Real-World Analysis of Symptoms, Diagnostic Patterns, and Provider Perspective on Acute Hepatic Porphyrias

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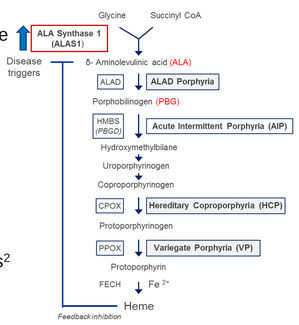
Background and Rationale

Acute Hepatic Porphyrias (AHPs)

- Family of rare, genetic diseases caused by deficient activity in one of the eight enzymes involved in hepatic heme biosynthesis (Figure 1); acute intermittent porphyria (AIP) is the most common subtype
- Accumulation of neurotoxic heme intermediates, urinary aminolevulinic acid (ALA) and porphobilinogen (PBG), can cause chronic debilitating symptoms and potentially life-threatening attacks
- First-line diagnostic biochemical tests include measuring urinary ALA and PBG as both are elevated in the majority of AHPs[1]; conversely, testing urinary porphyrins, alone, is less specific as elevations are observed in other more common disorders[1]; low awareness of optimal diagnostic tests leads to a delay in diagnosis[2]

Figure 1: Heme biosynthesis pathway



Objective

- To understand physician experiences diagnosing AHPs and characterize the AHP patient population in a real-world setting

Methods

Methodology

- Health Care Providers (HCPs) (N=175) from the US, EU-5, Canada, and Japan who had actively managed or treated patients with AHP (with and without recurrent attacks) in the year prior were recruited between September 15 to October 10, 2017 (until November 30th in Japan and EU-5). HCPs were included if they met the following criteria:
  - Board certified or eligible
  - Practice experience of 2-35 years
  - Able to provide at least 1 patient chart
  - At least slightly familiar with AIP, HCP, or VP
  - Spend at least 50% of time in direct patient management
  - Personally seen at least 1 AHP patient in the past year
  - Actively treats / is the primary care provider for at least 1 AHP patient
- HCPs completed an online survey collecting information on demographics, familiarity with AHPs and diagnostic tests, perspective on symptoms important to diagnosis, referral patterns, and treatment preferences
- HCPs were asked to provide 1-4 AHP patient charts; chart data included anonymized patient demographics, medical history, number of porphyria attacks, and symptoms

Results

HCP Demographics

- Mean of 18.1 years in practice
- HCPs were actively managing a median of 9 AHP patients (mean 21.3, SD 32.6) and have seen a median of 16 AHP patients in the past year (mean 35.0, SD 44.7)
- HCP location of practice included the US (29%), EU-5 (57%), Canada (9%), and Japan (6%)
- On average 3 AHP charts were provided per physician for a total of 546 charts (32% US) (Table 1)
- Majority of HCPs worked in academic settings (Figure 2a); most common HCP specialties were gastroenterology, neurology, and hepatology (Figure 2b)

Table 1: HCP countries of practice

	US	UK	Canada	France	Italy	Germany	Spain	Japan	*TOTAL*
HCPs (n)	50	20	15	20	20	20	20	10	***175***
Charts (n)	173	63	38	57	64	58	62	31	***546***

Figure 2a: HCP practice setting

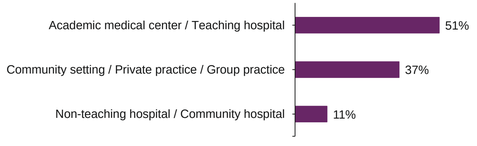
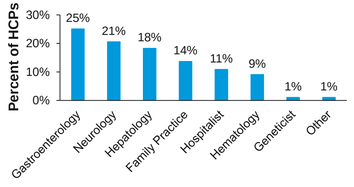


Figure 2b: Primary HCP specialty



Results (cont.)

Symptoms and Diagnostic Tests Considered Informative to AHP Diagnosis

- HCPs reported symptoms considered informative for AHP diagnosis, including abdominal pain, red/dark urine, muscle weakness, vomiting, fatigue, and nausea (Figure 3)
- AHP diagnostic tests considered informative included ALA in urine and PBG in urine; however, other nonspecific tests were also commonly considered informative (e.g., porphyrin in the urine) (Figure 3)

Figure 3: Symptoms & diagnostic tests considered informative to HCP's AHP diagnosis

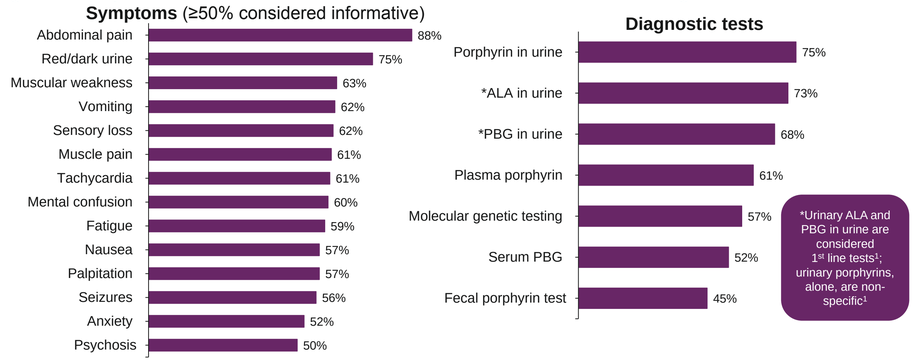


Chart Review: Patient Demographics

- 546 total AHP patient charts were abstracted
- Majority of patients were diagnosed with AIP, mean patient age was 40.3 years, slightly more patients were female (Table 2)
- According to patients' HCPs, the majority of patients were employed at some level (60%); however, over a quarter were unemployed or disabled (27%)

