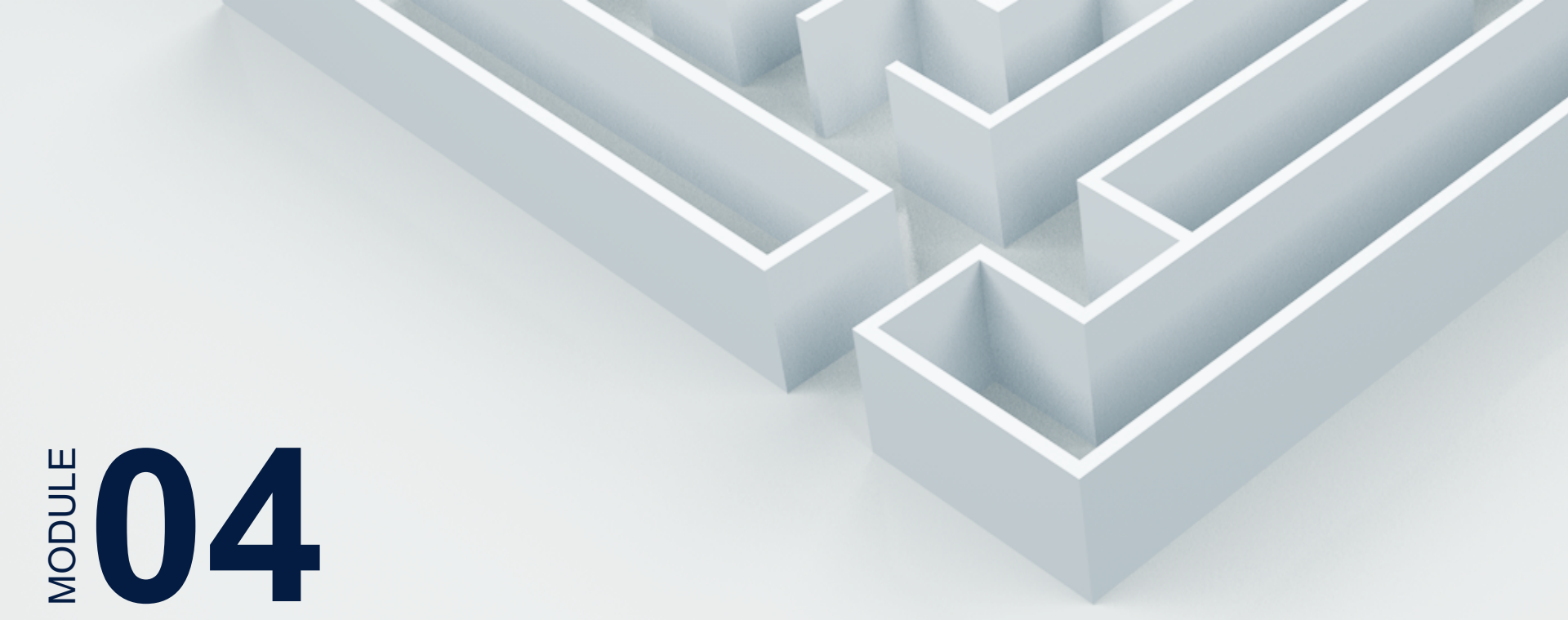


MODULE 04

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.

