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EXTENSIVE CLINICAL EXPERIENCE

Hypogonadism in Hereditary Hemochromatosis

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Hypogonadism, usually hypogonadotropic in origin, is the most common nondiabetic endocrinopathy in hereditary hemochromatosis (HH). Early studies, usually evaluating small numbers of patients with advanced HH, report prevalence rates of 10–100%. The clinical presentation of HH has changed in recent years as a result of increased awareness and screening. We assessed the prevalence of hypogonadism in a large group of patients with HH diagnosed in a single center over the past 20 yr, the period of follow-up spanning the time before and after widespread screening was introduced and the HFE gene was recognized. Abnormally low plasma testosterone levels, with low LH and FSH levels, were found in nine of 141 (6.4%) male patients tested. Eight of nine (89%) had associated hepatic cirrhosis; three of nine (33%) had diabetes. Inappropriately low LH and FSH levels were found in two of 38 females (5.2%) in whom the pituitary-gonadal axis could be assessed. This is the largest detailed study of hypogonadism reported in HH. The lower prevalence of hypogonadism compared with other reported series reflects the earlier diagnosis of HH in an unselected group of patients attending a single center. Patients with lesser degrees of hepatic siderosis at diagnosis are unlikely to develop hypogonadism. (*J Clin Endocrinol Metab* 90: 2451–2455, 2005)

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HEREDITARY HEMOCHROMATOSIS (HH) is a genetically transmitted disease characterized by excessive absorption of dietary iron, which may result in parenchymal iron overload and subsequent tissue damage. Early reports of HH recognized the frequent involvement of the endocrine system; iron deposition in pituitary gonadotrophs causes hypogonadotropic hypogonadism, which is the most frequently encountered nondiabetic endocrinopathy in HH, reported to occur in 10–100% of cases (1–9).

It is increasingly recognized that the clinical presentation of HH has changed significantly in recent years, and that many of the recognized complications are encountered less frequently (10). However, there has been no recent detailed study of hypogonadism in HH; therefore, it is not clear whether he prevalence of this complication has also declined. We now present the results of a detailed study of pituitary-gonadal function undertaken in a large group of unselected patients with HH, all of whom were followed by a single physician in a single center.

Patients and Methods

We studied 191 consecutive patients (144 men and 47 women) diagnosed with HH at a single institution and cared for by a single consultant endocrinologist between 1983 and the present day. The period of follow-up, therefore, spanned the time before and after the discovery of the HFE (the gene for hemochromatosis) mutations and the introduction of widespread familial screening.

HH was diagnosed by standard criteria. All patients had biochemical evidence of iron overload at diagnosis, with elevated serum ferritin values. Other possible causes for iron overload (*e.g.* porphyria cutanea tarda, disorders of erythropoiesis, and transfusional iron overload) were excluded. Patients admitting to excessive alcohol consumption, where this was felt to confound the diagnosis of HH, were excluded. All patients who consented to the study and were not taking anticoagulant medication had a liver biopsy performed; samples were examined to determine the presence or absence of cirrhosis or fibrosis, and the degree of siderosis was graded from 0–4 (11). Only patients with grade 2 or more siderosis were included in our study.

Genetic analysis for mutations in the HFE gene was performed in 170 of 191 patients. The remaining 21 patients were diagnosed before 1996, and genetic testing for the HFE mutation was unavailable at time of diagnosis. When the technique became available, these patients had either died or changed location.

All 18 patients who did not undergo liver biopsy had genetic testing performed; 14 were homozygous for the C282Y mutation, two were homozygous for the H63D mutation, and two were compound heterozygotes. Detailed analysis of the pituitary-gonadal axis was undertaken at diagnosis. Male patients had samples taken for basal serum testosterone, LH, and FSH determinations. An LH-releasing hormone (LHRH) stimulation test was performed on all patients with low basal testosterone levels. LH and FSH levels were measured in all postmenopausal women who were not receiving hormone replacement therapy.

