THE EXCRETION OF δ-AMINOLAEVULINIC ACID AND PORPHOBILINOGEN IN THE ACUTE ATTACK OF PROTOCOPROPORPHYRIA*

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The acute attack in protocoproporphyria is characterized by the excretion in the urine of the monopyrrole, porphobilinogen (PBG), and its precursor, δ-aminolaevulinic acid (ALA). These two substances are not usually excreted in abnormal amounts during remission.[1,2]

Attacks vary widely in their clinical severity. Apart from the findings in one case,[2] there have been no detailed studies of the urinary ALA and PBG. This investigation reports the findings in 15 patients. Serial determinations of ALA and PBG have been carried out and the relationship between alterations in urinary excretion of ALA and PBG and the clinical findings has been studied.

*South African genetic porphyria or porphyria variegata.

THE PATIENTS

Of the 15 patients, all of whom were White, 6 were male and 9 were female. In these patients a firm diagnosis of South African genetic porphyria was made — all had a grossly raised faecal porphyrin concentration, 14 of the 15 had cutaneous manifestations, and 12 of the 15 had unequivocal evidence of other affected members in their families. Three patients who had no family history of the disorder had cutaneous involvement and a raised faecal porphyrin concentration. These two features in a patient with an acute attack were regarded as sufficient evidence to support the diagnosis of South African genetic porphyria. Table I lists the relevant details.

TABLE I. DIAGNOSTIC DATA ON 15 PATIENTS WITH PROTOCOPROPORPHYRIA

Patient	*Age*	*Sex*	*Other affected members of family*	*Cutaneous involvement*	*Faecal porphyrin (μg./G.)*	
					*CP**	*PP***
1	23	F	Mother—biochemical +ve. 2 aunts—cutaneous	Incr. fragility—3 yrs.	2,393	1,940
2	26	M	Unknown—an orphan	Incr. fragility—12 yrs. Blisters, scars	1,260	915
3	32	F	Mother and 1 sister—cutaneous	Incr. fragility ± 5 yrs. Blisters, scars	590	468
4	28	F	1 aunt, 1 sister—cutaneous	Incr. fragility ± 5 yrs.	1,194	1,046
5	31	F	Sister, maternal aunt—cutaneous. Mother died at 35 yrs. with probable acute porphyria	Incr. fragility ± 10 yrs.	105	217
6	33	M	1 brother—cutaneous	Incr. fragility—16 yrs. Blisters and erosions	1,834	1,243
7	44	M	A brother and maternal uncle—cutaneous, the latter acute porphyria also	Incr. fragility ± 20 yrs. Blisters, erosions and scars	675	802
8	64	M	2 nephews, 1 brother and 1 sister—cutaneous	Incr. fragility—40 yrs. Scarring with pseudoscleroderma ++	611	1,110
9	32	F	Unknown	Incr. fragility—3 yrs. Blisters and scars	440	532
10	39	F	3 sisters, 1 brother—cutaneous. 2 sisters with acute porphyria	None	448	590
11	77	M	3 brothers—cutaneous	Incr. fragility—40 yrs. Scarring and pseudoscleroderma +++	774	788
12	50	M	Father, 1 brother and 1 sister—cutaneous	Incr. fragility—3 yrs. Scars	816	1,942
13	28	F	Unknown	Incr. fragility—2 yrs.	1,200	865
14	47	F	Uncle—cutaneous	Incr. fragility—17 yrs. Scars	262	700
15	32	F	Father, brother—cutaneous	Incr. fragility—8 yrs.	168	468

Normal range

* CP = coproporphyrin: O — 113 μg./G.
**PP = protoporphyrin: O — 37 μg./G.
Incr. = increased

The patients were graded according to their clinical severity. Severe abdominal manifestations are almost invariable during the acute attack and grading depended on the presence and extent of the following features: neuropathy, encephalopathy, electrolyte disorder (serum sodium 130 mEq./l. or less) and nitrogen retention (blood urea > 50 mg./100 ml.). The grading was as follows:

1. *Mild:* Abdominal presentation with or without evanescent mild neuropathy — rapid resolution of the attack with little or no azotaemia or hyponatraemia.

