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ORIGINAL RESEARCH

Patient Perspective on Acute Hepatic Porphyria with Sporadic Attacks: A Chronic Disease with Substantial Health-Related Quality of Life Impacts

Kristen Wheeden · Desiree Lyon Howe · Sue Burrell · Liz Gill · John Chamberlayne · Edrin R. Williams · Amy Simon · John J. Ko · Jordanna Mora · Ted Wells · Christopher Evans · Maggie Paulich · Stephen Meninger · Stephen Lombardelli

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ABSTRACT

Introduction: Acute hepatic porphyria (AHP) is a family of rare metabolic diseases characterized by potentially life-threatening acute attacks and, in some patients, chronic debilitating symptoms. While patients with frequent or recurrent attacks (three or more attacks annually) are known to have reduced health-related quality of life (HRQoL) as most aspects of daily living are impacted, limited data exist in patients with sporadic attacks. This research aims to identify porphyria-related symptoms between attacks, characterize the frequency, severity, and bothersomeness of these symptoms, and more generally understand the burden of this disease in patients who experience attacks sporadically.

Methods: Patients with AHP with sporadic attacks (AHP-SA) (at least one porphyria attack in the past 2 years, but no more than two attacks per year in the previous 2 years) were recruited, via outreach performed by patient advocacy groups, for participation in qualitative telephone interviews. Interviews were conducted using a semi-structured guide and were audio-recorded, transcribed, anonymized, coded, and analyzed to determine if saturation was reached.

Results: A total of 14 participants with AHP-SA were interviewed (mean age 45 years, 100% female). The most frequently reported chronic symptoms were fatigue, pain, heartburn, and constipation. The most frequently experienced chronic impacts were difficulty performing daily activities, difficulty exercising, negative impact on work, need for a special diet, anxiety, and depression. Beyond these chronic symptoms and impacts, participants also frequently described flares in their porphyria that were severe, did not qualify in their minds as an acute attack, but were nonetheless more severe than their typical chronic experience.

Conclusion: Patients with acute hepatic porphyria who experience sporadic attacks face

Patient authors: Kristen Wheeden (caregiver), Desiree Lyon Howe, Sue Burrell, Liz Gill, John Chamberlayne (caregiver).

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K. Wheeden · D. Lyon Howe · E. R. Williams
American Porphyria Foundation, 4915 St. Elmo Avenue, Suite 200, Bethesda, MD, USA

S. Burrell · L. Gill · J. Chamberlayne
British Porphyria Association, Durham, UK

A. Simon · J. J. Ko · J. Mora · S. Meninger · S. Lombardelli (✉)
Alnylam Pharmaceuticals, Cambridge, MA, USA
e-mail: slombardelli@alnylam.com

T. Wells · C. Evans · M. Paulich
Endpoint Outcomes, Boston, MA, USA

significant chronic symptoms and impacts that frequently require significant pharmacological and clinical treatment. The reported severity of these symptoms and impacts suggests that the humanistic burden of AHP-SA is substantial and may lead to a significant decrease in health-related quality of life in these patients between acute attacks. The presence of flares that do not reach the level of what is considered an acute attack by patients is a unique finding of this study not reported elsewhere and requires additional investigation.

Keywords: Porphyria; Acute hepatic porphyria; Quality of life; Burden of disease; Chronic symptoms

Key Summary Points

Patients with acute hepatic porphyria who experience sporadic attacks (AHP-SA) face significant chronic symptoms and impacts that frequently require significant pharmacological and clinical treatment.

The reported severity of these symptoms and impacts suggests that the humanistic burden of AHP-SA is substantial and may lead to a significant decrease in health-related quality of life in these patients between acute attacks.

The presence of flares that do not reach the level of what is considered an acute attack by patients is a unique finding of this study not reported elsewhere and requires additional investigation.

INTRODUCTION

Porphyria is a family of metabolic disorders arising from a defect in one of the eight steps involved in the biosynthesis of heme in the liver or bone marrow. Acute hepatic porphyria (AHP) includes four types: acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP), and δ-aminolevulinic acid dehydratase porphyria (ADP) [1, 2]. AIP represents 80% of symptomatic AHP cases and is prevalent in one of every 100,000 individuals [3].

