ABSTRACTS

International Congress on Porphyrins and Porphyrias (ICPP)

4- 7 September 2022

Sofia, Bulgaria

Recombinant porphobilinogen deaminase targeted to the liver corrects enzymopenia in a mouse model of acute intermittent porphyria

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Content Background

Correction of enzymatic deficits in hepatocytes by simple systemic administration of a recombinant protein is a desired therapeutic goal for hepatic enzymopenic disorders such as acute intermittent porphyria (AIP), an inherited porphobilinogen deaminase (PBGD) deficiency. An rhPBGD enzyme-replacement product (Porphozym®) was attempted as a therapeutic option to reduce serum PBG levels during an acute attack. However, the short half-life of rhPBGD protein in the circulation and lack of liver targeting lead to a prompt interruption of the trial (NCT00418795). Our aim was to evaluate the therapeutic efficacy of a recombinant PBGD protein conjugated to apolipoprotein A-I (ApoAI) in AIP mice.

Results

In vivo experiments showed that ApoAI conjugation increased serum half-life of the rhPBGD from 45 min (unconjugated) to 9.9h. We found that PBGD linked to apoAI (rhApoAI-PBGD), but not unconjugated PBGD, circulates incorporated into high-density lipoproteins, penetrates into hepatocytes and crosses the blood-brain barrier, increasing PBGD activity in liver and brain. Thus, rhApoAI-PBGD was able to abrogate acute porphyric attacks in AIP mice after intravenous or subcutaneous administration. ApoAI linked to a PBGD variant containing two amino acid substitutions (PBGDms) conferring it enhanced enzymatic activity, was still detected in the liver one month after a single intravenous dose and showed a long-lasting therapeutic effect.

Conclusions

Our findings support a new system for transferring functional enzymes into hepatocytes thus opening a new therapeutic avenue for AIP and other enzymatic deficiencies affecting the liver.

Givosiran therapy: adjusting treatment duration in patients with Acute Hepatic Porphyria

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Content Background
Givosiran, a small interfering RNA (siRNA) targeting the first step in hepatic heme biosynthesis, mediated by the ubiquitous 5-aminolevulinic acid synthase (ALAS1), is a novel therapeutic approved for the treatment of acute hepatic porphyria (AHP).
Materials and Methods
Since 2016, the Swedish Porphyria Centre has treated 19 AHP patients with givosiran, the majority (18) with acute intermittent porphyria (1 variegate porphyria). Nine patients were recruited in the ALNAS1-studies and ten in the Early Access Program. Mean age on treatment start was 37,5 (range 18-74). All patients had severe disease with recurrent attacks (>4/year) requiring hospitalization and treatment with hemin; 7 received hemin prophylactically prior to givosiran start. The duration of severe recurrent disease varied, ranging from <1 year in 6 patients, 1-4 years in 8 patients, 7-10 years in 3 patients and >10 years in 2 patients.
Treatment dose was at 2.5mg/kg. Two patients developed recurring liver aminotransferase elevation and received reduced dosing at 1.25mg/kg. Dosing interval was 4-8 weeks.
Results
Treatment was stopped in three patients due to adverse reactions (acute anaphylaxis, a 9,9-fold elevation of liver aminotransferases and severe fatigue, respectively). Of the remaining 16, 13 have completed treatment, 1 is completing treatment within the next 6 months whereas 2 are ongoing. Patients with a longer duration of recurrent disease received more doses (mean 52.8, range 47-57), whereas those with a shorter recurrency period received less (mean 26.6, range 14-51) before treatment completion.
The follow up period of those completing treatment is currently at 0-15 months, with no acute attacks and one completed pregnancy/live birth post-givosiran.
Conclusions
Duration of recurrence prior to treatment is a strong predictor of the treatment length required to reach remission.

Perspective of patients with erythropoietic protoporphyria treated with dersimelagon, a selective melanocortin receptor agonist: Results of the ENDEAVOR study exit questionnaire

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Disclosures: KB is an employee of MTDA, FT is an employee of MTPC, SM is an employee of RTI-HS, and TF is a paid consultant of MTDA and MTHA.

Background: Erythropoietic protoporphyria (EPP) imposes a significant burden on the quality of life (QoL) of patients. Dersimelagon, a novel synthetic, orally administered, selective melanocortin-1 receptor agonist, has demonstrated statistically and clinically significant improvement from baseline in average daily time to first prodromal symptoms in a phase 2 clinical trial.

Methods: ENDEAVOR was a multicenter, phase 2, randomized double-blind, placebo-controlled study with a 16-week treatment and 6-week follow-up period. Here we report the results of a post hoc analysis assessing the clinical benefit of dersimelagon treatment and patient perspective of QoL using an online exit questionnaire comprised of 28 close-ended questions completed after week 22 visit or post study completion. Participants rated their perceived change since the start of the study.

Results: Of 102 participants, 75 (placebo, n=24; dersimelagon, 100mg, n=28, 300mg n=23) completed the questionnaire. More recipients of dersimelagon (100mg, 57.6%; 300mg 31.4%) rated their EPP as “very much better” than placebo group participants (5.9%). They were also “much more often” (100mg, 69.7%; 300mg 48.6%) able to be outside at the end of the study than patients in the placebo group (8.8%). More participants who received dersimelagon (100mg, 72.7%; 300mg 62.9%) reported being “very satisfied” with the study drug vs placebo recipients (14.7%).

Conclusions: A greater proportion of patients who received dersimelagon reported improvements in their EPP and associated disease impacts than placebo group participants. The findings from the exit questionnaire support the results from the primary analysis and the potential use of dersimelagon for treatment of patients with EPP.

References

Naik H, Overbey JR, Desnick RJ, et al. Evaluating quality of life tools in North American patients with erythropoietic protoporphyria and X-linked protoporphyria. *JIMD Rep*. 2019;50(1):9-19.

Towards a FECH splicing dependent model of Erythropoietic Protoporphyria in the house mouse

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Content Abstract

Erythropoietic Protoporphyria (EPP) is a rare genetic disorder that manifests primarily through severe photosensitivity [1]. It is caused by an accumulation of protoporphyrin nine (PPIX), the penultimate product in the haem biosynthesis pathway; either due to a lack-of-function of the terminal enzyme (FECH) or an overregulation of the initial enzyme (ALAS). The most common underlying genotype is a loss-of-function FECH allele in trans to a single-nucleotide polymorphism (SNP) leading to aberrant splicing and subsequent degradation of FECH mRNA [2]. Current treatment options are sparse and disease management mainly focuses on avoiding exposure to sunlight, which comes with a tremendous decrease in quality of life [3].

It has previously been shown that antisense oligonucleotides (ASOs) directed against the detrimental SNP are able to correct splicing of FECH mRNA; thereby increasing FECH enzyme levels, leading to reduced accumulation of phototoxic PPIX [4–6]. Further development of these splice-switching oligonucleotides (SSOs) and other mechanistic therapies is however currently hindered by the lack of adequate model systems in-vivo.

Here we present our latest data towards the first model of splicing-dependent EPP in the house mouse; and its utility for the development of new therapies against EPP.

References

1. Magnus, I. A., Jarrett, A., Prankerd, T. A. J. & Rimington, C. Lancet (1961).

2. Gouya, L. et al. Am. J. Hum. Genet. (2006).

3. Naik, H., Shenbagam, S., Go, A. M. & Balwani, M. Mol. Genet. Metab. (2019).

4. Oustric, V. et al. Am. J. Hum. Genet. (2014).

5. Mirmiran, A. et al. Am. J. Hum. Genet. (2019).

6. Halloy, F. et al. Nucleic Acids Res. (2020).

Afamelanotide is associated with dose-dependent liver-protective effect in erythropoietic protoporphyria (EPP)

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Content Background: In animal models, melanocyte-stimulating hormones (MSHs) protect the liver from various injuries. EPP causes incapacitating phototoxic skin reactions due to the accumulation of protoporphyrin (PPIX). Additionally, 20% of EPP patients exhibit abnormal liver function tests (LFTs) and 4% liver failure, caused by the hepatobiliary elimination of excess PPIX. Skin symptoms are mitigated by the application of afamelanotide, an α-MSH analogue, as implant every sixty days. We recently showed improved LFTs in response to treatment with afamelanotide. Now, we investigate whether this effect is dose-dependent, as such a finding would further support a beneficial liver protective effect of afamelanotide.

Methods: In this retrospective observational study, we included 2933 LFTs, 1186 PPIX-concentrations and 1659 afamelanotide implant applications in 70 EPP patients. We investigated whether the number of days since the preceding afamelanotide dose or the number of doses during the preceding 365 or 730 days had an effect on LFTs and PPIX levels.

Results: Inter-patient differences exerted the strongest effects on PPIX and liver function tests. PPIX increased significantly with increasing number of days since last afamelanotide implant ($p<0.0001$). An increasing number of afamelanotide doses within the preceding 365 days correlated negatively with ALAT and bilirubin ($p=0.012$, $p=0.03$) and those within the preceding 730 days with bilirubin, ASAT and ALAT ($p<0.0001$; $p=0.015$, $p=0.005$), thereby more than 8-9 doses per 730 days were associated with the best response to elevated LFTs.

Conclusion: Our findings suggest that afamelanotide dose-dependently exerts liver protective effects in EPP, whereby more than four doses/ year and a treatment duration of two years are required to elicit a significant outcome.

NOD2-variants in Porphyria cutanea tarda

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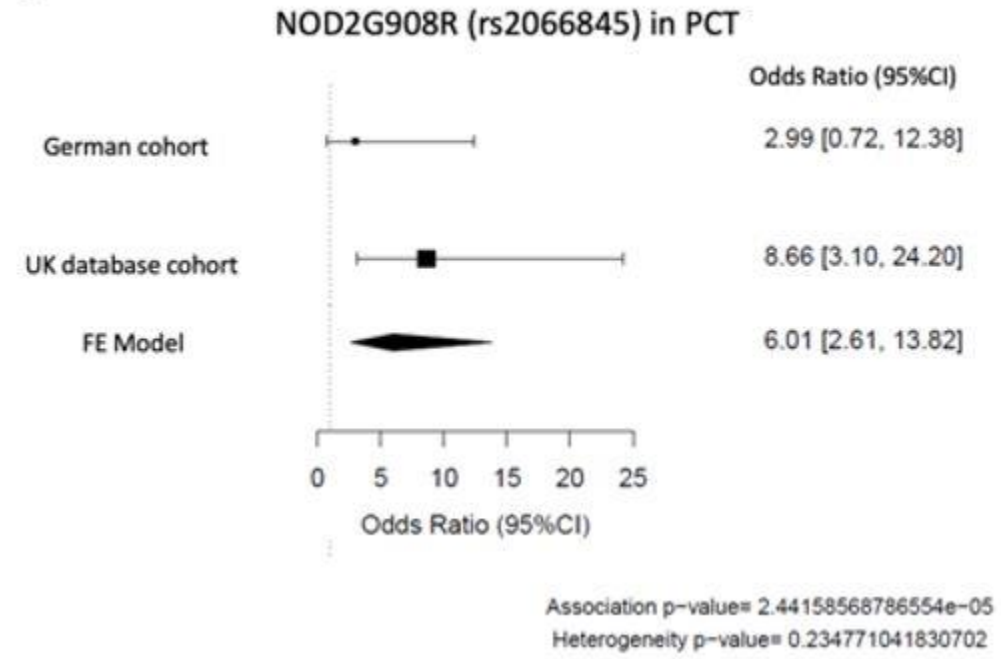
Content Background and Aims: Porphyria cutanea tarda (PCT) is associated with several metabolic and inflammatory liver diseases and increased risk of HCC. NOD2 is participating in the balance of the immune response and play a role in the development in HCC. We aimed to investigate NOD2 variants in PCT and compared with available data derived from large Caucasian population studies (gnomad and UK database).

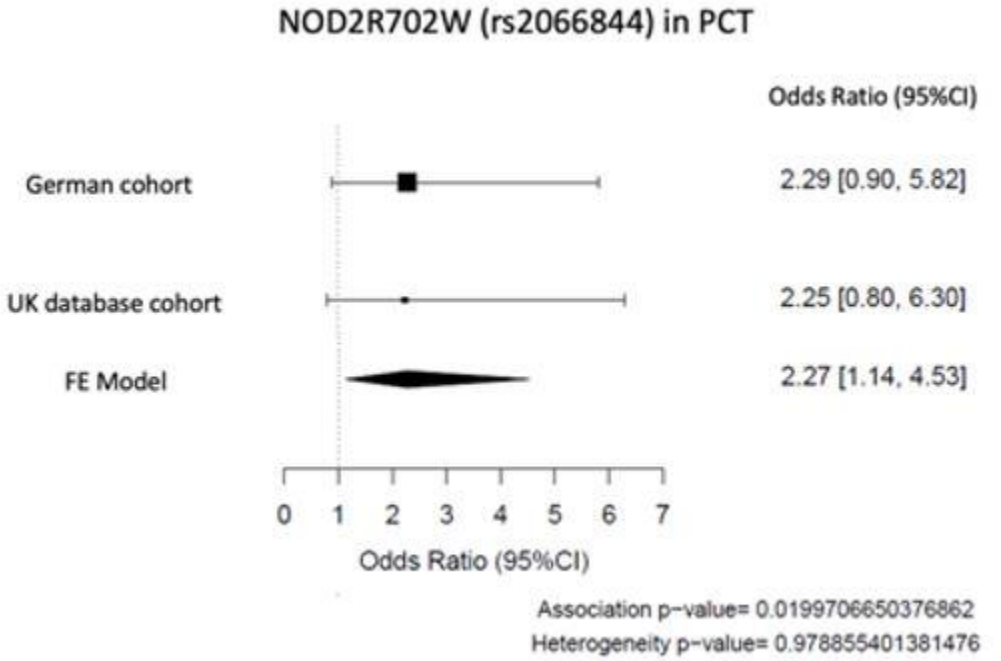
Method: The NOD2 variants rs2066844 (p.R702W), rs2066847 (c.3020insC), rs2066845 (p.G908R), rs72796367 (c.958T) and rs5743271 (c.866A) were genotyped in 20 patients with porphyria cutanea tarda. The European, non-Finnish cohort of the corresponding polymorphisms available at the gnomad database were used as control. We furthermore searched the UK database for patients with PCT and their minor allele frequency (MAF) for the mentioned NOD2-polymorphisms.

