MODULE
04

Patient Burden of Acute Hepatic Porphyria (AHP)

Alnylam PHARMACEUTICALS

The Burden of Disease for Patients in Their Own Words

The many dimensions of AHP adversely affecting patients' lives:

- Debilitating symptoms[1-3]
- Once an attack occurs, patients generally feel under constant threat of another[3]
- Patients' daily functioning is negatively impacted with increased disability and decreased employment[2-5]
  - 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.

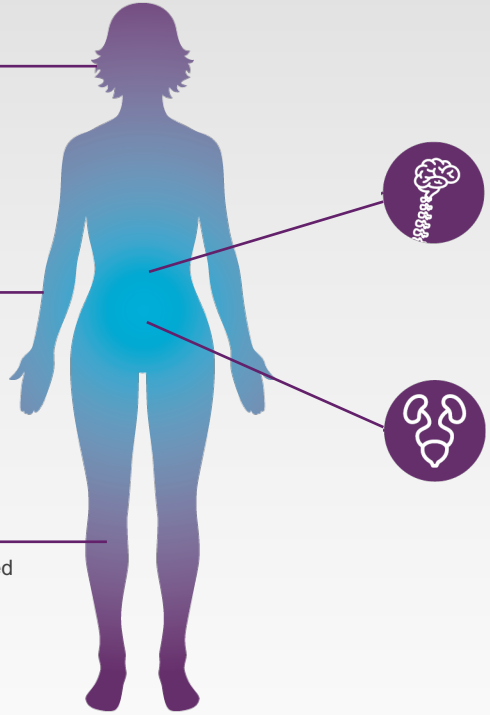
> **It's completely unpredictable**. There's no way I could be a reliable employee to somebody because I could not guarantee that I will be there tomorrow for work."
>
> Simon A, et al. Patient. 2018.

> 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



CENTRAL[1-3]
anxiety, depression, confusion, seizures, hallucinations, insomnia

PERIPHERAL[1,2]
muscle weakness, neuropathic pain in limbs, sensory loss, paralysis, respiratory paralysis

CUTANEOUS[2]
chronic, blistering lesions on sun-exposed skin primarily occur in hereditary coproporphyria (HCP) and variegate porphyria (VP)

AUTONOMIC[1,2]
nausea and vomiting, systemic arterial hypertension, tachycardia, constipation, severe diffuse abdominal pain, diarrhea, pain in back or chest

OTHER COMMON AHP SYMPTOMS[2,4]
hyponatremia, dark or reddish urine

*There are 4 types of AHP. Around 80% of cases are acute intermittent porphyria (AIP), followed by variegate porphyria (VP), hereditary coproporphyria (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.

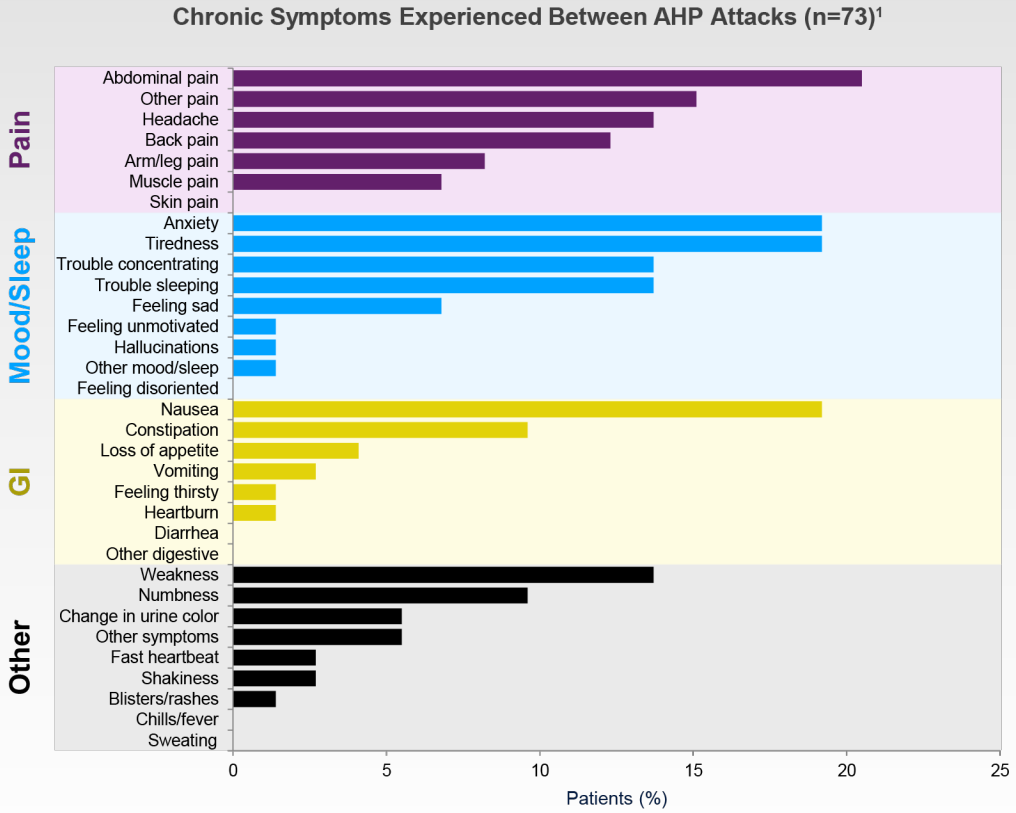
Symptoms of AHP Can Occur Chronically, Between Attacks

