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Diagnosing and Treating Hemochromatosis: Expert Insights

Dr. Buch:
This is *GI Insights* on ReachMD. I'm Dr. Peter Buch, and today I'm joined by Dr. Paul Adams for an update on the diagnosis and management of hemochromatosis. Dr. Adams is Professor in the Division of Gastroenterology at the Western University in London, Canada. He is passionate about the study of hemochromatosis. Dr. Adams, welcome to the program!

Dr. Adams:
Thank you, Peter.

Dr. Buch:
Dr. Adams, let's get started by giving an overview of the frequency and clinical manifestations of hemochromatosis.

Dr. Adams:
Well, that's an important question and not the easiest one to answer. And in order to talk about the frequency, you have to define what is hemochromatosis—the case definition—and you'd think by now that we'd have a working case definition, but it's a bit fuzzy. Perhaps the best-case definition involves the use of the genetic blood test for hemochromatosis, which was developed in about 1996. It's the most common genetic test done in Canada and the United States, and I'm sure it is in Europe too. And it's a simple test because it studies only one genetic mutation. This is unlike many other types of genetic testing, like cystic fibrosis, for example, where you're studying possibly hundreds of genetic mutations. So a typical patient has two copies of what's called the C282Y mutation, and that means they're homozygous for that mutation, and that means that each of their parents must be at least a carrier of that mutation.

So, what about the symptoms? This is another common problem we have here, because most of the people don't have any symptoms, or if they do have symptoms, they don't recognize them as symptoms of hemochromatosis because they're so common. Things like fatigue, diabetes, and arthritis, these are the most common symptoms, but as I mentioned, many people don't have these symptoms. When we did the big screening studies—and I was a PI of what was called the HEIRS study, which sampled 100,000 people in the US and Canada—we found that many of the people that were discovered by genetic testing had no idea that they had this.

Dr. Buch:
So, basically, let's talk a little bit about the non-Northern European population. When would we be considering evaluating this population for the possibility of hemochromatosis?

Dr. Adams:
So in the study of 100,000 mostly American people, we found none. So what we did find was a huge number of people that had an elevated serum ferritin blood test. And this has been misconstrued time and time again, meaning that the primary care doctor tells the patient they have iron overload, they have hemochromatosis, and almost always they don't. So we have been let down by these iron blood tests. Ferritin is one of them. Ferritin was developed in the 1970s as a test for iron deficiency, and it's much better at that than it is for iron overload, so there are way too many false positives with serum ferritin to consider that a good screening test. What do all these people have with high ferritin? They have, usually, what's called the metabolic syndrome, and this is probably the most common condition in North America, where people are overweight and they have high blood pressure and high cholesterol, and this can lead to an elevation in serum ferritin.

Dr. Buch:
So let's circle back to the genetics. You talked about homozygous. How about the heterozygous population?

Dr. Adams:
No, we don't think that heterozygous people get iron overload. Some of them have mild elevations in ferritin, but there's so much overlap with this metabolic syndrome because of our lifestyle and diet and lack of exercise and obesity and so on. People have speculated for years that maybe there's a genetic advantage to having these genes, because with many bad genetic diseases, the person dies in utero or they die in childhood, or the people are infertile, and these diseases sort of peter out. Well, that's not true in hemochromatosis. It's booming. There's all kinds of children being born with hemochromatosis every day. And people in France have shown that people who are heterozygotes are overrepresented on the French Olympic team and the French cycling team. They've gone into nursing homes in France and tested people over the age of 100 and found that the hemochromatosis genes are overrepresented there. And people have speculated that during times of great turmoil, like the Irish potato famine or the bubonic plague where everybody was dying, there might have been some advantage to being a heterozygote or a homozygote.

Dr. Buch:
Great. Let's circle back to another question that we need to elaborate further. You talked about ferritin on several occasions. How about iron binding capacity?

Dr. Adams:
Well, that's a combination test that leads to a quotient called the transferrin saturation. This is another iron test that has been overrated in the past and has led to a lot of confusion; it's a problem that both the transferrin saturation and the ferritin have great shortcomings. When we did the HEIRS study, where we tested 100,000 people, we had the opportunity in about 2,000 people who had an elevation in one of those tests to bring them back and repeat their test, usually within two months. And when we did that, we found that a great number of those people may have had an elevated transferrin saturation as the first test; two months later, you do it again, and it's completely normal or low.

So we went on and did a big study showing that the transferrin saturation has huge biological variability day-to-day, and we don't really know what that's related to. People have speculated that a lot of people are taking vitamins and supplements and things like this, but we can't rely on the transferrin saturation because it changes so much. So both of those tests are not appropriate for screening.

Dr. Buch:
So let's clarify this for our audience because, again, you've struck on several things that are really important. For our clinicians out there who are considering that their patients have hemochromatosis, what is the step-by-step approach that you would recommend?