Results: A significant higher frequency of the NOD2 c958T variant was detected in the German PCT cohort (p=0.032; OR 3.384 (95%CI: 1.038-11.027)). Moreover, we found significant more common carriers of the NOD2 G908R variant within the UK database PCT cohort. A further trend of an accumulation of the NOD2 variants NOD2 R702W, NOD2 G908R and NOD2 c866A was shown German PCT cohort. Meta-analysis of both, the German PCT cohort and PCT cases retrieved from the UK database cohort displayed another significant association of the NOD2 G908R (p=2.44x10-5; OR 6.01 (95%CI 2.61-13.82)) and the NOD2R702W (p=0.02; OR 2.27 (95%CI1.14-4.53)) variants and patients with PCT.

Conclusion: Identified variants in NOD2 gene may contribute to trigger overt PCT.

Figure:


NOD2G908R (rs2066845) in PCT
Odds Ratio (95%CI)
German cohort
2.99 [0.72, 12.38]
UK database cohort
8.66 [3.10, 24.20]
FE Model
6.01 [2.61, 13.82]
0 5 10 15 20 25
Odds Ratio (95%CI)
Association p−value= 2.44158568786554e−05
Heterogeneity p−value= 0.234771041830702


NOD2R702W (rs2066844) in PCT
Odds Ratio (95%CI)
German cohort
2.29 [0.90, 5.82]
UK database cohort
2.25 [0.80, 6.30]
FE Model
2.27 [1.14, 4.53]
0 1 2 3 4 5 6 7
Odds Ratio (95%CI)
Association p−value= 0.0199706650376862
Heterogeneity p−value= 0.978855401381476

HOMA score and periodontitis in acute intermittent porphyria - results from a case control study

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Content Background
Patients with acute intermittent porphyria (AIP) have been advised to a high carbohydrate intake due to the "glucose effect" since increased levels of glucose and insulin may lower AIP disease activity. Insulin resistance is a known risk factor for periodontitis. We hypothesized differences in Homeostasis model assessment (HOMA) scores for insulin resistance in AIP cases vs. controls and in those with periodontitis.
Materials and methods
Case-control study of 47 AIP cases and 47 controls matched for age, gender and place of residence. C-peptide in EDTA plasma was analyzed with A Bio-Plex pro human diabetes 10-plex kit and cytokines in EDTA plasma with a 27-plex kit, both on a Bio-Plex 200 system, from Bio-Rad Lab. Inc. An excel spreadsheet from the University of Oxford was used to estimate beta cell function, HOMA%B (%B), insulin sensitivity, HOMA%S (%S) and insulin resistance HOMA-IR (IR), based on serum glucose and plasma C-peptide. Periodontitis was assessed in 47 of the initial 50 AIP cases and 47 of their 50 matched controls, as three cases and one control were edentulous. Probing pocket depth (PPD), a marker of periodontitis, was assessed by probe UNC15. Wilcoxon matched-pairs signed rank test, Mann-Whitney U-test and Spearman correlation were performed in GraphPad Prism.
Results
Comparing all 47 AIP cases with 47 matched controls we found a lower %B in AIP cases (median 67 %) vs. controls (median 75 %), (p=0.005%), a higher %S (p=0.02) and a lower IR (p=0.04). The AIP cases with periodontitis (n=14) had lower %S and higher IR than AIP cases without periodontitis (n=33) (p=0.007). In AIP cases the %S correlated negatively with the periodontitis marker number of PPD > 5mm (p= 0.0006) and with missing teeth (n) (p=0.03). We found that %B in AIP cases was significantly negatively correlated with several cytokines in plasma, IL-5, IL-7, IL-10, IL-12, IL-15, CCL11, GM-CSF, MIP-1β, TNF (all $p < 0.05$).
Conclusions
In AIP cases beta cell function and insulin resistance was lower, and insulin sensitivity higher compared to matched controls. In AIP cases a lower beta cell function was associated with inflammation. Periodontitis in AIP was associated with a lower insulin sensitivity and higher insulin resistance.

Phase 2, Randomized, Open-label Trial of Bitopertin in Erythropoietic Protoporphyria: BEACON Trial Design

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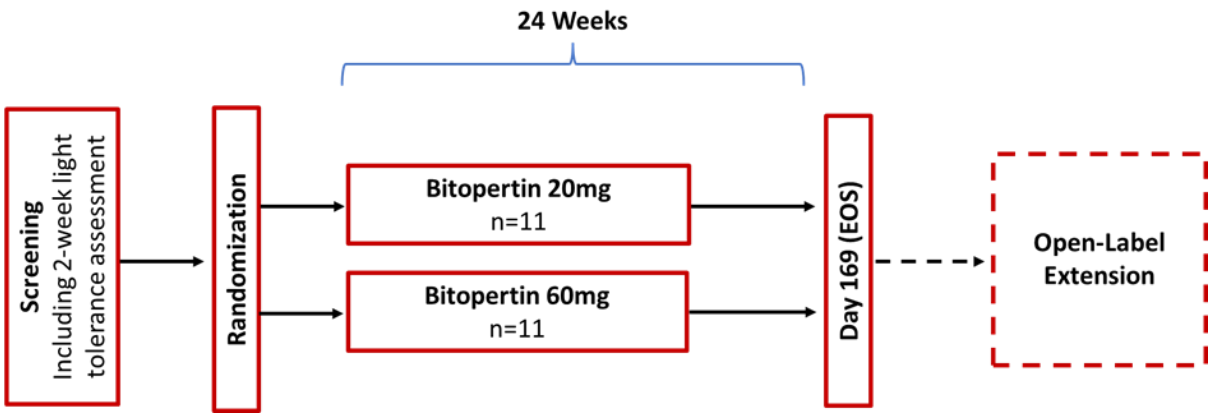
Content Background:
Erythropoietic protoporphyria (EPP) caused by FECH and ALAS2 mutations results in toxic accumulation of photoreactive protoporphyrin IX (PPIX). High levels of PPIX result in excruciating phototoxic reactions and hepatopathy caused by biliary stasis. Reduction of PPIX is associated with amelioration of disease in the settings of hematopoietic stem cell transplant, pregnancy and extracorporeal photoinactivation.

Bitopertin is a small molecule inhibitor of glycine transporter 1 (GlyT1), which imports large amounts of extracellular glycine into erythropoietic precursors. GlyT1 is needed to supply adequate amounts of substrate for the heme synthesis pathway to enable the large amounts of hemoglobin needed for normal red blood cell production. Treatment of EPP mouse models with FECH and ALAS2 mutations resulted in 45-73% reduction in PPIX, as compared to controls (Hong et al. 2021). These data, combined with a favorable safety profile that has previously been well-established in over 4,000 patients and healthy volunteers motivates the current study to evaluate this potentially disease-modifying treatment.

Study Design and Methods:
This is a Phase 2, randomized, open-label, parallel arm trial of 20 and 60 mg bitopertin daily for 24 weeks in EPP patients. The trial is being conducted at 2 sites in Australia. The primary endpoint is percent change in metal-free PPIX. Secondary endpoints include patient reported outcomes of light tolerance, safety and tolerability, and PK parameters. Eligibility criteria include: age ≥18 years with EPP by FECH/ALAS2 genotyping or porphyrin analysis, AST/ALT <2x upper limit of normal, normal bilirubin, and hemoglobin ≥100 g/L. Up to 22 participants will be randomized and stratified by baseline daily light tolerance (< or ≥ 30 minutes) and study site. Study sample size calculations were not performed for this first in EPP study. Endpoints will be summarized using descriptive statistics.

Results:
Subject enrollment is planned to begin mid-2022. Initial data may be presented at the meeting if available.



The impact of acute hepatic porphyria on mental health: Results from the Porphyria Worldwide Patient Experience Research (POWER) study

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Content Background and Aims
Acute hepatic porphyria (AHP) is a group of genetic diseases of haem biosynthesis characterised by acute pain attacks. AHP is also associated with psychiatric symptoms, including depression and anxiety. This study evaluated the effects of AHP on social life, personal life/goals, depression, and anxiety.

Methods
Adult patients who experienced >1 AHP attack within the past 2 years or were receiving intravenous hemin and/or glucose for attack prevention were recruited worldwide and administered an online survey. Patients taking givosiran were excluded. The Patient Health Questionnaire depression scale (PHQ-8) and the 7-item Generalized Anxiety Disorder scale (GAD-7) were used to screen patients for depression and anxiety among all patients as well as subgroups, including those with sporadic attacks vs recurrent attacks (0–5 vs ≥6 attacks over 2 years), those receiving vs not receiving prophylactic treatment, and those with an active disease duration of 0–5 years vs ≥6 years.

Results
Ninety-two patients with AHP completed the survey. Patients reported substantial impact on social life—76.1% of patients reported that most of their symptoms were hidden and that people in their social circle did not know they had AHP. Patients' personal life/goals were also impacted, with >80% of patients reporting having had to modify or give up goals important to them. PHQ-8 scores indicating moderate to severe depression were reported in more than half of patients with AHP (58.7%) regardless of attack rate or prophylactic treatment status. GAD-7 scores indicating moderate to severe anxiety were reported in 48.9% of patients and were highest in patients experiencing recurrent attacks (56.8%).

Conclusions
Patients with AHP, regardless of attack rate, treatment received, or duration of active disease, experience a high mental health burden on their personal and social life, highlighting the importance of mental health monitoring as part of disease management for AHP.

Funding: This study was funded by Alnylam Pharmaceuticals.
Acknowledgements: Editorial assistance was provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Alnylam Pharmaceuticals.

DISCLOSURES

Danielle Nance served on advisory boards for Aptevo Therapeutics, Bayer, HemaBiologics, and Medexus Pharmaceuticals; served on speaker bureaus for BPL and the National Hemophilia Foundation; provided consulting services to Goval; served as an author for Bayer; and had speaking engagements and received consulting honoraria from Alnylam Pharmaceuticals for participation in this research.

Desiree Lyon received grant and sponsorship funding to the American Porphyria Foundation from Alnylam Pharmaceuticals.

Sean Hegarty, Rocco Falchetto, and Jasmin Barman-Aksözen reported having nothing to disclose.

Joana E. Matos was employed by Kantar Health (now Cerner Enviza) at the time of the study.

Stephen Meninger and Stephen Lombardelli are employed by and own stock and stock options in Alnylam Pharmaceuticals.

Amy Dickey had speaking engagements and received consulting honoraria from Alnylam Pharmaceuticals for participation in this research and for other porphyria-related consulting.

Acute hepatic porphyria attack frequency and patient-reported outcomes: Results from the Porphyria Worldwide Patient Experience Research (POWER) study

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Content Background and Aims
Acute hepatic porphyria (AHP), a group of genetic diseases of haem biosynthesis, is characterised by neurovisceral attacks. This study evaluated the impact of AHP on patient-reported outcomes (PROs) and disease burden in AHP patients who experience sporadic or recurrent attacks.

Methods
Adult patients having >1 AHP attack in the past 2 years or receiving intravenous hemin and/or glucose for attack prevention were recruited worldwide and administered an online survey from January 19 to April 26, 2021. Patients taking givosiran were excluded. Descriptive and bivariate analyses were performed to evaluate differences between patients with sporadic attacks (annualised attack rate [AAR], <6 in past 2 years) and recurrent attacks (AAR, ≥6). PROs were assessed with the Generalized Anxiety Disorder-7 (GAD-7) scale (0–21) and the Patient Health Questionnaire (PHQ-8) scale (0–24). Burden of chronic symptoms was also reported.

Results
Of the 92 AHP patients who completed the survey, 55 reported sporadic attacks and 37 reported recurrent attacks. Most patients were female, and the most frequent diagnosis was acute intermittent porphyria. A majority of patients in the sporadic (52.7%) and recurrent (67.6%) attack groups reported a PHQ-8 score ≥10, indicating moderate to severe depression; 43.6% and 56.8% of patients in the sporadic and recurrent groups, respectively, reported a GAD-7 score ≥10, indicating moderate to severe anxiety. Pain was reported as one of the top 3 most burdensome chronic symptoms in the sporadic (50.9%) and recurrent (59.5%) groups. Of patients reporting their daily activities being limited by severe chronic symptoms, 83.3% of those in the sporadic and 90.6% in the recurrent group reported muscle weakness as a top 3 symptom having a moderate to severe impact.

Conclusions
Both sporadic and recurrent attack group patients experienced a substantial impact on physical, mental, and emotional quality of life.

Funding: This study was funded by Alnylam Pharmaceuticals.
Acknowledgements: Editorial assistance was provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Alnylam Pharmaceuticals.

DISCLOSURES

Amy Dickey had speaking engagements and received consulting honoraria from Alnylam Pharmaceuticals for participation in this research and for other porphyria-related consulting.

Kristen Wheeden was employed by the American Porphyria Foundation at the time of the study and currently is president of the United Porphyrias Association. She received grant and sponsorship funding to the American Porphyria Foundation from Alnylam Pharmaceuticals and served on a medical advisory board for Alnylam Pharmaceuticals.

Sue Burrell received grant and sponsorship funding to the British Porphyria Association as well as consulting honoraria from Alnylam Pharmaceuticals for participation on various patient advisory group leadership advisory boards.

Rocco Falchetto, Jasmin Barman-Aksözen, and Alison Bulkley reported having nothing to disclose.

