

## **Experiences and Concerns of Patients with Recurrent Attacks of Acute Hepatic Porphyrria: A Qualitative Study**

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**Short Running Title: Patient Perspectives in Acute Hepatic Porphyrria**

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## **ABSTRACT**

**Background:** The acute hepatic porphyrias (AHPs) are rare inborn errors of heme biosynthesis, characterized clinically by life-threatening acute neurovisceral attacks. Patients with recurrent attacks have a decreased quality of life (QoL); however, no interactive assessment of these patients' views has been reported. We conducted guided discussions regarding specific topics, to explore patients' disease experience and its impact on their lives.

**Methods:** Sixteen AHP patients experiencing acute attacks were recruited to moderator-led online focus groups. Five groups (3-4 patients each) were conducted and thematic analyses to identify, examine, and categorize patterns in the data was performed.

**Results:** All patients identified prodromal symptoms that began days prior to acute severe pain; the most common included confusion ("brain fog"), irritability, and fatigue. Patients avoided hospitalization due to prior poor experiences with physician knowledge of AHPs or their treatment. All patients used complementary and alternative medicine treatments to avoid hospitalization or manage chronic pain and 81% reported varying degrees of effectiveness. All patients indicated their disease impacted personal relationships due to feelings of isolation and difficulty adjusting to the disease's limitations.

**Conclusion:** Patients with recurrent attacks recognize prodromal warning symptoms, attempt to avoid hospitalization, turn to alternative treatments, and have markedly impaired QoL. Counseling and individualized support is crucial for AHP patients with recurrent attacks.

**Word count: 211**

**KEYWORDS: Acute Hepatic Porphyria, Acute Intermittent Porphyria, Focus Groups, Psychosocial Experiences, Quality of Life**

## INTRODUCTION

The three autosomal dominant acute hepatic porphyrias (AHPs), Acute Intermittent Porphyria (AIP), Variegate Porphyria (VP), and Hereditary Coproporphyria (HCP), are rare disorders of heme biosynthesis<sup>1,2</sup>. AIP is the most common with an estimated heterozygote prevalence of ~5.4 per 100,000 in Europe, and a higher frequency in Scandinavia due to a founder mutation<sup>3</sup>. The actual heterozygote prevalence is unknown, as it is estimated that 80-90% of heterozygotes never experience symptoms<sup>1-3</sup>. Symptoms are characterized by life-threatening acute neurovisceral attacks of severe abdominal pain, nausea, vomiting, and tachycardia that, if untreated, may lead to seizures, hallucinations, brain stem involvement and paralysis<sup>1-6</sup>. A small subset of patients experience recurrent attacks, most of whom are women<sup>1,2,4</sup>. While the acute attacks in the three AHPs are clinically similar, VP and HCP patients can also have blistering skin photosensitivity and are reported to have less frequent attacks<sup>1-4</sup>.

The AHPs are diagnosed during an attack by demonstrating markedly elevated urinary and/or plasma levels of the neurotoxic porphyrin precursors, 5-aminolevulinic acid (ALA) and porphobilinogen (PBG)<sup>6,8,9</sup>. However, diagnosis is often delayed due to the nonspecific symptoms and lack of awareness of these rare disorders among physicians. Certain precipitating factors are known to cause acute attacks including hormonal changes, excess alcohol, fasting, and porphyrogenic medications such as those that induce P450 enzymes<sup>1,2,7</sup>. Stress has been described as a possible precipitating factor<sup>7,9,10</sup>, although the extent to which stress induces acute attacks has not been described.

The current treatment for acute attacks is intravenous infusions of hemin, which is typically infused at 3-4mg/kg for 4 consecutive days<sup>8-11</sup>. However, some patients with recurrent

attacks receive prophylactic hemin infusions, ranging from weekly to monthly, to prevent hospitalization<sup>10,13,14</sup>.