Laboratory methods

Serum testosterone levels were measured by RIA using the TESTO-CT2 kit supplied by Cis Bio International (Gif-sur-Yvette, France). Internal quality control at three levels (low, medium, and high) was run at the beginning and end of each assay. The between-batch coefficients of variation throughout the assay ranged from 10% at the higher level to 14% at the lower level. Samples for testosterone were stored at −20 C before analysis. All samples were analyzed at the time of diagnosis.

LH and FSH levels were measured using two-site fluoroimmunometric assays (AutoDelfia, Wallac, Turku, Finland). Before analysis, samples for LH and FSH were stored at 4 C. The between-batch coefficient of variation ranged from 6% at the higher level to 8% at the lower level for both assays.

Ferritin levels were measured on the ACS 180 up until 1996 (which uses chemiluminescence to quantify the amount of antigen-antibody complex formed) and on the Autodelfia after 1996. Before analysis,

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Abbreviations: HH, Hereditary hemochromatosis; LHRH, LH-releasing hormone

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samples were stored at 4 C. The coefficient of variation was less than 5% over the measurement range of both methods.

Statistical analysis

One-tailed Fisher's exact test was used to test for the association between hypogonadism and other complications of HH, and two-tailed Fisher's exact test was used to compare the prevalence of hypogonadism before 1996 to the prevalence after 1996. A *t* test was used to compare the mean ages of the hypogonadal and nonhypogonadal males. Pearson's χ^2 test was used to test for an association between hepatic siderosis and hypogonadism.

Results

The characteristics of the 191 study patients are shown in Table 1. Rates of hepatic cirrhosis and diabetes mellitus at diagnosis are lower than those in previous studies of HH. The results of genetic testing for the HFE gene mutations are shown in Table 2.

Basal testosterone levels were low in 11 of 141 male patients. Two of the 11 had Klinefelter's syndrome and had elevated LH and FSH levels. The remaining nine patients (6.4% of the total) had low LH and FSH levels in association with the low testosterone levels, in keeping with hypogonadotropic hypogonadism. The characteristics of these nine patients are shown in Table 3. In one patient, initially low testosterone levels returned to normal after venesection.

The results of LHRH testing are also shown in Table 3. The amplitude of the LH and FSH responses to LHRH are reduced or inappropriately normal for the low basal testosterone levels, in keeping with hypogonadotropic hypogonadism.

Table 4 shows the clinical features of the nine males with hypogonadotropic hypogonadism.

Table 5 compares the hypogonadal males to the nonhypogonadal males. Hypogonadal males were more likely to have cirrhosis, ferritin levels greater than 1500 ng/ml at diagnosis, and grade 4 siderosis on liver biopsy. A greater proportion of hypogonadal patients had diabetes mellitus, but the difference was not statistically significant.

Table 6 compares male patients diagnosed before 1996 with those diagnosed after 1996. Patients diagnosed in the early period of the study were more likely to have hypogonadism, hepatic cirrhosis, or diabetes.

Hormonal data were available for 44 of the 47 female subjects. Primary amenorrhea due to a surgically resected craniopharyngioma was present in one case. Eight premenopausal subjects had normal menses. Five postmenopausal subjects were taking hormone replacement therapy. In the remaining 30 postmenopausal subjects, LH and FSH were appropriately elevated in 28 and inappropriately low in two, in both of whom estradiol levels were in the postmenopausal range, whereas serum prolactin levels and magnetic resonance imaging of the pituitary gland were normal. Thus, hypogonadotropic hypogonadism was found in two of 38 female subjects (5.2%) in whom the pituitary-gonadal axis could be assessed.

TABLE 1. Characteristics of study patients at diagnosis

	Male patients (n = 144)	Female patients (n = 47)	Total (n = 191)
Average age (yr) (range)	52 (24–77)	57 (24–82)	53
Hepatic cirrhosis	24/132 (18%)[a]	0/41 (0%)[b]	24/173 (13.8%)
Diabetes mellitus	35 (24%)	7 (14.9%)	42 (22%)

[a] Twelve not biopsied.
[b] Six not biopsied.