Methods

- EXPLORE study—an observational, multinational, prospective, natural history study of 112 people living with recurrent attacks of AHP[1]
- Key eligibility criteria
  - ≥3 attacks per year or use of prophylactic treatment[1]

Results

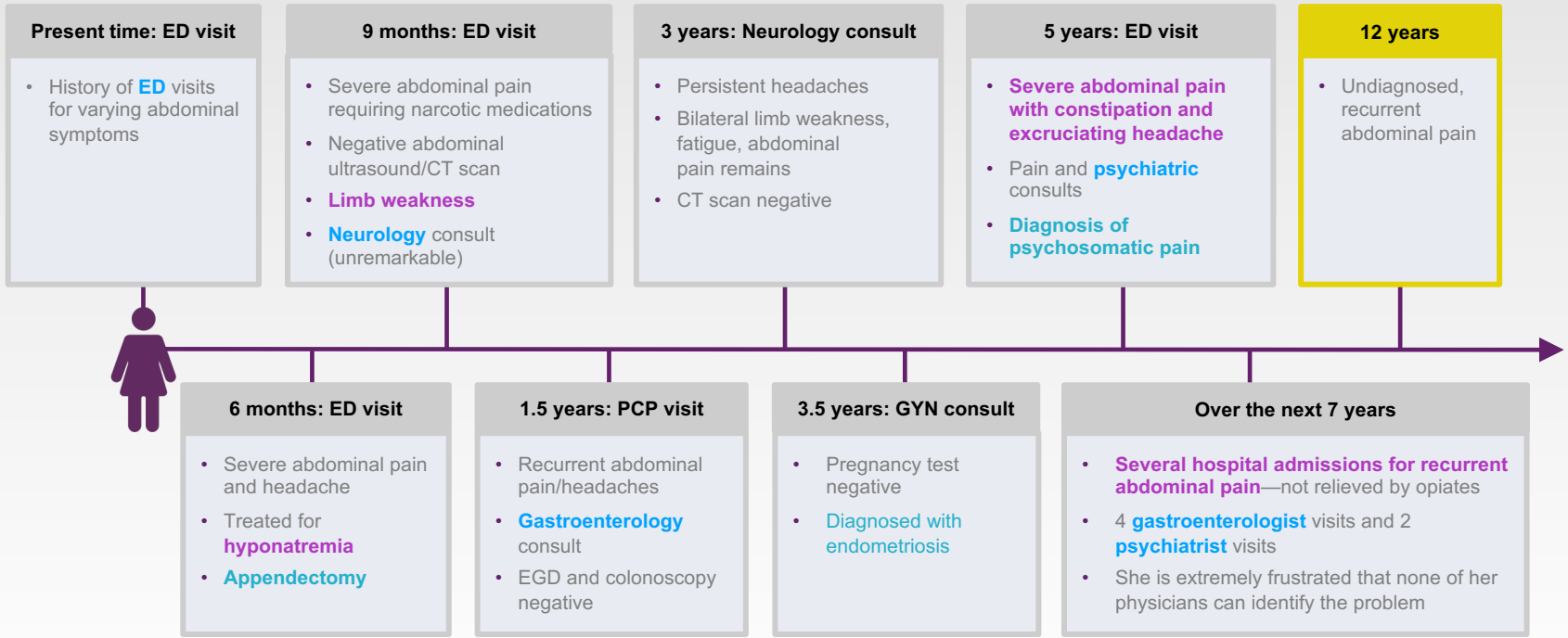
- 65% of patients reported chronic symptoms in between attacks (including pain)[1]
  - Some of these patients were treated with hemin or opioid prophylaxis[1]
- 46% of patients reported experiencing chronic symptoms every day[1]



