



MODULE
04

Patient Burden of Acute Hepatic Porphyria (AHP)



The Burden of Disease for Patients in Their Own Words

The many dimensions of AHP adversely affecting patients' lives:

- Debilitating symptoms¹⁻³
- Once an attack occurs, patients generally feel under constant threat of another³
- Patients' daily functioning is negatively impacted with increased disability and decreased employment²⁻⁵
 - 20% to 63% unemployment according to recent studies

“ My nausea is uncontrollable. And I—**my body just doesn't feel right anymore.** ”

Simon A, et al. *Patient*. 2018.

“ **It's completely unpredictable.** There's no way I could be a reliable employee to somebody because I could not guarantee that I will be there tomorrow for work. ”

Simon A, et al. *Patient*. 2018.

“ Some days I just feel like I hurt so bad that it's like I actually will think out loud, how is porphyria compatible with life...**You can't live like that.** ”

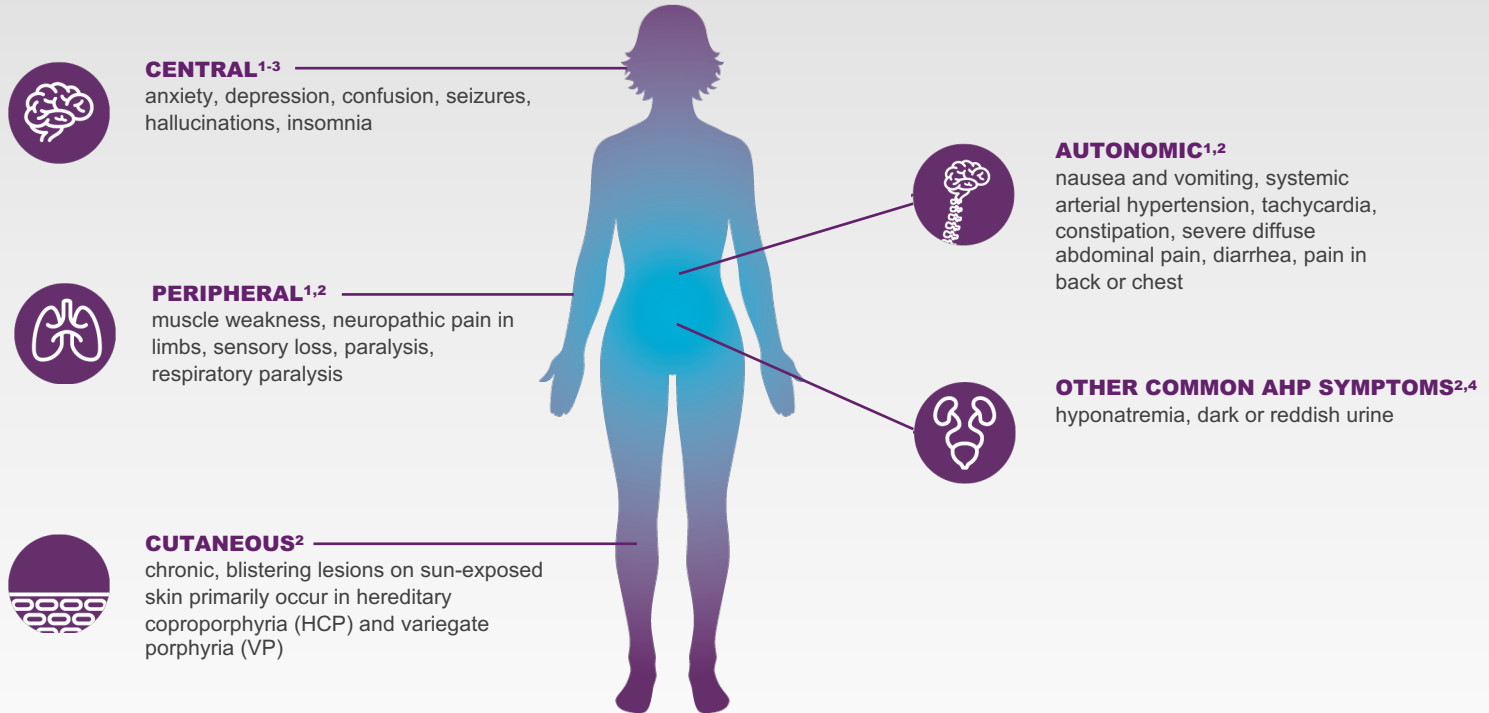
Simon A, et al. *Patient*. 2018.

“ **When I was still working,** I was a computer technician, and I had calls to make and didn't feel good. Calls would build up, customers would complain, **and that would lead straight into an attack.** ”

Naik H, et al. *Mol Genet Metab*. 2016.

References: 1. Bonkovsky HL et al. *Am J Med*. 2014;127:1233-1241. 2. Naik H et al. *Mol Genet Metab*. 2016;119:278-283. 3. Simon A et al. *Patient*. 2018;11:527-537. 4. Bylesjö I et al. *Scand J Clin Lab Invest*. 2009;69:612-618. 5. Ko JJ et al. ACG 2018. Poster.

