



Plasma porphyrins among end stage renal disease patients and cutaneous symptoms- is there still an association?

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ABSTRACT

Introduction: Several abnormalities of porphyrin metabolism leading to Porphyria Cutanea Tarda (PCT) have been described in early studies of End Stage Renal Disease (ESRD) patients, with a reported prevalence of 5–18%. We aimed to evaluate porphyrin levels and correlation to skin manifestations in modern dialysis era.

Methods: The study cohort included adult hemodialysis patients from a single center tertiary medical center. All patients underwent a full skin examination, completed the Dermatology Life Quality Index questionnaire, and provided a blood sample for porphyrin levels assessment.

Results: A total of 94 adult hemodialysis patients were recruited to the study. No clinical PCT was diagnosed. Porphyrin levels did not correlate with any clinical or dialysis quality parameters.

Conclusions: In modern hemodialysis era, possibly due to improved porphyrins' metabolism and dialysis removal, PCT is much less prevalent among hemodialysis patients than previously reported in the past.

1. Introduction

The porphyrias are a group of rare metabolic disorders — either inherited or acquired, which affect the heme biosynthetic pathway [1,2].

Porphyria Cutanea Tarda (PCT), caused by decreased activity of the enzyme uroporphyrinogen decarboxylase (UROD), is the most common cutaneous porphyria and is associated with cutaneous photosensitivity. Its clinical manifestations include signs of vesiculo-bullous lesions appearing on sun-exposed areas, milium, and may be accompanied by pruritus. The skin becomes very fragile, with superficial erosions covered by crust following minimal trauma. Hirsutism is another common sign.

This type of porphyria is most commonly acquired and arises from known risk factors including: alcohol abuse, estrogen therapy, chronic

hepatitis C virus (HCV), chronic hepatitis B virus (HBV), hepatic steatosis, HIV infection and hemochromatosis [3–5].

Several abnormalities of porphyrin metabolism leading to PCT have been described in early studies of end stage renal disease (ESRD) patients some by decreasing UROD activity such as iron overload, (HBV) and (HCV) and uremic toxins and some by accumulation of heme precursors due to impaired ability to excrete porphyrins [6]. It is not clear if abnormalities of porphyrin metabolism in ESRD patients are a consequence of their deficient kidney function or related to other accompanying risk factors prevalent among these patients. Early reports from the previous century demonstrated a 5–18% prevalence of PCT among ESRD patients [6,7]. Although there are no reliable documentations of current PCT prevalence in ESRD patients, it is probably not as common today due to the use of high-flux dialyzers, reduced blood transfusions and efficient treatment for HCV infections [8].

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ESRD patients demonstrate high prevalence of cutaneous manifestations such as: pruritus, xerosis, pigmentary changes, purpura and ecchymosis, bullous dermatoses, calcifications and fibrosis [9]. Another cutaneous manifestation seen in dialysis patients is pseudoporphyria, a photodistributed bullous dermatosis that resembles PCT clinically, but without biochemical porphyrins abnormalities in the serum, urine or stool [10]. While many of these manifestations negatively impact patients' quality of life, the etiology of many is still poorly understood.

Remarkably, there are no recent studies evaluating the prevalence of PCT among ESRD patients. Furthermore, there are no studies assessing a possible correlation between porphyrin levels and dermatological manifestations among dialysis patients.

2. Methods

2.1. Study design and patients

This is a cross sectional study including adult ESRD patients treated by hemodialysis in a tertiary medical center for at least three months. The study was approved by the local Institutional Review Board.

All patients, after filling a written informed consent, had a full skin examination and all cutaneous findings were documented. Then they were asked to complete the Dermatology Life Quality Index (DLQI) questionnaire regarding clinical cutaneous symptoms and signs and their impact on the patients' quality of life [11]. They were also asked about recent infectious diseases, residual renal function [yes or no] as well as sun exposure and smoking and alcohol consumption habits. Finally, a sample (10 ml) of whole blood prior to a mid-week dialysis was obtained, in order to quantify porphyrins levels and for plasma fluorescence scan. Samples were analyzed in the Israeli National Service for Biochemical Diagnoses of Porphyrins (INSP). Total plasma porphyrins were summarized as Uroporphyrin + Heptaporphyrin + Coproporphyrin + Protoporphyrin.