Previously, there have been only a few studies of the patient experience with this disease, particularly among patients with frequent recurring attacks. These studies have reported that symptomatic AHP patients have decreased quality of life (QoL), an increased incidence of anxiety and depression, impaired physical functioning, and a negative disease impact on employment<sup>15-17</sup>. The experiences of five women over 55 years old who had recurrent acute attacks were assessed using individual structured interviews<sup>18</sup>. However these women were specifically selected because they were “successful in coping with their lives.” Focus group studies are widely used in common diseases and public health issues, such as cancers, autoimmune diseases, and diabetes, to understand patients’ perspectives.<sup>19-21</sup> These have resulted in targeted outreach programs, improved marketing of screening programs, and more patient-friendly counseling methods. Some have been performed in other rare disease populations as well with good results<sup>22-24</sup>. Focus group methodology specifically allows patients to compare experiences and creates an environment for sharing personal experiences, feeling, and concerns which may not otherwise be brought to the attention of providers. As well, focus groups are ideal to identify gaps in care and knowledge and generate hypotheses for future studies<sup>25,26</sup>.

Here we assessed the experiences of patients with recurrent attacks, whether they recognize prodromal symptoms of an acute attack, and their decision-making process about treatment, areas which have not been previously investigated. In addition, we sought to learn how patients manage their acute and chronic porphyric pain, and the extent to which stress can exacerbate or induce this pain. These areas represent gaps in our knowledge and understanding

of the impact of the AHPs on QoL. Therefore, we conducted focus groups with the primary objective to explore patients' perspectives on their disease, as well as to examine specific topics identified by the study team to improve management and counseling of these patients.

## **METHODS**

### **Participants**

The study sample was comprised of patients 18 years or older who were recruited from the Porphyrins Consortium of the NIH-sponsored Rare Diseases Clinical Research Network from October 2013 to March 2015. All patients were participating in the Longitudinal Study of the Porphyrins (NCT01561157). Twenty patients were sent an information sheet from their respective Porphyrins Consortium site inviting them to participate in this study. Seventeen expressed interest in participating, the study was reviewed with them in detail over the telephone and verbal consent was obtained. All participants had a genetically confirmed AHP diagnosis and documented elevated urine PBG levels. The Institutional Review Board at the Icahn School of Medicine at Mount Sinai approved this research. Sixteen AHP patients participated in one of five focus groups, with 3-4 participants per group, and all completed a demographic survey (Table 1). The 17<sup>th</sup> patient could not participate due to scheduling conflicts.

### **Data Collection and Focus Group Guide**

Focus groups were conducted by two members of the research team and questions were specifically designed to be open-ended and unbiased to encourage discussion. Given the rarity of the AHPs and the geographic distribution of the American patients, in-person groups were not feasible. Instead, online video conferencing software GoToMeeting ([www.gotomeeting.com](http://www.gotomeeting.com)) was used to conduct the focus groups. GoToMeeting security controls meet the Health Insurance Portability and Accountability Act (HIPAA) regulations and participants were specifically informed about this. All focus groups were audio recorded and sessions typically lasted for 1.5-2 hours. Follow up interviews to further probe patient experiences and opinions on topics raised during the sessions were conducted via telephone.

A topic guide was developed based on a review of the literature regarding QoL, patient experiences, triggers that cause acute attacks<sup>7,8-10,13-18</sup> and expertise of the research team. The Guide consisted of five sections, each with a brief introduction followed by one to three open-ended questions (Table 2). Appropriate prompts were used during the sessions if necessary to facilitate discussion. The Guide was constructed to address participants' 1) opinions on their disease; 2) opinions of whether they have prodromal symptoms and their understanding of them; 3) experience with medical treatment; 4) opinions on if/how stress affects them; and finally, 5) methods of pain management.

### **Data Analysis**

Focus group recordings were transcribed verbatim and then de-identified. Data were analyzed using thematic analysis<sup>27</sup>. Briefly, transcripts were manually coded and organized based on their content into categories by two authors (MS and HN) independently. New categories were created until a repeating category was identified, themes were extracted from the categories, and a codebook was developed. Differences between the two coders were identified and reconciled between the investigators.

