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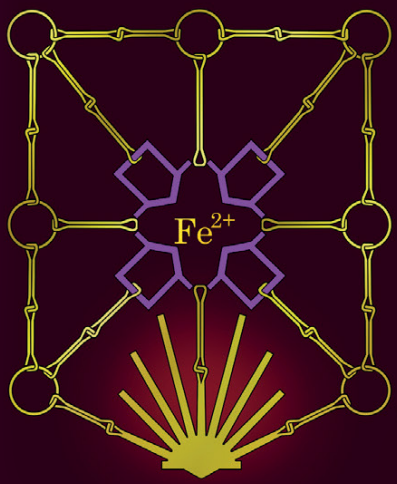

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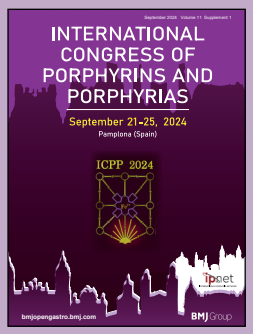

Abstracts of the International Conference of Porphyrins and Porphyrias, Pamplona, Spain, 21–25 September 2024

Session 1 – Guidelines for treatment and follow-up (September 22nd, 2024)

Thematic area: diagnosis and care in porphyrias

04089 A PILOT STUDY IN 77 EPP PATIENTS OF THE LIVER FIBROSCAN ('TRANSIENT ELASTOGRAPHY') TO IDENTIFY PATIENTS DEVELOPING FIBROTIC LIVER DISEASE. IDENTIFICATION OF OBESITY AS A RISK FACTOR

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Erythropoietic protoporphyria (EPP) is complicated by severe liver disease in 1–5% of patients. There is no means of identifying patients at risk of severe liver complications.

Histological analysis of the removed liver in EPP patients requiring liver transplantation, shows severe fibrosis and cirrhosis. The cirrhosis probably develops slowly and silently, terminating in the final illness.

Blood liver function tests are poor at identifying gradually progressive fibrosis, and are more useful for acute hepatic inflammation and obstruction. Liver biopsies are too invasive and hazardous for monitoring for developing fibrosis in EPP. In recent years liver fibroscanning ('transient elastography') has become widely used by Hepatologists for the detection and staging of liver fibrosis. It is non-invasive, and the machines can be used in an outpatient clinic by operators after minimal training.

We have carried out liver fibroscanning to assess its potential to identify early hepatic fibrosis in this exploratory pilot study.

We included all EPP patients over 18 years attending our Clinic in a 23 month period. No patient had XLDPP, 1 had previously had autoimmune hepatitis which was in biochemical remission. No patients developed severe liver disease or died during the study.

The fibroscan measure of fibrosis is the 'liver stiffness measure' (LSM). We used the normal and fibrotic ranges of LSM values established in Hepatitis C studies (normal <7.1 kPa; early fibrosis 7.1–12.5 kPa; advanced fibrosis > 12.5 kPa).

64 patients (83.1%) of patients had LSM values in the normal range. 13 (16.9%) had abnormal values indicating fibrosis, 8 (10.4%) in the mild fibrosis range, and 5 (6.5%) in the advanced fibrosis range.

This study did not include further fibrosis investigations, including liver biopsy histology.

We also examined other patient variables for correlations with fibroscan results indicating advanced fibrosis: age, alcohol intake, body mass index (BMI), liver function test results, and red cell protoporphyrin concentration. The only variable which correlated at the 5% significance with advanced fibrosis on fibroscanning, was BMI. BMI was significantly higher in patients with advanced fibrosis than the rest. Obesity has not previously been suggested as a risk factor for severe hepatic disease in EPP. However, it is a major risk factor for cirrhosis in the general population.

Our results suggest that liver fibroscanning may be of value to identify EPP patients developing liver fibrosis, of applications in routine clinical care and in drug trials. Our data also suggest that managing obesity may be important in EPP. Future studies are needed to confirm these findings with liver histology.

04104 PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS AT ENROLMENT IN ELEVATE, AN INTERNATIONAL REGISTRY OF ACUTE HEPATIC PORPHYRIA

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10.1136/bmjgast-2024-ICPP.2

Background Acute hepatic porphyria (AHP) is a group of rare genetic diseases that affect the haem biosynthesis pathway. Overproduction and accumulation of haem intermediates δ-aminolevulinic acid (ALA) and porphobilinogen (PBG) cause acute attacks and chronic complications in multiple organ systems, severely affecting patients' quality of life. Givosiran is a small interfering RNA molecule approved for the treatment of adults (USA) and adults and adolescents (≥12 years old; EU) with AHP.

Methods ELEVATE (NCT04883905), started in April 2021, is an international, prospective, observational registry. The primary objective is to characterize the long-term real-world safety of givosiran in patients with AHP. The secondary objectives focus on characterizing long-term real-world effectiveness of givosiran treatment and describing the natural history and clinical management of patients with AHP. Currently, there are 23 active sites in 6 countries in Europe and North America, with 2 sites in Asia to join. Data from routine clinical assessments of registry patients are collected at least once annually.

Results As of March 6, 2024, 166 patients with AHP (135 females [81.3%]) were enrolled in ELEVATE, with equal distribution between North American and European sites (n=83 in each). The median age (range) of patients at enrolment was 43 (12–77) years, with 54.2% in the 18–45 years age category. Most patients were white (71.1%), with a median (range) body mass index of 24.6 (15.9–53.1) kg/m2. Median age at diagnosis and/or testing (based on family history), as per the treating healthcare provider determination, was 29 (4–70) years. Among those with symptoms (n=151), median age of symptom onset was 29 (6–69) years. Of the 166 patients, 104 (62.7%) had at least one relative with known or suspected AHP. A total of 139 patients (83.7%) had acute intermittent porphyria, 20 (12.0%) had variegate porphyria, 4 (2.4%) had hereditary coproporphyria and 1 (0.6%) had ALA dehydratase-deficient porphyria; AHP type was not reported for 2 patients (1.2%). The majority of patients had unique mutations. A total of 117 patients (70.5%) reported ever having received treatment for AHP with any AHP medication. A total of 109 patients (65.7%) reported receiving treatment for AHP at the time of enrolment: 104 (95.4%) were treated with givosiran, 15 (13.8%) with hemin prophylaxis, 13

(11.9%) with intravenous glucose/dextrose, 6 (5.5%) with carbohydrate intake and 4 (3.7%) with other medications.
Conclusions The demographic and clinical characteristics of the patients enrolled in ELEVATE underscore the heterogeneous nature of AHP. The registry data collected will provide real-world evidence on the natural history and treatment of patients, helping to improve the clinical management of AHP. Safety and effectiveness endpoints will be analyzed in the future, during ongoing data collection as part of a post-authorization commitment. This study is funded by Alnylam Pharmaceuticals.

04150 USE OF HORMONAL CONTRACEPTIVES AND MENOPAUSAL REPLACEMENT THERAPY IN WOMEN WITH ACUTE PORPHYRIA

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10.1136/bmjgast-2024-ICPP.3

Background Therapeutic use of female sex hormones can potentially trigger acute attacks in genetically predisposed women, however, many women with acute porphyria tolerate this treatment well. Balancing the risks and benefits of hormonal drug treatment can be challenging in acute porphyrias, and there is a need for a more comprehensive knowledge base to establish robust guidelines.
Objective Our aim of this study was to investigate the current practices among porphyria specialists regarding recommendations for choice of contraceptive methods, menopausal replacement therapy (MHT) and follow-up in acute porphyrias. Additionally, we sought to assess the clinical experiences and outcomes associated with use of hormonal drugs in Norwegian porphyria patients.
Materials and Methods We circulated an electronic survey to porphyria specialist centers within the International Porphyria Network. The survey inquired about their recommendations and follow-up in different clinical scenarios related to use of hormonal drugs in patients with active or latent acute porphyrias. From the Norwegian Porphyria Registry, data reported from 2002–2022 were extracted to investigate patient-reported drug use, tolerance, and any associated acute attacks.
Results Among 24 respondents from 22 centers across Europe, North and South America, South Africa, Taiwan and Australia, 18 would recommend non-hormonal contraceptive methods for women with active porphyria, such as the copper intrauterine device (IUD), followed by the progestin IUD, which was recommended by 5. For treatment of menopausal symptoms, 21 recommended non-hormonal drugs or local hormonal therapy only. The majority recommended to monitor porphyrin precursors during any hormonal treatment, including MHT. However, there was significant variation in the suggested frequency and duration of this monitoring. In the Norwegian Porphyria Registry, 67 out of 196 women reported use of hormonal drugs. Twenty-two of these women reported attacks likely induced by these drugs, although the majority occurred prior to 2002, which is when the registry was established.
Conclusions Porphyria specialists tend to be cautious when recommending systemic hormonal therapy and often favoring IUDs for contraception. Regular monitoring of porphyrin precursors appears to be widespread. Data from the Norwegian Porphyria Registry suggest that hormonal medications are generally well-tolerated, with minimal reports of attacks in recent years. Menopausal hormone therapy has shown good tolerability, nevertheless many specialist centers do not recommend MHT. Our data indicate that there are variations in clinical practice among Ipnet specialist centres and the availability of common guidelines on hormonal therapy in acute porphyria would be beneficial for patients.

Session 2 – Genetic and molecular mechanisms of heme synthesis and regulation (September 23rd, 2024)

Thematic area: recent advances in the pathophysiology of porphyrias

04159 ACUTE INTERMITTENT PORPHYRIA ONSET: BIOINFORMATIC AND GENETIC ANALYSIS OF PORPHYRINOGENIC XENOBIOTICS AND DRUGS TRANSPORTER SYSTEM

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10.1136/bmjgast-2024-ICPP.4

Acute Intermittent Porphyria (AIP) is a metabolic disease in which the mutation in Porphobilinogen deaminase is not enough for the manifestation of the symptoms. Previous experimental results have shown that alternative variants in genes of ABC drug transporter (*ABCB1*: rs1045642, rs2032582, rs1128503; *ABCG2:* rs2231137) and *NR1I2* gene (rs12721613), regulator of *ABC* transcription, could be involved in the onset of AIP. The aim was to investigate further the influence of *ABCB1, ABCG2* and *NR1I2* on AIP onset in relation to porphyrinogenic drugs employing bioinformatics tools. For this purpose, three SNVs of *ABCB1* (rs1045642, rs1128503, rs20325822), two SNVs of *ABCG2* (rs2231137, rs2231) and four SNVs of *NR1I2* (rs12721613, rs2472677, rs12721607, rs12721608) were evaluated using different databases: gnomAD; UniProt; GenBank; PharmGKB, association between genetic variants, drugs and clinical manifestations; Gene Expression Omnibus, expression arrays; PreADMET and SwissADME, to estimate whether drugs are substrates/inhibitors of different transporters. Allele frequencies varied among different geographic regions and ethnicities, reinforcing the relevance of local control group analysis. For *NR1I2* gene, T allele of rs2472677 was associated with a phenotype of toxicity, an altered metabolism and/or a different efficacy for drugs contraindicated in AIP (Isoniazid, Rifampicin and Efavirenz). Considering models to infer liver toxicity, Rifampicin induced down expression of *ABCB1* and 8 *CYP* genes, including *CYP3A4*, in primary culture of human hepatocytes (GSE139896); Isoniazid caused differential expression of 11 *ABC* genes (27.3% down expressed) and 18 *CYP* genes

(61.1% down expressed) in a human liver cancer cell line (GSE168473). Analyzing Free Wilson's equations to find possible drugs to replace those insecure for AIP patients, some derivatives of Thiofeno[3,2]pyrimidine would represent therapeutic alternatives to Efavirenz. These derivatives would have a differential action as substrates/inhibitors of ABCB1 transporter and CYP. Associations between non-wild type variants of *ABCB1* and *ABCG2*, drugs contraindicated in AIP and a phenotype of toxicity or alteration of metabolism were also found: rs1045642, rs1128503 and rs1128503 for *ABCB1* (13, 2, and 2 xenobiotics, respectively); and rs2231137 and rs2231142 for *ABCG2* (2 and 10 xenobiotics, respectively). In conclusion, it was observed that contraindicated drugs for AIP patients are associated with toxicity and a differential metabolism in the presence of the studied variants. In turn, these drugs alter the gene expression of drug metabolizing and transporting systems. Bioinformatics tools are a valuable complement for experimental findings and for exploring new approaches and would be of relevance in personalized medicine and pharmacogenetics, a topic of upmost relevance in the pathophysiology of Hepatic Porphyrias.

Thematic area: heme synthesis and regulation

04124 SHAPES AND PATTERNS OF HEME-BINDING MOTIFS IN MAMMALIAN HEME-BINDING PROTEINS

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Porphyrins have been in the focus of research and intense studies for over a century. Heme is an iron-containing protoporphyrin that plays variety of roles by serving as a crucial prosthetic group in hemoproteins involved in various biological processes such as oxygen transport, storage, and miRNA processing as well as a signaling molecule regulating a wide array of cellular and molecular processes. Conversely, heme also exhibits the ability to temporarily associate with proteins, influencing biochemical pathways. Moreover, due to the association to a category of diseases known as porphyrias, scientists started exploring heme and its porphyrin precursors more extensively. These include proteins and enzymes in the heme biosynthetic pathway resulting in increased levels of heme precursors. Another set of heme-related disorders affecting a large cohort worldwide, is the broad category of hemolytic diseases, encompassing sickle cell disease and β-thalassemias, which involve premature rupture of RBCs leading to the release of excess amount of heme into the plasma. This available heme can bind to various proteins and regulate their functions. Nevertheless, the understanding of heme's contribution to these processes is still growing with increased efforts to gain insight into the mechanisms that initiate the interaction between heme and target proteins and the subsequent formation of complex structures. The presence of a distinct heme-binding motif (HBM) is a crucial requirement for the formation of such intricate complexes. While there are many short signature sequences that indicate specific protein functions, there is a lack of comprehensive analysis regarding the various patterns and structural characteristics of HBMs. Thus, the present investigation focuses on the evaluation of known heme-regulated proteins in mammals, specifically examining the specific recognition and structural patterns within their HBMs. Importantly, this analysis emphasizes the significance of Cys-Pro dipeptide motifs due to their higher frequency. Through this investigation, a comprehensive understanding of the sequence and structural similarities and differences observed during transient heme binding and the subsequent regulation of the respective proteins can be obtained.

Session 3 – Heme metabolism and cellular energy: inter-organ heme signaling and import/export systems (September 23rd, 2024)

Thematic area: heme synthesis and regulation

04146 ENHANCED ETB-DEPENDENT CONTRACTION MEDIATES INCREASED ET-1 RESPONSES IN MESENTERIC ARTERIES IN THE AIP MOUSE MODEL

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10.1136/bmjgast-2024-ICPP.6

Acute Intermittent Porphyria (AIP) is characterized by a deficiency of hepatic porphobilinogen deaminase (PBGD). Symptoms experienced by AIP patients, mostly women of reproductive age, include systemic arterial hypertension and tachycardia. The 21-aa peptide endothelin-1 (ET-1) is one of the more potent vasoconstrictors described and acts on vascular ET_A and ET_B receptors localized in smooth muscle (ET_A and ET_B) and in endothelial cells (ET_B). In symptomatic AIP patients increased plasma levels of Endothelin-1 (ET-1) have been reported (PMID: 35741113). In arteries of the AIP mouse model (T1/T2-AIP) we aimed to characterize the role of ET_A and ET_B receptors in mediating ET-1 contractile responses.

Mesenteric arteries were isolated from 8-month-old female C57Bl6 wildtype (WT, n=16) and T1/T2-AIP mice (n=16) and mounted on a Multi Wire Myograph for determination of isometric force (USA-DMT®). The contractile responses to K^+75 mM and ET-1 (10^{-11}-10^{-7}M) were measured at basal conditions. Parallel experiments were performed after pre-incubation with the ET_A specific blocker BQ123 (10^{-6}M) or the ET_B specific blocker BQ788 (10^{-6}M) in intact and endothelium denuded arteries. Maximal responses (ET-1_{MAX}) were expressed as% of contraction to 75mM KCl (%K_{MAX}) and sensitivity as pD_2 (-Log[EC_{50}]). Data were analyzed using Prism (GraphPad®).

In intact arteries, a greater ET-1 contraction was observed in AIP arteries (152±7 *vs.* 125±5 %K_{MAX}, $p<0.05$); this difference was abolished in arteries without endothelium (141±3 *vs.* 144±8 %K_{MAX}, $p>0.05$). In intact and endothelium

denuded arteries from both WT and T1/T2-AIP, blockade of ET_A or ET_B lowered ET-1 sensitivity. In intact arteries with ET_A blockade, T1/T2-AIP arteries displayed a greater contraction (145±7 *vs.* 120±8%K_{MAX} $p<0.05$) and lower sensitivity (7.47±0.07 *vs.* 7.8±0.09, $p<0.05$) with no differences in the presence of ET_B blockade. In endothelium denuded arteries with ET_A blockade, T1/T2-AIP arteries displayed a greater contraction (138±5 *vs.* 119±4%K_{MAX}, $p<0.05$) with no differences in sensitivity. Differences in ET-1_{MAX} and sensitivity were abolished in the presence of ET_B blockade in intact and denuded arteries.

We **conclude** that the increased ET-1-dependent contraction is due to a greater function of the smooth muscle ET_B receptor, with a higher function of the endothelial ET_B receptor only evident in the presence of ET_A blockade. An increased contraction in the presence of greater plasma levels of ET-1 will potentiate the prohypertensive effects of the peptide. Dual ET_A/ET_B antagonists may offer benefits in the control of hypertensive crisis in AIP patients. Possible effects of ALA, PBG, heme, and givosiran are in need of further study in this model system and are planned.

04190 ADRENAL INSUFFICIENCY ASSOCIATED WITH MUTATIONS IN HAEM BIOSYNTHESIS GENES

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10.1136/bmjgast-2024-ICPP.7

Mutations in the 8 haem biosynthetic pathway genes are traditionally known to cause a group of diseases known as porphyria. While Primary Adrenal Insufficiency (PAI), an intrinsic adrenal defect in glucocorticoid synthesis +/- mineralocorticoid synthesis, is linked to mutations in more than 25 genes, in our cohort, most commonly the melanocortin receptor gene (*MC2R*), its accessory protein (*MRAP*), steroidogenic enzymes (*STAR* and *CYP11A1*), and a gene involved in mitochondrial anti-oxidant defence (*NNT*). Over the last few decades, there have been tantalising case reports linking porphyria with defects in steroidogenesis.

We identified seven families (11 individuals) with defects in haem biosynthetic enzymes who exhibit flagrant adrenal insufficiency (AI), with or without porphyria. 1) a kindred (n=4) from Egypt with biallelic mutations in protoporphyrinogen oxidase (*PPOX*) p.(Glu339Lys), who have a spectrum of symptoms ranging from failure to thrive, focal neurology, cutaneous lesions of variegate porphyria along with severe AI. 2) Three kindreds with mutations in coproporphyrinogen oxidase (*CPOX*), (i) a preterm female of Asian descent homozygous for p.(Pro367Ala) mutation, who presented with anaemia, jaundice, focal neurology and cutaneous manifestations of Hereditary Coproporphyria (HCP) along with AI, (ii) siblings of Kurdish descent homozygous for p.(Ser28*) mutation, the boy had HCP along with AI and Disorder of Sex Development, while the girl has no clinical manifestations of HCP but has severe AI, and (iii) a patient with HCP from France who presented with AI aged 64, this patient had a urinary steroid metabolome that showed elevated levels of 11-deoxycorticosterone and 11-deoxycortisol. 3) Three adult patients with mutations in Hydroxymethylbilane Synthase (*HMBS*) who presented with AI during acute hepatic porphyria attacks.

This growing evidence suggesting a link between mutations in haem biosynthesis genes and PAI indicates that testing adrenal function in porphyria patients and their families might be warranted. Furthermore, haem biosynthesis genes should be considered for inclusion in genetic testing panels for adrenal insufficiency.

In order to understand the mechanism behind the link in patients, we plan a multicentre study that investigates different aspects of adrenal steroidogenesis biochemically and genetically in porphyria patients and their family members.

Session 4 – Heme in pathophysiology (September 23rd, 2024)

Thematic area: heme synthesis and regulation

04132 HEME-DRIVEN PATHOLOGIES IN THE CONTEXT OF INFECTIONS: FROM TLR4 SIGNALING TO COVID-19

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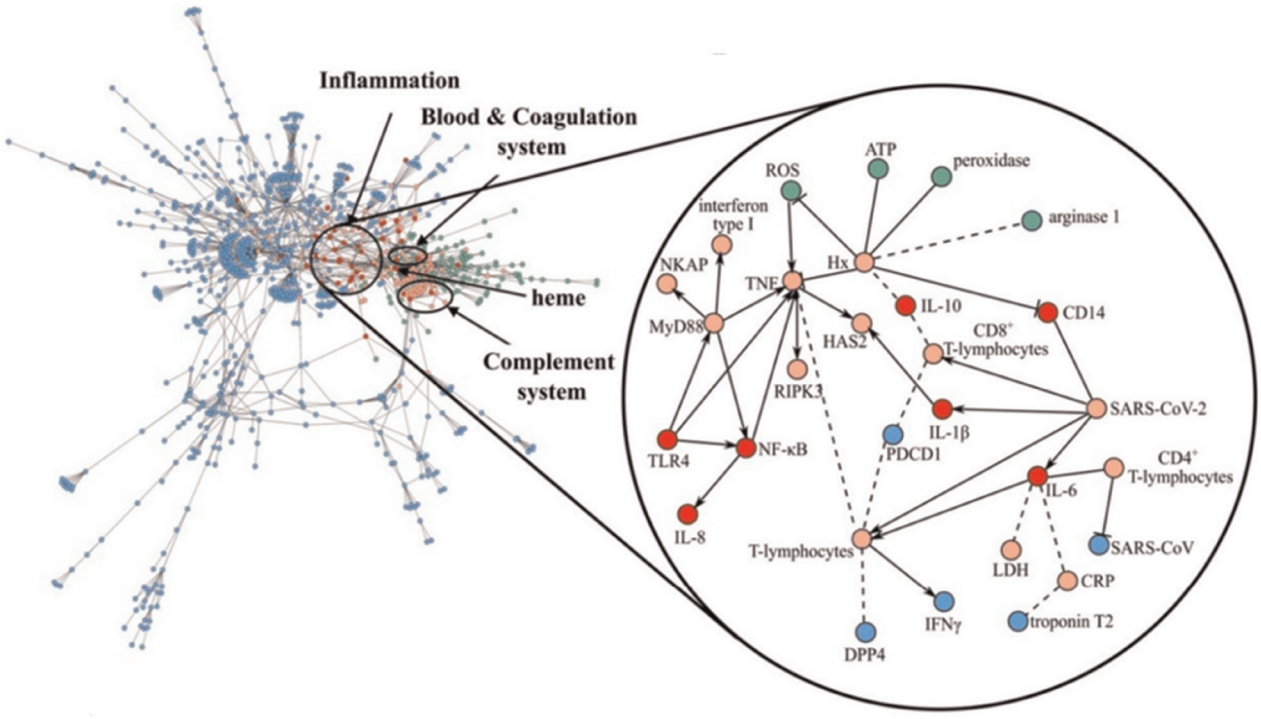
10.1136/bmjgast-2024-ICPP.8

Heme is not only a prosthetic group of hemoproteins, but also a potent effector molecule. This regulatory heme can bind to short nonapeptide sequences, i.e. heme-regulatory motifs (HRMs), on the protein surface. We studied >300 HRMs in detail employing peptides and proteins as well as a plethora of spectroscopic and bioinformatics methods. Apart from knowledge acquired for the physiological role of transient heme binding to proteins, its pathophysiological impact is still not completely understood. However, a considerable amount of heme is released under hemolytic conditions and causes pathological states such as thrombosis. On the other hand, the SARS-CoV2-triggered respiratory tract disease COVID-19 has been shown to lead to serious changes in clinical biomarkers like hemoglobin and interleukins, parameters, which are also altered during hemolysis. With various computational-experimental basic and advanced studies, we aimed at analyzing a potential link between heme-related and COVID-19 pathophysiologies. We performed a detailed analysis of the common pathways induced by heme and SARS-CoV-2 by superimposition of knowledge graphs covering heme biology (Heme-KG) and COVID-19 pathophysiology. Thereby, focus was laid on inflammatory pathways and distinct biomarkers as the linking elements. In a subsequent approach, four COVID-19-related proteins, the host cell proteins ACE2 and TMPRSS2 as well as the viral protein 7a and protein S as well as HRM-peptides derived thereof, were experimentally and computationally analyzed as potential heme-binding proteins. The results contribute to our understanding of the progression heme-related diseases in the context of infections in patients with different clinical



Abstract 04132 Figure 1

backgrounds and may allow for a more individual diagnosis and therapy in the future.

04108 CHARACTERIZATION OF HEME-INDUCED TOXICITY AND FERROPTOSIS IN PLACENTAL CELLS

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10.1136/bmjgast-2024-ICPP.9

The placenta is crucial for successful human pregnancy and fetal health. During pregnancy, the placenta plays pivotal roles in endorsing the mother's physiological adaptation to immunological acceptance, gas and nutrient exchange, and support of the developing embryo. Iron is an essential micronutrient through its participation in the structure of hemoproteins and its role in redox reactions. Free iron is a harmful pro-oxidant via the Fenton reaction that forms free hydroxyl radicals and increases oxidative stress and lipid peroxidation. Some pregnancy diseases have been associated with dysregulation in iron metabolism: pre-eclampsia is associated with higher iron maternal and ferritin concentrations. Ferroptosis is an iron-dependent, non-apoptotic programmed cell death. Emerging evidence supports the idea that ferroptosis may play a key role in placental dysfunction.

In this work, we aimed to explore the mechanism of heme and ferroptosis toxicity in human placental cells and to consider their potential reversibility using either antioxidant (Ferrostatin-1; Fer-1) or iron chelators (Deferoxamine, DFO). Therefore, we evaluated on BeWo cells (human trophoblastic cells model) treated either with heme (heme arginate 0.075 mg/mL) or ferroptosis inducer (erastin 5μM) the cell viability, the expression of markers specific to ferroptosis, and the effects on heme anabolism/catabolism and iron acquisition and storage.

Treatment with heme arginate and erastin showed a 40% decrease in BeWo cell viability assessed by MTT assay associated with an LDH release three times greater than for the untreated control group. DFO and Fer-1 partially reversed the cytotoxic effect of heme and erastin, respectively. Glutathione peroxidase 4 expression decreased by nearly 50% following heme arginate and erastin treatment. Lipid peroxidation was increased by erastin (45%), and co-treatment with 10 μM Fer-1 reduced the lipid peroxidation to the initial level, as evidenced using the BODIPY 581/591 C11 probe. Analysis revealed a significant change in the heme and iron metabolism pathways at transcriptional and post-transcriptional levels, with distinct patterns for heme and ferroptosis inducer treatments. Interestingly, compared to the untreated group, the expression of transferrin receptor 1 (TFR1) was upregulated by 1.5-fold in erastin-treated BeWo despite iron availability in this model. As expected, TFR1 protein and transcript markedly decreased in heme-treated cells; DFO significantly reversed this effect.

This study will help decipher heme dysmetabolism's impact on placental pathologies and develop personalized treatments.

04162 ROLE OF HEME AS A MODULATOR OF BLOOD COAGULATION PROTEINS

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Coagulation disorders display a major clinical concern of diseases accompanied by the intravascular release of high heme concentrations. In addition, early investigations on heme administration as a treatment of porphyria patients highlighted the thromboinflammatory side effects of locally high heme levels. As a regulatory molecule, heme is well-known to affect the function and/or stability of proteins through binding to short, surface-exposed amino acid stretches, so-called 'heme-binding motifs'. As such, the stimulation of the complement and coagulation system through direct heme binding to participating proteins (e.g., C3 and fibrinogen) has been described in the past and correlated with the respective clinical symptoms. Herein, we started to analyze the network of clotting factors as potential heme-regulated proteins by screening for heme-binding motifs using the webserver HeMoQuest. Subsequently, these motifs were synthesized as model peptides and analyzed for heme binding by UV/vis spectroscopy. Promising sites were further evaluated by molecular docking and dynamics simulations of the respective heme-protein complexes. Apart from these computational studies, the heme-binding capacity of these proteins was experimentally studied by UV/vis and/or SPR spectroscopy. Structural investigations were conducted by single-particle cryo-electron microscopy. Finally, the effect of heme binding towards the function of the respective protein was analyzed by diverse physiologically relevant as well as biochemical activity assays. In summary, heme binding to select blood coagulation proteins (e.g., FVIII) is demonstrated by applying a combination of biochemical, spectroscopic, bioinformatic, structural, and clinically relevant approaches. The results provided extend our understanding of heme as a regulator in the blood coagulation system on molecular level, which will support the knowledge on the progression of thrombosis under pathophysiological conditions of high intravascular heme levels.

Session 6 – Current therapies for acute hepatic porphyrias (AHP) (September 24th, 2024)

Thematic area: current and emerging therapies for porphyrias

04128 LONG-TERM CLINICAL OUTCOMES OF PATIENTS WITH ACUTE HEPATIC PORPHYRIA WHO WERE NOT ATTACK-FREE AFTER 6 MONTHS OF GIVOSIRAN TREATMENT: A SUBGROUP ANALYSIS OF THE PHASE 3 ENVISION STUDY

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Background Acute hepatic porphyria (AHP) is a group of rare, chronic, multisystem disorders characterized by acute attacks, chronic symptoms, progressive elements, and long-term complications requiring proactive management. Givosiran is an RNAi therapeutic approved for AHP treatment. In ENVISION (NCT03338816), givosiran treatment led to sustained reductions in annualized attack rate (AAR). Among patients who completed the study through month (M) 36, 58% were attack-free after their first 6M of givosiran treatment for the duration of the trial. In this analysis, we examined treatment outcomes in patients who were not attack-free after their first 6M of givosiran treatment.

Methods Eligible patients had AHP, were aged ≥12 years, and had experienced ≥2 attacks requiring hospitalization, urgent care, or intravenous (IV) hemin at home within 6M before study enrollment. A 6M placebo-controlled double-blind (DB) period was followed by a 30M open-label extension (OLE) period in which all patients received givosiran. This post hoc, descriptive analysis included patients who were randomized in the DB period and completed the OLE period. Subgroups were defined based on patient attack frequency after the first 6M of givosiran treatment (0 attacks, attack-free; ≥1 attack, not attack-free).

Results 94 patients were randomized, and 79 completed ENVISION; 46 (58%) were attack-free and 33 (42%) were not attack-free. Among patients who were not attack-free, the mean percentage reduction in composite AAR (attacks requiring hospitalization, urgent care, or IV hemin at home) per 6M interval were 57% after >6–12M of givosiran treatment and 85% after >30–36M, relative to historical composite AAR (mean [SD], 12.8 [9.6]). Of those patients who were not attack-free in the first 6M of treatment, the percentage of patients who were attack-free during 6M treatment intervals increased from 9% after >6–12M to 79% after >30–36M of further treatment. Quality of life improved in both groups: after 6M and 36M of treatment, mean SF-12 version 2 Physical Component Summary scores increased from baseline by 7.3 and 8.3 points (attack-free group) and 4.1 and 9.1 (not attack-free group); EQ-VAS scores increased by 6.9 and 19.9 points (attack-free group) and 2.2 and 17.5 points (not attack-free group). After 6M and 36M of givosiran treatment, median percentage reductions from baseline in aminolevulinic acid levels were 88% and 93% (attack-free group) and 85% and 92% (not attack-free group), and median percentage reductions from baseline in porphobilinogen levels were 88% and 97% (attack-free group) and 86% and 93% (not attack-free group).

Conclusions Both patient groups had reduced attacks and other treatment-related improvements within the first 6M of givosiran treatment. Those who were not attack-free after the first 6M of treatment experienced further attack reductions and quality of life improvements with longer-term givosiran treatment, similar to those observed in the attack-free group.

