Hypothalamic hypogonadism in hemochromatosis: A case report

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ABSTRACT: A 42-year-old man developed hypogonadotropic hypogonadism due to primary hemochromatosis. Endocrine evaluation indicated a hypothalamic defect in the control of gonadotropin secretion. Although cirrhosis was present on liver biopsy, other major features of the hemochromatosis syndrome were not manifest. Patients with hemochromatosis are now being diagnosed at earlier stages of disease. Clinicians should be alert to possible early development of hypothalamopituitary dysfunction and should be prepared to perform detailed endocrinological investigations in such patients. *Can J Gastroenterol* 1988; 2(1): 31-34

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PRIMARY IDIOPATHIC HEMOCHROMATOSIS is a slowly developing hereditary metabolic disorder characterized by excessive absorption of iron from the gut and its deposition within the parenchymal cells of the body. The liver, pancreas and skin as well as the heart, joints and the anterior pituitary gland appear to be particularly affected (1-3). Typically, patients are middle-aged men who present with unexplained cirrhosis accompanied by

diabetes mellitus and abnormally pigmented skin (1,3). Hypogonadotropic hypogonadism occurs in up to 64% of all individuals with advanced disease (2,3). Primary testicular dysfunction, although less frequent, also may occur (4,5).

The ready availability of laboratory techniques such as assays for serum iron, total iron binding capacity and ferritin, HLA typing and liver biopsy, has made it possible to diagnose this

disease in its early stages (5). Homozygotes can be diagnosed when there is little or no clinical evidence of disease (4,6). It is, therefore, likely that in the future many cases will be diagnosed before the classic manifestations of the syndrome have developed.

Present understanding of disease pathogenesis in advanced hemochromatosis may not be applicable to the syndrome in its earliest stages. A case of a 42-year-old man in whom a diagnosis of hemochromatosis was made during the investigation of acquired hypogonadotropic hypogonadism is presented. Endocrine investigations revealed evidence of hypothalamic dysfunction rather than the typical primary gonadotrope cell failure seen in advanced disease.

CASE PRESENTATION

A 42-year-old white man was referred to the Reproductive Endocrine Clinic at the University of Manitoba because of decreased libido and impotence which had developed over an 18-month period. He was subsequently referred to the Section of Gastroenterology for investigation of elevated liver

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enzymes. Prior to this time he had been in good health. Systematic inquiry relevant to his liver disease was negative; in particular, there had been no previous history of jaundice, drug or alcohol abuse, blood transfusions, pruritus, skin or eye complaints. There had been no foreign travel. There was no family history of liver disease or diabetes mellitus. He had previously fathered two children.

Physical examination showed him to be 188 cm tall, weight 75 kg. There were no peripheral stigmata of liver disease. In particular, there were no liver palms, spider angiomas or gynecomastia. Liver span was 12 cm in the mid-clavicular line and increased in consistency. He had normal body proportions and body hair. Visual fields and fundi were normal as was sense of smell. His penis was normal. The right testis was of normal size (5.0 × 3.0 cm) and consistency but the left testis was 2 cm in length and soft, probably related to surgery as a child for an undescended testis. The prostate gland was small.

Investigations revealed elevated serum aspartate transaminase at 79 iu/L (normal, less than 50), serum alanine transaminase at 81 iu/L (normal, 10 to 40) and serum alkaline phosphatase at 158 iu/L (normal, 30 to 125). Serum bilirubin and albumin levels were normal as were serum ceruloplasmin and α_1 -antitrypsin levels. Serology for hepatitis A and B, antinuclear and antimitochondrial antibodies was negative. However, his serum iron was 38 mmol/L (normal, 8 to 24), total iron binding capacity 39 mmol/L (normal, 45 to 72) and serum ferritin 2700 μ g/L (normal, 20 to 200). A liver/spleen scan showed hepatosplenomegaly with diminished activity throughout the liver consistent with diffuse parenchymal disease as well as moderate enlargement of the spleen with increased activity.

