Porphyrin Metabolism in Pellagra

Pellagra is an endemic disease in Egypt and other parts of the world. Pellagra involves deficiencies of calories, proteins and other components of the vitamin B complex besides nicotinic acid[1]. The clinical manifestations, including the cutaneous reactions such as hyperkeratosis and pigmentation, probably indicate disturbances in different metabolic processes, especially porphyrin metabolism. In fact, a rise in porphyrin excretion was previously reported by RIMINGTON and LEITNER[2] and by EL MOFTY et al.[3]. This was explained as due to the associated alcoholism, as no such rise was found in non-alcoholic pellagrins.

This stimulated the desire to study porphyrin metabolism in non-alcoholic pellagrins.

Materials and methods. 26 pellagrins were selected for this study; they included 3 females. The age of the patients ranged from 5 to 65 years. The duration of the cutaneous eruption ranged from 3 weeks to 3 years. All patients were examined clinically for evidence of any associated disease. Stools examination and urine analysis were performed. Standard liver function tests including alb/glob. ratio, serum bilirubin, thymol and zinc sulphate turbidities were done. Diarrhoea was observed in 8 patients (7 males and 1 female). Dementia was not observed in any of the patients. Cutaneous changes due to associated ariboflavinosis were seen in 14 patients.

For all patients, urinary, faecal and blood porphyrins were estimated. Quantitative determination of erythrocytic porphyrins were done by the method described by VISHWANATH, GORDON and JAMES[4]. Urinary and faecal porphyrins were determined according to the method of SANO and RIMINGTON[5]. Urinary porphobilinogen (PBG) was determined by the method of RIMINGTON[6].

Daily urinary excretion of nicotinamide methochloride was estimated under normal conditions and in the first 6 h urine after an oral administration of 100 mg nicotinamide by the method of HUFF and PERLZWEIG[7] as modified by ELLINGER and ABDEL KADER[8].

Results. The results of the urinary nicotinamide methochloride before and in the first 6 h after the administration of test dose of nicotinamide, and the urinary, faecal and erythrocyte porphyrins, are presented in Tables I and II.

In 21 cases, the values for urinary, faecal and erythrocyte porphyrins were within normal limits[9] (Table I). In 5 pellagrins out of the 26 cases, the urinary porphyrins

[1] R. PASSMORE and A. P. MEIKLEJOHN, *Biochemical Disorders in Human Diseases* (R. H. S. Thompson and E. J. King and A. Churchill Ltd. 1957), p. 627.
[2] C. RIMINGTON and Z. A. LEITNER, Lancet *2*, 494 (1945).
[3] A. M. EL MOFTY, L. SOLIMAN, M. NADA, M. A. ABDEL AAL and S. H. EMARA, Ind. J. Derm. *13*, 1 (1967).
[4] M. VISHWANATH, W. GORDON and M. JAMES, J. Haemat. *24*, 178 (1964).
[5] S. SANO and C. RIMINGTON, J. Biochem. *86*, 203 (1963).
[6] C. RIMINGTON, Ass. Clin. Path. Broad Sheet, N.S. *20* (1958).
[7] J. W. HUFF and W. A. PERLZWEIG, J. biol. Chem. *169*, 157 (1947).
[8] P. ELLINGER and M. M. ABDEL KADER, Biochem. J. *44*, 77 (1949).
[9] A. M. EL MOFTY, M. KHATTAB, L. SOLIMAN, M. A. ABDEL AAL, M. NADA and S. H. EMARA, J. Egypt. med. Ass. *50*, 285 (1967).

Table I. Values of urinary, faecal and erythrocytic porphyrins in pellagrins with normal porphyrin excretion