2. *Moderate:* Abdominal presentation and/or encephalopathy and neuropathy, often with azotaemia and hyponatraemia.

TABLE II. THE CLINICAL FEATURES OF THE ACUTE ATTACK

Case No.	*Days in hospital*	*Abdominal**	*Neuropathy*	*Encephalopathy***	*Blood urea (mg./100 ml.)*	*Serum sodium (mEq./l.)*	*Previous history*
Mild:							
1	9	+++	0	0	73	138	Salpingitis—2 days
2	10	+	0	0	31	134	Influenza—2 days
3	12	++	+	0	51	136	Varicose veins. 'Pentothal' 2 weeks before
4	16	++	0	0	41	133	Influenza—4 days
5	16	+++	+	0	28	136	2 months postpartum. 'Soneryl' 2 weeks before
Moderate:							
6	38	++	0	+	92	117	Respiratory infection 2 weeks. ? sulpha drug
7	37	0	0	+++	65	120	Soneryl 2 weeks before
8	45	+++	++	++	125	124	Hip injury treated 1 week before
9	47	+++	+	+++	51	125	'Doriden' 1 week before
Severe:							
10	42	+++	+++	+++	53	137	Pentothal for 'appendicitis' 2 weeks before
11	43	++	+++	+++	90	122	Bronchitis 1 month before. 'Seconal' 1 week before
12	185	+++	+++	+++	269	128	Influenza 3 weeks before. Seconal ± 10 days before
13	9	+++	+++	+++	54	130	Pregnant. Renal calculus. Phenobarbitone ± 7 days before
14	20	+++	+++	+	186	122	Gastrectomy for DU. Pentothal 2 weeks before followed by soneryl and seconal
15	10	+++	+++	+++	109	128	'Tercin' 3 weeks before

* Abdominal: + = mild, + + = moderate, +++ = severe symptoms.

** Encephalopathy + = confusion, + + = severe confusion and stupor, +++ = gross confusion with hallucinations, delusions or seizures, or coma.

3. *Severe:* Abdominal presentation with gross encephalopathy and profound neuropathy with bulbar involvement, often with azotaemia and hyponatraemia.

The major clinical features are summarized in Table II. Five patients were considered to have had mild, 4 moderate, and 6 severe attacks.

Three of the patients with mild attacks had neuropathy amounting to evanescent slight motor weakness and temporary areflexia. Only Case 1 had fleeting azotaemia. None had hyponatraemia. The stay in hospital varied from 9 to 16 days (mean 12).

The 4 moderate cases all showed azotaemia and hyponatraemia. Encephalopathy in the form of a confusional state was seen in all these patients. Case 7 became stuporose and Case 9 attempted suicide. Cases 8 and 9 had motor neuropathy. The hospital stay varied from 37 to 47 days (mean 41·7).

All the severe cases had quadriplegia with bulbar involvement and encephalopathy with stupor and confusion, often with hallucinations and delusions. Status epilepticus occurred in Case 13. All had azotaemia and 5 of the 6 had hyponatraemia. Three patients died: Case 13 — cardiorespiratory failure, Case 14 — peritonitis and septicaemia, and Case 15 — pulmonary embolism following femoral thrombosis.

METHODS

PBG and ALA were estimated by the method of Mauzerall and Granick.[3] After separation on an ion-exchange column, PBG is estimated with Ehrlich's reagent and ALA is converted to a monopyrrole by condensation with acetyl acetone and estimated with the same reagent. Normal values by this method are: for PBG up to 2 mg./24 hours and for ALA up to 5 mg./24 hours.

RESULTS

Table III summarizes the range of daily excretions of PBG and ALA in the urine. The maximal excretion of ALA + PBG is given as ALA equivalents.

