ISOLATED GONADOTROPE FAILURE IN THE POLYGLANDULAR AUTOIMMUNE SYNDROME

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Abstract

Hypogonadism is a component of the polyglandular autoimmune syndromes and usually results from primary gonadal failure. Isolated gonadotropin deficiency is a disorder of prepubertal onset that usually results from a failure of hypothalamic secretion of gonadotropin-releasing hormone (GnRH). We describe here two men with polyglandular autoimmune syndrome and isolated gonadotropin deficiency acquired after puberty. Plasma levels of lutinizing hormone and follicle-stimulating hormone in response to bolus doses of GnRH and to pulsatile GnRH injections (25 ng per kilogram of body weight intravenously every two hours) over a four-day period were subnormal. Pituitary secretion of thyroid-stimulating hormone, prolactin, growth hormone, and ACTH was not impaired. These data indicate that isolated gonadotropin deficiency may result from a selective pituitary gonadotrope failure. In addition, they suggest that autoimmune hypophysitis may be an integral part of the polyglandular autoimmune syndrome and can be selective, involving only one type of pituitary cells. (N Engl J Med 1995; 321:1535-40.)

primary adrenal insufficiency was made at that time and confirmed by loss urinary excretion of steroids, which did not respond to repeated infusions of ACTH. Tests for tuberculosis, histoplasmosis, and coccidiomycosis were all negative, and abdominal films did not reveal adrenal calcification. At the time of diagnosis the patient was noted to be hypogonadal, with no sexual hair and with soft, testes. His bone age was 15 years; skull roentgenograms, bony smear, and thyroid function were normal; urinary gonadotropin levels were low; and his sense of smell was intact. Treatment with hydrocortisone and fludrocortisone (Florinef, Squibb) in replacement doses resulted in complete correction of the hyposmegnism, but the patient's sexual maturation did not progress. Testosterone replacement had been recommended at the age of 25 years but had never been instituted. When we saw this patient in 1982, his height was 176 cm (lower segment, 90 cm; arm span, 160 cm), and his weight was 72 kg. He was taking 25 mg of hydrocortisone daily, divided doses and 0.1 mg of fludrocortisone daily. Clinically, the patient was severely hypogonadal, the tests were soft and measured less than 1 cm in length, but the length of the stretched penis was 10 cm. The complete blood count, fasting blood sugar level, serum concentrations of electrolytes, calcium, and phosphorus, and thyroid function were all within normal limits, and the skull roentgenogram revealed a normal pituitary fossa. The plasma testosterone level was less than 0.2 mg per milliliter (less than 0.7 nmol per liter; normal, 4.0 to 9.0 mg per milliliter [13.9 to 31.2 nmol per liter]), with a concomitant plasma luteinizing hormone level of less than 1.1 mIU per milliliter and a follicle-stimulating hormone level of 4.8 mIU per milliliter. Injections of human choriionic gonadotropin (Pregnyl, Organon) (200 units intramuscularly twice a week) were given, and six weeks later the testosterone level remained undetectable. Antithyroid and anti-Leu-vidig cell antibodies were not detected, but antitubercular and anti-ideal cell antibodies were detected in immunofluorescence assays using fresh gauze pig adrenal, and human pancreas, labelling in Bunn's fluid, respectively (performed in the Scripps Clinic, La Jolla, Calif.). The immunofluorescence assay to detect circulating pituitary antibodies was negative in three laboratories (Department of Clinical Immunology, Middlesex Hospital Medical School, London, U.K.; Laboratory of Oral Medicine, National Institute of Dental Research, National Institutes of Health; and Department of Pathology, University of Michigan, Ann Arbor). The patient was admitted to the Clinical Research Center at the University of Michigan Hospital for a detailed endocrine workup, and the results are shown below. Subsequently, he was started on testosterone enanthate (200 mg intramuscularly every two weeks), and three months later he reported an increase in general strength and energy, increased libido, growth of sexual hair, and a weight gain of 6.4 kg.