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

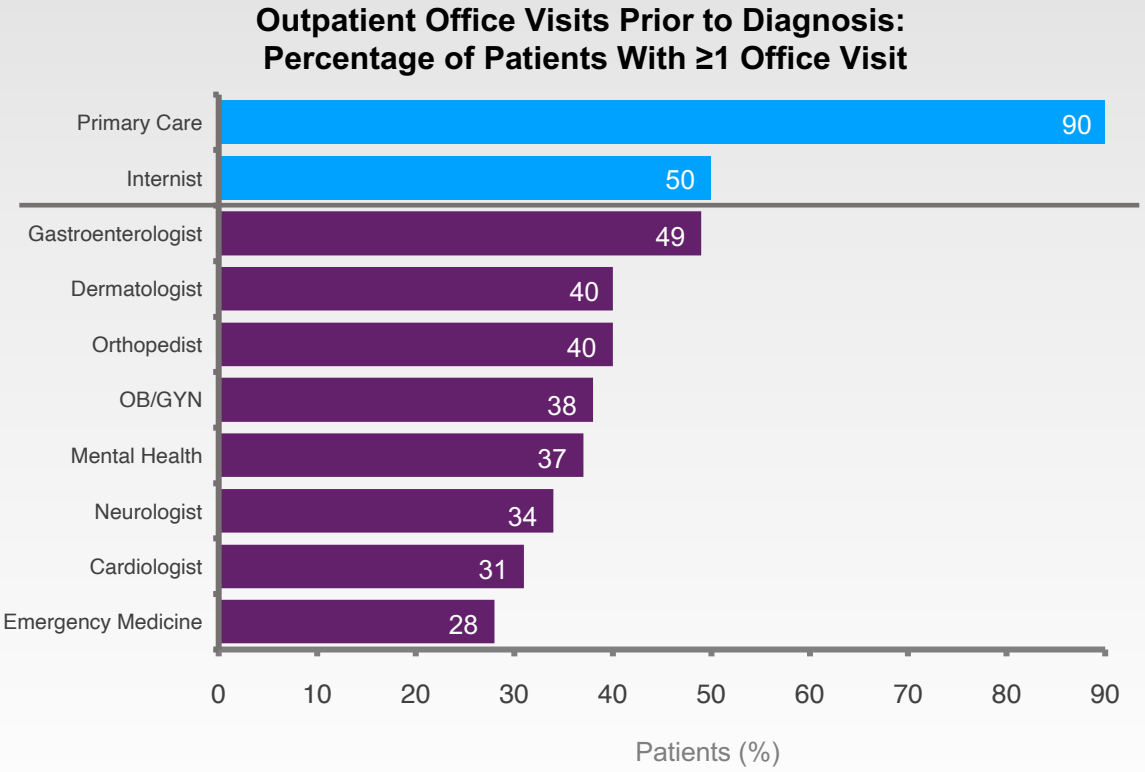
An Example of the Frustrating Journey of a Patient With AHP

Different specialties the patient may see | **Key signs and symptoms** | **Misdiagnosis**