Maximum values for PBG excretion varied from 203·0 to 17·0 and for ALA from 318·0 to 8·3 mg./day. Initially PBG substantially exceeded ALA in all except Cases 13 and 15, both of which were fatal. Furthermore, in Case 13 the ALA excretion of 318 mg./day far exceeded all other ALA values. On discharge from hospital the PBG values were normal or near normal in 8 patients and slightly elevated in 4 others. ALA excretion was normal in all except the 3 fatal cases. In these cases (13, 14, 15) the excretion of ALA and PBG had declined markedly by the time of death.

If the parameter ALA plus PBG is taken as the index of the degree of disturbance in the pyrrole metabolism, it is obvious that there is some correlation with the clinical grading of severity. Thus the mild cases have appreciably lower values (mean 70·6 mg./day). The difference between the moderate (mean 146·1 mg./day) and the severe cases (mean 218·7 mg./day) is less striking. There are discrepancies. Thus case 12, the most severe to survive, excreted only 57·5 mg. at the height of the attack, but spent 185 days in hospital, while case 5, a mild case, excreted 164·6 mg./day and spent only 16 days in hospital.

TABLE III. THE DAILY EXCRETION OF PBG AND ALA IN THE ACUTE ATTACK

Case No.	*Number of observations*	*PBG** *(mg./24 hrs.)*	*ALA** *(mg./24 hrs.)*	*Maximum ALA+PBG†* *(mg./24 hrs.)*
Mild:				
1	8	19·6– 0·4	11·8– 1·5	34·6
2	7	17·0– 2·3	11·5– 2·0	31·2
3	5	28·8– 2·6	8·3– 2·0	41·7
4	11	40·9– 3·9	33·4– 3·0	80·9
5	11	106·3– 0·0	57·4– 1·1	164·6
Moderate:				
6	33	132·5– 9·6	51·3– 0·7	205·0
7	7	28·5– 3·0	23·3– 2·8	56·3
8	44	203·0– 1·5	85·0– 1·8	322·0
9	8	66·0– 7·3	13·9– 3·9	91·1
Severe:				
10	21	126·1–11·9	76·7– 2·3	201·2
11	24	77·2– 0·5	51·3– 0·5	140·8
12	44	38·6– 0·2	16·6– 0·2	57·5
13	7	156·8–39·4	318·0–28·5	499·6
14	15	123·0–22·4	41·4–12·1	194·1
15	5	49·0–18·0	51·1‡	

* PBG and ALA — maximal and minimal excretions.

† PBG + ALA — expressed as ALA equivalents.

‡ Single determination when PBG was 24·7 mg./24 hours.

Representative Case Reports

Figs. 1 - 4 portray the biochemical and clinical features of 4 representative patients: 1 mild, 1 moderate, and 2 severe — one with a short and the other with a protracted course.

*Fig. 1, Case 5, a primipara (1 week).** Two months postpartum. Admitted with abdominal pain and mild motor weakness of the legs with areflexia. Pain settled by the 5th day and the neuropathy had resolved by the 12th day. There was neither azotaemia nor electrolyte disorder. Promazine, 150-300 mg./day, was given throughout, and stilboestrol (to supress lactation) from the 4th day. ALA and PBG fell rapidly to normal levels within 12 days.

Fig. 2, Case 8, a farmer (1 week). Admitted with severe abdominal pain and distension, and motor weakness of the proximal muscles of the legs with areflexia. Abdominal pain had subsided by the 10th day. The confusion had resolved, but the neuropathy persisted until the 20th day. The initial hyponatraemia was rapidly corrected, but the azotaemia subsided very slowly. The pulse rate throughout showed a marked lability. ALA and PBG were markedly elevated for the first 13 days, but reached normal values by the 31st day. Pyridoxine therapy was probably coincidental with spontaneous improvement.