Biochemical and molecular genetic testing are used to help establish a definitive diagnosis. However, the diagnosis of AHP is frequently delayed by years because of the non-specific nature of symptoms, which can easily be mistaken for other conditions [4]. During that time period, inappropriate treatments and medical procedures have been reported and are not an uncommon occurrence [4, 5]. The correct tests used to inform a diagnosis of AHP are not widely available or commonly utilized at hospitals, thereby often further delaying diagnosis [6]. The signs and symptoms associated with neurovisceral attacks are similar between the four types of AHP, and most often include severe neurovisceral pain in the abdomen, vomiting, muscle weakness, hypertension, and mental status changes. However, manifestations of attacks involve multiple organ systems and can be variable among patients [7].

During an acute attack, patients can experience multiple symptoms at the same time, which can lead to an exacerbation of the overall severity of a patient's condition over hours or days [8]. Attacks often require hospitalization and can be life threatening if not treated promptly or properly.

Many patients who experience recurrent attacks also report experiencing chronic symptoms including pain, fatigue, and nausea. Individuals may experience permanent neurologic damage which can result in paresis most commonly in the limbs, hands, and feet or in chronic neuropathic pain from repeated nerve damage [4, 9–11]. In addition, patients can have mental status changes during attacks (e.g., confusion, anxiety and hallucinations) as well as suffer from anxiety, depression, and trouble sleeping on a chronic basis [8, 12]. Additional long-term complications of AHP include chronic kidney disease, hypertension, and liver disease [13]. Individuals with AHP also experience a significant reduction in their health-related quality of life (HRQoL) as the clinical manifestations negatively impact many aspects of daily living, emotional burden,

difficulty sleeping, and increased medical expenses [14].

Current treatment focuses on trigger avoidance (e.g., certain medications, infection, alcohol use) to prevent attacks. If attacks occur, patients are treated with supportive care and pain management, and in more severe attacks intravenously administered hemin [7, 15–17]. In some cases, orally administered folic acid, propranolol, clonazepam, vitamin B complex, and carbohydrates are used as treatments depending on the case and symptoms [18]. For patients that have ongoing attacks despite trigger avoidance, an RNA interference therapeutic, givosiran, can be administered subcutaneously on a monthly basis. Liver transplants are considered a curative treatment but are rarely performed because of the highly invasive nature of transplantation, the need for lifelong immunosuppression, and the lack of available donor organs [1, 19, 20].

Current understanding of the attack-related symptoms and disease experience for individuals with AHP is primarily informed by studies of patients who suffer from recurrent attacks. While the burden of disease for these patients is well characterized in current literature [7], the chronic symptoms and resulting impact on HRQoL for individuals who suffer from AHP with sporadic attacks (AHP-SA) is not as clear. As such, there is a need to characterize the symptom experience in individuals with AHP-SA and identify the most important aspects of the disease in these individuals. The goal of this research was to conduct qualitative interviews to determine the most salient aspects of sporadic attacks in terms of patient burden, as well as to explore the overall burden of illness in AHP-SA.

METHODS

This was a qualitative research study that sought to understand the chronic symptoms and impacts of AHP-SA, as distinct from symptoms and impacts experienced during an acute attack. The research reported here is based on best practices in outcomes research [21] and is consistent with recommendations from authoritative regulatory bodies such as the US Food and Drug Administration (FDA)'s final guidance to industry on patient-reported outcomes [22] and patient-focused outcome measurement in clinical trials [23, 24].

This study was reviewed by the Reading Independent Ethics Committee (UK) and the Western Copernicus Group Independent Review Board (WCG IRB) (USA) for ethics review and approval prior to any contact with study participants (IRB tracking #20200869). The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All subjects provided informed consent to participate in the study.

Recruitment and Eligibility Criteria

Following IRB approval, participants were recruited through patient advocacy groups (American Porphyria Foundation [APF] and British Porphyria Association [BPA]). Participants recruited for the study were only enrolled if they met the following key inclusion criteria: diagnosed with AHP including AIP, VP, HCP, or ADP; experienced at least one porphyria attack in the past 2 years, with an attack frequency that did not exceed two attacks per year in the prior 2 years; and the participant was 18 years of age or older. Porphyria attacks were defined as an acute episode of neurovisceral pain in the abdomen, back, chest, extremities, and/or limbs. Additionally, attacks needed to require intravenous treatment with dextrose or hemin, carbohydrates, or analgesics (opioid or non-opioid), or other medications such as antiemetics at a dose or frequency beyond the patient's usual daily porphyria management.