A liver biopsy showed irregular bands of fibrosis with well defined nodules consistent with a diagnosis of cirrhosis without any active inflammation. Kupffer cells, liver parenchyma and bile duct epithelium showed heavy iron deposition; the overall picture was

TABLE 1
Results of anterior pituitary function tests

Serum hormone	Basal (normal)	Peak stimulated* (normal)
Testosterone (nmol/L)		
Mean of 10 samples	5.2 (8-35)	—
Range	2.3 - 7.5	—
Free testosterone index†	1.5 (2.8-11.7)	—
Estradiol (pmol/L)	50 (<180)	—
FSH (μ g/L)	210 (80-300)	290 (1.3-3x basal)
LH (μ g/L)	40 (30-110)	100 (2-6x basal)
Prolactin (μ g/L)	5 (<15)	19 (2-6x basal)
Growth hormone (μ g/L)	1.7 (<5)	18 (>5)
Cortisol (nmol/L)	630 (150-700)	1060 (>550)
TSH (mU/L)	<2 (<6)	13 (6-30)
Thyroxine (nmol/L)	116 (50-140)	—

* Following combined intravenous bolus injection of gonadotropin-releasing hormone (Factrel; Ayerst) 100 μ g, thyrotropin-releasing hormone (Relefact; Hoechst) 400 μ g and crystalline insulin 8 units (0.1 U/kg)

† Estimate of nonprotein-bound testosterone present in serum, calculated by multiplying the percentage free testosterone by the total testosterone concentration (7)

FSH Follicle stimulating hormone; LH Luteinizing hormone; TSH Thyroid stimulating hormone

consistent with a diagnosis of hemochromatosis.

Results of endocrine investigation are shown in Table 1. Serum testosterone levels were repeatedly below normal. The free testosterone index was also subnormal (7). Basal levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) were normal as was pituitary gonadotropin reserve when tested with synthetic gonadotropin releasing hormone (GnRH). Provocative tests of anterior pituitary function were within normal limits. The patient was biochemically euthyroid. An oral glucose tolerance test was within normal limits according to the criteria of the National Diabetes Data Group (8). A high resolution computerized tomographic scan of the pituitary fossa was normal.

The patient was started on a program of phlebotomy and testosterone enanthate injections, 200 mg intramuscularly every three weeks, with marked improvement in both his libido and potency.

DISCUSSION

This report represents the first description of hypothalamic hypogonadotropism in primary (genetic) hemochromatosis. The diagnosis of hemochromatosis was based on a history of minimal alcohol ingestion, the findings of elevated hepatic enzymes and increased serum iron and ferritin

concentrations. It was confirmed by pathologic findings consistent with this disorder on a liver biopsy specimen. The absence of portal hypertension, diabetes mellitus or cardiac abnormalities suggests that the diagnosis was made in the early stages of disease in this patient.

The presence of inappropriately normal serum gonadotropin levels in a setting of persistently low serum testosterone concentrations and a unilateral atrophic testis, indicates the presence of hypogonadotropism. Even though normal pituitary gonadotropin reserve has been demonstrated in patients with advanced primary and secondary hemochromatosis, typically, when basal serum testosterone concentrations are subnormal, as in this case, the pituitary is unresponsive to a single dose of GnRH (9,10). Pituitary unresponsiveness to an acute GnRH challenge cannot reliably differentiate a primary gonadotrope cell abnormality from a hypothalamic defect (11). However, a brisk response, as seen in this case, points towards the latter (12). Taken together, these findings suggest that, in this patient, the predominant defect in the control of gonadotropin secretion was at the hypothalamic, rather than the pituitary level.

In the past, pituitary dysfunction has been well documented in both primary and secondary hemochromatosis by both the anatomic demonstration

of iron deposition within gonadotrope cells (13) and the absence of pituitary gonadotropin reserve following challenge with repeated doses of GnRH (14,15). These studies were performed in patients with advanced disease, however, and primary gonadotrope cell failure in advanced hemochromatosis does not preclude the presence of hypothalamic dysfunction in the earlier stages of this disorder. Indeed, past studies performed using single dose, acute GnRH challenges may have overlooked individuals who actually had hypothalamic disease (9,10).

Data on hypothalamo-pituitary-gonadal axis function in the early stages of hemochromatosis are scanty. Edwards and colleagues (4) documented five cases of hypogonadotropism in a series of 21 patients diagnosed in the earliest stages of disease by pedigree analysis. However, GnRH challenge testing was not performed. In a similar, asymptomatic, group with early disease, Feller and co-workers (6) reported the presence of normal pituitary gonadotropin reserve to an acute GnRH challenge. However, only five individuals without clinical evidence of hypogonadism were evaluated. Therefore, the prevalence of hypothalamic dysfunction in the early stages of primary hemochromatosis is not known.

The cause of hypothalamic dysfunction in hemochromatosis is unknown. The authors are unaware of any reports of hypothalamic pathology in

this disorder. Data from *in vivo* studies on hypothalamic iron deposition using advanced techniques such as nuclear magnetic resonance imaging are as yet unavailable (16,17). Regardless of the mechanism of hypothalamic injury, the previous report of combined GnRH and thyrotropin-releasing hormone deficiency in a patient with secondary hemochromatosis (18) suggests that a number of hypothalamic hormones which regulate pituitary secretion may be affected.

