The Evolving Diagnosis and Care of Patients with Acute Hepatic Porphyria (AHP) in the UK: from 2006 to 2018

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Background and Rationale

Acute Hepatic Porphyria (AHP)[1-5]

- AHP, a subset of porphyria, refers to a family of rare, genetic diseases characterized by potentially life-threatening acute attacks and, for some patients, chronic manifestations that negatively impact daily functioning and quality of life (QoL)
- The four types of AHP are acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and 5'-aminolevulinic acid dehydratase deficiency porphyria (ADP)

Attacks, Chronic Manifestations, and Quality of Life[4,6]

- Patients can experience acute neurovisceral attacks, which can be life-threatening, that commonly manifest as severe, diffuse abdominal pain
- Patients may also experience nausea and fatigue, along with mental and autonomic symptoms
- Patients with AHP experiencing recurrent attacks report diminished QoL compared with population norms. There is also a significant economic burden in this patient group, with increased healthcare utilization and substantial numbers of lost work days, along with many patients not in full-time employment and receiving disability payments

Urgency to Diagnose[3,7-10]

- Patients experiencing acute attacks often present to emergency departments where rare diseases, such as AHP, are generally not considered as a part of the differential diagnosis when assessing for acute abdominal pain
- However, a timely diagnosis of AHP is crucial as untreated acute attacks can progress, become more severe and potentially lead to permanent neurological damage, or even be life-threatening
- Many drugs can increase hepatic heme requirements, meaning, undiagnosed patients may inadvertently be prescribed medications that induce or worsen attacks
- AHP diagnosis and treatment in the United Kingdom (UK) has evolved to include the creation of the National Acute Porphyria Service (NAPS) and associated regional care centers in 2012

Objective

- To describe the patient journey to AHP diagnosis, attack management, and satisfaction with treatment in the UK from 2006 to 2018

Methods

Methodology

- AHP patients identified through their British Porphyria Association (BPA) membership were invited to complete a descriptive, qualitative survey in 2006
  - The survey included only those with AHP (AIP, HCP, VP)
  - The survey contained 14 questions which was sent by mail to all BPA members
- A similar survey reviewed and approved by Alnylam Pharmaceuticals and the BPA was conducted in 2018 to explore the burden of illness of AHP and their caregivers (Figure 1)
  - Data collected in two phases; 1) web-based survey sent to members of the BPA to collect top-line information on the burden of illness associated with AHP 2) survey participants invited to telephone interviews to discuss their day-to-day experience of AHP
  - Web-based survey was open for 22 days and interviews followed shortly after
  - All patients aged 18 and over with a confirmed diagnosis of AHP and caregivers aged 18 or over of patients with a confirmed diagnosis of AHP were considered eligible to participate in the survey
- Both surveys assessed delay in diagnosis, disease management, and treatment satisfaction

Figure 1: 2018 Survey Design

*Response rate was calculated based on the BPA database which consists of 270 individuals with or affected by AHP. It was not possible to separate patients and caregivers
+Not all participants answered every question. Therefore, the number of participants varies for each question

Results

Patient Demographics

- Responses were collected from 92 patients in 2006, and 38 patients in 2018 (Table 1)
- The proportion of patients with AIP was higher in the 2018 survey than the BPA survey in 2006 (95% vs. 80%) and there was also a higher proportion of females (95% vs. 80%)

Table 1: Patient Characteristics and Diagnoses

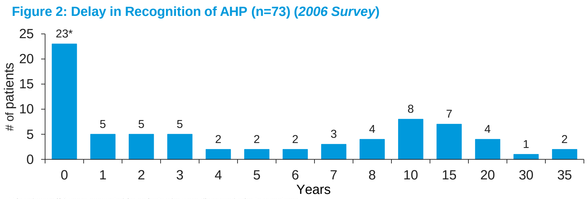
	Survey 2006 (N=92)	Survey 2018 (N=38)
Response Rate, %	22%	50%
Female, n (%)	74 (80%)	36 (95%)
AHP Type, n (%)		
AIP	51 (55%)	28 (74%)
VP	33 (36%)	9 (23%)
HCP	7 (8%)	1 (3%)
Two of these	1 (1%)	N/A

*The 2006 survey was mailed to all BPA members with AIP, HCP, and VP whilst the 2018 survey was shared via the BPA website and social media. Additionally, the 2018 survey included more questions. This may have affected response rates and population reached.