TABLE 2. Results of genetic analysis

Genotype	Male (n = 126)	Female (n = 44)	Total (n = 170)
C282Y/C282Y	111	37	148 (87%)
C282Y/H63D	7	0	7 (4%)
C282Y/normal	0	0	0 (0%)
H63D/H63D	4	2	6 (4%)
H63D/normal	4	2	6 (4%)
Normal/normal	0	3	3 (2%)

Discussion

After diabetes mellitus, hypogonadotropic hypogonadism is the most frequently encountered endocrinopathy associated with HH, with reported prevalence rates of 10–100% (1–9). Most of these reports involved small numbers of patients, and a notable feature has been the presence of hemochromatosis of advanced degree in many of the subjects. For example, Walsh *et al.* (2) and Charbonnel *et al.* (4) noted diabetes mellitus in 83% and 72% of cases, respectively, whereas hepatic cirrhosis was present in the majority of cases reported by others (3, 5).

These earlier reports are in contrast to our findings, where we observed a prevalence of hypogonadism of only 6.4% in men with HH. Unlike many of these previous studies, our findings derive from a large group of unselected patients attending a single center. Thus, we believe that these observations are a true reflection of the prevalence of pituitary-gonadal dysfunction in patients with HH at the present time. It is also interesting to note that although the number of patients with hypogonadism in each period of our study is quite small, the prevalence of hypogonadism appeared to decline over the period of our study, because 14.6% of patients diagnosed in the earlier period of the study had hypogonadotropic hypogonadism compared with 3% of those diagnosed in the more recent period (Table 6).

We specifically excluded patients with mutations in the HFE gene, but in whom siderosis of less than grade 2 was present at liver biopsy. Such lesser degrees of siderosis are nonspecific and may be found in a variety of conditions other than HH (11). These patients, therefore, although expressing the HH genotype, cannot be said to have HH in the conventional sense, because they do not express the HH phenotype. The natural history of such patients is unclear; it is not known whether all such patients will ultimately develop significant iron overload if left untreated. Although these patients were excluded from our final analysis, they were evaluated for the presence of hypogonadism, and no case of hypogonadism was found in this patient group.

It seems likely that the low prevalence of hypogonadism in our patients is a result of earlier diagnosis of HH in recent years; this, in turn, is due to a number of factors: increasing awareness of the disorder among physicians and general practitioners, more ready access to relevant biochemical screening for physicians in both primary care and hospital

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TABLE 3. Characteristics of hypogonadal males at diagnosis

Patient	Age (yr)	Serum ferritin (ng/ml)[a] (normal, 17–320)	Hepatic cirrhosis	Diabetes	Testosterone (nmol/liter)[b] (normal, 4.1–29.5)	LH basal (IU/liter)[c] (normal, 1.0–8.4)	LH 30 min (IU/liter)[c] (normal increment, 2.7–10 fold at 30–60 mins)	FSH basal (IU/liter)[c] (normal, 1.0–10.5)	FSH 30 min (IU/liter)[c] (normal increment, 1.5–2 fold at 30–60 min)
1	70	1596	Yes	No	3.4	1.5	2.6	3.4	1
2	69	>2000	Yes	Yes	1.9	1.5	1.8	1.0	3.4
3	64	2626	Yes	No	0.2	0.6	0.6	0.4	1.0
4	61	6180	No	No	1.9	1.5	1.8	3.4	3.4
5	59	>1500	Yes	Yes	0.88	1.4	1.3	0.91	1.0
6	55	1129	Yes	Yes	0.6	5.0	5.0	1.3	1.7
7	47	>1500	Yes	No	1.2	1.7	6.0	2.0	2.6
8	40	4614	Yes	No	3.4	3.1	7.1	4.3	5.1
9	36	477	Yes	No	0.7	2.9	4.0	1.5	1.5