Abnormal hypothalamic control of gonadotropin secretion has also been delineated in individuals with advanced alcoholic liver disease both by GnRH testing (19) and by analysis of pulsatile LH secretion (20). These patients exhibited findings of advanced liver disease such as portal hypertension, gynecomastia and increased serum estrogen levels. The absence of any of these findings in the present patient suggests that hepatic decompensation was not a major factor in the development of his hypogonadotropism, despite the presence of cirrhosis on liver biopsy.

It is likely that cirrhosis *per se* plays a minor role in the development of the hypogonadotropism seen in iron overload states. For instance, abnormally increased serum sex hormone binding globulin concentrations and peripheral aromatization of androgens to estrogens, typical of alcoholic cirrhosis, are not usually seen in hemochromatosis (21). In a recent large ret-

rospective study of patients with hemochromatosis (22), the prevalence of impotence was slightly greater in cirrhotics than in noncirrhotics. However, it is unlikely that this complication is causally related to the presence of cirrhosis as, in that study, the percentage of patients with diabetes mellitus and ethanol abuse was significantly greater in patients with severe liver disease. These latter two factors could have independently increased the prevalence of impotence in this group, especially because specific causes of erectile dysfunction such as hypogonadism, neuropathy and vascular disease were not detailed. Of interest, among the women in that study, the frequency of amenorrhea was similar in both the cirrhotic and noncirrhotic groups, suggesting that in iron overload states the prevalence of abnormal gonadotropin secretion is similar in those with and without severe liver disease.

Once established, hypogonadotropism in iron overload states is considered permanent (17). However, in view of the reports of reversal of hypogonadotropism with phlebotomy (23, 24) and of the diagnosis of this disease in its earliest stages with such techniques as HLA typing (4-6), prospective study of the function of the hypothalamo-pituitary-gonadal axis, and indeed all aspects of hypothalamo-pituitary function, in early hemochromatosis will be necessary to help judge the effectiveness of therapy.

REFERENCES

1. Finch SC, Finch CA. Idiopathic hemochromatosis, an iron storage disease. *Medicine (Baltimore)* 1955; 34: 381-430.
2. Lamon JM, Marynick SP, Rosenblatt R, Donnelly S. Idiopathic hemochromatosis in a young female. A case study and a review of the syndrome in young people. *Gastroenterology* 1979; 76: 178-83.
3. Milder MS, Cool JD, Stray S, Finch CA. Idiopathic hemochromatosis, an interim report. *Medicine (Baltimore)* 1980; 59: 34-49.
4. Edwards CQ, Cartwright GE, Skolnick MH, Amos DB. Homozygosity for hemochromatosis: clinical manifestations. *Ann Int Med* 1980; 93: 519-25.
5. Powell LW, Basset ML, Halliday JW. Hemochromatosis: 1980 update. *Gastroenterology* 1980; 78: 371-4.
6. Feller ER, Pont A, Wands JR, et al. Familial hemochromatosis: physiologic studies in the precirrhotic stage of the disease. *N Engl J Med* 1977; 296: 1422-6.
7. Stearns EL, MacDonnell JA, Kaufman BJ, et al. Declining testicular function with age: hormonal and clinical correlates. *Am J Med* 1974; 57: 761-6.
8. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes* 1979; 28: 1039-57.
9. Bezudova WR, Bothwell TH, Van Der Walt LA, Kronheim S, Pimstone BL. An investigation into gonadal dysfunction in patients with idiopathic haemochromatosis. *Clin Endocrinol (Oxford)* 1977; 6: 377-85.
10. Charbonnel B, Chupin M, Legrand A, Guillon J. Pituitary function in idiopathic hemochromatosis: hormonal study in 36 male patients. *Acta Endocrinol* 1981; 98: 178-83.
11. Spitz IM, Diamant Y, Rosen E, et al. Isolated gonadotropin deficiency: a heterogeneous syndrome. *N Engl J Med* 1974; 290: 10-5.
12. Hashimoto T, Kiyoshi M, Izumi K, Kumahara Y. Isolated gonadotropin deficiency with response to luteinizing hormone releasing hormone. *N Engl J*

