Int. J. Biochem. Vol. 12, pp. 873 to 877

0020-711X/80/1101-0873$02.00/0

STUDIES ON THE EXCRETION PATTERN OF PORPHYRINS AND ITS USE AS A TOOL FOR DIAGNOSING BOTH SYMPTOMATIC AND ASYMPTOMATIC CASES OF PORPHYRIA CUTANEA TARDA

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Abstract—1. A family investigation was performed in eleven cases of Porphyria Cutanea Tarda (PCT).

2. By using clinical findings, quantitative measurements and thin layer chromatography (TLC) of urinary porphyrins, overt and subclinical PCT patients have been identified.

3. In the overt type, skin manifestations are present, excretion of urinary porphyrins is increased and the TLC pattern of porphyrins in urine is characteristic for PCT.

4. In the subclinical type, patients have no clinical symptoms, excretion of porphyrins in urine might be normal or enhanced and TLC pattern of urinary porphyrins is typical for PCT.

5. By applying these criteria a clear distinction between hereditary and non-hereditary PCT was possible.

6. Among the 11 families studied, in four families where PCT was hereditary, four members have the overt type and ten relatives the subclinical type.

7. In seven families where PCT was non-hereditary only the propositus has overt PCT and not a single relative showed any clinical or biochemical abnormality.

INTRODUCTION

Porphyria Cutanea Tarda (PCT) has been regarded as acquired or non-hereditary because of its onset in middle or late life. The most important causative factor is usually considered to be abuse of alcohol and it is also associated with the use of other factors such as estrogens, halogenated hydrocarbons and iron. However it has long been suspected that PCT can be an inheritable disease (Waldenström & Haeger-Aronsen, 1963; Perrot & Thivolet, 1970; McEwin, 1973; Dehlin *et al.*, 1973; Prato *et al.*, 1974; Topi & D'Alessandro, 1977).

Specific enzymic defects have been assigned to each porphyria, among them PCT is characterized by a deficiency in the activity of Uroporphyrinogen decarboxylase and recently a reduction of this enzyme has been found in hepatic tissue and erythrocytes of patients and some of their clinically asymptomatic relatives (Kushner *et al.*, 1976; Benedetto *et al.*, 1978; Felsher *et al.*, 1978; Elder *et al.*, 1978; Verneuil *et al.*, 1978). This enzymic defect appears to be inherited as an autosomal dominant trait, with a low penetration; however, although measurements of erythrocyte UPG-Dcase levels in PCT patients and their relatives might allow a clear distinction between the acquired and inherited types of PCT, the technique is not always suitable for routine work; moreover, some of these studies have produced contradictory results (Blekkenhorst *et al.*, 1976).

It has been already reported that a systematic study of the urinary and fecal porphyrins using simple screening methods, such as thin layer chromatography (TLC) is a very useful technique for performing family studies, which can show any minor abnormalities in both clinically symptomatic and asymptomatic PCT patients (Doss *et al.*, 1971; With, 1975, 1976; Piñol-Aguadé *et al.*, 1975; Wider de Xifra *et al.*, 1979; Batlle *et al.*, 1979).

It is also clear that the hereditary of a case of Porphyria can only be elucidated by carrying out a study of both the patient and as many blood relatives as possible.

This report describes eleven cases of PCT, where a family investigation was performed with good collaboration from all relatives, to obtain further information about the existence of two forms of PCT: acquired and hereditary. The biochemical studies include analysis of the urine, blood and feces for porphyrins and for precursors, when available fine needle liver biopsy for porphyrins, and study of the TLC pattern of urinary porphyrins.

MATERIALS AND METHODS

Urinary, fecal and blood porphyrin determinations were performed by the solvent fractionation method described by Rimington (1971). The porphyrin methyl esters were analyzed qualitative and quantitatively by TLC (With, 1975; Wider de Xifra *et al.*, 1979). ALA and PBG were assayed in urine according to Mauzerall & Granick (1956). Porphyrins were investigated in liver biopsy smears by fluorescence microscopy and by solvent extraction, esterification and TLC.

RESULTS AND DISCUSSION

To establish a diagnosis of PCT the following criteria were used: (i) the presence of the clinical syn-

Table 1. Clinical and laboratory data of four families with porphyria cutanea tarda

