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THE PORPHYRIAS:
WEBINAR SERIES 2021

Diagnosing and managing porphyria cutanea tarda: the basics

Thursday 6 May 2021 (CET 13:00 - 14:00)

Additional Q&A responses

Question	Response
Can pregnancy precipitate PCT?	Pregnancy is associated with a marked increase in oestrogen levels and oestrogens are regarded as a risk factor for inducing or exacerbating PCT. However, most women with PCT develop symptoms when they are past the child-bearing age, and during pregnancy the foetus reduces the maternal iron stores. The panellists had rarely or never seen a pregnant woman with overt PCT. However, there have been some case reports on the subject. The treatment does not differ from that offered to non-pregnant women. (de Mola, J. Ricardo Loret; Muise, Kevin L.; Duchon, Method A. Porphyria Cutanea Tarda and Pregnancy, Obstetrical & Gynecological Survey: August 1996 - Volume 51 - Issue 8 - p 493-497)
Good afternoon, I would like to know if you have experience in hepatoerythropoietic porphyria, the recessive form of PCT especially the prognosis and treatment in children?	As hepatoerythropoietic porphyria is such a rare condition, none of the panellists had clinical experience with more than 1 or 2 HEP patients. In contrast to acquired PCT, in familial PCT and HEP the enzyme deficiency (UROD) is in all tissues and not only the liver. Trigger factors are required in familial PCT but less important for HEP where the activity is already often less than 20% of normal. In general, phlebotomy is not an option in treatment as most patients have been reported to have low or normal iron stores, and HEP patients may be anaemic. Hydroxychloroquine has been reported to be effective in one patient, but not in others. Therapy should be guided individually. Most important treatment is avoidance of sunlight, use of vitamin D supplements and support by a multidisciplinary team. (Liu LU, Phillips J, Bonkovsky H; Porphyrias Consortium of the Rare Diseases Clinical Research Network. Hepatoerythropoietic Porphyria. 2013 Oct 31 [Updated 2016 Dec 22]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/)
Is ultrasound, or other liver imaging, as “routine” monitoring appropriate. I have tended to think that if well controlled (clinically and biochemically) not much risk so have usually just asked for AFP and examined abdomen yearly. Fairly recently I had a patient whose PCT , which turned out to be due to homozygous C282Y haemochromatosis, was well controlled (no	The panellists advised long-term screening for primary hepatocellular carcinomas (HCC) in patients older than 50 years according to local guidelines, which generally will include ultrasound monitoring, Alfa-foetoprotein alone is not adequate. Since PCT is a hepatic disease, ultrasound covers diagnostic observation and HCC screening as well and is especially important in patients with pre-existent liver disease (e.g. cirrhosis or fibrosis and ongoing liver damage, hemochromatosis or viral hepatitis). Screening is not indicated in patients without these factors. See Baravelli CM, Sandberg S, Aarsand AK, Tollånes MC. Porphyria cutanea tarda increases risk of hepatocellular carcinoma and premature death: a nationwide cohort study. Orphanet Journal of Rare Diseases. 2019 Apr 3;14(1):1–10.