AHP* Features a Broad Range of Symptoms



*There are 4 types of AHP. Around 80% of cases are acute intermittent porphyria (AIP), followed by variegate porphyria (VP), hereditary coproporphryia (HCP), and the extremely rare ALAD-deficiency porphyria (ADP).^{5,6}

References: 1. Ventura P et al. *Eur J Intern Med.* 2014;25:497-505. 2. Anderson KE et al. *Ann Intern Med.* 2005;142:439-450. 3. Puy H et al. *Lancet.* 2010;375(9718):924-937. 4. Balwani M et al; Porphyrias Consortium of the Rare Diseases Clinical Research Network. *Hepatology.* 2017;66(4):1314-1322. 5. Simon A et al. *Patient.* 2018;11(5):527-537. 6. Bissell DM et al. *N Engl J Med.* 2017;377(9):862-872.

Symptoms of AHP Can Occur Chronically, Between Attacks

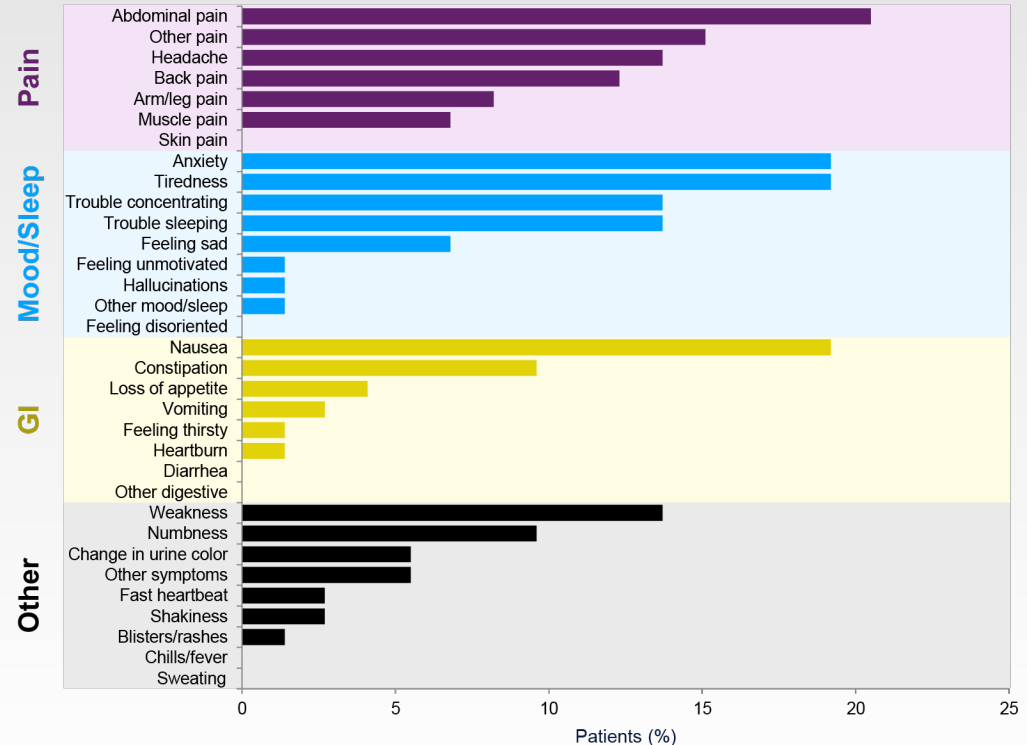
Methods

- EXPLORE study—an observational, multinational, prospective, natural history study of 112 people living with recurrent attacks of AHP¹
- Key eligibility criteria
 - ≥ 3 attacks per year or use of prophylactic treatment¹

Results

- 65% of patients reported chronic symptoms in between attacks (including pain)¹
 - Some of these patients were treated with hemin or opioid prophylaxis¹
- 46% of patients reported experiencing chronic symptoms every day¹