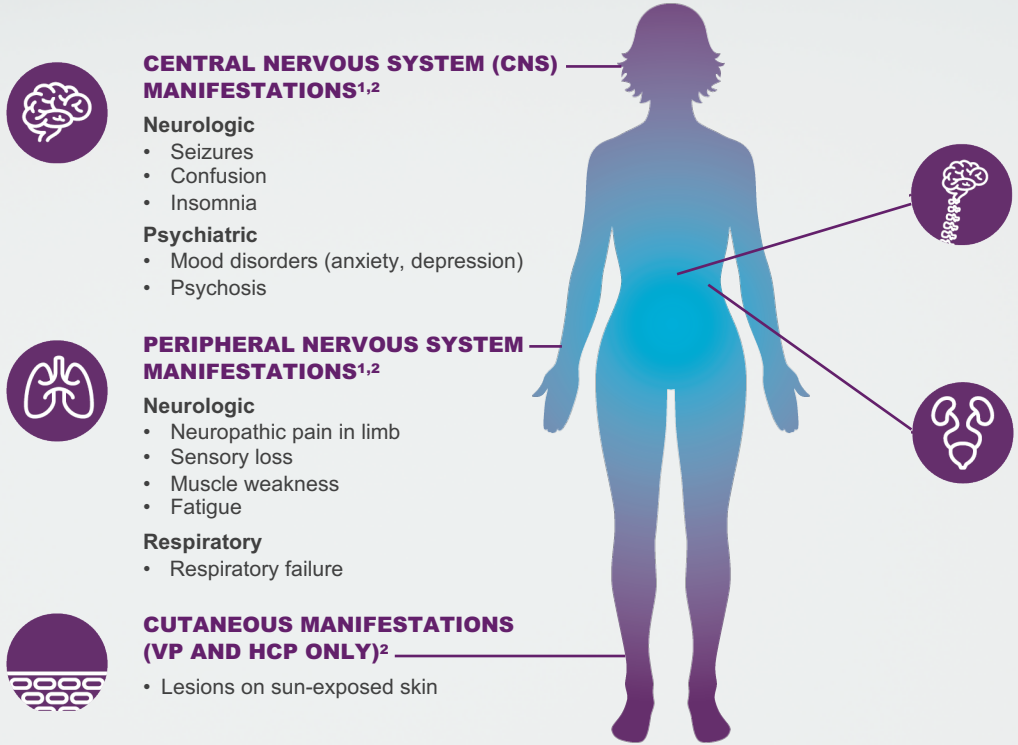
> "**It's completely unpredictable.** There's no way I could be a reliable employee to somebody because I could not guarantee that I will be there tomorrow for work."
>
> Simon A et al. *Patient*. 2018.

> "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.

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.

Multisystem Signs and Symptoms That May Be Associated with AHP



CENTRAL NERVOUS SYSTEM (CNS) MANIFESTATIONS[1,2]

Neurologic
- Seizures
- Confusion
- Insomnia

Psychiatric
- Mood disorders (anxiety, depression)
- Psychosis

PERIPHERAL NERVOUS SYSTEM MANIFESTATIONS[1,2]

Neurologic
- Neuropathic pain in limb
- Sensory loss
- Muscle weakness
- Fatigue

Respiratory
- Respiratory failure

CUTANEOUS MANIFESTATIONS (VP AND HCP ONLY)[2]

- Lesions on sun-exposed skin

AUTONOMIC NERVOUS SYSTEM MANIFESTATIONS[1,2]

Gastrointestinal
- Severe, diffuse abdominal pain, nausea, vomiting, constipation, diarrhea

Cardiovascular
- Hypertension
- Tachycardia

OTHER MANIFESTATIONS[1,2]

- Hyponatremia
- Reddish dark urine

HCP=hereditary coproporphyria; VP=variegate porphyria.

1. Pischik E, Kauppinen R. *Appl Clin Genet.* 2015;8:201-214. **2.** Anderson KE et al. *Ann Intern Med.* 2005;142:439-450.