Table 2: Patient demographics

Patient Characteristics	AHP Patients (N = 546)	
	n/Mean (SD)	%
Diagnosis		
AIP	447	82%
HCP*	56	10%
VP**	43	8%
Age	40.3 (14.2)	-
Gender, Female	288	53%
Ethnicity		
African	57	10%
Asian	59	11%
Caucasian	386	71%
Hispanic	39	7%
Employment Status		
Full-time	180	33%
Part-time	147	27%
Unemployed	125	23%
Retired	27	5%
Disabled	24	4%
Other, student, or unknown	43	8%

* HCP = hereditary coproporphyria
** VP = variegate porphyria

Chart Review: Patient Misdiagnosis

- 26% of AHP patients were initially misdiagnosed and 31% were diagnosed correctly (43% did not know this information) (Figure 4a)
- Most common misdiagnoses reported were nonspecific abdominal pain, irritable bowel syndrome (IBS), depression, and fibromyalgia (Figure 4b)

Figure 4a: Percentage of patients initially misdiagnosed

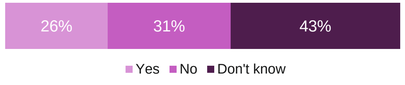
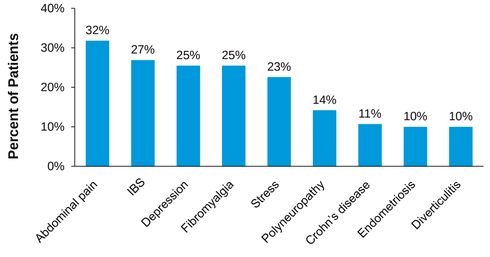


Figure 4b: Commonly reported misdiagnosis



Results (cont.)

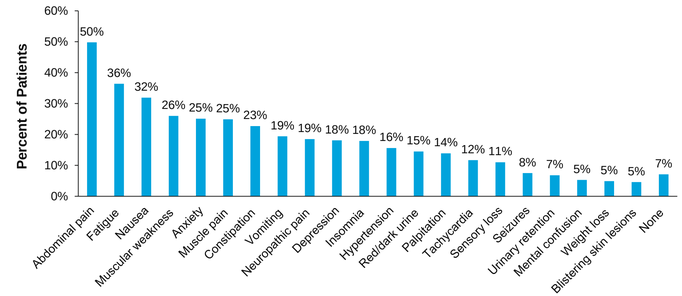
Chart Review: Acute Attacks and Hospitalizations

- Patients have a median of 2 attacks (mean 1.8, SD 1.5) and median of 1 hospitalization (mean 1.1, SD 1.1) in the year prior to survey completion
- Approximately half of patients (45%) were hospitalized in the year prior

Chart Review: Chronic Symptoms

- Most common chronic symptoms reported between attacks were abdominal pain, fatigue, and nausea (Figure 5)
- According to their HCPs, the majority of AHP patients (59%) rate their abdominal pain as moderate, causing a moderate interference in the patient's normal life in 34% of patients
- AHP physicians reported that 90% of their patients experienced 1 or more chronic symptoms occurring between attacks (7% reported no symptoms, 3% did not report data)

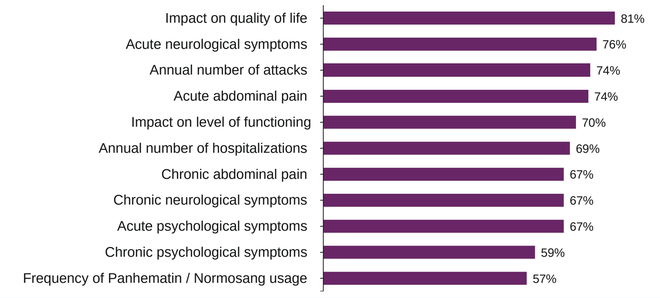
Figure 5: Chronic symptoms experienced between attacks



Factors Affecting Patient Severity

- Impact on quality of life, acute neurologic symptoms, acute abdominal pain, chronic neurologic symptoms, and chronic abdominal pain are considered important for HCP assessment of AHP severity (Figure 6)

Figure 6: Importance of characteristics in HCP assessment of AHP severity



Summary

- Data supports that AHPs are often underdiagnosed or misdiagnosed likely due to nonspecific symptomology and/or lack of understanding of optimal laboratory testing procedures
- AHPs have both acute and chronic manifestations impacting patient's quality of life; these symptoms play an important role in the diagnosis and assessment of severity amongst AHP patients
- Limitations include potential retrospective selection bias from HCPs pulling charts of their most severe patients and the greater proportion of males than cited in literature, limiting generalizability of results[3]

References: 1. Puy H, et al. Porphyrias. *Lancet.* 2010;375:924-37. 2. Bonkovsky, H.L., et al., Acute porphyrias in the USA: features of 108 subjects from porphyrias consortium. *Am J Med.* 2014;27(12):1233-41 . 3. Bissel DM, et al. Porphyria. *NEJM.* 2017;377:862-72.

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