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

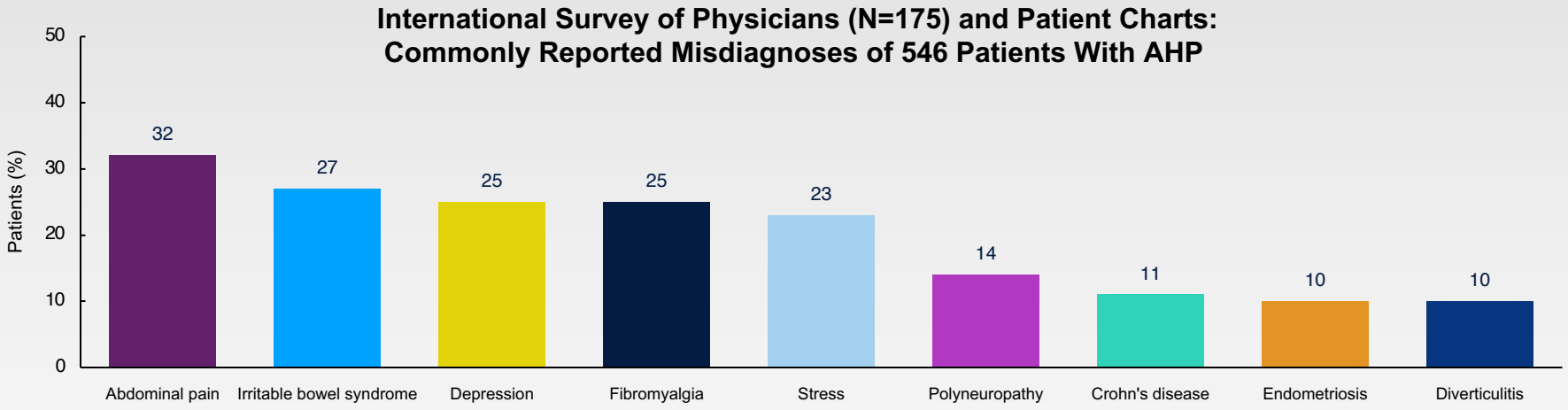
Patients With AHP Generally See Multiple Specialists Prior to Diagnosis



- Patients with AHP usually see multiple specialists prior to their diagnosis[1]
  - 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 assessed[1]
- 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 gastroenterologist[1]
  - These patients were seen on average 3.3 times during the observation period[1]

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 Common[1]

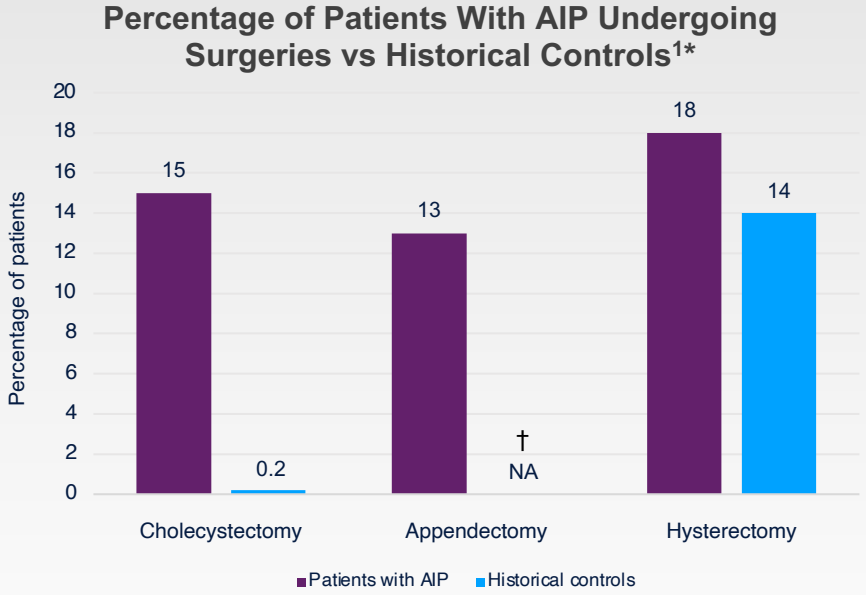


- A retrospective analysis of 546 AHP patient charts from 175 physicians from the United States, Europe, Canada, and Japan found that about 1 in 3 patients was correctly diagnosed with AHP[1]
  - The most common HCP specialists were gastroenterologists, neurologists, and hepatologists[1]
- A total of 26% of patients with AHP were initially misdiagnosed, and 31% were diagnosed correctly[1]
  - 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 misdiagnoses[1]

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 Prediagnosis[1]

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



*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]