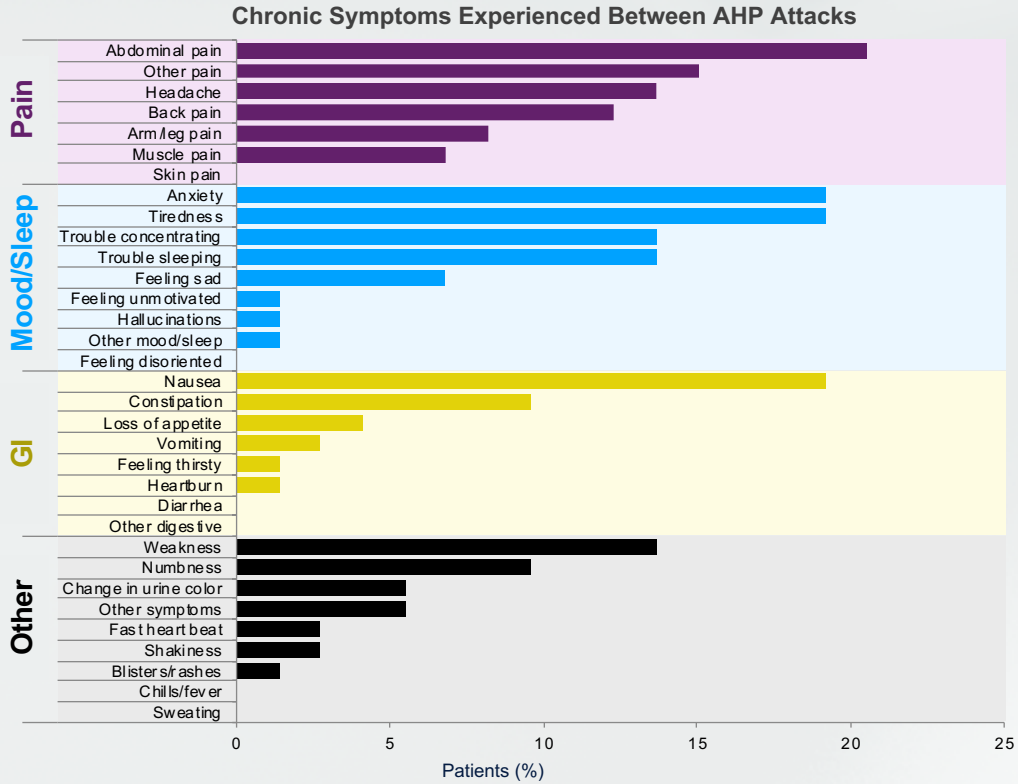
Chronic Symptoms Can Occur in Some Patients with AHP

Methods

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

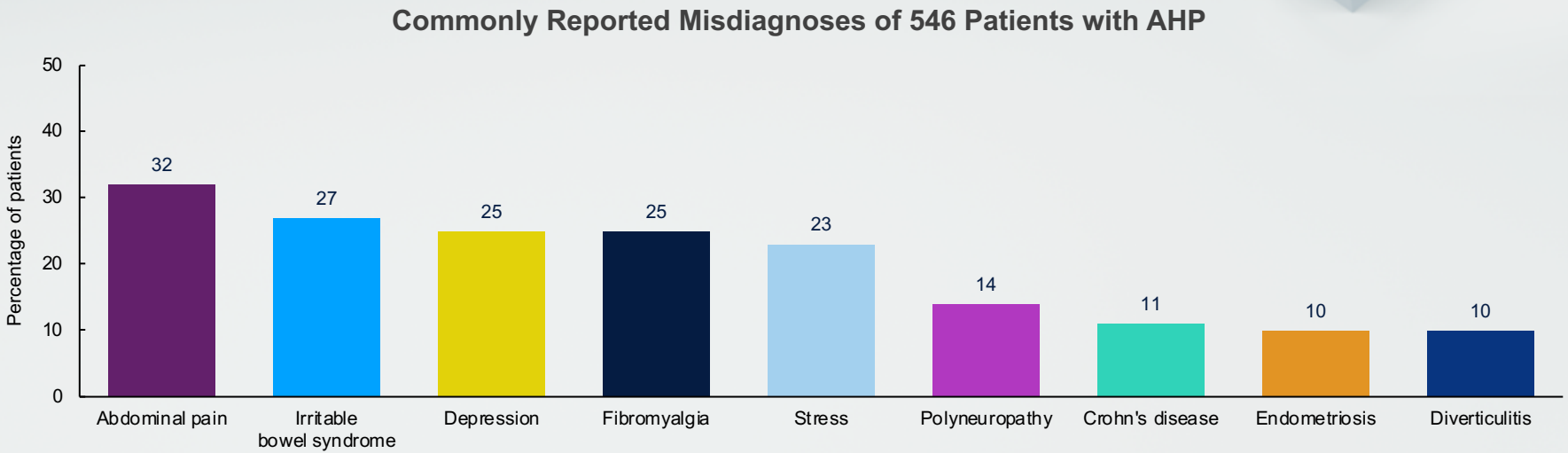
Results

- 46% of patients reported daily symptoms
- 65% of patients reported chronic symptoms in between frequent attacks
  - Some of these patients were treated with hemin or opioid prophylaxis



Bonkovsky HL et al. AASLD 2018. Poster.