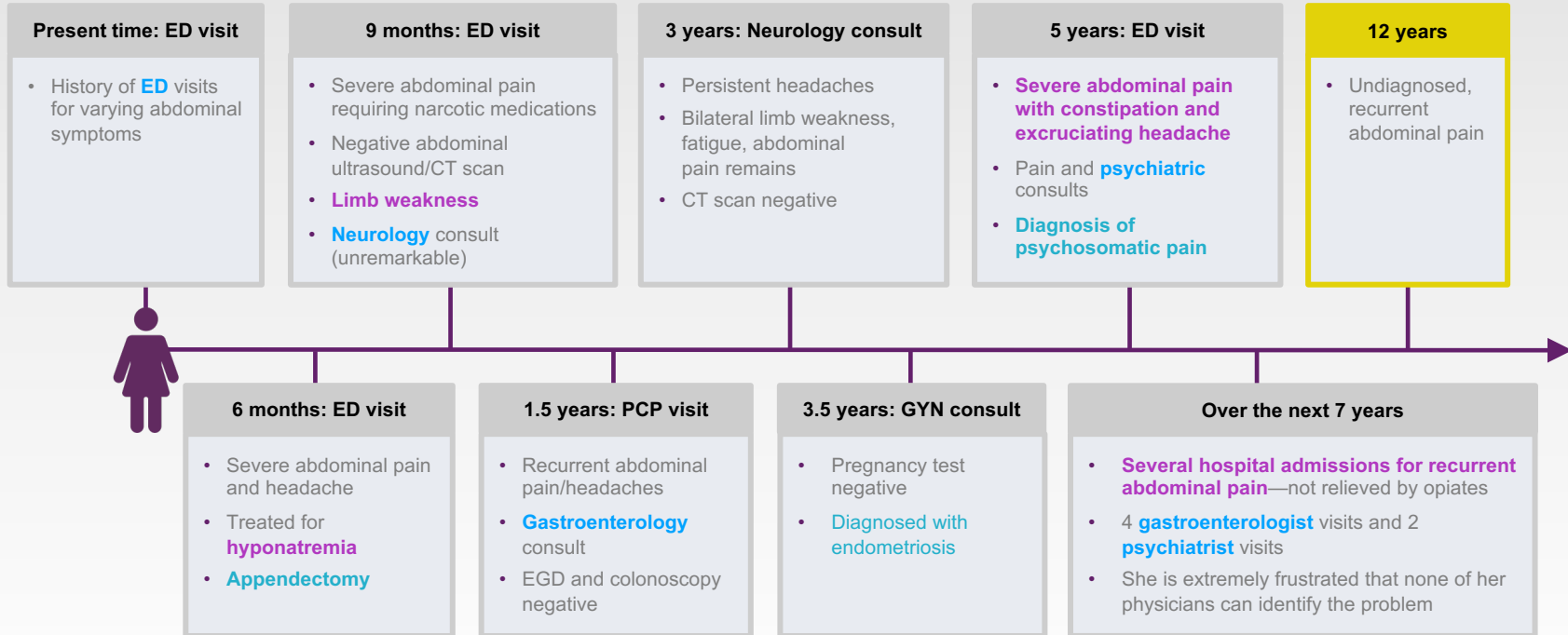
Chronic Symptoms Experienced Between AHP Attacks (n=73)¹



Reference: 1. Gouya L et al. *Hepatology*. 2020;71(5):1546-1558.

An Example of the Frustrating Journey of a Patient With AHP

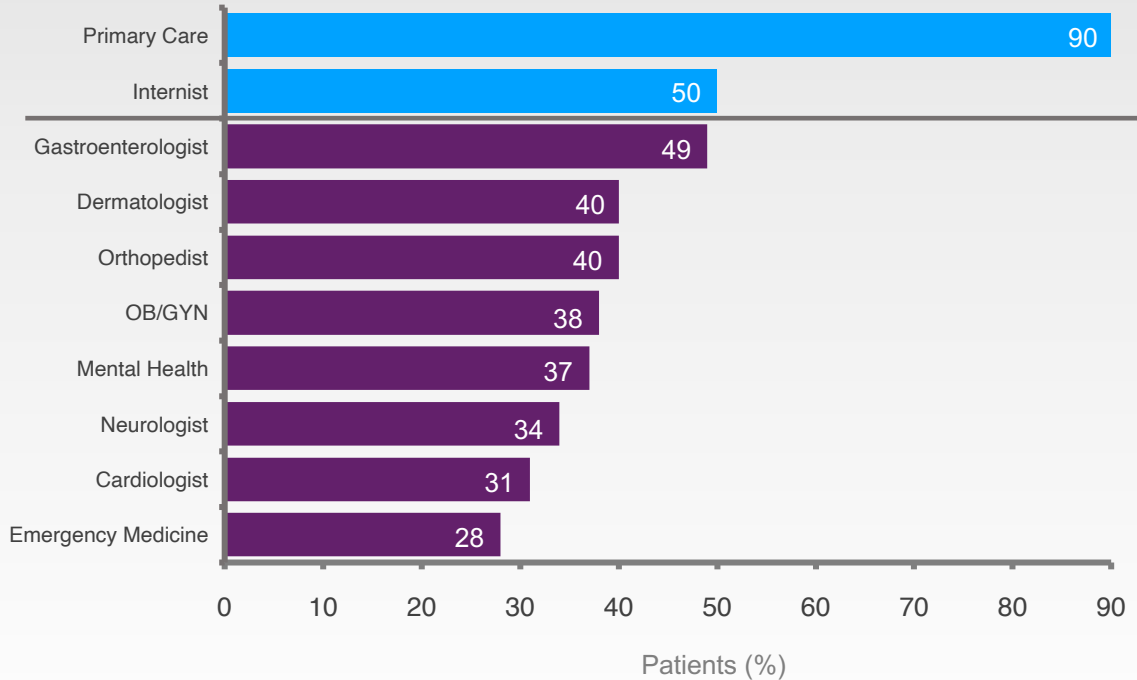
■ Different specialties the patient may see ■ Key signs and symptoms ■ Misdiagnosis



ED=emergency department; EGD=esophagogastroduodenoscopy; GYN=gynecologist; PCP=primary care physician.