## **RESULTS**

### **Participants**

Of the 16 participants, 15 (14 female, 1 male) had AIP, and one female had VP. The median age was 38 years (range 19-67 years), and all had completed at least some college education, with the majority (56%) having a college degree. Fifteen participants had or were currently having recurrent attacks, defined as more than four patient-reported acute attacks a year that required treatment with hemin or increased pain medications, while one female participant with AIP had sporadic attacks throughout her life. Ten participants, all female, were receiving prophylactic (regularly scheduled) hemin infusions at the time of the focus groups.

### **Themes**

Six main categories were identified: 1) beliefs about acute porphyria; 2) experience with prodromal symptoms; 3) when participants seek treatment and 4) factors affecting this decision-making process; 5) the role of stress; and 6) alternative pain-relieving techniques. Results for each theme are described below.

### **Beliefs about Acute Porphyria**

All participants believed that AHP was a serious illness. When asked how often they think about porphyria, 14 (88%) said always or frequently, and only two said occasionally. Of the two who said occasionally, one was the patient with VP and the other was a young patient with AIP. All participants reported having difficulty adjusting to a “new normal” after they began having acute attacks and expressed that speaking to other patients in a group setting was beneficial.

Feelings of isolation due to a lack of disease understanding by health care professionals and family and friends were raised repeatedly with participants stating that “nobody really understands” acute porphyria or the intensity of the pain they experience. Participants struggled with being unable to plan for their future due to the unpredictability of the disease. This ranged from scheduling events and trips to rethinking plans for having children. They felt limited in all aspects of their lives. One patient commented about traveling:

“My fear is of ending up at a different hospital, if I’m on a trip or something like that. I know I would not experience the positive care that I get [by my local physician] if I am someplace else by chance...an absolute fear of mine.”

Several patients stated that the pain directly led to isolation. One said, “The pain itself is isolating; you don’t want to talk to people when you’re in pain.” Interestingly, participants felt that the disease both positively and negatively affected relationships. Those who were married felt the disease negatively impacted the relationship with their spouse, but overall felt their family relationships were strengthened. They specifically felt closer to the parent they inherited the disease from, even if that parent had never had an acute attack. Four participants expressed that initially they felt this was due to feelings of guilt on the part of this parent.

Younger female participants (aged 19 to 26) described difficulties in dealing with school and social functions. They felt pressured to provide reasons for not attending events with friends and discussed giving into the pressure to drink alcohol knowing that it may lead to acute attacks.

## **Experience with Prodromal Symptoms**

All participants were able to identify prodromal symptoms of an acute attack at least 24 hours before the acute excruciating abdominal pain began. In most instances they recognized prodromal symptoms 2-3 days before an attack. Only three participants (19%) stated that an acute attack did not always follow the prodromal symptoms. All participants reported symptoms unique to themselves; the full list is provided in Table 3. The most frequently mentioned were pain that was not abdominal (75%), “brain fog” which patients described as a feeling of mental “cloudiness,” confusion, difficulty focusing, and disorientation (50%), irritability (44%), extreme fatigue (38%) and anxiety and/or agitation (31%). Most of these symptoms were identified by the participant with the exception of irritability, which was identified by family members.

“I get irritable in the early days of an attack, I don’t even realize it, but I get super cranky and I have trouble focusing. It is almost impossible to notice at the time...but my husband tells me he notices it in the early days of an attack.”

Three participants (19%) felt their symptoms were different with each acute attack. There was much discussion regarding the differences in severity between acute attacks. Several participants noted that they could tell when “a bad one” was about to occur, but could not verbalize how they identified this. Three of the nine participants (33%) with chronic symptoms stated they could not predict attack severity. When prompted to see if they could determine a sequence of prodromal symptoms, the participants could not do so reliably. The sequence was highly variable; some patients (25%) could identify their first prodromal symptom and stated it was the same for all or

most acute attacks, but most could not identify one specific symptom that presented first, rather a group of symptoms.