Participants were excluded if they met any of these key criteria: the participant was receiving off-label prophylactic treatment (e.g., hemin) to manage their AHP-SA at the time of screening or at the time of the interview; or the participant was receiving givosiran at the time of screening or at the time of the interview.

Twenty participants were initially targeted for recruitment as this sample size has been demonstrated to yield adequate, interpretable, and generalizable data for qualitative studies, although smaller sample sizes may be sufficient [25]. Given the rarity of AHP-SA, there were no

other recruitment targets for this qualitative interview study.

Data Collection

All concept elicitation interviews were conducted via telephone. Interviewers used a semi-structured interview guide, which included open-ended questions used to encourage spontaneous responses and robust qualitative data. Specifically, the guide included topics, questions, and probes to understand the disease experience from the participant's perspective. Each interview was audio-recorded, with the participant's prior consent and lasted approximately 90 min. In order to ensure that participants were able to distinguish chronic symptoms and impacts from acute attack symptoms and impacts, participant were first asked to identify what happened to them during an attack and then to comment separately on what their chronic experience was between attacks. It was felt that this line of inquiry would decrease the possibility of participants confusing aspects of their acute and chronic experiences so that the resulting data would represent an accurate reflection of their experience between attacks. Following the completion of the interview, participants were compensated for their time.

Data Analysis

Audio-recordings of the interviews were transcribed verbatim and anonymized by removing identifying information such as names and places. Each transcript was considered a unit of analysis, and data from all transcripts were aggregated following coding. An initial coding scheme was developed on the basis of the interview guide and research objectives. The coding scheme catalogued concepts that were reported by participants spontaneously (i.e., without prompting from the interviewer) or in response to probes (i.e., only reported following explicitly probing from the interviewer). Coding is an iterative process and therefore the initial code list was updated as necessary to reflect the actual terms participants used to describe concepts as well as to incorporate newly emerging data. The coding scheme was applied and operationalized using ATLAS.ti version 8 or higher (Atlas.ti GmbH, Berlin), a software program designed specifically for qualitative data analysis. This software was used to apply codes to specific text within each transcript and then to query for frequency across transcripts.

The coding process was guided by established qualitative research methods, including grounded theory and the constant comparative method. Specific grounded theory methods that were applied to this research included collecting and analyzing data in parallel (i.e., initiating coding of transcripts from completed interviews while the overall interview program is still in progress); allowing the coding scheme to naturally evolve outside of any preconceived notions; constantly comparing and contrasting concepts to inform relationships amongst the data (i.e., constant comparative method); and using memos within individual transcripts as necessary to explain findings and inform the next step of analysis (i.e., aggregating transcripts and harmonizing codes) [26]. Individual cases (e.g., unique concepts) were identified and ultimately formed broader categories (e.g., domains), which helped to identify and explain patterns and relationships within the data set (e.g., a conceptual framework) [27, 28]. Ultimately, frequencies of unique concepts (both spontaneous and probed) were reported, with accompanying illustrative verbatim quotes.

Intercoder reliability (ICR), or the extent to which independent coders are concordant in coding, was evaluated using percentage agreement. Specifically, percentage agreement was derived by dividing the total number of concordant codes by the total number of codes assigned and then multiplying by 100. Greater than or equal to 90% agreement amongst all coders was considered an acceptable threshold for ICR (i.e., percentage coder agreement) [29].

Qualitative data from the concept elicitation interviews was assessed for conceptual saturation. Saturation was considered to be achieved at the point when additional interviews were unlikely to yield new information (i.e., new concepts of importance and relevance to participants) [26]. In order to evaluate conceptual

saturation, concepts spontaneously emerging from the interviews were analyzed in cohorts based on the order in which the data were collected.

RESULTS

Study Population

Fifteen participants were found eligible and participated in concept elicitation interviews. As a result of ineligibility determined after review of the first completed interview (i.e., the participant disclosed during the interview that they were also diagnosed with a second rare disease and specifically noted that they were unable to attribute signs/symptoms and impacts to their AHP-SA alone), data for one participant was removed from analysis.

Demographic and Health Information

On the basis of the participant-reported data collected during screening and/or during participant interview, most participants (n = 12 of 14, 85.7%) had a current diagnosis of AIP with the remainder having a diagnosis of VP (n = 2, 14.3%). All participants (n = 14, 100.0%) were female and ages ranged from 23 to 72 years (mean 45.4). The majority of participants (n = 11, 78.6%) identified as white and all participants (n = 14, 100.0%) reported their ethnicity as non-Hispanic/Latino. The highest level of education most commonly reported for participants was Associate's degree (n = 4, 28.6%). Additionally, half of the participants (n = 7, 50.0%) self-reported their health status as "fair." During screening, the majority of participants (n = 9, 64.3%) reported experiencing one attack in the past year and more than half of the participants (n = 9, 64.3%) reported experiencing one attack in the year prior to that. Demographic and health information is reported in Table 1.