Patients With AHP Generally See Multiple Specialists Prior to Diagnosis

Outpatient Office Visits Prior to Diagnosis: Percentage of Patients With ≥ 1 Office Visit

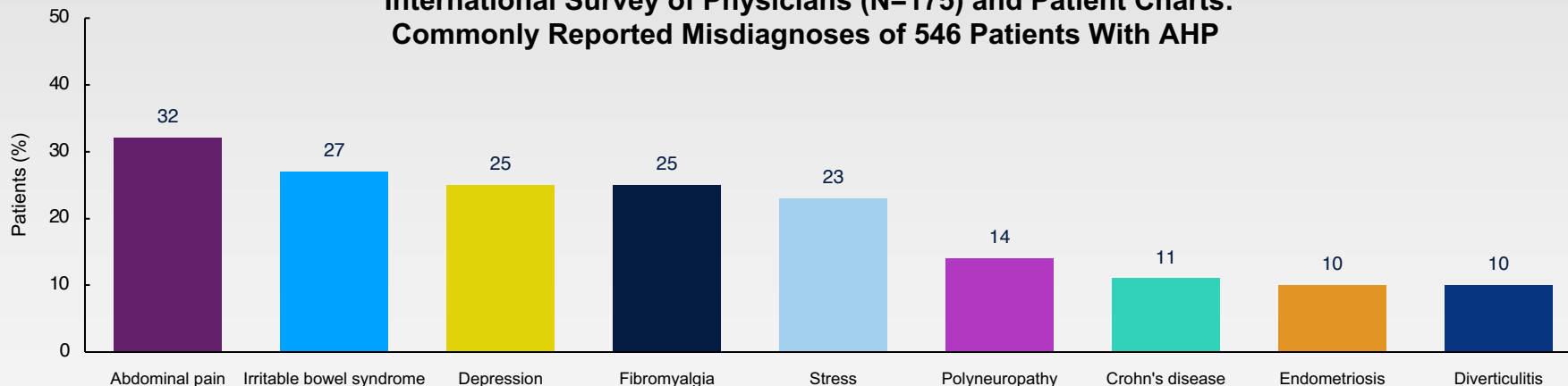


- Patients with AHP usually see multiple specialists prior to their diagnosis¹
 - Utilizing the IBM MarketScan Commercial Claims and Medicare Supplemental Databases, patients diagnosed with AHP/acute intermittent porphyria (AIP) between January 1, 2010, and June 30, 2017, were identified, and their healthcare journeys from first suspected symptom up to 5 years prior to diagnosis, referred to as the “observation period,” were subsequently assessed¹
- The most commonly seen physicians during the observation period were primary care physicians (90%) and internists (50%)¹
- The most commonly seen specialist during the observation period was a gastroenterologist¹
 - These patients were seen on average 3.3 times during the observation period¹

Reference: 1. Rudnick SR, et al. Poster presented at: American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

Initial Misdiagnosis of Patients With AHP Is Relatively Common¹

**International Survey of Physicians (N=175) and Patient Charts:
Commonly Reported Misdiagnoses of 546 Patients With AHP**

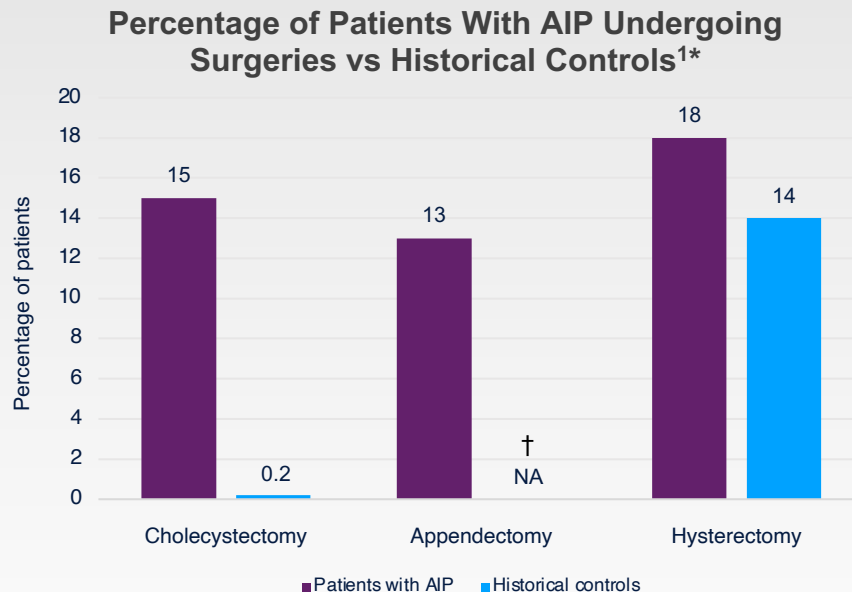


- A retrospective analysis of 546 AHP patient charts from 175 physicians from the United States, Europe, Canada, and Japan found that about 1 in 3 patients was correctly diagnosed with AHP¹
 - The most common HCP specialists were gastroenterologists, neurologists, and hepatologists¹
- A total of 26% of patients with AHP were initially misdiagnosed, and 31% were diagnosed correctly¹
 - 43% of patients had charts that did not clearly indicate whether a correct AHP diagnosis was made initially or whether it was preceded by any earlier misdiagnoses¹

Reference: 1. Ko JJ et al. Poster presented at: American College of Gastroenterology Annual Scientific Meeting; October 5-10, 2018; Philadelphia, PA.

