EXPLORE B *post hoc* analysis of chronic symptoms in patients with acute hepatic porphyria

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Conclusions

- **Patients with AHP experience chronic symptoms regardless of their attack frequency**
- **Disease burden and HRQoL should be monitored when managing patients with nonrecurrent AHP**

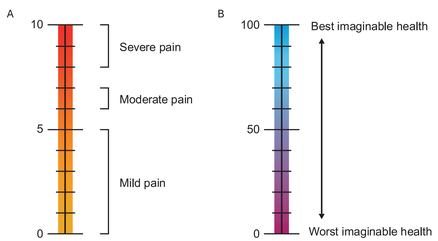
Introduction

- Acute hepatic porphyria (AHP) comprises 4 rare genetic diseases caused by defective heme biosynthesis:[1-3]
  - acute intermittent porphyria (AIP)
  - hereditary coproporphyria (HCP)
  - variegate porphyria (VP)
  - δ-aminolevulinic acid dehydratase deficiency porphyria (ADP)
- AHP manifests as acute neurovisceral attacks that:
  - are characterized by pain, dysautonomia, acute sensorimotor neuropathy, and encephalopathy
  - may lead to mild mental symptoms and chronic symptoms that can result in long-term complications[2-4]
- Current understanding of AHP disease impact is primarily informed by studies involving patients with recurrent attacks[3] (International Porphyria Network definition: ≥4 attacks/year)[5]
- Some patients experience chronic symptoms between attacks,[3,4] which may impair health-related quality of life (HRQoL)
- In the EXPLORE B observational study, 74% of patients with AHP had chronic symptoms regardless of attack frequency or prophylaxis[6]
- This *post hoc* analysis of baseline EXPLORE B data examined the relationship between attack frequency and chronic disease burden

Methods

- EXPLORE (NCT02240784) was a prospective observational study of the natural history of AHP
  - Part A followed up patients for ≤1 year using telephone and clinic visits
  - Part B was an optional long-term evaluation of pain intensity and disease activity for ≤3 additional years
  - EXPLORE B inclusion criteria:
    - ≥12 years old
    - ≥1 attack in last 12 months and/or hemin or gonadotropin-releasing hormone (GnRH) prophylaxis
- At baseline, patients completed survey questionnaires on chronic symptoms
  - Chronic symptoms were defined as symptoms experienced when not having an AHP attack

Figure 1. (A) BPI-SF and (B) EQ-VAS scales



BPI-SF, Brief Pain Inventory Short Form.

- Brief Pain Inventory Short Form (BPI-SF) used at baseline to measure pain intensity and impact in the past 24 hours (**Figure 1A**)
- EQ-5D and EQ-VAS assessments used at baseline to reflect the HRQoL of patients
  - EQ-5D categorizes health state across five dimensions and levels, which are used to calculate an overall index score
  - EQ-VAS captures overall health (**Figure 1B**)
  - Lower scores denote worse HRQoL
- EXPLORE B stratification by attack status (based on 12 months before enrollment):
  - <4 attacks/year and no hemin/GnRH prophylaxis
  - ≥4 attacks/year or hemin/GnRH prophylaxis
- Results are descriptive, and *p* values are nominal

Table 1. Baseline demographics and disease characteristics

Demographic/characteristic	<4 attacks/ year and no hemin/ GnRH (n=36)	≥4 attacks/ year or hemin/GnRH (n=100)	All patients (N=136)
Age at time of consent, years, mean (SD)	37.5 (10.9)	42.2 (13.0)	41.0 (12.6)
Female, n (%)	32 (88.9)	91 (91.0)	123 (90.4)
Years since diagnosis, mean (SD)	9.37 (11.69)	12.02 (11.62)	11.31 (11.65)
Race/ethnicity, n (%)			
White	29 (80.6)	86 (86.0)	115 (84.6)
Asian	3 (8.3)	6 (6.0)	9 (6.6)
Black/African American	3 (8.3)	3 (3.0)	6 (4.4)
American Indian/Alaska Native	0	1 (1.0)	1 (0.7)
Other	1 (2.8)	3 (3.0)	4 (2.9)
Not stated	0	1 (1.0)	1 (0.7)
Geographic region, n (%)			
Europe	23 (63.9)	47 (47.0)	70 (51.5)
North America	8 (22.2)	48 (48.0)	56 (41.2)
Other (Africa, Asia, Australia)	5 (13.9)	5 (5.0)	10 (7.4)
Porphyria type, n (%)			
AIP	32 (88.9)	91 (91.0)	123 (90.4)
HCP	1 (2.8)	1 (1.0)	2 (1.5)
VP	3 (8.3)	8 (8.0)	11 (8.1)
ADP	0	0	0
Attacks in last 12 months, mean (SD)	1.9 (0.9)	7.9 (9.1)	5.9 (8.0)

ADP, δ-aminolevulinic acid dehydratase deficiency porphyria; AIP, acute intermittent porphyria; GnRH, gonadotropin-releasing hormone; HCP, hereditary coproporphyria; SD, standard deviation; VP, variegate porphyria.