Stephen Meninger and Stephen Lombardelli are employed by and own stock and stock options in Alnylam Pharmaceuticals.

Danielle Nance served on advisory boards for Aptevo Therapeutics, Bayer, HemaBiologics, and Medexus Pharmaceuticals; served on speaker bureaus for BPL and the National Hemophilia Foundation; provided consulting services to Goval; served as an author for Bayer; and had speaking engagements and received consulting honoraria from Alnylam Pharmaceuticals for participation in this research.

Study design and methodology of ELEVATE, a global observational longitudinal registry of patients with acute hepatic porphyria

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Content Background and Aims
Acute hepatic porphyria (AHP) is caused by hepatic haem biosynthesis defects leading to accumulation of neurotoxic haem intermediates 5-aminolevulinic acid (ALA) and porphobilinogen (PBG). AHP is characterised by acute disabling, and sometimes life-threatening neurovisceral attacks, and chronic manifestations impacting daily functioning and quality of life. Givosiran is approved for treating AHP in adults in the US and adults and adolescents age ≥12 years in the EU. ELEVATE (NCT04883905) is a global, multicentre, prospective, longitudinal, observational registry being conducted to describe the natural history and real-world management of AHP patients and further characterise the safety and effectiveness of givosiran.
Methods
Patients with a documented AHP diagnosis are eligible to enrol. Patients are managed and treated per routine clinical practice. Specific treatments, visits, or procedures are not recommended; medication is not provided. Data are collected during routine encounters, or by referencing medical records, at least once every 12 months. Patients are followed for ≥3 years post-inclusion.
Results
Data collection began in Quarter 2, 2021 and includes patient demographics, medical history (including AHP signs and symptoms), AHP treatment, effectiveness (including urinary ALA/PBG results, attacks, and patient-reported outcomes), and safety outcomes.
Conclusions
The ELEVATE registry is a real-world data collection study designed to further elucidate the natural history and management of patients with AHP, and the long-term effectiveness and safety of givosiran for AHP treatment.

Funding: This study is funded by Alnylam Pharmaceuticals.
Acknowledgements: Editorial assistance was provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Alnylam Pharmaceuticals.

DISCLOSURES
Bruce Wang is a scientific advisor to Alnylam Pharmaceuticals and Recordati Rare Diseases.
Eliane Sardh received grant support and personal fees, paid to Karolinska Institute, from Alnylam Pharmaceuticals.
Michael Badminton is a scientific advisor to Alnylam Pharmaceuticals.
Laurent Gouya received travel support and financial support from Alnylam Pharmaceuticals.
Mary-Jean Fanelli is an employee of and owns stock and stock options in Alnylam Pharmaceuticals.

Manisha Balwani received grant support, consulting fees, advisory board fees, and lecture fees from Alnylam Pharmaceuticals; advisory board fees from Recordati Rare Diseases; grant support and advisory board fees from Mitsubishi Tanabe; and advisory board fees from Alexion, Genzyme/Sanofi, and Takeda. In addition, Mount Sinai faculty are named co-inventors with Alnylam on a patent related to the development of givosiran, the study drug. The Icahn School of Medicine at Mount Sinai receives payments related to this patent from Alnylam, and a portion of these payments are also distributed to faculty and other co-inventors.

Efficacy and safety of givosiran in patients with acute hepatic porphyria: 36-month results of the phase 3 ENVISION randomised clinical trial

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Content Background and Aims
Givosiran treatment in the ENVISION study (NCT03338816) open-label extension (OLE) period led to sustained clinical benefit in patients with acute hepatic porphyria (AHP). Data from the 36-month (M) analysis are reported here.

Methods
ENVISION is a phase 3, randomised, placebo-controlled trial in AHP patients age ≥12 years who had experienced ≥2 attacks requiring hospitalisation, urgent care, or intravenous hemin at home in the past 6M, with a 6M double-blind (DB) period followed by a 30M OLE period.

Results
Of 94 patients enrolled, 93 patients entered the OLE period. Givosiran led to sustained lowering of median urinary 5-aminolevulinic acid and porphobilinogen levels, and attacks and hemin use reduction, in the continuous givosiran and placebo crossover groups. The proportion of patients with 0 attacks and 0 days of hemin use improved during the OLE. Exploratory measures showed further improvements in quality of life (QoL) and daily living activities assessments during the OLE versus the DB period. Treatment-related adverse events (AEs) (>10%) were injection-site reactions, nausea, and fatigue. Six patients discontinued study drug due to AEs, 4 of whom for treatment-related AEs.

Conclusions
In AHP patients, long-term givosiran treatment led to sustained benefit, maintaining reduced attack frequency and hemin use and further improving physical functioning and QoL.

Funding: This study was funded by Alnylam Pharmaceuticals.

Acknowledgements: The authors present this abstract on behalf of the ENVISION investigators. Editorial assistance was provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Alnylam Pharmaceuticals.

DISCLOSURES
Susana Monroy received advisory board fees from Alnylam Pharmaceuticals.

David J. Kuter received grant support and consulting fees from Actelion (Syntimmune), Agios, Alnylam Pharmaceuticals, Amgen, Argenx, Bristol Myers Squibb, Protalix, Rigel, and Takeda (Bioverativ); grant support from Kezar and Principia; and consulting fees from Caremark, Daiichi Sankyo, Dova, Kyowa-Kirin, Merck Sharp Dohme, Momenta, Novartis, Pfizer, Platelet Disorder Support Association, Principia, Protalix, Sanofi, Genzyme, Shionogi, Shire, UCB, Up-To-Date, and Zafgen.

Herbert L. Bonkovsky received grant support and financial support, paid to Wake Forest University School of Medicine, from Alnylam Pharmaceuticals, Gilead Sciences, and Mitsubishi Tanabe, NA, and consulting fees from Alnylam Pharmaceuticals, Disc Medicine, Eiger Biopharma, Protagonist Pharma, and Recordati Rare Diseases.

Gayle Ross reported having nothing to disclose.

Encarna Guillén-Navarro received grants/research support, paid to the Fundación para la Formación e Investigación Biosanitaria-FFIS, from Alnylam Pharmaceuticals, and consulting fees from BioMarin, UCB, and Alnylam Pharmaceuticals.

Maria Domenica Cappellini received consulting fees, research funding, and honoraria from Novartis; research funding and consulting fees from Celgene; consultant fees from Vifor and IONIS Pharmaceuticals; and research funding from La Jolla, Protagonist Therapeutics, and CRISPR Therapeutics.

Anna-Elisabeth Minder received an unrestricted research grant from Clinuvel Pharmaceuticals.

Shangbin Liu and Marianne T. Sweetser are employed by and own stock and stock options in Alnylam Pharmaceuticals.

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PORPHYRIA CUTANEA TARDA AND HIV ASSOCIATION: INVOLVEMENT OF ABCG2 TRANSPORTER VARIANTS

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Content Background

Porphyria Cutanea Tarda (PCT) is caused by a deficiency in Uroporphyrinogen decarboxylase; there are 2 main types of PCT: hereditary and acquired. In Argentina, 16% of PCT patients are infected with human immunodeficiency virus (HIV). Genetic variants affect the expression of the ABCG2 transporter, altering the efflux of drugs and heme. NM_004827.3:c.34G>A and NM_004827.3:c.421C>A variants are present in a high frequency. Previously, we analyzed the influence of ABCB1 variants, a transporter of the same family as ABCG2, in the onset of PCT in HIV carriers. The aim was to evaluate the role of ABCG2 gene variants in the association of PCT-HIV.

Materials and methods

A population of Control, HIV, PCT and PCT-HIV individuals was studied. All of them had signed the corresponding Informed Consent. Genotyping was done by PCR-RFLP for c.421C>A and by direct sequencing for c.34G>A.

Results

For c.421C>A variant, non-wild type allele A frequency in PCT-HIV (0.16) was higher ($p<0.001$) than PCT (0.07), HIV (0.06) and Control (0,04) groups. Genotypic frequency in heterozygosis (CA) was higher in PCT-HIV (40%) than PCT (26%), HIV (21%) and Control (7.5%). The AA genotype (2%) was only found in PCT-HIV cohort. For c.34G>A variant, low frequency in heterozygosis (GA) in all groups (30-40%) compared to homozygosis (GG) (around 60%) was observed. The AA genotype was only found in PCT-HIV and PCT groups (7.1%). No significant variation was found among groups in allelic frequency for this SNV.

Conclusions

The presence of AA genotypes in both variants of ABCG2 gene could be associated with the onset of PCT. c.421C>A variant could be related to the trigger of this porphyria in HIV patients. Combining analysis of ABCG2 variants with those previously obtained for ABCB1 will enable us to further conclude about the risk haplotype for PCT manifestation. Due to the multifactorial nature of the triggering of porphyria, they are of utmost importance.

Clinical and biochemical evolution of five Acute Hepatic Porphyria patients under long-term givosiran treatment

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Content Background
Givosiran (Givlaari®) is a subcutaneously administered small interfering RNA approved for the treatment of patients with acute hepatic porphyrias suffering from recurrent attacks. Monthly administration was found to significantly reduce hepatic ALAS1 mRNA levels and the accumulation of porphyrin precursors, as shown by the ENVISION trial data. However, the treatment duration was not specified. Recent reports reveal unexpected metabolic crosstalks, such as the development of hyperhomocysteinemia (HHCy) associated with a potential dysfunction in the activity of cystathionine-β-synthase (CBS). Since CBS is a pyridoxal-5-phosphate-dependent enzyme, supplementation with pyridoxine could optimize this pathway, normalizing homocysteine levels in patients treated with givosiran. We describe the clinical and analytical follow-up of five patients treated with givosiran for up to 28 months.
Results
We analyzed the plasma levels of homocysteine, CBS activity, vitamin B12, folic acid and pyridoxine in patients treated at Hospital 12 de Octubre in Madrid, Spain. All five patients showed an improvement in quality of life, were free of acute attack episodes and underwent a sustained reduction in the use of hemin and opiates. All but one patient showed porphyrin precursors levels within the normal range. No thrombotic or cardiovascular events were observed during follow-up. Plasma homocysteine elevation was managed by supplementing the treatment with vitamin B6, B12, and folate.
After a period of more than 18 months of monthly administration, dose and administration frequency of the drug was individualized in each patient according to their clinical evolution and the excretion of porphyrin precursors. During this period, one of the patients suffered a mild acute crisis that required treatment with hemin.
Conclusions
Patients with severe acute porphyria receiving long-term givosiran treatment show good clinical and biochemical evolution. After long-term monthly treatment, an attempt was made to individualize the dosage frequency. The most prominent complication was a significant rise in blood homocysteine levels. The administration of pyridoxine and other vitamins that act as cofactors in the metabolic pathway of homocysteine, even in the absence of deficit, managed to reduce the levels of this amino acid.

CHARACTERIZATION OF A GENETIC MURINE MODEL OF ACUTE INTERMITTENT PORPHYRIA. AN OVER TIME STUDY

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Content Background
Acute intermittent porphyria (AIP) is an inherited disease due to Porphobilinogen deaminase (PBG-D) deficiency. AIP model is a knockout mouse with targeted disruption of PBG-D that exhibits the typical biochemical/neurological characteristics of human AIP. Considering that aging is a significant risk factor for impaired tissue functions and chronic diseases, the aim was to evaluate alterations in heme metabolism, hepatic damage and oxidative parameters in a genetic AIP model throughout life.

Materials and methods
The study was performed in liver and brain using three groups (males and females) of young mice: Wild type (C57BL/6), T1 (PBG-D activity 55% reduced) and AIP (PBG-D activity 70% reduced). For evaluating the effect of age, T1 mice 12-15 months old were used.

Results
In young mice, PBG-D activity in T1 and AIP was according to the model in liver being also reduced in brain (40-50%, $p<0.01$). As was expected, 5-Aminolevulinic acid synthetase activity (ALA-S) was elevated in liver in both genotypes (T1: 140%, $p<0.01$; AIP: 45%, $p<0.05$) and brain (T1: 257%, AIP: 95%, $p<0.05$). Heme oxygenase (HO) was 100% ($p<0.05$) higher than wild type in brain in both sexes and genotypes, being hepatic HO only induced in females (50-100%, $p<0.05$). HO alteration, GSH variation and Catalase reduction (140%, $p<0.05$) would indicate oxidative stress instauration. Glutathione S-Transferase (GST) varied depending on the genotype. Tryptophan pyrrolase (TRP) activity was elevated in liver and brain (87-140%, $p<0.05$) of AIP female. Comparing old T1 mice with young T1 mice, PBG-D mutation was unaltered; no variations were observed in ALA-S, PBG-D, TRP and GST while HO, GSH and Catalase activities were significant different, indicating that oxidative stress increased with aging.

Conclusions
The present study has demonstrated that the differences among wild type and genetic model were more striking in AIP genotype respect to T1 and age affected significantly oxidative stress parameters.

Catalytic fingerprinting on protein level of Norwegian AIP-associated variants

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Content AIP is caused by a partial deficiency in hydroxymethylbilane synthase (HMBS). HMBS binds porphobilinogen (PBG) into the intermediate complexes ES, ES2, ES3 and ES4 before product release. The distribution of intermediates gives a catalytic fingerprint of the elongation mechanism. Analysing the distribution of 12 AIP variants has served as the backdrop for the categorisation of mutational effects on the protein level.

Four variants, L238P, E250Q, A252P and A339D, resulted in complete folding defects and could not be purified: Important interdomain interactions were interrupted.