No.	Age	Sex	Urinary nicotinamide methochloride		Urine µg per day			mg/day	Stool µg/g dry weight				Blood µg/100 ml			
			24 h before dose mg	6 h after 100 mg dose mg	C	U	T	PBG	C	P	U	T	C	P	T	Haemat. (%)
1	50	♂	0.400	3.00	49.90	2.80	52.70	1.50	1.80	2.70	0.00	4.50	1.20	80.50	81.70	24.50
2	20	♂	0.60	8.00	30.20	0.00	30.20	3.50	–	–	–	–	–	–	–	–
3	55	♂	0.40	10.80	48.10	2.50	50.60	0.60	3.30	1.60	0.20	5.10	0.00	15.60	15.60	34.00
4	45	♂	1.60	12.80	35.20	0.80	36.00	0.40	1.20	1.20	0.00	2.40	2.40	51.00	53.40	24.40
5	35	♂	1.70	10.00	32.30	0.50	32.80	0.70	1.60	2.80	0.10	4.50	8.00	33.50	41.50	30.00
6	5	♂	1.20	–	34.40	4.10	38.50	0.80	2.80	5.40	0.10	8.30	0.00	73.10	73.10	21.20
7	25	♀	0.25	11.20	30.00	2.10	32.10	0.40	1.80	4.00	0.00	5.80	0.00	68.00	68.00	26.50
8	10	♂	0.70	–	61.80	3.30	65.10	1.40	2.10	5.20	0.00	7.30	0.00	40.80	40.80	35.00
9	36	♂	1.05	8.00	45.80	7.10	52.90	2.20	2.90	1.50	0.00	4.40	2.60	30.40	33.00	35.00
10	45	♂	0.90	5.90	29.40	5.80	35.20	0.90	1.30	22.70	–	24.00	0.00	11.30	11.30	32.50
11	65	♂	0.50	2.40	36.80	0.00	36.80	1.20	12.20	20.00	0.30	32.50	0.00	18.50	18.50	44.00
12	18	♀	0.45	2.40	32.70	0.00	32.70	1.00	6.70	11.00	0.00	17.70	–	–	–	–
13	18	♂	1.00	6.00	36.80	2.50	39.30	1.90	8.20	17.30	0.00	25.50	0.00	11.00	11.00	37.00
14	46	♂	0.67	6.80	61.20	13.30	74.50	3.00	6.70	14.70	0.00	21.40	0.00	15.70	15.70	33.30
15	50	♂	1.20	1.60	32.70	0.00	32.70	0.60	5.80	11.70	0.20	17.70	0.00	21.20	21.20	36.00
16	35	♂	4.50	8.40	49.00	5.10	54.10	0.80	7.70	21.70	0.10	29.50	0.00	25.00	25.00	33.30
17	25	♀	1.50	7.80	19.60	0.00	19.60	0.50	2.40	1.80	0.40	4.60	3.40	35.00	38.40	35.00
18	19	♂	1.80	1.20	19.20	–	19.20	1.70	3.10	2.50	1.10	6.70	3.70	102.00	105.70	32.60
19	27	♂	1.00	2.40	12.30	0.00	12.30	0.50	4.00	7.30	–	11.30	3.00	34.00	37.00	32.00
20	12	♂	–	–	66.20	4.90	71.10	4.60	–	–	–	–	0.00	36.00	36.00	36.00
21	40	♂	–	–	49.10	0.00	49.10	3.10	5.50	7.40	0.00	12.90	0.00	14.00	14.00	14.00
Mean			1.13	6.39	38.70	2.70	41.40	1.49	4.26	8.55	0.15	12.96	1.27	37.72	38.99	32.75

C, coproporphyrin; U, uroporphyrin; PBG, porphobilinogen; P, protoporphyrin; T, total.

Table II. Values of urinary, faecal and erythrocytic porphyrins in pellagrins with abnormal porphyrin excretion

No.	Age	Sex	Urinary nicotinamide methochloride		Urine µg per day			mg/day	Stool µg/g dry weight				Blood µg/100 ml			
			24 h before dose mg	6 h after 100 mg dose mg	C	U	T	PBG	C	P	U	T	C	P	T	Haemat. (%)
1	20	♂	0.50	6.00	74.80	15.40	90.20	1.80	21.20	104.10	0.20	125.50	0.00	59.80	59.80	29.00
2	17	♂	0.75	5.00	37.40	1.60	39.00	1.70	26.50	168.80	0.7	196.00	6.40	76.00	82.40	42.00
3	10	♂	1.05	–	17.20	0.00	17.20	1.90	12.30	21.50	0.4	34.20	0.00	175.40	175.40	26.50
4	19	♂	–	–	42.90	1.70	44.60	0.00	4.00	30.60	1.0	35.70	16.00	183.60	199.60	30.00
5	14	♂	3.60	20.50	81.70	0.00	81.70	3.90	11.60	10.20	0.0	21.80	8.50	217.00	225.50	28.20
Mean			1.40	10.50	50.80	3.74	54.50	1.86	15.14	67.04	0.46	82.64	6.18	142.36	148.54	31.14

were within the range for the normal individuals, while there was an apparent increase in faecal and blood porphyrin (Table II). 4 out of these 5 patients showed cutaneous signs of associated ariboflavinosis. Routine tests for liver function failed to show any significant impairment in hepatic function.

