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Updates on the Diagnosis & Management of AHP

Dr. Buch:
This is ReachMD *GI Insights*. I'm your host, Dr. Peter Buch. Today we are joined by Dr. Herbert Bonkovsky, who will be discussing an article he co-authored, "AGA Clinical Practice Update on Diagnosis and Management of Acute Hepatic Porphyrias: Expert Review," published in *Gastroenterology* March of 2023. Dr. Bonkovsky is Professor of Medicine and Molecular Medicine and Translational Science at Wake Forest University.

Welcome to the program, Dr. Bonkovsky.

Dr. Bonkovksy:
Thank you very much. It's great to be with you.

Dr. Buch:
Let's dive right in, Dr. Bonkovsky. Which patients with suspected irritable bowel syndrome should be screened for acute hepatic porphyrias, or AHP?

Dr. Bonkovksy:
The group of diseases called AHP, mostly acute intermittent porphyria, although there are rare instances of other types as well are mainly diseases of young women, women in the childbearing years. And so with that said, people with suspected or presumed irritable bowel syndrome with unusually severe episodes, and particularly, if women describe having monthly recurrence during the mid part of the menstrual cycle, around the time of ovulation, and it's severe enough that they need emergency room visits or urgent care visits certainly deserve at least a screening for the possibility that they actually have an acute hepatic porphyria. Now they may have elements of irritable bowel syndrome, as well as acute hepatic porphyria. They're not mutually exclusive. But those would be the patients in particular that deserve to be screened. And the screening is pretty simple, actually.

Dr. Buch:
Thank you for that. Now, Dr. Bonkovsky, when considering AHP, is there any additional testing that's necessary beyond what you discussed before?

Dr. Bonkovksy:
If there's an elevation of more than three times the upper limit of normal either in delta aminolevulinic or porphobilinogen in the urine, that is presumptive acute hepatic porphyria. For those that have elevations in porphobilinogen, perhaps with ALA, as well the next step would be to do genetic testing. And there are now very reliable and readily available tests for all of the genes of heme synthesis and heme-metabolism. In particular, INVITAE Laboratories in San Francisco has a 10-gene test that will sequence all of the genes that might be involved and be abnormal in people with acute hepatic porphyrias, so that would be the next step. If one is considering the possibility of variegate porphyria or hereditary coproporphyria, stool porphyrins are useful. And in variegate porphyria, another useful test is a fluorescence emission pattern of the plasma porphyrins.

Dr. Buch:
So with that under our belt, how should we be managing acute attacks?

Dr. Bonkovksy:
Acute attacks should be treated with intravenous heme. In the US, the form of intravenous heme that's available is called Panhematin. It's marketed by Recordati Rare Chemicals in Europe and several other countries and regions around the world. The predominant form that's available is called heme arginate, or Normosang, also marketed by Recordati. But this should be started as quickly as possible

during the acute attack, particularly, if the attack is severe enough that the patient needs to be in the emergency department or in the hospital.

The other important things are to avoid or stop any of the drugs that are known to be risky, that can trigger attacks. Alcohol should be avoided or used only sparingly in people with biochemically and clinically active acute hepatic porphyrias. Other things are good supportive care. Occasionally, people will present with pretty significant hyponatremia and/or hypomagnesemia, and these things may need to be treated, as well as the specific treatment of intravenous heme. And the idea of the intravenous heme is to downregulate the first and rate-controlling enzyme of the heme synthetic pathway, namely 5-aminolevulinic acid synthase, which in porphyria attacks is markedly upregulated.

Dr. Buch:
So, Dr. Bonkovsky, when we're talking about managing acute attacks, are there other medications that we should be aware of that may provoke acute attacks?

Dr. Bonkovksy:
Yeah, really anything that is capable of inducing cytochrome P450, or occasionally, there are chemicals that act as suicide substrates for cytochrome P450 and breaks down the heme of the P450; all of these are risky. Classically, the greatest risks have been from the barbiturates and from the hydantoins, but there are many other drugs that can induce cytochrome P450, increase the demand for heme by hepatocytes, and lead to this uncontrolled and unregulated induction of that first step, which is the biochemical sine qua non for occurrence of acute porphyric attacks.

Dr. Buch:
And a further question here, might the timing of one of these medications help us with differentiating irritable bowel syndrome from acute hepatic porphyrias?

Dr. Bonkovksy:
Well, certainly, there's a history of a patient having, say, started a barbiturate or rifampin or phenytoin or carbamazepine or one of these other drugs that are known to be risky in porphyria, that should really raise the level of suspicion, and it should become this acute hepatic porphyria until proven otherwise.

Dr. Buch:
So moving on from there, what is the best approach for patients with recurrent attacks?

Dr. Bonkovksy:
If patients are having more than three acute attacks per year, we now recommend that they be started on a relatively newly available medicine, called givosiran, and it is a selective and quite specific siRNA that downregulates ALA synthase 1, this key hepatic enzyme. The alternative is to treat patients with intravenous heme usually given once a week as a prophylaxis. The advantage of givosiran is that it may be given only once per month and can be given subcutaneously. In fact, patients can administer it themselves. In contrast, intravenous heme has to be given intravenously, and because of the possibility of things like thrombophlebitis, it really is best given into a high-flow central vein through a PICC line or through a central port.

Dr. Buch:
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Herbert Bonkovsky about the diagnosis and management of acute hepatic porphyrias, or AHP.

Dr. Bonkovsky, what's the risk of developing hepatocellular carcinoma?

Dr. Bonkovksy:
We've learned that these risks are substantially increased in people that have underlying acute hepatic porphyrias, it's of the order of 50 to 100 times increased risk compared with the general population. And the other thing to stress is that it seems to be related also to the degree of biochemical activity, so people who are chronically overproducing and over-excreting delta aminolevulinic acid or 5-aminolevulinic acid and porphobilinogen are likely at the highest risk. Probably, the main potential cause of hepatocellular carcinoma, as well as other adverse long-term effects is actually the delta aminolevulinic acid, which can increase oxidative stress in many, many tissues, but particularly, in hepatocytes.

Dr. Buch:
And with that in mind, what are some other consequences of AHP that we should be monitoring?

Dr. Bonkovksy:
The other big one is there's quite a marked increased risk of the development of chronic renal insufficiency, which can progress to renal

failure. Some of this is related to systemic arterial hypertension, and it's characteristic during acute attacks for people to have quite elevated blood pressures often as high as 200/120 or 130. Fortunately, as the attack is treated, these blood pressures tend to come back into the normal range, but certainly, eventual development of renal insufficiency possible need for hemodialysis or peritoneal dialysis is markedly increased in people with biochemically active and clinically active acute hepatic porphyrias.

Dr. Buch:
So before we conclude, are there any additional thoughts you'd like to share with our audience today?

Dr. Bonkovksy:
I guess the big take-home message, again, is if you are seeing patients who are returning time and again complaining of diffuse abdominal pain, you ought to think of the possibility of, 'Could my patient have acute hepatic porphyria?' And get the right screening test. And I can't stress too much that the right screening test is not to get a screening urinary porphyrin, but it's to get a single random urine or delta aminolevulinic acid, porphobilinogen, and creatinine.

Dr. Buch:
This was an excellent review on the diagnosis and management of acute hepatic porphyrias. I want to thank my guest, Dr. Bonkovsky, for sharing his insights.

Dr. Bonkovsky, thank you so very much for joining us today.

Dr. Bonkovksy:
It's my pleasure. Thanks for the invitation.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/GIInsights where you can Be Part of the Knowledge. Thanks for listening, and looking forward to learning with you next time.