

Leydig Cell Responsiveness with Germinal Cell Resistance to Gonadotropin Therapy in Kallman's Syndrome

JEROME H. CHECK, M.D.
JOSÉ F. CARO, M.D.
LOUIS CRIDEN, M.D.
RICHARD MELTZ, D.O.
KENNETH BROWNSTEIN, M.D.
Chester, Pennsylvania

Patient's with Kallman's syndrome have been divided into gonadotropin-sensitive gonadotropin-resistant types. This has been based on the testosterone response of the Leydig cells to human chorionic gonadotropin (HCG) and the resultant sexual characteristics. Whether the germinal epithelium is similarly sensitive has not been previously assessed. The present study was set up to see if a male with anosmia and hypogonadotropic hypogonadism could be made fertile by treating with human menopausal gonadotropins (HMG) in combination with HCG, a regime previously found effective in other types of hypogonadotropic hypogonadism.

The patient was previously shown to be HCG-responsive by the induction of secondary sexual characteristics following gonadotropin therapy. This was confirmed by measuring serum testosterone levels before and after the administration of HCG. Therapy with HMG, 75 IU intramuscularly, and HCG, 2,000 intramuscularly three times a week, was started. After six months, despite perfectly normal secondary sexual characteristics and near normal-sized testes, he still showed azoospermia. His HMG was increased to 150 intravenously thrice weekly. After an additional two months of therapy, his count was still zero.

A testicular biopsy was performed and disclosed Leydig cell hyperplasia but very little active spermatogenesis. Although this man was gonadotropin-sensitive as far as his Leydig cells are concerned, his germinal epithelium was resistant. Thus, HCG sensitivity does not ensure fertility.

The syndrome of anosmia or hypogonadism combined with hypogonadotropic hypogonadism was first defined by Kallman et al. in 1944 [1]. The failure to develop gonadotropic function is probably due to a defect in the development of the hypothalamus. Other associated abnormalities may also occur [2,3]. Pituitary responses to the injection of luteinizing hormone-releasing hormone (LH-RH) may also be subnormal in some cases [4]. The clinical difference between gonadotropin failure due to pituitary disease and that of Kallman's syndrome is important because patients with Kallman's syndrome may have a relative nonresponsiveness of the testes to exogenous gonadotropins. Bardin and colleagues [5] have suggested that both ends of the pituitary axis are abnormal in some patients based on the testosterone response of the Leydig cells to human chorionic gonadotropin (HCG).

A patient is presented with a history of hypogonadotropic hypogonadism and anosmia who previously demonstrated HCG respon-

From the Departments of Medicine, Obstetrics and Gynecology and Urology, Thomas Jefferson University School of Medicine, Philadelphia, Pennsylvania; and the Department of Obstetrics and Gynecology, Crozier-Chester Medical Center, Chester, Pennsylvania. Requests for reprints should be addressed to Dr. Jerome H. Check, The Jefferson Building, 1015 Chestnut Street, Philadelphia, Pennsylvania 19107. Manuscript accepted January 30, 1979.



Figure 1. Testicular biopsy specimen taken after eight months of gonadotropin therapy in a patient with Kallman's syndrome. A good number of Leydig cells are seen, but hypospermatogenesis is still present.

siveness as manifested by the development of secondary sexual characteristics after a series of injections. An attempt was made to induce spermatogenesis by treating him with a combination of human menopausal gonadotropins (HMG) and HCG in a therapeutic regimen previously demonstrated to restore fertility in 12 of 13 men with hypogonadotropic hyposonadism including four patients with Kallman's syndrome [6-12]. Although our patient was gonadotropin-sensitive as far as his Leydig cells are concerned, his germinal epithelium was resistant. Thus, HCG sensitivity does not ensure fertility. The clinical and histopathologic results are discussed.