Patients With AIP Can Have Multiple Surgeries and Hospitalizations Prediagnosis¹

- An observational study of 108 patients with AHP in the United States was conducted to describe demographic, clinical, and biochemical characteristics of the disease¹
 - Diagnosis was delayed by ~15 years for patients¹
- In the study, 90 patients had acute intermittent porphyria (AIP), the most common type of AHP¹
 - Of those who reported prior hospitalizations, 55% were hospitalized 1 to 5 times¹
 - Compared with historical controls, a higher percentage of patients with AIP underwent surgeries such as cholecystectomies and hysterectomies¹



*Indirect standardization methods were used to compare chronic medical conditions in subjects with AIP with data from the National Health and Nutrition Examination Survey 2009-2010 dataset or the United HealthCare database, 2009-2010.¹

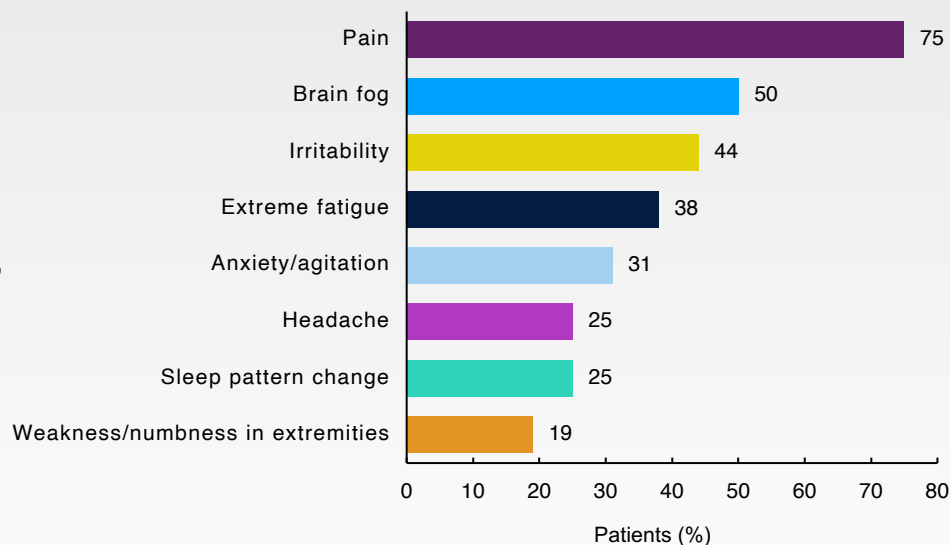
†Data not reported.

Reference: 1. Bonkovsky HL et al. *Am J Med.* 2014;127:1233-1241.

Patients With AHP May Experience Prodromal Symptoms Before an Attack

- In a National Institutes of Health (NIH)-sponsored longitudinal study of 16 patients with genetically documented AHP, 15 patients experienced recurrent AHP, defined as ≥ 4 attacks per year that required treatment¹
- Various prodromal symptoms were experienced by 100% of patients at least 24 hours before an attack involving severe, diffuse abdominal pain¹

Most Frequent Prodromal Symptoms ($\geq 19\%$) Experienced by Patients in NIH-Sponsored Trial (N=16)¹

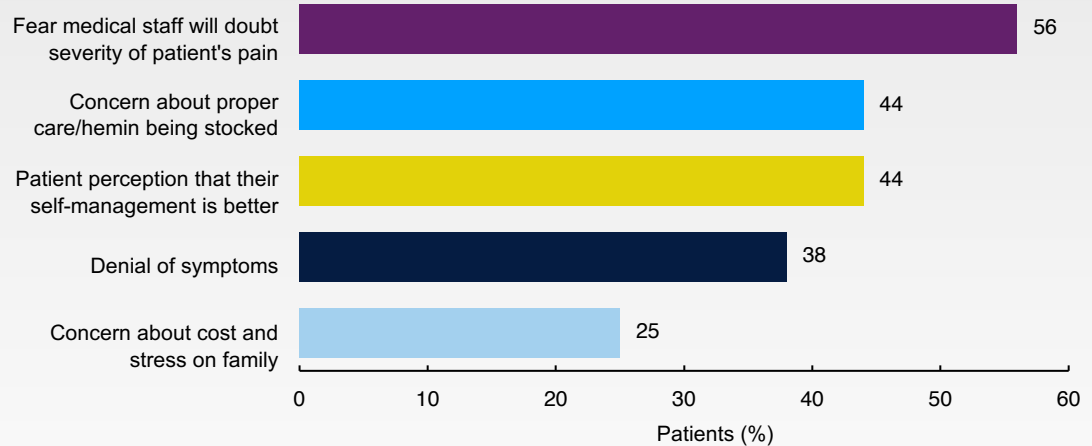


Reference: 1. Naik H et al. *Mol Genet Metab.* 2016;119:278-283.