Chronic Signs and Symptoms

Participants reported a total of 38 unique chronic symptoms. As part of their chronic experience, participants often described what they termed "flare-ups" or "episodes," when they experienced increased severity, frequency, and/or duration of one or more of their chronic signs/symptoms of AHP, but not to the levels that they considered the event as an attack (hereafter referred to as flares or flare-ups in their disease or in AHP). The majority of participants reported flares in their AHP (n = 7 of 13, 53.8%). Participants talked about flares in heterogeneous terms. One participant noted that the flares could be particularly bad: "I'd say, one episode that's wicked bad every, I'd say 6 to 8 weeks, where I feel like complete shit for several days and barely get out of bed… That's on an irregular basis, but it does not mean that I am getting an attack."

Another participant reported a milder experience: "For me, the flare-ups, I would say, are when I might have a day where my stomach's bothering me a little bit more—as in stomach pain—or my fingers and feet may have a little bit more pain than normal." Another participant spoke to the duration of a "flare-up" by stating "I have attacks. But then I also have what I refer to as a more, I guess, mild but long-lasting flare-ups. The flare-ups last anywhere from 7 to 14 days." Furthermore, participants described the potential of these episodes to turn into an attack and strategies they implement to prevent this. Specifically, one participant stated that during a flare "if I take it easy and—or take a day off work or do—you know, adjust what I'm eating or trying to get more sleep, it'll usually calm down. But it's when I try to do those things and the pain continues to get worse that it then turns more into an attack."

The most frequently reported chronic symptom was fatigue or tiredness, which was reported by 13 participants (92.6%). When asked to characterize their fatigue or tiredness, participants often provided descriptions noting the severity of the signs/symptoms: "you don't have a great deal of energy at times. At times, I don't have any energy at all. I am very sleepy. I sleep a great deal of the time—more so, I think, than most people," and "I will say some consider me in a coma because I sleep so much at times."

Participants also described the frequency at which their fatigue or tiredness occurs, ranging

Table 1 Concept elicitation interview participant-reported demographic and health information

Characteristic	Total sample (N = 14) n (%)
Diagnosis classification	
Acute intermittent porphyria (AIP)	12 (85.7%)
Variegate porphyria (VP)	2 (14.3%)
Country	
USA	13 (92.8%)
UK	1 (7.1%)
Age (years)	
Minimum–maximum	23–72
Average (SD)	45.4 (14.9)
Sex	
Female	14 (100.0%)
Race (all that apply selected)	
White	11 (78.6%)
Black or African American	2 (14.3%)
American Indian or Alaska Native	1 (7.1%)
Asian	1 (7.1%)
Ethnicity	
Not Hispanic/Latino	14 (100.0%)
Highest level of education	
High school graduate (or equivalent)	1 (7.1%)
Some college (no degree)	2 (14.3%)
Associate's degree	4 (28.6%)
Bachelor's degree	3 (21.4%)
Master's degree	3 (21.4%)
Other[a]	1 (7.1%)
Work status (all that apply selected)	
Working full-time	4 (28.6%)
Working part-time	4 (28.6%)
On disability	2 (14.3%)
Retired	2 (14.3%)
Unemployed	1 (7.1%)
Other[b]	1 (7.1%)

Table 1 continued

Characteristic	Total sample (N = 14)n (%)
General health status	
Poor	2 (14.3%)
Fair	7 (50.0%)
Good	3 (21.4%)
Very good	2 (14.3%)
Length of time since diagnosis (years)[c]	
Average (SD)	17.1 (16.9)
Range	0.5–47.0
Reported number of attacks within 1 year prior to interview	
0 attacks	3 (21.4%)
1 attack	9 (64.3%)
2 attacks	2 (14.3%)
Reported number of attacks between 1 and 2 years prior to interview	
0 attacks	3 (21.4%)
1 attack	9 (64.3%)
2 attacks	2 (14.3%)