04148 SINGLE-CENTER REAL-WORLD EXPERIENCE WITH GIVOSIRAN FOR ACUTE INTERMITTENT PORPHYRIA

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Givosiran, an ALAS1 targeted siRNA therapy, decreases the frequency of acute attacks in Acute Hepatic Porphyrias by lowering the neurotoxic heme precursors, aminolevulinic acid (ALA) and porphobilinogen (PBG). Here, we present real-world data on clinical, biochemical, efficacy and safety for 15 patients with Acute Intermittent Porphyria (ages 18–57 years,12F:3M) followed at our center. All but 1 patient had recurrent attacks (≥4/year) and 1 patient was started on givosiran for significant neuropathy likely secondary to AIP. Five patients were on prophylactic hemin before starting givosiran. Our experience shows that givosiran significantly reduces the frequency of acute attacks, with 12/14 being attack free after approximately 1 year of treatment. Of the 2 patients with recurrent attacks on givosiran, one had concurrent precipitating factors, including treatment interruption. Urine ALA normalized after starting givosiran in all patients with available data and remained normal during breakthrough attacks except for 3 patients. One of these patients had elevated urine ALA during an acute attack associated with treatment interruption. Three patients had normal urine PBG, and the remainder had elevations <4ULN. Pretreatment homocysteine levels were available for 6 patients and 3 were abnormal at baseline. All patients had elevated homocysteine level after commencing treatment. Four patients with normal ALT developed transient ALT elevations (<2.5 ULN) within the first year of treatment. Seven patients had alkaline phosphatase elevation (<2ULN) after starting givosiran, with 4 having concurrent normal AST and ALT. Elevated creatinine was noted in 8/15 patients within 6 months of treatment. Creatinine levels did not uptrend over time, 3 patients had transient elevations and 4 had intermittently abnormal creatinine. Creatinine levels remained abnormal in one patient with a baseline elevation.

Dose reduction was attempted in 8 patients due to adverse events, typically abnormal creatinine, and in 1 patient it was due to severe injection site reaction (ISR). Three patients had breakthrough attacks on a lower dose of 1.25 mg/kg/month which was well tolerated by the rest. One patient's attack was an isolated event precipitated by taking a porphyrinogenic drug and she remains stable on a lower dose. The most common side effects were nausea, fatigue, and headache. One patient developed ISR but was able to continue treatment on lower dose and premedications. One patient developed acute pancreatitis after 3 doses of givosiran which recurred on redosing. Dosing was resumed and well tolerated at a reduced dose and frequency.

Our experience suggests that treatment can be personalized, and a decrease in dose or frequency can be attempted in patients with adverse events. Homocysteine levels, liver enzymes and renal function should be closely monitored. Long term data are needed to determine the efficacy, safety, and risk benefit profile of modified dosing regimens.

Session 7 – New insights and potential treatment approaches in erythropoietic porphyrias (September 24th, 2024)

Thematic area: current and emerging therapies for porphyrias

04118 RESULTS OF THE AURORA STUDY: A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF BITOPERTIN IN ERYTHROPOIETIC PROTOPORPHYRIA

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Background Erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP) are caused by pathogenic variants in the ferrochelatase (FECH) or 5-aminolevulinate synthase 2 (ALAS2) genes, respectively, resulting in accumulation of photoreactive protoporphyrin IX (PPIX). In the protoporphyrias, elevated levels of PPIX cause debilitating phototoxic skin reactions following exposure to sunlight and may lead to potentially life-threatening protoporphyric hepatopathy in some patients. Reduction of PPIX is associated with amelioration of disease in the settings of hematopoietic stem cell transplant, pregnancy, and extracorporeal photoinactivation.1–3

Glycine transporter 1 (GlyT1) supplies extracellular glycine for the initial step of heme biosynthesis in erythroid cells.4 Bitopertin is an investigational small molecule inhibitor of GlyT1. It is hypothesized that GlyT1 inhibition leads to a decrease in heme pathway intermediates, including PPIX, and can improve light tolerance.5 In murine models of EPP and XLP, treatment with bitopertin lowered blood PPIX levels by >40% compared to controls.6 Bitopertin treatment in mice with EPP also lowered liver PPIX levels and reduced histopathological evidence of liver cholestasis and fibrosis compared to controls.7

These data, combined with a favorable safety profile observed in prior clinical studies of bitopertin with cumulative enrollment of >4000 participants, provided rationale for AURORA.

Methods AURORA is a Phase 2, randomized, double-blind, placebo-controlled study (NCT05308472) that randomized 75 participants (1:1:1) to receive oral, once-daily administration of 20 mg, 60 mg bitopertin, or placebo for 17 weeks. Participants ≥18 years of age with a confirmed diagnosis of EPP by PPIX analysis and/or genetic testing were enrolled. Exclusion criteria included alanine aminotransferase/aspartate aminotransferase values ≥2x the upper limit of normal, hemoglobin <10

g/dL, or concurrent treatment with afamelanotide or dersimelagon. Randomization was stratified by baseline light tolerance (time to prodrome < or ≥30 minutes), as assessed during a 2week run-in period.

The primary endpoint is percent change from baseline in whole blood metal-free PPIX in participants randomized to bitopertin compared to placebo. The key secondary endpoint is the total hours of sunlight exposure to skin on days with no pain from 10:00 to 18:00 hours. Upon completion of the double-blind treatment period, participants may continue in an open-label extension study.

Results Unblinded topline safety and efficacy data, including changes from baseline in wholeblood metal-free PPIX and measures of light tolerance, will be presented.

Conclusion Bitopertin has been shown to significantly reduce PPIX levels in prior clinical and nonclinical studies of EPP. The AURORA study evaluates whether reductions in PPIX with bitopertin can improve measures of light tolerance in adults with EPP. Topline safety and efficacy data will be presented.

04117 RESULTS FROM THE BEACON TRIAL: A PHASE 2, RANDOMIZED, OPEN-LABEL TRIAL OF BITOPERTIN IN ERYTHROPOIETIC PROTOPORPHYRIA

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10.1136/bmjgast-2024-ICPP.14

Background Erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP) are associated with accumulation of photoreactive protoporphyrin IX (PPIX) in the skin and other organs, causing debilitating phototoxic skin reactions following exposure to sunlight, and potentially life-threatening protoporphyric hepatopathy in some patients. Reduction of PPIX is associated with amelioration of disease in the settings of hematopoietic stem cell transplant, pregnancy, and extracorporeal photoinactivation.[1–3]

Glycine transporter 1 (GlyT1) supplies extracellular glycine for the initial step of heme biosynthesis in erythroid cells.[4] Bitopertin is an investigational, orally administered inhibitor of GlyT1. It is hypothesized that GlyT1 inhibition leads to a decrease in heme pathway intermediates, including PPIX, and can improve light tolerance.[5]

Methods BEACON is a Phase 2, randomized, open-label, parallel-arm trial (ACTRN12622000799752) of 22 participants who will receive oral, once-daily administration of 20 mg or 60 mg of bitopertin for 24 weeks. The trial is being conducted at 2 sites in Australia and includes participants ≥12 years of age with a confirmed diagnosis of EPP or XLP.

Results As of data cutoff (20 October 2023), a total of 22 adults had been enrolled. For the primary endpoint, treatment with bitopertin resulted in significant, sustained, dose-dependent reductions in PPIX levels; mean reduction >40% ($p<0.001$ versus baseline). For the key secondary endpoint, the mean (± SD) cumulative total time in light observed over the 6-month treatment period on days without pain was 222.6 ± 129.3 hours, which represents approximately a 3-fold increase with bitopertin treatment relative to historical control.[6]

Other aggregate measures of light tolerance also improved over time. The proportion of days without symptoms (with sun exposure) increased from 33% during screening to 78% while on treatment, and patient-reported phototoxic reactions decreased by 92% with bitopertin compared to baseline (n=22). This functional benefit was also associated with improvements in quality of life; in the Patient Global Impression of Change, nearly all participants who completed treatment (12/13) reported their EPP was much better or a little better at the end of the study.

Bitopertin was generally well tolerated at both dose levels with no serious adverse events (AEs), stable mean hemoglobin levels, and no anemia AEs reported. The most common AEs (reported in >1 participant) were dizziness, lightheadedness, headache, and nausea.

Conclusion By reducing PPIX levels, bitopertin targets the underlying pathophysiology of EPP, resulting in consistent improvements in multiple measures of light tolerance and quality of life. Bitopertin has been well tolerated to date. Final adult results from the study will be presented at the meeting.

04111 PHLEBOTOMY AND AFAMELANOTIDE AS AN EFFICIENT COMBINED TREATMENT OF HEPATOERYTHROPOIETIC PORPHYRIA

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Background Hepatoerythropoietic porphyria (HEP) is a rare type of inherited porphyria and results from severe uroporphyrinogen decarboxylase (UROD) deficiency. Patients usually suffer in early childhood with extreme skin fagility, cutaneous lesions with fluid-filled blisters that break and heal slowly, hypertrichosis in periorbital areas, and scarring over the light exposed areas. Repeated sun exposure can lead to scleroderma-like changes that can result in photomutilation. There are no effective treatments for individuals with HEP.

Aims Development of the first therapy based on iterative phlebotomies and concomitant administration of afamelanotide 16 mg every two months.

Methods A therapeutic protocol was set up for a 47 years old male HEP, combining administration of Afamelanotide 16 mg with iterative phlebotomy. In a first phase 200 ml of blood were removed every month until iron depletion. Subsequently, treatment was administrated every two months as for maintenance therapy. Concomitant off label use of afamelanotide was performed as photoprotective measure since it stimulates melanogenesis and reduces severity of cutaneous symptoms in erythropoietic protoporphyria.

Results Therapy reduced porphyrins accumulation. Urine porphyrins decreased from 1303 to 240 µmol/mmol creatinine (ULN, upper limit of normal 35 µmol/mmol creatinine), plasma porphyrins decreased from 1376 to 311 nmol/l (ULN 15 nmol/l). Chronic epathopathy was ameliorate as shown

from liver function analyses (transaminases decreased from 3x ULN to normal values). Ferritin was used as index to monitor iron status obtaining a significant reduction after 2 months from 700 ng/ml to 81 ng/ml (v.n.= 13–400 mg/ml). Patient had an improvement of lesions on the scalp and in photoexposed areas. The clinical tolerance was excellent for patient without any adverse effect to report.

Conclusion This is the first report in the literature applying a successfull protocol in a higly uncommom form of porphyria, hence the importance of the case. Higher tolerance to the sun induced by afamelanotide reduced phototoxic chronic damage. If therapy was established precociously, some irreversibile damages, such as phalanges mutilation, could have been reduced and also palpebral ectropion. It suggests that early diagnosis and treatment might prevent the occurrence of devastating and severe consequences of HEP.

Session 9 – Rational approach(es) to diagnosis and care in AHPS (September 25th, 2024)

Thematic area: current and emerging therapies for porphyrias

04172 FUNCTIONAL CHANGES IN THE CENTRAL NERVOUS SYSTEM IN A NON-HUMAN PRIMATE MODEL OF AIP CAN BE FULLY RESCUED BY SYSTEMIC MESSENGER RNA REPLACEMENT THERAPY

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Functional brain changes in acute hepatic porphyrias has been described in various experimental models. However, direct evidence linking neurological alterations to hepatic porphobilinogen deaminase (PBGD) deficiency, the recurrence of acute attacks, or their potential reversion in response to available therapies is lacking. Given the limited availability of patients eligible for clinical studies in rare disorders such as acute intermittent porphyria (AIP), physiopathological information from relevant animal models is of paramount importance for improving clinical trial design and endpoints assessment. In this work, we replicated AIP in adult non-human primates (NHPs) through selective knockdown of the hepatic *PBGD* gene. Our aim was to asses neural GABAergic activity and glucose metabolism in the brain of these animals before and after the induction of AIP, as well as after the administration of current and emerging therapies.

The benzodiazepine receptor antagonist flumazenil binds to the benzodiazepine binding site of γ-aminobutyric acid-type A (GABAA) receptors, which are the most prominent inhibitory neurotransmitter receptor in the central nervous system (CNS). Flumazenil can bind GABA receptors that are not activated by GABA, providing a surrogate index for assessing the activation status of these receptor in the brain. At baseline, PET/CT imaging revealed a prominent distribution of the radiotracer [^{11}C]flumazenil in the brain cortex and hippocampus. A significant reduction of [^{11}C]-flumazenil uptake was observed in the brain of AIP NHPs, starting one month after AIP induction. Reduced uptake remained consistent following recurrent attacks in untreated animals, whereas multi-dose administration of hPBGD mRNA uniformly restored baseline uptake across all regions.

The prefrontal motor cortex and subcortical ganglia at the brain's base, which are associated with movement initiation and planning, showed the highest uptake of the glucose radiotracer [^{18}F]-fluorodeoxyglucose ([^{18}F]FDG). Induction of AIP in NHPs led to a notable reduction in the radiotracer signal, further declining with repeated attacks. Notably, treatment with hPBGD mRNA significantly improved brain [^{18}F]FDG uptake and restored baseline levels.

In conclusion, our novel clinically relevant AIP model confirmed alterations in glucose uptake and GABAergic activity in the brain. Importantly, since PBGD expression in our model is specifically impaired only in the liver, our findings represent the first experimental demonstration of the hepatic origin of the functional alterations observed in the CNS of AIP patients.

04138 POTENTIAL CAUSES OF DYSREGULATED HOMOCYSTEINE METABOLISM IN PATIENTS AFFECTED BY ACUTE INTERMITTENT PORPHYRIA

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Homocysteine (Hcy) is an intermediate of sulfur amino acid metabolism and increased plasma levels are potentially associated with greater risk for thromboembolism, vascular and neurological diseases. Hcy elevation in plasma has been previously reported in Acute Intermittent Porphyria (AIP) patients leaving the reasons unclear. Moreover, several scientific papers have confirmed the observation that treatment with Givosiran, a molecular inhibitor of heme biosynthetic pathway, may further increase Hcy levels in some patients. This upsurge seems to be mediated by a decrease in activity of Cystathionine B-Synthase (CBS), which uses Hcy as a substrate, but the mechanism underlying this reduction remains unknown.

In this study, we evaluated genetic asset, vitamin status and levels of Hcy cycle derivatives in a cohort of 23 untreated AIP patients (10 low and 13 high excreters), in order to determine the potential causes of Hyperhomocysteinemia (HHcy).

Total porphyrins and heme precursors were detected in urine; biochemical analysis for Hcy, folic acid, and vitamin B12 were performed in serum. ELISA or colorimetric assays were used for vitamin B6, S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH) and heme measurements. Genotyping was applied to define the inherited status for c.C677T MTHFR polymorphism.

We found 14 patients (60.9%) with HHcy (>15.40µmol/L) of which 9 mild (<25µmol/L) and 5 moderate (<50µmol/L). HHcy was frequently associated with low blood concentrations of folate and values were inversely correlated as expected (r=-0.65, p=0.0008). Despite the allele distribution of MTHFR polymorphism was comparable to those in the Italian population (53% vs 50%), the Hcy average values were higher than normal even after stratification for polymorphism: 18.7 and 35.2 µmol/L for CC and TT genotype respectively. On the contrary, the average values of vitamin B12 (434.2 ± 198.8ng/L), B6 (64.6 ± 41.6 nmol/L) and folate (7.9 ± 5.3 µg/L) were similar to those of healthy population. Of note, the AIP high excreters showed increased levels of B12 and significantly reduced levels of both folate and B6 compared to low excreters, but no difference in Hcy values. Finally, heme and SAM were significantly reduced ($p < 0.01$ and $p=0.037$ respectively) while SAH was increased (p= 0,014) in AIP patients compared to healthy subjects.

This study confirms that HHcy is very frequent in AIP patients and that higher values are significantly associated with lower values of folic acid and the presence c.C677T MTHFR polymorphism in homozygous as expected. However, the high frequency of HHcy in AIP cohort is not directly due to a greater T allele frequency or a greater vitamins deficiency compared to the general population but rather to a pathophysiological mechanism of AIP itself. Considering that CBS is a heme- containing enzyme regulated by SAM, these results demonstrate that a combined depletion of heme and SAM metabolite is the most likely cause of HHcy in AIP cohort.

Thematic area: diagnosis and care in porphyrias

04152 THE PREVALENCE AND PENETRANCE OF ACUTE INTERMITTENT PORPHYRIA IN THE MASS GENERAL BRIGHAM BIOBANK

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Background Acute Intermittent Porphyria (AIP) is characterized by neurovisceral attacks including abdominal pain and neuropathy, resulting from heterozygous pathogenic variants in hydroxymethylbilane synthase (HMBS). Three studies found the prevalence of pathogenic HMBS variants in genetic datasets to be 1:1299, 1:1675, or 1:1782, but did not include clinical information for the individuals in those large general population genetic datasets. Based on these studies and the prevalence of diagnosed AIP, the penetrance of AIP was described to be low (<1%); however, the prevalence of diagnosed or undiagnosed patients in those population datasets was unknown. A higher prevalence of symptomatic individuals might be expected in a patient population sample. The Mass General Brigham (MGB) Biobank is a database containing clinical data and biologic samples of over 135,000 patients, including annotated exome data for 13,000, collected through the MGB hospital system. The aim of this study was to evaluate the genetic prevalence and disease penetrance of AIP using the MGB Biobank exome dataset in parallel with clinical information obtained from patient medical records.
Methods Patients evaluated at MGB were eligible to enroll in the MGB Biobank research protocol. We identified individuals with disease-associated HMBS pathogenic variants in the dataset, and the medical charts of these individuals were reviewed.
Results Among the 13,000 annotated exomes, 8 patients were identified with pathogenic HMBS variants, corresponding with a genetic prevalence of 1:1625. These 8 patients had 3 well-described pathogenic variants in HMBS (NM_000190.3): p.Arg167Gln, p.Arg173Trp, and p.Arg225X. Two of the 8 patients had been previously diagnosed with AIP. However, detailed review of the 6 remaining undiagnosed patients revealed that 4 had a history of at least one episode of unexplained abdominal pain, 3 had unexplained neuropathy, 3 had hyponatremia, and 3 had hypertension. Further, at least 4 patients were exposed to common AIP triggers such as porphyrinogenic medications, anesthesia, or tobacco.
Conclusion Using the MGB Biobank, we found the prevalence of pathogenic AIP variants to be 1:1625, which is consistent with previous studies in general population databases. AIP disease penetrance in our patient database was at least 25% but may be higher due underdiagnosis and failure to recognize the nonspecific disease symptoms. After recent approval to recontact patients, we will pursue biochemical testing of the 6 patients with pathogenic HMBS variants but no AIP diagnosis. Similar studies in other datasets are essential to better characterize the prevalence, penetrance, and underdiagnosis of the acute porphyrias and achieve earlier diagnosis. At ICPP, we plan to present additional data for the 50,000 exomes now available in the MGB Biobank and results of outreach to the undiagnosed patients for clinical evaluation and biochemical testing for AIP.

04083 EMBRYO SELECTION IN THE ACUTE HEPATIC PORPHYRIAS: CLINICAL, ETHICAL AND ECONOMIC ISSUES

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Assisted reproductive technology (ART) can be used to avoid passing on genetic conditions to subsequent generations but it is generally reserved for conditions with high morbidity or mortality. This is especially true in resource constrained, publicly funded health systems such as New Zealand, Australia and the United Kingdom. Hereditary coproporphyria (HCP) is the rarest of the autosomal dominant acute hepatic porphyrias (AHP) and is usually characterised by low penetrance and limited impact on health and quality of life. We present a case

from an HCP family in Wellington, New Zealand with high penetrance, recurrent attacks and severe complications who has successfully undergone pre-implantation testing for a monogenetic disorder (PGT-M) and embryo selection for her first planned pregnancy to avoid passing the genetic variant to future generations. We argue that although ART should not be used routinely in AHP, it should be considered in cohorts with high prevalence or evidence of significant impact on health or quality of life. We discuss both the clinical and ethical issues associated with embryo selection in AHP. We also provide costings of the recurrent admissions to hospital for presentations associated with AHP in this family as well as the cost of the tax-payer funded ART. We are not aware of other published reports of embryo selection in AHP and hence this case represents an opportunity to discuss a rare management strategy that may benefit severely impacted families in other countries.

Thematic area: current and emerging therapies for porphyrias

04182 PREVENTION OF CYCLICAL ATTACKS WITH GNRH-AGONISTS AND HORMONAL CONTRACEPTIVES AMONG PATIENTS WITH ACUTE PORPHYRIA

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Clinical manifestations of acute porphyria (AP) are precipitated by the menstrual cycle in around half of the female patients. Attacks occur after menarche and are most frequent in the mid 20's. The risk of attacks diminishes after 35-years of age, but the perimenopausal period can provoke attacks. Around 5% of the patients have recurrent attacks, defined as $\geq$ 3 attacks per year.

The purpose of this study was to explore recurrent attacks triggered by the menstrual cycle or perimenopause among 70 symptomatic female patients. We evaluated retrospectively the preventive use of combined hormonal contraceptives (CHC) and gonadotropin-releasing hormone agonists (GnRHa) among 33 patients. Clinical, biochemical, and genetic data was obtained from the medical reports, registry data and patient interviews during 1996 - 2023.

48 patients (69%) had recurrent attacks precipitated by the menstrual cycle. 15 patients (31%) had genetic counselling, but no preventive treatment. 33 patients (69%), who had 1–20 severe attacks prior to intervention, received medical treatment: 19 patients CHC and 14 patients GnRHa. One patient was excluded since she did not reach amenorrhea during GnRHa treatment.

23 patients responded to medical intervention, 5 partially and 4 patients were non-responders. During GnRHa treatment (3–12months) 9 patients (69%) became asymptomatic. Four patients had 8 attacks, most of which occurred during the first 3 months suggesting longer, 6- 12-month, treatment duration for better clinical response. 11 patients continued with CHC (3–42 months) after GnRHa treatment. 12 patients (63%) became asymptomatic during CHC treatment (2–109 months), and 7 patients had 9 attacks, half of which occurred during the first 3 months.

During the 1st year of intervention, excluding first 3 months in all groups, the proportion of attack free patients was 36% in the control group, 62% in the GnRHa and 74% in the CHC group. Follow-up of five years demonstrated a decrease in attack rate in all groups.

Based on these results, hormonal intervention should be considered among female patients with recurring attacks ($\geq$ 2 attacks/6 months) precipitated by the menstrual cycle.

Thematic area: recent advances in the pathophysiology of porphyrias

04183 REDUCED EXPRESSION OF PPOX, THE VARIEGATE PORPHYRIA GENE, CAUSES INTRINSIC PATHOLOGICAL CHANGES TO KERATINOCYTES

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Variegate porphyria, caused by monoallelic mutations in protoporphyrinogen oxidase (*PPOX*), causes acute visceral attacks and skin photosensitivity, presenting in blistering and skin fragility, a more severe phenotype is seen with rare biallelic mutations. This fragility is due to accumulation of intermediate porphyrins from the liver, such as 5'-aminolevulenic acid (ALA), close to the skin surface that are oxidised by sunlight. Oxidised porphyrins cause oxidative stress and degranulation of mast cells resulting in the release of proteases that cause blistering. We hypothesise that PPOX deficiency causes intrinsic pathological changes to keratinocytes that contribute to the skin phenotype.

To test this, we created two *PPOX* shRNA knockdown cell lines, KD1 and KD2 (50 & 25% residual expression respectively). Both KD lines displayed significantly reduced proliferation with KD2 having reduced migratory capacity. KD clones expressed reduced levels of involucrin in monolayer, proportional to the amount of knockdown, suggesting decreased differentiation. To mimic porphyrin accumulation keratinocytes were treated with ALA and deferoxamine (an iron chelator), resulting in an increase in fluorescent porphyrins in KD2. Treatment of keratinocytes to induce porphyrin accumulation caused intracellular oxidative stress, evidenced by reduced expression of 4 of the 5 electron transport chain complexes, in shC and both KDs. The differentiation phenotype was corroborated by 3D organotypic cultures where KD models expressed less keratin 10 and involucrin, proportional to knockdown, while KD2 models also displayed reduced stratification. Treatment of 3D organoids with ALA and DFO further reduced differentiation and stratification in KD models compared to shC.

In conclusion, we show that keratinocytes have an active haem synthetic pathway and contribute to porphyria pathology with >50% PPOX KD causing significant changes in keratinocyte proliferation, differentiation, and epidermal stratification, with >75% KD also affecting migration and reducing epidermal thickness, which could facilitate the oxidation of porphyrins under the skin. The more severe effects seen with >75% KD reflects the phenotype seen in individuals with biallelic

mutations in *PPOX*. These 3D organotypics could therefore serve as models to trial therapeutic interventions to improve patient skin care.

Thematic area: current and emerging therapies for porphyrias

04170 DIETARY INTERVENTIONS TARGETING GLUCOSE METABOLISM AND HYPERINSULINEMIA: A NEW TRANSLATIONAL PERSPECTIVE FOR THE MANAGEMENT OF PATIENTS WITH ACUTE INTERMITTENT PORPHYRIA

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Background Glucose intolerance and hyperinsulinemia are emerging risk factors in patients affected by Acute intermittent porphyria (AIP), a metabolic rare disorder caused by the haploinsufficiency of PBGD activity, the third enzyme of heme biosynthesis. Previously, we found that lipoic acid (α-LA), an insulin-mimetic, improved glycolysis and ATP production in *PBGD*-silenced hepatocytes. Here, we investigated whether nutritional interventions may correct carbohydrate metabolic dysfunctions in a murine model of AIP.

Methods Firstly, we assessed the short (2 weeks) and long-term (3 months) α-LA efficacy on glucidic and energy balance in the liver and insulin-sensitive tissues. Secondly, we explored new dietary options, previously tested in metabolic disorders, on the same targets by evaluating the effects of live organisms (*Bacillus coagulans*, BC-30™), postbiotics (heat-treated *Bifidobacterium animalis* subsp. *lactis* CECT8145, BPL1® HT) and a lipoteichoic acid (LTA: metabolite derived from *B. animalis* strain) orally administered for 3 months. Compositional and functional changes in fecal microbiota before and after supplementation were assessed using shotgun metagenomic sequencing.

Results After 2 weeks, α-LA normalized GTT, insulin levels and reduced the aberrant hepatic insulin signaling activation in fasted AIP mice. Glycogenolysis/gluconeogenesis and Glut2, which mediates glucose-dependent transport into the blood, were upregulated in AIP+α-LA group, sustaining that α-LA ameliorates glucose handling. Glut3/4 transporters were higher in brain, muscle and white adipose tissue (WAT) of AIP+α-LA mice. At 3 months, PET/CT scan revealed enhanced glucose uptake in the liver, brain, muscle and WAT of AIP+α-LA mice. The administration of BC-30, BPL1® HT, and LTA increased glucose uptake in skeletal muscle, resulting in improved glucose tolerance, insulin sensitivity, and muscular energy utilization. Additionally, LTA, BC-30 and α-LA improved lean/fat ratios and increased muscle mass by stimulating fat disposal in both brown (BAT) and WAT tissues. Lipid breakdown can be facilitated by muscle contractions during exercise and heat dissipation by BAT. Analysis of fecal microbiota revealed that metabolic improvements observed with the diets may be related to changes in intestinal flora. AIP mice plus BC-30 showed an enrichment in species involved in glucose control (i.e. *Odoribacter laneus)* and reduced *Lachnospiraceae* abundance, regulating carbohydrate digestion. LTA treatment lowered harmful gram-negative bacteria like *E. coli*, and α-LA and LTA enhanced those with protective activities against hyperglycemia (*Clostridium cocleatum* and *Alistipes communis*), potentially explaining the improvement in glucose tolerance.

Conclusions Oral insulin sensitizers (α-LA) or intervention with LTA, life BC-30 or BPL1® HT restored hyperinsulinemia and improved carbohydrate metabolism in AIP mice.

Thematic area: diagnosis and care in porphyrias

04137 NUTRITIONAL ASSESSMENT AND BODY COMPOSITION IN ACUTE INTERMITTENT PORPHYRIA (AIP) PATIENTS

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AIP is a rare metabolic disorder characterized by neurovisceral symptoms resulting from the accumulation of heme precursors. Acute attacks can be triggered by porfirinogenic drugs and a low-glucose diet as well. Thus, nutrition is crucial in managing AIP, especially with recent findings highlighting chronic symptoms.

This study focused on the interplay between nutritional, metabolic, and biochemical data in 16 females with AIP. We hypothesized that increased glucose consumption might lead to imbalanced nutrition and metabolism, serving as a strategy to prevent AIP crises. Nutritional assessment was conducted by direct counselling with an online food frequency questionnaire Grana Padano Observatory (OGP); anthropometric measures including BMI, bioelectrical impedance analysis (BIA Dex® Mascaretti) and blood samples were also collected. Nutritional analysis revealed that 14 on 16 AIP had a high intake of simple sugars (v.n.<15%) and saturated fatty acids (v.n.<10%). This unbalanced diet led to overweight conditions in 50% of AIP patients (BMI>25), which significantly correlated with an increase in waist circumference ($r=0.86$, $p<0.0001$). For BIA analysis, patients were divided into 2 groups based on age.

Group (A) 11 patients (30–49 ys) and (B) 5 patients (51–70 ys). This analysis confirmed, better than BMI, an excess of fat mass (FM) in 64% of patients in A (7 on 1) and 40% in B (2 on 5). Excessive consumption of simple sugars, SFA results in an increase of 36% (4 on 7) in A and 80% (4 on 1) in B of blood LDL levels above the reference range (<100 mg/dL).

The HDL level is above the normality (x=83±20.3, >45 mg/dL) even though it is consumed by 7 on 16 AIP in low amounts with diet. Moreover, HDL correlates with age (r=0.56, p=0.02). Recent literature demonstrates that low and high HDL values have the same predisposition to mortality changing the paradigm that high HDL levels provide greater protection against cardiovascular diseases. This could suggest that high HDL may not play a completely protective role in AIP. In addition, by detecting BIA water distribution we found the ratio of extracellular water (ECW) to total body water (TBW) was above the normal range in 9 patients in A and 4 in B (v.n.0.36–0.4), indicating over-hydration in ECW. This data suggests inflammatory and stress status, as supported by the ECW/TBW ratio correlation with cortisol (r=0.67, p=0.008). In contrast, we did not find a correlation with ALA, PBG, or total porphyrins vs data on nutrition and BIA.

In conclusion, we confirm our hypothesis that AIP patients excessively consume simple sugars and SFA. This behaviour is reflected in their body composition and biochemical markers. This finding highlights the importance of providing nutritional support to prevent metabolic syndrome. Particular attention should be paid to a larger sample size cohort to assess the significance of high HDL and the TBW/ECW ratio as markers of disease progression based on age or stress.