Misdiagnosis of Patients with AHP Is Relatively Common

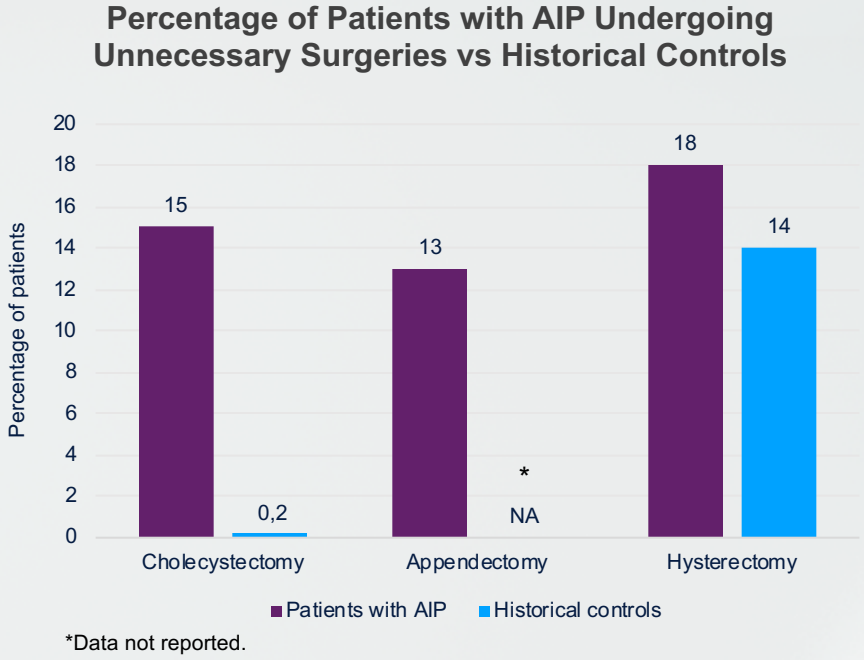


- From a retrospective review of 546 AHP patient charts submitted by 175 healthcare providers (HCPs) from the US, EU, Canada, and Japan
  - The most common HCP specialists were gastroenterologists, neurologists, and hepatologists
- 26% of patients with AHP were initially misdiagnosed while 31% were initially diagnosed correctly
  - 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

Ko JJ et al. ACG 2018. Poster.

Misdiagnosis or Delayed Diagnosis Can Involve Multiple Hospitalizations and Unnecessary Surgeries

- In an observational study of 108 patients with documented AHP from the US Porphyria Consortium
  - 90 patients had acute intermittent porphyria (AIP), the most common AHP
  - Diagnosis was delayed by a mean of 15 years
  - Among patients who reported a history of prior hospitalization, 55% were hospitalized 1 to 5 times in their lifetimes for attacks
  - Significantly more patients with AIP experienced unnecessary cholecystectomies ($p<0.0001$) compared to age and sex matched controls



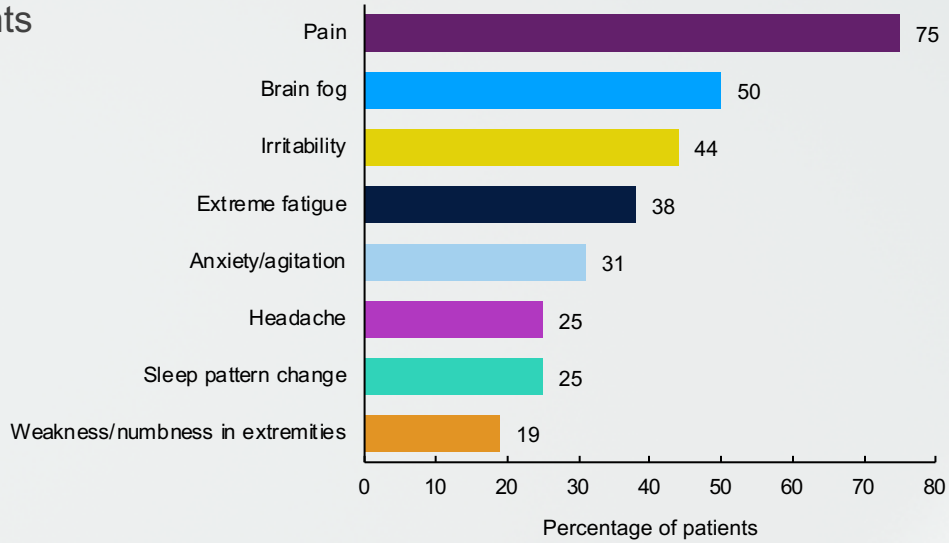
*Data not reported.