[a]One participant (7.1%) selected "Other" and reported the following: UK equivalent schooling of high school graduate
[b]One participant (7.1%) selected "Other" and reported the following: furloughed
[c]One participant (7.1%) did not report date and/or age of diagnosis at time of interview and is not incorporated into calculations for length of time since diagnosis (years)

from daily (n = 7 of 13, 53.8%), to weekly (n = 1 of 13, 7.7%), to monthly (n = 1 of 13, 7.7%), to every 2 months (n = 1 of 13, 7.7%). Other participants also noted the systemic impact, the severity, and frequency their chronic tiredness and fatigue has on their life, "[w]ell, it causes chronic fatigue, so I'm always tired and I try everything I can to try and get through the whole day and it's really hard to keep a full-time job and try to do normal daily activities due to the pain that I feel, as well as being tired." Participants also commented on the severe nature of their fatigue by explaining, "I never feel well-rested when I wake up, ever. I can't remember the last time I felt rested." Participants who suffered from fatigue reported working with a psychologist and taking drugs, "I take a lot of drugs. I know that sounds terrible, but I take Adderall, so I've really gone the medication route to try and solve a lot of my problems."

Participants reported experiencing eight different types of chronic pain (i.e., back pain, headache, muscular body pain, extremity pain, abdominal pain, nerve pain, chest pain, and stomach pain). Five of the eight types of chronic pain were frequently reported symptoms (i.e., back pain, headache, muscular body pain, extremity pain, and abdominal pain). Patient

quotes ranged from a type of chronic background pain to pain that gets progressively worse. For instance, one participant noted: "During an attack, it'll—I mean it [pain] would bring me to my knees. But just kind of every day, it's more of like just—it's more of abdominal pain. It just kind of hurts as far as compared to debilitating during an attack." Another participant noted: "the pain in my legs have—has increasingly gotten worse with time, which is scary to me, like it started out a little bit, and then it became a little bit more, and now it's a little bit more often and it just feels like I just don't want to stand for long periods."

Overall, 13 out of 14 participants (92.8%) reported experiencing some form of pain chronically. Back pain, headaches, muscular body pain, and extremity pain were each reported as chronic symptoms by eight participants (57.1%). Chronic abdominal pain was reported by half of the participants ($n = 7$, 50.0%). Chronic nerve pain was reported by five participants (35.7%). Lastly, chest and stomach pain were reported as chronic symptoms by two participants (14.3%). For back pain, two participants reported taking medications: hydrocodone/oxycontin when needed and a daily fentanyl patch. For body pain, treatments reported by three participants included Tylenol, muscle relaxers, and hydrocodone. Three participants reported taking medication for pain in the extremities which included over the counter medications and morphine. Abdominal pain treatments were reported by two participants and included fentanyl patches, oxycodone, and Advil.

Nausea, another frequently reported chronic symptom, was reported by eight participants (57.1%). When asked to characterize nausea, participants described the symptom in terms of frequency and duration: "I almost always wake up nauseated, and 24-h struggle with pain and nausea" and "The nausea, I get a lot after I eat food, which I think is also why I have a loss of appetite, because I know if I eat, then I'm going to feel sick." In regard to frequency, participants reported that the nausea occurred daily ($n = 2$ of 8, 25.0%), weekly ($n = 1$ of 8, 12.5%), monthly ($n = 1$ of 8, 12.5%), or less than monthly ($n = 1$ of 8, 12.5%). One participant reported experiencing nausea "on a regular basis. It's a joke with me and my friends. I'm definitely the puker in the group." When discussing the duration of chronic nausea, one participant ($n = 1$ of 8, 12.5%) reported the symptom lasting only 5 min and three participants ($n = 3$ of 8, 37.5%) reported the symptom lasting half a day. Specific anti-nausea treatments reported by two participants were Zofran and prochlorperazine.

Constipation was reported as a chronic symptom by seven participants (50.0%). Participants described chronic constipation with a focus on its frequency. One participant noted, "I've had a physical—I don't know—handful of years ago where the doctor inquired how often I go and I only go once or twice a week and she seemed very concerned about that. But I relate that to being porphyric as well is that my bowel movements are maybe twice a week. I'm not as regular—as like a normal regular person might be. I—that could be constipation. I don't know if that would fit into that category" and "I had severe stomach pain and a couple times, mom had to take me to the hospital, because I was just bent over in pain and I didn't know why and the doctors would always come back and say it was due to being so backed-up." Another participant reported, "I can't go to save my life… It feels like you're giving birth trying to go to the bathroom. It's horrific." In terms of frequency, participants reported they experienced constipation daily ($n = 3$ of 7, 42.9%), monthly ($n = 2$ of 7, 28.6%), or always ($n = 1$ of 7, 14.3%). Three participants specifically reported taking treatments for constipation: docusate, ispaghula husk, linaclotide, magnesium citrate, and magnesium oxide.