clinical activity and urine porphyrins long quantitatively and also qualitatively, on HPLC) for decades who died of primary hepatocellular carcinoma. This was just one case, but should I change what I advise?	
Apart from estrogens at unusually high dose, as in treating advanced prostate cancer, that can cause liver upset I have always been unsure about oestrogens as a cause. Most women who present with PCT seem to present older than men (I have assumed menstrual blood loss a bit protective against liver iron overload). So, as many post-menopausal women are on HRT anyway, I have not been convinced actually causative. Is there proof that estrogens are causative?	The clinical evidence for HRT or oral contraceptives contributing to PCT in women derives from observations that stopping the treatment can lead to remission of the PCT without phlebotomy, and from the very high percentage of female patients with PCT who are taking exogenous estrogens (most commonly in HRT). These reports suggest that the chance of remission on cessation of estrogens is higher in patients who had only used estrogens for a year or less. Transdermal HRT was found to be safe in a small study. Experimentally, estradiol has been shown to induce or worsen porphyria in hexachlorobenzene-treated rats.
How significant are factors such as smoking, high BMI, type 2 diabetes in the pathogenesis of PCT?	Smoking of > 10 cigarettes/day is regarded by some as a risk factor and has been shown to be associated with earlier onset on disease in sporadic PCT. Fontanellas A, Martínez-Fresno M, Garrido-Astray MC, Perucho T, Morán-Jiménez MJ, García-Bravo M, Méndez M, Poblete-Gutiérrez P, Frank J, Henriques-Gil N, de Salamanca RE. Smoking but not homozygosity for CYP1A2 g-163A allelic variant leads to earlier disease onset in patients with sporadic porphyria cutanea tarda. Exp Dermatol. 2010 Aug;19(8):e326-8. The prevalence of diabetes mellitus is increased in patients with porphyria cutanea tarda, but it is not clear to what extent the diabetes mellitus or obesity associated steatohepatitis contribute to the porphyria. (Christiansen AL, Bygum A, Hother-Nielsen O, Rasmussen LM. Diagnosing diabetes mellitus in patients with porphyria cutanea tarda. Int J Dermatol. 2018 Jul;57(7):763-769. Muñoz-Santos C, Guilabert A, Moreno N, Gimenez M, Darwich E, To-Figueras J, Herrero C. The association between porphyria cutanea tarda and diabetes mellitus: analysis of a long-term follow-up cohort. Br J Dermatol. 2011 Sep;165(3):486-91. Ergen EN, Seidler E, Parekh S, Parker SR. Is non-alcoholic steatohepatitis a predisposing factor to porphyria cutanea tarda? Photodermatol Photoimmunol Photomed. 2013 Apr;29(2):106-8.) **Conclusion**: The advice is to manage the smoking and diabetes mellitus and obesity at the same time as treating the PCT by phlebotomy, low-dose hydrochloroquine or both.
Do we need to send plasma sample for all patients suspected of porphyria? And is measurement of different fractions of porphyrin in plasma give added values as compared to urine porphyria?	This would depend on the practice of your (referral) laboratory. Most porphyria centers ask for both plasma and urine, to exclude other some forms of acute hepatic porphyrias with cutaneous symptoms similar to PCT, especially variegate porphyria. Differentiation of these porphyrias can be done by plasma fluorescence and be analysis of faeces. The presenye of protoporphyrin in plasma, or an excess of coproporphyrin together with increased ALA and PBG can lead to a diagnosis of variegate porphyria or hereditary

	coproporphryia. The relative pattern of uro-, hepta-, hexa-, penta-, and coproporphyrins is usually similar in plasma to that found in urine. The pattern is in general pathognomonic for PCT.
Do you know if the precipitating factors known in acute hepatic porphyria such as fasting and drugs can also trigger PCT?	The short answer is no. PCT is not an acute hepatic porphyria.
Sir, is there any role of Enzyme analysis Urodecarboxylase in the diagnosis and monitoring?	There is big overlap of urodecarboxylase (which is measured in the erythrocytes) between healthy and patients with hereditary PCT. The enzyme has therefore presently no role in differentiation between hereditary and sporadic PCT. This differentiation is best done by DNA-analysis. Remember also that the assay is performed in erythrocytes whereas the overproduction of porphyrins occurs in the liver. Erythrocyte UROD is not indicated for monitoring as it has no therapeutic consequences for patients with PCT.
Why is it important to test for ALA and PBG in this non-acute porphyria?	To help exclude variegate porphyria, hereditary coproporphyria or a very rare combination to two porphyrias. However, the diagnostic pitfall is that occasionally variegate porphyria patients have a PCT biochemical pattern in their urine ('dual porphyria'). So PCT can only be diagnosed on the basis of urine analysis plus analysis of either plasma or faecal porphyrins.
What about hormonal contraception causes an increase in reactive oxygen species?	It is still not clear what mechanism is involved in the relationship between hormonal contraception, hormonal replacement therapy and PCT. A increase in reactive oxygen species induced by the hormones may be involved but we are not aware of any publications on this specific subject.
Would all of panel recommend measuring urine PBG and ALA in diagnostic workup for PCT? Mentioned by second speaker whereas first speaker noted urine and plasma porphyrins, not precursors	No, if the urine findings are absolutely typical for PCT. However, if there are any unusual features (young age, acute porphyria complaints, absence of predisposing factors for PCT) then PBG and ALA assays should be performed. Often urine PBG (and ALA) are routinely performed in every patient suspected of porphyria.
But if the samples were not collected during an acute attack for VP, will ALA/PBG even be raised?	Urinary ALA and PBG may normalize within weeks of an attack, plasma values remain raised for longer. A plasma fluorescence spectrum typical for variegate porphyria will usually values remain raised for longer. A patient can be asked to send samples for u-ALA and PBG if having a new acute attack.
Thanks for another brilliant session.	Thank you for your compliments.
Is it possible to get a copy of the presentation slides?	A full recording of the webinar will be made available at 2021 Webinar Series: The Porphyrias | European Porphyria Network in the next few days. This link will also allow you to access the other webinars in the series. EPNET does not hold a copy of the slides used in the presentations. We would therefore recommend contacting the presenter directly if you require a copy of the PowerPoint delivered during either of the presentations.