Delayed Diagnosis: 2006

- According to the 2006 survey, just over half of people were diagnosed with AHP within 3 years of experiencing symptoms, but a third of respondents waited 10 years or more for diagnosis (Figure 2)

Figure 2: Delay in Recognition of AHP (n=73) (*2006 Survey*)



*It is unknown if 0 years accounted for patients who were diagnosed prior to symptoms

Delayed Diagnosis: 2018

- Excluding those diagnosed before experiencing symptoms, respondents of the 2018 survey reported a mean delay between first experiencing symptoms and diagnosis of 4.2 years (SD=5.9)
- Patients first experienced symptoms of AHP at a mean age of 22.4 years and were diagnosed at a mean age of 23.7 years (Figure 3,4)

Figure 3: Age of First Experienced Symptoms (n=36) (*2018 Survey*)

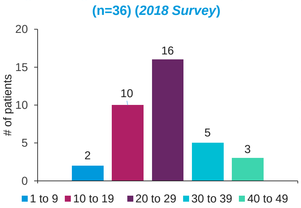
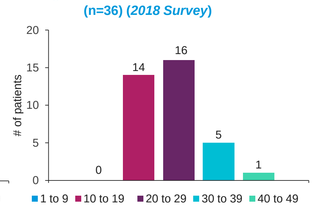


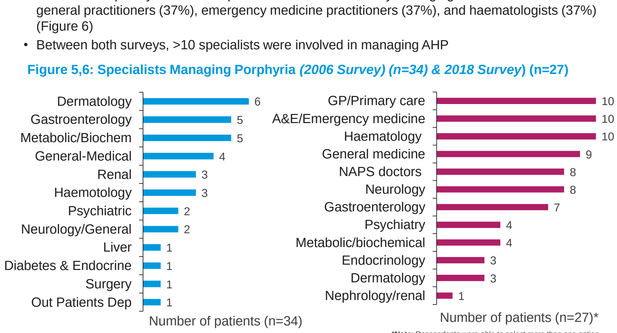
Figure 4: Age of Diagnosis of AHP (n=36) (*2018 Survey*)



Physician Demographics

- Specialists managing patients' AHP in 2006 reflected a range of professionals with dermatology the most commonly seen specialist (17.6%) followed by gastroenterology (14.7%) (Figure 5)
- The most frequently mentioned specialists in the 2018 survey managing AHP attacks 2018 were general practitioners (37%), emergency medicine practitioners (37%), and haematologists (37%) (Figure 6)
- Between both surveys, >10 specialists were involved in managing AHP

Figure 5,6: Specialists Managing Porphyria *(2006 Survey) (n=34) & 2018 Survey)* (n=27)



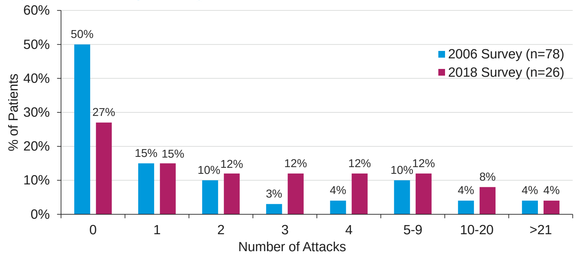
*Note: Respondents were able to select more than one option

Results (cont.)

Experience of Acute Attacks

- 85% (78/92) of 2006 survey respondents and 84% (32/38) of 2018 survey respondents reported having experienced an attack in their lifetime
- Of those who reported having experienced a previous attack, 50% (39/78) and 73% (19/26) of patients responding to the 2006 and 2018 surveys, respectively, had at least one attack in the last 2 years
- One 2006 survey respondent reported experiencing 100 attacks in the last two years (max) and one 2018 survey respondent reported experiencing 50 attacks in the last two years (max)

Figure 7: Patients Experiencing 1 Attacks in Last 2 Years



"The very first attack I ever had, it was six months in hospital and then the previous ones I've had, it was five days and then the last one I had was ten days"

2018 respondent on attacks requiring hospitalization

"I have not had a very bad attack since 1999. However I have quite a few illnesses and symptoms…from porphyria. Weakness is a constant one, and I find they [illnesses] are not often viewed as part of porphyria symptoms"

2006 respondent on symptoms between attacks

"Everyone has been no shorter than three weeks. Sometimes it's three weeks, sometimes it's four, sometimes it's ten, sometimes it's months"

2018 respondent on length of attacks

Hospitalization Due to Acute Attacks

- Of those experiencing at least one attack in the 2 years prior to the 2006 survey, 41% (16/39) of patients indicated needing hospital treatment (Figure 8)
- In the two years prior to the 2018 survey, 146 attacks were experienced by 23 respondents
  - 25% of attacks required hospital admission, 11% required emergency department services, 3% were manged at the clinic, and <1% required ICU admission; the remainder of attacks (61%) were managed at home (Figure 9)