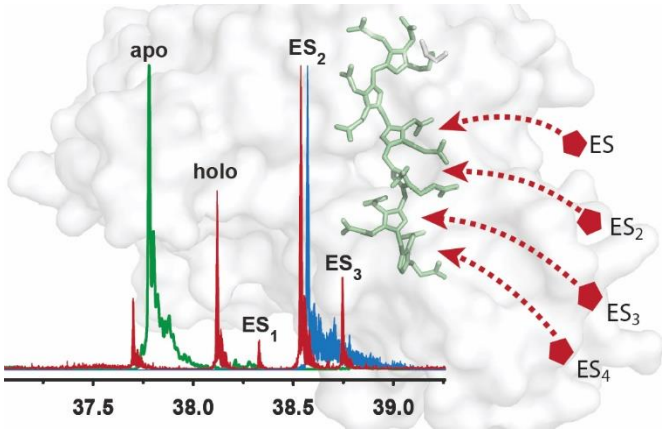
Variants K98N and R149Q are only detected in the apo-from, however, the substitutions did not cause detrimental folding effects.

Both R26H and D99N are trapped in the ES2-state. R26H is inactive with a thermostability that resembles ES2 of wildtype. D99N holds ~1% residual activity and is more thermolabile, indicating a larger conformational effect.

Four variants produced all intermediates, suggesting residual activity and turnover. R167Q and R195C have minimal residual activity (0.1% and 0.7%, respectively). With excess PBG, R195C accumulated ES4, indicating an extreme delay in product release. No such accumulation was seen for R167Q. Variants L30P and E223K were inactive, which is counterintuitive since all intermediates were present.

We conclude that the variants could be grouped in four major categories: Variants i) with complete folding defects, ii) as stable apoenzymes, iii) accumulating in a single intermediate, and iv) yielding a distribution of enzyme-intermediate complexes.

Acknowledgements: This work is part of PredPor – Predictors of symptomatic disease and long-term complications in AIP. The poster is supported by grant to HJB from Bioingeniørfaglig institutt.



CAN LIVER CYST AFFECT THE OUTCOME OF ACUTE PORPHYRIA – A CASE REPOR

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Content BACKGROUND: The purpose of the liver cyst fenestration was to see whether diminishing the size
and potential pressure of the large non-malignant cyst in the liver would affect the clinical outcome and porphyrin metabolism in a 50-year-old woman with acute intermittent porphyria.
MATERIALS AND METHODS: Acute intermittent porphyria was revealed by the mutation analysis in the family screening in her 20s. She had premenstrual acute symptoms since teenager for a week 4-5 times a year which resolved after 2 normal pregnancies in her 30s. She remained asymptomatic thereafter but in her 40s, moderate attacks reoccurred 3-4 times a year but became more longlasting with the years causing chronic pain syndrome in the abdomen and extremities, and tiredness.
Urinary PBG and ALA levels increased substantially (10-fold for U-PBG, 4 -fold for U-ALA,) during acute symptoms. Estradiol patches helped for some extend for a year. Progesterone combination induced acne, and she stopped both preparations. Menopause was confirmed by high FSH and low estrogen levels. Further hormonal therapy was inefficient to prevent attacks. Acute attacks reoccurred more severe than ever, and she was hospitalized for an attack for the first time in her life in her 50s. Hepatoma was excluded by abdominal CT. The patient had a large 3-lobar cyst (max 10 cm) in the segment IV of the left hepatic lobe reaching the central part of the liver. The liver function was normal. The multilobe cyst was fenestrated laparoscopically. After two months the size of remnants was max 5 cm.
RESULTS: After recovering from the operation, she was symptom-free for 6 months. Thereafter, mild attacks have occurred 3-4 times a year. Urinary PBG, ALA and porphyrin levels have been mildly increased in remission during the follow-up of two years, and chronic symptoms have stopped.
CONCLUSION: Large liver cyst may have caused relative cholestasis, and thus also affect porphyrin metabolism. Clinical response was surprisingly prompt but other factors such as hormonal changes can be associated with the good response.

High-throughput screening of chemical libraries identified therapeutic molecules in cellular models of porphyria with enhanced ALAS2 expression

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Content Background

Erythropoietic porphyrias are inherited metabolic disease caused by enzymatic dysfunctions in the heme biosynthetic pathway, resulting in porphyrin accumulation in red blood cells. Recent studies identified ALAS2, the first and rate-limiting enzyme of the pathway, as a therapeutic target in substrat reduction therapy for erythropoietic porphyria. In this work, we developed cellular models with enhanced ALAS2 expression for a phenotypic high-throughput screening of chemical libraries as a treatment of erythropoietic porphyria.

Materials and methods

We developed HEK cellular models of porphyria by overexpression (stable transfection of lentiviral transduction) of ALAS2WT and gain of function hALAS2Q548X proteins leading to spontaneous porphyrin accumulation. We further characterized isolated cellular clones for ALAS2 expression (mRNA and protein) and porphyrin metabolite profile (flow cytometry and spectrofluorometric assays of cellular extracts). We then optimized a 96-well phenotypic assay based on porphyrin fluorescence measurement in living cells to screen a chemical library in order to identify drugs that lowered porphyrin accumulation.

Results

We used lentiviral-transduction or stable transfection into HEK cells to reach high level ALAS2WT and gain of function hALAS2Q548X enzyme expression, which were characterized by RT-PCR and Western Blot analysis. ALAS2 expression led to spontaneous accumulation of high amount of protoporphyrin IX-Zn (PPIX-Zn) as determined by spectrofluorometric analysis. We developed a high-sensitive functional assay based on porphyrin fluorescence quantification in living cells using flow cytometry analysis and spectrofluorometric phenotypic assay in 96-wells plates. We reverted porphyrin accumulation by ALAS2-targeted shRNA expression in dose-dependent manner. We then implemented a drug repurposing high-throughput screen of FDA and EMA-approved chemical libraries in a phenotypic assay based on porphyrin quantification in living cells. We identified 21 compounds that significantly reduced porphyrin accumulation (up to 95% vs control).

Conclusions

In this work, we developed cellular models of porphyria based on ALAS2 expression to serve as functional assays in high-throughput screening of therapeutic chemical libraries. We present the molecular and metabolic characterization of these cellular models and the development of a high-throughput screening assay in living cells based on highly sensitive porphyrin measurement. We screened chemical libraries and identified 21 candidate molecules with therapeutic potential. We are pursuing a hit to lead study of the compounds in patient-derived cells and animal models.

Severe perinatal presentations of Günther's disease: review and perspectives drawn from the history of 20 cases from the French cohort

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Content Background
Günther's disease (CEP congenital erythropoietic porphyria) is one of the rarest porphyria, resulting from deficient uroporphyrinogen III synthase (UROS), the fourth enzyme of heme biosynthesis. The disease is inherited as a recessive trait; the phenotype ranges from extremely severe perinatal onset, with life-threatening haemolytic anaemia, to mild or moderate cutaneous involvement in late-onset forms. This work aimed at reviewing the perinatal CEP cases published so far or recorded by the French Center for Porphyrias.

Materials and methods
We systematically reviewed the data available from 17 families including 20 cases, previously published except 3 families, and attempted a classification according to three main presentations: antenatal manifestations (6), acute neonatal distress (3) and early post-natal diagnosis (8).

Results
Prenatal presentations have in common hydrops foetalis caused by anaemia leading to abortion, except in the more recent case report who benefited from early intensive care after premature delivery. Hydrops and malformations suggestive of thalassaemia, were present in two families. Acute neonatal distress as initial presentation is challenging and may rely on precise analysis of available erythroid samples. Bone marrow aspirate was the key to diagnosis in the most recent case. All reported severe post-natal CEP patients were treated by stem cell transplantation, but fatal issue due to hepatic dysfunction occurred in two patients.

Conclusions
This review enlightens the progress made in both diagnosis and therapeutic care from pregnancy survey to specific intensive care, including hematopoietic stem cell transplantation. Unusual situations including severe malformations associated with CEP disease were recently encountered, revealed by novel NGS sequencing strategies for genetic diagnosis. More investigations are needed to explain these features in a physiopathological way, helped by a larger registry of these severe presentations to be developed by collaborative work through the Epnet members.

Acknowledgements
We are grateful to the whole staff of the French Center for Porphyrias as well as clinicians and geneticists who referred CEP cases, with a special mention for C Desage, P Mahe (CH Montpellier), I Harzallah (CH Saint-Etienne), B. Sudrié-Arnaud (CH Rouen), A Salhi (Dermatology, Alger)

All families were referred to the French Center for Porphyrias and informed consent was obtained for each step of the diagnosis and use of anonymised data.

PATHOGENESIS OF ACUTE PORPHYRIC ENCEPHALOPATHY

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Content OBJECTIVE: The pathogenesis of acute encephalopathy, which can be a symptom of a protracted acute attack is still obscure.
METHODS: The clinical, laboratory data, neuroimaging and PEPT2 polymorphisms were evaluated in 33 patients with encephalopathy during an acute attack and compared with patients with peripheral neuropathy but no encephalopathy, n=17, and patients with no neurological complications during an acute attack, n=12.
RESULTS: The typical clinical manifestations of porphyric encephalopathy included triade of seizures, confusion and blurred vision. Posterior reversible encephalopathy syndrome (PRES) was identified in 8 of 20 attacks studied by neuroimaging. Of five patients studied by MR angiography, reversible segmental vasoconstriction was found only in one. Clinical and neuroradiological findings of porphyric encephalopathy had no major difference with PRES of other origin except of frequent hyponatremia and rarity of headaches probably due to co-existence of severe abdominal pain masking headache.
Despite blood pressure during encephalopathy was commonly elevated (200–125/116–80mmHg), no statistical correlation was seen between hypertension and encephalopathy (P=0.182).
There was no statistical difference of urinary ALA (P=0.722) or PBG excretion (P=0.813) in patients with and without encephalopathy during the attack.
Routine laboratory examination revealed only few common findings including hyponatremia in most of the cases, mild elevation of serum liver transaminases (94% of the cases, 56-317 mmol/l, normal <45 mmol/l) and creatinine (26%, 122–193 µmol/l, normal <90 µmol/l). Of the patients with PRES, 88 % were hyponatremic and 50 % severely hyponatremic (S-Na < 125 mmol/L). The mean sodium values did not differ in patients with or without PRES.
No correlations between PEPT2 haplotypes and encephalopathy, polyneuropathy, or chronic kidney disease, could be identified, which may be due to insufficient number of patients. The PEPT2*2/2 haplotype was less common among patients with encephalopathy and/or polyneuropathy.
CONCLUSION: Acute endothelial dysfunction causing PRES could be explained by a combination of abrupt hypertension, SIADH and inflammatory factors of hepatic origin.

Variegate Porphyria With Verrucous Carcinoma Diagnosed after Chronic Renal Failure: A Case Report

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Content Background :
Variegate porphyria (VP) is an autosomal dominant porphyria characterized by both cutaneous and neurovisceral symptoms.A form of acute porphyria, VP is caused by mutations in PPOX, a gene that carries instructions for making an enzyme called protoporphyrinogen oxidase.
Case report :
In this case we discuss a 65-year-old female patient with bullous lesions on hands, lethargy, increased facial hair and darkened facial skin. Here, we report a heterozygous mutation of the PPOX gene in a Turkish female VP patient who has been diagnosed with chronic renal failure secondary to porphyria. A 65-year-old female patient came in with bullous lesions on hands, lethargy, increased facial hair and darkened facial skin.
Conclusion :
Our case is unique in the way that porphyrin precursors were accumulated both in the liver and kidney. Due to delayed diagnosis, chronic kidney failure was observed less than 5 years after the initial high creatinine levels making our patient dialysis-dependent. This case is a clear reminder that porphyria should be kept in mind in the differential diagnosis in order to avoid attacks that will bear long-term complications.

Differentiating Guillain-Barre Syndrome from Porphyria Neuropathy: ENDEAVOR® Study

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Content Background
Guillain-Barre Syndrome (GBS) is an inflammatory disorder that curse with acute flaccid paralysis (AFP), and it is an important differential diagnosis for acute attacks of weakness in Acute Hepatic Porphyria (AHP). There is a lack of large clinical and biochemical data for differentiate GBS from AHP on clinical practice.
Materials and methods
We analyzed the medical records of 52 patients with GBS evaluated at our institution in the last 5 years and compared with the clinical profile of 50 porphyria attacks that presented with acute weakness on 36 patients with AHP in regular clinical follow-up at the same center.
Results
The clinical features of neuropathic pain, encephalopathy, constipation, headache and preserved facial movements are more common in patients with AFP due to AHP than in patients with GBS ($p<0.05$). Regarding biological biomarkers, hyponatremia at clinical presentation was more common in AFP due to AHP than GBS and cytoalbuminological dissociation (the combination of a normal cell count and increased protein level) it is not reliable biomarker to distinguish GBS from AHP. The profile of anti-gangliosides antibodies was very different in patients with GBS compared with AHP. High mortality rate and elevated motor disability at 6-month and 12-month after the AFP were more common in patients with AFP due to AHP than GBS.
Conclusions
This is the first report of the ENDEAVOR study that show clinical findings, laboratory abnormalities and outcomes that can help physicians differentiate GBS from AHP in the context of AFP.

Next Generation Sequencing in the Diagnosis of Acute Hepatic Porphyrias (AHP): Unraveling the Molecular Basis of AHP in Brazilian Patients

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Content Background

In Brazil, analyses of clinical and laboratory features of patients with acute porphyrias are until recently limited to biochemical testing since genetic testing was expensive and not covered by national health system neither private insurance. In partnership with Brazilian Porphyria Association (ABRAPO), during February 2020 until March 2022, genetic testing was offered to patients registered in the patients database to better allow a specific diagnosis for the families.

Materials and methods

Individuals aged ≥16 years from a Brazilian national referral center for porphyrias with a suspected diagnosis or a confirmed history of AHP that underwent genetic testing via ABRAPO between February 2020 and March 2022 were included. Extracted DNA samples from saliva and buccal swabs were analyzed using a short-read next-generation sequencing gene panel.