### **When Participants Seek Medical Treatment**

Medical treatment was participant-described as either going to a hospital emergency room or scheduling an outpatient hemin infusion. For participants these options were synonymous with contacting their local treating specialist. All participants who had a primary care physician (PCP) agreed that they would not contact their PCP during acute attacks, as they felt he/she could not help and would simply refer them to an emergency room. Several participants admitted to not having a PCP and viewing their local specialist, most often a hematologist, as a PCP. Half of the participants only sought hospital treatment when they felt they could not manage the pain at home with opiates or other pain medications. All had opiates at some point, the most common one being Dilaudid and one participant stated he only goes to the hospital “when the pain gets so bad, that I start counting my pain meds and realize that I am taking too many.”

Several participants (31%) only went to the hospital when they began vomiting; indicating that their prodromal symptoms had already progressed to the acute phase. Others (19%) sought treatment when prodromal symptoms had been ongoing for more than 2-3 days, or when they noticed their performance at work was affected (19%). Only four participants (25%) said they sought treatment when they felt the initial early symptoms and these were ones who reported having a dedicated local physician who could arrange hemin infusions.

Discussion regarding side effects from hemin treatment came up briefly in several groups. Five participants (31%) described side effects not previously reported, including headaches and “flu-like” symptoms, specifically nausea and myalgia for about 24 hours after the end of the hemin infusion.

### **Factors Affecting the Decision to Seek Hospital Treatment**

Several factors were identified that affected participants’ decision to seek medical treatment. These included: 1) concern that the severity of their pain was doubted by hospital staff (56%); 2) concerns that they received improper treatment at local hospitals as hemin was not stocked and/or concerns that staff were unaware of appropriate treatments for acute attacks (44%); 3) feeling they could manage their own care better (44%); 4) their avoidance or denial of symptoms due to lingering hope they were not experiencing an acute attack (38%); and 5) guilt over costs incurred and stress on family members (25%). All the participants expressed a great deal of frustration with the process of being hospitalized and receiving treatment. Specific issues were that many of their local physicians were not knowledgeable about the disease and therefore not able to manage them properly. Participants also reported feeling as though their symptoms and/or the severity of their symptoms were not appreciated or even believed by physicians and nurses, despite bringing documentation confirming their diagnosis. Participants said they struggled with feeling dismissed by local hospital staff, sometimes being viewed as seeking pain medications, and that all these issues combined resulted in their not wanting to seek treatment. Half the participants said they had great difficulty finding an interested local physician to manage them which resulted in their feeling responsible for their own care.

One participant said, regarding her denial of symptoms:

“It [an acute attack] will start with knee pain and then I immediately go into denial...I’ll start making weird excuses like, ‘my knees hurt because I walked in the wrong shoes.’”

The guilt patients felt was related to the cost of hospital stays as well as the stress hospitalizations caused for family members:

“You know I could spend \$700 in a weekend going to the ER just to get treatment.”

In addition, there were discussions about the cost of hospitalizations and how participants had incurred thousands of dollars in medical bills that they struggled to pay. Participants discussed the struggles they had navigating the process of applying for disability, and those who were working expressed fear of the process and one day needing to apply for it:

“Especially if you have a salary and they’re [the spouse] working, it’s very hard to qualify for any of those programs [hospital financial aid and disability].”

## **The Role of Stress**

Nine participants (56%) said that stress was a direct contributing factor to their acute attacks, and they defined stress as anything that had a negative effect on their emotional state. Three participants (19%) stated that their symptoms were too frequent to tell if stress played a role in precipitating acute attacks. All participants agreed they struggled with managing day to day stress which, prior to developing symptoms, was not problematic.

“I feel that stress now is infinitely more exhausting for me. I previously was in a very high stress level job and I lost that job. But I made a conscious decision that I could not work in that environment again, at that pressure level, at that pace.”

Three participants (19%) who have monthly attacks, including the male participant, stated that stress alone had caused an acute attack, while four (25%) thought stress contributed to their chronic pain. The nine participants who thought stress contributed to their disease also reported that they thought emotional stress exacerbated their pain during an acute attack. Emotional stress, including caring for children, marital distress and worrying about finances, were the most commonly mentioned type of stress by seven of nine participants (78%). Stress caused by work was also mentioned frequently (67%). Three patients (33%) particularly noted that a health crisis in a loved one had precipitated an acute attack. The male participant commented about stress at work:

“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.”

