PORPHYRIA CUTANEA TARDA AND DIABETES

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The association of porphyria cutanea tarda with diabetes mellitus has previously been noted, and is perhaps not unusual. The case here reported illustrates the association of these conditions, and is of particular interest in that the tolbutamide prescribed for the treatment of the diabetes may have induced the clinical manifestation of the porphyria.

Case Report

The patient, a farmer aged 68, has 13 siblings, but knows of no similar condition in his family. After "shell-shock" in 1918 he developed a tremor which has persisted unchanged and for which he has taken phenobarbitone, 1 gr. (65 mg.) daily, for five years. His consumption of alcohol has been heavy for over 40 years. He has experienced no attacks of abdominal pain and no organic nervous symptoms.

In 1956, after several attacks of balanitis, he was found to have persistent glycosuria and a fasting blood-sugar of 270 mg./100 ml., and was diagnosed as a diabetic of the elderly obese type. He neglected his diet for the next 18 months, during which he felt vaguely unwell but suffered no loss of weight, polyuria, or polydipsia. In June, 1958, he was again advised to diet, and tolbutamide, 0.5 g. t.d.s., was prescribed. The glycosuria was soon controlled, and the dose was reduced to 0.5 g. b.d. and then to 0.5 g. daily.

Four weeks after he began to take tolbutamide he first noticed blisters on the backs of the hands and fingers. These appeared singly at intervals of a few days and were associated with slight burning pain. Their development was usually spontaneous, occasionally related to trauma but never to exposure to light. They were tense blisters, 1-2 cm. in diameter, sometimes haemorrhagic, arising on normal skin and healing to leave scars; they at once suggested the diagnosis of porphyria cutanea tarda.

On general examination the patient was obese and plethoric. The liver was enlarged one fingerbreadth below the costal margin and was firm. Slight gynaecomastia and palmar erythema were present but no spider telangiectasia. Body hair and pigmentation were normal. No abnormality was detected in cardiac, respiratory, or central nervous systems.

Investigations

Glucose-tolerance Test (50 g. glucose).—Blood-sugar estimations at half-hourly intervals showed 140, 193, 248, 268, 206 mg./100 ml. Glucose 1% was present in the urine at one and two hours.

Liver-function Tests.—Serum alkaline phosphatase, 4.3 Bodansky units; thymol turbidity, 3 units; thymol flocculation, nil; plasma bilirubin, 0.9 mg./100 ml.; plasma protein, 6.2 g./100 ml.; electrophoresis pattern normal.

Porphyrin Studies.—(a) The urine showed a slight orange coloration. No porphobilinogen could be detected with the method of Watson and Schwartz (1941). The urine, untreated and after extraction with amyl acetate, showed a strong red fluorescence in ultra-violet light, with bands at 540 Å and 575 Å. Exhaustive extraction with ether acidified with acetic acid demonstrated the fluorescence of uroporphyrins in the residual fluid phase (Varley, 1954). (b) A filtered

20% suspension of faeces in 10% acetic acid gave a strong red fluorescence in ultra-violet light. (c) Serum: no red or pink fluorescence was seen in ultra-violet light.

Progress

While the patient was in hospital the alcohol and barbiturate were stopped. After one week there was no decrease in the porphyrinuria, as shown by comparison spectroscopically with a standard solution of quinine, and one new blister appeared. He was then placed on a controlled low-carbohydrate diet and the tolbutamide was stopped. After 48 hours there was a detectable decrease in the ultra-violet fluorescence of the urine, and this continued up to the patient's discharge four days later.

For the past eight months the diabetes has been controlled by diet alone, and no further blisters have developed, though he has resumed the consumption of alcohol. Further examination of the urine showed a raised uroporphyrin (880 µg./day—normal 5-30 µg.), but normal coproporphyrin (34 µg./day) and no porphobilinogen. The faeces showed a rise in the coproporphyrins (158 µg./g. dry weight—normal 0-20 µg.) and in the total protoporphyrin (42 µg./g. dry weight—normal 0-30 µg.).