- Med 1972; 287: 1059-62.
13. Bergeron C, Kovacs K. Pituitary siderosis: a histologic immunocytologic and ultrastructural study. *Am J Pathol* 1978; 93: 295-306.
 14. Kletzky OA, Costin G, Marrs RP, Bernstein G, March CM, Mishell DR. Gonadotropin insufficiency in patients with thalassemia major. *J Clin Endocrinol Metab* 1979; 48: 901-5.
 15. Snyder PJ, Rudenstein RS, Gardner DF, Rothman JG. Repetitive infusion of gonadotropin-releasing hormone distinguishes hypothalamic from pituitary hypogonadism. *J Clin Endocrinol Metab* 1979; 48: 864-8.
 16. Valberg LS, Ghent CN. Diagnosis and management of hereditary hemochromatosis. *Ann Rev Med* 1985; 36:27-37.
 17. Lufkin EG, Baldus WP, Bergstrath EJ, Kao PC. Influence of phlebotomy treatment on abnormal hypothalamic-pituitary function in genetic hemochromatosis. *Mayo Clin Proc* 1987; 62: 473-9.
 18. Williams TC, Frohman LA. Hypothalamic dysfunction associated with hemochromatosis. *Ann Int Med* 1985; 103: 550-1.
 19. Van Thiel DH, Lester R. Further evidence for hypothalamic-pituitary dysfunction in alcoholic men. *Alcoholism Clin Exp Res* 1978; 2: 265-70.
 20. Bannister P, Handley T, Chapman C, Losowsky MS. Hypogonadism in chronic liver disease: impaired release of luteinizing hormone. *Br Med J* 1986; 293: 1191-3.
 21. Kley HK, Niederau C, Stremmel W, Lax R, Strohmeyer G, Kruskemper HL. Conversion of androgens to estrogens in idiopathic hemochromatosis: Comparison with alcoholic liver cirrhosis. *J Clin Endocrinol Metab* 1985; 61: 1-6.
 22. Niederau C, Fischer R, Sonnenberg A, Stremmel W, Trampisch HJ, Strohmeyer G. Survival and causes of death in cirrhotic and noncirrhotic patients with primary hemochromatosis. *N Engl J Med* 1985; 313: 1256-62.
 23. Kelly T, Edwards CQ, Meikle AW, Kushner JP. Hypogonadism in hemochromatosis: reversal with iron depletion. *Ann Int Med* 1984; 101: 629-32.
 24. Siemons LJ, Mahler C. Hypogonadotropic hypogonadism in hemochromatosis: Recovery of reproductive function after iron depletion. *J Clin Endocrinol Metab* 1987; 65: 585-7.

Clinical quiz – Answers

PANCREAS

1. Clinical or laboratory features at admission or during first 48 h of hospitalization which correlate with severe or complicated course and increased risk of mortality in acute ethanol-associated pancreatitis

At admission

- Older than 55 years
- White blood cell count more than 16,000/mm³
- Blood glucose more than 200 mg/dL (no history of prior hyperglycemia)
- Serum lactate dehydrogenase more than 350 iu/L
- Aspartate aminotransferase levels above 250 iu/L

During initial 48 h

- Hematocrit falls more than 10%
- Blood urea nitrogen rises more than 5 mg/dL
- Arterial pO₂ less than 60 mmHg
- Base deficit greater than 4 mEq/L
- Serum calcium less than 8 mg/dL
- Estimated fluid sequestration

2. Complications of cystic fibrosis

Gut

- Meconium ileus – constipation
- Rectal prolapse – obstruction
- Intussusception

Liver

- Gallstones
- Focal biliary cirrhosis
- Fatty liver
- Cirrhosis and portal hypertension
- Cholecystitis

Pancreas

- Pancreatic atrophy
- Diabetes
- Pancreatitis

STOMACH

1. Phases of gastric acid secretion and probable mechanisms of control

Phase	Control mechanism
Spontaneous or basal	Vagus gastrin
Cephalic	Vagus stimulation of parietal cells stimulation of gastrin-secreting cells
Gastric	Vagus stimulation of parietal cells stimulation of gastrin-secreting cells Vasovagal reflexes distension Local reflexes distension chemical (protein, amino acids)
Intestinal	Intestinal gastrin release Distension of jejunum Intestinal chyme

2. Causes of hypergastrinemia

Hypersecretion of acid

- Gastrinoma
- Antral G cell hyperplasia
- Retained gastric antrum
- Massive small bowel resection

Variable acid secretion

- Chronic renal failure
- Pheochromocytoma
- Hyperthyroidism

Hyposecretion of acid

- Pernicious anemia
- Atrophic gastritis
- Gastric carcinoma
- After vagotomy and pyloroplasty