Results

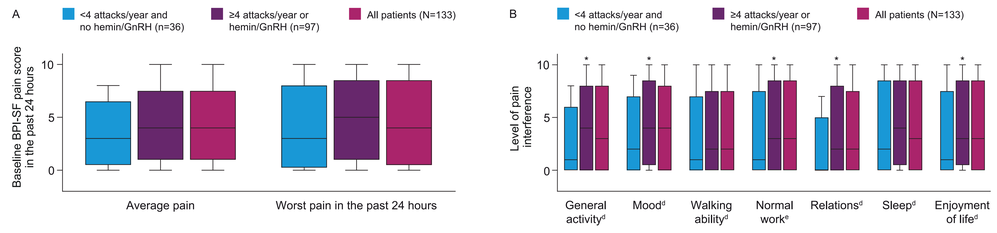
- Patients included: N=136 (**Table 1**)
  - <4 attacks/year n=36 (26%)
  - ≥4 attacks/year n=100 (74%)
- Demographics were broadly similar
  - Most common porphyria type in all groups was AIP
  - Patients with ≥4 attacks/year were older, with more time since diagnosis
- Most patients reported chronic symptoms at baseline (**Table 2**)
  - Reports of 'trouble sleeping' or 'other' symptoms were more likely for patients with ≥4 attacks/year vs <4 attacks/year
  - No other notable between-group differences in the odds of reporting chronic symptoms
- Average and worst BPI-SF scores were similar between groups (**Figure 2A**)
  - Patients with ≥4 attacks/year reported a greater level of pain interference than patients with <4 attacks/year for 5 of the 7 individual items (**Figure 2B**)
  - Mean between-group differences did not exceed the minimal clinically important difference (2 points) for any item
- EQ-5D-5L index scores: lower for patients with ≥4 attacks/year vs <4 attacks/year (**Figure 3A**)
- EQ-VAS scores: similar between groups (**Figure 3B**)
- EQ-5D dimension scores (odds of experiencing moderate or worse problems): no difference between groups for any dimension (**Figure 4**)

Table 2. Commonly reported chronic symptoms

Chronic symptom	Odds ratio[a] (95% CI)	*p* value
Any pain symptoms	2.83 (0.14, 56.55)	0.2785
Abdominal pain	1.18 (0.35, 4.02)	0.7919
Back pain	1.01 (0.39, 2.65)	0.9846
Muscle pain	0.74 (0.30, 1.79)	0.5035
Headache	0.54 (0.22, 1.33)	0.1791
Any mood or sleep symptoms	5.49 (0.30, 100.72)	0.1196
Tiredness	1.98 (0.52, 7.49)	0.3112
Trouble sleeping	**3.52 (1.10, 11.24)**	**0.0276**
Anxiety	0.71 (0.29, 1.76)	0.4612
Any digestive symptoms	1.57 (0.17, 14.64)	0.6938
Nausea	0.65 (0.23, 1.85)	0.4192
Urine color change	1.38 (0.51, 3.71)	0.5239
Constipation	0.83 (0.33, 2.07)	0.6880
Any nervous system symptoms	0.64 (0.17, 2.37)	0.4998
Weakness	1.01 (0.39, 2.65)	0.9846
Sensitive nerves	0.54 (0.22, 1.33)	0.1791
Tingling	0.57 (0.23, 1.40)	0.2215
Any other symptoms	**0.18 (0.05, 0.62)**	**0.0037**
Fast heart rate	0.81 (0.33, 1.93)	0.6293
Trouble breathing	0.44 (0.15, 1.31)	0.1373
Other	**0.12 (0.02, 0.97)**	**0.0211**

[a]Odds ratios for <4 vs ≥4 attacks/year. Odds ratios, 95% CIs, and *p* values were calculated from a Mantel–Haenszel chi-square test. Nominally significant between-group differences are shown in bold text.
CI, confidence interval.