Patients With AHP Symptoms May Delay Going to the Hospital for Medical Care

- In the same NIH-sponsored study, patients with AHP reported delaying seeking medical treatment despite prodromal symptoms¹
- Patients who had access to porphyria specialists and local knowledgeable physicians to manage their care had more favorable healthcare experiences¹

Top Reasons for Patients' Delay in Seeking Medical Treatment Despite Experience of Prodromal Symptoms in NIH-Sponsored Trial (N=16)¹



Reference: 1. Naik H et al. Mol Genet Metab. 2016;119:278-283.

Symptomatic AIP Is Associated With Chronic Impairment

Background

- A retrospective, population-based study of 356 patients with latent and manifest/symptomatic AIP in Sweden¹
 - Patients with latent AIP were defined as gene carriers with no history of AIP symptoms¹
 - Patients with manifest AIP experienced clinical symptoms during an attack, with 87% reporting at least 1 or 2 symptoms in addition to abdominal pain¹
 - Follow-up study assessed long-term disability/sick leave due to symptomatic AIP (N=133)¹
 - Mean age for receiving disability was 45 years (range 21-61 years)¹

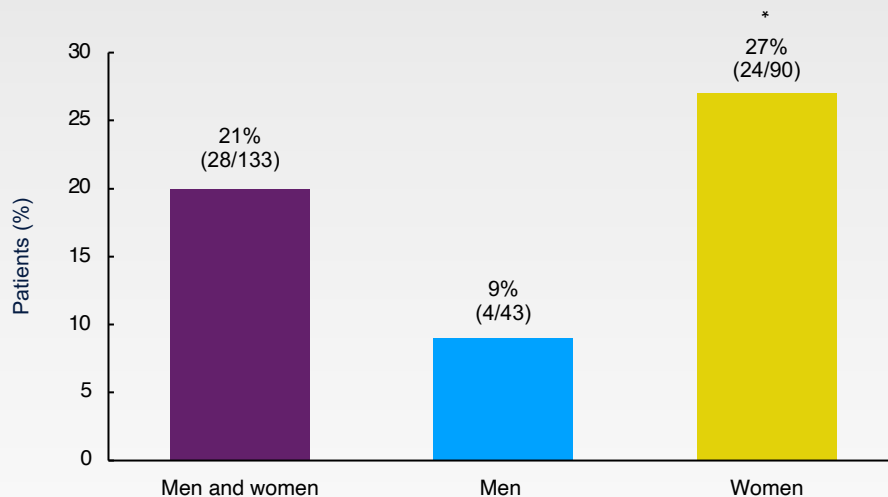
Results

- 54% of patients with long-term disability/sick leave reported >10 attacks¹
- 46% reported chronic impairment¹
- Levels of urinary PBG and ALA remained above upper reference limit of normal in 79% and 42% of patients, respectively, with long-term sick leave or disability¹

ALA=aminolevulinic acid; PBG=porphobilinogen.

Reference: 1. Bylesjö I et al. *Scand J Clin Lab Invest.* 2009;69:612-618.

Percentage of Symptomatic Patients According to Gender Claiming Long-Term Sick Leave or Disability Pension Due to AIP (N=133)¹



* $P < 0.05$ vs men.

EXPLORE Natural History Study: Patients With AHP Have Diminished Quality of Life—Even Between Attacks