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

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

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

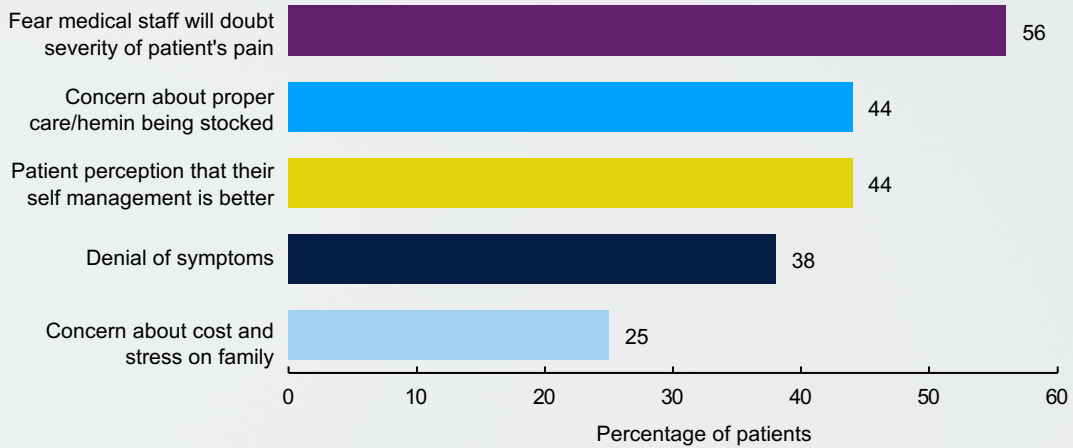


Naik H et al. *Mol Genet Metab.* 2016;119:278-283.

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

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

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



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

Symptomatic AIP Associated with Chronic Impairment

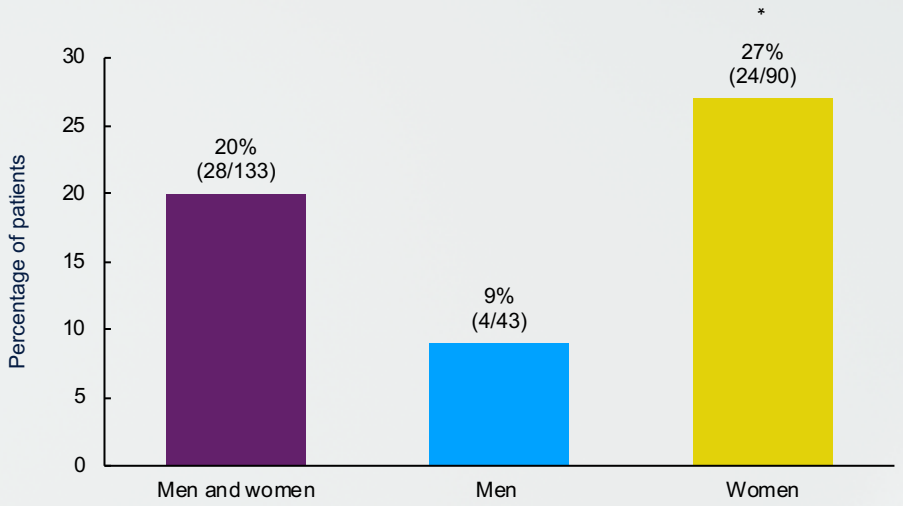
Background

- A retrospective, population-based study of 356 latent and manifest/symptomatic AIP patients in Sweden over 4 years
  - Latent AIP patients were defined as gene carriers with no history of AIP symptoms
  - Manifest AIP patients experienced clinical symptoms during an attack, with 87% reporting at least 1 or 2 symptoms in addition to abdominal pain
  - Follow-up study assessed long-term disability/sick leave due to symptomatic AIP (N=133)
  - Mean age for receiving disability was 45 years (range 21-61 years)

Results

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

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



*$p<0.05$ vs men.

