you don't even need an MRI. You know that they have a risk for hemochromatosis. I use my FibroScan to tell me about what the risk of cirrhosis is in this clinic today.

Matt: So, you mentioned no MRI. Why wouldn't you want an MRI in this case? Or what case would you find the MRI helpful? It is important to quantify, like, how much iron is in the liver if you're testing, like if you do the FIB-4 or you do the elastography and you're worried, okay, this person has advanced fibrosis, do you even need to do any further testing?

Elliot: Yeah. In this case, if we don't have any other competing diagnoses that could be manifesting in part as this dysmetabolic iron overload syndrome. Then I would feel comfortable and guidelines would allow me the privilege of providing this diagnosis face to face without any additional testing like MRI. But where the diagnosis is in question or there are competing probabilities and you need to know if there is iron in the liver to provide this person with the positive diagnosis of hemochromatosis, then you will go to that MRI. Once I know that they have advanced fibrosis or cirrhosis based on the FibroScan, and after my limited laboratory evaluation, I'm done, I can tell them everything that they need to know about how clinic with me is going to go on a semiannual basis.

People with hemochromatosis who present like this, who is otherwise asymptomatic if they have cirrhosis, they're at increased risk of developing liver cancer. That risk will decline if we can remove the iron from their blood and get them down to a ferritin of like 50 but it will never go away.

Paul: That leads into my next question about concretely, what does management look like from here? Obviously, the broader answer is, it depends, but it sounds like it's mostly kind of I'm not sure if this is the right term, like liver preservation, that protection from viruses, minimization sort of toxin exposure, that kind of thing. But when are you pulling the trigger on phlebotomy and is there anything else that you're sort of in your [unintelligible [00:44:10], I guess, when are you making these decisions and what guides, sort of what happens next?

Elliot: Yeah, so the key branch point is cirrhosis or no cirrhosis. Once you're in cirrhosis, you get that whole package where we start to think about liver cancer screening for varices, like you said, general liver care, make sure that they're vaccinated against hepatitis A, hepatitis B, and then we'll talk about phlebotomy. But the sort of the general practice that anybody has for someone with hemochromatosis is to tell them to-- if they're taking a multivitamin, make sure there's no iron in it, to try to keep cut back on things like red meat, and then three, because people with high transferrin saturations are at high risk of getting serious invasive infections from bacteria that require transferrin to get the iron for their own metabolism, like Vibrio vulnificus. We tell all people like this to avoid the coastal waters in the spring and summer as well as to avoid eating uncooked or raw shellfish like oysters.

When it comes to phlebotomy, the goal is to get that ferritin to 50 to 100 that's our goal. Typically, I'll make a decision about how fast I want to get there, based on how robust the patient is. If they come to me with a ferritin of 1000 and they're 36 years old, we'll do phlebotomy once every week or two weeks until we get down to that low ferritin. If I'm a little bit worried about them, I'll space it out. Sometimes what I'll find when I'm doing phlebotomy is that the ferritin will plummet very quickly. In that case, I've actually learned that the person probably didn't have penetrant hemochromatosis in the first place. I was probably phlebotomizing NASH, which is something that a lot of people would have done. If you can normalize a very high ferritin very quickly, you're probably putting that person at risk of iron deficiency anemia even with a high ferritin. You can start to see that as the transferrin saturation will start to plummet and the iron will be very low. There's no hard and fast rule about how many units of blood need to come out before that person will normalize, but if you watch the kinetics for your given patient, you can get a better sense of what their total iron stores are and what the underlying biology that drove their presentation in the first place was.

Matt: I'm curious. I met a patient with hemochromatosis once that told me that when they drank alcohol, they felt bad and that when they donated blood, they felt very good. They didn't have someone like yourself, like, following them. They were just kind of on their own going for phlebotomy.

Paul: They're self-titrating their ferritin. [laughs]

Matt: Yeah, I tried to convince them to go to see hematology to get some official-- someone actually doing this in a systematic way.

Elliot: Okay, so I have heard this story several times myself and I have learned the hard way to never take a placebo effect away from a patient. Some people get hooked on phlebotomy. Even the people who don't have penetrant hemochromatosis will still like to go give blood. If they are giving the blood to the Red Cross, then that is phenomenal. It's very hard when somebody will retire and then they'll come to see me, and then I'll say, I'm not sure that you need phlebotomy because you went six months and your ferritin went from 50 to 45. So, I'm not sure. And then they'll get upset, but I need my phlebotomy, I feel so much better. In this case, I've definitely seen that. I cannot fully explain it, but we also pump it up for the patient that it's good for them. I don't know where it starts for anybody, but I am not one to question that.

Matt: All right, okay. The person was very convincing and I was like, look, if it feels good then I would just have someone check your levels, make sure you're not going to become anemic from this.

Paul: It's always great, primary care counselling. If it feels good, you should be doing it, just keep it up.

[laughter]

Elliot: I really like it when people are in maintenance phase if they can give their blood. There's something profoundly sad about doing it in the apheresis center and we just throw the blood away. There was, for a time, a kind of stigma from the Red Cross about whether or not it was okay to donate blood if you had hemochromatosis. I'm not sure why they were saying that. I know that they don't want to be serving as, like, providing a medical service, but for patients who are in the maintenance phase where they might only need to do a phlebotomy a few times a year, this is the perfect opportunity to make it count twice.

Matt: Love that. That's great. All right, Elliot, and we're running down to the wire here, but I did want to ask about-- because I had seen this-- our first case, Bill, was a man that we gave you, and in this case, Francesca, this is a female. What are the sex differences, if any, in patients of hemochromatosis? Can you speak to that a little bit?