Session 10 – Rational approach(es) to diagnosis and care in cutaneous porphyrias (September 25th, 2024)

Thematic area: diagnosis and care in porphyrias

04092 LIVER FUNCTION, IRON STATUS, AND HEMOPOIESIS IN ERYTHROPOIETIC PROTOPORPHYRIA (EPP): INSIGHTS INTO A COMPLEX INTERPLAY

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Background Despite its dramatic cutaneous manifestations, EPP is a systemic disease with multi-organ involvement. In fact, protoporphyrin IX (PPIX) accumulates in multiple sites beside the skin, chiefly the bone marrow and the liver. Therefore, EPP patients display mild hematological alterations and are at risk of developing cholestatic liver disease, which may evolve to liver cirrhosis. Several patients show thrombocytopenia with increased spleen dimensions, which in the presence of hepatic alterations may raise the suspicion of portal hypertension.
Aim To characterize the phenotype of clinically stable EPP from a multi-system perspective.
Methods To test phenotypic correlations, 15 patients were enrolled: liver status, hematology and spleen parameters, and PPIX levels were collected at the same timepoint.
Results Increased spleen dimensions (SplD: bipolar diameter, BP; area-at-hilus, Ah) are common in EPP (7/15). Free PPIX levels predicted liver stiffness (LS, β=0.71, p=0.004), erythropoietin levels (β=0.63, p=0.020), SplD (BP: β=0.76, p=0.001; Ah: β=0.81, p<0.001), and platelet count (β=−0.60, p=0.017); SplD predicted platelet count (BP: β=−0.64, p=0.014; Ah: β=−0.82, p<0.001); when both SplD and PPIX levels were tested, platelet count was significantly correlated to SplD only (Ah: β=−0.95, p=0.008). Spleen stiffness was within normal ranges in all patients and not significantly associated with SplD. Instead, it showed significant correlations with hemoglobin (Hb, β=0.62, p=0.03), hypochromic red blood cell percentage (HypoRBC, β=−0.77, p=0.003), and ferritin (β=0.60, p=0.038). Hb was inversely related to HypoRBC, (β=−0.64, p=0.010). HypoRBC was inversely related to reticulocyte Hb content (β=−0.65, CHr, p=0.008) and mean corpuscular Hb (MCH, β=−0.51, p=0.047). Serum ferritin predicted the iron status of red blood cell lineage (HypoRBC: β=−0.64, p=0.010, CHr: β=0.72, p=0.002), but did not significantly reflect on Hb. Alterations in liver biochemistry were significantly associated with increased LS.
Discussion Taken together, these findings support the following phenotype model: in EPP, hypersplenism is likely an expression of compensatory extramedullary erythropoiesis, independent of protoporphyric hepatopathy; thrombocytopenia may be directly linked to increased spleen dimensions, rather than direct PPIX-driven impairment on platelet production; the erythropoietic drive is directly dependent on the disease activity; HypoRBC, MHC, and CHR could support a diagnosis of iron-restricted erythropoiesis better than serum ferritin or transferrin saturation.
Conclusion Although further studies are needed to confirm these findings, this is the first description of a complex multisystem interplay in protoporphyria. These findings could help better define the phenotype of EPP patients, particularly in the context of protoporphyric hepatopathy with spleen or hematological alterations.

Thematic area: recent advances in the pathophysiology of porphyrias

04112 QUANTITATIVE ANALYSIS OF POLY-UNSATURED FATTY ACIDS PROFILES IN ERYTHROPOIETIC PROTOPORPHYRIA

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Background Erythropoietic Protoporphyria (EPP) is an inherited metabolic disorder due to ferrochelatase activity deficiency and it is characterized by the accumulation of protoporphyrin

IX (PPIX) in erythrocytes, plasma and tissues. PPIX is a photosensitizer agent that can cause cytotoxic oxidative damage directly or through the generation of Reactive Oxygen Species (ROS). Unsatured membrane lipids, including phospholipids and cholesterol are recognized targets of oxidative modifications. Oxidized lipids originating from poly-unsaturated fatty acids (PUFAs) have gained increasing relevance as modulators of inflammation and have been associated with a large number of biological processes including tissue damage.

Aims In order to investigate on PUFAs involvement in patients with EPP, we applied a lipidomics strategy to characterize blood samples taken from these subjects particularly exposed to oxidative damage.

Methods Fatty acid methyl esters profiles were obtained from whole blood samples from 10 EPP patients and 10 controls by a sequential procedure which involved the simultaneous saponification and methylation of bound fatty acids, butylated hydroxytoluene (BHT) derivatization and gas chromatography-mass spectrometry (GC-MS) analysis. Integrated areas of single peaks were extracted from Total Ion Chromatogram (TIC) and used for the quantitative analysis. Fatty acids identification was obtained by matching with spectral library data and verified by comparison with the authentic standards.

Results Whole blood samples were characterized on the basis of their content of PUFAs including arachidonic acid (AA), linoleic acid (LA), dihomo-gamma-linoleic acid (DGLA), alpha-linoleic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Blood samples from EPP patients showed increased ratio of omega-6/omega-3 PUFA by comparison with controls thus indicating higher consumption of omega-3 PUFA to support the synthesis of pro-inflammatory lipid mediators.

Conclusion This work represents a first step towards a deeper characterization of lipid asset in EPP patients since this topic is fundamental for a full comprehension of inflammatory processes underlying the clinical manifestations of EPP.

04094 QUALITY OF CARE AND RISK OF RELAPSE IN PORPHYRIA CUTANEA TARDA: A STUDY FROM THE NORWEGIAN PORPHYRIA REGISTRY

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Background Most patients with porphyria cutanea tarda (PCT) may be successfully treated to remission, but are at risk of relapse. In Norway, patients are therefore recommended yearly follow-up including measurement of urinary porphyrins in order to identify a biochemical relapse prior to symptoms. However, there is little data on the risk of relapse and the usefulness of yearly controls. The aims of this study were therefore to utilize data from the Norwegian Porphyria Registry (NPR) to describe the clinical presentation, treatment and follow-up of PCT in Norway, and to investigate the frequency of biochemical and clinical relapse.

Methods All patients with PCT are invited to participate in the NPR. The registry contains both patient- and physician reported data. For this study, data on diagnosis, treatment and follow-up for all patients diagnosed with PCT in the period from July 2009–2023 were included (n = 359). To assess the relapse rate, data from patients with follow-up urinary samples drawn at least three years after the time of diagnosis were retrieved (n = 239). Patients were classified as having a biochemical relapse if the sum of uroporphyrin + heptaporphyrin $\geq$ 25 nmol/mmol creatinine.

Results The mean age at diagnosis was 60 years and 54% were women. Out of 352 patients where UROD sequencing had been performed, a likely disease-related variant was identified in 48%. At the time of diagnosis, 27% were smokers and 14% drank > 10 units alcohol per week. Based on patient-reported data, the following symptoms were most prevalent: blisters 92%; fragile skin 82%; red/brown urine 62%; excessive hair growth 34%; and increased skin pigmentation 28%. At the time of diagnosis, women had higher urinary porphyrin concentrations than men, with median uroporphyrin + heptaporphyrin of 621 nmol/mmol creatinine in women (n = 193) and 399 in men (n = 166), p = <.001). Phlebotomy was the most commonly treatment. In total, 239 patients had control samples analyzed more than 3 years after the PCT diagnosis was made, and the average time of study observation was 7 years. The number and frequency of control samples varied. When assessing the most recently analyzed sample, 25% (n = 60) had increased urinary porphyrin concentration, consistent with biochemical relapse, though most (n = 39) had moderately increased porphyrins (uroporphyrin+ heptaporphyrin <100 nmol/mmol creatinine).

Conclusion In this national cohort study, we have included more than 350 patients with PCT and followed them prospectively in the NPR. Increased urinary porphyrin concentrations were demonstrated in 25% of this cohort during follow-up, in samples taken more than 3 years after the diagnosis was made, when assessing their most recently submitted sample. Thus, a high proportion of the PCT patients in our study presented with biochemical relapse, indicating that routine follow-up may be beneficial to identify patients in whom closer follow-up or treatment should be initiated.

04116 PORPHYRIA PATIENTS AND THE ROLE OF UV AND VISIBLE SUNSCREENS IN THEIR PHOTO-PROTECTION

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Porphyria patients face a difficult dillema every day: how best to protect themselves from harmful light (photo-protection). Medicines, sun-avoidance, and protective clothing all play a part in a patient's photo-protection strategy, but so too do sunscreens. Therein lies another struggle, which is the choice of sunscreen. Available in hundreds of brands, at a variety of prices, and with myriad claims on photo-protection efficacy across the Ultraviolet (UVB and UVA) and visible bands of the spectrum, the decision-making can prove difficult even for non-photosensitive individuals. Moreover, porphyria patients are sensitive across the PPIX spectrum, which has multiple peaks across the breadth of the UV and visible spectrum. Therefore, whilst a UV-sunscreen will protect from some of these bands, it will be ineffective against others. Similarly, whilst visible sunscreens provide broad protection in both the

UV and visible bands, they come with their own range of drawbacks. Compared to their UV counterparts, visible sunscreens are not so widely known, are often not available on the supermarket shelves, and, importantly, are pigmented. This means that a patient must match the pigment of their skin to that of the sunscreen, and given the limited choices available, this can prove difficult from person to person, and even across areas of the body. Furthermore, sunscreen is no guarantee of protection, but rather increases the time allowed until a photosensitive reaction occurs. This will also vary depending on the manner in which the individual has applied the sunscreen; how light or how heavy, in patches, over make up, in wet or dry conditions.

Our research brings these issues into focus in a number of areas. Firstly, we have been routinely testing sunscreens of all types using our spectrophotometer in order to analyse their protective qualities, some of which has been previously published (Eadie et al., 2023, doi.org/10.1093/bjd/ljac112). We have found that protection varies from product to product, which is a particular issue for porphyria patients who may have to test multiple products before settling on the best protection for them. Secondly, we have been polling our photosensitive patients to understand more about the role sunscreens play in their photo-protection strategies. Through this type of patient-engagement, we have learned about the value patients place on factors such as cost, availability and application against other photo-protection methods such as sun-avoidance and protective clothing. We are extending this to porphyria patients in conjunction with the British Porphyria Association (BPA) and will present the results of this survey. Thirdly, we have begun building a public-access database of sunscreens with the intention of allowing patients to discover the protective qualities of these products for themselves, whilst comparing them side-by-side. We plan to engage with the BPA to facilitate patient-friendly guidance on photo-protection.

04129 QUALITY OF LIFE IN PATIENTS WITH PORPHYRIAS – FIRST DATA FROM THE GERMAN PORPHYRIA REGISTRY (POREGER)

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Background Porphyrias, as most rare diseases, are characterized by complexity and scarcity of knowledge, particularly symptom burden and quality of life. The German Porphyria Registry (PoReGer) was set up to close this gap nationally. Here we present the results of our first evaluation on patient reported outcome measures on quality of life (QoL).

Methods PoReGer was founded in 2023 by four German centers with longstanding porphyria expertise. In a specified data matrix for three subgroups [acute (AP), chronic blistering cutaneous (CBC), acute non-blistering cutaneous (ANC)] data on demographics, symptoms, clinical course and history, follow-up assessments, therapies, and life circumstances are collected longitudinally, at least once a year. Ethics approval and patient´s informed consent were obtained. Enrolment into the registry started in August 2023. To evaluate QoL the EQ-5D-5L questionnaire was used. The results were compared to the population based EQ-5D-5L visual analog scale (VAS) norm for Germany across all age groups, which is 77%.

Results Until May 2024, 23 patients were included, 14 with APs (13 acute intermittent porphyrias, 1 variegate porphyria), 9 with CBCs (all Porphyria cutanea tarda) and 1 with an ANC. In APs median age at inclusion in registry was 40 years; while median age at diagnosis was 27 years. 13 (93%) were female and 6 (43%) reported comorbidities. Median self-rated health status using EQ-5D-5L VAS was 73 (IQR 58;90) in APs. In the subitem pain or discomfort, 71% of patients with APs reported experiencing any pain/discomfort and 28% reported moderate or severe pain/discomfort. In CBCs median age at inclusion in registry was 64 years; while median age at diagnosis was 59 years. 7 (78%) were female and 7 (78%) reported comorbidities. Median self-rated health status using EQ-5D-5L VAS was 60 (IQR 31;75) in CBCs. In the subitem pain or discomfort, 67% of patients with CBCs reported experiencing any pain/discomfort and 33% reported moderate pain/discomfort. In both APs and CBCs, the values for EQ-5D-5L VAS were lower in patients with pre-existing comorbidities and older age. [*More patients from all groups and also an analysis of the 'AP treated with Givosiran' subgroup are expected until September 2024*]

Conclusions This analysis showed QoL in patients with different forms of porphyrias being lower than in the general German population. Not only the porphyria diagnosis, but also other comorbidities and age have an impact on the results of the score. Two thirds of patients reported experiencing any pain or discomfort in everyday life, which highlights a substantial chronic disease burden. With more patients being included in the registry, further longitudinal data on QoL and influencing factors will be gained

Session 10 – Expert panel: diagnostic and clinical conundrums. critical issues to resolve and future directions (September 25th, 2024)

Thematic area: diagnosis and care in porphyrias

04147 C-TYPE LECTIN 10A AS A POTENTIAL BIOMARKER IN ACUTE INTERMITTENT PORPHYRIA

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Background Acute intermittent porphyria (AIP) is a rare inherited metabolic disorder characterized by neurological

manifestations, including abdominal pain. Identifying new biomarkers is crucial for improving the diagnosis and monitoring of AIP. We sequenced blood mRNA from 12 individuals, comprising six symptomatic AIP patients and six matched controls, to identify differentially expressed genes between the two groups.

Methods StarSeq (Mainz, Germany) performed total RNA sequencing using the Illumina NextSeq 500™ platform on samples from 12 individuals, comprising six matched controls and six symptomatic AIP patients. Participants were chosen from a case-control study that included 50 AIP cases and 50 controls matched for gender, age, and place of residence. The six AIP cases, three women and three men, aged 20–75 years—were selected based on currently elevated urine porphobilinogen (PBG)/creatinine levels and having had AIP attacks. Differential mRNA expression analysis was conducted using the R package edgeR (version 3.42.4). Plasma cytokines and several diabetogenic hormones were measured using multiplex technology. Urine PBG and plasma kidney and liver function tests were conducted using routine methods. Results were compared with the Wilcoxon matched-pairs signed rank test.

Results EdgeR analysis showed that C-type lectin domain family member 10A (CLEC10A) mRNA was differentially expressed in the 6 AIP cases compared to matched controls (log fold-change = 1.05, p = 2.09E-06, adj. p = 0.0519). No other significant mRNA expressions were found. As anticipated, the 6 AIP cases had significantly elevated porphyrin PBG/creatinine levels in urine compared to the 6 matched controls. Additionally, they had significantly elevated levels of 23 different cytokines and growth factors in plasma compared to their matched controls ($p < 0.05$). The selected AIP cases and their matched controls did not have diabetes. No significant differences were observed in S-glucose, B-HbA1c, P-C-peptide, P-insulin, S-ALT, S-Creatinine, or BMI between cases and controls (all $p > 0.05$). These results highlight CLEC10A's potential as a biomarker for diagnosing and monitoring AIP-related inflammation.

Conclusion CLEC10A mRNA was significantly upregulated (p-value = 2.09E-06) in symptomatic AIP compared to matched controls, although the adjusted p-value (adj.p.val = 0.0519) was on the boundary of statistical significance. Hence, further qPCR and ELISA analyses are underway to verify CLEC10A as a potential AIP biomarker.

CLEC10A is linked to glucose metabolism and inflammation; supporting the hypothesis that differences in these pathways may be associated with AIP disease activity. Our RNA dataset shows no significantly increased cytokine mRNA in blood samples, suggesting that the elevated plasma cytokines in AIP come from organ damage, e.g. in liver or kidneys, and not from blood leukocytes.

04186 51-YEAR-FOLLOW-UP OF A PATIENT WITH DOSS-PORPHYRIA IN TIMES OF GIVOSIRAN

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Introduction Aminolevulinic acid dehydratase porphyria (ADP/Doss-Porphyria) is a very rare autosomal recessive disease leading to severe deficiency of the second enzyme in the heme synthesis (ALAD). As in other acute porphyrias, lead intoxication and tyrosinemia type 1, neurovisceral symptoms are probably driven by excessively upregulated ALAS1. Thus, down regulating ALAS1 with heme is considered to be a therapeutic option of choice. Notably, in one case with ADP, Givosiran, was observed to be not effective. We report here long-term follow up of one case with ADP and recurrent attacks, that significantly affected quality of life. Givosiran was started in order to prevent attacks.

Case We followed-up the one of the first patients diagnosed with ADP in the 1973 by Manfred Doss. Known as patient H in previous publications, ADP manifested at the age of 15 years with mainly abdominal and neurological symptoms, latter leading to paralysed extremities. Significant urinary ALA elevation, an extremely low ALAD activity in red blood cells and genetic analysis (compound heterozygocity for V153M and delTC mutations) led to the diagnosis of ADP. Interestingly, also in asymptomatic periods between attacks, urinary ALA-concentrations were found to be permanently elevated (aprox. > 10 times of ULN).

Over five decades, most acute attacks were treated with heme and glucose. In 2022, the patient suffered in 4 attacks within 6 months. Together with the desperate patient, we decided to initiate givosiran (50% of dose). Givosiran was applied four times, leading to a reduction of elevated ALA 60% (mean) within 6 days and 54% at day 21 after application. However, after 4 weeks urinary ALA concentration returned to baseline. Treatment with heme in twof formerly observed acute attacks displayed a reduction of ALA of 80%, 60% respectively. In treatment with heme as well as with givosiran ALA reduction never turned to normal and almost returned to baseline within days. Furthermore, Givosiran did not protect the patient against a severe attack, triggered by polymyalgia rheumatica following COVID-19 vaccination. This attack worsened the paresis and a prolonged rehabilitation was needed. After Givosiran has been withdrawn, another attack one year later, caused by a cholecystitis, was treated with heme.

Discussion Due its phenotype ADP is classified as an acute hepatic porphyria. However, the erythropoietic component may obviously contribute to highly elevated urinary ALA-levels that were monitored over five decades, Moreover, patients with ADP seem to be exposed and somewhat tolerate - lifelong - extremely high ALA concentrations. Givosiran showed a similar but lesser effect on ALA reduction, when compared with heme treatment. In addition, the clinical effect of heme in acute attack could point toward a role of heme deficiency, per se, in the pathogenesis of acute porphyria.

Manfred Doss characterized ADP as an erythro-hepatic porphyria (US, MDF personal communication).

04244 MENTAL HEALTH IN THE PORPHYRIAS

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This study investigates the mental health challenges across the Porphyrias through focus group discussions. The primary aim was to identify emotional and psychological issues, coping strategies, and support needs. Both groups reported significant mental health struggles. Recommendations include enhanced mental health support, mentorship programs, and community-building initiatives to improve the quality of life for those affected by porphyria.

Methods Focus groups were conducted for individuals with Cutaneous Porphyria on May 13, 2024, and Acute Hepatic Porphyria on June 13, 2024. Discussions covered mental health struggles, coping strategies, and the impact of the disease on daily life. The sessions were transcribed and analyzed to identify recurring themes and key takeaways.

Results Key Common Challenges:

Mental Health Struggles: Anxiety, Isolation and Abandonment, Loss of Identity, Frustration and Grief, Guilt and Shame

Impact of the Condition: Emotional Toll of Clinical Trials, Unpredictability, Medical Trauma, Invisible Disease, Self-Advocacy

Varying Themes Reported among Porphyrias:

Cutaneous Porphyria: Depression and Therapy, Building Emotional Walls Adjusting After Setbacks: Balancing Needs During Reactions, Support for Families.

Acute Hepatic Porphyria: Pendulum of Extremes, Grieving Past and Future, Identity and Productivity, Slowing Down, Feeling Out of Control, Lack of Medical Guidance.

Potential Resources

Several resources were discussed as potential solutions:

1. Mental Health Professionals
2. Support Groups
3. Educational Materials
4. Financial Assistance Programs
5. Community Building

Next Steps

To address the identified needs and challenges, the following steps are recommended:

Develop and Implement Resources
Enhance Support Systems
Advocacy and Education
Financial Support
Community Engagement

Conclusion The focus group discussions with individuals across the Porphyrias reveal overlap in their mental health struggles, coping strategies, and advocacy needs. However, the differences in specific challenges highlight the necessity for tailored resources and separate discussions and community-building initiatives for each group. Both communities emphasized the importance of self-compassion, robust support systems, and practical resources to manage their conditions effectively.

Poster 1

Thematic area: current and emerging therapies for porphyrias

04191 INHIBITION OF GLYCINE TRANSPORTER 1 REDUCES EPP PHOTOTOXICITY IN A MOUSE MODEL OF ERYTHROPOIETIC PROTOPORPHYRIA (EPP)

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Erythropoietic protoporphyria (EPP) is a genetic disorder typically caused by reduced activity of ferrochelatase (FECH), the enzyme that catalyzes the final step in heme biosynthesis. EPP phototoxicity occurs when the photosensitive metal-free protoporphyrin IX (PPIX) in erythrocytes and skin is exposed to irradiation from sunlight, absorbs photons, and produces reactive oxygen species (ROS) that damage the skin and subdermal layers. EPP patients suffer from acute and severe phototoxicity after sun exposure, significantly impacting their quality of life.

The $Fech^{m1Pas}/Fech^{m1Pas}$ homozygous mice (EPP mice) retain approximately 5% residual ferrochelatase activity due to a severe homozygous loss-of-function mutation. EPP mice develop protoporphyria characterized by elevated PPIX levels in red blood cells (RBCs) and liver, liver fibrosis, and cutaneous phototoxicity, manifested as skin lesions when these mice are exposed to light with excitation wavelength of PPIX (395 to 410 nM) (Wang, 2019).

Glycine transporter 1 (GlyT1) mediates the import of glycine, a precursor for heme synthesis, to erythroid cells. The GlyT1 inhibitor bitopertin has been shown to reduce whole blood PPIX levels in EPP patients in Phase 2 clinical studies (Dickey, 2024; Ross, 2024) and in animal models (Wu, 2022).

This study evaluated whether GlyT1 inhibition can ameliorate phototoxicity via downregulating PPIX levels in the $Fech^{m1Pas}/Fech^{m1Pas}$ EPP mice. The EPP mice were administered vehicle or a selective small molecule inhibitor of GlyT1, DISC-C, at 15 mg/kg, p.o., twice per day, for 18 days. GlyT1 inhibition reduced PPIX levels in RBCs by 43% and 37% on Day 14 and Day 18, respectively. On Day 14 of treatment, hair was removed from the backs of the EPP mice, and all mice were exposed to light with wavelength of 395 nM, 588 $\pm$10% lumens (lm)/m^2 for 30 minutes. Mice administered vehicle developed progressively worsening skin lesions over the observation period from Day 14 to Day 18, with 51.2% exposed skin area developing skin lesions at 4 days post light exposure (Day 18). In contrast, mice administered DISC-C developed skin lesions in 9.2% of exposed skin area, suggesting GlyT1 inhibition reduced phototoxicity in $Fech^{m1Pas}/Fech^{m1Pas}$ homozygous mice. Additionally, lower percentage of the area with skin lesions correlated with lower PPIX levels in RBCs.

In conclusion, this study demonstrated that by inhibiting glycine uptake into erythroid precursors and reducing PPIX levels in RBCs, GlyT1 inhibitor treatment could reduce EPP

phototoxicity in the EPP mouse model. These data support the rationale for treating EPP patients with GlyT1 inhibitors.

REFERENCES
1. Dickey A, *et al.* EHA Library. 06/13/2024; 419662; P1575.
2. Ross G, *et al.* EHA Library. 06/13/2024; 419656; P1569.
3. Wang P, *et al. Sci Adv*. 2019;5(9):eaaw6127.
4. Wu M, *et al. Blood*. 2022;140(Suppl1):8192–8193.

Poster 2

04121 AFAMELANOTIDE FOR THE TREATMENT OF CUTANEOUS PHOTOTOXICITY OF ERYTHROPOIETIC PROTOPORPHYRIA: THE SCOTTISH EXPERIENCE

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Afamelanotide has been licensed for the phototoxicity of erythropoietic protoporphyria (EPP) in Europe since 2014. However, it has not yet been approved for use in the National Health Services of the United Kingdom (UK) countries. In Scotland, a framework has recently been developed by the Scottish Medicines Consortium (SMC) to assess 'ultra-orphan' medicines for very rare conditions. Through this route, the SMC has allowed some use of Afamelanotide in Scotland by making it available for a period of up to three years while clinical effectiveness data are gathered.

To be considered as an ultra-orphan medicine four criteria must be met:

- the condition has a prevalence of 1 in 50,000 or less in Scotland
- the medicine has a Great Britain (GB) orphan marketing authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA)
- the condition is chronic and severely disabling
- the condition requires highly specialised management
- Additionally, the criteria for use of Afamelanotide in Scotland in this pathway are:
- recommendation by Scottish Cutaneous Porphyria Service (SCPS) and two consultant dermatologists
- visual analogue score for quality of life (QoL) effects $\geq$7/10 (on a 0 to 10 scale, with 10 being worst effects)
- time to prodrome $\leq$ 30 minutes
- inadequate response to narrowband ultraviolet B phototherapy.
- Response criteria that must be met if it is to be continued for a patient are
- doubling of time to prodrome and
- at least a 2 point improvement of QoL VAS

The first patient was treated in Scotland in 2022. By the end of 2023, 8 patients (7 treated in Dundee; 1 in Glasgow) had been treated in Scotland with 4 more being treated in 2024. So far, all individuals have continued treatment as responses have been good, with patients noting major improvements in quality of life for themselves and their families. This has been exemplified by one of our patients within a podcast as part of a patient engagement project to raise awareness and improve the lives of our patients: https://www.youtube.com/watch?v=Kkg0_T2sWs8

Three patients have now had treatment for 3 consecutive years. We have observed a phenomenon of longer lasting improvement after the initial year of treatment with all but one patient and one patient has requested just two implants last year (2023) as she is doing so well.

A number of challenges have been encountered, including:

- difficulty sourcing equipment to administer Afamelanotide implants
- obtaining agreements for reimbursement from the patient's resident Health Board
- time-consuming nature of implanting and documenting post-marketing study information which has been largely unfunded

Overall, our experience so far has been positive and the use of Afamelanotide has currently been extended until September 2025 to enable further data to be collected. We remain hopeful that a favourable decision will be made by the SMC after this time to continue to make Afamelanotide available in Scotland.

Poster 3

04173 METHIONINE CYCLE, POLYAMINE SYNTHESIS, AND TRANSSULFURATION PATHWAY IN THE LIVER OF A NOVEL AIP MODEL IN NON-HUMAN PRIMATES AND THE EFFECT OF SYSTEMIC MRNA THERAPY

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The detection of elevated blood levels of homocysteine in patients with acute intermittent porphyria (AIP), particularly in symptomatic individuals with high excretion of porphyrin precursors, suggest an impairment of one carbon metabolism (OCM). To investigate the impact of AIP and therapies on hepatic OCM, we conducted transcriptomic and metabolomic analyses in an AIP model developed by *PBGD* expression knockdown upon intrahepatic delivery (rAAV vector) of specific shRNA in non-human primates (NHP).

One month after AIP induction, hepatic PBGD inhibition led to 2-fold increase of porphyrin precursors despite normal *ALAS1* gene expression. From month 1 to 7, NHPs (n = 8) were challenged with porphyrinogenic drugs to intensify precursor accumulation (up to 4-fold), replicating recurrent acute attacks. Multi-dose (MD) administration of hemin (n=1)(15 doses of 2 mg/kg, iv, with 3 doses every two weeks), givosiran (n=1)(5 doses of 2.5 mg/kg, sc, with one dose every 3 weeks), and hPBGD mRNA formulated in lipid nanoparticles (n=3)(7 doses of 0.5 mg/kg, iv, with one dose every 2 weeks)

was implemented from month 3 to the end of the study (7 months post-rAAV injection). At sacrifice, hepatic levels of S-adenosyl-L-methionine (SAMe) decreased sharply, while those of polyamines, particularly putrescine, were increased. Given the critical role of SAMe in polyamine synthesis pathway, its reduced levels could be associated with polyamine accumulation. Accordingly, the hepatic levels of methylthioadenosine (MTA), a molecule generated from SAMe during polyamine synthesis, were also drastically reduced. Regarding the transsulfuration pathway, the hepatic enzymatic activity of cystathionine beta-synthase (CBS) was not altered in AIP NHPs. Consequently, metabolomic analyses showed no changes in cystathionine levels, a product of CBS, but low levels of reduced glutathione (GSH), the downstream product of this pathway. Transcriptomic studies showed no changes in the expression of *MAT1A*, coding for methionine adenosyltransferase (MAT I/III), the enzyme responsible for SAMe synthesis in the liver. However, MAT I/III is readily inactivated under oxidative stress conditions, which likely occur in the liver of AIP NHPs as indicated by the low GSH levels and the increased expression of *SOD2* (superoxide dismutase 2). Interestingly, a significant induction of *ODC1* (ornithine decarboxylase 1), together with decreased SAMe availability, may explain the accumulation of putrescine in AIP NHPs. Remarkably, hepatic levels of SAMe and GSH were restored only in hPBGD mRNA-treated animals.

In conclusion, our data demonstrate a significant impairment of OCM in the liver of AIP NHPs. Given the key role of SAMe in numerous hepatic and systemic metabolic pathways, its reduced availability may contribute to the progression of the disease and the alteration of central liver functions. OCM pathway tended to be normalized following MD administration of hPBGD mRNA.

Poster 4

04136 FAIRNESS OF FUNDING DECISIONS OF INNOVATIVE THERAPIES FOR THE PORPHYRIAS IN ENGLAND AND WALES: COMPARISON OF THE PARAMETERS FOR THE CALCULATION OF QUALITY-ADJUSTED LIFE YEARS ACCEPTED BY THE NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

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Background A quality-adjusted life year (QALY) is a measure that combines the size of the clinical benefit of a treatment, measured as health-related quality of life, with the time over which the patient benefits from it, i.e., the time horizon. The National Institute for Health and Care Excellence (NICE) in England use QALYs to assess the cost-effectiveness of treatments and to formulate recommendations for their funding in the National Health Service (NHS) of England and Wales. Treatments evaluated under the Highly Specialised Technologies (HST) programme for very rare diseases at NICE benefit from a QALY modifier which increases the odds of patient access in case $\geq$10 QALYs are gained. Our investigation takes a closer look at the consistency of how QALYs of treatments assessed under the HST programme are determined.

Method The time horizon is one of the factors that determines how many total QALYs are gained. For our analysis, we therefore extracted the length of the time horizons used for the calculation of the QALY gains from publicly available documents of evaluations conducted under the HST programme. These evaluations include two innovative treatments for the porphyrias: afamelanotide for treating erythropoietic protoporphyria (HST27) and givosiran for treating acute hepatic porphyria (HST16).

Results In the initial assessment of afamelanotide in 2018, a time horizon of 35 years was used to calculate the QALY gain. Afamelanotide is approved for use from age 18 and is a lifelong treatment. For givosiran, during the evaluation at NICE clinical experts estimated a treatment duration of 13 years for most patients, i.e., a starting age of treatment of 37 years and a stopping age of 50 years. However, for the calculation of the QALY gain, a 60-year time horizon was accepted by the NICE committee. When analyzing all completed evaluations conducted under the HST programme (n=29), we found a time horizon of median 97.5 years (range: 35 to 125 years).

Discussion Our analysis shows that most time horizons accepted for calculating the QALY gains of treatments evaluated under the HST programme are longer than either the expected treatment duration or the estimated general life expectancy of 81 years. In contrast, for afamelanotide, the only treatment with a negative funding decision, a time horizon shorter than the expected treatment duration was applied. In 2023, after presenting preliminary results of our analysis, the NICE committee adjusted the time horizon to 60 years. While more realistic, a 60-year time horizon also does not cover the entire treatment duration with afamelanotide.

Conclusion The fairness and consistency of the evaluation process of treatments for very rare diseases at NICE is not ensured and should be reviewed. However, access to treatments for patients with very rare diseases with an already positive recommendation by NICE must not be compromised.

Poster 5

04158 ASSESSING DISEASE IMPACT AND QUALITY OF LIFE: INSIGHTS FROM A PATIENT SUPPORT PROGRAM FOR ACUTE HEPATIC PORPHYRIA

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Acute hepatic porphyria (AHP) is a group of rare, chronic, progressive, multisystem disorders with acute attacks and long-term complications. Patients with AHP can experience potentially life-threatening acute attacks and chronic manifestations (e.g., pain, fatigue, nausea between attacks), impacting daily functioning and quality of life. Treatment options for patients with AHP were limited before the approval of Givosiran.