In regard to severity, one participant noted that the constipation was so bad "[t]o where I have hemorrhoids." Table 2 reports on the frequency of all chronic symptoms, the average (median) severity, and bothersomeness ratings.

Chronic Impacts

Participants reported a total of 35 unique chronic impacts across 12 conceptual domains (i.e., activities of daily living, appearance, diet and weight management, emotional, financial,

Table 2 Summary of chronic signs/symptoms

Frequency of report classification	Chronic signs/symptoms	(*N* = 14) *n* (%)	Severity rating Median[a]	Bothersomeness rating Median[a]
Frequently reported	Fatigue or tiredness	13 (92.9%)	6	7
	Back pain	8 (57.1%)	6	7
	Headache	8 (57.1%)	6	6
	Heartburn	8 (57.1%)	6	7
	Muscular body pain	8 (57.1%)	6.5	7
	Nausea	8 (57.1%)	7	8
	Pain in extremities	8 (57.1%)	5	6
	Abdominal pain	7 (50.0%)	6.5	6.5
	Constipation	7 (50.0%)	7	6
Somewhat frequently reported	Difficulty sleeping	6 (42.9%)	5.5	7
	Changes in urine color	5 (35.7%)	8	5
	Loss of appetite	5 (35.7%)	8	8
	Muscle weakness	5 (35.7%)	5	7
	Nerve pain	5 (35.7%)	4.5	5.5
	Topical skin issues	5 (35.7%)	8	8
	Numbness	4 (28.6%)	3	3
Infrequently reported	Lack of mental clarity	3 (21.4%)	9	6
	Chest pain	2 (14.3%)	4	5
	High blood pressure	2 (14.3%)	5.5	5.5
	Rapid heartbeat	2 (14.3%)	7.5	6.5
	Sensitivity to sunlight	2 (14.3%)	NR	8
	Stomach pain	2 (14.3%)	3	5
	Sweating	2 (14.3%)	9	9
	Vomiting	2 (14.3%)	3.5	4.5
	Arthritis	1 (7.1%)	8	8
	Cold sores	1 (7.1%)	7	8
	Diarrhea	1 (7.1%)	10	8
	Dizziness	1 (7.1%)	NR	NR
	Gas	1 (7.1%)	6	6
	Hallucinations	1 (7.1%)	1	1
	Hunger	1 (7.1%)	4	NR
	Inability to urinate	1 (7.1%)	9	8
	Increased production of saliva	1 (7.1%)	NR	NR
	Itching	1 (7.1%)	10	9
	Low blood pressure	1 (7.1%)	9	7
	Unexplained changes in mood	1 (7.1%)	7	NR
	Shakiness	1 (7.1%)	NR	NR
	Watery eyes	1 (7.1%)	8	8

NR not rated by any participants

[a]Not all participants provided a severity or bothersomeness rating. Scale range was 0 (not at all)–10 (extremely)

Table 3 Summary of chronic impacts

Impact	(*N* = 14) *n* (%)	Bothersomeness rating Median[a]
Activities of daily living		
Increased difficulty performing daily tasks	11 (78.6%)	6.5
Difficulty planning for future	4 (28.6%)	10
Difficulty planning for daily tasks	3 (21.4%)	5
Requires assistance completing daily tasks	2 (14.3%)	7.5
Challenges with healthcare system	2 (14.3%)	9
Limitations traveling	2 (14.3%)	6
Avoiding sunlight	1 (7.1%)	NR
Avoid being outdoors	1 (7.1%)	6
Difficulty caring for child	1 (7.1%)	6
Appearance		
Negative impact on appearance	4 (28.6%)	6.5
Diet and weight management		
Special diet	7 (50.0%)	6
Difficulty eating	2 (14.3%)	NR
Difficulty losing weight	2 (14.3%)	NR
Weight loss	2 (14.3%)	5.5
Emotional		
Anxiety	9 (64.3%)	6.5
Depression/sadness	8 (57.1%)	9
Frustration	3 (21.4%)	8
Stress	2 (14.3%)	NR
Self-conscious	2 (14.3%)	NR
Hopelessness	1 (7.1%)	9
Financial		
Negative impact on finances	7 (50.0%)	9
Medical complications		
Medical complications attributed to porphyria	5 (35.7%)	NR

