A Qualitative Analysis of Disease Burden in Patients with Acute Intermittent Porphyria and Recurrent Attacks

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Background, Objective and Methods

Acute Intermittent Porphyria (AIP)

- Rare, serious, life-threatening metabolic disorder caused by genetic mutation in heme biosynthesis, resulting in elevated levels of neurotoxic porphyrin precursors porphobilinogen (PBG) and 5-aminolevulinate (ALA)[1]
- Characterized by occurrence of acute disabling neurovisceral attacks, requiring hospitalizations (average length of stay 5-7 days), and also by chronic debilitating disease symptoms that have significant impact on patients' daily functioning and quality of life [2]
- Disease course often results in chronic use of narcotics, high rates of unemployment, and increased risk of severe depression and suicidality[3]
- Most severe patients (5-10%) have recurrent attacks (≥ 4 per year)[4]
- Clinical aspects of acute attacks include severe abdominal pain, nausea, vomiting, hypertension, tachycardia, neuropathy and fatigue[5]
- Experience of AIP from the patient perspective is limited[6]

Objective

- Characterize overall symptom experience and disease impact of AIP from the perspective of patients living with AIP with recurrent attacks

Study population

- Adults, ≥18 years of age diagnosed with AIP by a porphyria specialist
- ≥ 3 porphyria attacks over last 12 months, at least 1 requiring hemin treatment OR currently receiving hemin treatment prophylactically to prevent attacks
- Cognitive and linguistic abilities necessary to participate in interview (English-speaking)

Methods

- Patients recruited in partnership with American Porphyria Foundation, a patient advocacy group
- 2-hour telephone interviews using semi-structured interview guides with open-ended questions about AIP and symptom experiences both acutely (during an attack) and chronically (in between attacks) and impact of AIP on patients' lives

Analysis

- Interviews anonymized, transcribed and coded qualitatively using inductive coding[7]
- Transcripts analyzed chronologically, saturation analysis conducted to determine whether little to no information emerged in last set of interviews

Results

Participant Characteristics

Table 1. Participant demographics and clinical information

Characteristics	Total (n=19)
Age	
Mean (SD); range	39.8 years (±11.1); 24-61
Gender	
Female	15 (79%)
Male	4 (21%)
Porphyria diagnosis	
<3 years ago	5 (26%)
3 – 10 years ago	10 (53%)
≥ 10 years ago	4 (21%)
Taking hemin prophylactically	
Yes	11 (58%)
No	8 (42%)
Number of patients reporting chronic symptoms between attacks	
Symptoms between attacks	18 (95%)
Taking pain medication between attacks	
Yes	12 (63%)
No	7 (37%)

Attack experience

- Attacks were described as extreme events having progressive and uncontrollable symptoms that preclude usual daily activities
- Attacks generally last 3-5 days and require hospitalization/treatment
- Most common symptoms during attacks reported include pain (100%), nausea (42%), memory loss (21%) and vomiting (16%) (**Figure 1**)
- Additional reported attack symptoms included flu-like symptoms, headache, numbness, tingling, limb weakness, paralysis and seizures

Figure 1. Patient experience of porphyria attacks

"…and then the worst days is like being disemboweled, having a hot pan shoved into your intestines or into your abdomen while having your ribs filleted" (Patient 03)

"I'll lose feelings in my hands and my stomach will be - it feels like someone's kicking me in the stomach. It's very, very sore and very tender. And then my liver area will start burning really badly. I can't eat because anything that I eat will come back up. And, I'm dizzy at times and disoriented and the biggest thing is that it robs me of my quality of life" (Patient 01)

"I had seizures after seizures … about three of them within about four hours" (Patient 8)

"I had like paralysis also in my legs, and I couldn't walk. I mean like I was dragging a leg. And also I had difficulty breathing. I almost got put on the ventilator" (Patient 16)

"I describe mine as having the worst flu you ever had in your life, that whole body ache and everything else that goes along with it and multiply that by about a hundred times" (Patient 02)

Chronic disease symptoms between attacks

- 18/19 patients reported chronic symptoms
- Most frequently reported were include pain, neuropathy (numbness or tingling), nausea, insomnia, numbness, tingling, and fatigue (**Table 2**)