Givosiran is a newly siRNA-based treatment of AHP targeting the first and rate-limiting δ-aminolevulinic acid synthase 1 (ALAS1) enzyme of the heme biosynthetic pathway. The ENVISION (NCT03338816), placebo-controlled phase 3 study proves the long-term efficacy and safety of Givosiran treatment in patients aged ≥12 years with AHP, leading to a reduction in porphyria attacks and days of hemin use, improving patient-rated physical and mental quality of life. This study aims to investigate the disease burden and the health-related quality of life (HRQoL) in patients with AHP in 18 months. Thus, we report data on patients with AHP enrolled in the Patient Support Programs by PHDlifescience. We used the Physical (PCS) and Mental (MCS) Composite Scores from the SF-12v1 Italian version questionnaire to assess the perception of HRQoL. PCS and MCS range from 0 to 100, with higher scores indicating better functioning. Pain intensity and its impact on patients' lives were assessed by the Brief Pain Inventory (BPI) questionnaire, which measures both pain interference in patients' lives (PIS) and pain severity (PSS), with high values indicating severe interference/completely debilitating pain. Additionally, we used the Brief Fatigue Inventory (BFI) questionnaire to swiftly assess the severity of patients' fatigue, with higher scores indicating more pronounced fatigue. Descriptive statistics include median, 1st, and 3rd quartiles. Differences over time were assessed using Friedman's analysis. All statistical analyses were conducted using the R environment (R Foundation for Statistical Computing, Vienna, Austria). Significance was set at $p < 0.05$ for all two-sided tests. The sample has a median age of 47.8 (34.7; 54.3). The clinical variables: blood pressure, heart rate, respiratory rate, oxygen saturation, body temperature, dose, and adverse events, were under control until the last follow-up. Despite no statistically significant changes, from baseline to 18 months of 7 patients with no missing values, four increased in PSI and PSS. The median PSI change was 1.8% (0.0%;34.0%) from baseline and PSS of 5.3% (-5.9%;36.5%). MCS and PCS change was 6.3% (0.1%;12.7%) and 5.3% (-5.9%;36.5%), respectively. BFI increase of 8% (-22%;13%). Although there were no statistically significant changes due to missing values and the small sample size, the clinical parameters were under control with a stable trend at 18 months. HRQoL and pain improved at the last follow-up to the baseline values.

Poster 6

04171 VALIDATION OF ANATOMICAL AND BRAIN PERFUSION DYNAMICS IN AIP NON-HUMAN PRIMATE MODEL USING NON-INVASIVE MRI, AND ASSESSMENT OF EFFICACY WITH HPBGD MRNA THERAPY

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A previous observational study (NCT02076763) reported that 7 out of 8 patients diagnosed with acute intermittent porphyria (AIP) and experiencing recurrent acute attacks showed significant enlargement of brain ventricles compared to healthy volunteers. Among them, 2 patients also showed reduced cerebral blood flow (CBF) during and acute episodes. Similarly, AIP mice demonstrated reduced CBF and developed chronic dilatation of cerebral ventricles compared to wild type controls, a condition worsened following acute attacks. However, overexpression of PBGD by means of gene therapy successfully alleviated both symptoms.

In this study, we evaluated alterations in CBF and cerebral ventricles volume in a clinically relevant Non-Human Primates (NHPs) model before and after induction of AIP, while comparing current (hemin and givosiran) and emerging (hPBGD mRNA) therapies using a 3T Magnetic Resonance Imaging (MRI) scanner (Magnetom Skyra, Siemens Healthcare, Germany) equipped with 32-channel head array coil.

Perfusion quantification was performed using custom MATLAB scripts (The MathWorks, Inc). MRI images and quantification revealed a reduction in CBF in AIP NHPs starting one month after AIP induction. This hypoperfusion persisted during acute attacks triggered by administration of porphyrinogenic drugs such as sulfamethoxazole and phenobarbital. Remarkably, increased PBGD expression in the liver achieved through multidose administration of hPBGD mRNA was the unique treatment capable of restoring baseline CBF levels.

Ventricular volumes in NHPs were obtained using AFNI (Analysis of Functional NeuroImages, https://afni.nimh.nih.gov/), with voxel counts converted to cubic centimeters. NHPs exhibited an increase in ventricular volume following the induction of porphyria and recurrence of acute attacks. Only multidose administration of hPBGD mRNA therapy showed potential to restore normal volume values.

In conclusion: MRI proved to be a non-invasive and safe medical imaging technique capable of validating anatomical changes and brain perfusion dynamics in AIP. Our findings support the safety and translatability potential of multiple systemic administration of hPBGD mRNA as a promising therapeutic approach for addressing ventricular enlargement and CBF alterations in AIP.

Poster 7

04167 HEMIN TREATMENT DURING ATTACKS IN ARGENTINEAN PATIENTS WITH ACUTE PORPHYRIAS

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10.1136/bmjgast-2024-ICPP.38

Acute Intermittent Porphyria (AIP), Variegate Porphyria (VP) and Hereditary Coproporphyria (HCP) are Hepatic Acute Porphyrias inherited as autosomal dominant traits caused by a

defect in the genes that encode porphobilinogen deaminase, protoporphyrinogen oxidase or coproporphyrinogen oxidase, respectively. Clinical expression typically occurs after puberty; environmental and other factors as fasting, drugs, alcohol, steroid hormones are potentially triggers of acute attacks. These attacks often begin with abdominal pain followed by the development of peripheral neuropathy and central nervous system manifestations. During 2021–2023, eleven women between 25 and 50 years old developed attacks of AIP, another woman developed VP and a man developed HCP. All patients were treated with Normosang (3–4mg/kg for four days). In AIP group, five patients received only one treatment, five received two and one patient received Hemin treatment in three occasions. For nine patients, Hemin was used during the first attack, at the date of diagnosis; eight of them were the first case in their families. Genetic study of the HMBS gene (NM_000190.4, LRG_1076), revealed that four of these patients carried the most prevalent variant in Argentina, c.331G>C (p.Gly111Arg). Each of the other patients presented different variants: c.849G>A (p.Trp283Ter), c.145delp. (Leu49Cysfs*49), IVS8–1G>T (c.423–1G>T), c.913–1G>A (p.?, causing deletion of exon 15), c.517C>T (p.Arg173Trp), c.652–2A>G (p.?, causing deletion of exon 12). The VP patient developed her first attack at 32 years old and was the first member of her family. The HCP patient triggered his first attack at 39 years old, being also the first in his family. In these two cases, as well as in two of the AIP patients, Hemin treatment was administered more than one month after the onset of the attack due to the delay in the diagnosis, as clinicians did not initially consider Porphyria. These cases required more time for remission. Currently, all patients are in recovery, maintaining an adequate diet and receiving prescriptions for folic acid, vitamin B and glucose. Although it is recommended that Hemin must be administrated within the first fifteen days of the acute attack, our experience suggests that Hemin treatment can still be effective even when is administered later.

Poster 8

04133 PATERNAL SPLIT-LIVER TRANSPLANTATION FOLLOWED BY HAPLOIDENTICAL HEMATOPOIETIC CELL TRANSPLANTATION IN AN ADULT PATIENT WITH PROTOPORPHYRIA-INDUCED LIVER FAILURE

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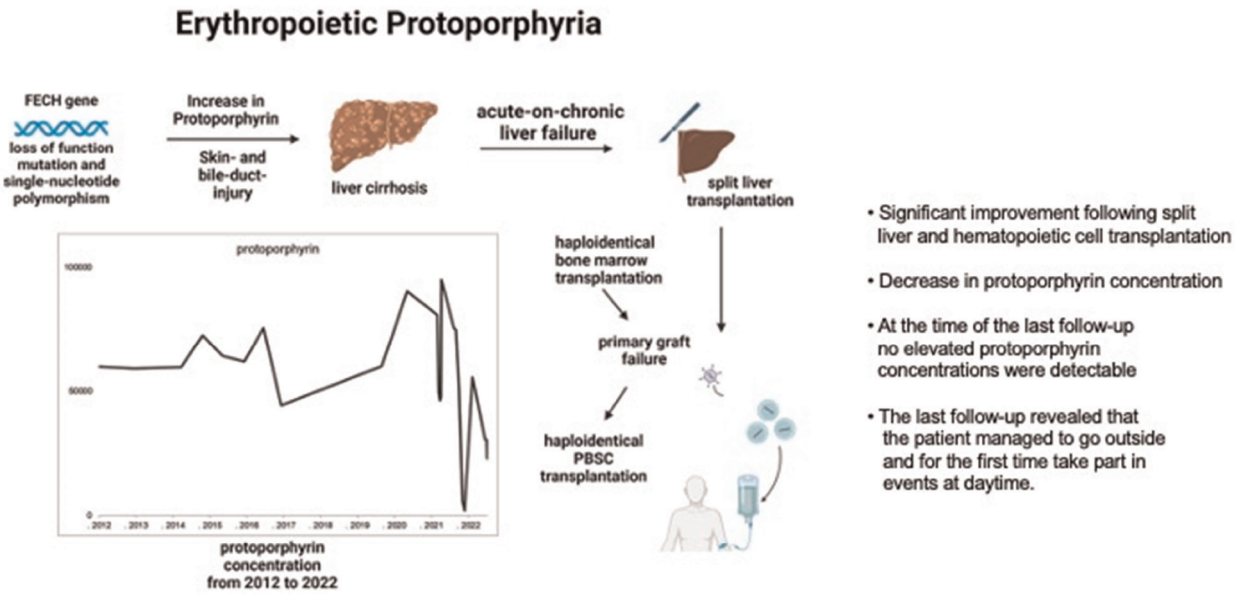
10.1136/bmjgast-2024-ICPP.39

Erythropoietic Protoporphyria (EPP) caused lifelong grave light sensitivity on skin and induced liver cirrhosis with liver-failure in a 35-year-old patient. Since an unrelated donor search for hematopoietic cell transplantation (HCT) was not successful, the haploidentical and otherwise healthy father was identified as an alternative stem cell donor. However, during the Covid-19 pandemic HCT was postponed and the patient developed severe liver dysfunction and subsequent liver-failure. The 60-year-old father consented in donating split liver and hematopoietic stem cells and was cleared medically for donating both. Repeated plasma- and erythrocyte-apheresis were used to diminish toxic protoporphyrin IX (PP) and as a bridging strategy to paternal split-liver transplantation (SLT). Six months after SLT and with improved liver function, a first paternal haploidentical bone marrow transplantation resulted in non-donor-specific-antibody-associated primary graft failure (PGF)



Abstract 04133 Figure 1

with subsequent autologous recovery. For a second successful paternal haploidentical peripheral-blood HCT, hydroxyurea was implemented and a more immunosuppressive total-body irradiation-based conditioning regimen was applied.

After haploidentical HCT, PP levels decreased to normal blood concentrations and light sensitivity of the skin disappeared.

The results presented herein describe the successful treatment of a patient with EPP causing lifelong grave light sensitivity on skin and induced liver cirrhosis with life-threatening complications.

This is a) the first patient reported with EPP who underwent haploidentical HCT using post-transplant cyclophosphamide as immunosuppressive backbone, and b) the first adult patient with EPP in general who has been treated with this subsequent SLT-HCT regimen.

The report might be of high interest for clinicians and currently discussed guidelines for management of protoporphyria-induced liver failure.

Poster 9

04103 EFFECT OF GIVOSIRAN FOR HEREDITARY COPROPORPHYRIA: 2 CASES REPORT

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10.1136/bmjgast-2024-ICPP.40

Background The effect of Givosiran on persistent symptoms of hereditary coproporphyria (HCP) is unclear. We report 2 sisters of HCP treated with Givosiran.

Case Case 1: A 23-year-old Japanese female was diagnosed as HCP in the neonatal period. Her diagnosis was established on the base of clinical symptoms; UV-sensitization and dark-brown urine. Abdominal pain, headache, general fatigue, and photosensitization were observed and gradually worsen. He was referred to our hospital for the treatment with Givosiran at 22 years old. Excretion of coproporphyrin, d-aminolevulinic acid (ALA) and porphobilinogen (PBG) was 2927 mg/g CRE, 1.3 mg/L, and 2.7 mg/L respectively. The persistent symptoms were improved immediately and the values of coproporphyrin, ALA and PBG were decreased to 1754 mg/g CRE, 1.3 mg/L, and 0.8 mg/L respectively 4 months after Givosiran treatment.

Case 2: The patient is 12 years old girl. She had abdominal pain from 4-years-old. Abdominal pain gradually deteriorated every year, nausea, numbness in limbs, weakness, headache, dizziness, and light-headedness began to occur frequently. The skin symptoms caused by sunlight were not strong, but dizziness, abdominal pain, and headache worsened when exposed to sunlight. She diagnosed HCP by genetic analysis. She arrived at our hospital for administered Givosiran. Coproporphyrin, ALA, and PBG was 238μg/g CRE, 1.5mg/L, and 2.3mg/day respectively before Givosiran administration. After the start of Givosiran, the persistent symptoms improved immediately, and the value of Coproporphyrin, ALA, and PBG decreased to 99μg/g CRE, 0.6mg/L, and 1.0mg/L after 3 months.

Conclusion Givosiran has been shown to be effective for persistent symptoms of HCP. The changes in ALA and PBG are slight, and it is necessary to investigate the factors that contributed to the improvement of symptoms in the future.

Poster 10

04156 RECURRENT ACUTE INTERMITTENT PORPHYRIA ATTACKS AFTER NORMALIZATION OF PORPHOBILINOGEN ON GIVOSIRAN PROPHYLAXIS

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10.1136/bmjgast-2024-ICPP.41

Background Givosiran is an interfering RNA therapeutic targeting hepatic ALAS1 mRNA, and the first-in-its-class drug approved for treatment of acute hepatic porphyrias (AHP). It reduces ALAS1 expression, thus reducing delta-aminolevulinic acid (ALA) and porphobilinogen (PBG) over-production and accumulation. Here, we present a case of a patient with acute intermittent porphyria (AIP) who is on prophylaxis with givosiran and continues to have sporadic acute attacks in spite of normalization of ALA and PBG.

Case This 21-year-old Black female initially presented with multiple episodes of abdominal pain, nausea, and emesis associated with the luteal phase of the menstrual cycle. After several months she was diagnosed with AIP and responded to treatment with hemin for amelioration of attacks. She was admitted for an acute attack shortly after relocating to Texas. Labs at that time showed a PBG of 67.3 mg/g creatinine (ref 0–7) and ALA of 45 mg/g creatinine (ref 0–4). The attack resolved with treatment that included hemin and opioids. Givosiran 2.5mg/kg subcutaneously was started after discharge. She has received 21 doses of givosiran over 612 days, with dosing intervals ranging from 26–38 days. Initially her PBG was 43.2 mg/g Cr, but normalized on givosiran and has remained normal during treatment (range 0.7–2.7). Attacks have been less frequent, but she was hospitalized with acute attacks between doses 4–5, 7–8 and 15–16. PBG levels on these admissions were normal, at 1.1, 2.7, and 1.0 mg/g Cr respectively, and the attacks resolved after treatment with hemin (1–4 doses). ALA levels were also normal at the time of the attacks. She remains well between less frequent attacks on prophylactic givosiran with normal PBG and ALA levels.

Discussion An elevation in urine PBG is the hallmark of a porphyria attack and is considered a criterion for diagnosis of AHP attacks. Additionally, PBG levels are expected to decrease as symptoms resolve. The goal of givosiran prophylaxis is normalization of urine PBG and prevention of attacks. In clinical trials of givosiran, attack rates were substantially reduced in AHP patients, but levels of ALA and PBG that occurred during infrequent attacks were not described. In this case, occasional acute AIP attacks were observed during givosiran treatment in spite of sustained normalization of PBG and ALA levels. This suggests that mechanisms additional to elevation in levels of ALA and PBG, which are potentially neurotoxic, may contribute to symptoms during attacks of AHP.

Poster 11

04157 ADMINISTRATION OF HEMIN AND TIME-RELATED EFFECTS ON FERRITIN IN ACUTE HEPATIC PORPHYRIA

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10.1136/bmjgast-2024-ICPP.42

Background Accurate assessment of iron status is important in patients with acute hepatic porphyrias (AHP) since iron overload may develop after repeated administration of hemin. Serum ferritin is a useful measure of iron status; however, ferritin is also an acute-phase protein that may be elevated by inflammation or dysmetabolic conditions. We considered that ferritin elevation after hemin administration could result from an acute phase response in AHP rather than sustained iron overload. We examined data from five patients with acute intermittent porphyria (AIP) who were treated with hemin and had multiple ferritin measurements, providing an opportunity to assess time relationships between hemin administration and serum ferritin.

Study findings The dose-time relationship between hemin administration and serum ferritin for each patient is shown in the figure 1. Patients 1 and 2 received prophylactic and treatment doses of hemin, while patients 3,4, and 5 received prophylactic givosiran and treatment doses of hemin. All patients had normal baseline serum ferritin levels, increase in ferritin post-hemin, and a decline in ferritin levels over time. Sustained ferritin elevations were not noted even after repeated hemin administration. Also, serum ferritin rise post-hemin administration varied widely – hemin given to a patient in iron-deficient state did not raise ferritin as dramatically as when it was given in iron-replete state.

Conclusion Our observations suggest that serum ferritin increases rapidly after hemin administration and decreases slowly over several days or weeks, and during that time may not be a reliable indicator of iron overload. Prospective, larger studies are needed to assess the time course of ferritin elevation after hemin administration, relationship with serum iron status, and measurement of hepatic iron concentrations in order to determine risk for iron overload and hepatic damage in AHPs.

Poster 14

04153 CLINICAL AND BIOCHEMICAL EVOLUTION OF EIGHT ACUTE HEPATIC PORPHYRIA PATIENTS UNDER GIVOSIRAN TREATMENT

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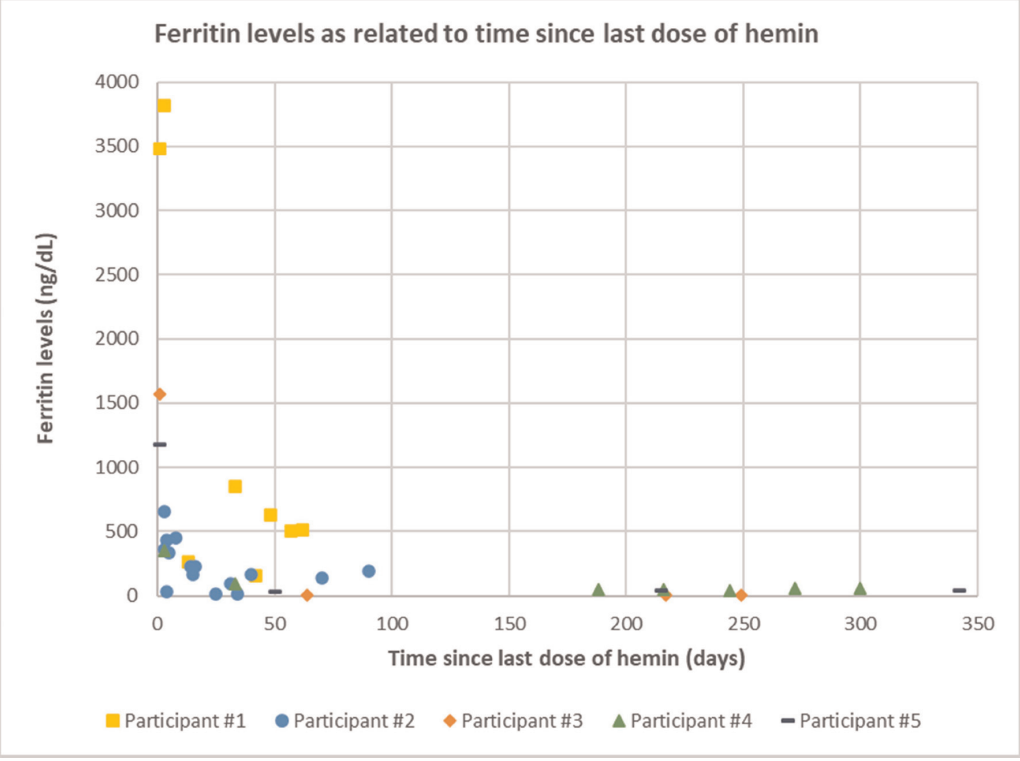
10.1136/bmjgast-2024-ICPP.43

Acute hepatic porphyrias (AHPs) are rare inherited disorders characterized by enzyme dysfunctions in the hepatic pathway of heme biosynthesis, leading to recurrent life-threatening



Abstract 04157 Figure 1

neurovisceral attacks due to the accumulation of neurotoxic porphyrin precursors, including delta-aminolevulinic acid (ALA) and porphobilinogen (PBG). Givosiran (Givlaari®), a subcutaneously administered small interfering RNA, targets hepatic aminolevulinate synthase 1 (ALAS1) activity, thereby reducing porphyrin precursor levels and mitigating attack frequency.

This study conducted a comprehensive clinical and analytical follow-up of eight AHP patients treated with Givosiran for at least 17 months. Analyzed parameters encompassed urinary ALA and PBG excretion, plasma levels of homocysteine (HCy), transaminases, glomerular filtration rate (GFR), lipase, amylase, vitamin B12, folic acid, vitamin B6, plasma cystathionine-β-synthase (CBS) activity, methylenetetrahydrofolate reductase (MTHFR) and hemopexin mutations.

The majority of patients exhibited notable improvements in quality of life and a sustained reduction in hemin and opiate usage. Treatment discontinuation occurred in two patients: one due to nausea and fatigue (resulting in increased opiate use and the occurrence of moderate porphyric crises) and another due to pregnancy. Plasma homocysteine elevation was frequent and managed by supplementing the treatment with vitamins B6, B12, and folate. Although elevated pancreatic enzyme levels were observed in 50% of patients, clinical pancreatitis was not evident. Individualized dosing adjustments were implemented based on clinical evolution and precursor excretion profiles.

Long-term Givosiran treatment in severe AHP patients demonstrated favorable clinical and biochemical outcomes. Elevated homocysteine levels and pancreatic enzyme elevation were effectively managed through vitamin supplementation and dose adjustments respectively. Close monitoring for adverse effects remains paramount for optimizing patient outcomes, while tailored treatment approaches may further enhance therapeutic efficacy in acute hepatic porphyria.

Poster 15

Thematic area: diagnosis and care in porphyrias

04110 PORPHYRIA REGISTRY PADOVA – START UP

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10.1136/bmjgast-2024-ICPP.44

Porphyrias are a group of rare, predominantly hereditary, metabolic diseases, characterized by the absence of pathognomonic symptoms. The creation of a Registry of patients affected by the various types of porphyria in Veneto Region (Italy) is a useful tool for collecting clinical, biochemical, genetic, epidemiological and psychological information with the aim of improving knowledge of these rare pathologies, facilitating and reducing the diagnosis times and identifying an interdisciplinary path that these patients and their families need.

The Porphyria Center in Padova was recently established. The first diagnosis dates back to 2010, but in a short time numerous new diagnoses of both acute and cutaneous porphyria were performed with the advantage of making use of professionals with experience in internal medicine, hepatology, dermatology, nutrition, gynecology, nephrology, neurology, biochemistry and genetics to respond to the patient's multiple needs. Diagnosis of all forms of porphyria is made by identifying specific patterns of porphyrin metabolites and porphyrin precursors in urine, feces, and blood. Genetic analysis is the gold standard, available to all patients. Padova's experts currently follow more than 80 patients. During the summer at least 10 patients suffering from EPP are treated with *Afamelanotide*; in 2020, the center was authorized to treat 2 young women with *Givosiran* and currently, there are 5 patients on therapy (4 AIP, 1 VP). The Porphyria Registry Padova, prepared with the and shared among the center's specialist, will only be accessible with a password. The Registry will contain patient data in anonymous form with demographic information, information on the characteristics and severity of symptoms, presence of associated pathologies, laboratory analysis data, use and response to therapies and other aspects deemed useful in order to improve knowledge of these rare pathologies. The project was approved by the local Ethics Committee. Patients will be included only after signing the informed consent. Delays in the diagnosis of acute porphyrias can reach up to 15 years from the onset of clinical manifestations. The symptoms are often similar to those of other gastrointestinal, gynecological, neurological or neuropsychiatric diseases and can lead to frequent and prolonged hospital admissions and even unnecessary surgical procedures. Data in the literature are still scarce regarding the natural history of the disease, its onset, progression and complications, including the disabling impact on the daily and social life of patients. The introduction of drugs based on new technologies capable of treating and improving the quality of life of these patients, reducing the frequency of attacks and chronic pain, makes the support of a porphyria registry of primary importance. Patients undergoing new therapies must also be monitored from the point of view of liver and kidney function and regarding the levels of porphyrin metabolites.

Poster 16

04188 HEREDITARY COPROPORPHYRIA WITH CEREBRAL ANEURYSMS: SUCCESSFUL DIAGNOSIS AND TREATMENT WITH GIVOSIRAN

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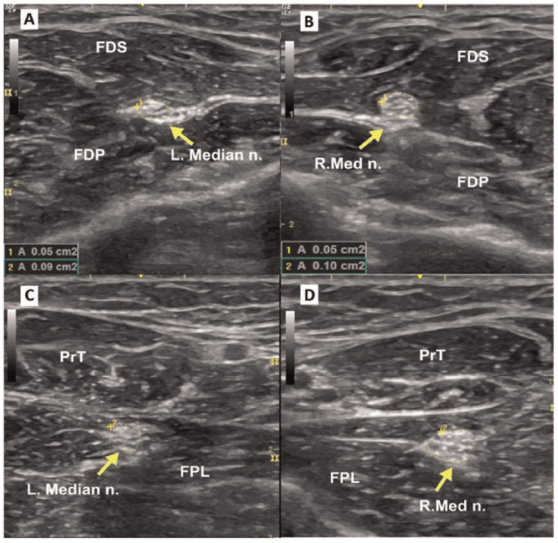
10.1136/bmjgast-2024-ICPP.45

We present a clinical case of a 56-year-old woman who developed bullous lesions on the dorsum of her hands in August 2022, prompting a biopsy revealing features consistent with bullous dermatitis such as porphyria cutanea tarda. Subsequently, she was referred to our unit for further evaluation.

Her medical history included hyperthyroidism, post-anesthesia recovery difficulties following two surgeries, recurrent episodes of diffuse abdominal pain radiating to the lumbar and inguinal regions accompanied by tachycardia, worsening

asthenia, reduced diuresis, constipation, and insomnia. She also experienced episodes of lower extremity paresthesias and clonus.

Hospitalization in January 2023 included instrumental examinations to assess potential organic abnormalities related to reported symptoms, alongside genetic testing revealing a pathogenic variant c.917dup in the CPOX gene, confirming hereditary coproporphyria. Imaging studies identified two small aneurysms: one dysmorphic at the bifurcation of the right middle cerebral artery, and the other sac-like at the bifurcation of the left middle cerebral artery. Despite no apparent association with coproporphyria, these findings underscored the importance of preventing acute porphyria crises to mitigate aneurysmal rupture risk. Neurosurgical consultation recommended regular MRI monitoring.Initiation of Givosiran therapy was planned but delayed due to hospitalization in April 2023 for acute hepatitis secondary to initial HCV infection. After completing eradication therapy, she commenced Givosiran therapy in July 2023, resulting in prompt subjective symptom improvement and normalization of ALA and PBG levels. She remained asymptomatic, reporting enhanced quality of life post-treatment. This case highlights the co-occurrence of hereditary coproporphyria with multiple cerebral aneurysms, emphasizing the necessity for comprehensive diagnostic evaluations to exclude other underlying pathologies. Notably, it underscores the significant symptomatic improvement and enhanced quality of life achieved withGivosiran therapy, reflecting its efficacy in managing porphyria-associated symptoms.



Legends: Figure 2.

A) Right median nerve between the flexor digitorum profundus and flexor digitorum superficialis muscles with a CSA of 0.05 cm^2.

B) Left median nerve between the flexor digitorum profundus and flexor digitorum superficialis muscles with a CSA of 0.05 cm^2.

C) Right median nerve between the pronator teres and flexor pollicis longus muscles with a CSA of 0.09 cm^2.

D) Leftmedian nerve between the pronator teres and flexor pollicis longus muscles with a CSA of 0.10 cm^2.

Abstract 04134 Figure 1

Poster 17

04134 AN UNUSUAL CASE OF VARIEGATE PORPHYRIA WITH NERVE ENLARGEMENT, CONDUCTION BLOCK AND IDIOPATHIC INTRACRANIAL HYPERTENSION

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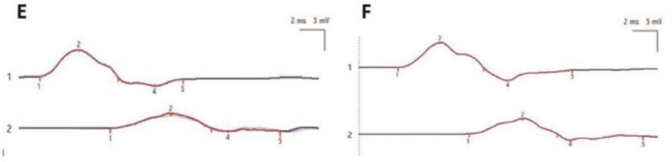
10.1136/bmjgast-2024-ICPP.46

Background Acute porphyrias are associated with chronic symptoms which are frequently reported but still poorly investigated. We report a patient with variegate porphyria with unusual findings during follow up.

Case Report Female patient with previous history of acute attack (abdominal pain, urinary retention and tetraplegia) at age 27. She was evaluated at age 42 and as sequelae she had mild distal weakness and neuropathic pain in both hands and feet. She was diagnosed after genetic panel showed a pathogenic variant on PPOX - c.503G>A. Electrodiagnostic studies (EDX) were performed and revealed reduced compound motor action potential (CMAP) amplitudes in nerves of the lower limbs and both median nerves. Also, conduction block in both median nerves suggested acquired demyelinating neuropathy. Late responses showed absence of F waves and H reflexes in the tibial nerves. Sensory studies were normal. Neuromuscular ultrasound showed enlarged cross-sectional



Legends: Figure 1

E) Conduction block of the left median nerve between the distal stimulus in the wrist (1) and the stimulus in the arm (2).

F) Conduction block of the right median nerve between the distal stimulus in the wrist (1) and the stimulus in the arm (2).

area in both median nerves in the forearm, consistent with neural thickening outside typical compression site. Six months later, she presented with psychosis and reported migrainous headache. Brain MRI suggested idiopathic brain hypertension. Lumbar puncture demonstrated increased opening pressure of 32 cmH2O. A new attack was discarded with biochemical exams.

Discussion Acute porphyric neuropathy is described as an axonal predominantly motor neuropathy. Secondary demyelinating findings have been described. A primary demyelinating neuropathy and partial conduction block, as seen in our case, have been reported in the acute phase and related to more severe acute attacks. A chronic distal axonal sensory-motor polyneuropathy can persist. Specific ultrasonography features of porphyric neuropathy have not been reported. This unpredicted finding can be a source of misleading diagnosis as inflammatory neuropathy. Finally, intracranial hypertension is not usually seen and further studies are needed to establish a relationship.

Poster 18

04149 THREE YEARS LATER: HOW THE PREVIOUSLY DEFINED VISUAL THRESHOLD OF THE HOESCH TEST WORKS

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Background Hoesch test is a rapid test based on porphobilinogen (PBG) reaction with Erlich reagent. The method is available 24/7 in our hospital due to its quite simple measurement protocol. The rapid test has several limitations caused by difficulties in visual assessment of the resulting coloured solution, as well as interferences that cause false positive or false negative results. We have previously validated the Hoesch test in our laboratory conditions and determined the threshold value to be around 20.8 µmol/L. In our hospital, the trueness of the rapid test results are usually confirmed as soon as possible by the PBG measurement on commercial solid phase extraction (SPE) method separating with an anion-exchange column, treatment Ehrlich's reagent and photometric measurement.

The aim of our investigation was to evaluate the actual performance of the previously found threshold value of the Hoesch test in a routine working process.

Methods We analysed the qualitative results of all Hoesch tests performed during recent 3 years together with the corresponding results of the quantitative SPE measurement. Urine PBG (U-PBG) values measured by the SPE method were divided into positive and negative groups based on the results of the Hoesch test. Receiver operating characteristic (ROC) curve analysis was performed by a statistical program MedCalc V19.1.

Results U-PBG data (n=272) were distributed between groups with corresponding positive (n=37) and negative (n=235) Hoesch test results. ROC curve analysis showed that the optimal threshold level for U-PBG, as determined by the Youden index, was >13.6 µmol/L (sensitivity 100%, specificity 94.9%), area under the curve 0.993. Our previously established threshold value of about 20.8 µmol/L fits well between closest to optimal the ROC curve points of 19.72 µmol/L and 21.41 µmol/L with a sensitivity of 97.3 and 91.9%, a specificity of 96. 6% for both points.