Dr. Adams:
Okay, well, the first question would be, why do they think the patient has hemochromatosis? The best nugget from the history would be that their sibling has hemochromatosis and is having treatment already. That's a very high yield that the patient you're looking at could have it: one in four statistically. So that's not always available, that information. So if the patient has some kind of symptom like arthritis in their hands or in their ankles, then you would start with a ferritin and transferrin saturation blood test—widely available, not very expensive—and you see what that is. And if they're a C282Y homozygote and they have an elevation in these iron tests, then the next step starts to try to determine how severe the iron overload is. This is a type of staging.

And we have some advantages now in staging the liver. There are some noninvasive tools that look like ultrasound machines, but aren't quite. These are things like FibroScan and shear wave scanning. They bounce sound waves off your liver, and if your liver is hard, it bounces back very quickly, and if your liver is soft, like fatty liver, it's just absorbed into the liver. And those started in Europe, and they were a bit slow to be introduced in the US, but they're everywhere now, and this would be the next step—to see if the person has significant liver disease, which seems to be less common now. It used to be that people were dying with liver cancer and cirrhosis and so on, and there were publications from England where it looked like everybody was on death's door. Now, since we started screening the general population, most of the people have no symptoms and no significant liver disease.

Dr. Buch:
Wow. For those just tuning in, you're listening to *GI Insights* and ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Paul Adams about the diagnosis and management considerations for hemochromatosis. So moving on, Dr. Adams, what should we know about the treatment of hemochromatosis?

Dr. Adams:
Okay. Well, the treatment of hemochromatosis is rather medieval. It's a phlebotomy, or venesection. It's like a person's donating a pint of blood. That's the treatment. And if you have significant iron overload at the time you're diagnosed, that would usually be done weekly until your serum ferritin comes down to the low normal range, which could be 50 to 100 micrograms per liter.

There are a number of companies in Europe and around the world who are trying to develop biological-type treatments for this that

involve creating synthetic hepcidin. Hepcidin is a relatively new molecule if you're an oldster in medical school like I am, but this is an important regulator of iron balance in the body, and it's made in the liver. And in most people with hemochromatosis, they have a low hepcidin, so by giving synthetic hepcidin, you can decrease iron absorption in your intestine.

Then there are other approaches that are using new chelators. Chelators have been difficult in the past. If you look back at deferoxamine, it had a considerable toxicity. You had to take it as an all-night infusion. A lot of children were on it. It's still around, but there have been some advances in oral chelation—Exjade is a product like that—and there are new ones being developed. There are compounds that you take orally—sort of slurries that you take with a meal—and the iron in your food binds to these compounds, and then that's excreted in your stool. It's a little bit like the product for high potassium, kayexalate. So those would be some of the new treatments.

Gene therapy—it's a disease that can certainly be treated by CRISPR gene therapy. It's been done in animals. Since these patients are relatively well, who wants to sign up to be the first patient to have this done, you know? So it's one of these things where it's just around the corner and maybe always will be. But, I mean, we've seen some movement on some more symptomatic diseases, like sickle cell disease, thalassemia, and Huntington's chorea just recently. So it's an exciting field, gene therapy, but we have to move slowly because there has been some toxicity and deaths associated with these treatments historically.

Dr. Buch:
Thank you. We're in the last few moments of our conversation, Dr. Adams. Do you have any additional thoughts you'd like to share?

Dr. Adams:
Well, I mean, people often say, "Well, how come this is so common and I don't know anything about it?" This comes from doctors. This comes from patients. I don't think it's that students haven't been told about this. Certainly, in my years of medical training, there's been an increased emphasis on genetic diagnosis and genetic consultations in the hospital. These, in some places, were always pediatric clinics, but that's not true now. There are adult genetic clinics with genetic counselors. People like Anne Landers, who used to write a column all the time in the newspapers, she loved writing about this. Oprah Winfrey's show called me about going on, and she thought that I had discovered this disease. Well, I told her that there had been a book written about this on 300 cases in 1934, so that kind of shocked them. So this has been around. I would say it's more well-known in Europe than it is here. I went to France to work, and I moved into a middle-class neighborhood, and all my neighbors, who were not medical, they knew all about this disease. They had family members with it and uncles and aunts that were having phlebotomy and so on, so it should be more on the radar than it is. We don't have television commercials and so on, partly because there's not a pharma product for it. But it's a very treatable disease, and if your brother calls you up and says, "I've just been diagnosed with this; you should go and be tested," you should go and be tested because you could have a treatment that could save your liver.

Dr. Buch:
Those are great insights for us to think about as we come to the end of our program, Dr. Adams. Thanks so very much for this very informative presentation on hemochromatosis.

Dr. Adams:
Well, thank you for inviting me, Peter. It's been a great honor for me.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit *GI Insights* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening, and looking forward to learning with you again very soon.