Other clinical and laboratory data such as ferritin levels, HCV and HIV status, dialysis clinical and laboratory data and Charlson comorbidity score were extracted from patient's files.

Exclusion criteria: patients unable or unwilling to fulfil one of the study requirements; dialysis due to indications other than ESRD; patients with active infection in the prior two weeks; patients with active malignancy or with a chronic skin disease unrelated to ESRD.

2.2. Statistical analysis

Baseline characteristics and categorical variables were summarized using descriptive statistics and compared with the Independent-samples *t*-test, exact Fisher's *P* test and Mann-Whitney *U* test as appropriate. *P* < 0.05 was considered to indicate statistical significance. The data were analyzed using SPSS, version 19.0 for Windows (SPSS, Inc).

3. Results

A total of 94 patients were included in the study. Mean age was 67.8 ± 13, 30.1% were female. Median dialysis vintage was 55.9 ± 42.3 months. The characteristics of the patients included in the study are presented in Table 1.

No dialysis patients were diagnosed with clinical PCT. No patients were found to have cutaneous manifestations commonly associated with PCT such as bullas, vesicles, erosions and ulcers.

23 dialysis patients (24.5%) had slightly above normal total porphyrin levels (level > 20 nmol/l, normal < 15 nmol/l). Patients with elevated total porphyrin levels were younger (mean age 58.9 Vs 70.7, *P* < 0.001). Elevated total porphyrin levels did not correlate with clinical and dialysis quality parameters including gender, smoking, residual renal function, dialysis KTV, dialysis length; Charlson co-morbidity score; laboratory parameters including hemoglobin, ferritin, albumin; treatment with erythropoietin or iron (Table 2). Skin manifestations that

Table 1
characteristics and demographics of patients included in the study.

Characteristic	Number
Age, mean ± SD	67.8 ± 13
Gender- Female, No. (%)	28 (30.1)
Past transplant, No. (%)	12 (12.9)
Dialysis vintage, m, mean ± SD *until 1/2021	55.9 ± 42.3
KTV, mean ± SD	1.37 ± 0.23
Dialysis length, mean ± SD	3.9 ± 0.3
Dialysis UF, mean ± SD	2 ± 0.9
Access, No. (%)	
Central line	42 (45.2)
Arterio-venous fistula/graft	51 (54.8)
Smokers and past smokers, No. (%)	27 (29)
Residual renal function, No. (%) *1 missing	58 (62.3)
Positive HIV, No. (%) *30 missing	0 (0)
Positive HCV, No. (%)	3 (3.2)
Positive HBV, No. (%)	0 (0)
Primary renal disease, No. (%)	
Glomerular disease	10 (10.8)
Diabetes with/without biopsy	44 (47.3)
Nephrosclerosis with/without biopsy	8 (8.6)
PCKD	5 (5.4)
Other	33 (35.5)
Co-morbidities, No. (%)	
Coronary artery disease	51 (54.8)
Peripheral vascular disease	20 (21.5)
Diabetes mellites - Uncomplicated	5 (5.4)
Diabetes mellites with target organ damage	50 (53.8)
Charlson score, mean ± SD	5 ± 1.8
Laboratory indices:	
PTH, mean ± SD	374.7 ± 246.7
Hemoglobin, mean ± SD	10.7 ± 1.3
Albumin, mean ± SD	4 ± 0.3
Corrected calcium, mean ± SD	8.6 ± 0.7
Phosphor, mean ± SD	5 ± 1.24
CRP, mean ± SD	2.17 ± 3.31
Ferritin, mean ± SD	654.1 ± 436.8
HBV Antibody level, mean ± SD	179.1 ± 285
Treatment:	
Treatment with EPO, No. (%)	73 (78.5)
Treatment with iron, No. (%)	51 (54.8)
Treatment with heparin, No. (%)	88 (94.6)
Treatment with activated vitamin D, No. (%)	55 (59.1)
Treatment with calcium, No. (%)	43 (46.2)
Gabapentin, No. (%)	1 (1.1)
Lyrica, No. (%)	14 (15.1)
Gabapentin + Lyrica, No. (%)	15 (16.1)

UF ultrafiltration; PCKD polycystic kidney disease; PTH parathyroid hormone; CRP C-reactive protein; EPO erythropoietin.

could be attributed to PCT, including dermatoheliosis, milia, excoriations, excoriated papules, scarring and post inflammatory changes, did not correlate with porphyrin levels either. There was no correlation between DLQI nor specific items in the questionnaire to total porphyrins levels (data will be shared on request to the corresponding author).