Fig. 3, Case 11, a farmer (2 weeks). Admitted with severe confusion and quadriplegia with rapid deterioration despite improvement in the azotaemia and rapid correction of the hyponatraemia. Decline in the excretion of ALA and PBG commenced on the 5th day and reached normal levels by the 11th day. The confusion had resolved, but the neuropathy persisted until the 16th day. Urinary tract infection was successfully treated with 'furadantin'. The administration of adenosine monophosphate (AMP) coincided with improvement in the mental status, but ALA and PBG values had already shown a decline.

*Figures in brackets refer to estimated duration of the acute attack before admission to hospital.

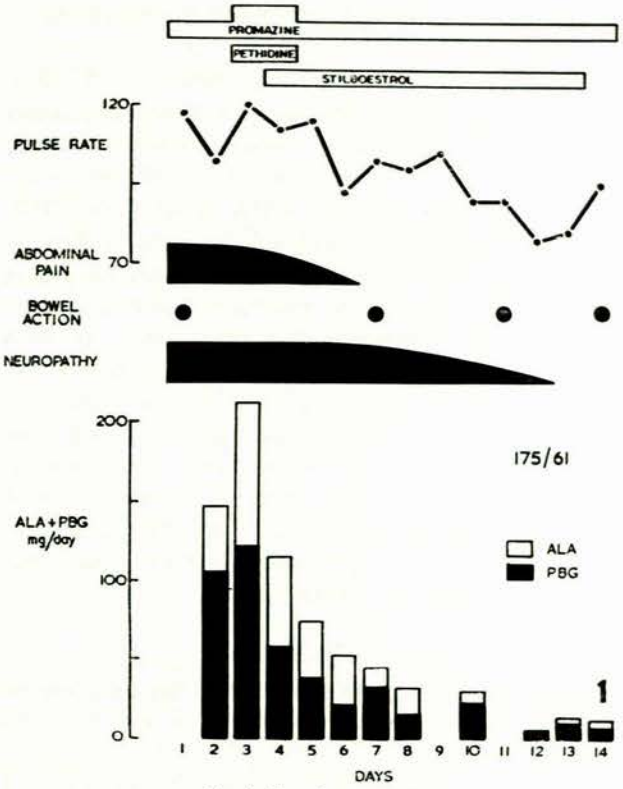

Fig. 1. Case 5 — see text.

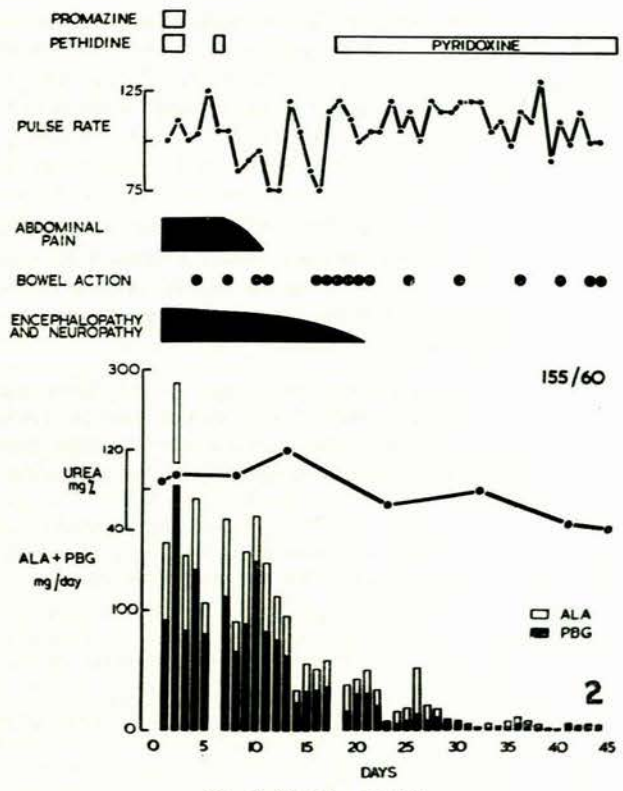

Fig. 2. Case 8 — see text.