Figure 2. BPI-SF scores for (A) average and worst pain and (B) pain interference in the past 24 hours by domain

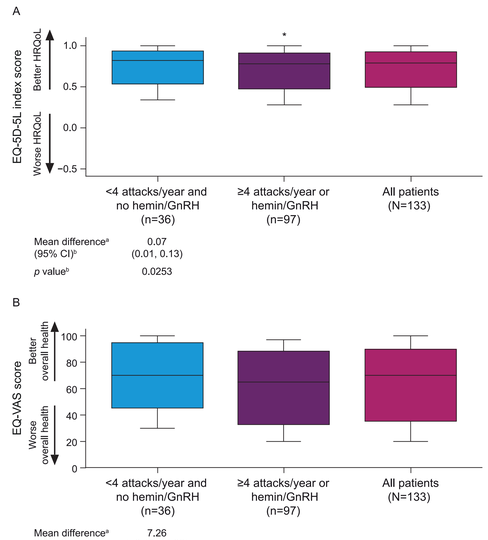


	Average pain	Worst pain in the past 24 hours
Mean difference[a] (95% CI)[b]	−0.63 (−1.54, 0.29)	−1.12 (−2.29, 0.06)
p value[c]	0.1772	0.0636

	General activity[d]	Mood[d]	Walking ability[d]	Normal work[e]	Relations[d]	Sleep[d]	Enjoyment of life[d]
Mean difference[a] (95% CI)[b]	−1.95 (−3.15, 0.75)	−1.66 (−2.89, 0.42)	−0.82 (−1.90, 0.26)	−1.45 (−2.78, 0.12)	−1.91 (−3.10, 0.72)	−1.14 (−2.50, 0.21)	−1.84 (−3.14, 0.54)
p value[c]	0.0016	0.0089	0.1355	0.0323	0.0019	0.0978	0.0058

Box plot reports median, interquartile range; error bars indicate min/max range. *Nominal significant difference (<4 vs ≥4 attacks/year).
[a]<4 vs ≥4 attacks/year. [b]Mantel–Haenszel chi-square test. [c]Two-sample t-test. [d]n=35 for <4 attacks/year, total N=132. [e]n=35 for <4 attacks/year, n=96 for ≥4 attacks/year, total N=131.
BPI-SF, Brief Pain Inventory Short Form; CI, confidence interval; GnRH, gonadotropin-releasing hormone.

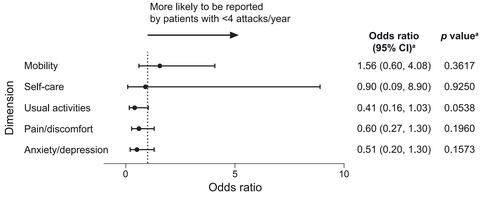
Figure 3. HRQoL assessed by (A) EQ-5D-5L index score and (B) EQ-VAS score



	A	B
Mean difference[a] (95% CI)[b]	0.07 (0.01, 0.13)	7.26 (−0.45, 14.98)
p value[b]	0.0253	0.0648

EQ-5D score is derived using the US reference value given for that particular set of responses in the five dimensions. Box plot reports median, interquartile range; error bars indicate min/max range.
*Nominal significant difference (<4 vs ≥4 attacks/year).
[a]<4 vs ≥4 attacks/year. [b]Two-sample t-test.
CI, confidence interval; GnRH, gonadotropin-releasing hormone; HRQoL, health-related quality of life.

Figure 4. Odds of experiencing moderate or worse problems in EQ-5D dimensions



The EQ-5D has five possible severity levels: no problems, slight problems, moderate problems, severe problems, and extreme problems/inability to carry out task. The odds (<4 vs ≥4 attacks/year) of experiencing problems worse than moderate (EQ-5D rating of >2) are shown. Odds ratio >1 indicates the odds of the outcome are higher for patients with <4 attacks/year.
[a]Odds ratio, 95% CI, and *p* values were calculated from a Mantel–Haenszel chi-square test.
CI, confidence interval.

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SM has received advisory board and speaker fees from Alnylam Pharmaceuticals, and speaker fees from Medison Pharma. **MT** is a consultant for Alnylam Pharmaceuticals and has served as a consultant for Disc Medicine, Mitsubishi Tanabe, and Recordati Rare Diseases. **RK** has been an Orion Pharma stockholder and Alnylam Pharmaceuticals expert consultant. **EG-N** received grants/research support, paid to the Fundación para la Formación e Investigación Biosanitaria-FFIS, from Alnylam Pharmaceuticals, and consulting fees from Alnylam Pharmaceuticals, BioMarin, and UCB. **DM**, **TLK**, and **WD** are employees of and own stock and stock options in Alnylam Pharmaceuticals. **DC** and the University of Leuven and University Hospitals Leuven have received speaker fees, and consultancy and advisory board compensations from Alnylam Pharmaceuticals and Recordati.

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