Conclusion Our previously determined U-PBG threshold value of approximately 20.8 µmol/L, which corresponded to a positive Hoesch test by visual assessment, performed very well in routine working process. When compared to the optimal threshold value determined by Youden index, it demonstrated a slight loss of sensitivity but an increase in specificity. The better specificity of the threshold value is especially important in the management of this group of diseases with low prevalence.

Poster 20

04095 HORMONAL TREATMENTS IN ACUTE HEPATIC PORPHYRIA

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Acute attacks in patients with acute hepatic porphyria (AHP) have long been associated with female hormones and the use of hormone containing contraceptives. Females with acute hepatic porphyria have traditionally been advised to avoid all forms of exogenous forms of oestrogen and progesterone due to the risk of causing an acute attack. This leaves patients in a difficult position when it comes to choosing contraception, or treating symptoms such as menorrhagia, dysmenorrhoea, menopause symptoms. There is limited research on the effect of specific hormonal contraceptives, with just one study in 2003 finding 1 in 4 AIP patients experienced an attack with contraceptives containing progesterone, oestrogen or a combination.[1]

We designed a questionnaire which was sent to all female patients with a diagnosis of AHP - acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), in our hospital database, and distributed via the Australian Porphyria patient support group. Participation was voluntary and unidentifiable. Patients were asked their previous experience with hormonal treatments. Thirty responses were obtained (AIP 12, VP 12, HCP 6). 23 patients had used hormonal treatments. 7 patients had not used hormonal treatments, with 5/7 (71%) of this group reporting the reason for this being due to fear of side effects including a flare of porphyria.

HCP was the most common porphyria type to experience a flare with hormones (66%), and approximately 20% of VP and AIP patients. No patients flared with hormone replacement therapy (HRT), the progesterone-only pill, or progesterone implant. The progesterone-containing intrauterine device (IUD) resulted in a flare in 2/7 (28.5%), whilst 7/15 (46.6%) flared with the combined oral contraceptive pill. Drospirenone-containing pills, Yaz and Yasmin were the most likely brands to cause a flare. Levonorgestrel in the Mirena IUD and Levlen, were more likely to be tolerated, particularly by patients with VP compared to HCP. In terms of treatments that were reported to have helped porphyria symptoms, the Mirena IUD was most likely to be of benefit, likely as a result of keeping hormone levels stable. Many patients reported being unsure of whether they received any benefit from the medication.

This study, although limited by small sample size and the retrospective nature of the questionnaire, add to the literature and aid in our ability to effectively counsel patients and prescribe much-needed hormonal treatments.

REFERENCE

1. Andersson C, Innala E, Bäckström T. Acute intermittent porphyria in women: clinical expression, use and experience of exogenous sex hormones. A population-based study in northern Sweden. *Journal of Internal Medicine*, 2003;**254**(2):176–183.

Poster 21

04243 BRIDGING THE GAP: ENHANCING PATIENT ENGAGEMENT THROUGH ACCESSIBLE MEDICAL INFORMATION IN THE PORPHYRIAS. A CASE STUDY IN ERYTHROPOIETIC PROTOPORPHYRIA

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Introduction Patients with rare diseases often encounter difficulties accessing and comprehending medical information due to the complexity and rarity of their conditions. This communication barrier between medical professionals and patients can impede patient engagement and informed decision-making. Erythropoietic protoporphyria (EPP) exemplifies this challenge, lacking sufficient patient-centric research.

Objectives Our initiative seeks to demystify medical research in the porphyrias by translating complex publications into patient-friendly summaries, written at an 8th-9th grade level. We aim to bridge the knowledge gap, enabling patients, caregivers, and non-specialists to access and understand the latest EPP research. Our goal is to foster patient engagement and involvement in their healthcare journey.

Methods We have developed a series of easy-to-understand summaries of recent porphyria research, reviewed and endorsed by the United Porphyrias Association's Scientific Advisory Board. These summaries offer comprehensive insights into advancements while ensuring accessibility for patients and caregivers. Additionally, collaboration with healthcare providers ensures the utility of these summaries in facilitating improved doctor-patient communication.

Results Our initiative, 'Summing UP,' has received positive feedback from the porphyria patient community. Patients and caregivers appreciate the accessibility of the summaries, resulting in heightened engagement and informed decision-making. We observe increased patient interest in understanding and actively participating in their care plans.

Conclusions and Future Directions Accessible medical information is pivotal in enhancing patient engagement. Going forward, we aim to expand 'Summing UP' to cover a broader spectrum of rare diseases, ensuring more patients have access to relevant research. We will explore additional formats and platforms to enhance accessibility, such as videos, podcasts, and interactive webinars. Furthermore, ongoing collaboration with medical professionals will maximize the impact of our initiative on patient knowledge, engagement, and health outcomes.

Case Study in erythropoietic protoporphyria (EPP):

- Published in Hepatology, July 2023
- Summing UP, October 2023
- Published in Chronic Liver Disease, February 2023

Poster 22

04107 THE EPP LIGHT STUDY: UNDERSTANDING THE BURDEN OF ERYTHROPOIETIC PROTOPORPHYRIA (EPP) FROM THE PATIENT PERSPECTIVE

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10.1136/bmjgast-2024-ICPP.50

Introduction Erythropoietic protoporphyria (EPP) is a rare, inherited disorder caused by accumulation of a toxic metabolite, protoporphyrin IX (PPIX), which can lead to severe, painful phototoxicity and potential liver disease. EPP can have significant impacts on health-related quality of life (HRQoL) and healthcare resource utilization (HRU). To date, little has been published on the burden of EPP from the patient perspective.

Objective A cross. sectional, online survey study is currently underway with adolescents (12–17 years of age) and adults ($\geq$ 18 years of age) with EPP and X-linked protoporphyria (collectively, EPP) that seeks to describe the burden associated with EPP in terms of symptoms, HRQoL, HRU as well as preferences for treatment.

Methods Participants, recruited by an advocacy group, are $\geq$ 12 years of age, report a diagnosis of EPP, reside in North America, are able to speak, read and write English, and able to complete a one-time online questionnaire.

The online questionnaire, which could take up to 60 minutes to complete, includes existing validated and newly developed patient-reported outcome (PRO) measures to assess HRQoL, including the EPP Impact Questionnaire (EPIQ), items assessing early warning symptoms and pain from the Sunlight Exposure Diary, PROMIS Satisfaction with Social Roles and Activities-8a, PROMIS Peer Relationships-8a (adolescents only), PROMIS Social Isolation-4a, and original items assessing physical functioning, anxiety, depression, fatigue, bullying/unfair treatment, work/school loss/productivity, and need for accommodations when doing daily activities. Original items were also developed to assess the EPP diagnostic journey and HRU, including hospitalizations, emergency room visits, physician visits, and prescription and over-the-counter medication use. The questionnaire also includes items assessing preference for various types of EPP treatment. The questionnaire was developed based on qualitative research conducted with individuals with EPP, in collaboration with EPP clinical experts, a patient advocacy group, and PRO research experts.

All participants are required to provide informed consent (adults) or assent and parental permission (adolescents). Each participant will be remunerated for their time.

Results The study has been approved by an institutional review board (WCG IRB), and was initiated in May 2024. Enrollment is currently ongoing. The plan is to enroll a minimum of 100 adults and 25 adolescents. Preliminary data will be presented at this meeting.

Conclusion Currently, there is a lack of available data describing the burden of EPP from the perspective of the patient. Results from this study will provide comprehensive insight regarding the HRQoL and HRU impact on the lives of adolescents and adults with EPP in North America.

Poster 23

04100 PORPHYRIA CUTANEA TARDA IN SCOTLAND: UNDERLYING ASSOCIATIONS AND TREATMENT APPROACHES

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10.1136/bmjgast-2024-ICPP.51

Please note that this work has been accepted for publication in the International Journal of Dermatology and is available online ahead of print: doi: 10.1111/ijd.17205

Background Despite its rarity, porphyria cutanea tarda (PCT) is globally recognized as the most common form of cutaneous porphyria. This study aims to review the underlying associations and treatment of PCT in Scotland.

Methods We retrospectively reviewed data on 27 patients diagnosed with PCT between 1987 and 2022 at the Scottish Cutaneous Porphyria Service.

Results Males slightly predominated (66.7%). The mean ± standard deviation (SD) age at diagnosis was 55.6 ± 12.5 years. Common associated factors were heavy alcohol intake (88.5%), genetic hemochromatosis (72%), smoking (45.5%), and hepatitis C virus infection (16%). Most had multiple associated factors (70.4%). Patients with genetic hemochromatosis with the C282Y genotype exhibited higher median transferrin saturation (69.5 vs. 35, P = 0.004) and ferritin levels (observed in males only) (1175 vs. 339; P = 0.014) than those with the H636D genotype. Most (52%) received combination therapy of venesection and antimalarials, followed by venesection monotherapy (32%) and antimalarial monotherapy (16%). Overall, 95.2% achieved biochemical improvement. Median time to improvement was 7, 5, and 9 months with venesection, antimalarial, and combined treatments, respectively (P = 0.173). Biochemical remission was achieved in 50% of patients. Remission occurred in 2/4 of patients with antimalarial monotherapy (median time 19 months) and 9/13 patients with combined treatment (median time 26 months). Biochemical relapse was found in three patients, all of whom received combination therapy.

Conclusion Excess alcohol intake and genetic hemochromatosis were the most common underlying associations with PCT in our Scottish cohort. Treatment for PCT should be individualized, and long-term follow-up is needed to monitor for disease relapse.

Poster 24

04127 MENSTRUAL CYCLE-DEPENDENT SYMPTOMS IN PATIENTS WITH ACUTE HEPATIC PORPHYRIA – DATA FROM THE GERMAN PORPHYRIA REGISTRY (POREGER)

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10.1136/bmjgast-2024-ICPP.52

Introduction Acute Porphyrias (APs) pose particular challenges to physicians due to non-specific symptoms requiring specific diagnostics. Irreversible damage can be prevented by early detection. The German Porphyria Registry (PoReGer) was set up to gain differentiated knowledge about all forms of porphyrias.

APs manifest in episodes that are often triggered by factors such as infections, certain medications, but also sex hormones, and can present in a menstrual cycle-dependent manner. In this project, we aim to analyze , whether the pattern of complaints in AP patients can be distinguished from typical menstrual and/or endometriosis complaints.

Materials and Methods In close cooperation with the Charité Berlin Endometriosis Center, a specified, detailed questionnaire was developed to gather information on menstrual cycle-dependent and menstrual cycle-independent symptoms and symptom perception in adult, premenopausal AP patients with a focus on abdominal pain. The information from the questionnaire was then combined with the information from the PoReGer. All adult, premenopausal women included in the registry were additionally asked to complete the questionnaire.

Results Of 13 patients who completed the questionnaire, 4 (31%) suffer menstrual cycle-dependent lower abdominal pain due to their AP, 4 (31%) suffer only typical menstrual pain and 5 (38%) do not experience any menstrual cycle-dependent symptoms. The AP-associated lower abdominal pain occurs mainly before menstruation and is localized umbilically and suprapubically radiating to the back. The quality of the pain ranged from localised to diffuse and the average pain was given as 6.6/10 on the Numeric Rating Scale. [*More patients are expected until September 2024*]

Summary One third of patients with APs suffer from menstrual cycle-dependent lower abdominal pain, which can also become a more severe relapsing symptom. Therefore, menstrual cycle-dependent pain also marks an initial symptom to think of porphyria before diagnosis. Strategies for the short- and long-term management of this special patient population will be developed in the course of this project.

Poster 25

04088 VARIEGATE PORPHYRIA CASES WITH FAECAL ISOCOPROPORPHYRIN – NOT DUAL PORPHYRIA

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10.1136/bmjgast-2024-ICPP.53

We wish to present two cases of variegate porphyria with faecal isocoproporphyrin. It is not expected for VP patients to demonstrate the presence of faecal isocoproporphyrin, and textbooks state that this is pathognomonic for porphyria cutanea tarda (PCT). Both of our patients have a clear diagnosis of variegate porphyria (VP) clinically, on Plasma Spectrofluorimetry (Peptide X) and genetic testing. The authors postulate that patients with acute hepatic porphyrias, including VP, could express faecal isocoproporphyrin in the setting of liver dysfunction or hepatic iron overload. Both patients had mildly elevated liver function tests. When the one patient's liver function normalised and iron levels dropped, the faecal isocoproporphyrin was no longer able to be detected. The other patient has remained positive for faecal isocoproporphyrin over time, and is completely asymptomatic, in keeping with latent VP.

CUMULATIVE REPORT

Laboratory:	**MH**	**MH**	**MH**		
Date:	**13-Oct-21**	**14-Oct-21**	**21-Sep-22**		
Time:	**09:10**	**00:00**	**12:00**		
Episode No.:	**12444930**	**12448548**	**13450558**		
Spec. Type:	**PORPHYRINS**	**PORPHYRINS**	**PORPHYRINS**	**Units**	**Ref. Interval**
Urine Porphyrins					
PBG Screen	--	Negative	--		
Creatinine	--	**1.3 L**	--	mmol/L	(4.2 - 9.7)
Total Porphyrin	--	**503 H**	--	nmol/L	(< 300)
Porph/Creat ratio	--	**386.9 H**	--		(< 35.0)
Uroporphyrin	--	**380 H**	--	nmol/L	(< 40)
Coproporphyrin	--	98	--	nmol/L	(< 150)
Faecal Porphyrins					
Total Porphyrin	--	**435 H**	**413 H**	umol/Kg	(< 200)
Total Coproporphyrin	--	152	145	umol/Kg	(< 180)
Isocoproporphyrin	--	**65 H**	**58 H**	umol/Kg	(< 2)
Protoporphyrin	--	**183 H**	149	umol/Kg	(< 180)
Copro 3/1 ratio	--	**2.2 H**	**1.9 H**		(< 1.5)
Plasma Porphyrins					
Total Porphyrin	**50 H**	--	--	nmol/L	(< 10)
Porphyrin Peptide	Present	--	--		
Red Cell Porphyrins					
Total Porphyrin	0.8	--	--	umol/L rbc	(< 1.8)

NOTES:

Episode 13450558 21-Sep-22 12:00
Comments: This patient has previously been diagnosed as having Porphyria Varigata.
NOTE: C3/C1 RATIO The ratio of coproporphyrin III to coproporphyrin I in the faeces (C3/C1 Ratio) is greater than 1.5 in patients who have inherited the gene for hereditary coproporphyria or porphyria variegata. In other porphyrias and normal subjects the ratio is less than 1.5 . This ratio is usually calculated only when the total faecal porphyrin level is >100umol/kg.

Episode 12448548 14-Oct-21 00:00
Comments: NOTE: PBG SCREEN A negative screen has been shown to correlate with porphobilinogen levels less than 10 umol/L.
NOTE: C3/C1 RATIO The ratio of coproporphyrin III to coproporphyrin I in the faeces (C3/C1 Ratio) is greater than 1.5 in patients who have inherited the gene for hereditary coproporphyria or porphyria variegata. In other porphyrias and normal subjects the ratio is less than 1.5 . This ratio is usually calculated only when the total faecal porphyrin level is >100umol/kg.

Episode 12444930 13-Oct-21 09:10
Comments: These results are consistent with a diagnosis of variegate porphyria.
NOTE: PORPHYRIN PEPTIDE X Porphyrin protein complex (P Peptide X) if present, is diagnostic of porphyria variegata.

BIOCHEMISTRY

Abstract 04088 Figure 1

Poster 26

04169 THE FIRST CASES OF δ-AMINOLEVULINATE DEHYDRATASE PORPHYRIA (ADP/DOSS PORPHYRIA) IN ITALY

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10.1136/bmjgast-2024-ICPP.54

This clinical case involves two siblings, a 6 year old girl and a 13 year old boy, children of consanguineous parents, diagnosed with acute porphyria due to ALA-dehydratase deficiency. They have been followed at our center since the summer of 2022. Diagnosis was confirmed through exome sequencing, which revealed a homozygous variant in the ALAD gene in both siblings, resulting in reduced enzyme activity and elevated urinary ALA and coproporphyrin III, along with increased blood levels of protoporphyrin-Zn. The male presents with axonal polyneuropathy, difficult-to-control arterial hypertension, mild cognitive deficit, sensorineural hearing loss requiring a prosthesis and mood swings. The female exhibits axonal polyneuropathy, tetraparesis with tendon contractures, resistant arterial hypertension, psychomotor retardation, prosthetic sensorineural deafness, and requires PEG for nutritional support. Since age 8 for the boy and age 5 for the girl, both have experienced monthly acute crises characterized by headache, nausea, abdominal and limb pain, and hypertensive episodes necessitating hospitalization and sometimes intensive care to manage pain and high blood pressure. On one occasion, the girl required intubation and ventilatory support due to severe respiratory failure. Following their diagnosis, the treatment regimen included hemin (4 mg/kg/day iv) during exacerbations and subsequently as prophylaxis, givosiran (2.5 mg/kg sc) during exacerbations and periods of well-being, continuous hydroxyurea (10–20 mg/kg/day orally), plasmaexchange/erythroexchange during acute phases and as prophylaxis, and continuous opioid therapy. In the boy, painful crises subsided for about a year, allowing near-complete neuromotor recovery, but recurred following psychophysical stress, resulting in severe motor deficits and dysphonia, making him wheelchair-dependent. The girl's monthly neurovisceral crises, more severe and frequent than her brother's, were consistently accompanied by resistant hypertensive crises. Over the past 20 months, both siblings have endured severe monthly neurovisceral crises involving significant peripheral, central, and autonomic neurological impairment. Triggers for these crises remain unidentified, and ALA levels have persistently remained high, even during periods of well-being. Hemin, administered during acute phases and subsequently as bi-weekly prophylaxis, effectively resolved acute crises (latency of 48–72 hrs) and reduced urinary ALA levels but did not ensure prolonged well-being. Givosiran had no effect on clinical symptoms or urinary ALA reduction. Hydroxyurea significantly reduced erythrocyte protoporphyrins but did not impact clinical symptoms or urinary ALA levels. Plasmaexchange/erythroexchange were ineffective in reducing or preventing acute crises, providing only temporary reductions in urinary ALA. Frequent changes in opioid medications (morphine, methadone, fentanyl) were necessary to manage chronic pain and flare-ups.

Poster 27

04178 DUAL PORPHYRIA: INITIAL PORPHYRIA CUTANEA TARDA IN A PATIENT WITH VARIEGATE PORPHYRIA

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10.1136/bmjgast-2024-ICPP.55

Beginning in her 20s, this 70-year-old female experienced episodes of abdominal pain accompanied by nausea, fatigue, and fecal and urinary urgency. Porphyria was considered in her 30s, but urine porphobilinogen (PBG) was normal. At age 60, she developed blistering on sun-exposed skin when taking an estrogen-medroxyprogesterone combination for menopausal symptoms. Laboratory findings suggested porphyria cutanea tarda (PCT), including: a) elevated urine porphyrins, predominance of uroporphyrin and heptacarboxyl porphyrin and an increased uroporphyrin/coproporphyrin ratio, b) normal urine PBG, c) elevated total fecal porphyrins and isocoproporphyrin/coproporphyrin ratio, and d) normal erythrocyte uroporphyrinogen decarboxylase (UROD) activity. Four phlebotomies over 2 years reduced serum ferritin levels and achieved clinical remission. A variety of intermittent neurovisceral symptoms continued. At age 64, findings were diagnostic for variegate porphyria (VP), with: a) intermittent PBG elevation, b) elevated urine porphyrins (predominantly coproporphyrin III), c) elevated fecal porphyrins with an increased coproporphyrin III/I ratio and d) normal total plasma porphyrins but a peak fluorescence at 626 nm at neutral pH. Mutation analysis revealed a protoporphyrinogen oxidase (PPOX) gene mutation (c.1123C>T, p.375*), previously associated with VP, and predicted to result in premature protein termination. She has since been hospitalized several times for acute attacks, and treated with hemin. Prophylactic hemin was partially successful in preventing attacks.

This case is consistent with reports from South Africa and elsewhere that some VP patients may, usually early in their course, develop biochemical and clinical features of PCT. Although rarely recognized, this may occur more often than expected, and suggests that VP may predispose to reversible inhibition of hepatic UROD by a mechanism that remains to be elucidated.

Abstract 04178 Table 1 Porphyrin precursors and porphyrins in urine and feces in a female that supported a diagnosis of PCT at age 60 and VP at age 64 years. Results from 3 different laboratories have been recalculated for purposes of comparison, when possible, and abnormalities are in bold font

	Age 60	Age 64	Units	Range
URINE				
Delta-aminolevulinic acid (ALA):	-	1.6-5.2	mg/g creatinine	0-7
Porphobilinogen (PBG):	<0.7	1.8-**11.7**	mg/g creatinine	0-4
Total Porphyrins:	**1,786**	**329**	nmol/g creatinine	0-300
Uroporphyrin-total:	68.3	*20.8*	% of total p'yrins	See comments
Uroporphyrin I:	-	*16.2*	"	"
Uroporphyrin III:	-	*4.6*	"	"
Heptacarboxyl porphyrin-total:	14.4	*4.0*	"	"
Heptacarboxyl porphyrin I:	-	*0.0*	"	"
Heptacarboxyl porphyrin III:	-	*4.0*	"	"
Hexacarboxyl porphyrin-total:	-	*0.0*	"	"
Pentacarboxyl porphyrin-total:	-	*0.0*	"	"
Coproporphyrin-total	17.3	75.2	"	"
Coproporphyrin I:	3.0	*6.2*	"	"
Coproporphyrin III:	14.4	*69.0*	"	"
Uroporphyrin/coproporphyrin	**3.9**	0.3	Ratio	<1
FECES				
Total porphyrins:	**8719**		nmol/24h	<4600
		209	nmol/g dry wt.	<200
Uroporphyrin-total:	*1.2*	*0.1*	% of total p'yrins	See comments
Uroporphyrin I:	*0.8*	*0.1*	"	"
Uroporphyrin III:	*0.4*	*0*	"	"
Heptacarboxyl porphyrin-total:	*9.3*	*0*	"	"
Heptacarboxyl porphyrin I:	*0.3*	*0*	"	"
Heptacarboxyl porphyrin III:	*9.0*	*0*	"	"
Hexacarboxyl porphyrin-total:	*1.2*	*0*	"	"
Hexacarboxyl porphyrin I:	*0.6*	*0*	"	"
Hexacarboxyl porphyrin III:	*0.6*	*0*	"	"
Pentacarboxyl porphyrin-total:	*8.0*	*0.6*	"	"
Pentacarboxyl porphyrin I:	*5.8*	*0.1*	"	"
Pentacarboxyl porphyrin III:	*2.2*	*0.6*	"	"
Coproporphyrin-total:	*14.4*	*59.5*	"	"
Coproporphyrin I:	*6.4*	*12.3*	"	"
Coproporphyrin III:	*8.0*	*47.2*	"	"
Coproporphyrin III/I:	*1.2*	***3.8***	Ratio	<2.5
Isocoproporphyrin(s):	***57.5***	*1.2*	% of total p'yrins	See comments
Isocoproporphyrin/coproporphyrin:	***2.1***	*0.02*	Ratio	<0.1
Total di- & tricarboxylated porphyrins	*8.5*	*38.6*	% of total p'yrins	See comments
Protoporphyrin	*8.5*	*10.1*	"	"
Other di- & tricarboxylated porphyrins	*0*	*28.5*	"	"

Poster 28

04135 EVALUATING THE IMPACT OF A FAMILY CAMP FOR ERYTHROPOIETIC PROTOPORPHYRIA (EPP) AND OTHER RARE SUN DISORDERS

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Pediatric rare disorders are known to be isolating for affected individuals and family members. Sun disorders in particular have significant impacts on quality of life as they limit 'normal' activities and are difficult to navigate in childhood. Family camps for common and rare conditions can increase children's self-esteem, emotional functioning, and socialization, as well as build community. However, camps for rare sun disorders are not consistently available. Two patient advocacy groups, Shadow Jumpers and the United Porphyrias Association, established a camp weekend for 20 families. We assessed the experiences of attendees and potential psychosocial benefits of the camp session. Pre- and post-camp anonymous online surveys were sent to the primary adult contact (parent), the primary camper (child with a sun disorder), and any unaffected siblings. A post-camp survey only was also sent to volunteers. Data was analyzed descriptively, and using content and codebook thematic analysis for open ended questions. All 20 parents and primary campers completed the pre-camp survey, as well as 12 unaffected siblings. Post-camp surveys were completed by 17 parents, 9 primary campers, 10 unaffected siblings, and 26 volunteers. Preliminary results are presented from the parent and primary camper surveys. 84% (16/19) of primary campers had a diagnosis of EPP, and the remainder had congenital erythropoietic porphyria, xeroderma pigmentosum, and solar urticaria. The majority (76%) had never attended a family camp for sun disorders before, and were hoping to participate in activities that are generally difficult for them to do (82%). Parents' camp expectations included hoping to build connections with other parents (community), having their affected child feel less isolated (realizing they are not alone, have fun doing things they normally could not), and learning from other parents how to manage their child's condition. Post-camp, 88% of parents reported they made new friends at camp, and 76% thought their child with a sun disorder made new friends. All parents reported feeling understood as a key theme about what they enjoyed most during camp, and their affected child was able to do 'normal' activities. Parents also reported benefits to unaffected children, including not feeling left out and enjoying family time together. All parents reported that attending camp improved their mental health, in many cases significantly, and that they observed improvements in their affected child's mental health, including decreased isolation, anger, and self-consciousness. 76% (7/9) of affected children reported making new friends. 100% of attendees reported enjoying the camp activities and wanted the session to be longer, as well as wanted to attend future camp sessions. These preliminary results show the benefits of a dedicated sun disorders family camp to coping and socialization of parents and affected children.

Poster 29

04166 UNDERSTANDING VARIEGATE PORPHYRIA IN AN HIV PATIENT: A DETAILED CASE STUDY

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Variegate Porphyria (VP) is a rare metabolic disorder characterized by deficient activity of the protoporphyrinogen oxidase (PPOX) enzyme, leading to the accumulation of neurotoxic porphyrin precursors. Managing VP becomes increasingly challenging in patients with coexisting conditions, such as HIV, due to potential drug interactions. Here, we present a comprehensive case study of a 32 years old HIV-positive female, who exhibited multiple neurological and psychiatric symptoms, initially interpreted as secondary to an infectious condition. Recurrent seizures, acute psychotic episodes, and polyneuropathy marked the patient´s clinical course. Magnetic resonance imaging revealed characteristic findings suggestive of vasogenic edema, prompting suspicion of autoimmune encephalitis. Despite initial treatment attempts with immunomodulatory therapy, the patient´s condition continued to deteriorate, culminating in episodes of sepsis. Further investigation revealed the underlying diagnosis of VP. Biochemical analysis consistently showed elevated levels of aminolevulinic acid (ALA), porphobilinogen (PBG), and total urinary porphyrins (TUP). Additionally, the chromatographic profile of fecal porphyrins and the plasma porphyrin index (PPI) at l: 626nm supported the diagnosis of VP. Genetic analysis identified a pathogenic mutation in the *PPOX* gene (NM_001365398.1):c.428A>T, further confirming the diagnosis of VP. This mutation, while not previously reported in ClinVar or HGMD, has been documented in various publications and databases, emphasizing its significance in porphyria pathogenesis. Biochemical data correlated with clinical symptoms, showing a notable decrease in ALA, PBG, and TUP levels following hemin therapy. However, a few months later, she experienced two more attacks and received a second and third successful course of hemin. Although the patient was clinically stable, her ALA and PBG levels rose once again. Consequently, Tenofovir, a possible porphyrinogenic agent used in HIV management, was discontinued, coinciding with a marked improvement in her condition. This emphasizes the importance of medication review and the consideration of potential drug interactions in porphyria management. In conclusion, this case highlights the intricate interplay between genetic predisposition, environmental factors, and comorbidities in the manifestation and management of VP. Genetic testing, coupled with biochemical analysis, facilitates accurate diagnosis and customized treatment strategies, optimizing outcomes for patients facing the complex junction of VP and HIV.

Poster 30

04165 MANAGEMENT OF HEREDITARY COPROPORPHYRIA: A CASE REPORT OF A NEW PATHOGENIC VARIANT, HIGHLIGHTING THE SIGNIFICANCE OF HEMIN THERAPY AND MAINTENANCE TREATMENT COMPLIANCE

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Hereditary Coproporphyria (HCP) is an uncommon autosomal dominant disorder characterized by neurological and/or dermatological symptoms resulting from mutations in the *CPOX* gene. Successful management depends on precise diagnosis, biochemical control, and treatment adherence. Here we report the clinical course of a 39 years old male finally diagnosed with HCP, emphasizing the pivotal role of Hemin therapy and the maintenance treatment. The patient, afflicted by a history of urolithiasis and notable familial medical antecedents, initially manifested with abdominal distress needing opioid analgesia. Subsequent presentation with generalized tonic clonic seizures and neurological deterioration prompted extensive diagnostic scrutiny, including neuroimaging and biochemical assays, initially suggestive of acute intermittent porphyria (AIP). A key diagnostic indicator was the presence of dark urine. The laboratory results showed elevated levels of urinary aminolevulinic acid (ALA), porphobilinogen (PBG), total urinary porphyrins and total fecal porphyrins, both with a preponderance of coproporphyrin. Genetic analysis identified a novel pathogenetic variant (c.200_204del p.(Thr67LysfsTer36)) in the *CPOX* gene (NM_000097.7; LRG_1077), confirming HCP. Although the identified variant has not been previously reported, it presents criteria supporting evidence of pathogenicity. It is a null variant, absent from controls in public databases and showing co-segregation with disease in two affected family members. Administration of hemin therapy elicited notable clinical progress, accompanied by a decrease in urinary ALA and PBG levels. However, recurrent symptoms correlated with inadequate adherence to prescribed folic acid, vitamin B, and glucose. Longitudinal data illustrated fluctuating urinary porphyrin and PBG levels, strongly associated with treatment adherence. This case highlights the significance of hemin therapy in managing acute HCP episodes and stresses the crucial role of patient adherence to therapeutic protocols. Regular biochemical surveillance and patient education are imperative in preventing symptoms recurrence and enhancing quality of life. Biochemical monitoring is important to evaluate hemin therapy's efficacy in acute management and the imperative of sustained maintenance therapy for symptomatology control. Additionally, genetic diagnosis is essential in familial screening and counseling, while the identification of a novel mutation highlights the ongoing importance of genetic research in elucidating the pathogenesis of HCP.

Poster 31

04084 A CHALLENGING DIAGNOSIS FOR A POTENTIALLY FATAL DISEASE: 2 YEARS OF PORTUGUESE EXPERIENCE IN BIOCHEMICAL AND MOLECULAR DIAGNOSIS OF PORPHYRIAS

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Heme, like chlorophyll, is a primordial molecule and one of the basic pigments of life. Disorders in the normal heme synthesis can cause human diseases, including certain anemias and porphyrias. The porphyrias are a group of eight rare diseases caused by inherited defects, each resulting from a defect in a different enzymatic step of the heme biosynthesis. These disorders are multisystemic, with variable symptoms, and represent a major burden for patients and families because of the unusual course of the disease, with disabling chronic symptoms scattered with life-threatening acute attacks. Acute porphyrias are often misdiagnosed because of their multiform clinical manifestations, which may mimic other (and more common) diseases. This under-recognized disease also reflects a lack of medical and disease awareness, as well as a lack of biochemical guidelines and laboratory methods for diagnosis. As clinical features alone are not specific enough to confirm the diagnosis of acute porphyria or to distinguish between the different forms of acute porphyria, knowledge and correct interpretation of the appropriate tests are essential for accurate diagnosis and subsequent management of the disease. Delayed diagnosis and inappropriate treatment of acute porphyrias can be fatal.