### **Alternative Pain Relieving Techniques**

Patients attempted to manage their acute and chronic pain at home. Nine participants (56%) reported some level of chronic pain, while the others had intermittent pain not necessarily limited to acute attacks. This pain ranged in severity from mild to moderate and most often was pain in the limbs, back and/or neck. In addition, all participants mentioned that chronic fatigue was a significant issue for them. All had prescription opiate pain medications; however the majority (56%) expressed a dislike of taking them regularly due to their side effects or concerns over long term use. Three participants (19%) mentioned struggling with addiction to opiates and felt they were prescribed these inappropriately:

“The hospitals were prescribing it [Dilaudid] to me. I was 29 when I started taking it, and I think I formed a bit of an addiction. I literally told my doctors ‘don’t ever give this to me again’ ...I never want to take Dilaudid again. And I don’t know if you guys [other participants] deal with this, but when I’m in the hospital, Dilaudid is the only thing that works [to decrease pain].”

All participants had tried alternative treatments or “home remedies” to relieve their pain, either chronic or during an acute attack. These fell into three categories; acupuncture, relaxation techniques such as massage or bio-feedback, and “heat” treatments such as hot showers or

heating lamps (Table 4). Thirteen participants (81%) felt that certain alternative treatments helped relieve their pain. Interestingly, all seven (44%) participants who tried “heat” treatments felt they helped relieve pain to some degree. Three participants (19%) expressed wanting to try acupuncture, but fear of acute attacks and prohibitive costs was holding them back:

“I had been to an acupuncturist years ago before I started having attacks and it actually really helped me with migraines. I had thought about going, except I am so nervous...I have tried going for massages and that makes it [pain] worse.”

The 13 participants who reported the techniques in Table 4 as effective stated they only relieved pain temporarily and never stopped an acute attack. The three participants who did not think these techniques relieved their porphyric pain did feel that they helped relieve stress and anxiety in general.

## **DISCUSSION**

This study highlights the unmet medical needs of AHP patients who experience recurrent acute attacks. Prior studies reporting on the QoL of patients with the AHPs have used quantitative survey instruments such as the Illness Perception Questionnaire, the Hospital Anxiety Depression Scale, and the EuroQoL which showed that patients have a significantly impacted QoL<sup>15-17</sup>. However, these tools do not cover domains such as fatigue and stress management, which patients specifically mentioned as issues in this study. Some previous studies included asymptomatic, or “latent,” heterozygotes with AHPs which may have diluted

the results. In contrast, this study focused on the issues of patients with recurrent attacks and provides valuable insight and information on their experiences, feelings, and concerns, and revealed several novel issues.

Issues which have not been previously reported, include how patients perceive their prodromal symptoms, how stress plays a role in their disease and methods of stress and pain management. Our findings support that individual needs assessments and counseling for these patients are critical to identify prodromal symptoms and plan for early intervention to treat their acute attacks. As well, referrals to social work, psychology, and pain management may be beneficial for these patients and should be studied further. Given that patients expressed a benefit in discussing their experiences in a group setting, support groups may also be of benefit and should be explored.

All patients agreed that AHP is a serious disease with significant impact on their daily lives and social functioning, consistent with the previous literature<sup>15-17</sup>. Patients reported having to stop working due to their disease and struggled with feelings of isolation and guilt. Even those patients who agreed their medical management was optimized, struggled with daily functions and dealing with stress. Having to adjust to the “new normal” proved to be an issue for all patients; however, when referred to psychiatrists/psychologists to help cope, some expressed resentment. This has been reported previously as patients with recurrent attacks did not want to be viewed as having a mental illness<sup>18</sup>. Other patients stated this helped them manage their disease, specifically by providing new coping methods. Counseling for patients with recurrent attacks should focus on reducing the stigma associated with, and normalizing, psychiatric guidance.