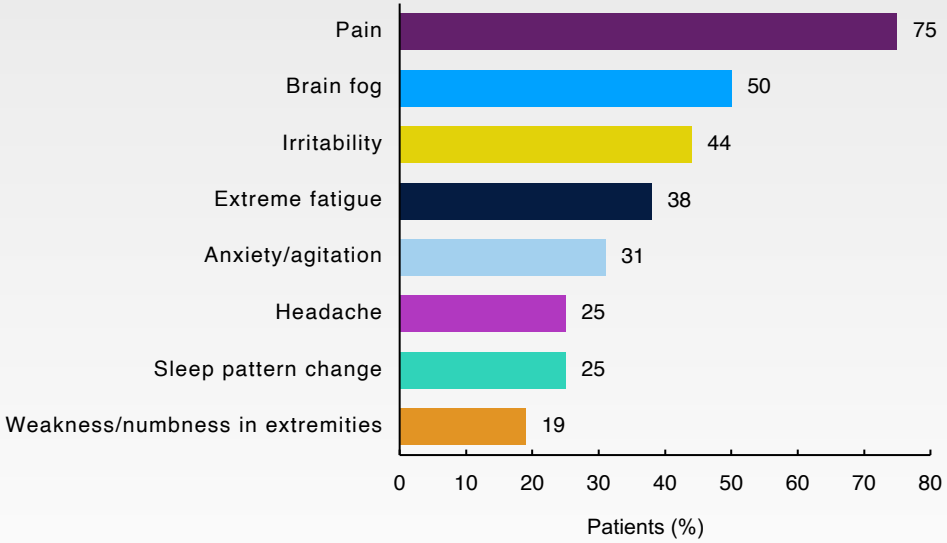
†Data not reported.

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 treatment[1]
- Various prodromal symptoms were experienced by 100% of patients at least 24 hours before an attack involving severe, diffuse abdominal pain[1]

Most Frequent Prodromal Symptoms (≥19%) Experienced by Patients in NIH-Sponsored Trial (N=16)[1]

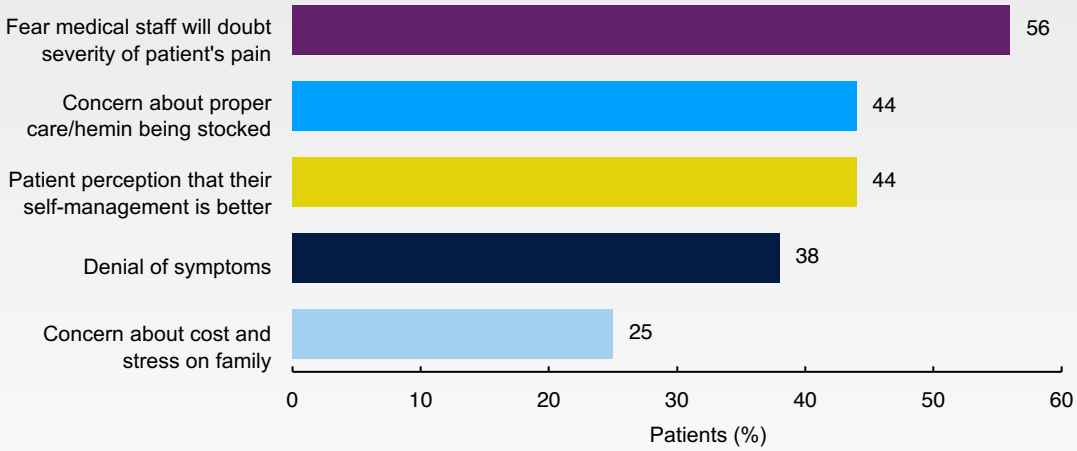


Reference: 1. Naik H et al. *Mol Genet Metab.* 2016;119:278-283.

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 symptoms[1]
- Patients who had access to porphyria specialists and local knowledgeable physicians to manage their care had more favorable healthcare experiences[1]