Elliot: Well, I think there're two ways of looking at this, and the first is epidemiologically. It is that men are more likely to present with severe iron overload, that the penetrance of this condition is higher in men. The other thing is that they're going to present at an earlier age because their cumulative exposure to iron is higher, because in contrast women are more likely to have menstruation through a large part of their life, which is effectively preventing that iron overload. This is modified by a variety of things, behavior, environmental exposures that may have led to men being more classically associated with iron overload, alcohol or obesity in those studies from times in the past.

Nowadays, I'm more likely to make a diagnosis of penetrant hemochromatosis in a younger woman, even in her 20s, because patterns of birth control have changed such that there's now continuous forms, like IUDs or oral contraceptives without interruption that result in a cessation of menstruation for many, many years. And so, you're much more likely to pick up an elevated ferritin in younger woman now. A lot of these sex differences might be rooted in just differing trends, secular trends. It is probably more likely that there're differences in cancer risk that you might pick up, but I'm not sure how solid those associations are.

Matt: So, probably two more questions here. I think anytime anyone gets a genetic test, it can always be a little scary or if somebody's family member got a genetic test and you're operating for incomplete information, someone says, "Oh, my family member has it." Maybe the family member was heterozygous or maybe the patient was heterozygous and they just see that they have the gene, so now they're telling people they have hemochromatosis. How do you sort that out or how do you talk to the patient about that?

Elliot: So, the issue here is that we rarely have perfect information about what our patient has heard about their loved one's genetic history. Responding to that, I think our society guidelines tend to say, if you have diagnosed hemochromatosis, then recommend that first-degree relatives be tested but we know that this is an autosomal recessive condition and that it is variably penetrant. Our responsibility is to tell people that not everyone in their family is going to end up with this disease. It should not affect anything like family planning and that people with one copy of this genetic condition are not likely to present with any disease.

Matt: I like it. Elliot last question here is, in primary care I tend to get the person and you told us this great term, dysmetabolic iron overload. Now that I know that, I feel like I have a better handle of what's probably going on. I tend to get these people who have either a high ferritin, let's say 500 or above, or they have a high just randomly transferrin saturation in the 40% to 50% range and I'm just like, is this hemochromatosis? How should I follow this up? How would you handle that if you were us in primary care?

Elliot: I think there's at least a couple of considerations. The first is whether you think that this is a touchstone for you to help counsel your patient. If they can see that this ferritin reflects inflammation and that what's happening with that iron is that it is effectively kindling for the fire that is going on in their liver or their heart or their joints and that if they improve their underlying health, they can cool that fire off, then that's great. Not everybody responds to blood tests in that kind of productive way.

You might be stuck thinking about when is the threshold where you're no longer comfortable just watching or forgetting about it, and you have to consult hepatology, and if you watch it for a couple of years and you watch it go up to 600, 700, 800, then I'm not going to be mad at you, give me a call. Here at Kashlak Hospital, we are there for each other. If you've watched someone's ferritin go up, this is probably somebody with severely inflammatory liver disease more often than not. It actually brings up a sidebar here, which is that if NASH is the most common thing that's driving this, and the ferritin is a sign of the inflammation, and that there's actual iron being deposited in the liver, it might be the case that if we lowered that ferritin, if we lowered that iron, there'd be less kindling for the liver fire.

There's actually been a randomized trial of phlebotomy in just this patient by Adams, et al, and we're talking about people with ferritins of like 400 or so, not greater than 1000 and drum roll, it made no difference to the patient's liver enzymes or their liver histology.

[laughter]

Matt: Aww man.

Elliot: So, it would have been awesome.

Matt: Yeah.

Elliot: But unfortunately, I'm super glad they did that study because we see this all of the time, but the ferritin will come down if they lose weight or stop drinking and so forth. It is still a reliable biomarker of liver health in this case.

Matt: Okay, so I can add this to my metabolic syndrome checklist when I tell patients, because I do think it's helpful to say to patients, they're saying, "Am I sick from my obesity?" I'm like, "Well, let's go through the checklist." Now, this is going to be on there with diabetes and blood pressure and sleep apnea all the other ones I tick off on there. So, great. Well, I think at some point we have to let you go, certainly, what is it a Wednesday night Paul? [Paul laughs] It's a Wednesday night. [crosstalk] I'm sure you have better things to do. Thank you so much for your time. Let's get some take-home points here. If people had to remember just like two or three things about this discussion, what would they be?

Elliot: Well, for me, the most common causes of an elevated ferritin are still going to be alcohol use disorder and metabolic syndrome/NASH. If you want to diagnose hemochromatosis, you're

looking for significantly elevated ferritin and the elevated transferrin saturation, greater than 45 for women, greater than 50% for men. Finally, although this is a super common genetic condition, perhaps the most common autosomal recessive genetic condition, its penetrance is low, somewhere around 10%.

Matt: Beautiful.

Elena: Yeah. Thank you. That's helpful.

Matt: Always great to hang out with you. A big fan of your Twitter. Even though I'm not on Twitter that much anymore, I do, I always enjoy reading your Tweetorials whenever I'm on there and that's it. We'll let you get on with the rest of your evening. Thank you so much.

Elliot: Thanks for having me, guys.

Paul: This has been another episode of the Curbsiders bringing you a little knowledge food for your brain hole.

Elena: Yummy.

Paul: [laughs] we knew it was you. You can get your show notes at *thecurbsiders.com*. And while you're there, sign up for our mailing list to get our weekly show notes in your inbox plus twice each month you'll get our Curbsiders Digest, which recaps the latest practice-changing articles, guidelines, and news in internal medicine.

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Elena: Elena Gibson, here. Good night.

Paul: And as always, I remain Dr. Paul Nelson Williams. Thank you and goodbye.

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