Table 3 continued

Impact	(*N* = 14) *n* (%)	Bothersomeness rating Median[a]
Mental state		
Difficulty remembering	1 (7.1%)	10
Physical		
Difficulty exercising	7 (50.0%)	7
Walking/movement more difficult	2 (14.3%)	10
Difficult to participate in tasks that increase exposure to sunlight	1 (7.1%)	10
Needs physical therapy	1 (7.1%)	NR
Sex life		
Negative impact on sex life	4 (28.6%)	10
Sleep		
Increased need for sleep	2 (14.3%)	NR
Trouble falling asleep	1 (7.1%)	4
Social		
Feeling isolated	5 (35.7%)	8
Negative impact on relationships with family/spouse	6 (42.9%)	8
Limited social activities	4 (28.6%)	5
Difficulty maintaining friendships	3 (21.4%)	9
Work or school		
Negative impact on ability to work	10 (71.4%)	7

NR not rated by any participants

[a]Not all participants provided a severity or bothersomeness rating. Scale range was 0 (not at all)–10 (extremely)

medical complications, mental state, physical, sex life, sleep, social, and work or school) (Table 3).

The most frequently reported chronic impact was in the activities of daily living domain: increased difficulty performing daily tasks (*n* = 11 of 14, 78.6%). Participants described not having "the fine motor skills" they used to and tasks took "twice as long" as they normally would have. One participant described experiencing increased difficulty with "bend[ing] over," "going up and down steps," and "yard-work." Another participant explained that there are days where they feel so "lousy" they are unable to "get out of bed" to "go to the grocery store and get some chores done." This impact was closely followed by an impact in the work or school domain: negative impact on ability to work (*n* = 10 of 14, 71.4%). Participants reported that it is "really hard to keep a full-time job," they are "no longer able to work," and whatever work they do "has to be extremely flexible." One participant described a loss of an important opportunity: "And then I got my dream job with the international [company]. I went to [company] and then I had my second attack. And then I had recurrent attacks after that, and the [company] said they would never have me again. So that was the end of that. That's what I trained for, for many years and had been my

lifelong ambition. So that's what it means to me. More than the pain and everything else, it's the fact that I lost the opportunity." Another participant described not being able to keep their chosen vocation: "I was a teacher. That would definitely not be an option for a couple reasons, because I don't mentally completely trust myself. And if I were to have an attack and things were to get fuzzy, I certainly wouldn't want to be responsible for a group of children. And, also because just feeling well enough to get through the day."

Other frequently reported impacts (defined as reported by seven or more participants [at least 50.0%]) included anxiety (n = 9 , 64.3%), depression/sadness (n = 8, 57.1%), negative impact on finances (n = 7, 50.0%), difficulty exercising (n = 7, 50.0%), and special diet (n = 7, 50.0%). Somewhat frequently reported impacts included medical complications (e.g., ulcers, infections) attributed to porphyria (n = 5 , 35.7%), feeling isolated (n = 5 , 35.7%), negative impact on relationships with family/spouse (n = 5 , 35.7%), difficulty planning for future (n = 4, 28.6%), negative impact on appearance (n = 4, 28.6%), negative impact on sex life (n = 4, 28.6%), and limited social activities (n = 4 , 28.6%). The frequency of impacts and average bothersomeness rating (severity ratings were not collected for impacts) are reported in Table 3.

DISCUSSION

Various terms may be used to describe this studied patient population with acute hepatic porphyria that do not experience frequent attacks: intermittent-, less recurrent-, or sporadic-acute hepatic porphyria. Regardless of terms used, they do not adequately capture the impact of AHP on this group of patients' lives. This research has demonstrated that in patients with AHP-SA, the symptoms and impacts are not limited to just the attack period but occur on a chronic basis between attacks, even when the annual attack frequency is infrequent.

This research is the first to describe the average severity and bothersomeness of symptoms in patients with AHP-SA and average bothersomeness of impacts. In this study, the severity of symptoms were, overall, moderate to severe and the bothersomeness of the symptoms was often rated slightly higher than the severity rating. In terms of impacts, patients consistently reported that all impacts caused them moderate to a high level of bother, with limited exceptions. Many of the symptoms reported by participants required treatments with medications, often prescriptions.

