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Co-Existent Klinefelter's Syndrome, Acquired Cutaneous Hepatic Porphyrria and Systemic Lupus Erythematosus

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A patient is reported with Klinefelter's syndrome, systemic lupus erythematosus (SLE) and acquired cutaneous hepatic porphyria. Although patients with chromatin positive Klinefelter's syndrome may have elevated auto-antibodies, this patient had definite diagnostic criteria for SLE. Furthermore, evidence of disturbed porphyrin metabolism compatible with acquired cutaneous hepatic porphyria was found. It is speculated that the major disturbance in our patient's porphyrin biosynthesis may be distal to Δ -ALA synthetase. Any association between the three diseases is conjectural; however, it is noteworthy that both SLE and porphyria are more common in the female and that our patient had two X chromosomes in addition to a Y chromosome in his karyotype.

Klinefelter and co-workers¹ in 1942 first reported nine males with eunuchoid habitus, gynecomastia, small testes, aspermatogenesis, moderately reduced function of the Leydig cells and increased gonadotrophins. Jacobs and Strong² and Ford et al³ demonstrated in 1959 that Klinefelter's syndrome was due to an X-chromosome polysomy. Although various other karyotype patterns have since been reported, the basic chromosomal abnormality is the supernumerary X-chromosome in at least one line of somatic cells.

Co-existent with Klinefelter's syndrome, many diseases have been reported. K. L. Becker⁴ reviewed their

Mayo Clinic experience of 50 patients with Klinefelter's syndrome and listed 53 associated diseases. While two of their cases had rheumatoid arthritis, none had systemic lupus erythematosus (SLE) or porphyria. However, SLE and porphyria have also been associated and recently Harris et al⁵ collected six such cases. The chromosome patterns were not described.

This report describes a patient with Klinefelter's syndrome associated with both SLE and acquired cutaneous hepatic porphyria.

Case Report

R.T., a 35-year-old press operator, was admitted to the Henry Ford Hospital for complaints of recurrent postprandial epigastric distress with seasonal variation for 15 years, irritation in his eyes for 10 years, unsatisfactory sexual performance for 10 years, migratory arthralgia for six months, and a pink urine for two months.

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A duodenal ulcer had been previously diagnosed radiographically; it had responded to antacid and diet therapy but had recurred with ingestion of alcoholic beverages. The patient's eyes had always been dry and even as a child he had been unable to produce tears. He was married at the age of 17 and allegedly fathered a child a year later. His second marriage has been infertile. Joint complaints started with a painful swelling of the left ankle; subsequently involved were the right ankle, both knees, wrists, the metacarpal-phalangeal and proximal interphalangeal joints of both hands in a migratory, polyarticular pattern. Treatment was initiated at another hospital with corticosteroids two months prior to his admission here, but the joint symptoms increased and he noticed a pink color to his urine for the first time. His mother had undergone many abdominal operations but no details are available.

On physical examination, this garrulous man was 69 inches tall and weighed 207 pounds. The skin was tanned; an acneform eruption was present on his face. The facial, axillary, and pubic hair were sparse. Examination of the ears, nose and throat was unremarkable. The optic fundi were normal but slit-lamp examination revealed filamentous sloughing of the corneal epithelium. Schirmer's test indicated a deficiency of tears. The heart and lungs were normal, but bilateral gynecomastia was noted. The abdomen was slightly protuberant, the liver and spleen were of normal size, and no abdominal masses were felt. The penis and prostate were normal; however, both testes were small, measuring 1½ cm in greatest diameter. There were effusions in the proximal interphalangeal joints of the left fourth finger, of the third and fourth right fingers and in the right knee. The range of motion was normal. Neurologic examination was normal except for borderline mental retardation.

Laboratory Data

Hemoglobin 13.5 gms%; WBC 7,200/ccm with normal differential; reticulocytes 1%; red blood cells were normocytic and normochromic. BUN, serum electrolytes, uric acid, calcium, phosphorus, blood cholesterol, 2-hour post prandial blood sugar, serum bilirubin, alkaline phosphatase, SGOT, and serum protein electrophoresis were normal. BSP retention was 7.5% at 45 minutes.

Urine was pink in color, with a pH of

5.0 and no sugar or albumin. Urinary delta aminolevulinic acid (Δ -ALA) and porphobilinogen (PBG) were negative; but, uroporphyrin was elevated to 4.5 mgm/24 hours and coproporphyrin was normal at 140 μ g/24 hours (Table I).