Patient 2 was a 21-year-old man whose sister was known to have Addison's disease. Addison's disease and primary hypothyroidism developed in the patient when he was 19. At that time the plasma cortisol level was undetectable, and the plasma ACTH level was 1445 pg per milliliter (normal, less than 100). The plasma thyroxine level was low at 0.6 µg per deciliter (23.2 nmol per liter); normal, 4.5 to 11.5 µg per deciliter (38 to 166 nmol per liter); and the level of thyroid-stimulating hormone was 134 µU per milliliter (normal, less than 7). The patient was treated with hydrocortisone, thio-
cortisone, and synthetic levothyroxine (Synthroid, Eli Lilly) in replacement doses, with complete resolution of symptoms and return of thyroid indexes to normal levels. Sexual maturation was complete, and before the onset of this illness the patient had been sexually active and had shaved daily. His plasma testosterone concentration at the age of 20 was 6.6 ng per milliliter (22.3 nmol per liter). At the age of 21, the patient presented to our clinic reporting a decline in libido, rare erections, and a decrease in sexual hair. Physical examination revealed thin, soft skin; sparse facial, chest, and pubic hair; and soft testes measuring 4.5 by 3.0 cm. The penis was 15 cm in length (stretched). The complete blood count, fasting blood sugar level, and serum electrolyte, calcium, and phosphorus levels were all normal. Tests for antidiuretic and antithyroid antibodies were positive. The plasma testosterone level was low, between 2.1 and 2.5 ng per milliliter (7.3 and 8.7 nmol per liter) on three occasions. A GnRH test (100 μg intravenous bolus) demonstrated a decreased luteinizing hormone response, with undetectable levels of follicle-stimulating hormone. Stimulation by human chorionic gonadotropin (two intramuscular injections of 2000 units 48 hours apart) increased the plasma testosterone level to normal (4.6 ng per milliliter [22.9 nmol per liter]). A computerized axial tomographic scan of the hypothalamo-pituitary area was normal. Circulating pituitary-cell antibodies were negative in three laboratories (the same laboratories as for Patient 1). The patient was admitted to the Clinical Research Center, and the results of the investigations are shown below. After discharge the patient was lost to follow-up, but one year later he returned to our clinic reporting a further decrease in sexual potency. At that time, his sexual hair was noted to be more sparse, and his testes were softer on palpation, albeit of the same size. The plasma testosterone level was 1.5 ng per milliliter (5.2 nmol per liter), and a repeat GnRH test (100 μg intravenous bolus) demonstrated a further decrease in luteinizing hormone responsiveness and an undetectable serum level of follicle-stimulating hormone. The patient was started on replacement therapy with testosterone enanthate (200 mg intramuscularly every two weeks).

**Study Protocol**

The nature of the studies was explained to the patients, and written consent was obtained. Replacement therapy with hydrocortisone and fludrocortisone in both patients and levothyroxine in Patient 2 was continued throughout the study. On the day of admission (Day 0), a forearm heparin lock was inserted, and plasma luteinizing hormone and follicle-stimulating hormone were measured in samples drawn every 20 minutes for the next 24 hours (from 8 a.m. to 8 a.m.). Plasma testosterone was measured in samples taken at 8 a.m., 12 noon, and 8 p.m. on each day of the study. On Days 1 to 4, GnRH (29 ng per kilogram of body weight) was injected intravenously every two hours, and luteinizing hormone and follicle-stimulating hormone were measured in preinjection samples. GnRH was stopped at 8 a.m. on Day 5, and on the last day of the study (Day 6) plasma luteinizing hormone and follicle-stimulating hormone were measured every 20 minutes for 24 hours. Short-term responses of luteinizing hormone and follicle-stimulating hormone to GnRH were assessed in samples obtained every 20 minutes for two hours after the 8 a.m. injection of GnRH (25 ng per kilogram) on Days 1 through 5 and on Day 7 of the study.

A combined insulin hypoglycemia—thyrotropin-releasing hormone test was performed in both patients to assess other pituitary function. Crystalloid insulin (0.15 unit per kilogram) and thyrotropin-releasing hormone (200 μg) were injected as a rapid intravenous bolus, and blood samples were obtained at 0, 15, 30, 60, and 90 minutes.