In Portugal, porphyrias are underdiagnosed. In 2017, the National Health Institute Dr Ricardo Jorge (INSA) started to implement the biochemical diagnosis of porphyrias, and since 2023 almost complete biochemical and molecular characterization of porphyrias has been available. INSA is now a reference laboratory for biochemical and molecular characterization of porphyria but it took a lot of hard work to convince the medical community that porphyrias existed and that it was 'easy' to make a porphyria diagnosis, mostly a biochemical one if the right specimens were collected. So, with some porphyria awareness campaigns, medical meetings, workshops, and leaflets, the medical community was awakened to these interesting diseases.

In 2023, a multidisciplinary panel elaborated a consensus paper to consolidate this awareness of Porphyria, aiming to provide guidance for an efficient and timely diagnosis of acute porphyrias and evidence-based recommendations for treatment and monitoring patients and their families in Portugal. ('Portuguese Consensus on Acute Porphyrias: Diagnosis, Treatment, Monitoring and Patient Referral- Acta Med Port 2023 Nov;36 (11):753–764').

So, briefly, in 2022, of the 24 samples for porphyria request, we characterized 4 patients with porphyria. In 2023, of the 69 requests for porphyria, we characterized 12 patients with porphyria from the biochemical and molecular point of view. Last year, the National Authority of Medicines and Health Products, I.P. (INFARMED) approved the ribonucleic acid interference (RNAi) therapy (givosiran; GIVLAARI®, Alnylam Pharmaceuticals, Cambridge, MA, USA).

Porphyria exists, we just have to look for it!

Poster 32

04139 ACQUIRED CONGENITAL ERYTHROPOIETIC PORPHYRIA SECONDARY TO TREATMENT FOR HAEMATOLOGICAL MALIGNANCY

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Congenital erythropoietic porphyria (CEP) is a rare autosomal recessive disease caused by a mutation of *UROS* gene in chromosome 10 leading to deficiency of cytosolic enzyme uroporphyrinogen III synthase which converts hydroxymethylbilane into uroporphyrinogen III. The reduced enzyme activity results in the disorder of haem biosynthesis in which hydroxymethylbilane spontaneously condenses into uroporphyrinogen I which accumulates in bones, erythrocytes, skin, and teeth (erythrodontia). Onset typically occurs at birth or early infancy. The porphyrin deposition in CEP is primarily characterised by severe cutaneous photosensitivity whereby exposure to ultraviolet light induces blistering and lesion formation leading to significant scarring and disfigurement of sun-exposed sites.

A 76-year-old female presented with painful blisters, increased facial hair growth and dark urine 7–10 days following an erythropoietin infusion for 5q deletion myelodysplastic syndrome. Physical examination showed large fluid filled blisters on her hands, wrists, and lower arms and lesions on the scalp. No further erythropoietin infusions were given, and her symptoms resolved after 4 months. The patient had no history of similar blistering or lesions in the past and no erythrodontia.

Plasma porphyrin scan showed a positive peak with maximum fluorescence at 618 nm. Urine porphyrin fractionation showed markedly elevated uroporphyrin of 1048.7 nmol/mmol (reference range 0 - 4.4) and coproporphyrin of 243.2 nmol/mmol (reference range 0 - 41.0) with a predominance of isomer I, and borderline raised 7-carboxyporphyrin of 35.4 nmol/mmol (reference range 0 - 2.2). Faecal analysis showed an increased total coproporphyrin of 124 nmol/g (reference range 0 – 46) with an elevated I:III isomer ratio. There was no significant increase in faecal 7-carboxylate porphyrin nor any evidence of isocoproporphyrins. Repeat urine porphyrin analysis 6 months later showed a similar pattern but with much lower levels of uroporphyrin (346.9 nmol/mmol) and coproporphyrin (70.4 nmol/mmol). The biochemical findings were consistent with CEP.

Only a small number of late-onset CEP, secondary to an underlying haematological malignancy, have been reported. The onset of symptoms in this patient was triggered by erythropoietin infusion stimulating haem biosynthesis. The increased rate of haem formation overwhelms the deficient enzyme, triggering the accumulation of porphyrins, photosensitivity and cutaneous symptoms.

Poster 33

04091 VERIFICATION AND IMPLEMENTATION OF CHROMSYSTEMS HPLC KIT FOR URINARY PORPHYRINS AT NORTH ESTONIA MEDICAL CENTRE

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10.1136/bmjgast-2024-ICPP.61

Background High-Performance Liquid Chromatography (HPLC) coupled with fluorescence detection has been the gold standard for the differential diagnosis of porphyria for nearly 40 years. Analysing porphyrins in urine is a robust way to identify most forms of porphyrias. In the age of looming In Vitro Diagnostics Regulation (IVDR), the development of in house HPLC methods remains for the most adept clinical chemistry laboratories. Fortunately, companies like Chromsystems are making IVDR kits for the analysis of porphyrins in urine by HPLC. The North Estonia Medical Centre laboratory has recently incorporated the aforementioned kit and tried to verify the manufacturers claims.

Materials and Methods Verification of the Chromsystems Porphyrins in Urine IVDR kit was performed on a Shimadzu LC-20A Prominence HPLC system equipped with an RF-20A fluorescence detector. All required and optional components of the kit were used including the analytical column, precolumn and the prefilter. Samples were separated into uroporphyrin, heptacarboxyporphyrin, hexacarboxyporphyrin, coproporphyrin I, coproporphyrin III and quantified using a calibrator and an internal standard. Precision (repeatability and within-laboratory precision) was assessed using internal quality controls (IQC) (n=14 for each analyte) and evaluated with Analysis of Variance (ANOVA) statistics against the manufacturers reported Coefficient of Variation (CV) and the target ranges of the IQC materials. Accuracy was established by participating in external quality assessment (EQA) scheme by Instand.

Results The ANOVA statistics showed that we were not able to achieve the same precision results with all parameters as the manufacturer of the kit. Chromsystems had results with a CV of 0.5–1.6% for repeatability and 1.5–2.4% for within-laboratory precision while our numbers were within a range of 0.5–13% and 7.8–17% respectively. However, the results were well within the target ranges of the control materials. Participation in the INSTAND EQA show that we were able to get similar results as others within our group as the average difference was 2.4%.

Conclusions Even though we did not achieve the same results as the manufacturer of the kit, our results were far from unacceptable. Discrepancy was likely due to using lyophilized urine control materials instead of freezing aliquots of a single sample. EQA results and patient cases prove that this kit is producing reliable results. Chromsystems has taken a good

step forward to provide a simple to implement method to separate and identify relevant porphyrins in urine. Unfortunately, kits for the analysis of different biological matrices for porphyrins are hard to come by, using only urine, as a diagnostic tool does not cover the entirety of porphyria diagnostics. To rule out all forms of porphyrias, laboratories must either forward a sample to a different laboratory or delve into the world of developing an in house method for either plasma, blood or stool.

Poster 34

04120 HAEMATOPOIETIC STEM CELL TRANSPLANT FOR SEVERE 'DOUBLY HOMOZYGOUS' ERYTHROPOIETIC PROTOPORPHYRIA: EARLY OUTCOME

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A boy experienced episodes of photosensitivity with rash and swelling on sun exposed sites from 6-months old. A diagnosis of EPP was made when he was 2-years old following monochromator photo-testing showing marked 7-hour sensitivity at 400±27nm [half maximum band width] nm and 430 ± 27 nm and biochemical testing showing positive porphyrin plasma scan, raised free blood protoporphyrin (99% metal-free) and highly elevated total erythrocyte porphyrins (146.7µmol/L, normal <1.7). Unusually in EPP, he also showed mildly increased urine porphyrins.

Genotyping showed homozygosity for 2 different variants in the ferrochelatase gene. The patient is homozygous for the likely pathogenic variant FECH c.502C>T, p.(Pro168Ser) and homozygous for the low expression variant c.315–48T>C. Having both mutations and such high levels of porphyrins present a high risk of phototoxicity and likely also present a high risk of serious liver disease. A younger sister, initially biochemically diagnosed on cord blood, has the same mutations alongside comparable porphyrin biochemistry. Their parents and two siblings are heterozygous carriers of both variants.

His mother reported a history of her mother's cousin (her second cousin, once removed) dying of liver disease aged 9, and EPP is on his death certificate. Another 'cousin' died at age 3 years old, probably of the same disease.

Liver transplant has been used to treat EPP severe liver disease but is not curative as recurrence of liver disease occurs when the bone marrow continues to produce excess protoporphyrin. Additionally, liver function can deteriorate acutely making patients poor candidates for transplant. For this reason, Haematopoietic Stem Cell Transplant (HSCT) may be recommended in patients who have undergone a liver transplant or for those considered to be at higher risk of liver failure, to remove the primary source of the excess protoporphyrin.

After multi-national discussion this boy had an unrelated donor HSCT in early 2024 after intensive conditioning. He had mild liver veno-occlusive disease post-transplant but is doing well now. Total erythrocyte porphyrin levels have gradually reduced with time following his transplant and are now well within the normal range. The proportion of metal-free protoporphyrin has also decreased to normal levels and, following an initial increase post-transplant, his total urine porphyrins have now also decreased to normal levels. There has also been marked improvement in repeat photo-testing and he has been able to gradually reduce precautions against painful cutaneous phototoxicity, such as wearing gloves all the time. His younger sister, who carries the same severe variant of EPP and is therefore also at risk of severe protoporphyria liver disease, is now being 'worked up' for HSCT. To our knowledge, this is the first case of HSCT in EPP in Scotland.

The input from colleagues throughout IPNET is gratefully acknowledged in the management of this case

Poster 35

04187 THE GENETIC LANDSCAPE OF PORPHYRIA IN IRELAND

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The Porphyria Laboratory in the Biochemistry Department, St James's Hospital, Dublin, has operated as a national service for porphyria in Ireland for over 40 years. During this time a comprehensive database integrating genetic, biochemical, and clinical data on more than 100 Irish kindreds affected by porphyria has been developed. This unique resource has been curated to facilitate the analysis of the genetic landscape of a range of porphyrias in Ireland. This analysis identified 87 families with a biochemically confirmed porphyria phenotype, among whom 74% had at least one member with a confirmed genetic diagnosis through Sanger sequencing-based variant. The primary presenting phenotypes included Acute Intermittent Porphyria (AIP, 27%), Erythropoietic Protoporphyria (EPP, 27%), Variegate Porphyria (VP, 20%), familial Porphyria Cutanea Tarda (fPCT, 11%), and Hereditary Coproporphyria (HCP, 10%). Correspondingly, the majority of genetic variants were found in the *HMBS*, *FECH*, *PPOX*, *UROD* and *CPOX* genes, with additional novel rare variants identified in *ALAS1 and UROS*. To aid in annotating and predicting the pathogenicity of identified variants, an in-house genetic reference database, PorphyriaDB, built on a cloud-native publicly-facing infrastructure (PorphyriaDB.com) has also been developed.

The findings highlight a heterogeneous genetic landscape of both acute and non-acute Porphyrias in Ireland, including the rare incidence of conditions such as XLP and CEP. Overall, an integrated molecular diagnostic service, underpinned by accurate variant annotation and interpretation, is critical in ensuring that genetic susceptibility to porphyrias is appropriately identified and monitored in affected families accordingly.

Poster 36

04184 'CASSANDRA CURSE' OR A MODERN 'SISYPHUS BURDEN'? RECURRENT ATTACKS IN A COHORT OF BRAZILIAN PATIENTS WITH ACUTE HEPATIC PORPHYRIAS

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10.1136/bmjgast-2024-ICPP.64

Background Acute Hepatic Porphyrias (AHP) are mostly autosomal dominant inborn metabolic errors of one of the enzymes involved in the heme biosynthetic pathway. Clinical manifestations in acute attacks comprise abdominal pain, autonomic features, progressive peripheral neuropathy, PRESS-like syndrome, hyponatremia, hypertension, psychiatric features, encephalopathy and coma. Nevertheless, a subset of patients can experience recurrent acute attacks that can be not only life-threating, but also chronically debilitating.
Methods Retrospective data from patient records and clinical questionnaires with patients with acute porphyrias followed in a reference center in Brazil
Results 24 patients (20 females and four males) were enrolled. Media age of symptons onset was 22 years (range: 12–47 years). All patients reported recurrent porphyria related symptoms, such as pain, neurological and/or psychiatric disorders, nevertheless other systemic complications as hypertension and chronic kidney disease were seen in 10 patients. All patient – but one - had high levels of delta-aminolevulinic acid and porphobilinogen measured in 24 hours urine collection. 10 out of 20 female patients were treated with induced menopause lasting 1–2 years, and 4/27 received the treatment of hematin All patients had ate least one acute attack in t three months. The median frequency of acute attacks in the last year was 3 times (0–12 times), and the duration of every attack was 8 days (4–20 days). Analgesic dependency to opioid was a problem in 12 patients. Heme therapy was initiated in all patients with remission of the symptoms in most of the patients for more than 6 months in its first use; recurrent attacks followed by repeated heme injections seemed to alleviate symptoms for a shorter period of time. Orthotopic liver transplant was performed in three patients with recurrent attacks (one of the patients passed away one month after liver transplant due to fulminant heart attack, apparently not related to porphyria).
Conclusions Our cohort of patients showed frequent recurrent attacks of acute porphyria (>3 per year) requiring in most of them intravenous heme therapy. Although for patients with recurrent attacks prophylactic heme infusions may be benefic in remitting the symptoms, a subset of patients showed less response to this therapy overtime. Not only facing a debilitating disease state, but patients with recurrent attacks can also bear a significant burden on health care systems. Acute porphyria patients who suffer from recurrent attacks also report a low quality of life (QoL) and a negative impact on several aspects of everyday life, such as unemployment, personal relationships and long-term disability.

Poster 37

04097 WHOLE EXOME DIAGNOSIS FOR CLARIFIES THE CONCOMITANT PATHOLOGIES OF A PATIENT WITH PORPHYRIA

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10.1136/bmjgast-2024-ICPP.65

Background She is born hypotonic and maintains muscle weakness and digestive problems with vomiting, recurrent anemia, photosensitivity, fatigue, drowsiness and respiratory failure associated with outbreaks suffering numerous hospital admissions; with age appear muscular tonic problems and osteopenia (resistant to treatment). She was clinically and biochemically diagnosed of Porphyria without having found the causal gene after various targeted studies.
Material and Methods Starting from a blood sample in EDTA, the DNA was extracted by automatic thecnique based on magnetic beads. The human whole exome was performed by massive sequencing with 'Twist Human Core Exome' that amplifies 21,528 genes; using Illumuna's NextSeq 2000™ Sequencing System Platform.
Results Three heterozygous variants were found in relation to their pluripathological involvement: a novel *PPOX* gene variant (NM_001122764) c.604del; p.Leu202Cysfs*32, (Not described in ClinVar nor in dbSNP, with ACMG criteria PVS1,PM2 it is probably pathogenic). Another in gene *LGR4* (NM_018490) c.1087G>T; p.Gly363Cys, described as pathogenic in ClinVar rs117543292. And in gene *MYO1H* (NM_001101421) c.242 +1G>A, rs559770546 (Not described in ClinVar, with ACMG criteria PVS1, PM2 it is probably pathogenic).
Conclusions The *PPOX* gene explains Variegata Porphyria by dominant inheritance; The *LGR4* gene explains the decreased in bone mineral density with dominant inheritance and the *MYO1H* gene would explain its respiratory failure, although recessive inheritance. It is not ruled out that in situations of metabolic stress the penetrance may be partial even in heterozygosity. Concluding that each patient is unique and their different symptoms become clearer as more of their genome is studied.

Poster 38

04193 THE INCIDANCE OF TYPES OF PORPHYRIA AND THEIR SYMPTOMS IN TURKEY

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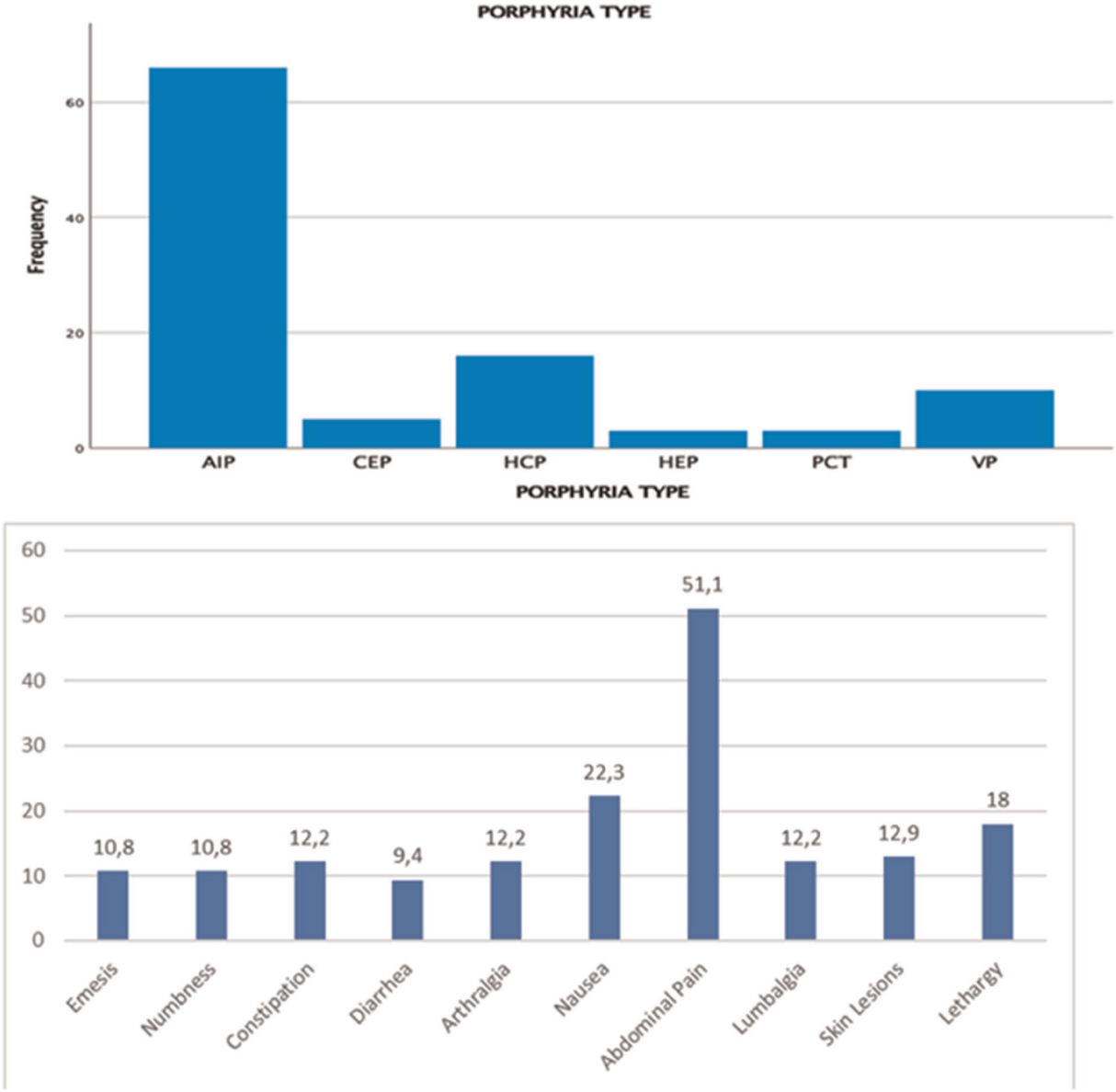
Aim Porphyria is the accumulation of substrate in nervous system, gastrointestinal system, kidney, liver, and skin. It is a uncommon illness that is seen when there is absence or insufficient action of 8 enzymes in making heme molecule. The

purpose of this research is to assess the types and symptoms incidence of porphyria patients in Turkey.

Method There are 139 patients who are followed by our hospital's internal medicine department, and outpatients. Some patients are not diagnosed yet but they have family history and symptoms which cause to suspect about Porphyria. 103 of 139 patient's type of Porphyria is known and genetic test is done to 61 of them. 53 patients are men and 86 are women. 139 patients average age is 35.4 and average body mass index is 22.6. Mutation seen in 81.9% patients who took genetic test. Obtained informations taken from our Hospital's Pusula system and examined in SPSS.

Results There are 103 patients whose type of porphyria are known. It is seen that 64% of patients are AIP, 2.9% of patients are PCT, 4.8% of patients are CEP, 15.5% patients are HCP, 9.7% patients are VP. In our research, the most typical type of porphyria is determined as AIP with the percentage of 64. When we searched for the patients informations on the system Pusula, we found that 75% of patients have symptoms. Observed as most common symptoms are; 51.1% abdominal pain, 22.3% vomiting, 18% lethargy, 12.9% skin lesions, 12.2% constipation, 12.2% arthralgia, 12.2% lumbalgia, 10.8% emesis, 10.8% paresthesia and 9.4% diarrhea.

Conclusion Our research indicates that acute intermittent porphyria (AIP) is the most common type. Confirmed that abdominal pain is the most typical accompanying symptom of a prophyria patient. The most commonly seen symptoms of patients are not specific. Therefore the conclusion is, there should be more research done for the rare disease porphyria which can't be noticed easily.



Abstract 04193 Figure 1

Poster 40

04195 CONCOMITANT AIP AND SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) – COINCIDENCE OR CLINICAL ASSOCIATION?

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A 38 year old HIV negative man of mixed ancestry, with a history of smoking, alcohol use, and previously treated pulmonary tuberculosis, presented with severe, constant abdominal pain, arthralgia, swollen hands and skin lesions. Clinically he had marked abdominal pain but no peritonism with discoid type lesions on the scalp as well as auricular ulcers. Raynaud's phenomenon with digital infarcts of his fingers and toes and a vasculitic rash on his nail beds, palms, soles, and legs, were noted. BP was 155/95 with a tachycardia of 113 bpm. Lower limb weakness was evident with 4/5 globally reduced power demonstrated. Knee and ankle reflexes were reduced. No sensory fall-out was evident. Serum sodium was 128 mmol/L. A diagnosis of a possible acute porphyria, likely variegate, was made. However, the Raynaud's phenomena, arthralgia, vasculitic rash and digital infarcts were atypical. A Watson-Schwartz test was positive. Urinary ALA and PBG were 68 (upper limit of 1.6) and 79 umol/mmol creatinine (upper limit of 4.5), respectively. Porphyrin plasma fluorescence peaked at 619nm (excitation at 405nm). An *R59W PPOX* mutation (associated with the South African VP founder effect) was negative. AIP was thus probable, the exact *HMBS* gene mutation as yet, not identified. Haem arginate was given for 6 days. An autoimmune screen was positive for an antinuclear factor, ANF 1:1280; elevated double stranded DNA 149IU/ml (normal <10IU/ml); elevated total IgG 30.8g/L (normal <16g/L) and low complement C3 and C4. Proteinuria was present (0.8g/day) and serum creatinine normal (65 umol/L). Renal biopsy demonstrated ISN class II Lupus Nephritis. Skin biopsy of the vasculitic lesions confirmed small vessel vasculitis. An SLE diagnosis was made from positive criteria present. Prednisone, Azathioprine and Chloroquine were initiated. Urinary porphyrin activity and acute porphyria symptoms were monitored for. He was discharged a month after admission. Coexisting acute porphyria and SLE is rare. A handful of cases are reported in the literature with most reported cases occurring in women. The putative mechanisms for concomitance invariably are medications used in SLE. However, in our patient, the SLE therapy followed the porphyria presentation, there was a history of alcohol use as well as previous TB treatment with no clinical expression of porphyria. This may suggest an evocative effect of the SLE. In established SLE, triggers of SLE flares often include infections, often viral, physiological, emotional or traumatic stress. How lupus could trigger acute porphyria is unclear, however a 'perfect storm' of multiple factors – infection, marked inflammation, carbohydrate depletion may all coalesce to trigger an acute attack. The issue of whether SLE was potentiated by acute porphyria, is a moot point. In summary, we present a case of a man with a rare co-existing presentation of SLE and acute porphyria. The intertwining mechanisms remain unclear.

Poster 41

04125 DETECTION AND QUANTIFICATION OF LABILE INTRAVASCULAR HEME IN THE PRESENCE OF HEMOGLOBIN

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Heme, iron protoporphyrin IX, is one of the most abundant molecules of aerobic life. As a prosthetic group of proteins it is highly important for numerous biological reactions and processes, such as oxygen transport, electron transfer, and catalysis. Heme also has modulating properties that go beyond the regulation of its own biosynthesis. In addition, serious conditions are provoked in case of malfunctioning endogenous heme production. Hemolytic events caused by various disorders (e.g., sickle cell disease), infections (e.g., malaria) or injuries and trauma lead to an accumulation of intravascular labile heme, whereas the different types of porphyrias are characterized by a lack of heme. Porphyria is the umbrella term for a group of hereditary metabolic disorders that involve one of the eight enzymatic steps of the heme biosynthesis pathway. Specific for each impaired enzyme is the accumulation of certain heme precursors in the blood, urine or stool, accompanied by various symptoms. As a possible treatment strategy, the substitution of heme is utilized in acute porphyria incidences or prophylactically. The accumulation of heme precursors is stopped e.g. by end product inhibition of 5-aminolevulinic acid synthase and at the same time restores the essential heme pool. Monitoring the administered heme and therefore, an individualized treatment can be targeted for advanced therapy. Until recently there was no quantification method available, which distinguished between labile heme and protein-bound heme and hence could help to monitor labile heme after administration. To close this gap of knowledge, we conducted a study to evaluate the validity and applicability of methods for quantification of heme levels in the presence of hemoglobin as well as to assess the differentiation of hemoglobin-bound heme and labile heme. In total, 10 direct and indirect primarily spectroscopic methods were examined regarding their linearity, accuracy, and precision, as well as their ability to distinguish between hemoglobin-bound heme and labile heme. Thereupon, the different approaches have been used to quantify heme and Hb solutions as well as mixtures thereof. The determination of a broad concentration range, heme ~0.02–45 µM and hemoglobin ~0.002–17 µM, was possible using the investigated indirect and direct methods. Nevertheless, a clear distinction between hemoglobin-bound heme and labile heme applying only one method was, however, not feasible, suggesting the use of a combined approach. In consequence, a combination of two spectroscopic methods, one direct and one indirect, including a newly established equation was used to quantify the labile heme content in porcine plasma samples as well as human plasma samples in healthy and varying hemolytic states. In conclusion, our study can

accelerate porphyria treatment by aiding to monitor the administration of the proper heme dosage, improving the compatibility to and compliance of the patients.

Poster 42

04176 RETHINKING ACUTE INTERMITTENT PORPHYRIA NUTRITIONAL GUIDELINES: A NEW APPROACH PROPOSAL

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Introduction Upon receiving a diagnosis of AIP, patients are often advised by their healthcare providers to adopt a high-carbohydrate diet. This recommendation prompts many patients to seek further nutritional advice and guidance in major patient foundations. However, not all patients who access this information are at the same stage of the disease, nor do they present the same symptoms or ability to ingest and assimilate food.

Material and Methods With educational purposes in nutrition for AIP patients, it is proposed to divide the disease into three stages: acute (AS), intermediate (IS) and chronic (CS). Patients can classify themselves into one of these stages, and nutritional advice can be tailored to align with the stage of their disease. The most representative symptoms of these stages are:

- AS: severe vomiting, constipation, intense pain, and neurological symptoms.
- IS: patients begin to feel better but may experience an 'aura of crisis' episode with nausea, vomiting, and high fatigue.
- CS: patients have not had a porphyria crisis for a long period.

Results Development of a nutritional guideline aligned with AIP patients by symptomatic stage. For the AS, recommendations include an easily digestible, high-carbohydrate diet. Cold or room temperature meals are preferable to prevent strong odours from triggering nausea. Patients should be aware that sensations of hunger and satiety can be distorted during this stage. It is advised to eat small quantities regularly, even if appetite is reduced, and a gradual increase in portion sizes is recommended. Dehydration and adherence to hydration guidelines, as well as recognition of symptoms of hyponatremia, are highlighted in this part of the guideline. In the IS nutritional guidance focuses on understanding how various factors, such as medications, hormones, physical and emotional stress, can impact glucose regulation in AIP patients. Patients should be educated about recognizing their body's signals indicating the need for nourishment (that may include among others symptoms such as low energy, elevated resting heart rate, mental fog, and difficulty concentrating). Education on different types of carbohydrates and their combination with other macronutrients and their impact on glucose and insulin levels in AIP patients is crucial. Understanding insulin resistance and its main symptoms is very important too. For the CS, it is advised to consume complex carbohydrates, which provide a sustained release of glucose, as well as a high variety of fruits and vegetables, legumes, eggs, lean proteins, and healthy fats into their diet.

Conclusion This new nutritional guideline approach could align better with patients' symptoms implementing real solutions for every stage of the disease and emphasizes the importance of continuous education for both patients and healthcare providers in the management of AIP.

Poster 43

04196 PREVALENCE OF ACUTE HEPATIC PORPHYRIA IN THE FRENCH POPULATION: FIRST RESULTS OF THE PREVPHA PROSPECTIVE STUDY

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Introduction Acute hepatic porphyria (AHP) comprises a group of rare genetic diseases caused by mutations in genes encoding enzymes involved in heme biosynthesis. AHP is characterized by acute neurovisceral crises including violent abdominal pain, dysautonomia, central and peripheral neurological symptoms. This disease remains underdiagnosed. Identifying AHP is therefore a major challenge for early and appropriate care of patients and their families.

The primary objective was to determine the prevalence of patients with AHP from different hospital departments and referred to an internist referent for a suggestive clinical picture with a first negative etiological assessment. **The secondary objective** was to define and characterize the profile of patients according to their initial symptomatology.

Patients et methods This was an observational, multicenter, and ambispective study. 160 patients from 13 French hospital centers were included in the study between 09/2021 and 12/2023. The diagnosis of AHP was based on the urinary dosage of the neurotoxic precursors of heme: delta-aminolevulinic acid (ALA) and porphobilinogen (PBG). A patient was diagnosed with AHP (AHP+) if: ALA $\geq$ 3 µmol/mmol of creatinine and/or PBG $\geq$ 1 µmol/mmol of creatinine. In all other cases, the patient was considered not to suffer from AHP (AHP-).

Results Among the 152 patients included in the analyses, 9 (5.9%) patients were diagnosed AHP+. All were female, mean age was 34.3 years and they were referred by a neurologist (2), an internist (2), an emergency physician (1), a gastroenterologist (1), a gynecologist (1) or another physician (1). One third of AHP+ patients had a family history of AHP. The factors triggering attacks were stress (6), menstrual cycle (4), medications (4), infections (1), alcohol or tobacco consumption (1+1). The mean delay between inclusion and

first severe, diffuse and apyretic abdominal pain was 28.4 months. Eight patients had dysautonomia (nausea, vomiting, constipation and/or tachycardia), 5 patients had peripheral neurological symptoms and 6 patients had central neurological symptoms.

Conclusion This study found a 5.9% prevalence of AHP in patients with suggestive clinical picture in France. It confirms the main symptoms of AHP including severe, diffuse abdominal pain over several days, without fever, and possibly associated with neurological symptoms.