Results

Overall, of the 122 unrelated individuals referred for AHP molecular diagnostic testing, 80 had an AHP mutation. Although most mutations identified were in hydroxymethylbilane synthase gene (HMBS n=43), there was an unexpected great number of pathogenic variants in protoporphyrinogen oxidase (PPOX n=31) in patients with a previous biochemical diagnosis of Acute Intermittent Porphyria (AIP). Just one heterozygous variant in ALAD gene was seen in our cohort in a patient with a pathogenic mutation in PPOX gene. Of the 250 family members of mutation-positive individuals tested for an autosomal dominant AHP, 104 (46.8%) had their respective family mutation. All patients with documented increase in aminolevulinic acid and porphobilinogen had a confirmed molecular diagnosis of AHP.

Conclusions

This is the first report describing genetic variants for all four acute porphyrias in Brazilian individuals under AHP investigation . It was worthy of note that a high number of cases of VP was identified with PPOX mutations, being a frequent cause of AHP in our population. These data expand the molecular genetic heterogeneity of the AHP and document the usefulness of molecular testing to confirm the positive biochemical findings in symptomatic patients and identify at-risk asymptomatic family members. A correct genetic diagnosis allows not only better understanding of such disorders but also genetic counseling for affected and at-risk individuals.

An Overview Project of 55 Diagnosed Porphyria Patients

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Content Background:
Porphyria is a metabolic disorder that occurs as the result of accumulation of the substrates in the nervous system, the gastrointestinal system, liver, kidney and skin, multisystemically due to the deficiency or inadequate functioning of one of the eight enzymes taking part in the production of the heme molecule.
Although this disease can affect many systems and cause symptoms, it is a rare disease.
Porphyria, emerged clearly in Turkey around the 1950s, but nowadays it can be diagnosed faster and treated more specifically thanks to the increase in the methods used in diagnosis today, the more conscious employees and the developments in the technological field.
In the diagnosis, checking for the spot urine porphobilinogen, especially at the time of the attack, is effective for us in making quick decisions, and the presence of genetic tests also provides the opportunity to follow up and control individuals at risk of developing the disease.
Material and Methods, Results:
Our study is an overview of 55 diagnosed patients with confirmed genetic results diagnosed, treated and followed up by the specialists in our organization and to learn from individuals who have not been diagnosed in the past and perhaps have this disease, with an overview of the time taken from the appearance of symptoms to treatment, the commonality and frequency of symptoms, the main complaints which they reached the doctors for and their family history. It is aimed to pay attention to the issues that we need to pay attention to, to emphasize the types of symptoms. The average age of patients is 32.5 (SD:15.1). On gender basis 9 male and 46 female patients are in our study. Average BMI of patients is 22.5 (SD:4.4). Gene mutation is detected in 89% of the patients.
Conclusions:
The important point here is that such a comprehensive study has not been carried out in Turkey and many other countries before, it is a precedent for other studies and useful to draw attention to the points to be considered while making a diagnosis from symptoms in the community. Also to reveal the rates of endemic elements or symptoms. We hope that this study will guide other studies as well.

Molecular and clinical aspects of a Brazilian cohort of patients with variegate porphyria

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Content Molecular and clinical aspects of a Brazilian cohort of patients with variegate porphyria

Michelle Abdo Paiva, Andre Macedo Serafim Silva, Rodrigo de Holanda Mendonça, José Pedro Soares Baima, Beatriz Carneiro Gondim Silva, Angelina Maria Martins Lino, Edmar Zanoteli

Background:
Variegate porphyria (VP) is an autosomal dominant hereditary form of acute hepatic porphyria (AHP) and it is believed to be the second most common AHP. Data from Brazil are scarce due to lack of available specific biochemical exams and genetic studies.
Objectives:
To describe epidemiological, clinical, and genetic profile of patients with VP in a tertiary center in Brazil.
Methods:
We included patients based on clinical history (recurrent abdominal pain, altered colored urine and peripheral or central nervous system manifestation) and confirmatory genetic study. We reviewed medical records of all patients. A severe attack was defined as need of hospitalization for management.
Results:
A total of 16 AHP genetically confirmed patients were identified in our hospital. VP was diagnosed in nine patients from five families.
All patients were female, medium age of 37 (25-54). Age at first symptoms ranged from 12 to 45. Three patients had two severe attacks, five patients had one severe attack and one patient had a mild attack.
During an attack, six patients had acute flaccid paralysis. Five patients had associated psychiatric symptoms (anxiety or depression). Electrophysiologic studies was available for two patients with findings of axonal sensory motor polyneuropathy. ALAd/creat relation was available for two patients, both more than 2x de UNL. PBG was not available in all patients.
Chronic symptoms of pain were present in seven patients. Skin lesions and/or photosensitivity was reported in four patients.
Four families shared the same missense variant in exon 6, c503G>A (p.Arg168His), and one had a deletion in exon 5-6.
Conclusion:
Data from our center may suggest that VP is more common in our population than previously reported since more than half of our patients with AHP had pathogenic variant for PPOX. Clinically patients may present similarly to other forms of AHP. Skin lesions may not be present in all patients. Lack of biochemical studies in our country may influence diagnostic accuracy.

High molecular variability in the ALAD gene associated with intense abdominal pain: not always acute porphyria.

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Content Background

Acute hepatic porphyria is suspected in the differential diagnosis of unexplained abdominal pain. A marked porphyrinuria and the pathognomonic detection of elevated urinary PBG concentration strongly support its presumptive diagnosis.

Here, we present four adult patients who required hospital admission due to repeated intense abdominal pain in whom the suspected diagnosis was acute porphyria due to the presence of marked porphyrinuria greater than 1000 µg/L. However, urinary PBG excretion was surprisingly normal. We also present a young patient with an early onset of severe abdominal pain, sometimes accompanied by weakness of his hands and legs, and progressive renal failure.

Results

Adult patients showed low activity of the erythroid enzyme δ-aminolevulinic acid dehydratase (eALAD), yet in vitro addition of zinc and DTT produces a full recovery of enzyme activity. Molecular studies confirm three SNPs within the ALAD gene that confer increased sensitivity to lead poisoning.

Young patient showed a profound deficiency of eALAD (16% compared to controls), which increased up to 30% with the in vitro addition of Zinc and DTT. He was classified as compound heterozygous for ALAD porphyria carrying non-described deleterious G280R mutation and hipomorphic V242I ALAD allele in cis. Parents were asymptomatic and had an eALAD activity of 25% and 75% when compared to healthy controls.

Conclusions

Lead poisoning can manifest as intense abdominal pain associated with marked porphyrinuria that is not associated with acute porphyria. These data extend the information available regarding the molecular basis of ultrarare ALAD porphyria and the use of ALAD polymorphisms to identify individuals with a high susceptibility to lead exposure and potentially refractory to chelation therapy.

Porphyria Cutanea Tarda in Argentina. An update

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Content Background

Porphyria Cutanea Tarda (PCT) is the most common porphyria in Argentina (prevalence 1:20,000). There are two main types: PCT-A (acquired, sporadic or type I) and PCT-H (hereditary or type II). Type I is the most common form of PCT (70-80%) and the deficiency in Uroporphyrinogen decarboxylase (URO-D) is restricted to the liver. In PCT type II blood URO-D activity is reduced by 50%. The manifestation of PCT is associated with triggering factors: alcohol consumption, hormones and iron overload. The association between PCT and other pathologies is remarkable: hereditary haemochromatosis (HH), HCV and HIV. The aim of this study was to analyze the patients diagnosed in CIPYP with PCT to date, to evaluate the incidence of the different types of PCT in our population. All patients signed the Informed Consent.

Results
Among 2230 PCT cases analyzed, 92% were PCT-A; 79% male and 21% female, in a 3.7:1 ratio. In the PCT-H cohort, 179 were symptomatic and 43 were latent in a 1.3:1 male:female ratio in both cases. 16.4% of the PCTs were HIV+ and 34% were HCV+. Only 4.3% were HH, 31.6% carried p.H63D (26.5% heterozygous, 5.1% homozygous). 6.8% carried the p.C282Y mutation (5.1% heterozygous, 1.7% homozygous) and 2.6% were heterozygous for both mutations.
In the 84 unrelated PCT-H families, 45 different pathogenic variants were found, of which 16 were reported for the first time in CIPYP. In 23 families, the c.10-12insA variant (27%) was detected, being the most frequent in the country. The second was p.M165R (8%) and in third place p.N304K (7%), which together represent 38% of the allelic variants characterized. We also diagnosed 25 cases of childhood PCT, carrying c.10-12insA (8 cases) and p.M165R (2 cases).

Conclusion
Although PCT-H is inherited in an autosomal dominant manner with low penetrance, there are multiple triggering factors. Genetic diagnosis is of utmost importance as it allows counselling about contact with such agents to avoid the clinical expression in latent cases.

Quantification of blood ALA and PBG by LC-MSMS: a new tool for monitoring acute porphyria

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Content Quantification of blood ALA and PBG by LC-MSMS: a new tool for monitoring acute porphyria

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Background
The quantifications of delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) in urine are the first-line tests for the diagnosis and monitoring of acute hepatic porphyrias. While quantification in urine has long been the reference analysis due to the limitations of the historical method, the development of new methods by LC-MSMS now enables to monitor these biomarkers in plasma. Here we present our routine method of plasma ALA and PBG measurement and highlight the relevance of monitoring porphyrin precursors in blood.
Material and Methods
ALA and PBG were derivatized using a commercial reactant (Waters) before being quantified using a UPLC coupled with Xevo-TQMS (Waters). The calibration scale ranged from 0.05 to 25 µmol/L. Blood were collected from 37 healthy donors, 97 AIP asymptomatic carriers, 116 AIP patients (mild and severe phenotypes).
Results
Urine and plasma showed a good correlation with both metabolites. However, the urine/plasma concentration ratio decreases with the progress of kidney disease. Furthermore, PBG/ALA ratio in plasma was clearly correlated with the same ratio in urine. The median of ALA concentrations was 0.08 µmol/L in control group and 0.19 µmol/L in healthy carriers. In patients, ALA concentration ranged from 0.09 to 4.7 µmol/L outside an acute attack and can reach up to 12.6 µmol/L during a severe attack. PBG was undetectable in healthy people and ranged from undetectable to 24.2 µmol/L with significant difference between healthy carriers, mild and severe patients.
Conclusions
The good correlation of ALA and PBG concentrations between urine and plasma means that the analysis in urine, an easily collected biofluid, will remain the first indication. However, we show that renal function affects significantly the urine level compared to plasma. With the advent of new therapies associated with a need for detecting fine variations of precursors and to be independent of renal function, the plasma quantitation will become a necessary tool for clinicians.

A FEMALE WITH ERYTHROPOIETIC PROTOPORPHYRIA (EPP) WITH LIVER DAMAGE – CLINICAL AND GENETIC CHARACTERISTICS

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A case of erythropoietic portoporphyria (EPP) with severe liver damage and acute appendicitis is reported. A 21 year old female with wax-like skin lesions on the dorsum of the hands, feet and on the face, severe abdominal pains, subileus and jaundice of 1 week duration was referred to our clinic. She suffered from skin lesions related to sun exposure since childhood. Laboratory tests revealed liver dysfunction - icterus and cholestasis, mild anemia and inflammation. On the second day after admission appendectomy was performed due to increased intensity of abdominal pains and fast elevation of leucocyte count. They subsided after the surgery, but icterus and cholestasis persisted. Porphyrin measurements revealed markedly elevated erythrocyte protoporphyrin level. These findings were consistent with EPP with advanced porphyric liver disease. Histological evaluation of the skin biopsy confirmed the diagnosis of EPP. The patient was evaluated for liver transplantation. Meanwhile, ursodeoxycholic acid and ademetionine treatment was initiated and gradual improvement was established. During the two year follow-up period resolution of icterus and cholestasis was observed. Direct sequencing of all the coding exons of the ferrochelatase gene was performed. A heterozygous nucleotide change c.101G>A [p.W34X] and a hypomorphic allele IVS48-3C>T trans were identified in the proband.

The above report suggests that in patients with similar development of liver involvement and photodermatosis, clinicians should perform in due time investigation of porphyrin metabolism. Early treatment by UDCA and ademetionine could play essential beneficial role.

mtDNA copy number drives the penetrance of Acute Intermittent Porphyria (AIP)

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Content Background: An oligogenic inheritance model, combined with environmental modifiers, can efficiently explain the variability in AIP clinical presentation although the involved genes have not yet been identified. Transcriptomic analyses in AIP mice revealed an upregulation of genes involved in the mitochondrial biogenesis pathway, specifically during attack induction. Moreover, mitochondrial functional abnormalities have been reported in both animal models and AIP patients thereby suggesting that mitochondria content may play a role in the AIP clinical penetrance.
Methods: Through a relative quantification of the peripheral mtDNA copy number, this study aimed to estimate the number of mitochondria in 34 AIP patients and 37 healthy subjects matched for age and sex. By using qPCR-based assays, specific for an mtDNA region and a selected nuclear gene, we calculated the average mitochondria content per cell with the Ct comparative method.
Results: We observed that the mtDNA copy number was significantly lower in AIP patients than in healthy subjects and that this reduction was more pronounced after classification into symptomatic and asymptomatic patients. Indeed, symptomatic patients showed a significant reduction of the 75% of the mtDNA content respect to healthy subjects, while the asymptomatic ones showed a reduction of the 40%. However, the mtDNA integrity showed comparable levels between AIP patients and healthy controls, suggesting that the observed reduction was not due to the mutational damage of the mtDNA itself.
Conclusion: In this study, we demonstrated that all AIP patients show a reduced number of mitochondria, reason why remains to be elucidated and that the penetrance of disease is closely associated with the mitochondria content. This could justify different individual responses to environmental stimuli and bioenergetic demands. Ethics committee approved the study (n.0051832) and all included subjects signed the informed consent.