Comment

The biochemical investigations were incomplete, but the findings were typical of the cutanea tarda type of hepatic porphyria. Porphobilinogen characteristic of the acute and so-called mixed types is absent in cases without abdominal or neurological symptoms (Waldenström, 1957).

The association of porphyria and diabetes has been recognized for some years. Sterling, Silver, and Ricketts (1949) found diabetes in three out of eight patients with acute porphyria. Freedman (1956), in reporting a case of diabetes with the "mixed" form of porphyria, suggested that the association was fortuitous. Berman and Bielický (1956), however, found that 15 of their 36 patients with porphyria cutanea tarda were diabetics. Berman (1956) drew attention to the frequency of diabetes in other published cases of porphyria cutanea tarda. Seven of the 26 men, but none of the eight women, with this condition reported by Brunsting (1954) were diabetic, as were two of the patients of Borda and Campins (1950). Berman and Bielický (1956) examined diabetic-clinic clientele for porphyrinuria and for clinical evidence of porphyria cutanea tarda. They found the latter in 13 (1%) of 1,250 male diabetics, but in none of 1,430 females. Further they found porphyrinuria in eight patients without skin lesions. As examination of the urine alone may fail to detect cases of hepatic porphyria in remission (Rimington, 1952), the association of porphyria with diabetes may be still higher than these figures suggest, and a routine search for abnormal faecal porphyrins, particularly in male diabetics over 40 years of age, would be of interest. The clinical manifestations of hepatic porphyria could possibly be confused with those of diabetic neuropathy, and the combination of diabetes, hepatomegaly, and cutaneous pigmentation may suggest haemochromatosis (Freedman, 1956).

It seems probable that the association of diabetes and porphyria should no longer be regarded as fortuitous. Diabetes has been reported with all forms of hepatic porphyria—that is, using Waldenström's (1957) classification, with acute intermittent porphyria, porphyria cutanea tarda hereditaria, and porphyria

cutanea tarda symptomatica. It has been most frequently reported with the last, whence the great predominance of males. Clinical or biochemical evidence of porphyria has usually followed the diagnosis of the diabetes by several years, but has occasionally preceded it (Berman and Bielický, 1956). There would seem to be no evidence that the conditions are genetically linked. The nature of their biochemical relationship is still a matter for speculation.

The drugs most commonly implicated in the provocation of porphyria are alcohol, barbiturates, and sulphonamides. Circumstantial evidence, in particular the decrease in the ultra-violet fluorescence of the urine only after the tolbutamide was stopped, suggests that this drug may have been responsible in our patient, though it would be unreasonable to place the responsibility on the tolbutamide alone in a patient regularly consuming alcohol and barbiturates.

Summary

A case is reported of porphyria in association with diabetes mellitus.

The possibility that the clinical manifestation of porphyria cutanea tarda was induced by tolbutamide is considered.

The association between porphyria and diabetes is discussed.

We are indebted to the late Dr. N. Lawrie for the biochemical investigations.

REFERENCES

- Berman, J. (1956). *Z. ges. inn. Med.*, **11**, 186.
 — and Bielický, T. (1956). *Dermatologica (Basel)*, **113**, 78.
 Borda, J. M., and Campins, H. (1950). *Prensa méd. argent.*, **37**, 697.
 Brunsting, L. A. (1954). *A.M.A. Arch. Derm. Syph.*, **70**, 551.
 Freedman, A. L. (1956). *Ann. intern. Med.*, **44**, 391.
 Rimington, C. (1952). *Acta med. scand.*, **143**, 177.
 Sterling, K., Silver, M., and Ricketts, H. T. (1949). *Arch. intern. Med.*, **84**, 965.
 Varley, H. (1954). *Practical Clinical Biochemistry*, 1st ed., p. 408. Heinemann, London.
 Watson, C. J., and Schwartz, S. (1941). *Proc. Soc. exp. Biol. (N.Y.)*, **47**, 393.
 Waldenström, J. (1957). *Amer. J. Med.*, **22**, 758.

