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HEMOCHROMATOSIS AND PORPHYRIA CUTANEA TARDA

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In 1953 Bolgert, et al,[1] mentioned, for the first time, the coexistence of iron abnormalities in cases of porphyria cutanea tarda. Eight of their nine cases showed a significant hypersideremia, and in one of these, a patient with diabetes and diffuse hyperpigmentation, the liver biopsy demonstrated excessive parenchymal iron.[2-7] This constellation of findings has been repeatedly found thereafter. A search of the American literature discloses only one case in which this association is explicitly discussed.[8] In another[9] the biopsy displayed "rather large amounts of hemosiderin in the liver and Kupffer cells", but this finding was not further referred to in the article. In 1960 Lamont, et al.,[10] in South Africa, published their findings pertaining to plasma iron and liver pathology in African porphyrics of the nongenetic variety and stressed the overwhelming frequency of elevated serum iron and increased siderotic deposits in the liver. In striking contrast to the cases of so-called African siderosis, the iron-binding capacity approached complete saturation giving a picture "almost identical with that found in idiopathic hemochromatosis and transfusion siderosis". Unaware of the European literature, they mentioned that "it would be of great interest to know whether similar disturbances in iron metabolism occur in other groups of porphyric patients, both in South Africa and elsewhere".

We wish to call attention to this interesting association in the following case report.

Case Presentation

A 50 year old white lady was seen for the first time in June 1963, with the chief complaint of tension and irritability. In 1958 she had become aware of skin darkening on exposed areas and increasing facial hair. In 1961, in another hospital, the diagnoses of cirrhosis and diabetes mellitus were made on the basis of a liver biopsy and a two hour postcibal blood sugar of 180 mgm.%.

The patient had had a hysterectomy for endometriosis in 1946 at which time she had received three blood transfusions. She denied the use of alcoholic beverages. The family history revealed maturity onset diabetes in both the mother and father.

Physical examination revealed a middle-aged woman with a tanned appearance. She displayed facial hirsutism, conjunctival injection, erythema palmaris and several spider nevi. The blood pressure was 120/75 and the cardiovascular examination was within normal limits. The liver was palpated 10 cm. below the right costal margin and demonstrated slight tenderness with increased consistency. The spleen was palpable 5 cm. below the costal margin. The remainder of the physical examination was unremarkable.

Fifth Medical Division.

Laboratory studies revealed: Hemoglobin 14.3 grams%, WBC 5,200; differential: polymorphonuclears 38%, eosinophils 2%, lymphocytes 48%, leukocytoid lymphocytes 10%, monocytes 2%, normal urinalysis; non-reactive serology. BUN 13 mgm.%; S-GOT 36 u.; alkaline phosphatase 3.1 Bodanski units; BSP 15% retention at 45 minutes; serum iron 150 mcg. (normal 60-120); iron-binding capacity 167 mcg.%; sodium 142 mEq/1.; potassium 4.0 mEq/1.; chlorides 104 mEq/1.; CO_2 23.5 mEq/1. Three-hour glucose tolerance test: fasting glycemia 80 mgm.%, one hour 280 mgm.%, two hours 330 mgm.%, three hours 240 mgm.%. Serum protein electrophoresis: total protein 6.4 gm.%, albumin 2.93 gm.%, alpha-1 0.45 gm.%, alpha-2 0.44 gm.%, beta 0.93 gm.%, gamma 1.65 gm.%. Bone marrow: myeloid/erythroid ratio was low 1.4:1. There was a slight increase in overall marrow cellularity with moderate erythroid hyperplasia. Gastric mucosa: Chronic inflammatory changes. Iron stains were negative. Electrocardiogram was normal. Chest x-ray and upper GI series were unremarkable. The liver biopsy revealed changes consistent with cirrhosis plus excessive iron deposition.

In September 1963, the patient was seen in the Dermatology Department with complaints of hyperpigmentation, easy bruisability and alopecia of the scalp. Examination revealed a scarring alopecia of the scalp, heliotrope eyelids, hyperpigmentation in sun-exposed areas, palmar erythema, spider angiomata over anterior chest, atrophic scars of the forearms and facial hypertrichosis. Questioning revealed that the patient had noted a reddish tinge to her urine and during the preceding summer, she had noticed some "blisters" over her fingers. The diagnosis of porphyria cutanea tarda was confirmed by the urinary finding of 5.18 mgm. of uroporphyrins/24 hours and 3.38 mgm. of coproporphyrins/24 hours. A scalp biopsy showed scarring alopecia and a skin biopsy of the right forearm demonstrated increased melanin.