Clinical experience with afamelanotide for the protoporphyrias in the United States

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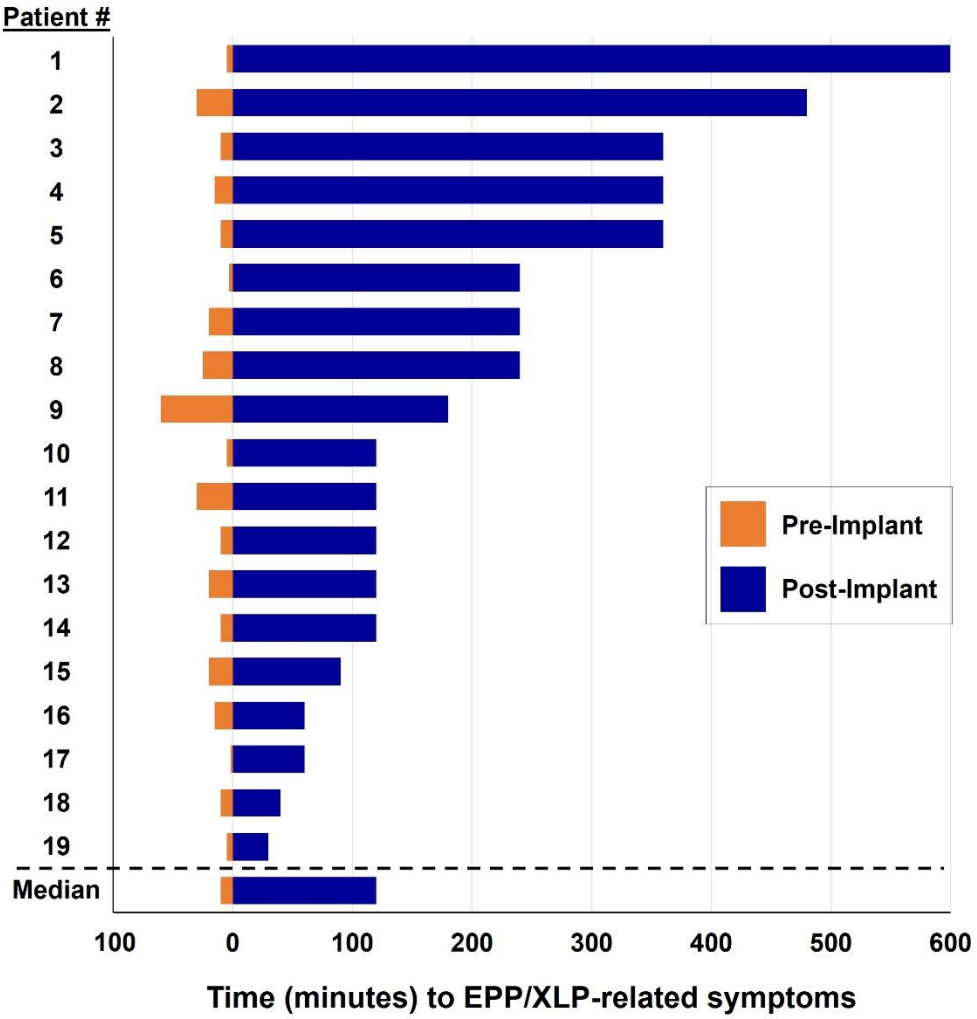
Content Background: The protoporphyrias, comprised of erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP), are rare photodermatoses characterized by phototoxic reactions and, in a subset of patients, hepatic failure. In 2019, the U.S. Food and Drug Administration approved afamelanotide (Scenesse®, Clinuvel), an α-melanocyte stimulating hormone analogue, dramatically changing the clinical management of patients with EPP/XLP. However, little is known about post-marketing experience with this medication in the U.S.

Methods: This was a single-center retrospective cohort study of all patients with EPP/XLP treated at the Massachusetts General Hospital Porphyria Center from March 2021 through May 2022.

Main outcomes: Time until phototoxic reaction and frequency and severity of symptoms pre- versus post-treatment with afamelanotide, and side effects of afamelanotide.

Results: A total of 30 patients with EPP/XLP were evaluated during the period of interest, 24 of whom (n=23 [EPP], n=1 [XLP]) received at least one afamelanotide implant. The median age for patients who received afamelanotide was 40 years (interquartile range [IQR], 32-57), and 19 (79%) were female. The median number of implants received was 4 (IQR, 2-5). Among the 19 patients who received at least 2 implants, the median time to symptom onset after light exposure was 10 minutes (IQR, 5-20) prior to initiation of afamelanotide, and 120 minutes (IQR, 105-300) after initiation of afamelanotide ($P<0.001$). All patients who received at least 2 doses of afamelanotide reported a decrease in frequency and severity of phototoxic reactions. Adverse events were generally mild and included nausea, vomiting, flushing, and bruising at the implant site. Of the 6 patients who did not receive afamelanotide, one was scheduled to receive afamelanotide after the data lock period, one was receiving afamelanotide at another center, three were on a clinical trial with an orally administered selective melanocortin-1 receptor agonist, and one was unable to afford the medication.

Conclusion: In this U.S. single-center cohort, afamelanotide lead to a significant increase in median time to phototoxic reaction in patients with EPP/XLP, and a decrease in symptom frequency and severity. Afamelanotide was generally well-tolerated with limited side effects.


Patient #
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Median
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100
0
100
200
300
400
500
600
Time (minutes) to EPP/XLP-related symptoms

Variegate Porphyria With Verrucous Carcinoma Diagnosed after Chronic Renal Failure: A case report

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Content Background :
Variegate porphyria (VP) is an autosomal dominant porphyria characterized by both cutaneous and neurovisceral symptoms.A form of acute porphyria, VP is caused by mutations in PPOX, a gene that carries instructions for making an enzyme called protoporphyrinogen oxidase.
Case report :
In this case we discuss a 65-year-old female patient with bullous lesions on hands, lethargy, increased facial hair and darkened facial skin. Here, we report a heterozygous mutation of the PPOX gene in a Turkish female VP patient who has been diagnosed with chronic renal failure secondary to porphyria. A 65-year-old female patient came in with bullous lesions on hands, lethargy, increased facial hair and darkened facial skin.
Conclusion :
Our case is unique in the way that porphyrin precursors were accumulated both in the liver and kidney. Due to delayed diagnosis, chronic kidney failure was observed less than 5 years after the initial high creatinine levels making our patient dialysis-dependent. This case is a clear reminder that porphyria should be kept in mind in the differential diagnosis in order to avoid attacks that will bear long-term complications.

GIVOSIRAN IN THE TREATMENT OF SYMPTOMATIC PATIENTS AFFECTED BY ACUTE HEPATIC PORPHYRIAS: "REAL LIFE" DATA FROM THE EXPERIENCE OF ITALIAN PORPHYRIA CEN

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Content Background:Givosiran is an ALAs1-directed small interfering RNA approved in Europe for the treatment of acute hepatic porphyrias (AHP) patients > 12 years. The Envision Study demostrated that this treatment is associated with a sustained decrease in urinary delta aminolevulinic acid(ALA) and porphobilinogen(PBG) levels, together with a sustained reduction in annualized acute attack rate(AAR) and annualized hemin use.
Aims:to report the preliminary results of "real life" experience on Givosiran-treated patients within the Italian network of porphyria expert centres (Gruppo Italiano Porfiria,GrIP).
Results:To date,in Italy 27 patients(21 females,mean age 46±13 years;range 15-70) have been treated by givosiran.Mean time from diagnosis to treatment was 9.5 years(range 0-35).One patient died due to vascular drug-unrelated causes.25 patients were affected by AIP,2 by HCP; diagnosis was genetically confirmed in 22/27 cases(81.5%).Before treatment, all patients had had acute attacks requiring Hospital admission(45%) or glucose(7.5%) and/or Hemin infusion(47.5%) in outpatient clinics;the AAR before treatment mean was 4.9(range 1-12). Before treatment,only 2 patients(7.4%) were not under prophylactic treatment, whereas 11(40.7%),4(14.8%) and 10(37%) were under heme, glucose or heme/glucose prophylaxis,respectively.Mean Urinary ALA and PBG(out from Acute attacks) before treatment were 13.5±9 and 25.4±22 mmol/g creatinine,respectively(24/27 patients had Urinary ALA and PBG at least two times normal range).During Givosiran treatment(20 months of median observation, range 2-52)all patients stopped any prophy treatment, no patients suffered for a documented acute attack ,up to now, none needed heme arginate infusion. Urinary ALA was normalized in 23/27(85.2%) and PBG in 11/27(40.7%) patients. All patients significantly reduced (>60%) with respect to pre-treatment levels urinary ALA and PBG levels. No significant side effect leading to treatment withdrawal was observed up to now.17/27(63%) patients had hyperhomocysteinemia(HHcy) before treatment, and 24/27(88,8%) showed an important increase in Hcy levels early after givosiran treatment (in 7 cases reaching levels>100 mmol/l). All patients with HHcy under treatment were supplemented by Hcy-related vitamins: in all cases homocysteine levels

significantly reduced to very mild levels/or completely normalized. 11 patients(40.7%) showed a significant decrease in GFR,but never so severe to reduce or suspend the treatment.
Conclusions:real life available data seems to confirm the biochemical and clinical benefit of givosiran treatment in AHP symptomatic patients.

Psychiatric Aspects of Porphyria: Clinical Manifestation, Comorbidity or a secondary Condition? The Historical Case of Mathilde Schleicher

Rouska Nenov *

Background

Broad psychiatric symptoms have been associated to acute porphyria (AP) and correspond to a spectrum of heterogeneous manifestations such as anxiety, affective alterations, behavioral changes, personality, and psychotic symptoms. These symptoms may be difficult to identify as being related to porphyria since symptoms may arise at any time during the disease process. In addition, these patients may present psychiatric conditions secondary to the disease, such as adjustment disorders and substance use disorders.

We present and discuss a historical case of Sigmund Freud, that can be assumed as a case of comorbidity between porphyria and a bipolar disorder.

A Historical Case

In his report Sigmund Freud describes the patient Mathilde Schleicher with a "nervous illness" who developed mania in July 1889. Freud committed her on October 1889 to a private clinic with a diagnosis of "cyclical mood alteration".

For seven months patient was given all kinds of hypnotics and sedatives, occasionally she was also given sulfonal, a new hypnotic introduced in 1888 which had been described in medical journals as non-addictive, unlike other products in use.

In September, Freud found Mathilde "anemic", with vomiting, urinary retention, abdominal pain and red urine. On September 24, 1890, Mathilde Schleicher died in horrible abdominal cramps.

A few weeks later an article appeared under the signature of Hermann Breslauer who warned for the first time against the dangers of sulfonal: this product might cause acute porphyria, a liver damage signaled by the red color of the urine.

Conclusions

It is unclear whether porphyria is causally related to psychiatric disorder or not. It is possible that porphyria modifies an already present psychiatric condition and vice versa. A presented historical case can be assumed as a case of comorbidity between porphyria and a bipolar disorder.

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Impact of Acute Hepatic Porphyria on pregnancy, maternal postpartum and neonatal outcomes: A Swedish national cohort study

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Content Background
Our knowledge concerning morbidity in women with acute hepatic porphyria (AHP) during pregnancy, labor and the puerperium is largely based on biochemical disease models, case reports and case series. Larger observational studies are much needed for the establishment of updated evidence-based clinical guidelines.
Materials and Methods
We performed a national cohort study where the study base consisted of all women included in the Swedish Porphyria Register with confirmed AHP aged 18 years or older between 1987 and 2015. The women with AHP were matched with up to ten comparator subjects based on sex, birthyear and county of residence.
Risk ratios with corresponding 95% confidence intervals were estimated using Poisson regression among exposed (AHP) compared with the unexposed (non-AHP). Analyses were adjusted for maternal age at delivery, area of residency, birthyear and parity.
Results
214 women with AHP were included in the porphyria register and had ≥ 1 registered birth in the Medical Birth Register (MBR) during the study period.
2,174 matched comparator women, the comparison cohort, had ≥ 1 registered birth in the MBR during the study period.
Women with AHP presented with a higher risk for pregnancy-induced hypertensive disorder (aRR 1.73, 95% CI 1.12-2.68), gestational diabetes (aRR 3.41, 95% CI 1.69-6.89) and small-for-gestational-age (SGA) birth (aRR 2.08, 95% CI 1.26-3.45).
Conclusions
Pregnancy in women with AHP is associated with increased risks of adverse pregnancy outcomes, necessitating controls for the early identification and correct management of complications.

A 25 hour fast among quiescent herediatary coproporphyria and variegate porphyria patients is associated with a low risk of complications

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Content Background: Prolonged fasting is a known trigger of an acute hepatic porphyria (AHP) attack. Despite this, some Jewish AHP patients - mainly Hereditary coproporphyria (HCP) and Variegate porphyria (VP) patients - fast for 25 consecutive hours during a Jewish traditional holiday known as "Yom Kippur" (YK). In this study, we evaluated the effect of the fast on these patients. Methods: A retrospective study and survey of AHP patients in Israel. Patients were asked whether they have fasted since the age of 18 and whether any symptoms were induced by this fast. Patients' medical records were reviewed for an Emergency Department (ED) visit following YK between 2007-2019. Since only 3 Acute intermittent porphyria patients reported fasting- they were excluded. Results: 21 HCP patients and 40 VP patients completed the survey; 30 quiescent patients reported they fast while 31 didn't. Majority of fasting patients (96.67%) reported no symptoms following a fast. Data extracted from medical records were available for 383 patient fasts for each group. We found no statistically significant correlation between ED visits 1 week (0.26 % in both fasting and non-fasting patients) or 1 month (2.1% visits in non-fasting vs 0.78 % in fasting patients) following YK. Of the symptomatic ED visits following a fast, none were defined as severe attacks. Conclusion: A 25 hours fast in stable HCP and VP patients did not increase the chance for an acute attack and can probably be regarded as safe.