ALA=aminolevulinic acid; PBG=porphobilinogen.

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

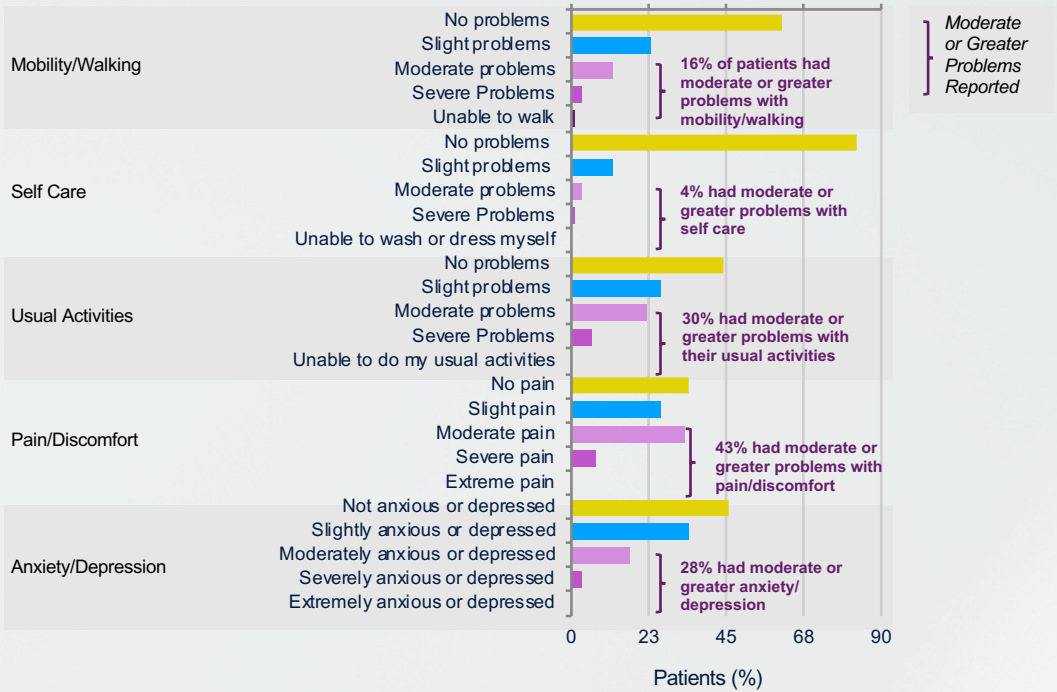
Background

- Patient-reported outcomes substudy of 74 recurrent attack patients 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

Results

- The 0.80 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[2]
  - 0.79 mean score in patients with chronic obstructive pulmonary disease (COPD)[3]

Rating of Quality of Life Parameters Between Attacks by People with AHP (N=74)[1]



1. Gouya L et al. ICPP 2017. Presentation OC13. **2.** Van Assche G et al. *Dig Liver Dis.* 2016;48:592-600. **3.** 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
  - Median 1.7 attacks in the past year
  - Compared to 2410 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

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

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

Comparison of SF-36 Subscale Scores in 27 Women with Confirmed AIP vs Historical Healthy Controls

Scale	Score in AIP Patients*	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.

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Clinical and Lifestyle Burden of AHP

Clinical burden of disease

- AHP—a group of rare genetic diseases almost universally associated with acute attacks involving severe, diffuse abdominal pain (neurovisceral pain)[1,2]

Challenges with diagnosis

- Patients are frequently misdiagnosed with other more common diseases (26% in one recent study) or undiagnosed[3,4]
- Delay in diagnosis can result in multiple hospitalizations and unnecessary surgeries[4]

Lifestyle burden of disease

- Patients with AHP can have a high burden of disease, which limits employment, daily functioning, and quality of life[5-8]

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**. Ko JJ et al. ACG 2018. Poster.
4. Bonkovsky HL et al. *Am J Med.* 2014;127:1233-1241. **5.** Naik H et al. *Mol Genet Metab.* 2016;119:278-283. **6**. Simon A et al. *Patient.* 2018:11:527-537.
7. Bylesjö I et al. *Scand J Clin Lab Invest*. 2009;69:612-618. **8**. Gouya L et al. ICPP 2017. Presentation.