TABLE I

Precursors of Heme in Urine/24 hours

Precursors	Excretion in Patient's Urine	Normal
1. Porphobilinogen	Negative	Negative
2. Uroporphyrin	4.5 mg	15 mcg
3. Coproporphyrin	140 mcg	100-300 mcg

Endocrine studies: Protein bound iodine (PBI), plasma cortisol, urinary 17-OH corticosteroids and 17-ketosteroids were normal. Growth hormone suppressed normally with exogenous glucose as against reported inappropriate secretion of some hormones in acute intermittent porphyria.⁶ Urinary testosterone was low at 21.2 μ g/24 hours (normal 40-100 μ g/24 hours for males). Urinary gonadotrophins were elevated (positive at 96 MUU).

Chromosome analysis revealed an XXY pattern (Fig 1).^{*} An LE preparation was positive with 31 and 32 LE cells on two different occasions. ANF was positive exhibiting a strong homogeneous, strong peripheral type pattern.^{7, 8} Differential rheumatoid agglutination titer was negative and serum complement titer was normal. In a skin biopsy, the direct immunofluorescent band test was positive for a stippled band; the indirect test using the patient's serum was negative.⁹ (Fig 2)[†]

Discussion

A diagnosis of Klinefelter's syndrome was suspected because of the history of progressive impotence, infertility, gynecomastia, and small testes.¹ It was supported by low urinary testosterone and elevated gonadotrophins and was substantiated by an XXY karyotype (Fig 1). Although the

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†Kindly provided by Dr. T. Burnham

Klinefelter's Syndrome, Cutaneous Hepatic Prophyria, Lupus Erythematosus



Figure 1

Karyotype of a peripheral blood cell in metaphase, prepared from the patient. The extra "X" chromosome is paired with the normal X-chromosome between the top two rows.

patient claimed to have fathered a child, a history of past fertility does not necessarily exclude a diagnosis of Klinefelter's syndrome.¹⁰ The child and the mother were not available for genetic studies to determine the probability of paternity.

The diagnosis of acquired cutaneous hepatic porphyria is supported by the elevated uroporphyrins, and normal PBG, Δ -ALA, and coproporphyrins (Fig 3). The diagnosis of congenital erythropoietic porphyria was discarded because that disorder usually manifests itself in childhood and is frequently associated with hemolytic anemia and splenomegaly, both being absent in our patient. Furthermore, the possible diagnosis of congenital cutaneous hepatic

porphyria was discarded because of a negative family history and the absence of acute abdominal attacks.

Porphyria is a metabolic disorder characterized by increased excretion of porphyrins and/or their precursors. Granick¹¹ demonstrated in liver cell cultures that chemicals which can induce porphyria will elevate the levels of ALA synthetase. Tschudy¹² demonstrated increased levels of ALA synthetase in the livers of patients with acute intermittent porphyria, and Levere and Kappas¹³ suggested that a defective operator mechanism in the gene (Fig 3) results in this elevated level, characteristic of the hereditary porphyrias. Furthermore, they speculate that congenital ery-

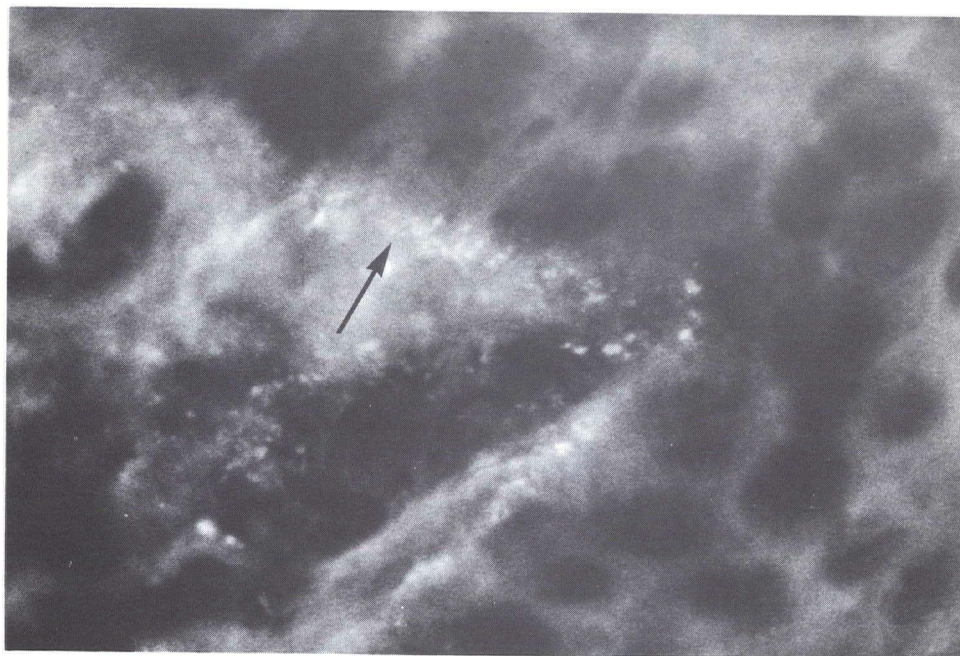


Figure 2

Clinically normal skin from the patient was incubated with fluorescein conjugated goat anti-human IgG. A discontinuous stippled band is seen at the dermal-epidermal junction (arrow). The epidermal side of the specimen is to the right.