Table 2. Number of patients reporting each chronic AIP symptoms

Chronic AIP symptom codes	N (%)
Pain	17 (90%)
"Neuropathy"*	9 (47%)
Nausea	7 (37%)
Insomnia, or Numbness, or Tingling with Crawling Sensation	6 (32%)
Fatigue**	5 (26%)
Flu-like, or Lack of energy**, or Memory loss, or Tired**, or Weakness	4 (21%)
Fatigability**, or Hypersensitivity, or Paralysis	3 (16%)
Bowel obstruction, or Cognitive processing problems, or Concentration, or Constipation, or Dizziness, or Itching, or Loss of appetite, or Photosensitivity	2 (11%)
Confusion, or Diarrhea, or Exhausted, or Heat sensitivity, or Muscle weakness, or Rapid heartbeat, or Shortness of breath, or Swelling, or Tightness, or Urine color changes, or Vomiting	1 (5%)

*Neuropathy coded as a unique concept as patients used it to describe symptom experience. It was double coded within "neuropathy" as well as specific symptoms such as tingling, numbness
** While these concepts fall within larger fatigue experience, these are distinct, patient-reported aspects of fatigue; terms are not necessarily interchangeable

Pain is a cardinal symptom experienced during and between attacks

- 19/19 reported pain during attacks, 17/19 reported chronic pain
- 13/19 reported pain (attack or chronic) as most bothersome symptom
- Attack pain described as 'severe' and 'completely incapacitating'
- Many patients spontaneously assigned acute and chronic pain a 1-10 rating; 2-6 range is 'good' or 'typical' day living with porphyria (**Figure 2**)

Figure 2. Patient experiences with pain during acute attacks and chronic pain in between attacks

Acute pain (blue boxes)

"… it's always a belly pain, and then I would get weak in the hands and I couldn't stand up on my own … I'll be in so much pain that I won't be able to move" (Patient 10)

"It's a real hot feeling like it feels like there's hot coals packed in there. And it feels like someone's like poking in more of them, and there's all this pressure, you know, like stretching and burning … sometimes also I'll feel like hot knives stabbing me, and that's when I feel back pain. I'll feel like someone's stabbing a hot knife and it went out through my back, like a hot knife coming out" (Patient 16)

Chronic pain (red boxes)

"Some days I just feel like I hurt so bad that it's like I actually will think out loud, like how is porphyria compatible with life, you know? When you get to that point where you're in that much pain, it's not compatible with life. You can't live like that" (Patient 20)

"I have pain disassociation so that my level of pain is at a 5 all the time, which is probably someone else -- a normal person's 10, because I' m so used to the pain" (Patient 04)

AIP impact on patients

- Attack symptom severity affects basic activities of daily living, and mobility
- Between AIP attacks, symptoms, unpredictability of knowing when next attack would come, and treatment factors impacted work/education, social relationships and roles, leisure and exercise, diet and nutrition, healthcare and treatment, and psychological factors

Comprehensive experience elicited

- Final 5 interviews in this patient sample generated limited additional information, suggesting that saturation was reached in these 19 interviews for acute symptoms; however saturation was not reached for non-pain chronic symptoms

Limitations

- Results should be interpreted carefully given small sample; Clinical data were reported by patients and no confirmation clinical diagnosis; Interviews were not originally designed to explore chronic symptoms in depth and non-pain chronic symptom saturation was not achieved

Conclusions

- Study highlights high disease burden in patients with AIP whom experience recurrent attacks through qualitative feedback on their experiences
- Porphyria attacks are severe and disabling events that typically require hospitalization and treatment
- AIP is not just an "intermittent" disease as its name implies, but has chronic manifestations that impact patients' lives and their ability to function
- Wide variety of chronic symptoms were reported in addition to pain, which appear to align with attack symptoms; i.e., no chronic symptoms appeared that are not also experienced in more severe form as an attack symptom, supporting acute-on-chronic nature of porphyrias
- This qualitative patient study supports EXPLORE natural history study findings (NCT02240784) that AIP is an acute on chronic disease[8]

Disclosures: Amy Simon, William Querbes, Craig Penz, Sonalee Agarwal, Alex Wei, and Rena Denoncourt are employees of Alnylam Pharmaceuticals. Farrah Pompilus, Sara Strzok and Patrick Marquis are employees of Modus Outcomes, which received payment from Alnylam to conduct the qualitative research.

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