**Methods**

Plasma luteinizing hormone, follicle-stimulating hormone, and testosterone were measured by established radioimmunoassays. All samples from each patient were run in the same assay. Gonadotropin concentrations are reported in milliinternational units (mIU) by the Second International Reference preparation of human menopausal gonadotropin after conversion from LER 907, which was used as the assay standard. The lowest detectable levels were 0.1 ng per milliliter for luteinizing hormone and 1.3 mIU per milliliter for follicle-stimulating hormone. Spontaneous luteinizing hormone pulses were defined as a rise from nadir to peak within 40 minutes, more than three times the intraassay coefficient of variation of repeat samples. Plasma human growth hormone, prolactin, thyrotropin-stimulating hormone, and ACTH were all measured by established radioimmunoassays.

Data are expressed as means ± S.D., and statistical analysis was performed with Student's t-test.

**Results**

A combined pituitary-function test was performed in Patient 1, 12 hours after the last dose of hydrocortisone, and his basal concentration of plasma cortisol was undetectable. Patient 2 took 10 mg of hydrocortisone two hours before the test, and his basal plasma cortisol concentration was 12 μg per deciliter (0.3 μmol per liter). His plasma thyroxine level was 29 μg per deciliter (162.5 nmol per liter) while he was taking 0.15 mg of levothyroxine daily. Normal responses of growth hormone, prolactin, and thyroid-stimulating hormone occurred in both patients. Basal ACTH levels were elevated and increased even further in response to hypoglycemia (Table 1).

A GnRH test (100 μg as an intravenous bolus) in Patient 2 was performed on two occasions (see Case Report), and the results were compared with the range of responses observed in nine healthy men. Initially, the patient's basal luteinizing hormone level was 2.4 mIU per milliliter, and the level increased to 110 at 30 minutes. One year later, the basal luteinizing hormone level was undetectable, and the level increased to 8.3 mIU per milliliter at 30 minutes (the lower limit of the normal luteinizing hormone response at 30 minutes is 27.3). The plasma level of follicle-stimulating hormone was undetectable throughout both tests.

Data (means ± S.D.) obtained in four healthy young men studied under conditions identical to those of Day 0 of the protocol were used as reference points in assessing spontaneous hormone secretion: luteinizing hormone, 9.0 ± 3.0 mIU per milliliter; follicle-stimulating hormone, 3.3 ± 2.0 mIU per milliliter; testosterone, 5.85 ± 1.47 ng per milliliter (20.3 ± 5.1 nmol per liter); number of spontaneous luteinizing hormone pulses, 11.75 ± 1.0 per 24 hours; and amplitude of luteinizing hormone pulses, 6.04 ± 3.12 mIU per milliliter.

In Patient 1 (Fig. 1), only seven values of luteinizing hormone were above the assay detection level on Day 0. Three spontaneous luteinizing hormone pulses were detected, with an average amplitude of 0.95 ± 0.1 mIU per milliliter (P < 0.01). Plasma levels of follicle-stimulating hormone fluctuated between 1.8 and 4.2 mIU per milliliter (mean, 2.9 ± 0.54). On Day 6, the mean luteinizing hormone level was low at 1.8 ± 0.5 mIU per milliliter (P < 0.001), with 10 spontaneous pulses detected (amplitude, 1.1 ± 0.4 mIU per milliliter, P < 0.001). The plasma testosterone level was low.
Table 1. Results of Combined Pituitary-Stimulation Tests.

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient</th>
<th>Normal Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid-stimulating hormone (μU/ml)</td>
<td>2</td>
<td>&lt;7</td>
</tr>
<tr>
<td>Basal</td>
<td>2.8</td>
<td>6.7</td>
</tr>
<tr>
<td>Maximal</td>
<td>13.2</td>
<td>36.0</td>
</tr>
<tr>
<td>Prolactin (ng/ml)</td>
<td>2</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Basal</td>
<td>20.4</td>
<td>12.6</td>
</tr>
<tr>
<td>Maximal</td>
<td>137</td>
<td>91</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>2</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Basal</td>
<td>291</td>
<td>1120</td>
</tr>
<tr>
<td>Maximal</td>
<td>1170</td>
<td>1940</td>
</tr>
<tr>
<td>Growth hormone (ng/ml)</td>
<td>2</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Basal</td>
<td>7.7</td>
<td>1.7</td>
</tr>
<tr>
<td>Maximal</td>
<td>38.3</td>
<td>13.4</td>
</tr>
</tbody>
</table>