Figure 8: Setting of Attack Management (n=39) (*2006 Survey*)

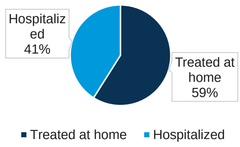
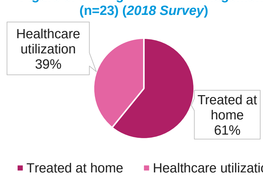


Figure 9: Setting of Attack Management (n=23) (*2018 Survey*)



*Healthcare utilization: Hospital admission (25%), ED without admission (11%), Clinic without admission (3%), and ICU admission (1%)

Treatment of Acute Attacks

- Of the 39 patients in 2006 who had experienced an acute attack in the past 2 years, glucose alone was the most commonly used treatment (49%) followed by no treatment (26%); treatment with hemin and glucose was used less frequently (15%) (Figure 10)
- Twenty seven of 32 patients in 2018 who had ever experienced an acute attack reported if they received treatments for the management of acute attacks
  - Hemin (30%) and hemin with glucose (33%) were the most commonly used treatments in 2018, followed by symptomatic relief (19%); treatment with glucose alone was used less frequently (7%) (Figure 11)

Figure 10: Treating Acute Attacks (n=39) (*2006 Survey*)

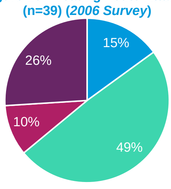
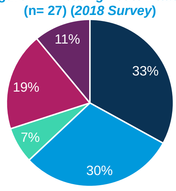


Figure 11: Treating Acute Attacks (n= 27) (*2018 Survey*)



Satisfaction with Treatment

- Thirty-four of 51 respondents (67%) were overall satisfied with treatment per the 2006 survey (Figure 12)
- Sixteen of 25 respondents (64%) reported that better knowledge of the disease among those treating patients would improve treatment according to the 2006 survey
- Twenty-seven patients reported their satisfaction with the management of acute attacks in the last 2 years in the 2018 survey (Figure 13)
  - In the 2018 survey, 29% of respondents reported being dissatisfied or very dissatisfied with knowledge of those treating patients

Figure 12: Satisfaction with Management of Acute Attacks (*2006 Survey*)

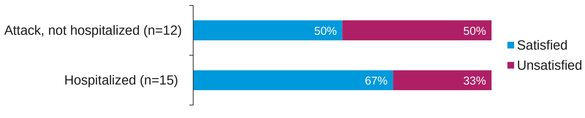
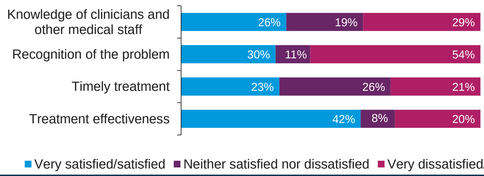


Figure 13: Satisfaction with Management of Acute Attacks (n=27) (*2018 Survey*)



Limitations

- Respondents were members of the BPA and may not be representative of the AHP population
- The sample size was small and there were variable response rates for each question as respondents had the option to not respond to every question
- The 2006 and 2018 surveys differed and therefore can not be directly compared
- The 2006 survey was shorter, less detailed, and mailed to participants while the 2018 survey was longer, more detailed, and available online which may have affected response rates and population reached
- The 2018 survey potentially captured responses from a more severely affected population than the 2006 population due to a smaller percentage of patients not having experienced a recent attack

Summary

- AHP delay in diagnosis varied widely in both studies with some patients being diagnosed years after first symptom onset
- Both surveys reflected that numerous specialists were involved in managing patients' AHP
- Patients reported varying levels of satisfaction in AHP treatment and management in both surveys
- The 2018 survey showed increase in hemin utilization for attack management compared to the 2006 survey
- Increasing disease awareness and availability of treatment options may help address unmet needs of patients

Acknowledgments & References

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1. Puy H et al. *Lancet* 2010;375:924–37; 2. Balwani M. Desnick RJ. *Hematology Am Soc Hematol Educ Program* 2012;2012:19–27; 3. Bonkovsky HL et al. *Am J Med* 2014;127:1233–41; 4. Wang B et al. *Hepatol Commun* 2018;3:193–206; 5. Balwani M et al. *Hepatology* 2017;66:1314–1322; 6. Pischik E, Kauppinen R. *Appl Clin Genet* 2015;8:201-14; 7. Wang B et al. *Hepatol Commun* 2018;3:193–206. 8. Anderson KE et al. *Ann Intern Med* 2005;142:439–450. 9. Stein PE et al. *Br J Haematol* 2017;176:527–538. 10. Stein PE et al. *Clin Med* 2012;12:293–4