Family	Case	Sex	Age (years)	Clinical syndrome	Liver biopsy	Urine Porphyrins (g/24 hr)	TLC	Type of PCT
CM	IIb	F	47	No		705	Abn†	Subclinical
	IIc	M	45	No		154	Abn	Subclinical
	IId	M	48	No		415	Abn	Subclinical
	IIIb	M	21	No		50	N‡	—
	IIIc (pr.)*	M	29	Yes	+	1165	Abn	Overt
	IIId	F	29	No		20	N	—
	IVa	M	3	No		10	N	—
	IVb	M	4	No		16	N	—
	IVc	F	6	No		934	Abn	Subclinical
CJ	IIa	F	64	No		16	Abn	Subclinical
	IIb	F	66	No		23	Abn	Subclinical
	IIc (pr.)	M	52	Yes	+	1633	Abn	Overt
	IIIa	F	18	No		36	N	—
	IIIb	F	24	No		18	N	—
FB	Ia (pr.)	M	70	Yes	+	573	Abn	Overt
	IIb	F	42	No		104	Abn	Subclinical
	IIIa	F	10	No		58	Abn	Subclinical
	IIIb	F	16	No		65	Abn	Subclinical
CMI	Ib (pr.)	F	66	Yes	+	4476	Abn	Overt
	IIa	M	38	No		620	Abn	Subclinical
	IIb	F	40	No		13	N	—

* pr. = propositus.
† Abn = abnormal.
‡ N = normal.

drome, skin fragility and blisters on the sun exposed skin areas, occasionally hypertrichosis and hyperpigmentation; (ii) increased urinary excretion of porphyrins, particularly highly carboxylated porphyrins, uro and heptacarboxylic porphyrins; (iii) abnormal and characteristic fluorescence pattern of the urinary methyl ester porphyrins on TLC, with strong bands at the uroporphyrin (8-COOH porphyrin) as well as at the 7-carboxyl porphyrin zone.

By applying these criteria we can identify two types of PCT: overt and subclinical. In the overt type, skin lesions are present, excretion of urinary porphyrins is increased and the TLC pattern is characteristic. Patients with subclinical PCT have no cutaneous manifestations, excretion of highly carboxylated porphyrins in urine might be normal or increased but TLC of the methyl esters of that urine shows the typical pattern for PCT.

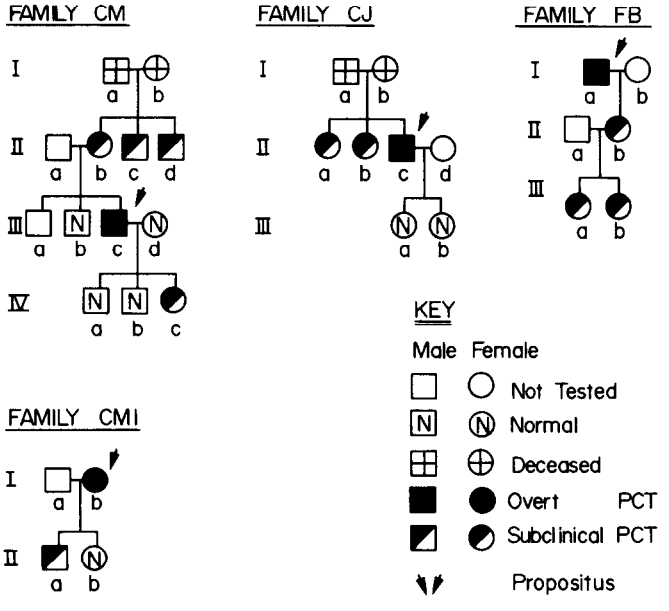

Fig. 1. Pedigree of four families with hereditary PCT.

In both PCT patients and all their relatives urinary excretion of PBG and ALA was normal. Free erythrocyte protoporphyrin was also within the normal range in all cases. Liver biopsy specimens were only available from some of the PCT patients, which showed intensive red autofluorescence, and contained large amounts of uro and heptacarboxylic porphyrins.

For the purposes of discussion we have divided the 11 families studied in two groups: Group I comprises four families where PCT has been defined as hereditary and Group II includes seven families, where PCT was non-hereditary or acquired.

In Table 1 and Fig. 1, the clinical and laboratory data and the pedigree of families of Group I are shown respectively. If we carefully analyze these findings it is clear that among the 21 members examined, four were the patients (CM IIIc, CJ IIc, FB Ia and CMI Ia) having overt PCT, blistering photo-enhanced dermatosis was present, porphyrin fluorescence was intense in liver biopsy smears, porphyrinuria was high and the TLC urinary pattern was typically abnormal. Ten other relatives (CM IIb, IIc, IId, and IVc; CJ IIa and IIb; FB IIb, IIIa and IIIb; CMI IIa) have never developed any cutaneous symptoms, urinary porphyrin excretion was normal or increased but in all ten, TLC of porphyrins in urine was characteristic of PCT, showing that they have subclinical disease. The remaining seven members studied were completely normal.

These four families are therefore an example of hereditary PCT in which ten individuals not having any cutaneous manifestations and some of them having normal urinary excretion, could be diagnosed as subclinical cases, because the TLC pattern of porphyrins in urine was characteristic of PCT.

