When Carbohydrates are Not Enough: Acute Intermittent Porphyria Treated with Givosiran

Rahimian, Shoja; Kushwah, Akanksha; Kate, Yugandhara; Rettew, Andrew

Department of Hematology & Oncology, Tower Health Reading Hospital, West Reading, PA

INTRODUCTION

Acute intermittent porphyria (AIP)

- Most common of the rare acute porphyrias
- Autosomal dominant disease of heme synthesis enzymes and their deficiency in the liver (Figure 1).
- Resultant pathologic levels of porphyrins induce neurovisceral attacks, often with abdominal pain, nausea, vomiting, and wide variety of neuropsychiatric symptoms.
- Can be precipitated hormonally (estrogen, progesterone) or by certain medications (sulfonamides).
- Often misdiagnosed, and delay in diagnosis leads to patient morbidity such as chronic pain and neurologic symptoms.

CASE DESCRIPTION

An 18-year-old woman was admitted to the hospital for the second time in two months for abdominal pain and intractable nausea and vomiting.

Significant findings upon hospitalization:

- Diffusely tender abdomen, no skin lesions on examination
- Low ferritin of 26 ng/mL
- Unremarkable CT and MRI of the abdomen
- EGD and colonoscopy which revealed mild chronic duodenitis with negative celiac disease testing.

→ Diagnosis of a functional gastrointestinal disorder was suspected and antimotility and antiacid agents were prescribed.

→ After discharge, serum and urine porphyrin studies sent during the hospitalization returned elevated (Table 1).

Hematology evaluation & management:

- Upon further interview, patient had been experiencing abdominal pains, worst mid-menstrual cycle, along with paresthesia at fingers.
- Confirmatory gene testing revealed a pathogenetic variant of the hydroxymethylbilane synthase gene, consistent with AIP.
- In the six months that followed, she required four carbohydrate loading and hemin treatments for exacerbations. She gained 25 pounds during this time.
- Due to persistence of disease, she was initiated on the novel givosiran, a heme synthesis gene interference agent. She tolerated this well without any side effects.
- In the months that followed she had notable reduction of her symptoms and did not require any further hemin or carbohydrate treatments.

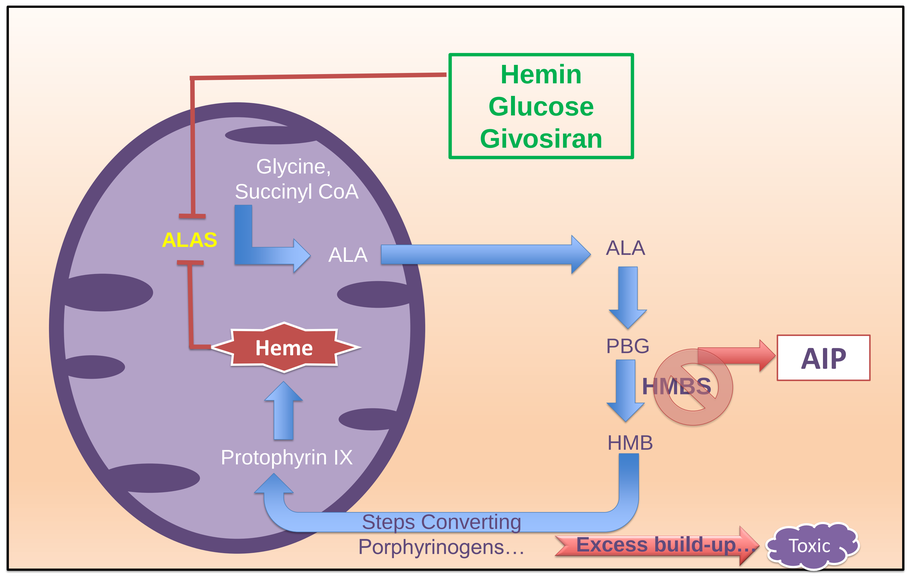

Figure 1: Delta-aminolevulinic acid (ALA) is formed by ALA synthase (ALAS2 in the liver) while inside mitochondria. Unless its product of porphobilinogen (PBG) is converted to hydroxymethylbilane (HMB) by HMB synthase then toxic porphyrins are formed causing symptomatology of AIP. ALAS can be inhibited by the heme product or AIP treatments.

LAB RESULTS

Lab test	Result	Reference range
Plasma studies:		
PBG Deaminase	5.7	>=7.0 nmol/L/sec
Plasma Total Porphyrins	20.1	1-5.6 mcg/L
Urine studies:		
Random Porphobilinogen	76.06	<0.22 mg/ g creatinine
Total Porphyrins	15754.3	27-153.6 mcg/ g creatinine
Coproporphyrin III	846	4-88.6 mcg/ g creatinine
Coproporphyrin I	188.4	6.5- 33.2 mcg/ g creatinine
Heptacarboxyporphyrin	286	<= 3.4 mcg/ g creatinine
Hexacarboxyporphyrin	54.4	<= 6.3 mcg/ g creatinine
Pentacarboxyporphyrin	242.5	<= 4.1 mcg/ g creatinine
Uroporphrin I	7164.3	3.6- 21.1 mcg/ g creatinine
Uroporphrin III	6972.7	<= 5.6 mcg/ g creatinine

Table 1: Serum and urine porphyrin studies

DISCUSSION

- Unexplained and refractory abdominal and neuropsychiatric symptoms in a young female should prompt consideration of checking serum and urine porphyrin levels.
- The 5 P's are helpful for recognition of AIP (figure 2).
- In the case of AIP, treatment with hemin and carbohydrate loading may alleviate attacks while more frequent manifestations may necessitate trial of novel gene modulating therapies such as givosiran.
- Glucose loading: 300g per 24hrs in form of D10 or PO glucose loading, however usually not helpful in severe attacks
- Hemin: 3-4 mg/kg daily x 4 days or symptoms improve

Givosiran

- FDA approved November 20, 2019
- In the RCT, patients with AIP on givosiran experienced 74% (P<0.001) fewer porphyria attacks compared to placebo. Givosiran also led to significant decrease in levels of neurotoxic heme intermediates including ALA, PBG.[2]
- The recommended givosiran dose is 2.5 mg/kg once monthly by subcutaneous injection.
- May not be cost effective in all cases, difference of around $500,000 compared to hemin treatment alone.

5Ps: Features in Porphyria

- P: Pain in abdomen
- P: Polyneuropathy
- P: Psychological abnormalities
- P: Pink urine
- P: Precipitated by medications

Figure 2: Features in porphyria

REFERENCES

1. Balwani, M., Sardh, E., Ventura, P., Peiró, P. A., Rees, D. C., Stölzel, U., Bissell, D. M., Bonkovsky, H. L., Windyga, J., Anderson, K. E., Parker, C., Silver, S. M., Keel, S. B., Wang, J. D., Stein, P. E., Harper, P., Vassiliou, D., Wang, B., Phillips, J., Ivanova, A., … ENVISION Investigators (2020). Phase 3 Trial of RNAi Therapeutic Givosiran for Acute Intermittent Porphyria. *The New England journal of medicine*, *382*(24), 2289–2301
2. Massachi, S., Epstein, J., Hurd, J., & Bonkovsky, H. L. (2020). Cost savings with hemin versus givosiran for the treatment of patients with acute intermittent porphyria (AIP). Journal of medical economics, 23(12), 1441–1449.