[a] Conversion factor to micrograms per liter = 1.
[b] To convert to nanograms per deciliter, divide by 0.035.
[c] Conversion factor to milli IU per milliliter = 1.

practice, and identification of mutations of the HFE gene, which has resulted in widespread screening of asymptomatic relatives of patients with HH. A number of facts support this view. Firstly, diabetes mellitus and hepatic cirrhosis, both complications known to be associated with significantly greater body iron stores (12) and therefore more advanced disease, were present at diagnosis in only 22% and 14% of the patients in this series, respectively, in marked contrast to the studies mentioned above, in which the prevalence of these complications was markedly greater. Secondly, in parallel with the higher prevalence of hypogonadism in patients diagnosed in the early period of our study, both of these complications were more frequent in those patients diagnosed in the earlier period of our study, when awareness of HH was not so widespread and before genetic testing was available (Table 6). Finally, when we evaluated the factors that led to the diagnosis of HH in our patients, we found that significantly more patients presented in the earlier period of the study because of the presence of symptoms or complications of the disease, such as skin pigmentation, joint pains, diabetes, or abnormal liver blood tests, rather than through familial screening or serendipity (65% before 1996 *vs.* 41% after; by Pearson's χ^2 test, $P = 0.018$). This indicates that in the later period of our study, more patients were indeed being diagnosed at an earlier, asymptomatic stage of the disease.

A possible confounding factor in any analysis of male hypogonadism is the natural decline in testosterone that occurs with aging, a subject that has received much recent attention. The largest longitudinal study into the effects of healthy ageing on male testosterone levels, the Massachusetts Male Aging Study (13), followed 1156 men for a period of 7–10 yr and demonstrated an average decline in total testosterone levels of 1.6%/yr. There is no doubt, therefore, that some healthy elderly males will have testosterone levels that are below the normal reference range for a given laboratory, but are normal compared with testosterone levels from men of similar age. The decline in testosterone with aging is less when total testosterone is measured, as in our study, compared with when free testosterone is measured, due to the coexisting increase in SHBG that occurs with aging.

A number of factors suggest, however, that this natural decline in testosterone does not confound our analysis. Firstly, the apparent decline in the prevalence of hypogonadism over the period of our study occurred despite the fact that there was no significant difference in average patient age for the two periods of study (Table 6). Also, although some studies of male aging have suggested that the decline in testosterone with aging is not associated with a rise in LH and FSH values (14), the Massachusetts Male Aging Study, a well conducted, longitudinal study of a large number of male subjects, demonstrated rises in LH and FSH of 0.9% and 3.1%/yr, respectively, in association with the decline in testosterone, and similar results were reported in the New Mexico Aging Process Study (15). Therefore, although LH and FSH levels may not necessarily rise above the normal range

TABLE 4. Clinical features of hypogonadal males

Patient	Testosterone (nmol/liter)[a] (normal, 4.1–29.5)	Body hair	Testicular examination	Erectile dysfunction
1	3.4	Reduced	Normal	Yes
2	1.9	Reduced	Normal	Denied
3	0.2	Greatly reduced	Small, soft	Denied
4	1.9	Reduced	Small, soft	Yes
5	0.88	Reduced	Soft, normal size	Yes
6	0.6	Reduced	Normal	Yes
7	1.2	Reduced	Small, soft	Yes
8	3.4	Reduced	Normal	Yes
9	0.7	Greatly reduced	Normal	Denied

[a] To convert to nanograms per deciliter, divide by 0.035.

TABLE 5. Characteristics of hypogonadal *vs.* nonhypogonadal males at diagnosis

	Hypogonadal males (n = 9)	Nonhypogonadal males (n = 132)[a]	*P*
Average age (yr)	56	51.6	NS
Hepatic cirrhosis	8 (89%)	16/121 (13%)[b]	<0.001
Diabetes mellitus	3 (33%)	32 (24.2%)	NS
Ferritin >1500 (ng/ml)[c]	5 (77%)	26 (19%)	<0.001
Grade 4 siderosis	8/8 (100%)[d]	49/115 (42%)[d]	0.007

NS, Not significant.
[a] Includes two patients with hypogonadism due to Klinefelter's syndrome.
[b] Eleven not biopsied.
[c] Conversion factor to micrograms per deciliter = 1.
[d] Significant siderosis but not graded accurately in seven patients.