POWER (Porphyria Worldwide Patient Experience Research) study: Humanistic impact of prophylactic treatment among patients with acute hepatic porphyria

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Content Background and Aims
Acute hepatic porphyria (AHP) is a group of rare genetic diseases of haem biosynthesis resulting in severe neurovisceral attacks and complications that negatively impact quality of life. This study evaluated the impact of prophylactic and non-prophylactic treatment on patient-reported outcomes.

Methods
Adult patients from US, Italy, Spain, Australia, Mexico, and Brazil with AHP with >1 porphyria attack within the past 2 years or receiving intravenous hemin and/or glucose for attack prevention completed an online survey between January 19 and April 26, 2021. Descriptive analyses of demographics, health characteristics, and patient-reported outcomes (utilizing Generalized Anxiety Disorder-7 [GAD-7; scale, 0–21] and Patient Health Questionnaire [PHQ-8; scale, 0–24]) were conducted on all patients and separately among those who did and did not receive prophylactic treatment, defined as routine or scheduled hemin, routine or scheduled intravenous glucose, and/or a gonadotropin-releasing hormone agonist. Patients receiving givosiran were excluded.

Results
Ninety-two patients with AHP completed the survey (mean age, 41.1 years; 90.2% female). Prophylactic treatment was used by 38.0% of patients. Participants receiving and not receiving prophylactic treatment reported their current physical (88.6% and 71.9%), emotional (68.6% and 73.7%), cognitive (54.3% and 52.6%), financial (74.3% and 68.4%), and social health (62.9% and 49.1%) as either poor or fair, respectively. Mean GAD-7 and PHQ-8 scores for patients receiving prophylaxis were 10.3 and 12.4, respectively, and for those not receiving prophylaxis were 10.3 and 11.8, respectively.

Conclusions
Regardless of current treatment approach, AHP patients experience high disease burden and decreased quality of life.

Funding: This study was funded by Alnylam Pharmaceuticals.
Acknowledgements: Editorial assistance was provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Alnylam Pharmaceuticals.

DISCLOSURES

Amy Dickey had speaking engagements and received consulting honoraria from Alnylam Pharmaceuticals for participation in this research and for other porphyria-related consulting.

Edrin Williams, Rocco Falchetto, Jasmin Barman-Aksözen, and Marc DeCongelio reported having nothing to disclose.

Sue Burrell received grant and sponsorship funding to the British Porphyria Association as well as consulting honoraria from Alnylam Pharmaceuticals for participation on various patient advisory group leadership advisory boards.

Stephen Meninger and Stephen Lombardelli are employed by and own stock and stock options in Alnylam Pharmaceuticals.

Danielle Nance served on advisory boards for Aptevo Therapeutics, Bayer, HemaBiologics, and Medexus Pharmaceuticals; served on speaker bureaus for BPL and the National Hemophilia Foundation; provided consulting services to Goval; served as an author for Bayer; and had speaking engagements and received consulting honoraria from Alnylam Pharmaceuticals for participation in this research.

Changes in acute hepatic porphyria health impacts since diagnosis: Results from the Porphyria Worldwide Patient Experience Research (POWER) study

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Content Background and Aims
Acute hepatic porphyria (AHP) is a disease caused by mutations in the haem biosynthetic enzymes. This study evaluated AHP patient perceptions of changes in disease characteristics and impacts in quality-of-life domains since diagnosis.
Methods
Adults with >1 AHP attack within the past 2 years or receiving intravenous hemin and/or glucose for attack prevention were recruited worldwide and were administered an online survey from January to April 2021. Patients taking givosiran were excluded. Patient perceptions of changes in overall health and disease characteristics since diagnosis were evaluated. Patient-reported outcomes to evaluate anxiety and depression were assessed among subgroups of patients experiencing active disease for 0–5 years or ≥6 years using the Generalized Anxiety Disorder-7 (GAD-7) scale and the Patient Health Questionnaire (PHQ-8) scale, respectively.
Results
A total of 92 patients with AHP completed the survey. Most patients experienced negative impacts on emotional health (90%), physical health (87%), financial health (75%), social health (70%), and cognitive health (66%) since their diagnosis. Patients described disease characteristics as worsening since their diagnosis, including chronic pain (66%), kidney disease (55%), and acute pain (48%). In subgroup analyses, 22% (N=20) of patients were found to have had active disease for 0–5 years, and 73% (N=67) had active disease for ≥6 years. Thirty-five percent of patients experiencing AHP for 0–5 years reported a GAD-7 score ≥10, indicating moderate to severe anxiety, compared with 51% of patients experiencing AHP for ≥6 years. On the PHQ-8 scale, 30% of patients experiencing AHP for 0–5 years reported a score ≥10, indicating moderate to severe depression, compared with 66% of patients experiencing AHP for ≥6 years.
Conclusions
Patients with AHP experience negative impacts across multiple health domains and worsening in some disease characteristics since initial diagnosis.
Funding: This study was funded by Alnylam Pharmaceuticals.
Acknowledgements: Editorial assistance was provided by Peloton Advantage, LLC, an OPEN Health company, and funded by Alnylam Pharmaceuticals.

DISCLOSURES
Danielle Nance served on advisory boards for Aptevo Therapeutics, Bayer, HemaBiologics, and Medexus Pharmaceuticals; served on speaker bureaus for BPL and the National Hemophilia

Foundation; provided consulting services to Goval; served as an author for Bayer; and had speaking engagements and received consulting honoraria from Alnylam Pharmaceuticals for participation in this research.
Desiree Lyon received grant and sponsorship funding to the American Porphyria Foundation from Alnylam Pharmaceuticals.
Sean Hegarty, Rocco Falchetto, Jasmin Barman-Aksözen, and Tarek Mnif reported having nothing to disclose.
Stephen Meninger and Stephen Lombardelli are employed by and own stock and stock options in Alnylam Pharmaceuticals.
Amy Dickey had speaking engagements and received consulting honoraria from Alnylam Pharmaceuticals for participation in this research and for other porphyria-related consulting.

Underlying Causes of Porphyria Cutanea Tarda in Tayside

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Content Porphyria Cutanea Tarda (PCT) is the most common cutaneous porphyria in the UK and presents mainly with visible light–exposed site blisters and fragility. Sporadic PCT is most common due to reduced activity of uroporphyrinogen decarboxylase in the liver due to multifactorial chronic liver inflammation and iron deposition.

We investigated the underlying causes of PCT in 21 patients diagnosed in the Tayside Health Board area of Scotland in the last 30 years, by interrogating the medical records for evidence of excess alcohol consumption, viral infection, iron stores and haemochromatosis genetic status.

57% of patients were male, with the median age at diagnosis of 57 (range 32 -72) years. The most common contributing factor was excess alcohol consumption in 95% of patients (median/mean consumption 40/68 (range 27-210) units/week; maximum recommended intake 14 units/week).

Genetic haemochromatosis was identified in 42.9% of patients (28.6% homozygous C282Y, 4.8% compound heterozygous C282Y/H63D and 9.5% homozygous H63D). Additionally, 9.5% were heterozygous for C282Y, 14.3% were heterozygous for H63D and 23.8% had neither C282Yor H63D mutation. Genetic results were not available for two patients.

Four patients (19%) had chronic hepatitis C infection (76% negative and 5% unknown), whilst 90% were Hepatitis B negative (10% unknown). No patients were documented as HIV positive, although data were unavailable for 86% of patients.

76% of PCT patients had increased iron stores as evidenced by raised ferritin (median 820 [range 168-1973] μg/L in males, normal range 30-400 μg/L and median 427 [range 90-829] μg/L in females, normal range 13-150 μg/L). 29% of patients had raised transferrin saturation by iron (median 36%, range 16-93%, normal range 22-55%). Abnormal liver function tests were documented in 90% of patients, with either ALT and/or GGT elevated above the normal reference range.

In line with PCT being multifactorial in origin, 38% of Tayside patients were found to have both excess alcohol consumption and genetic haemochromatosis. All four patients with Hepatitis C infection also had excess alcohol consumption and one was additionally heterozygous for H63D.

These data help us to have a clearer understanding of the underlying causes of PCT in Tayside.

Porphyria during pandemic in Argentina

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Content Background

In early 2020 when pandemic started, some reports indicated that SARS-CoV-2 attacked β-hemoglobin chain releasing heme that cleaves to protoporphyrin IX and Fe, favoring virus infectivity by interaction with porphyrin. Porphyric patients usually have high content of porphyrins. The aim was to analyze how COVID-19 could affect manifestation and evolution of both pathologies in comorbidity. Porphyria incidence in patients diagnosed in CIPYP was studied during pandemic phases comparing it with last ten years. All patients signed the Inform Consent.

Results

Pandemic affected diagnosis during 2020, only 6 cases were registered: 4 Porphyria Cutanea Tarda (PCT), 1 Erythropoietic Protoporphyria (EPP), 1 Congenital Erythropoietic Porphyria. During 2021 we diagnosed: 35 PCT, 8 Acute Intermittent Porphyria (AIP), 3 Variegate Porphyria (VP) and 2 EPP. A last 10 years survey showed that AIP cases in 2021 were around median value (4.5±2.2) while PCT were significantly below (64±9.6). Until 20/5/2022, SARS-CoV-2 infected 111 patients: 58 AIP, 29 PCT, 14 VP, 8 EPP and 2 Hereditary Coproporphyria. 5 AIP and 2 PCT were hospitalized; among AIP, 1 needed ventilation, 2 has an attack during hospital care and 1 suffered a crisis 2 months after COVID-19 positive. For AIP, where most COVID-19 cases were reported, biochemical data showed no significant differences pre and post SARS-CoV-2 infection even in individuals with bilateral pneumonia or respiratory deficiencies.

Conclusion

COVID-19 does not have a different expression in porphyrics than in general population. We observed no worsening due to Porphyria and no different Porphyria manifestation during infection even in latent AIP/VP. Considering that COVID-19 is a systemic pathology with different levels of severity including long COVID and post COVID stress, a long-term medical control post-COVID in Porphyria is especially relevant to Acute Porphyrias where stress plays a key role.

Brazilian Registry of Patients with Porphyria: REBRAPPO® Study

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Content Background
There is a lack of large epidemiological and clinical data for porphyria in Brazil. We report results from the REBRAPPO® Study, a national Brazilian registry of Brazilian patients with the diagnosis of porphyria.
Materials and methods
The Brazilian Registry of Patients with Porphyria (REBRAPPO) is a clinical registry that collected retrospective self-reported medical data from Brazilian patients with porphyria through a specific electronic form developed by the authors.
Results
A total of 172 patients fully completed the registry form, 147 (85.4%) are female, 96 (55.8%) are Caucasian and 82 (47.6%) are unmarried. 69 (40.1%) patients had higher education degrees, 35 (20.3%) are unemployed and 79 (45.9%) depend exclusively on the Brazilian public health system. 148 (86%) had Acute Hepatic Porphyria (AHP) and 4 (2,3%) had Erythropoietic Porphyria (EP). Regarding AHP patients, 118 (79.7%) had Acute Intermittent Porphyria (AIP), 16 (10.8%) had Variegate Porphyria and 2 (1.3%) had ALAD porphyria. 36 (24.3%) of the AHP patients reported more than 4 attacks at last year and 139 (93.9%) reported chronic symptoms. Anxiety (69%), neuropathic pain (61%), insomnia (61%), constipation (58%), nausea (50.4%) and abdominal pain (48%) were the most common chronic symptoms reported by AHP patients. A total of 93 (62.8%) report opioid use for analgesic relief with a subset of 28 (30.1%) with daily use opioid. 66 (44.5%) had ever been treated with hemin therapies and 5 (3.3%) are on treatment with Givosiran.
Conclusions
This is the first report of the REBRAPPO study that constitutes a national cohort of Brazilian patients with Porphyria and shows important data about the natural history, chronic symptoms and quality of life in a large number of patients with AHP.

Quality of care in Norwegian porphyria patients, a Norwegian Porphyria Registry study

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Content Background

The Norwegian Porphyria Registry, a national quality registry, monitors whether patients receive treatment and follow-up as recommended by best-practice guidelines developed by the Norwegian Porphyria Centre. A patient questionnaire, a physician questionnaire and relevant guidelines for the patient's diagnosis are distributed annually to all patients included in the registry, and patients are asked to bring the guideline and physician questionnaire to their next follow-up appointment. The aim of this study was to assess the quality of care received by Norwegian porphyria patients, based on data reported to the Norwegian Porphyria Registry.

Materials and methods

All porphyria patients, including those with predictively tested acute hepatic porphyria, are invited to participate in the Norwegian Porphyria Registry. The registry includes 71% of the total Norwegian porphyria patient population. Patient and physician reported data on frequency, content and quality of annual follow-ups in 2021 were used to assess the quality of care.

Results

A total of 495 patients reported to the registry in 2021. Out of the 434 previously or currently symptomatic patients, 77% reported that they had been to an annual check-up that year. Physician reported data were received from 68% of the follow-up appointments, most of these adhered to the guidelines. About half of the patients with acute hepatic porphyria (AHP) >50 years of age (n=53) had received liver surveillance biannually as recommended. The majority of the patients were very satisfied with the follow-up they received (78%, n=346).

Conclusions

The majority of porphyria patients received high quality patient care, but more awareness towards liver surveillance biannually for AHP patients >50 years of age is needed. The distribution of guidelines and physician questionnaires can be helpful tools to ensure best practice follow-up in accordance with recommendations.