Medical Memoranda

Onchocerciasis Presenting without Dermatitis

It is well known that a patient from tropical Africa complaining of an irritating skin rash requires investigation for onchocerciasis, but it is not generally known that the presenting symptom may be a swollen limb in the absence of skin rash or irritation. The swelling is diffuse and firm, like a Calabar swelling, and may involve the limb completely or in part. Dubois and Forro (1939) observed non-pitting oedema of the lower leg in association with other signs of onchocerciasis, and Chartres (1955) described swelling of the upper limb as part of a reaction to the treatment of onchocerciasis with diethylcarbamazine, but the following case histories indicate that swelling of a limb may be the first clinical manifestation of infection with *Onchocerca volvulus*.

CASE REPORTS

Case 1.—An Englishman aged 37, who had spent 15 years in Uganda, returned to Britain on leave in April, 1953. The following month he developed pain in the right shoulder and a diffuse swelling of his right hand and forearm. The pain and swelling persisted. Two months later the swelling increased, and he observed that the right shoulder was also swollen. There was no skin rash or irritation. One month later (August, 1953) the swelling began to subside and had disappeared by the time he reported at the Hospital for Tropical Diseases at the end of August. No clinical abnormalities were detected, and routine tests for filariasis were as follows: Day and night blood, no microfilariae found; white-cell count, 15,300/c.mm. (eosinophils 60%); filarial skin test, positive; filarial complement-fixation test (C.F.T.), strongly positive; skin shavings, scanty embryos of *O. volvulus* found.

Case 2.—An Englishwoman aged 31, who had spent six years in Uganda, finally left Africa in March, 1956. Six months later she noticed aching pain in her right shoulder, and two months later the shoulder became swollen. Swelling and pain persisted, the pain being aggravated by lying on the right side, by exercise, and by carrying anything heavy in the right hand. After exercise such as tennis the swelling of the right shoulder increased temporarily and involved the upper arm. Dermatitis and pruritus were absent. She was seen at the Hospital for Tropical Diseases in April, 1959, two and a half years after the onset of her symptoms, and was found to have a diffuse swelling of her shoulder, which was firm, non-pitting, and of normal skin colour, resembling a Calabar swelling. The skin appeared normal. Investigations: day and night blood, no microfilariae found; white-cell count, 7,600/c.mm. (eosinophils 18%); filarial C.F.T., weakly positive; numerous embryos of *O. volvulus* found in skin shavings from the right shoulder but absent from other sites; on x-ray examination of right shoulder, the joint appeared normal.

COMMENT

In both patients the swelling was localized to the right upper limb, lasting for three months and two and a half years respectively, and the diagnosis of onchocerciasis was confirmed by demonstrating embryos of *O. volvulus* in skin shavings. Loiasis cannot be excluded on the grounds of absence of microfilariae of *Loa loa* in the day blood, but this finding, taken in conjunction with the fact that both patients had lived in Uganda, one of the regions of tropical Africa in which loiasis is not endemic, almost certainly excludes loiasis. In addition, a Calabar swelling usually disappears in a few days, but even when it remains for a longer period it is very unlikely to persist for three months or more. Bancroftian filariasis can be excluded by the absence of microfilariae of *Wuchereria bancrofti* in the night blood, and by the fact that the oedema cleared up spontaneously in one patient and involved the proximal, not the distal, part of the limb in the other patient; furthermore, there was no history of lymphangitis and no enlarged lymph nodes were palpated.

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REFERENCES

- Chartres, J. C. (1955). *W. Afr. med. J.*, **4**, 130.
 Dubois, A., and Forro, M. (1939). *Ann. Soc. belge Méd. trop.*, **19**, 13.