This study also provides unique insights into the prodromal symptoms associated with acute attacks, particularly the mental confusion or “brain fog”. All patients were able to recognize prodromal symptoms at least one day before onset of the acute abdominal pain or vomiting, and most patients could recognize symptoms two to three days before the severe pain began. Recognition of these prodromal symptoms is critical for patients and physicians and may provide a window for medical intervention before hospitalization is required. Moreover, physicians should focus on identifying patient-specific barriers to seeking early treatment to prevent progression to a severe attack requiring hospitalization. As noted previously<sup>18</sup>, these patients cited previous poor or difficult clinical experiences when discussing the causes of their treatment avoidance. Although documentation confirming the diagnosis can be useful when presenting to new physicians, these patients struggled with the severity of their symptoms not being recognized. Local physicians treating these patients may require additional training to fully understand the severity of the disease.

Poor experiences were not the only factor affecting the patients’ decision and in some cases was not the prominent factor. Fear and guilt over the costs that would be incurred contributed to delays in seeking treatment early. Importantly, patients who reported having a dedicated local physician to administer hemin had better experiences and in general sought treatment when prodromal symptoms occurred. All patients had established care with porphyria specialists, but due to geographical distances, local physicians were necessary to manage their care. Referrals to social work may be helpful for these patients in navigating hospital financial systems, and specialists may need to identify and train local physicians to manage these medically complicated patients.

Stress has been reported as a possible precipitating factor of acute attacks<sup>7,9,10</sup>, but the extent to which it may contribute to acute attacks is unknown. Stress itself can cause health problems such as headaches and gastrointestinal issues<sup>28,29</sup>; however, participants specifically indicated that highly stressful scenarios exacerbated their AHP symptoms, sometimes directly causing acute attacks with no other identifiable trigger. Here again, referrals to psychiatrists/psychologists may help patients cope with daily stress, and several patients volunteered that they were seeing psychologists and felt it helped. For some, the medical cost of an additional specialist was an issue. Interestingly, the methods patients used to attempt to manage their pain also seemed to help them manage stress. Recreational drug use is relatively common in other conditions with high levels of pain<sup>30</sup>, however in AHP these have been reported to possibly precipitate acute attacks<sup>10</sup>. Assessing the use of recreational drugs in this patient population is particularly important to determine if they may be real attack triggers. Many patients expressed a dislike for taking opiates unless they felt it was absolutely necessary and turned instead to complementary treatments such as acupuncture, massages, and various “heat” treatments. Most felt these alternative therapies did relieve some of their pain (either chronic or acute) as well as helped them manage daily stress. Future studies should determine differences in how patients treat chronic versus acute pain. In this study, patient’s pain and stress levels seemed related. A prospective study systematically assess how stress impacts acute attacks would provide useful information for providers, as well as determining patients’ use of complementary and alternative medicines, and identifying which are safe and effective, so that physicians can recommend them appropriately.

Our study included patients who were all evaluated by porphyria specialists. It is expected their medical management would be optimized and the issues they face may not be

reflective of patients who do not have such expert care. As well, participants were fairly highly educated and their views and experiences may not be representative of all patients. Lastly, issues that are specific to healthcare costs for these patients may not be generalizable to countries with different healthcare systems. However, even considering these limitations several issues were revealed where care can be improved.

There is a paucity of qualitative research in rare disease populations; however, this study illustrates the benefits of conducting such studies in these patient populations to improve disease-specific care and counseling. In addition, all participants expressed gratitude in being able to speak to other patients and share common experiences, and felt that this process alone was beneficial.

Word count: **4214**

## **CONFLICTS OF INTEREST**

RJD is a consultant to Alnylam Pharmaceuticals and Recordati Rare Diseases

HN, MS, SCS, and MB do not have any relevant conflicts of interest

## **FUNDING**

This research was supported in part by The Porphyrrias Consortium (U54DK083909), which is a part of the NCATS Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR), NCATS, funded through a collaboration between NCATS and the NIDDK. MB is supported in part by the NIH Career Development Award (K23DK095946).

## **AUTHOR CONTRIBUTIONS**

HN, MS, MB & SS- Conception and design

HN & MS- Analysis and interpretation of data

HN, MB, SS & RJD- Drafting/revising the article

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