Unusually high levels of hydrocortisone were observed at the start of the test, with the highest level being 1200 ng/ml, while the normal range is 200 to 500 ng/ml. Blood pressure was also higher than normal, reaching 120/80 mm Hg, typical of patients with elevated levels of thyroid hormones. Basal blood glucose levels were lower than normal, at 80 mg/dl, compared to the normal range of 90 to 110 mg/dl. Changes in plasma levels of testosterone were also observed, with a decrease from 1000 ng/ml to 500 ng/ml in the first hour, typical of patients with hypogonadism. In conclusion, the patient was diagnosed with primary hypothyroidism and hypogonadism, requiring further medical intervention.

Oral glucose-tolerance tests (100 g) in both patients showed normal dynamics of both serum glucose and insulin (data not shown).

Discussion

Five patients studied presented with a Type II polyglandular autoimmune syndrome. In Patient 1, Addison’s disease was associated with primary hypogonadism, as documented by his inability to respond to the long-term administration of human chorionic gonadotropin; in Patient 2, Addison’s disease was associated with primary hypothyroidism. The autoimmune nature of the disease was substantiated by the presence of circulating antiadrenal antibodies in both patients and of antithyroid antibodies in Patient 2. Hypogonadism may be an integral component of the polyglandular autoimmune syndrome and has invariably been due to primary gonadal failure, with decreased plasma concentrations of gonadal steroids and elevated plasma levels of gonadotropins. In both patients studied here, hypogonadism was associated with low levels of plasma luteinizing hormone and follicle-stimulating hormone, suggesting a hypothalamic or pituitary defect. This was especially striking in Patient 1, who also had documented primary gonadal failure.

In Patient 1 hypogonadism was diagnosed at the age of 19 years, but the delayed bone age at that time
confirmed by the declining levels of plasma testosterone, pituitary secretion of thyroid-stimulating hormone, prolactin, ACTH, and growth hormone was not impaired in either patient.

Thus, these patients presented with an isolated gonadotropin deficiency acquired after puberty. This condition may result either from a failure of GnRH secretion or from the inability of the pituitary to respond to GnRH. The latter mechanism has been described in some patients with pituitary tumors and usually represents a transient stage in the development of more extensive hypopituitarism. Prolonged administration of GnRH allows differentiation of the two forms of gonadotropin deficiency, and the pulsatile GnRH regimen used in this and other studies has been employed successfully to induce puberty in patients with isolated gonadotropin deficiency.

The occurrence of spontaneous luteinizing hormone pulses both before and after GnRH therapy in Patient 2 and after GnRH priming in Patient 1 suggests that the hypothalamic mechanisms controlling GnRH secretion were intact in both patients. The low amplitude of spontaneous luteinizing hormone pulses as well as the poor responses to GnRH indicate an impaired ability of the pituitary gland to respond to GnRH stimulation, this was confirmed by the inability of both patients to augment secretion of luteinizing hormone and follicle-stimulating hormone after four days of GnRH stimulation, which contrasts with the response seen in patients with GnRH deficiency. These data, together with the blunted or absent responses to the supraphysiologic dose of GnRH (100 μg) in Patient 2, strongly suggest that the hypogonadotropic hypogonadism in these patients was due to selective gonadotrope failure.

The cause of the isolated gonadotrope failure in these patients is uncertain, but negative radiologic studies and the selectivity of the process over a long period make the possibility of a tumor or vascular abnormality unlikely. Also, the presence of primary adrenal insufficiency is unlikely to be a factor, since patients with adequately treated Addison's disease undergo normal puberty and have normal fertility. In addition, low-dose pulsatile GnRH given over 26 hours elicited normal levels of luteinizing hormone and follicle-stimulating hormone in patients with congenital adrenal hypoplasia and isolated gonadotropin deficiency. Thus, the development of selective gonadotrope failure in patients with the polyglandular autoimmune syndrome may suggest that the pituitary failure is also due to autoimmune mechanisms.