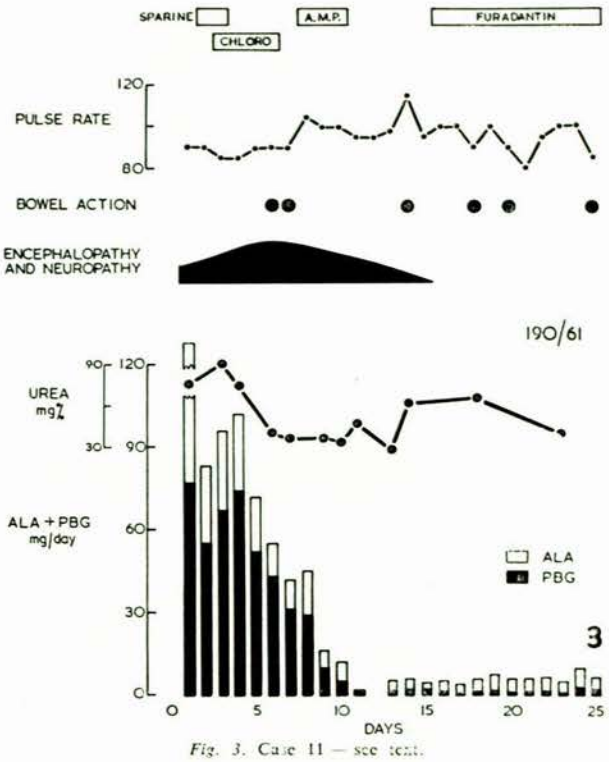

Fig. 3. Case 11 — see text.

Fig. 4, Case 12, a brandy distiller (2½ *weeks*). Admitted in a critical condition with profound quadriplegia and bulbar involvement. In addition he had bronchopneumonia and peripheral circulatory collapse. Tracheotomy was performed and intermittent positive-pressure respiration (IPPR) was commenced. Although ALA and PBG excretions had declined markedly by the 3rd day, azotaemia was progressive and was accompanied by acidosis and purpura and the later development of paroxysmal auricular fibrillation. Following haemodialysis on the 6th day, improvement commenced and by the 9th day IPPR was no longer necessary. By the 16th day he had slight knee movement and ALA and PBG had reached normal levels. Progress was very slow and marked by recurrent urinary infection. By the 56th day the tracheotomy wound was closed. On the 77th day he sat up for the first time and on the 123rd day was able to walk 25 yards unassisted. He was discharged on the 185th day with residual weakness of the extensors of the thighs, shoulders and wrists. A vesical calculus was successfully removed 3 months later.

Progress

In all cases the daily excretion of the two precursors declined to normal within 1 - 4 weeks. The initial fall in PBG and ALA excretion was generally rapid with marked parallel improvement in the abdominal manifestations, the encephalopathy, the azotaemia and the hyponatraemia. Improvement in the neuropathy was frequently dissociated from the biochemical improvement, gross disability persisting for weeks or months despite a normal urinary ALA and PBG excretion. The tachycardia, too, often outlasted the biochemical disturbance.

DISCUSSION

Although varying considerably in magnitude, excretion of ALA and PBG was raised during the acute attacks in all 15 patients. The first random specimen analysed has usually contained the highest concentration. It is probable that excretion was considerably higher at an earlier stage,