In Table 2 the clinical and laboratory data of Group II are shown. Figure 2 illustrates the pedigree of seven families in which PCT was Non-hereditary. From these results, among the 32 members studied, it is clear that in the seven overt PCT patients (TM Ia, LN Ia, TJ Ia, PO Ia, PJ Ia, MRJ Ib and MF IIa) the disorder was acquired because cutaneous manifestations, porphyrinuria and characteristic TLC urinary pattern were only present in the propositus; none of the relatives have ever developed any clinical symptom, and both their urinary porphyrin excretion and TLC pattern were normal.

Therefore, by using clinical data and quantitation

Table 2. Clinical and laboratory data of seven families with non hereditary porphyria cutanea tarda

Family	Case	Sex	Age (years)	Clinical syndrome	Liver biopsy	Urine Porphyrins (g/24 hr)	TLC	Type of PCT
TM	Ia (pr.)	M	54	Yes	+	3197	Abn†	Overt
	IIa	M	16	No		19	N‡	—
	IIb	F	18	No		20	N	—
	IIc	F	19	No		10	N	—
LN	Ia (pr.)	M	57	Yes	+	1243	Abn	Overt
	IIa	M	26	No		18	N	—
	IIb	F	28	No		52	N	—
	IIc	F	30	No		10	N	—
	IId	F	37	No		6	N	—
TJ	Ia (pr.)	M	60	Yes	+	1538	Abn	Overt
	IIa	F	17	No		38	N	—
	IIb	F	21	No		10	N	—
	IIc	F	25	No		12	N	—
PO	Ia (pr.)	M	32	Yes		4727	Abn	Overt
	IIa	F	4	No		32	N	—
	IIb	F	6	No		12	N	—
	IIc	F	8	No		11	N	—
PJ	Ia (pr.)	M	60	Yes	+	2032	Abn	Overt
	IIa	M		No		7	N	—
	IIb	M		No		13	N	—
	IIc	F		No		10	N	—
	IId	F		No		21	N	—
	IIe	F		No		22	N	—
	IIf	F		No		20	N	—
	IIg	F		No		18	N	—
MRJ	Ib (pr.)	F	39	Yes		686	Abn	Overt
	IIa	M	14	No		17	N	—
	IIb	M	20	No		10	N	—
	IIc	F	17	No		9	N	—
MF	Ia	M	80	No		29	N	—
	IIa (pr.)	M	22	Yes		7157	Abn	Overt
	IIIa	M	1	No		10	N	—

* pr. = propositus.
† Abn = abnormal.
‡ N = normal.

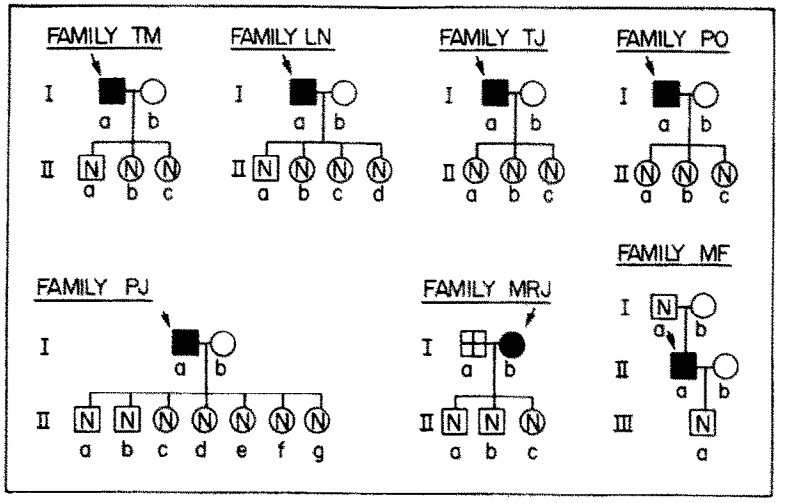

Fig. 2. Pedigree of seven families with non-hereditary PCT.

and TLC of urinary porphyrins we have been able to identify overt and subclinical PCT patients. Among the 11 families studied, in four of these, PCT was a hereditary disease, while in seven other families PCT was a non-hereditary disorder.

These findings are in agreement with the hypothesis on the existance of an acquired and an hereditary form of PCT and stress the importance of carefully performing complete clinical and biochemical investigations of both the patients and all their blood relatives, to be able to determine whether or not there is a pattern of heredity in the family and consequently institute proper therapy and prophylaxis.

Acknowledgements—This work was supported by grants from the CONICET, the University of Buenos Aires and the SECYT. A. M. del C. Batlle and E. A. Wider de Xifra hold the post of Scientific Researchers in the CONICET. We are very grateful to Dr. A. A. Juknat de Geralnik, Dr M. V. Rossetti and Dr V. E. Parera for their valuable help and also to Miss H. Gasparoli, Mr F. Ortega, Mrs I. Jaievsky and Mr D. Sachetti for their skilful technical assistance.

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