Poster 44

04123 EARLY, QUICK AND ACCURATE IDENTIFICATION OF ACUTE PORPHYRIAS IN HEALTH CENTERS: PBG REAGENT

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10.1136/bmjgast-2024-ICPP.71

Clinical features of the acute attack in Acute Porphyrias include neuroabdominal and neurological psychiatric symptomatology. Due to these symptoms are commonly observed in other pathologies, Porphyrias are usually underdiagnosed. They are considered rare diseases with a global prevalence around 0,5–10 per 100000 people worldwide. Acute attacks in latent individuals can be induced by a variety of environmental factors such as medications, stress, ethanol uptake, low carbohydrates diet, nutrition and hormones. Biochemical characterization of acute attacks is the detection of elevated values of urinary aminolevulinic acid and porphobilinogen (PBG). PBG determination is the first approach when an Acute Porphyria is suspected; a positive result leads to an early identification of the disease. The aim was to provide a reagent for PBG that could be available in Argentinean Health Centers in the event of a probable case of Acute Porphyria. For this purpose, an agreement was signed between CONICET and Tuteur (CONVE-2022–102083786-APN-GVT#CO). CIPYP (UBA-CONICET) carried out the assessment about the preparation of the reagent to Farmacoop, a national laboratory who produced and packaged the reagent; we also performed quality and stability analyses. Tuteur take care of the free distribution of the reagent. Experimental design involved stability studies at different store times and temperatures in the final container of PBG reagent (light protected vial) (4°C for one year; room temperature for 30 days; 45°C for one week) evaluating colour, turbidity and pH changes. Moreover, PBG determination was performed in urine of controls and Acute Porphyria individuals during all the different experimental conditions. Results indicated that the reagent is stable at 4°C at least 6 months protected from light. If storing at room temperature is necessary, it must be no more than 4 days. A colour scale was stablished for qualitative results: negative (yellow) or positive (mild to deep pink). We also advised on the design of the packaging and the corresponding data sheet. During 2023–2024 Tuteur distributed 188 PBG reagents (123 in Buenos Aires and 65 in the rest of the country) to 41 public and 36 private Health Centers. Consequently, 5 new patients came to CIPYP for diagnosis of Porphyria. In conclusion, results were evaluated considering country distribution and its contribution to the increase of Acute Porphyria diagnosis. Respect to the total of test distributed, 0.3% became new diagnosis during this first year. Moreover, an increase of inquiries about the disease happened at the time of reagent delivery. We consider that the reagent is a fundamental strategy for Porphyrias diffusion and a relevant tool for Medical Doctors to do a possible pre-diagnosis and without delay contact CIPYP to achieve differential diagnosis, confirming Porphyria crisis to apply the specific treatment.

Poster 45

04151 ERYTHROPOIETIC PROTOPORPHYRIA: EXPLAINING THE NORTH-SOUTH GAP

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10.1136/bmjgast-2024-ICPP.72

Erythropoietic protoporphyria (EPP) is a rare genetic disorder associated with mutations in the FECH gene. EPP is characterized by photosensitivity, resulting in severe skin reactions upon exposure to sunlight. While this condition affects individuals worldwide, notable demographic differences have been observed between northern European countries and those in southern regions.

In northern countries, the prevalence and incidence of EPP tend to be higher (Norway $27.7/10^6$ and $0.36/10^6$; Switzerland $27/10^6$ and $0.35/10^6$; United Kingdom $25.4/10^6$ and 0.33 x 10^6 respectively) compared to southern countries (Spain $2.3/10^6$ and $0.03/10^6$; Italy $5.4/10^6$ and $0.07/10^6$). The factors that could explain this difference may be genetic: the frequency of mutations in the FECH gene in the north could be higher than in the south. Environmental conditions may also play a role: clinical expression could be reduced due to a 'hardening' phenomenon secondary to sun exposure, which makes it easier for patients to live with the disease without the need to seek attention from a healthcare provider.

We present a series of 37 patients diagnosed with EPP in the main two tertiary reference centers for porphyrias in Spain. Mean average age of symptom onset was 15 years with 51% making their debut in the first decade of life while 16% made their debut over 40 years. Mean age at diagnosis was 16 years and 4 months.

This study aims to present and compare sociodemographic and genetic data between a series of Spanish patients with data from Nordic European countries. Understanding these

demographic variations could be crucial for comprehension, effective management, and support for individuals living with EPP.

Poster 47

04140 DRUGS STIMULATING ERYTHROID COMPARTMENT CAN INDUCE HEPATIC DAMAGE IN ERYTHROPOIETIC PROTOPORPHYRIA

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10.1136/bmjgast-2024-ICPP.73

Erythropoietic ProtoPorphyria (EPP) is an autosomal recessive disorder caused by the deficiency of the ferrochelatase (FECH) enzyme resulting in the systemic accumulation of protoporphyrin IX (PPIX) in blood, erythrocytes and tissues. EPP is characterized by acute, painful and non-blistering phototoxicity on sun exposure and, in a small proportion of patients, by liver disease with the development of liver failure in 1–5% of cases.

Our clinical vignette describes the case of a 71-year old man who received a diagnosis of low risk myelodysplastic neoplasm with ring sideroblasts in 2018. Due to anemia, erythropoietin (EPO) 40000 U once a week was started. Four years later, he presented to gastroenterology unit because of jaundice, asthenia and nausea. Blood tests revealed an increase in hepatobiliary enzymes and an ultrasound diagnosis of liver cirrhosis was made. Investigating more deeply his past medical history, he reported cholelithiasis and photodermatosis, with painful erythema and edema since childhood, and therefore a form of chronic porphyria was suspected. Erythrocyte protoporphyrins (PP), predominantly metal-free PPIX, resulted markedly increased, spectrofluorimetric plasma scan showed an emission peak at 634 nm and molecular analysis of *FECH* gene revealed the presence of a pathogenetic variant (c.215dupT) trans to the hypomorphic allele (c.-252A>G, c.68–23C>T and c.315–48T>C), thus confirming the diagnosis of EPP.

During hospitalization, a further increase in serum transaminases, total and conjugated bilirubin and erythrocyte PPIX level concomitantly to EPO administration was observed. For this reason, EPO was interrupted and seven cycles plasma- and erythro-exchange were performed with improvement in liver enzymes and PP levels. Treatment with ursodeoxycholic acid was also promptly started as well as regular blood transfusions to reduce protoporphyrin production by suppressing erythropoiesis. Symptoms improved but, due to liver failure, the patient was transplanted. A year later, due to the worsening of the transfusion need, Luspatercept was started at 1 mg/kg/day every 3-week. Two doses were administered with a good response on Hb levels but, the exponential increase in PP levels (from 15 to 36.8 to 137.5 mg/gHb) and liver enzymes (ALT from 30 to 36 to 168 U/L and AST from 10 to 66 to 99U/L) prompted treatment cessation with subsequently normalization of serum markers.

The treatment with EPO has been already reported to be contraindicated in EPP. Luspatercept acts in the late-stage of erythropoiesis and, unlike EPO, that mainly stimulates the proliferation of erythroid compartment, it improves anemia enhancing erythroid differentiation. To the best of our knowledge, this is the first case of an EPP patient treated with Luspatercept and it suggests that not only EPO but also this drug, can induce exacerbations of EPP phenotype, even in a liver transplant patient.

Poster 48

04141 INVESTIGATION FOR PORPHYRIA IN DENMARK

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10.1136/bmjgast-2024-ICPP.74

Introduction The biochemical investigation for porphyria is performed only at one site in Denmark: The Department of Clinical Biochemistry, Odense University Hospital. This descriptive study investigated the number of requested porphyrin analyses from 2020 to 2023. The aim of the study was to elucidate whether Danish citizens are equally tested for porphyria based on geography. The generated knowledge will help us to locate areas, where porphyria may be underreported.

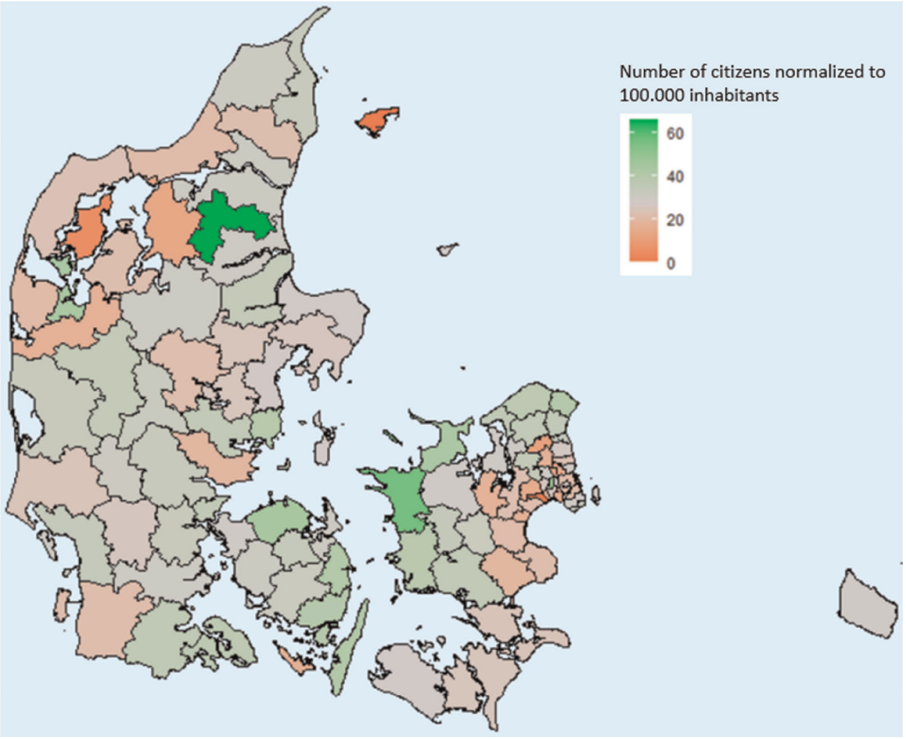
Method Data was collected for citizens having any biochemical porphyrin analysis requested from January 1st 2020 to December 31st 2023. Collected data: 'The unique civil registration number, living district (commune) and date of sampling'. If a citizen during the period had more than one commune registered, only the first commune was used. Exclusion criteria: 'Unknown commune, fictive civil registration numbers (e.g. foreign citizens) and citizens from Greenland or Faro islands. From the webside of the Danish Statistics, we collected the average number of citizens living in each commune (2020 to 2023).

Results A total of 1627 unique Danish citizens were included. The number of citizens was normalized to 100.000 inhabitants, and is illustrated on the map. No patients had a porphyrin analysis request in the following communes: Ishoej, Laesoe and Christiansoe (23,201; 1,777 and 90 citizens per commune, respectively).

Discussion/Conclusion There are areas in Denmark, where porphyrin analyses are not requested, and there is not an equal distribution for requested porphyrin analyses.

Some of the areas with low requests seem to resemble areas, where the number of doctors is low, but further studies needs to be performed to investigate this theory.

The map indicates that there are areas in Denmark, where more knowledge of porphyria could be beneficial. Web based educational initiatives should be consider; it is a simple/effective method to reach the remote geographical areas.



Abstract 04141 Figure 1

Poster 49

04163 **FUNCTIONAL CHARACTERIZATION OF NEW PATHOGENIC AND LEAD-POISONING PREDISPOSING VARIANTS IN ALA DEHYDRATASE PORPHYRIA (ADP)**

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Hepato-erythropoietic ALA dehydratase porphyria (ADP) is the rarest form of inherited porphyrias, with only eight cases reported worldwide. This condition exhibits significant molecular heterogeneity, as evidenced by the identification of fourteen pathogenic variants in the *ALAD* gene located on chromosome 9q34. Here, we present the case of three young patients, including a brother and a sister, experiencing early-onset clinical and biochemical symptoms of ADP.

Genetic analysis revealed three previously unreported variants in the gene. The two siblings inherited the variant c.440_441delinsTT in homozygosis. This variant resulted from two adjacent nucleotides substitutions at the same codon: the c.440G>T substitution, causing a mutated protein p.(Arg147Leu) and the c.441C>T, which does not affect the wild type protein p.(Arg147Arg) sequence. The simultaneous presence of both substitutions always results in the p.(Arg147Leu) mutated protein. The third patient exhibited compound heterozygosity for the c.839G>A (p.Gly280Glu) and c.724G>A (p.Val242Ile) variants.

The *in vivo* characterization of these previously unreported variants was performed using vector transfer by hydrodynamic tail vein injection-based procedures into hepatocytes of C57BL/6 mice. The expression of the c.440G>T variant showed approximately 5% of the wild-type enzyme activity. However, the protein with both c.440G>T and c.441C>T changes displayed no further decrease, confirming the pathogenetic role of the first substitution. Conversely, the c.724G>A (p.Val242Ile) variant alone exhibited substantial residual enzyme activity (60% of the wild-type) compared to the c.839G>A (p.Gly280Glu) variant, which showed minimal residual activity (2.7%). However, co-expression at a 50/50 ratio in mouse livers resulted in lower activity (~12%) than theoretically expected (~30%), suggesting a dominant effect

of the c.839G>A variant on the already hypomorphic c.724G>A allele.

Additionally, we report the molecular characterization of the *ALAD* gene in five adult patients presenting clinical and biochemical symptoms of acquired ADP porphyria. Four of five patients shared the rs1805313T>C common variant: one patient carried the variant alone in homozygosis, two of them carried also the less frequent rs8177800G>A variant, and one also presented both the rs1139488T>C and rs1805312G>C variants. The last patient was heterozygous for the rs1800435G>C variant alone. These results confirm the significant molecular heterogeneity of *ALAD* gene and suggest that several common variants, alone or in combination, could confer increased susceptibility to lead exposure. All these variants have been reported to modulate the accumulation and/or distribution of lead in the body through an unknown mechanism. The majority of these variants are located in introns or near to splicing junctions, suggesting a putative effect on *ALAD* mRNA processing. Further studies are needed to evaluate presence and activity of new *ALAD* isoforms.

Poster 51

04126 FATIGUE IN PATIENTS WITH PORPHYRIAS – FIRST DATA FROM THE GERMAN PORPHYRIA REGISTRY (POREGER)

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Background Porphyrias, as most rare diseases, are characterized by complexity and scarcity of knowledge, particularly symptom burden and quality of life. The German Porphyria Registry (PoReGer) was set up to close this gap nationally. Here we present the results of our first evaluation on patient reported outcome measures on Fatigue.

Methods PoReGer was founded in 2023 by four German centers with longstanding porphyria expertise. In a specified data matrix for three subgroups [acute (AP), chronic blistering cutaneous (CBC), acute non-blistering cutaneous (ANC)] data on demographics, symptoms, clinical course and history, follow-up assessments, therapies, and life circumstances are collected longitudinally, at least once a year. Ethics approval and patient´s informed consent were obtained. Enrollment into the registry started in August 2023. To evaluate fatigue the Fatigue-assessment-scale (FAS) questionnaire was used, categorizing patients in 3 different groups (no fatigue, substantial fatigue and extreme fatigue) depending on their answers to 10 Likert-scaled questions.

Results Until May 2024, 23 patients were included, 14 with APs (13 acute intermittent porphyrias, 1 variegate porphyria), 9 with CBCs (all Porphyria cutanea tarda) and 1 with an ANC. In APs median age at inclusion in registry was 40 years; while median age at diagnosis was 27 years. 13 (93%) were female and 6 (43%) reported comorbidities. Median (IQR) total score of the FAS questionnaire was 23 (20;36) in the AP group, with 5 (36%) patients in the category no fatigue, 4 patients (29%) with substantial fatigue and 4 patients (29%) with extreme fatigue. In CBCs median age at inclusion in registry was 64 years; while median age at diagnosis was 59 years. 7 (78%) were female and 7 (78%) reported comorbidities. In the CBC group 4 (44%) patients were categorized with no fatigue and 4 (44%) patients with substantial fatigue. [*More patients from all groups and also an analysis of the 'AP treated with Givosiran' subgroup are expected until September 2024*]

Conclusions This analysis showed fatigue being a relevant comorbidity in patients with different forms of porphyrias. Patients with APs seem to be affected more than patients with CBCs with a third of patients with AP reporting extreme fatigue. With more patients being included in the registry further longitudinal data on fatigue and influencing factors will be gained.

Poster 52

04143 A REAL-LIFE OVERVIEW OF DIET PATTERNS AND ACUTE HEPATIC PORPHYRIA

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Acute hepatic porphyrias (AHP) are rare metabolic diseases caused by enzyme defects along the heme biosynthesis pathway. In addition, in attacks the first and speed limiting enzyme ALAS1 is upregulated in liver cells. In patients with AHP, malnutrition with low caloric intake and moreover, some xenobiotics, such as herbs and spices added to meals, may induce hepatic ALAS1 transcription. Thus, diet may impact disease severity and quality of life in AHP. In this pilot study we focused on disease related dietary characteristics and body weight oscillations. Moreover, we report here on nutrition related triggers for porphyria attacks, body weight, stress-eating behaviour, and on how patients with AHP him-or herself perceive importance of diet in disease managing. In our Porphyria Centre a detailed questionnaire was applied to a cohort of 37 consecutive patients (30 females, 7 males, mean age of 45.4 years) with clinically and laboratory (urinary ALA and PBG, porphyrins) confirmed AHP. Notably, 13 of our patients reported specific foods such as garlic (24,3%), sauerkraut (10,8%) and alcohol (24, 3%), as triggers for attacks, and 31 modified their diet during an attack (avoid eating 30 or eating more foods rich in carbohydrates 10. Furthermore, 11, 18 and 8 of participants rated their diet as highly important, important, and not important, respectively. Additionally, 23 (62%) of patients paid attention to their diet also during latency phases. On average, patients gained 6.3 kilograms since the onset of the disease (mean of 50,6 months), with men gaining more weight (8.9 kilograms) compared to women (5.7 kilograms). Male patients exhibited a higher tendency to gain weight compared to female patients. Notably, 20 patients on Givlaari treatment for 24 months (range 3 to 66 months)

reported a lower average weight gain (4,1 kg) compared to those not on the medication (8.9 kg), indicating towards to a potential metabolic stabilizing effect of Givlaari. Stress, defined as a physical and emotional response to situations perceived as threatening or challenging (APA, 2024), was reported to influence eating behaviours, with 20 of patients eating less and 11 eating more, often increasing their intake of sweets and fast food. These stress-induced dietary changes may lead to an unbalanced diet. When less eating, the risk of triggering porphyria attacks is increased. A substantial proportion of patients identified specific foods as potential triggers for porphyria attacks. Most patients modified their diet during attacks. Surprisingly, weight gain was common among patients with AHP, with men more than women. Notably, patients on Givlaari treatment experienced less weight gain, suggesting potential metabolic benefits of that medication. Stress-induced changes in eating behaviour further underscore the importance of dietary management in AHP. These findings suggest that comprehensive dietary counselling should be an integral part of managing AHP.

Poster 53

04142 SLEEP AND STRESS IN PATIENTS WITH ACUTE INTERMITTENT PORPHYRIA

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Lifestyle factors, such as sleep and stress are suspected to be trigger for attacks in acute intermittent porphyria (AIP). Stress response is physiologically displayed along the Hypothalamic-pituitary-adrenocortical (HPA) axis. Hypothetically, stress may increase heme biosynthesis in liver cells, leading to accumulation of porphyrin precursors in acute porphyrias. Therefore, stress managing may be effectively in reducing the frequency and severity of acute attacks. Chronic stress can cause disturbed sleep with insomnia and poor sleep quality. In a vicious circle, a sleep disorder can - in turn – reduce individual capacity to limit HPA related stress reactions. Therefore, the bidirectional relationship between sleep and stress management could play a role in coping with the disease and improving quality of life. This study aimed to investigate sleep quality and stress levels in biochemically confirmed patients with AIP.

A total of 26 consecutive patients (mean age = 39 years; 17 women and 9 men) from the Chemnitz Porphyria Center were included. A subjective questionnaire was used, incorporating well-established instruments: the Pittsburgh Sleep Quality Index (PSQI), the Trier Inventory for Chronic Stress (TICS), the Stress Processing Scale (SVF 120), the Social Support Questionnaire (F-SoZu), and the Hospital Anxiety and Depression Scale – German Version (HADS-D).

Thirty-six percent of patients with AIP reported to sleep less than recommended (minimum: = six hours per night, Sleep Foundation, 2024). On average, patients fell asleep within 38 minutes (range = 10 to 110 minutes). Poor subjective sleep quality (measured by the PSQI) was strongly correlated with higher perceived stress levels ($r = .53$; $p = .005$). Significant correlations were also found between stress and job dissatisfaction ($r = .55$; $p = .004$), work overload ($r = .43$; $p = .029$), lack of social recognition ($r = .47$; $p = .015$), social isolation ($r = .57$; $p = .002$), and chronic worry ($r = .54$; $p = .004$). Sleep duration significantly influenced both subjective sleep quality and stress levels ($r = .77$; $p < .001$). Both male and female patients exhibited a similar pattern of stress impacting sleep quality. The correlation was slightly stronger for females ($r=0.534$) compared to males ($r=0.477$), but this difference was not statistically significant.

The findings support the hypothesis that stress significantly impacts sleep quality in patients with acute porphyria. This bidirectional relationship can create a feedback loop. Increased stress leading to poorer sleep. Thus, further elevating stress levels and potentially triggering acute porphyria attacks. The moderate correlation here observed, underscores the importance of managing both stress and sleep.

Poster 54

04145 PROFOUND HYPOTONIA IN A NEWBORN WITH BIALLELIC δ-AMINOLEVULINIC ACID DEHYDRATASE (ALAD) MUTATIONS

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Background ALAD-Porphyria (ADP) is an ultrarare porphyria, with only eight documented cases previously reported in literature. Infantile onset of symptoms was reported in only 2 cases. Herein, we report another such case, and the second known case of ADP in the Western hemisphere.

Case Presentation A male Hispanic neonate presented on day three of life with profound hypotonia, pinpoint pupils, absent deep tendon reflexes, and anemia. Whole genome sequencing revealed two pathogenic missense ALAD variants each inherited from one parent: c.397G>A (p.Gly133Arg) and c.415G>A (p.Gly139Arg). Biochemical testing on day 21 of life (15 days after erythrocyte transfusion) showed substantial elevation in urinary ALA (30 mg/g creatinine, ref <7) and total porphyrins (5,038 nmol/g creatinine, ref <300; 96% coproporphyrin III) and erythrocyte protoporphyrin (total 286 ug/dL (ref <80, 85% zinc protoporphyrin, 15% metal-free protoporphyrin), as expected in ADP. Erythrocyte ALAD enzyme activity was mildly decreased; however, this was measured after packed red blood cell transfusion. With supportive care in the neonatal intensive care unit his hypotonia improved gradually until he was safely discharged home on day 34 of life. He has continued to improve during outpatient follow up, and additional transfusions were not required.

Discussion Ultrarare autosomal recessive forms of porphyria, such as ADP, should be suspected as a cause of neonatal-onset hypotonia. Diagnosis is made by biochemical testing, but is facilitated by broad genetic testing methods. Both the marrow and liver may contribute to overproduction of ALA and porphyrins in ADP. Improvement in this patient may have resulted from erythrocyte transfusion and decreased erythropoiesis and less overproduction of ALA and porphyrins by the marrow, and this may be an important consideration for long term management.

Poster 55

04130 ACUTE PORPHYRIAS AS A PRIME EXAMPLE FOR (UNRECOGNIZED) RARE BUT TREATABLE DISEASE IN THE EMERGENCY DEPARTMENT: A PATIENT SURVEY AND SYSTEMATIZED LITERATURE REVIEW

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Background Rare diseases (RD) like akute porphyrias (APs) present a particular challenge for emergency physicians (EP), as their acute symptoms are usually nonspecific and resemble common clinical presentations. This is compounded by low awareness and limited training of EP regarding RD, often leading to patients with RD being discharged without an accurate diagnosis. Consequently, despite the availability and necessity of targeted diagnostic and treatment options, RD patients may experience further complications and fatal outcomes. This study aimed to characterise patients with RD, such as APs, in the ED and to raise awareness of the problem of unrecognised rare but treatable diseases in the ED.

Methods The BEAWARE study conducted from July 2023 to June 2024 surveyed patients with RD throughout the German-speaking area, focusing on acute symptoms and presentations in the ED. A select group of RD, including AHP, was chosen to meet the following criteria: (a) causing acute symptoms, (b) diagnosable in the ED for adolescents or adults and (c) availability of therapeutic options. In addition, Embase and MEDLINE were searched up to November 2023 in a systematized literature review of articles on the clinical characteristics of patients with AHP in the ED.

Results A total of 147 RD patients (15 with APs) participated in the survey. Except for one patient, all AP patients (93.3%) reported that they did present to the ED prior to diagnosis. 8/14 of AP patients presented to the ED 1–2 times, 4/15 3–5 times, 1/15 11–20 times and 1/15 more than 20 times with symptoms of their later diagnosed AP.

Of 327 identified articles, 3 could be included that described the clinical presentation of 59 AP patients in the ED. The most common symptoms were abdominal pain (53/59) and neurological symptoms (confusion, paresis, numbness of the extremities, and seizures). The main reported trigger factors included menstrual cycle (28/36) and medication (8/49). Imaging typically yielded unremarkable results. Vital signs were within normal ranges for most patients and hyponatremia was observed in 32/46 patients. The patients‘ outcomes ranged from hospital release after two days to respiratory paralysis (in 3/59 patients) followed by three months of recovery and death in one patient due to a delay in diagnosis for a month.

Discussion and Conclusion Patients with APs frequently present to the ED prior to diagnosis and remain often undiagnosed for several visits. The sometimes serious and even fatal consequences emphasize the need for immediate diagnosis and treatment of APs in the ED.

Awareness and knowledge of rare diseases such as APs should be increased in the emergency department. So far, little is known in the literature about the presentation of AP patients in the emergency department. Perhaps AI-supported algorithms can support rapid diagnosis in the future.

Poster 56

04131 INCREASED PANCREATIC ENZYMES IN A PATIENT WITH ACUTE INTERMITTENT PORPHYRIA

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We report a case of a 62 year old female patient followed at our rare disease center for acute intermittent porphyria (AIP). The diagnosis of AIP was made in 1977 as a result of unexplained abdominal pain. She was doing well until 2015 when the clinical picture worsened with the appearance of motor and sensitive peripheral neuropathy and anxiety. In 2021, the patient could start therapy with the recently approved drug givosiran, which led to an improvement of symptoms and a drop in ALA and PBG urinary values right after the first dose. Pre-therapy tests showed amylase (Am) 192 U/L [v.n.28–100] and lipase (Lip) 63 U/L [v.n.13–60]. During three years of specific treatment, there was a constant alteration of pancreatic enzymes values measured just before infusions (median Am 185 U/L, median Lip 82 U/L) with a peak of Am 443 U/L and Lip 1167 U/L, which spontaneously reduced (Am 150 U/L; Lip 67 U/L) two days after givosiran injection. No symptoms attributable to pancreatitis have ever been detected. On repeated abdominal ultrasound, the pancreas was normal. There was no history of alcohol abuse, and the gallbladder was acalculous.

In 2024, we decided to interrupt givosiran to evaluate the effect of the drug on pancreatic enzymes. To date, on therapeutic washout, the patient has taken four blood samples one month apart each, with persistent increases in Am (median 204 U/L) and Lip (median 92 U/L). Furthermore, urine exams have shown an increase in PBG values, and the patient complains of a relapse of neurovisceral symptoms attributable to porphyria.

Despite the absence of abdominal pain, to rule out pancreatitis we performed CT scan which showed the presence of pancreas divisum.

In the ENVISION trial,[1] one of 94 patients discontinued treatment with givosiran for pancreatitis. In another study,[2] one patient discontinued treatment after the occurrence of acute pancreatitis, and another patient presented an isolated increase in lipase levels under treatment, without any symptoms. However, both pancreatitis and amylase/lipase elevation are also reported in AIP, regardless of givosiran treatment.[3] Finally, pancreas divisum is a known cause of increased pancreatic enzymes on laboratory tests.

In our patient, we are in favor of an amylase/lipase elevation due to the underlying disease and/or the patient‘s congenital anatomic alteration (pancreas divisum) rather than the drug’s effect. This is because the pancreatic enzyme peak was just before the administration of givosiran, and values

spontaneously decreased after a few days of treatment. Moreover, at several blood tests after drug withdrawal, the enzymes remained persistently altered. This clinical case reminds us of the importance of an accurate differential diagnosis in properly assisting the patient, especially in rare diseases for which knowledge is limited.

REFERENCES
1. Kuter DJ, *et al. J Hepatol*. 2023 Nov.
2. Poli A, *et al. Mol Genet Metab*. 2022 Mar.
3. Marcacci M, *et al. Orphanet J Rare Dis*. 2022 Apr.

Poster 57

04144 FIRST REPORT OF CLINICALLY MANIFEST VARIEGATE PORPHYRIA (VP) AFTER MATERNAL SPLIT LIVER TRANSPLANTATION IN A ONE-YEAR-OLD GIRL WITH IDIOPATHIC BILIARY ATRESIA

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A six-month-old girl with extrahepatic biliary atresia received living-donor liver transplantation [LTX] (segments II/III) with donor biliary-recipient enteric anastomosis from her 37-year-old healthy mother.

Immunosuppression after LTX was with cyclosporine and prednisolone. The infant did not receive trimethoprim/sulfamethoxazole. Six weeks after LTX acute rejection (RAI 5) was treated with prednisolone pulse therapy for six days. Eight weeks after LTX significant stenosis of the biliary-enteric anastomosis required percutaneous trans-hepatic cholangiography and dilatations. Recurrent cholangitis was treated with piperacillin, tazobactam, and meropenem.

5 months after LTX, the child developed very fragile skin on light exposed areas in (face and hands/fingers) (pictures will be shown). 4 months later she developed bullae, some of which broke and led to blisters that were slow to heal. Milia, hyperpigmentation and scars developed. As a result, the child had a mixed appearance of her skin: blisters, wounds, crusty erosions, milia, hyperpigmentation and scars. Salient biochemical results are summarized in the table 1.

Mutational analysis of *PPOX* gene revealed heterozygous *c.471_ 471+4del, p.(?)* variant in the mother and the girl. Her mother has done well after donating part of her liver with no skin lesions or other clinical features of VP, despite elevated urinary and fecal porphyrins [table 1].

Taken together, the skin lesions, plasma fluorescence screen results, high proportion of fecal Copro isomer III, and mutational findings establish the diagnosis of VP, which became clinically manifest only after LTX, complicated by chronic cholestatic liver disease.

Conclusion This observation clearly shows the influence of endogenous (mutation, PPOX deficiency) and exogenous factors that may lead to the clinically manifest VP even in early childhood We thank Daniela Jakob for strongly supporting this report and kindly providing pictures from her daughter.

Poster 58

04087 ACQUIRED ERYTHROPOIETIC PROTOPORPHYRIA DUE TO MYELODYSPLASTIC SYNDROME

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We present the case of a 71-year-old female with acquired erythropoietic protoporphyria (EPP) associated with myelodysplastic syndrome (MDS). She had been diagnosed 3 years prior to initial presentation with myelodysplastic syndrome and was receiving cycles of venetoclax and azacytidine. She presented with a one-year history of severe pain and swelling in her face and hands on exposure to sunlight. Within 10 minutes of sun exposure tingling and pruritus would develop. This would then progress to pain that could last up to 3 days. Minor relief was provided by immersing hands in cold water and pregabalin 150mg BD. Symptoms reportedly improved over winter and with chemotherapy cycles. She had previously seen an immunologist who diagnosed angioedema and commenced her on regular antihistamines and weaning courses of oral prednisolone 25mg for flares. When she did not respond to this treatment she was referred to dermatology. There was no family history of similar issues.

Examination of the skin was unremarkable, with no erythema, purpura, oedema, thickening or scarring. Based on her classic symptoms, a porphyrin screen was sent, which

Abstract 04144 Table 1 Selected laboratory characteristics in a 1-year-old girl with biochemically and clinically manifest VP 18 months after related living-donor liver transplantation*

	Urinary 5-ALA/Crea (mmol/mol)	Urinary PBG/Crea (mmol/mol)	Urinary URO/Crea (µmol/mol)	Urinary COPRO/Crea (µmol/mol)	Fecal Porphyrins (µg/g)	Fecal COPRO-isomer III/I (%)	Peak Plasma-Fluorescence (nm)	URO Plasma (µg/l)	COPRO Plasma (µg/l)	PROTO Plasma (µg/l
Child	7,34	0,63	5,12	23,59	12,2	90,9	625	11,3	5,8	9,2
Mother	0,22	0,14	3,44	28,5	121,1	80,4	626	-	-	-
Normal	< 2,66	< 1,01	< 4,33	< 20,68	< 85	< 35	negative	< 2	< 4	< 7

* At the time of these studies, the child displayed cholestatic chemistries (serum gamma GT and Alkaline Phosphatase activities > 10-fold and > 2-fold upper limit of normal, respectively)

demonstrated elevated total red blood cell porphyrin of 36.1 umol/L RBC (reference range <1.8) with normal levels of zinc protoporphyrin 1.3 umol/L RBC (reference range <1.6). Liver function tests were unremarkable. She was mildly anaemic, in keeping with MDS. A diagnosis of erythropoietic protoporphyria was made. She was able to cease prednisolone and antihistamines. We counselled her on the need to avoid sun exposure and implement strict sun protection strategies. Presently, she continues venetoclax monotherapy. A bone marrow transplant would potentially be curative for both MDS and EPP however, she has previously been deemed inappropriate due to her age.