Analysis of whole blood protoporphyrin and plasma porphyrin in patients on Dapsone

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Content We conducted this study to determine whether dapsone is associated with elevated protoporphyrins in blood, prompted by an observation in one of our patients who had phototesting with suspected chronic actinic dermatitis. Previously he had been diagnosed with urticarial vasculitis and was on dapsone for this. Along with monochromator phototesting, which confirmed chronic actinic dermatitis (CAD), he had blood porphyrin biochemistry which showed moderately elevated total erythrocyte porphyrin, which was proportionately unchelated, although no plasma porphyrin peak was detected. His phototesting did not show features of a cutaneous porphyria. Blood tests repeated twice after that, whilst he was still on dapsone, showed the same but testing repeated after he was off dapsone was normal.
We considered that dapsone might be the explanation for raised erythrocyte porphyrin, possibly related to increased turnover in his bone marrow to compensate for dapsone haemolysis or impact on ferrochelatase activity.
This was a retrospective study measuring blood protoporphyrin and plasma porphyrin levels in patients on dapsone on samples stored, with permission of patients, by the Scottish Health Research Register (SHARE). None of the samples were light protected prior to storage, but were wrapped in foil upon retrieval. 10 samples for both blood and plasma porphyrin levels were analysed by the Scottish Cutaneous Porphyria Service. Plasma, blood porphyrin and total erythrocyte protoporphyrin levels were analysed by fluorescence spectroscopy using standard, published methods.
The plasma scan of all the samples showed no porphyrin peak. The blood protoporphyrin scan of 50% of patients on dapsone showed increased free protoporphyrin levels ranging from 54-65% (normal <70%). The total erythrocyte porphyrin levels in packed red blood cells were normal for all ten patients (<1.4 μmol/L)
We found that the increased unchelated protoporphyrin was not isolated to the original patient, but that this was increased in half of the ten patients on dapsone whose blood samples were analysed. Further prospective light protected studies are needed to explain this finding.

Acknowledgement: The study was funded by the British Porphyria Association

Treatment of severe liver disease in a patient with a rare combination of erythropoietic protoporphyria and factor VII deficiency

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Content Treatment of severe liver disease in a patient with a rare combination of erythropoietic protoporphyria and factor VII deficiency

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Introduction
Erythropoietic protoporphyria (EPP) is a rare inherited metabolic disease caused by a reduced activity of the last enzyme of the heme biosynthesis pathway, ferrochelatase. In a small subset of patients, hepatic accumulation of protoporphyrin IX (PPIX) is responsible for a progressive liver disease that could lead to liver failure.

Case description
We described the case of a female EPP patient who was treated for 3 episodes of liver involvement related to EPP in the span of 3 years. Firstly, she presented with jaundice following oral iron supplementation. Treatment discontinuation and ursodeoxycholic acid administration led to normalization of hepatic function. Secondly, seven months later, she underwent a liposuction, which resulted in an important blood loss that stimulated her erythropoiesis and resulted in massive accumulation of PPIX. She then presented with severe cholestasis that was treated with combination of iterative blood transfusions, erythrapheresis, hydroxycarbamide and ursodeoxycholic acid. Recurring epistaxis were responsible for erythropoiesis stimulation that contributed to PPIX accumulation. Finally, more than two years after the initial episode, the patient showed further deterioration of her liver function despite hydroxycarbamide and ursodeoxycholic acid treatment. Iterative erythrapheresis and plasma exchange, associated with blood transfusions, were able to normalize the liver function. Liver biopsy showed portal and sinusoidal fibrosis. A hematopoietic stem cell transplantation was then successfully performed.

Discussion and Conclusion
Our case highlights the different treatment options for EPP-related liver involvement. There are two main mechanisms of action: promoting the elimination of PPIX (ursodeoxycholic acid, erythrapheresis and plasma exchange) and inhibiting erythropoiesis (iterative blood transfusions, erythrapheresis and hydroxycarbamide).

Liver involvement in Bulgarian patients with porphyria

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Background: Porphyria is a group of metabolic diseases due to the impaired synthesis of hem. They are divided in two main types: hepatic and erythropoietic. Liver involvement is most common in porphyria cutanea tarda(PCT) and erythropoietic protoporphyria (EPP). Clinically hepatic disorders can range from mild hepatitis, hepatic steatosis, cholelithiasis, to development of cirrhosis, hepatocellular carcinoma, acute liver failure. In patients with PCT the frequency of chronic hepatitis C, alcohol consumption and hemochromatosis is high and contributes to liver involvement.
Material and methods: We have studied 17 patients with different types of porphyria in "St. Ivan Rilski University Hospital". Predominance were the women 65% and men 35%. Most of the patients were with AIP-8, followed by PCT-6 and 3 with PV. The aim was to investigate the frequency of liver involvement. We calculated the biomarker FIB-4, which can predict the possibility of developing severe liver disease. An increase in the FIB-4 over time it can be associated with higher risk, while a decrease in the FIB-4 was associated with reduced risk. Under 1.3 is with low chance of developing severe liver disease, upon 2.67 high and between 1.3 and 2.67- is an intermediate risk for advanced disease . Exclusion criteria were metabolic syndrome, excessive alcohol / drugs consumption.
Results: In the study 100% of the patients had hepatic steatosis, without having diabetes nor dyslipidemia. Liver enzymes were slightly above average ranges, dominantly GGT, which is an inducible enzyme. There were found 29% with asymptomatic cholelithiasis and 17 % polyp of the gallbladder, mainly in PCT and AIP, due to the insoluble porphyrins. Frequently were found hepatic cysts and hemangiomas in women around 29%. There were 4 male patients with PCT and viral hepatitis: one with HBV and tree with HCV. In 12% of all patients was liver cirrhosis was diagnosed, both of them with HCV. The average value of FIB-4 index was 1.37. Around 55% of the patients had a score under 1.3, which is associated with low possibility of advance hepatic disease and 45% an intermediate risk.
Conclusions: Porphyria are diseases with multiple organ involvement. Frequently diagnosed are hepatic steatosis and asymptomatic cholelithiasis. Most of the patients with PCT have liver involvement associated also with viral hepatitis or alcohol consumption. The index FIB-4 is non-invasive marker for predicting hepatic disease. By multiple measuring in the years, it can assess the risk of cirrhosis or HCC. This could be a useful tool for screening liver involvement or disease in patients with porphyria.

The role of a patient's association in patient care

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Content The role of a patient's association in patient care

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Background

In Brazil, since 2014 there is a policy geared at people with rare diseases. However, there are still many gaps for its implementation, as genetic tests are not available for most, and only very few diseases have specific treatment policies. For people with porphyria, access to diagnosis nor treatment guaranteed in public or private health system. In the scenario, rare disease patients' association play a major role since they are the main voice for the patients.

Brazilian Porphyria Association (ABRAPO) and "What your genes say?" project

ABRAPO has been representing people with porphyria since 2006. It's an information source for health professionals, patients, and families. In 2019, ABRAPO participated in a selection process for a grant from a pharmaceutical industry with a project aimed at providing genetic testing for its associates. Two doctors specialized in medical genetics offered pre and post testing genetic counseling sessions for patients and family members interested in the test. Family members were offered testing after positive results.

Results of the project

60 patients participated and acute porphyria diagnosis was confirmed in 39 (28 acute intermittent porphyria, 8 variegate porphyria, and 3 hereditary coproporphyria). 10 cases revealed variants of unknown significance and in 13 cases the test was negative. Clinical history and biochemical results of negative cases revealed that diagnosis was based on atypical symptoms, qualitative porphobilinogen urinary test or fecal porphyrins.

Conclusion

This experience is an example of a patients' association action, occupying spaces where the state is absent. The result of this investigation suggests that clear guidelines, access to proper testing and training health professionals are needed in the country

Acknowledgements

We thank Alnylan Pharmaceuticals for this grant.

Severe hyperhomocysteinemia induced by givosiran: should systematic vitamin treatment be offered?

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Content Background

Homocysteine (HCy) is an intermediate of methionine metabolism, and its elevation is correlated with an increased risk for vascular disease. In patients with acute intermittent porphyria (AIP) and long-term excretion of heme precursors, 62.5% presented hyperhomocyteinemia (HHCy) (1). We report a case of major HHCy under givosiran.

Case report

A 72-year-old woman is affected by a first attack of AIP at the age of 63 in the form of a PRES syndrome (porphyria-induced posterior reversible encephalopathy syndrome). She relapsed 5 years later with rapidly resolving transient blindness. She presented 6 months ago with a 3rd acute attack following pyelonephritis. Her brother, sister and 2 daughters are carriers of the HMBS gene mutation. Biologically, one month after the last crisis treated with human hemin, the levels were: ALA/creat: 49 micromol/mmol, N<3 and PBG/creat: 63 micromol/mmol, N<1. Fasting HCy was measured at 79 micromol/l. The patient is treated with givosiran® by subcutaneous injection monthly for 2 months. One month after the 1st injection ALA/creat: 2.8 and PBG/creat: 11.4, HCy: 447. Treatment with vitamin B6 is started (250 mg 3 times a day and one cystine tablet per day) for 60 days. The 2nd injection of givosiran is performed. One month later the plasma HCy is measured at 317 and two months later at 13. Two months after the 2nd injection of givosiran ALA/creat: 2 and PBG/creat: 8.5. A month later the levels rise to 15.5 and 33 micromol/mmol respectively, a 3rd injection of givosiran is carried out with the continuation of the vitamin treatment.

Conclusion

The rhythm of givosiran injections is adapted according to the evolution of urinary heme precursors with the aim of reducing the side effects, healthcare costs, and improving patient comfort (2). It has now been clearly demonstrated that AIP patients can present HHCy potentiated by givosiran (3). It is therefore important in the management of these patients to measure systematically plasma HCy level before treatment, to administrate an appropriate vitamin treatment based mainly on vitamin B6 and to monitor the evolution of the Hcy levels according to the frequency of administration of givosiran.

Bibliographie

1. To-Figueras J, Lopez RM, Deulofeu R, Herrero C. Preliminary report: hyperhomocysteinemia in patients with acute intermittent porphyria. Metab Clin Exp 2010; 59:1809-1810.
2. Poli A, Schmitt C, Moulouel B, Mirmiran A, Talbi N, Rivière S et al. Givosiran in acute intermittent porphyria: A personalized medicine approach. Med Genet Metab 2022;135:206-214.
3. To-Figueras J, Wijngaard R, Garcia-Villoria J, Aarsand AK, Aguilera P, Deulofeu R et al. Dysregulation of homocyteine homeostasis in acute intermittent porphyria patients receiving heme arginate or givosiran. J Inherit Metab Dis 2021;1-11

A survey of acute and chronic symptoms of acute intermittent porphyria in a French cohort

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Content Background
Acute intermittent porphyria (AIP) is an inherited disorder of heme metabolism responsible for acute neurological symptoms and chronic complications (mainly chronic kidney disease, hepatocellular carcinoma). We characterized the natural history of the disease, focusing on the onset of chronic complications and investigating the presence of mild symptoms in patients and asymptomatic carriers.
Methods
A survey was sent to AIP carriers and patients, including questions regarding epidemiological data, patients' history, the rate, nature, and severity of the symptoms, and an evaluation of the patients' quality of life. The screening included blood and urine laboratory tests and liver ultrasound. Patient's spouses completed an adapted survey to constitute a control group.
Results
Among 833 AIP subjects contacted, 388 AIP (191 patients, 197 carriers) and 113 controls completed the survey. In the symptomatic patient's group, 23.2% patients declared having symptoms equivalent to their initial crisis at least four times a year, 32.1% between 1 and 3 times and 44.6% less than one time.
In gender-separated subgroups, long-lasting moderate abdominal pain at least four times a year was reported by 34.8% symptomatic male patients, 21.1% male carriers, and 8.5% male controls, whereas it was reported by 41.6% symptomatic female patients, 28.4% female carriers and 39.5% female controls. The presence of moderate abdominal pain was not correlated with precursor concentrations. High blood pressure was reported by 47.6% of symptomatic patients, 29.9% of carriers and 21.9% of controls. Chronic kidney disease was diagnosed in 20.9% symptomatic patients, 3.1% carriers and 1.7% controls. Hepatocellular carcinoma was diagnosed in 4 AIP patients and two carriers.
Conclusion
We confirm the high prevalence of chronic complications. Patients and carriers experience moderate long-lasting abdominal pain that is not correlated to ALA and PBG concentrations. This raises questions regarding physiopathology and patient management.

Pregnancy, childbirth and use of hormonal replacement therapy and contraception among patients with acute hepatic porphyria

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Content Background:
Clinical manifestations of acute hepatic porphyria occur mainly among female patients. This is commonly due to hormonal changes during their fertile years. The purpose of this study is to explore the menstrual cycle, pregnancies, childbirths, and use of exogenous sex hormones among female patients with acute hepatic porphyria.
Materials and methods:
107 Finnish female patients were enrolled into a retrospective, longitudinal study during 2015. Clinical, biochemical, and genetic data was obtained from the medical reports, registry data and a questionnaire designed for the study. A total of 205 pregnancies resulting in 172 live births were reported among 85 patients.
Results:
Menarche began at the average age of 13 years, and 87% of the patients had a regular cycle. Of the 70 patients with manifest acute porphyria, 48 had symptoms during the luteal phase of the menstrual cycle. Typical symptoms were abdominal pain accompanied by pain in the back and limbs starting one week before menstruation. Acute symptoms were relieved by menstruation. 32 patients reported relief of acute symptoms by menopause.
Most pregnancies were uneventful and resulted in a normal vaginal delivery. The cesarian section rate was 16%, which is in line with the normal Finnish population. Five patients reported porphyric symptoms during pregnancy, and additional seven patients up to six months after delivery. Acute attacks were commonly not triggered by pregnancy or delivery alone, but in combination with rapid weight loss, infections, and use of porphyrinogenic medications. Nine patients reported infertility, and four patients received hormonal treatment which did not cause acute symptoms.
96 subjects reported use of contraception. 76 used hormonal contraceptives, most commonly combined methods. Four attacks were associated with hormonal contraception. Hormonal replacement therapy (HRT) was used by 29 post-menopausal women, none of whom reported acute symptoms during use.
Conclusions:
The risk of an acute attack during pregnancy, delivery or postpartum is low. The risk for a cesarian section is not increased among patients with acute hepatic porphyria in Finland. Most patients use hormonal contraceptives, which is rarely a triggering factor for acute attacks.