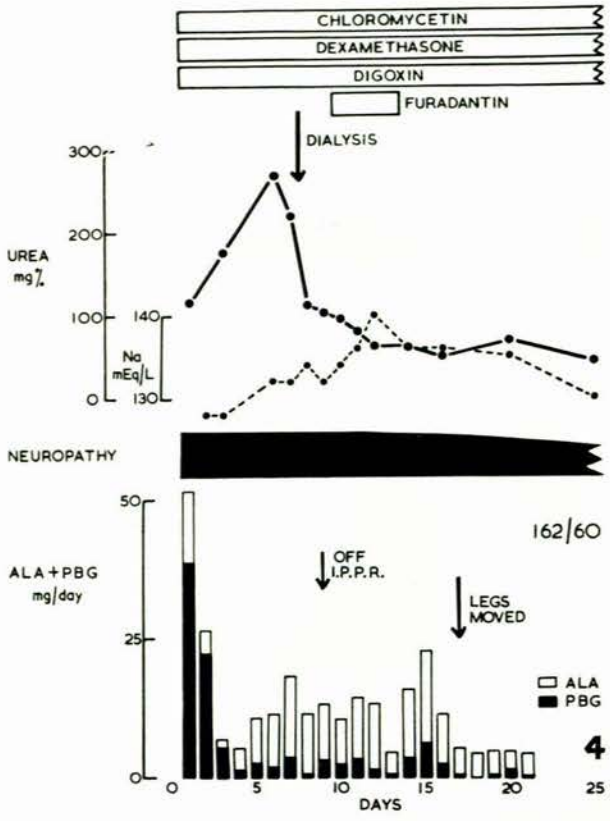

Fig. 4. Case 12 — see text.

since most of these patients had had acute symptoms for many days before admission to hospital. This may well be the explanation of the relatively low figures for Case 12, one of the most severe cases we have seen. He had developed suggestive signs and symptoms at least 14 days before admission.

The pattern of excretion has been one of relatively rapid decrease within a period not usually exceeding 4 weeks. Normal or near normal figures are reached in the majority of patients. Some patients continue to excrete small amounts of ALA and PBG for longer periods. Such patients need to be observed further to ascertain whether this will eventually resolve. Thus in Case 10, at follow-up 3 months after discharge, no PBG was detectable. Numerous reports of the beneficial effects of various therapeutic agents must be treated with the greatest reserve. Sudden improvement in the clinical status is not infrequent, but serial determination of ALA and PBG may show that biochemical improvement has preceded therapy. This is well illustrated in Case 11, where the excretion of both substances had already declined substantially during the 4 days before treatment with adenosine monophosphate.

The ALA and PBG excretions have been comparable in magnitude to those recorded in the acute phase of Swedish genetic porphyria.[4] The Swedish patients excrete ALA and PBG in the latent phase and in remission.[1,4-7] Therefore, the finding of these substances in the urine of such patients (even with suggestive symptoms) cannot be taken as proof of an acute attack. However, the finding of ALA and PBG in the urine of a South African patient is best regarded as reliable evidence of an acute attack.

When due allowance is made for the probable duration of the attack, the urinary ALA and PBG are reasonably good indices of its severity, but there appeared to be a better correlation between ALA plus PBG (as ALA equivalents) and the clinical severity. Attention is drawn to the fact that in two of the fatal cases initially ALA excretion exceeded PBG and, furthermore, in Case 13, ALA amounted to 318 mg./24 hours. This may be interpreted as the result of an acute overload of ALA which has exceeded the capacity of the ALA dehydrase system. This reversal of the usual ALA/PBG ratio may have serious prognostic significance.

SUMMARY

The daily excretion of ALA and PBG has been studied in 15 cases of South African genetic porphyria of varying severity.

There is some correlation between the excretion of these precursors and the clinical severity, lower values being encountered in the mild cases.

The pattern of excretion in the acute attack is one of rapid fall to normal in a period of 1 - 4 weeks with resolution of the abdominal manifestations, the encephalopathy and electrolyte disorder. Improvement in the neurological disorder is frequently dissociated and disability persists after ALA and PBG excretions have returned to normal.

PBG exceeds ALA, but they both show the same trend, and in South African patients raised excretion is best regarded as evidence of an acute attack. The possible serious prognostic significance of the finding of an excess of ALA over PBG is mentioned.

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