thropoietic porphyria results from a relative deficiency of PBG isomerase, because in this disorder uroporphyrin I and coproporphyrin I are produced excessively in the circulating erythrocytes, while amounts of the type III isomers are normal.

ALA synthetase activity has not been proven to be elevated in acquired cutaneous hepatic porphyria. Since Δ -ALA and PBG were normal in our patient, one may speculate that the basic defect in the biochemical pathway is distal to Δ -ALA synthetase and therefore extra mitochondrial.¹⁴

It is possible to precipitate porphyria by a number of chemical agents: Arsenic, bismuth, copper, gold, iron, lead, silver, phosphorus, zinc, carbon tetra-

chloride; drugs: Chloroform, sulfonamides, nitroglycerine, sulfonal; and the sex hormones or their metabolites. No history of exposure to these substances could be obtained in our patient. He admitted to heavy ethanol ingestion which may have played an etiologic role in the development of porphyria. However, the only evidence of hepatic disease was the slightly elevated BSP retention of 7.5%. To our knowledge, an association has not been demonstrated between chromosomal abnormalities and porphyria.

The diagnosis of SLE was documented by the arthritis, the positive LE cell tests, and a homogeneous positive ANF. It was further substantiated by the demonstration of a stippled im-

Klinefelter's Syndrome, Cutaneous Hepatic Prophyria, Lupus Erythematosus

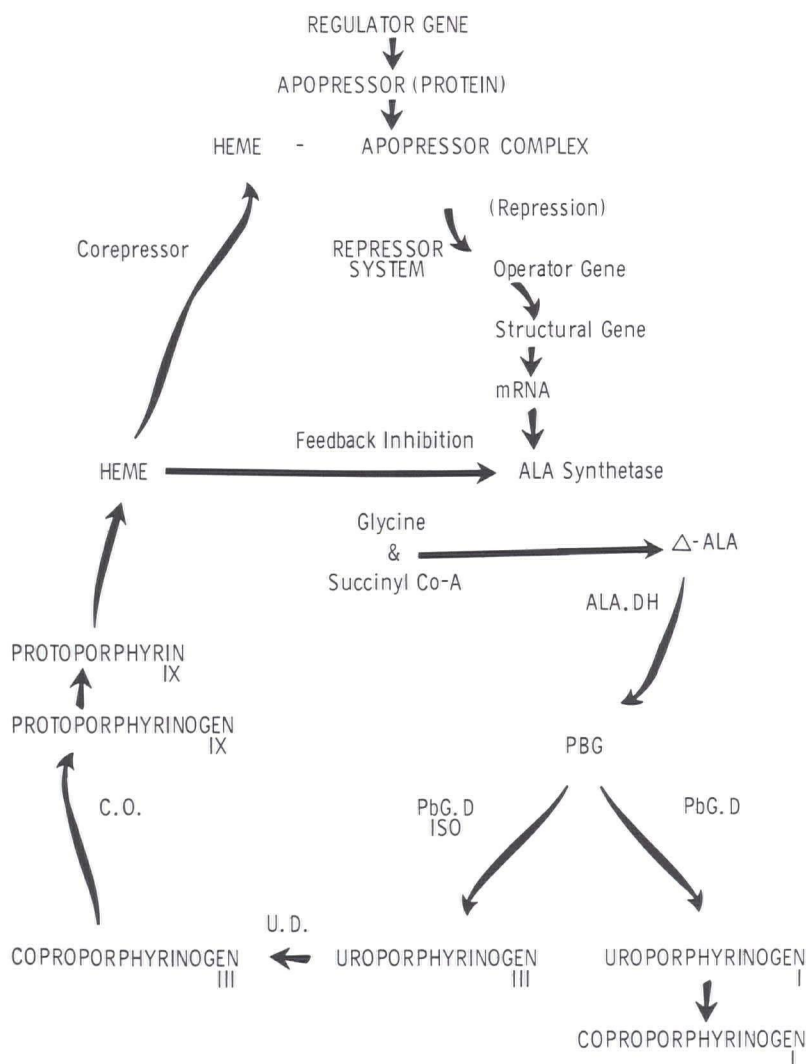


Figure 3

Scheme depicting the control mechanisms of heme synthesis and stages in the biosynthesis of heme. (Adapted from Granick¹¹ and Kappas¹³) The following abbreviations are used: Δ -ALA, delta amino levulinic acid; Δ -ALA DH, delta amino levulinic acid dehydrogenase; PBG, porphobilinogen; PBG D, porphobilinogen deaminase; ISO, isomerase; U.D., urogen decarboxylase; CO, coprogen oxidase; ALA Synthetase, amino levulinic acid synthetase. ALA synthetase is considered to be the rate limiting enzyme operating in a system with two types of inhibition—feedback control and operon. A protein (apopressor) generated by the regulator gene forms a complex with heme (co-repressor) which in turn represses the operator gene. Inducers can displace heme from the heme-apopressor complex, rendering the repressor mechanism inactive. Then, the structural gene becomes available to code more messenger RNA.

munofluorescent anti-IgG band in the skin biopsy.⁹ In the six previously reported patients⁵ with co-existent SLE and porphyria, four demonstrated the LE cell phenomenon. It is noteworthy that all of these patients were females and that our patient had a supernumerary X chromosome.

The frequency of autoantibodies in Klinefelter's syndrome is disputed. While Ferguson-Smith¹⁵ reported no