An autoimmune cause of hypopituitarism has been suspected since the 1960s, but only in 1975 were Bottasso et al. able to demonstrate the presence of circulating autoantibodies to prolactin-secreting cells in patients with known autoimmune endocrine diseases. Lymphocytic hypophysitis of pregnancy was described as a distinct clinicopathological entity, and its autoimmune origin has been postulated. It has
been suggested that several cases of acquired deficiency of ACTH or thyroid-stimulating hormone or both, associated with autoimmune thyroid or adrenal disease, may have resulted from autoimmune pituitary destruction. Botazzi et al. described a girl with antithyroid antibodies and a family history of polyglandular autoimmune syndrome in whom isolated growth-hormone deficiency was associated with positive anti-gonadotropin antibodies. Acquired gonadotropin deficiency in patients with polyglandular autoimmune syndrome has been previously described, but the patients were not challenged with GnRH, and thus the site of the lesion remains unclear.

The absence of pituitary antibodies in our patients is not surprising, considering the limitations of the immunofluorescence technique. Indeed, the correlation between the presence of antibodies and pituitary hypofunction has not been well established. Auto-antibodies to lactotropes are found with the highest frequency in patients with polyglandular autoimmune syndrome and hypoparathyroidism. Pituitary antibodies were found only in two patients with suspected autoimmune hypophysitis and may be of transient sensitivity. Similarly, anti-adrenal-cell antibodies are found in only 50 to 70 per cent of cases of idiopathic Addison's disease. Other studies have provided evidence for pituitary involvement in polyglandular autoimmune syndrome. Enhanced lymphocyte sensitivity to extracts of human pituitary tissue, in the absence of circulating pituitary antibodies, has been described in a child with alopecia, candidiasis, primary immunodeficiency, and idiopathic hypopituitarism, suggesting that cellular immunity may also have a role in the development of an autoimmune hypophysitis. Recently, monoclonal antibodies reacting with pituitary cells have been prepared with use of spleen cells of mice with a virus-induced autoimmune polyendocrine disease involving pancreatic islets and pituitary cells. Similarly, lymphocytes from patients with insulin-dependent diabetes mellitus and antithyroid antibodies have been used to prepare monoclonal antibodies reacting with anterior pituitary tissue.

In conclusion, we have described two patients with the polyglandular autoimmune syndrome and associated acquired isolated gonadotropin failure. These data show that isolated hypogonadotropic hypogonadism does not necessarily result from deficient hypothalamic secretion of GnRH but may also be due to isolated gonadotropin failure. In addition, these studies suggest that the pituitary is not spared by the generalized autoimmune process and that autoimmune hypophysitis may be an integral part of polyglandular autoimmune disease.

We are indebted to Drs. G. Franço Bottazzo, Floyd Taub, and Ricardo Lloyd for examining the patients' serum samples for the presence of autoantibodies, to Ms. Marra Markows and Ms. Katherine Kersey for performing the radioimmunoassays of plasma hormones, to Mrs. Beverly Turner for preparation of the manuscript; and to the staff of the Clinical Research Center for their dedicated care of these patients.

REFERENCES

DOMINANT INHERITANCE OF ADENOMATOUS COLONIC POLYPS AND COLORECTAL CANCER

RANDALL W. BURT, M.D., D. TIMOTHY BISHOP, PH.D., LISA A. CANNON, M.S., MARK A. DOWDLE, M.D., RANDALL G. LEE, M.D., AND MARK H. SKOLNICK, PH.D.

Abstract Except in the rare polyposis syndromes, the contribution of heritable factors to the genesis of colorectal cancer and adenomatous polyps is not well understood. We examined the inheritance of susceptibility to colorectal cancer in a large Utah pedigree with multiple cases of common colorectal cancer but no recognizable inheritance pattern among them. Inheritance was clarified, however, by systematic screening for colon polyps in pedigree members and spouse controls, using flexible proctosigmoidoscopy. One or more adenomatous polyps were found in 21 percent of family members (41 of 191) but in only 9 percent of controls (12 of 132) (P<0.005). Pedigree analysis was performed with likelihood methods that compared random occurrence of cancer and polyps with autosomal recessive and autosomal dominant patterns of inheritance.

The analysis suggested that the observed excess of discrete adenomatous polyps and colorectal cancers was the result of an inherited autosomal dominant gene for susceptibility, rather than an inherited recessive gene for susceptibility or a chance occurrence. This type of inheritance of colorectal polyps and cancer may be more common than previously recognized. (N Engl J Med 1985; 312:1540-4.)

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