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TABLE 6. Subgroup analysis based on year of diagnosis in male patients

	1983–1995	1996–2003	*P*
No. of patients	42	102	
Patient age (yr)	52.51	53.29	NS
Hypogonadism	6/41 (14.6%)[a]	3/100 (3%)[b]	0.018
Hepatic cirrhosis	13/40 (32.5%)	11/92 (12%)	0.001
Diabetes mellitus	15 (35.7%)	20 (19.6%)	0.055
Serum ferritin >1500	9 (21.4%)	22 (21.7%)	NS

NS, Not significant.
[a] No data available in one patient.
[b] No data available in two patients.

with aging, one would expect values to rise at least into the mid to high normal range. All of our elderly hypogonadal males, however, had LH or FSH levels in the below normal or low normal range in association with their low testosterone levels (patients 1–6; Table 3). The results of LHRH testing are also supportive of our conclusions (Table 3). Previous studies of the response to LHRH in elderly males (14, 16) found that LH values rose at least 4–5 times above their basal value 30 min after administration of LHRH, unlike the results in our patients. Notwithstanding the above arguments, in the absence of a control group of healthy males followed over the same time period, it is difficult to be absolutely certain that our group of hypogonadal patients does not contain a patient(s) with low testosterone due to the natural decline in testosterone with aging. However, the inclusion of such patients would merely result in our reported rates of hypogonadism being an overestimation and, therefore, would not weaken our conclusion that the prevalence of hypogonadism in HH is lower than that in previous studies.

In contrast to their female counterparts, our male patients with hypogonadism did not have imaging of their pituitary gland performed. Hypogonadism is a well recognized complication of advanced HH in males and, therefore, was certainly considered a more likely cause of hypogonadism in our patients than a pituitary lesion. All of our patients had a metyrapone test performed to assess the integrity of their hypothalamo-pituitary-adrenal axis, and all were normal, as were prolactin levels. Thyroid function tests were performed in all patients at diagnosis, and no patient had abnormalities in thyroid function testing suggestive of pituitary disease. One patient, as mentioned, had a return of gonadal function after venesection, making a pituitary tumor an unlikely cause of his hypogonadism. None of the remaining patients developed any symptoms or signs of a pituitary tumor on follow-up.

Although occasional cases of hypogonadism, invariably hypogonadotropic in type, have been recorded in females with HH (9, 17–20), the subject has received relatively little attention, and there have been no studies of adequate size to indicate the likely prevalence of the problem. This is the largest series of females reported to date in which the subject has been evaluated. Of the 38 patients in whom it was possible to assess pituitary-gonadal function, hypogonadotropic hypogonadism associated with HH was observed in two (5.2%). Because isolated gonadotropic deficiency in postmenopausal females may not be associated with signs or symptoms, it is likely to be overlooked if not specifically sought.

In summary, we report a prevalence of hypogonadotropic hypogonadism of 6.4% among a large series of male patients with HH. Our data suggest that the prevalence of hypogonadism may be decreasing, probably as the result of earlier diagnosis of HH. Despite the low prevalence of hypogonadism, it still remains an important complication and should be considered in all patients with HH. The diagnosis must be based on hormonal evaluation, because clinical assessment can be misleading (2, 6). Its presence has important implications for the patient, because testosterone replacement (21) together with aggressive venesection (7, 22) can significantly improve the quality of life and restore sexual function and may have an important effect on bone mass (23). Our study suggests, however, that patients with lesser degrees of hepatic siderosis on liver biopsy who do not have hepatic cirrhosis, diabetes mellitus, or markedly elevated serum ferritin levels are unlikely to have hypogonadism. In these patients, there may be no immediate need for hormonal evaluation.

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