increase in the incidence of ANF, Engleberth and co-workers¹⁶ found a 28% increase. In our patient the combination of clinical and laboratory evidence is sufficient for diagnosis of SLE. The association of SLE and Klinefelter's syndrome has not been reported and it is only speculative that the chromosomal abnormality in our patient predisposed to the abnormality of porphyrin metabolism.

REFERENCES

1. Klinefelter, H.F., Jr.; Reifstein, E.C., Jr. and Albright, F.: Syndrome characterized by comastia, aspermatogenesis without A-Leydigism, and increased excretion of follicle-stimulating hormone. *J Clin Endocr* 2:615-627, 1942.
2. Jacobs, P.A., and Strong, J.A.: A case of human intersexuality having a possible XXY sex-determining mechanism. *Nature* 183:302-303, 31 Jan 1959.
3. Ford, C.E., et al: The chromosomes in a patient showing both mongolism and the Klinefelter syndrome. *Lancet* 1:709-710, 4 Apr 1959.
4. Becker, K.L., et al: Klinefelter's syndrome. *Arch Intern Med* 118:314-321, Oct 1966.
5. Harris, M.Y.; Mills, G.C., and Levin, W.C.: Coexistent systemic lupus erythematosus and porphyria. *Arch Intern Med* 117:425-428, Mar 1966.
6. Waxman, A.D., et al: Isolated adrenocorticotrophic hormone deficiency in acute intermittent porphyria. *Ann Intern Med* 70:317-23, Feb 1969.
7. Burnham, T.K.; Neblett, T.R., and Fine, G.: The application of the fluorescent antibody technic to the investigation of lupus erythematosus and various dermatoses. *J Invest Derm* 41:451-456, Dec 1963.
8. Burnham, T.K., et al: The immunofluorescent tumor imprint technique. IV. The significance of "thready" nuclear immunofluorescence. *Arch Derm* 99:611-616, May 1969.
9. Burnham, T.K., and Fine, G.: The immunofluorescent "band" test for lupus erythematosus. I. Morphologic variations of the band of localized immunoglobulins at the dermal-epidermal junction in lupus erythematosus. *Arch Derm* 99:413-420, Apr 1969.
10. Williams, R.A., (ed): *Textbook of endocrinology*, ed 4, Philadelphia, Saunders, 1968, p. 422.
11. Granick, S.: The induction in vitro of the synthesis of delta-aminolevulinic acid synthetase in chemical porphyria: A response to certain drugs, sex hormones, and foreign chemicals. *J Biol Chem* 241:1359-1375, 25 Mar 1966.
12. Tschudy, D.P., et al: Acute intermittent porphyria: The first "overproduction disease" localized to a specific enzyme. *Proc Nat Acad Sci USA* 53:841-847, 1953.
13. Levere, R.D., and Kappas, A.: The porphyric diseases of man. *Hosp Practice* 5:61-73, Mar 1970.
14. Matteis, F. de: Disturbances of liver porphyrin metabolism caused by drugs. *Pharmacol Rev* 19:523-557, Dec 1967.
15. Ferguson-Smith, M.A., et al: Frequency of autoantibodies in patients with chromatin-positive Klinefelter's syndrome and their parents. *Lancet* 2:566-568, 10 Sept 1966.
16. Engelberth, O., et al: Autoantibodies in chromatin-positive men. *Lancet* 2:1194, 26 Nov 1966.