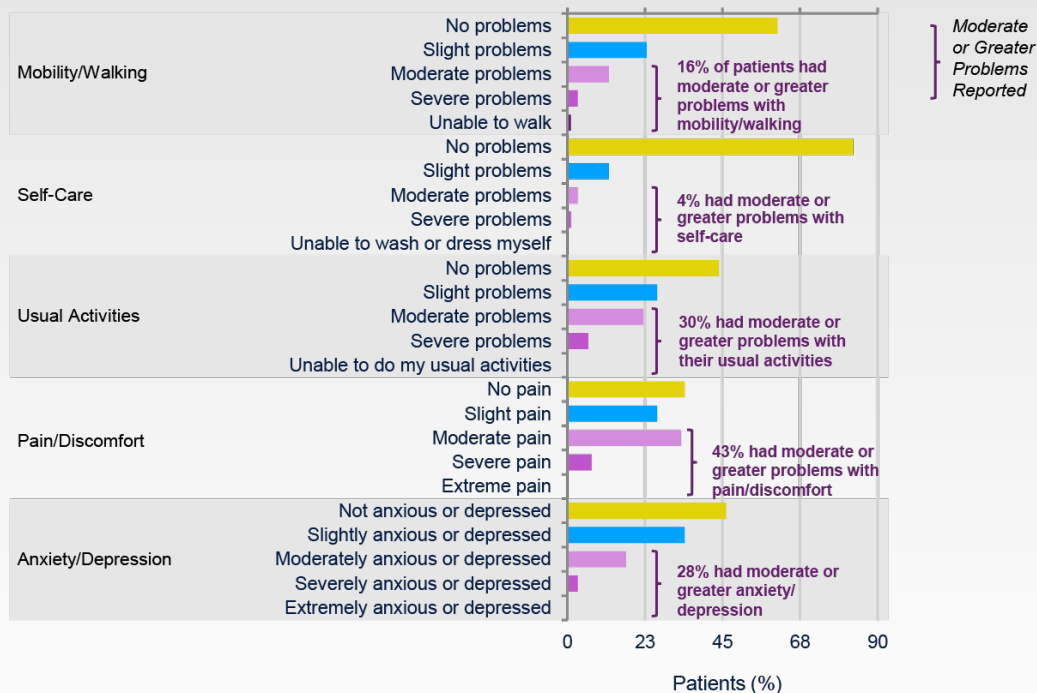
Background

- Patient-reported outcomes substudy of 73 patients with recurrent attacks who were surveyed using the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) assessment tool¹
 - Key eligibility criteria: ≥ 3 attacks per year or use of prophylactic treatment¹

Results

- The 0.78 EQ-5D-5L mean summary score was similar to diminished quality of life seen with common chronic diseases¹
 - 0.77 mean score in patients with ulcerative colitis³
 - 0.79 mean score in patients with chronic obstructive pulmonary disease (COPD)⁴

Rating of Quality of Life Parameters Between Attacks by People With AHP (N=74)²



References: 1. Gouya L et al. *Hepatology*. 2020;71(5):1546-1558. 2. Gouya L et al. ICPP 2017. Presentation OC13. 3. Van Assche G et al. *Dig Liver Dis*. 2016;48:592-600. 4. Lin F-J et al. *BMC Med Res Methodol*. 2014;14:1-12.

Recent Single-Center Study Demonstrated Diminished Quality of Life and Posttraumatic Stress Disorder Symptoms in Patients With AIP

Background

- 27 female patients of reproductive age with genetically confirmed AIP from mainland China were evaluated¹
 - Median 1.7 attacks in the past year
 - Compared with 2,410 healthy Chinese adults
- Quality of life assessment tool: Short Form-36 (SF-36, Chinese version)
- Posttraumatic stress disorder (PTSD) symptoms assessment: Impact of Event Scale–Revised (IES-R)

Results

- Patients with AIP had significantly lower scores compared with the general population on 2 components of SF-36: physical functioning and mental health¹
- Patients with AIP had significantly higher scores on the IES-R ($P<0.001$), indicating PTSD symptoms¹
 - In a qualitative assessment, some patients stated that they were fearful of future attacks and even of menses as a potential precipitating factor

Comparison of SF-36 Subscale Scores in 27 Women With Confirmed AIP vs Historical Healthy Controls¹

Scale	Score in Patients With AIP*	Norm-Based Score* (N=2410)	P value
Physical functioning	85.74 ± 11.67	91.83	0.01
Role physical	64.81 ± 57.74	82.43	0.13
Bodily pain	77.96 ± 22.81	83.98	0.18
General health	51.67 ± 25.84	55.98	0.39
Vitality	57.96 ± 18.96	60.27	0.53
Social functioning	85.65 ± 23.44	91.19	0.23
Role emotional	69.13 ± 54.64	71.62	0.81
Mental health	65.19 ± 19.15	72.79	0.049

*Scores for each category range from 0 to 100, where 100 represents the best health status.

Reference: 1. Yang J et al. *Biomed Res Int.* 2018;2018:1-6.

Reproduced with permission from Yang J et al. *Biomed Res Int.* 2018;2018:1-6.

Long-Term Complications Associated With AHP

Primary liver cancer (PLC)



In national cohort studies:

- Multiple studies have shown that symptomatic patients have 30 to 100x higher risk of PLC over the lifetime of AHP patients vs controls^{1-4*}
 - In a nationwide cohort study of 251 patients with AHP, the annual incidence rate of PLC was 0.35% compared to 0.003% in reference controls¹
- 36x higher risk of HCC over 7 years among AHP gene carriers vs controls^{2†}

HCC=hepatocellular carcinoma.