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

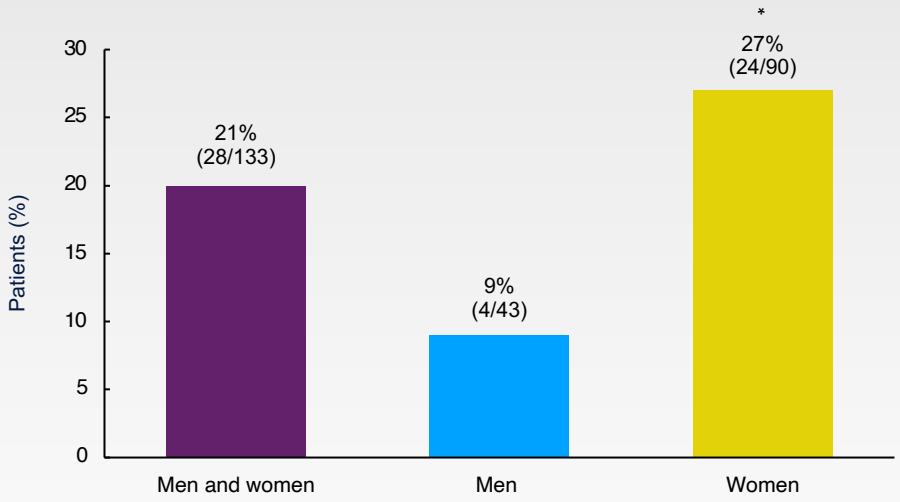
Background

- A retrospective, population-based study of 356 patients with latent and manifest/symptomatic AIP in Sweden[1]
  - Patients with latent AIP were defined as gene carriers with no history of AIP symptoms[1]
  - Patients with manifest AIP experienced clinical symptoms during an attack, with 87% reporting at least 1 or 2 symptoms in addition to abdominal pain[1]
  - 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 attacks[1]
- 46% reported chronic impairment[1]
- 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 disability[1]

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.

ALA=aminolevulinic acid; PBG=porphobilinogen.

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

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

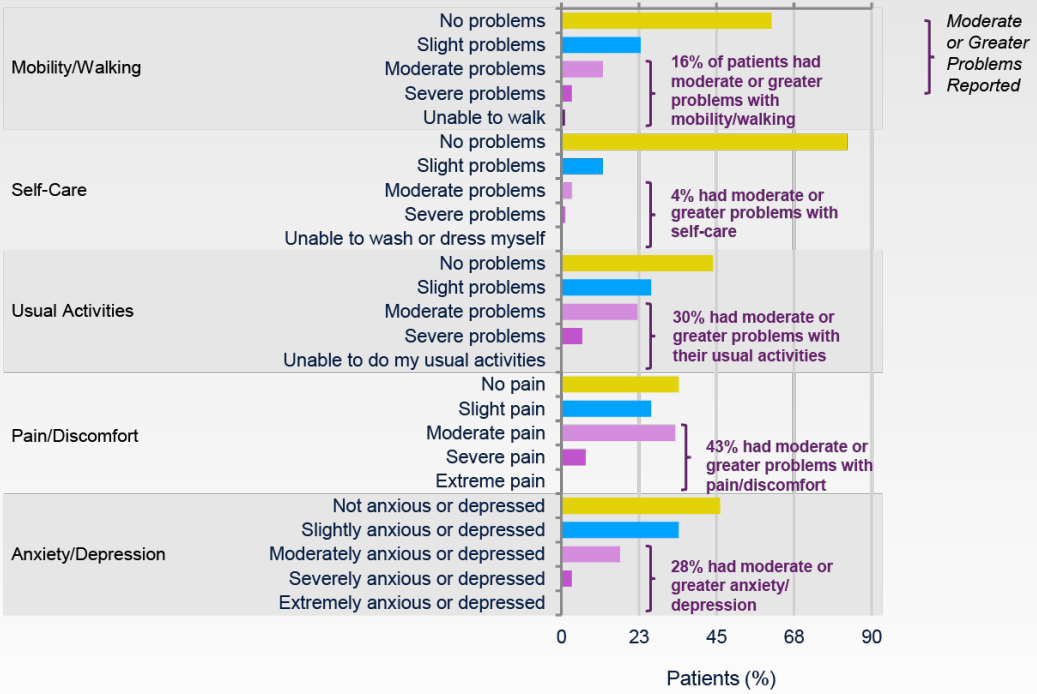
Background

- 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 tool[1]
  - Key eligibility criteria: ≥3 attacks per year or use of prophylactic treatment[1]

Results

- The 0.78 EQ-5D-5L mean summary score was similar to diminished quality of life seen with common chronic diseases[1]
  - 0.77 mean score in patients with ulcerative colitis[3]
  - 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 evaluated[1]
  - 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 health[1]
- Patients with AIP had significantly higher scores on the IES-R (P<0.001), indicating PTSD symptoms[1]
  - 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 Controls[1]

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.

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 controls[1]
- 36x higher risk of HCC over 7 years among AHP gene carriers vs controls[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]

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]

‡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 AHP[3]
- As the risk of hypertension is high in the general population, further research is required to detect the true excess risk in patients with AHP[4]

Anxiety, Depression, and Suicidality

- Patients with AHP may have an increased risk of suicide related to comorbidities of psychiatric symptoms and chronic pain[5]

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 surgeries[6]

Lifestyle burden of disease

- Patients with AHP can have a high burden of disease, which limits employment, daily functioning, and quality of life[7-10]
- 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.