We had the chance of re-estimation of porphyrins in 4 of those patients who showed increased porphyrin excretion after the clinical signs and symptoms have disappeared following replacement therapy. Increments in porphyrin could still be demonstrated.

Discussion. The biochemical findings, cited here, with regard to the urinary nicotinamide methochloride confirms the clinical identification of the pellagrous condition. This runs parallel with previous findings of ABDEL KADER et al.[10] and EL RIDI et al.[11].

The results obtained in this study indicate that, in about 20% of cases of non-alcoholic pellagrins, there was increase in faecal and erythrocytic porphyrins, particularly proto- and coproporphyrins. In contrast to alcohol-induced porphyria, the urinary porphyrins were within normal limits.

The relation of this type of disturbed porphyrin metabolism to pellagra is too difficult to elucidate and no plausible explanation for this increment in faecal and erythrocyte porphyrin in some pellagrins could be advocated. There was no correlation between the severity of the cutaneous lesions and the increase in porphyrins. Moreover, this increase in porphyrin could be demonstrated after the disappearance of the cutaneous lesions following replacement therapy.

The associated mild degree of iron deficiency anaemia not uncommonly associated with pellagra may be responsible for such a rise. However, there was no such rise in the other 21 cases of pellagra who suffered from this type of anaemia of more or less the same intensity as indicated by the mean haematocrit value.

The relation of the pellagrous lesions of the skin to nicotinic acid deficiencies in the skin has been established by many workers[12–17]. Many vitamins of the B-complex are, involved in intermediary porphyrin metabolism, namely B 12, pteroylglutamic acid[18], pyridoxal and pantothenic acid[19]. It may thus be suggested that increment in porphyrin excretion associated with pellagra is due to either associated vitamin deficiencies or to an impaired hepatic function. The failure to detect such impairment by routine liver function tests may be due to the fact that the latter are not sensitive enough to show mild impairment in liver function. Normal liver function tests have been obtained in many cases with hepatic porphyrias[18].

That a disturbed porphyrin metabolism may be involved in the mechanism of the photosensitive cutaneous reaction in pellagra seems unlikely. This is suggested by the fact that the increase in faecal and erythrocytic porphyrine could be demonstrated after the disappearance of the cutaneous lesions following replacement therapy.

It has been established that photosensitivity associated with some types of porphyrias is due to formed porphyrins present in the skin namely uro-, copro- and protoporphyrins and that all have similar absorption spectra in the visible light[20]. The study of action spectrum of the skin in pellagra seems essential before any definite conclusion can be reached.

Résumé. La quantité de porphyrins faecaux et sanguins trouvée dans 21 cas de pellagrins normale comparée à celle des cas normaux observés en Egypte. Cependant, dans 5 cas les porphyrins sanguins et faecaux furent plus nombreux et les porphyrins urinaires restèrent en quantité normale.

M. M. ABDEL KADER,
ANGEL H. ZAKI, S. H. EMARA,
A. EL MOFTY and M. M. NADA

Departments of Biochemistry and Dermatology, Faculty of Medicine, Cairo University (Egypt), 20 August 1970.

[10] M. M. ABDEL KADER, A. HABIB and F. YOUSSEF, J. Egypt. med. Ass. *34*, 98 (1951).
[11] M. S. EL RIDI, M. M. ABDEL KADER, A. HABIB, A. HASSABALLAH, C. HAZZI, M. ZAKI and Y. RIAD, Acta physiol. hung. *17*, 429 (1960).
[12] D. T. SMITH and J. M. RUFFIN, Archs. int. Méd. exp. *59*, 631 (1937).
[13] T. D. SPIES, Archs. int. Méd. exp. *56*, 920 (1935).
[14] A. B. ALPORT, P. GHALIOUNGUI and G. HANNA, J. Egypt. med. Ass. *21*, 750 (1938).
[15] G. A. GOLDSMITH, H. P. SARETT, U. D. REGISTER and J. GIBBENS, J. clin. Invest. *31*, 533 (1952).
[16] G. H. FINDLAY, Br. J. Derm. *75*, 249 (1963).
[17] G. H. FINDLAY, L. REIN and D. MITCHELL, Br. J. Derm. *81*, 345 (1969).
[18] A. GOLDBERGE and C. RIMINGTON, *Diseases of Porphyrin Metabolism* (Charles C. Thomas, Springfield, Illinois 1962), p. 150.
[19] M. P. SCHULMAN and D. A. RICHERT, J. biol. Chem. *226*, 181 (1956).
[20] I. A. MAGNUS, Proc. R. Soc. Med. *21*, 196 (1958).