4. Discussion

The correlation between ESRD and PCT has been evaluated and published during the middle and late decades of the previous century. Since, treatment of ESRD patients have dramatically changed for the better. Advancements include higher specification of hemodialysis machines, improvement in dialysis membranes (biocompatible membrane, higher transport capabilities), improvement in water purification process, treatment of HCV and decreased number of blood transfusions due to treatment availability of erythropoietin stimulating agents [8,12,13]. These changes are bound to change porphyrins' metabolism [HCV treatment and lower number of blood transfusions] and dialysis removal [High flux membranes] [8]. However, PCT is still quoted as a common co-morbidity in ESRD patients. In the current study we evaluated 94 ESRD hemodialysis patients, treated in a tertiary hospital and found no clinical PCT. We also evaluated for elevated porphyrin levels and while

Table 2

Comparison analysis between normal total porphyrin levels and elevated total porphyrin levels.

Characteristic	Normal total porphyrin levels (N = 70)	Elevated total porphyrin levels (N = 23)	P Value
Age, mean ± SD	70.7 ± 11.3	58.9 ± 13.9	P < 0.001
Female, No. (%)	22 (31.4)	6 (26.1)	0.8
KTV, mean ± SD	1.37 ± 0.24	1.39 ± 0.2	0.77
Dialysis length, median (range)	4 (3–4.5)	4 (3.5–4.5)	0.29
Smoker, No. (%)	11 ^a (15.9)	6 (26.1)	0.35
Residual renal function, No. (%)	44 ^a (63.8)	14 (60.9)	0.81
Positive HCV, No. (%)	2 (2.9)	1 (4.3)	NA
Charlson co-morbidity score, median (range)	5 (2–9)	5 (2–7)	0.21
Co morbidities – No. (%)			
Diabetes - uncomplicated	4 (5.7)	1 (4.3)	NA
Diabetes with target organ damage	38 (54.3)	12 (52.2)	NA
Hemoglobin, mean ± SD	10.7 ± 1.1	10.5 ± 1.7	0.36
Albumin, mean ± SD	3.9 ^a ± 0.3	4 ± 0.2	0.19
Ferritin, mean ± SD	654 ± 420	651 ± 496	0.98
Treatment with erythropoietin, No. (%)	55 (78.6)	18 (78.3)	NA
Treatment with iron, No. (%)	39 (55.7)	12 (52.2)	0.81

a. Out of 69 patients due to lack of information

we found only mildly elevated levels in 24.5% of patients, these levels did not correlate neither to any of the common skin manifestations in ESRD patients nor with skin manifestations possibly related to PCT. Furthermore, these elevated porphyrins levels did not correlate with quality of life or comorbidities either.

An incidental finding was correlation between age and porphyrin levels. This finding may be due to porphyrin metabolism changes with age [14], however it is beyond the scope of this study, and should further be evaluated in future studies.

The strength of our work is the thorough skin evaluation and comprehensive testing of porphyrins levels among hemodialysis patients. Several limitations merit consideration. First, this is a single center study, therefore care should be taken in applying the results to other hemodialysis patient's population. Second, a study in a tertiary hospital may not represent all ESRD patients in non-hospital setting. However, we found no correlation to dialysis KTV, length or access. Furthermore, we believe this study can represent porphyrin metabolism and removal in most modern centers. Third, the cohort is limited by size, and unknown risk factors to PCT might not be represented in our cohort. However, even if PCT is still occasionally relevant in ESRD, our cohort is sufficient to demonstrate PCT is not as common as previously described.

In conclusions, this study shows, for the first time, that in modern hemodialysis era, possibly due to improved porphyrins' metabolism and dialysis removal, PCT is much less prevalent than previously reported in the past.

Authors' contributions

Conception and study design: SG, OZ, YE, BRZ, AL. Acquisition, analysis, and interpretation of data: SG, OZ, YE, AS, TM, EH, SC, RM. Drafting and revising the manuscript: SG, OZ, YE, AL, AS, TM, EH, SC, RM, BRZ. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

Disclosure

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The results presented in this paper have not been published previously in whole or part, except in abstract format.

Compliance with ethical standards

The study was approved by the local Institutional Review Board with the principles of the Declaration of Helsinki.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

Data availability

Data will be made available on request.

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