In addition, to the best of our knowledge, this is the first study where participants described the presence of flares between their acute attacks, characterized by increased severity, frequency, and/or duration of one of their chronic signs/symptoms, but not defined as a full-blown attack necessitating hospitalization. Disease flares were heterogeneous in nature: some were characterized as a worsening of a single symptom while others caused a significant change in health status that did not (by the patient's definition) quite reach the level of an attack. Nevertheless, the flares caused significant health burden and should be further studied and monitored by treating physicians.

Previous research into the burden of recurrent AHP found similar symptoms and impacts to those described here. For instance, pain, nausea, fatigue, and aspects of neuropathy were considered key chronic symptoms and sleep difficulties, inability to work, negative financial impact, difficulty walking, and decreased socialization were main impacts identified in previous studies [19, 30]. Only one study was identified that examined a population broadly similar to the patient population examined here [31]. In this Spanish study of sporadic acute intermittent porphyria (SA-AIP; defined as having no history of neurovisceral attacks and an annual rate of attacks lower than four per year), abdominal pain, fatigue, muscle pain, insomnia, paresthesia, dyspepsia, anxiety, and depression were identified as core signs and symptoms. Overall, these studies, and this research, suggest that even patients who only experience attacks sporadically also experience significant impairment. The findings here are also consistent with those reported in the EXPLORE natural history study [12]. Many of the attack-related symptoms identified in

EXPLORE were also found to be experienced chronically by patients with AHP who experience less frequent attacks. However, participants in EXPLORE experienced a median of 6 attacks in the 12 months prior to study enrollment and therefore the time between attacks was relatively short. In contrast, the time between attacks in this study's sample was greater, as the average number of attacks in the past year and the year prior was 0.9 (SD 0.6). Further supporting evidence of the presence of chronic symptoms and impacts comes from a report from an FDA patient-focused drug development meeting [32].

There are several limitations to this study. The sample size was lower than originally targeted, although the final sample size (n = 14) is consistent with what is reported in the literature for an adequate sample in qualitative research to achieve saturation. For instance, it has been estimated across a wide range of diseases that 92% of concepts may emerge by the 15th interview, 97% of concepts by the 20th interview, and 99% by the 25th interview [25]. A saturation analysis was run on the 14 interviews and saturation was achieved for all but one symptom ("rapid heartbeat") and two chronic impacts ("difficulty remembering" and "hopelessness"), which indicates that the sample size was generally adequate for this study. Another limitation is that the diagnosis of AHP and the number of reported acute attacks were self-reported, and did not rely on biochemical data (such as ALA and PBG levels) and medical records were not obtained to confirm the diagnosis or the number of attacks, respectively. As patients were recruited from engaged and knowledgeable patient advocacy groups, it can be reasonably concluded that the patients had AHP; however, recall of the number of acute attack episodes is subject to recall bias and there is no guarantee that patients did not have more or fewer attacks than that reported here. In addition, patients who elected to take part in this research may be more motivated to share their experiences if they have more severe disease than if their disease was mild. This may skew the results reported here to be representative of patients with a higher burden of disease and it should be noted that the data is generally subjective and based only on participant reports: additional research using more objective indicators of outcomes would be useful in more fully describing the burden of AHP-SA, and a study that compared the results to an age- and sex-matched control could demonstrate the extra disease burden associated with AHP-SA. Moreover, the patient population in this study was predominantly AIP, with a couple of participants with VP; therefore, chronic manifestations of VP and HCP may not have been fully recognized in this sample.

CONCLUSION

This study done in patients with AHP with sporadic attacks demonstrated that the burden of their disease was substantial despite having a lower number of attacks than those with recurrent attacks. The symptom burden and impact on daily function, on a chronic basis, are still significant. Patients described chronic symptoms of fatigue and pain and described flares of disease activity that did not reach the level of what they experienced during attack, but that nonetheless were associated with limitations in their daily functioning. Other important symptoms include gastrointestinal problems (i.e., heartburn, nausea, constipation, and loss of appetite) and sleep problems. The chronic impacts experienced by patients are wide ranging: from difficulty planning for daily and future activities to need for a special diet, to anxiety and depression.

AHP should not be considered only as an acute disease in patients experiencing sporadic attacks, as the patients also experience chronic disease impacts. These data also highlight why regular monitoring of patients with AHP regardless of attack rate may be required and underscores the need for additional research to further understand the unmet need in the sporadic attack population.

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Data Availability. Authors can confirm that all relevant data are included in the article and/or its supplementary information files. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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