*Historical cohort study in 251 Norwegian patients with AHP vs reference controls.¹

†Prospective French cohort study in 650 AHP gene carriers vs reference controls followed for 7 years.²

Chronic kidney disease (CKD)



In European and US clinical studies:

- Up to 64% of symptomatic AHP patients had CKD^{5-7‡§||}
- ALA and PBG are associated with nephrotoxicity in patients with AIP^{7,8}

‡Retrospective Dutch case-controlled study (N=88) in patients with recurrent AIP attacks (>4/year) vs occasional attacks (1-4/year) or no attacks.⁶

§Among symptomatic AIP patients (n=74) in a 10-year follow-up to a 2003 French population-based study of AIP gene carriers (N=415).⁷

||Based on 90 patients with AIP in an observational study of 108 patients with AHP from the US Porphyria Consortium.⁵

References: 1. Baravelli CM et al. *J Intern Med.* 2017;282:229-240. 2. Andant C et al. *J Hepatol.* 2000;32:933-939. 3. Sardh E et al. *J Inherit Metab Dis.* 2013;36:1063-1071. 4. Kauppinen R et al. *Br J Cancer.* 1988;57:117-120. 5. Bonkovsky HL et al. *Am J Med.* 2014;127:1233-1241. 6. Neeleman RA et al. *J Inherit Metab Dis.* 2018;41:809-817. 7. Pallet N et al. *Kidney Int.* 2015;88:386-395. 8. Pallet N et al. *Clin Kidney J.* 2018;11:191-197.

Long-Term Complications Associated With AHP (cont'd)

Hypertension

In published reports:

- 60% to 70% of patients with AHP had chronic sustained hypertension^{1,2*†}
- Hypertension may be due, in part, to dysautonomia related to AHP³
- As the risk of hypertension is high in the general population, further research is required to detect the true excess risk in patients with AHP⁴



Anxiety, Depression, and Suicidality

- Patients with AHP may have an increased risk of suicide related to comorbidities of psychiatric symptoms and chronic pain⁵
- ### *In national cohort studies:*
- 22% of patients reported moderate or severe anxiety, and 15% reported moderate or severe depression^{6‡}
 - High rates of suicide were observed among patients with AIP over a 50-year period (1940 to 1988)^{5§}
 - 10% (5/50) of deaths were by suicide
 - The suicide rate was 3.7% (5/136), 370x that of the general population^{||}



*Retrospective Dutch case-controlled study (N=88) in patients with recurrent AIP attacks (>4/year) vs occasional attacks (1-4/year) or no attacks.¹

†Among symptomatic patients with AIP (n=74) in a 10-year follow-up to a 2003 French population-based study of AIP gene carriers (N=415).²

‡Questionnaire survey of 138 adults in the UK who tested positive for porphyria. The study focused on mental health, including anxiety and depression.⁶

§Retrospective study examining the prognosis of patients with AIP (N=136) in the US who were hospitalized for porphyric attacks.⁵

||Rates were compared using US census numbers from 1970.⁵

References: 1. Neeleman RA et al. *J Inherit Metab Dis*. 2018;41:809-817. 2. Pallet N et al. *Kidney Int*. 2015;88:386-395. 3. Pallet N et al. *Clin Kidney J*. 2018;11:191-197. 4. Stewart MF. *J Clin Pathol*. 2012;65:976-980. 5. Jeans JB et al. *Am J Med Genet*. 1996;65:269-273. 6. Millward LM et al. *J Inherit Metab Dis*. 2005;28:1099-1107.

Clinical and Lifestyle Burden of AHP

Clinical burden of disease

- AHP—a group of rare genetic diseases associated with acute attacks involving severe, diffuse abdominal pain (neurovisceral pain)^{1,2}
- AHP features a combination of symptoms such as nausea and vomiting, limb weakness or pain, anxiety, and more^{3,4}

Challenges with diagnosis

- Patients are frequently misdiagnosed with other more common diseases or undiagnosed^{5,6}
- Delay in diagnosis can result in multiple hospitalizations and unnecessary surgeries⁶

Lifestyle burden of disease

- Patients with AHP can have a high burden of disease, which limits employment, daily functioning, and quality of life⁷⁻¹⁰
- Long-term complications associated with AHP may include chronic kidney disease, hypertension, hepatocellular carcinoma, and psychological problems^{6,11-15}

References: 1. Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26. 2. Ramanujam V-MS, Anderson KE. *Curr Protoc Hum Genet*. 2015;86:17.20.1-17.20.26. 3. Anderson KE et al. *Ann Intern Med*. 2005;142(6):439-450. 4. Ventura P et al. *Eur J Intern Med*. 2014;25(6):497-505. 5. Ko JJ et al. ACG 2018. Poster. 6. Bonkovsky HL et al. *Am J Med*. 2014;127:1233-1241. 7. Naik H et al. *Mol Genet Metab*. 2016;119:278-283. 8. Simon A et al. *Patient*. 2018;11:527-537. 9. Bylesjö I et al. *Scand J Clin Lab Invest*. 2009;69:612-618. 10. Gouya L et al. ICPP 2017. Presentation. 11. Neeleman RA et al. *J Inherit Metab Dis*. 2018;41:809-817. 12. Pallet N et al. *Kidney Int*. 2015;88:386-395. 13. Andant C et al. *J Hepatol*. 2000;32:933-939. 14. Jeans JB et al. *Am J Med Genet*. 1996;65:269-273. 15. Millward LM et al. *J Inherit Metab Dis*. 2005;28:1099-1107.