While acquired EPP is a rare entity, our case exemplifies the need to screen for EPP in patients of any age where there is clinical suspicion, especially in patients with an underlying haematological disorder. Treatment of the abnormal bone marrow clone with chemotherapy temporarily reduces EPP symptoms.

Poster 59

04093 PORTAL HYPERTENSION IN ADVANCED PROTOPORPHYRIC HEPATOPATHY: A CASE REPORT

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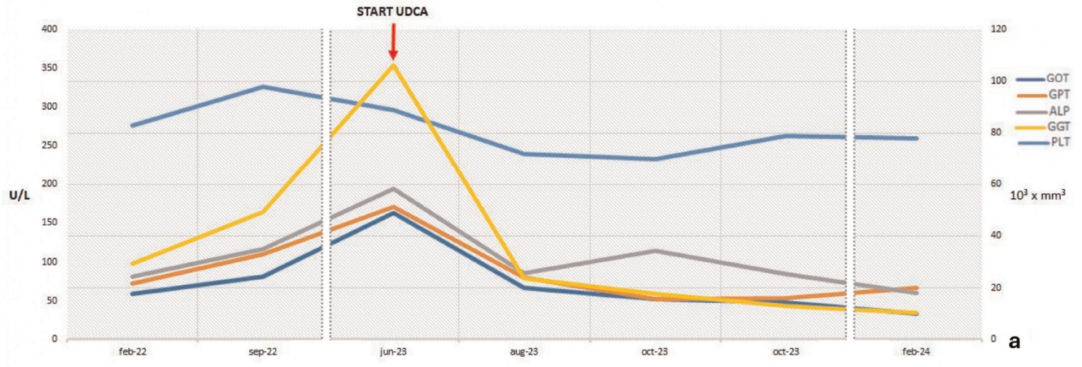


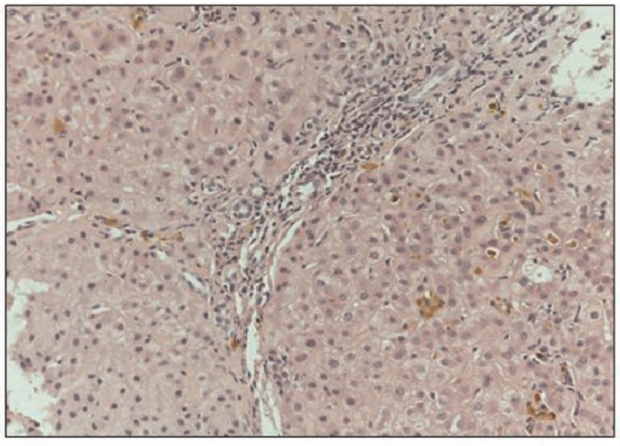
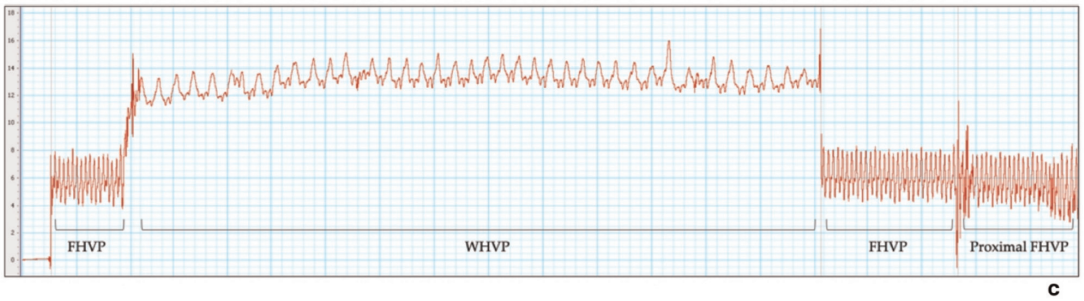


Figure 1. a) Follow-up in liver biochemistry in a patient with advanced protoporphyric hepatopathy. A dramatic improvement in liver biochemistry was noted after starting UDCA. *Please note that, for graphic purposes, GGT values have been halved.* b) Liver biopsy with fibrous septum and cholestasis (courtesy of Dr Pamela Sighinolfi, Pathology Department, Policlinico of Modena). c) Pressure waveform recorded during HVPG measurement (FHVP: 5 mmHg, WHVP: 12 mmHg). HVPG measurement of 7 mmHg indicates the presence of non-clinically significant sinusoidal portal hypertension. Permanent tracings were obtained with PowerLab (ADInstruments, Inc, Colorado Springs, CO).

Abbreviations: ALP, alkaline phosphatase; FHVP, free hepatic vein pressure; GOT, serum glutamic oxaloacetic transaminase; GPT serum glutamic pyruvic transaminase; GGT, gamma-glutamyl-transpeptidase; PLT, platelets. HVPG, Hepatic venous-portal gradient; WHVP, wedge hepatic vein pressure.



Abstract 04093 Figure 1

Protoporphyric hepatopathy (PPHep) can be a dreaded, long-term complication of erythropoietic protoporphyria (EPP). In fact, PPHep may go unnoticed for years until advanced chronic liver disease (ACLD) develops, leading to cirrhosis and portal hypertension (PH). We present a case of a 31-year-old, lean (BMI 18 Kg/m2) Caucasian male EPP patient, who presented at our Centre with altered liver biochemistry parameters (figure1a) and normal liver function (MELD score 7, Child-Pugh score 5). He had microcytic anaemia, low platelet count (<80000/mm3), and marked splenomegaly (spleen bipolar diameter 15.9 cm, area 93.8 cm2). Although an abdominal ultrasound did not provide clear evidence of ACLD, a liver biopsy was performed, which revealed a picture of cholestatic cirrhosis with fibrous septa, slight chronic inflammation, and diffuse cholestasis, both intracanalicular and intraductal (figure 1b). A gastroscopy detected mild congestive gastropathy without varices. The patient underwent hepatic venous-portal gradient (HVPG) measurement, which revealed a gradient of 7 mmHg, indicating the presence of non-clinically significant sinusoidal portal hypertension (figure 1c). No evidence of vein-to-vein communications was found during venography, which could have led to an underestimation of the gradient. Liver and spleen stiffness were 17.6 kPa and 27.7 KPa, respectively, consistent with the HVPG and other findings. After 3 months of follow-up, during which therapy with ursodeoxycholic acid was started, a dramatic improvement in liver biochemistry abnormalities was observed (figure 1a) with a reduction in liver stiffness (11.6 KPa). Although a definitive confirmation of the type of PH would have required a direct puncture of the portal vein, this case provide indirect evidence that PH in PPHep appears to be strictly sinusoidal, unlike other cholestatic liver diseases such as primary biliary cholangitis.

Poster 61

04109 THE IMPACT OF ERYTHROPOIETIC PROTOPORPHYRIA (EPP) ON FAMILY QUALITY OF LIFE

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Erythropoietic protoporphyria (EPP) adversely affects the quality of life (QoL) of patients, due to the requirement for strict sun protection measures and debilitating pain during acute episodes, often limiting educational and career choices. Few data exist regarding the effect of EPP on the QoL of close relatives. There are no previous published reports of the FROM-16 or FDLQI in EPP families.

Close family members of n=252 adults with EPP in England and Wales were surveyed during summer 2023. Questionnaires included: the 16 item Family Reported Outcome Measure (FROM-16), utilised across medical and surgical specialties, comprising emotional and personal/social life domains (score 0–32). The Family Dermatology Life Quality Index (FDLQI) includes 10 items assessing the secondary impact of skin disease on the families of dermatology patients. FDLQI scores range from 0–30, higher scores indicating a greater impact on QoL.

The response rate was 29.4% (n=74), the mean age was 51.5 years (SD 15.8, range 20 to 91) and 52.7% were female. Spouses/civil partners represented 67.6% (n=50), parents 23% (n=17) and adult son or daughter 6.8% (n=5). The majority of respondents were White British (90.5%, n=67), with 5.4% (n=4) White other background, and 2.8% (n=2) Asian or Asian British Indian and Other ethnicity.

The mean total FDLQI score was 6.8 (SD 5.9, range 0–21). The highest impact was on recreation and leisure activities, social life and emotional distress. There was no significant gender difference in overall scores, however males reported having to do significantly more extra housework than females due to their relative's EPP (p=0.03).

A very or extremely large impact on QoL was seen in 13.6% (N=10) for the FROM-16 and a moderate impact was seen in 37.8% (N=28). There was no significant gender difference. Highest mean scores were for problems going on holiday, followed by adverse impact on family activities. The lowest impact reported in both tools was the effect of EPP on the family member's work and studying.

We have shown a previously undocumented, substantial impact of EPP on patients' family members. A greater understanding of the effect of EPP on patients' relatives may lead to improved holistic care of this rare, lifelong and severe photodermatosis.

Poster 62

04194 IN-DEPTH BIOCHEMICAL INVESTIGATIONS IN A NEW CASE OF ALAD DEFICIENCY: BETTER UNDERSTANDING FOR BETTER TREATMENT

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Introduction Delta-aminolevulinic acid deshydratase (ALAD) deficiency porphyria (ADP) or Doss porphyria is an autosomal recessive disease caused by a profound deficiency of the second enzyme in the heme biosynthesis pathway. ADP is the rarest porphyria with only eight documented cases. Different therapeutic strategies aimed at slowing down heme biosynthesis have been described with varying level of efficacy, suggesting a complex pathophysiology.

Clinical Description We report the case of a 3-year-old boy whose two unrelated parents came from the same village in Cape Verde. He was hospitalized in neuropediatric department for recurrent generalised tonic-clonic seizures in a viral

context. Examination revealed a mild neurodevelopmental disorder with language delay, agitation and impaired social interaction No motor disorder was reported and no significant abnormality were found on brain MRI or CT-scan. Seizures were controlled by treatment with levetiracetam and valproic acid.

Biological Investigations Metabolic screening revealed a massive accumulation of delta-aminolevulinic acid (ALA) in urine and plasma. Lead intoxication was ruled out by a negative quantification of blood lead levels. Investigations for porphyria diagnosis were then initiated. We confirmed the high accumulation of ALA in urine and plasma (75 µmol/mmol creatinine ; 4.16 µmol/L respectively) associated with a moderate increase in PBG level (7 times less than ALA). Porphyrin concentrations were also significantly increased in urine, essentially coproporphyrin III, but normal in plasma and stool. Erythrocyte zinc-protoporphyrins level was also increased (10N). The similarity of this biological phenotype with published cases led us to consider the diagnostic of ALAD deficiency or Doss porphyria. *ALAD* gene sequencing revealed unreported homozygous ALAD variants classified as likely pathogenic (class 4). ALA concentrations were also elevated in cerebrospinal fluid (CSF) and in red blood cells (RBC). In order to determine the most appropriate treatment, a therapeutic challenge using heme arginate was carried out for 3 days while monitoring ALA levels in urine, blood and CSF. Urine ALA level fell by 35% after first injection, then stabilised. A slight decrease was also observed in plasma. CSF and RBC ALA levels did not appear to be not impacted by heme treatment.

Discussion and Conclusion We report here the 9th case of ADP, with clinical and biological features resembling those of previously described patients. Metabolic investigations confirmed limited efficacy of heme arginate, suggesting that the liver contributes only partially to ALA accumulation. Furthermore, elevated ALA concentrations in RBC and CSF were not significantly modified by heme treatment. Therefore, interventions aimed at slowing down the erythroid heme pathway could be beneficial.

Poster 63

Thematic area: heme synthesis and regulation

04185 THE GOOD, THE BAD AND THE UGLY: GLUCOSE, INSULIN AND HEME DEFICIENCY – IMPAIRMENT OF GLUCOSE METABOLISM IN PATIENTS WITH ACUTE HEPATIC PORPHYRIAS PRESENTING WITH RECURRENT ATTACKS

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Background Heme deficiency in the liver of patients with Acute Hepatic Porphyrias (AHP) stimulates an increase in ALA-synthase which triggers an escalating metabolic chain reaction, leading to an increase in toxic metabolites such as ALA and PBG. Therapy with heme infusions or glucose infusions are usually first line therapies for AHP patients presenting with an acute attack. Furthermore, several experimental models have been confirming that alterations of glucose metabolism and mitochondrial bioenergetics are part of the many metabolic dysfunctions seen in this disease. Nevertheless, their actual role in precipitating the AHP symptomatology is not completely understood.

Methods Retrospective data from AHP patients records and their general biochemical laboratory results compared with ALA and PBG levels from a reference center in Brazil were analyzed

Results 13 patients (10 females and three males) were enrolled. All patients reported recurrent porphyria attacks in combination with hypoglycemia. All patient had chronic increased levels of delta-aminolaevulinic acid and porphobilinogen with normal insulin levels. None of the patients had diabetes mellitus or decreased glucose tolerance previous to the onset of the first crisis. Nevertheless, after several glucose infusions without concomitant insulin administration and before heme therapy, all patients but one developed abnormal glucose metabolism, oscillating hypo and hyperglycemia usually with normal insulin levels. Recurrent hypoglycemia was a constant finding in patients before - and even after - a new acute attack and correlated with its recurrence. Paradoxically, treatment strategies using high carbohydrate diet combined with glucose infusions did not bring any apparent benefit and seemed to worsen hypoglycemia in most of the patients.

Conclusions The characterization of carbohydrate metabolic profiles in experimental acute porphyria models has highlighted alterations in glucose metabolism, hyperinsulinemia, and abnormal hepatic glycogenolysis, gluconeogenesis and mitochondrial bioenergetics that could be associated with AHP pathophysiology Our cohort of patients showed a striking relationship involving chronic hypoglycemia and frequent recurrent attacks of acute porphyria (with most of the patients displaying chronic symptoms between attacks). In particular, glucose loading therapy seemed to worsen clinical symptomology in some patients which can be consequence of increased gut permeability (followed by increased translocation of bacterial products and insulin resistance) caused by a high-glucose diet, pointing out to the gut-liver axis as a likely contributing factor to the physiopathology of acute attacks recurrence.

Poster 64

04154 THE RELATIONSHIP BETWEEN PROTOPORPHYRIN IX AND HEMATOLOGIC PARAMETERS IN PATIENTS WITH PROTOPORPHYRIA

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Introduction Erythropoietic protoporphyria and X-linked protoporphyria, collectively referred to as the protoporphyrias, result in accumulation of protoporphyrin IX, causing severe

cutaneous pain and, in a minority of patients, liver failure. Approximately half of patients with protoporphyria have microcytic hypochromic anemia, which may be related to reduced iron availability or decreased heme biosynthesis. Several reports have described mild thrombocytopenia in patients with protoporphyria as well, though the mechanism for this remains unknown. In this study, we characterize the relationship between erythrocyte metal-free protoporphyrin IX (PPIX) levels, platelet count, and iron status in patients with protoporphyria.

Methods We analyzed hematologic parameters in patients with protoporphyria treated at the Mass General Brigham (MGB) hospital system. Patient-level data across multiple time points were collected. Generalized Estimating Equation (GEE) models with an identity link and Gaussian family distribution were performed to determine the association, accounting for within-participant associations. A separate analysis was performed using linear regression for a cohort of patients with protoporphyria in Sweden, with one value per patient.

Results A total of 118 patients with protoporphyria were included in the analysis including 65 patients from MGB and 53 from the Swedish cohort. In the MGB cohort, the median PPIX level was 1482 ug/dl (min 265- max 4897, ref <20). A 1mg/dl increase in PPIX was associated with a 0.02 $x10^9$/L decrease in platelet count on average (p< 0.0001). This relationship was consistent when adjusting for alanine transaminase (ALT) and ferritin. There was no association between PPIX and ferritin (p = 0.57), PPIX and soluble transferrin receptor (p=0.31), or PPIX and hemoglobin (p =0.40). Higher PPIX levels were associated with lower MCV (p = 0.019) and higher ALT (p <0.0001). Similarly, in the Swedish cohort, a 1 mmol/L (ref <1.2) increase in PPIX was associated with a 1.4640 $x10^9$/L decrease in platelet count (p = 0.01224), a relationship that remained consistent when adjusting for ALT and ferritin. PPIX was not significantly associated with hemoglobin (p=0.102), ferritin (p=0.352), MCV (p=0.063), or ALT (p=0.068), but the trends for MCV and ALT were present in the same direction as for the US cohort.

Conclusion In this study of 118 patients with protoporphyria in the US and Sweden, we demonstrated a linear relationship between PPIX and platelet count that remained consistent when controlling for ALT and ferritin. The PPIX level was not associated with hemoglobin or markers of iron stores. Moving forward, we plan to present data for matched controls in the MGB cohort as well as data on the iron regulatory hormones, hepcidin and erythroferrone, in this group of patients.

Poster 65

04160 OBSERVED AND PREDICTED EFFECTS OF HMBS VARIANTS – RESULTS FROM THE PREDPOR STUDY

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Introduction Characterisation of hydroxymethylbilane synthase (*HMBS*) variants contribute to genotype descriptions and may give an increased understanding of pathomechanisms in AIP. As part of the prospective clinical study Predictors of symptomatic disease and long-term complications in AIP (PredPor), we characterised and categorised identified *HMBS* variants based on their predicted and observed molecular effects and assessed markers of disease activity and kidney function across gene variant groups.

Method Norwegian patients with latent and current/previously active AIP were invited to participate in PredPor. Health data were recorded for 103 participants via standardised questionnaires, and urine and blood samples were collected. In vitro studies of 12 missense HMBS variants registered in PredPor were conducted using mass spectrometry, native-PAGE, and enzymatic activity. We extracted the highest ever recorded values for urinary porphobilinogen (uPBG) and estimated glomerular filtration rate (eGFR) at inclusion.

Results In the PredPor population, we identified 21 different *HMBS* variants (NM_000190.4), most common were c.593G>A (n=33) and c.644T>A (n=14). For all other variants, the number of occurrences was 6 or less. Increased uPBG was recorded in 64% of participants. Among women (n=67), 76% had increased uPBG, with 25% higher than 10 times the upper reference limit, as compared to 14% among the men (n=36). 45% of participants (n=102) had normal eGFR above 90ml/min at inclusion, whereas 45% had slightly reduced eGFR (60–89ml/min; G2) and 10% had eGFR of 30–59 ml/min (G3a/b).

Based on biophysical features of the expressed HMBS variants studied *in vitro*, we categorised them as i) unstable with folding defects; ii) stable apoenzyme; iii) catalytically inactive with accumulation of a single intermediate; and iv) with a distribution of intermediates and a degree of activity.

We established gene variant groups, taking observed features in expressed enzyme into account: 1) predicted to have no gene product through non-coding, null variants, and nonsense-mediated decay (8 variants, n=52); 2) gene product was expressed but unfunctional (categories i-iii above, 9 variants, n=30); and 3) gene product was expressed and relatively functional (category iv above, 4 variants, n=21). No clear differences in uPBG or eGFR classification were observed between the variant groups.

Conclusion There is a lack of genotype-phenotype correlations in AIP, but few studies have investigated relationships between clinical disease and variant groups established on observed and predicted molecular effects. In the PredPor study, we categorised *HMBS* variants into three groups. Although we were unable to demonstrate significant differences in metabolic activation or kidney function between the groups, further studies are warranted. Furhtermore, increased knowledge on *HMBS* variants on a molecular level can contribute to our understanding of disease mechanisms in AIP.

Poster 66

Thematic area: recent advances in the pathophysiology of porphyrias

04122 COEXISTENCE OF WILSON'S DISEASE AND HEREDITARY COPROPORPHYRIA: EFFECT OF COPPER ON THE HEME PATHWAY

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Introduction Porphyria and Wilson's disease are genetically inherited metabolic diseases that can show multisystem involvement. Hereditary coproporphyria (HCP) can manifest itself with a wide range of symptoms such as abdominal pain, diarrhea, blisters on the skin, neuropathy, psychosis, and paraplegia as a result of the mutation of coproporphyrinogen oxidase (CPOX), one of the heme biosynthesis enzymes. Wilson's disease, which is transmitted in an autosomal recessive manner, is characterized by the accumulation of copper (Cu2+) in the tissue as a result of inadequate excretion into plasma and bile owing to a mutation in the ATP7B gene. Depending on the organ where copper accumulates, the patient may present with tremors, jaundice, cirrhosis, early osteoporosis, heart failure, renal tubular dysfunction, Kayser-Fleischer ring, and behavioral disorders. In this study, a case report was compared with the literature, and the effect of copper accumulation on HCP was investigated.

Clinical Findings Our 26-year-old male patient was found compatible with the CPOX gene mutation as s result of the genetic test requested upon suspicion of Wilson's Disease. The dry copper weight in the patient's tissue was recorded as 609 µg/g. Through literature review it was established that copper (Cu2+) suppresses the heme pathway, and this suppression is especially pronounced in the performance of ATP7B. In the Wilson's disease where the copper accumulation in the tissue is excessive, it is expected that the heme pathway will be suppressed and the CPOX enzyme will be decreased. Thus in line with this thought, our hypothesis based on the synergistic progression of our patient's Wilson and HCP diseases was supported; and the existence of a pathophysiological condition in which Wison's disease, where both the heme pathway and the CPOX enzyme are suppressed, and HCP exacerbate each other has been revealed.

Conclusion The association of hHCP and Wilson, which has not been previously reported in the literature to the best of our knowledge, is discussed in terms of liver mechanisms and common pathophysiology. Although the effects of Wilson and HCP diseases on each other are not yet known, the mechanism of this synergistic relationship can be explained through biochemical and pathological studies in future studies. The existence of patients diagnosed with Wilson's disease, which resembles porphyria, and experimental studies are strong evidence that heme metabolism should be investigated in Wilson's disease.

Poster 68

04164 HEPATIC PORPHYRIAS ONSET. THE ROLE OF NR1/2 GENE VARIANTS

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Porphyrias are due to heme enzymes deficiencies: Porphobilinogen deaminase in Acute Intermittent Porphyria (AIP) and Uroporphyrinogen decarboxylase (URO-D) in Porphyria Cutanea Tarda (PCT). In Argentina, AIP and PCT are the most common hepatic Porphyrias. Many triggering factors are involved such as therapeutic medications, alcohol, abuse drugs, estrogens and iron levels. Nuclear receptors such as the Pregnane X Receptor (PXR) are key regulators of ABC drug transporters and CYP3A4. Previously we investigated the role of ABCB1 and ABCG2 in AIP and PCT triggering. The aim was to continue analyzing variants of *NR1I2* gene that encodes for PXR. For this purpose rs12721613 (NM_022002.3: c.196C>T) and rs2472677 (NM_003889.4:c.-22–7659C>T) variants were genotyped in Control, symptomatic AIP (S-AIP), asymptomatic AIP (L-AIP) and acquired PCT (A-PCT) by PCR-RFLP. Individuals signed informed consent. When AIP was evaluated, c.196C>T allelic frequency for S-AIP (0.129) was lesser than Control (0.288, $p<0.01$) and L-AIP (0.273, $p<0.05$). A different genotypic profile was observed: S-AIP showed a less value in heterozygosis (25.93%) vs Control (45.45%, $p<0.01$) and L-AIP (48.48%, $p<0.01$); TT had in S-AIP a null value and very low in both Control (6%) and L-AIP (3%). For c.-22–7659C>T, no differences were found in the allelic and genotypic frequencies among AIP groups and Control. In PCT cohort, T allele frequency for c.196C>T was very low (0.021, $p<0.01$) respect to Control (0.288). Genotypic frequency in heterozygosity was lower in PCT group (4.14%, $p<0.01$) than in Control (31.57); concordantly a high proportion was observed in homozygosity for wild type in this Porphyria. For c.-22–7659C>T, allelic frequencies were similar for PCT and Control while genotypic profile showed less proportion of CT (36.4%, $p<0.05$) in PCT and high levels although no significant for TT vs Control. In conclusion, for AIP, the higher presence in latent patients of c.196C>T would suggest that T could be a protector allele, probable related to a minor demand of heme due to the downregulation of PXR on CYP3A4. For A-PCT, the major presence of TT genotype found in c.-22–7659C>T could be related to its onset considering that the negative regulation of PXR on ABCB1 and CYP3A4 transcription affects detoxification and transport of xenobiotics promoting a hepatotoxic environment that inhibits URO-D activity. Considering the importance to study local population, further investigation to compare allele frequencies in Argentinean Control cohort using gnomAD was done. The frequency of rs2473677 was significantly higher in

Argentinean population than in Americans who have null value, and Africans, being similar to Europeans and global population. For rs12721613, T frequency was higher in Argentina than in the other populations included global one. Finally, *NR1I2* gene variants could be considered as a possible modulator in the pharmacological induction of Hepatic Porphyrias.

Poster 69

04098 SMART METABOLIC METRO-MAP: DYNAMICS OF THE BIOCHEMICAL CHAIN REACTIONS AND ITS CORRELATION TO PATHOPHYSIOLOGY OF METABOLIC DISORDERS

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Smart metabolic metro-map refers to a dynamically stimulable model of the metabolic pathways. F. Hoffmann-La Roche Ltd provides a static version of the biochemical pathways.

A static biochemical pathways map is a good guideline to understand the general functions and connections. It is however not sufficient to capture the time dependencies of the biochemical interactions.

We are developing a stimulable electrical model predictive of the flow of the forward and backward reactions in time domain when a defect on a pathway is present.

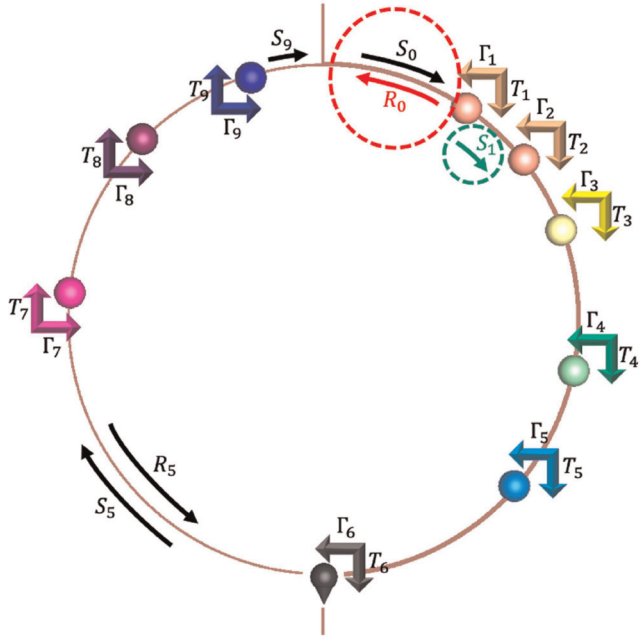
In the case of rare metabolic disorder, the dysfunctional enzyme results in a partial forward reaction as well a partial backward reaction. The backward signaling results in substrate accumulation in the previous step. This in turn induces another partial backward reaction. The sum of these time dependent behavior creates a continuous backward signal. The induced backward signal is a crucial consideration which could predict the rate of accumulation and congestions of the defective pathways.

In the case of a defect on a pathway, periodic stimulation of the biochemical pathways results in a periodic accumulation of the intermediate metabolites. The peak (maximum) point of accumulation causes the acute phase of a disease.

An electrical software model of the biochemical pathways is constructed to be able to simulate scenarios with several metabolic excitations simultaneously or sequentially. The model is excitable by launching user-defined electrical signals at specified input ports.

We use periodic and non-periodic electrical signals to illuminate the pathway and to detect the congestion on a pathway , following the backward signal flow and its interaction with an incoming signal. These interactions are illuminated using high-end visualization techniques and CAD models.

We developed a technique to effectively identify the triggers and subdue the acute attacks of a defect of heme biosynthesis in 3 members of a family with a defect on CPOX gene.



Abstract 04098 Figure 1

- Enzyme activity coefficient: T_n
- Enzyme deficiency coefficient: $\Gamma_n = 1 - T_n$
  equiv. substrate accumulation coefficient
- S : transmitted signal
- R: reflected signal

- $S_1 = S_0 \times T_1$
  $R_0 = S_0 \times \Gamma_1 = S_0 \times (1 - T_1)$
- $S_2 = S_1 \times T_2 = S_0 \times T_1 \times T_2$
  $R_1 = S_1 \times \Gamma_2 = S_0 \times T_1 \times (1 - T_2)$
- $S_3 = S_2 \times T_3 = S_0 \times T_1 \times T_2 \times T_3$
  $R_2 = S_2 \times \Gamma_3 = S_0 \times T_1 \times T_2 \times (1 - T_3)$
- .
- .
- .
- $S_n = S_{n-1} \times T_n = S_0 \times (T_1 \times T_2 \times \ldots \times T_n)$
  $R_{n-1} = S_{n-1} \times \Gamma_n = S_0 \times T_1 \times T_2 \times \cdots \times (1 - T_n)$

Poster 70

04174 A CONGENITAL ERYTHROPOIETIC PORPHYRIA CASE OF UNKNOWN GENETIC MUTATION

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Congenital erythropoietic porphyria (CEP) is an autosomal recessive metabolic disorder of which less than 300 cases are

reported in the literature. It is caused by mutations in the *UROS* gene or rarely, mutations in the X-linked *GATA1*gene leading to deficiency of the enzyme uroporphyrinogen III synthase, the fourth enzyme in the heme biosynthesis pathway. This multi-system disorder is characterised by the build-up of uroporphyrin I and coproporphyrin I which causes extreme photosensitivity from birth. CEP can cause severe skin fragility including blisters and scarring, ophthalmologic complications including loss of vision, haemolytic anaemia, and dental and skeletal abnormalities. Disease severity is variable and dependent on the type of mutation, unknown genetic factors, environmental factors and photoprotective behaviour. CEP is normally managed by strict photoprotection and vitamin D supplementation. Blood infusions, splenectomy, stem cell and bone marrow transplantations, and gene therapy are also potential treatment options.

A 5-year-old patient presented to the dermatologist after his non-consanguineous parents noticed blisters and scarring on photo-exposed areas and darkly coloured urine during a holiday. On examination, he was found to have scarring and post inflammatory hyperpigmented patches on sun exposed areas, hypopigmentation on his nose and cheeks as well as slightly discoloured teeth. The patient is not known to have a family history of CEP.

Initial investigations included urinary, plasma and faecal porphyrin screens. Results showed raised urinary porphyrin: creatinine (2383 nmol/nmol, reference range <40) with markedly increased uroporphyrin I (96.3%) compared to uroporphyrin III (3.7%), as well as an increased coproporphyrin I (85.7%) compared to coproporphyrin III (14.3%) isomer ratio.

The plasma porphyrin screen showed a distinct immunofluorescence peak at 618 nm. His total faecal porphyrins were raised (310 nmol/g, reference <200) with a significantly increased coproporphyrin I (91.5%) to coproporphyrin III (8.5%) isomer ratio.

The pattern of results confirmed a biochemical diagnosis of CEP, however genetic analysis of known mutations was negative. The latter was performed using Nonacus enrichment technology (RCGPv5) and Illumina DNA sequencing to detect known pathogenic variants in the *UROS* and *GATA1* genes.

In conclusion, this patient had a biochemical and clinical diagnosis of CEP, however negative genetic analysis demonstrates current genetic testing may not be able to detect all mutations causing CEP. RNA sequencing is planned to investigate gene expression in more detail.

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