

Research letter

Hair cortisol is elevated in patients with erythropoietic protoporphyria and correlates with body mass index and quality of life

DOI: 10.1111/bjd.16341

DEAR EDITOR, Erythropoietic protoporphyria (EPP) is a rare, inherited disorder of haem biosynthesis, characterized by severe photosensitivity from early childhood.¹ In most countries, no effective treatment is available and the behavioural adaptations needed to avoid sunlight, in addition to pain and sleep deprivation associated with phototoxic episodes, are important stressors in patients with EPP.² This might be reflected in increased long-term cortisol levels, which can be measured in scalp hair. Hair cortisol concentrations (HCC) have previously been shown to be positively correlated with chronic stress.³ In this study, we investigated HCC in patients with EPP and the possible relationship with body mass index (BMI), self-reported perceived stress, quality of life (QoL) and disease severity.

Adults with a confirmed diagnosis of EPP, attending our Porphyria Center at the Erasmus Medical Center (Rotterdam, the Netherlands), were invited to participate in the study. At the time of inclusion, patients were not receiving any treatment for EPP. Patients were age- and sex-matched to controls from our historical cohort⁴ with a ratio of 1 : 3. Participants with insufficient hair growth, concomitant disorders of the hypothalamus–pituitary–adrenal (HPA) axis or continuous exogenous corticosteroids use in the past 3 months were excluded.

In both groups, a lock of scalp hair was cut from the posterior vertex and processed for determination of long-term cortisol exposure as described elsewhere.⁴ We further collected

data on age, sex, BMI, medication use and hair-related factors in all participants. In addition, the EPP group were asked to fill out the 14-item Perceived Stress Scale (PSS),⁵ the EPP-specific QoL questionnaire (EPP-QoL)⁶ and to report the time they could spend in direct sunlight without symptoms.

This study was approved by the local medical ethics committee and was conducted in accordance with the Declaration of Helsinki; all participants gave written informed consent. Statistical analyses were performed with IBM SPSS Statistics version 21 (IBM, Armonk, NY, U.S.A.). Differences between groups were assessed with ANCOVA and correlations were tested using Pearson's or Spearman's rho correlation coefficient. The level of significance was set at $\alpha = 0.05$.

Fifteen participants with EPP and 45 controls were included. There were no significant differences between the groups in baseline or hair characteristics, except for natural hair colour ($P = 0.022$). The EPP group had significantly higher HCC than matched controls [geometric mean, 17.06 pg mg^{-1} , 95% confidence interval (CI) 13.02–22.35 vs. 8.28 pg mg^{-1} , 95% CI 5.88–11.64, Cohen's $d = 0.83$, $P = 0.021$, Fig. 1]. Adjustments for age, sex and hair colour did not change the results. Scores on the EPP-QoL, PSS-14 and sunlight sensitivity were available in nine, 15 and 13 patients, respectively. There was a strong inverse association between long-term cortisol exposure and EPP-QoL scores ($\rho = -0.703$, $P = 0.035$). No correlation was found between HCC and PSS scores, or between HCC and the time that could be spent in sunlight. In the EPP group, we additionally observed a positive correlation between HCC and BMI ($r = 0.672$, $P = 0.012$).

In this study, we have demonstrated that patients with EPP have higher long-term cortisol levels than age- and sex-matched

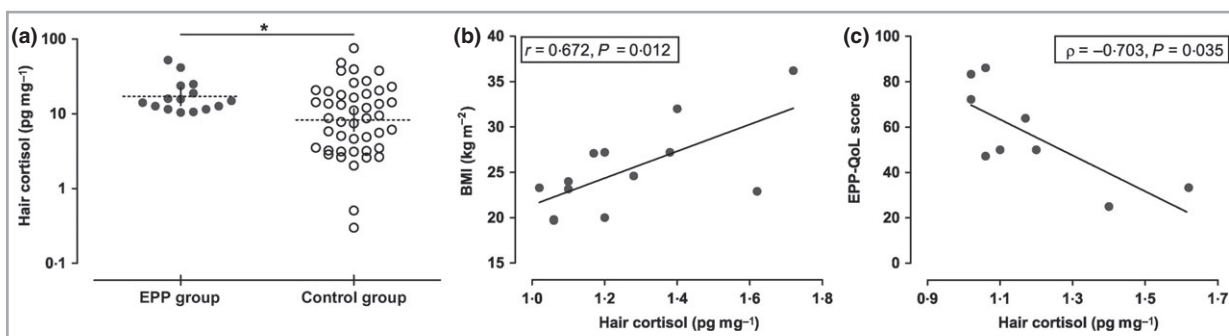


Fig 1. Long-term cortisol exposure as measured in scalp hair of study and control participants. Hair cortisol concentrations in the erythropoietic protoporphyria (EPP) group and the age- and sex-matched control group (a), and their associations with body mass index (BMI) (b) and EPP-specific quality of life (EPP-QoL) questionnaire score (c) in the EPP group. Hair cortisol concentrations are shown as geometric mean (95% confidence interval) on a logarithmic scale or as log-transformed data. * $P < 0.05$.


controls and that this was correlated with lower QoL and higher BMI. Stress in patients with EPP is related to limitations in their social and professional life, but also to pain from phototoxic reactions and a deep-rooted fear of sunlight.⁶ In addition, reduced light exposure and alterations in the day–night rhythm, common in these patients,² could disturb the circadian cortisol rhythm and induce alterations in HPA-axis activity.

The strong correlation between HCC and scores on the EPP-QoL suggests that the measurement of hair cortisol could be a useful addition in the study of EPP and the efficacy of new treatments, such as afamelanotide,⁶ as it assesses all aspects of stress, including biological stress. Furthermore, the association between HCC and BMI, as found in the EPP group, has previously been described in other study participants.^{7,8} It could be suggested that there is a vicious circle in patients with EPP in which weight gain because of stress, pain or reduced physical activity may lead to greater stress-induced cortisol production, thereby promoting further weight gain.

The main limitation of this study is the small sample size, which is related to the rarity of EPP.¹ Furthermore, we did not take into consideration the seasonal variance of EPP-related symptoms or potential seasonal effects on hair cortisol levels in both groups. Whether EPP-related symptoms affect cortisol production should be assessed in further studies.

In conclusion, we show that long-term cortisol levels, as measured in hair, are elevated in patients with EPP and that these are associated with a lower QoL and higher BMI. Hair cortisol analysis might be a valuable tool to monitor stress-related comorbidities and disease-related QoL in patients with EPP.

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Funding sources: E.F.C.v.R. is supported by a Vidi grant from the Netherlands Organization for Scientific Research (grant number 91716453).

Conflicts of interest: none to declare.