Discussion

With the exception of rare instances in which there is a familial incidence with strong suggestion of simple mendelian patterns,[11,12] most investigators feel that in adult cutaneous porphyria,[1] also referred to as porphyria cutanea tarda and urocoproporphyria,[13] exogenous factors are of the utmost etiologic importance. Watson[11] has stressed the importance of constitutional or idiosyncratic factors that appear to be necessary for the overt manifestation of the disease. Environmental factors, notably the prolonged use of alcohol,[1,7,14,15] seem to be of paramount importance.

Schmid, et al.,[16] have designated that porphyria cutanea tarda belongs to the group of hepatic porphyrias. In spite of this, the disease is still thought of either in terms of a skin disorder or a biochemical aberration with a nebulous organic substratum. The validity of Schmid, Schwartz and Watson's view has been confirmed by more recent work[6] indicating that the earliest and most constant finding in urocoproporphyria is the increased porphyrin content of the liver which is present even in the absence of skin changes or excretory abnormalities.

The next most common morphologic alteration in urocoproporphyric livers is hemosiderosis,[6,18] which can be present when routine methods of study fail to disclose other abnormality. However, in contrast to the increased hepatic porphyrins, it is not an obligatory finding and may be absent in far-advanced cases even when specifically sought. It is also well-known that when the usual histological techniques are revealing, the morphologic picture of the liver may range from that of fatty metamorphosis, to chronic hepatitis, portal fibrosis and different forms of cirrhosis.[6,7,15]

As indicated above, the finding of both a hypersideremia and an abnormally saturated iron-binding capacity, as in our case, is quite frequent in patients with porphyria cutanea tarda.[1,6,7,10]

The explanation for the intriguing association of porphyrin and iron abnormalities was at one time based on a notion of a metabolic block in the main pathway of porphyrin biosynthesis with secondary defective utilization and ensuing accumulation of iron.[19] Evidence to support this view is wanting. Currently, it is believed that in porphyria cutanea tarda there is an actual overproduction of physiologically inactive porphyrin side-metabolites brought about by prompt oxidation of porphyrin precursors with deviation of the latter from the main synthetic pathway.[20,21]

Unless it is shown in the future that increased porphyrinogenesis of itself effects an excessive iron absorption, it would appear that a simple causal connection between these two substances is hard to uphold. In regard to this point, it is pertinent to recall that the prevailing view with respect to the etiology of secondary or nutritional, nongenetic hemochromatosis,[22] involves a combination of hepatic damage plus the presence of dietary factors. Secondary hemochromatosis[23] is a rather nonspecific finding in the sense that it has been found in a multiplicity of liver disorders: toxic, nutritional, infectious and neoplastic.[23,24] It is our contention that porphyria cutanea tarda is another example of secondary increase in iron absorption and liver deposition resulting in the pathologic picture of hemosiderosis, if the liver is otherwise normal; or hemochromatosis, if there is an underlying cirrhosis.

Excesses of both liver iron and porphyrins are, therefore, related to each other but as effects of a common, probably multiple causal combination. They are co-ordinated phenomena, presumably dependent upon either genetic factors or acquired vulnerability from previously established disease. Their isolated or combined excesses may well be due to variations in the etiologic constellation.

With the foregoing in mind, one can understand the "resemblances" between porphyria cutanea tarda and hemochromatosis that have been noted in the literature:[18] similar age at onset, sex partitioning, geographic distribution, antecedent alcoholism, frequency of diabetes mellitus and diffuse pigmentation. In porphyria cutanea tarda there is, to be sure, a real but secondary derangement in iron metabolism. The porphyria itself is secondary. Both are effects; neither necessarily complicates or implicates the other. The source of most of the confusion and vagueness concerning both of these entities stems from the fact that they have been regarded as diseases rather than — what they actually are — complex and fascinating symptoms.

It is hoped that this change in perspective will tend to clarify the relationship between prophyria cutanea tarda and hemochromatosis and possibly stimulate experimental verification of the concept proposed.

SUMMARY

A case of porphyria cutanea tarda exhibiting diabetes mellitus, cirrhosis and features of pathologic iron storage is presented. The relationship between porphyria and altered iron metabolism is discussed, and an explanation for the resemblance between porphyria cutanea tarda and hemochromatosis is suggested.

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