CASE REPORT

The patient, a 26 year old man, had congenital anosmia and no secondary sexual characteristics until he received (at age 21) a series of HCG injections—2,000 U twice weekly for three months—when his voice deepened and a male muscular pattern and male hair pattern developed. He stopped receiving these injections after six months and by age 26 he only shaved occasionally, had scant axillary and pubic hair, and had lost some of his muscular habitus. He claimed to have no difficulty in maintaining an erection but was unable to ejaculate. The rest of his history was negative except for color blindness. He has one brother without gonadal dysfunction or anosmia, but he is also color blind. No other family members are color blind.

His physical examination disclosed no abnormalities with the exception of small 1 by 1.5 cm testes bilaterally, a slightly eunuchoid habitus, and scant axillary, pubic and facial hair.

At age 14 he had a lumbar puncture, electroencephalogram, skull roentgenogram and pneumoencephalogram, none of which disclosed any abnormalities. Since his neurologic examination remained status quo, these studies were not repeated.

Laboratory evaluation revealed both serum LH and FSH to

be undetectable. Serum testosterone was 33 ng/100 ml (normal male = 300 to 800 ng/100 ml). Serum thyroxine and triiodothyronine uptake were normal.

Therapy with HMG, 75 IU intramuscularly three times a week, and HCG, 2,000 IU three times a week, was started.

After 91 days of therapy the patient had gained 25 pounds, most of which seemed secondary to increased muscle mass, had a normal male hair pattern and shaved daily. He was now able to produce a 1.5 ml ejaculate. However, he still had azoospermia.

His serum testosterone level rose to 625 ng/100 ml after five injections and was 1972 ng/100 ml after six months of therapy, but still no mature sperm were seen in the ejaculate.

After six months of HMG injections 75 mIU three times a week, the injections were increased to 150 mIU three times a week; he was evaluated after a total of eight months of therapy, but azoospermia persisted. His testicular volume was just slightly subnormal now, 3.5 cm by 2 cm.

A testicular biopsy specimen was obtained after eight months of therapy and is seen in **Figure 1**. Leydig cell hyperplasia is seen thus explaining the supranormal levels of testosterone. A good level of Leydig cells is seen but very little active spermatogenesis.

COMMENTS

Patients with Kallman's syndrome have been divided into those with and without gonadotropin resistance depending upon their testosterone response to HCG [2].

This case demonstrates that a man with Kallman's syndrome who shows a good testosterone response to HCG may still fail to induce spermatogenesis despite a prolonged course of HMG in conjunction with HCG.

After eight months of therapy, the biopsy specimen still showed hypospermatogenesis despite a good

number of Leydig cells. Although it might have been nice to have a pretherapy biopsy specimen, since testicular biopsy specimen from patients with Kallman's syndrome have been similar to those from prepubertal boys and since this patient clinically resembled a prepubertal male, we ruled out a pretherapy biopsy. This procedure would have subjected the patient to surgical risk and pain without the likelihood of providing very useful information.

Whether this failure of gonadotropin therapy represents resistance of the germinal epithelium to gonadotropins in this condition or whether some other mechanism is responsible cannot be determined at this time.

It is unlikely that antihormone antibodies are responsible in view of previous studies involving prolonged gonadotropin therapy [13].

The response to gonadotropins in our patient resembles the response of the prepubertal testis. The inactive fibroblasts of the interstitial tissue of the prepubertal testis are capable of synthesizing testosterone within 48 to 72 hours after the administration of HCG. A 15- to 20-fold increase in plasma testosterone level may be achieved even before these cells completely differentiate to mature Leydig cells. Longer stimulation (three to six months) transforms the immature cells into Leydig cells [14].

However, the seminiferous tubules do not respond in the same manner. In prepubertal boys, using different doses and ratios of FSH and LH for prolonged periods of time up to eight months, full spermatogenesis was not induced. It appears that the germinal epithelium may not be stimulated up to the first meiotic division very easily, but it was impossible to stimulate the spermatogenic process any further [15]. This may be similar to what happened in our patient.

The fact does remain, however, that a very large dose of gonadotropins, a dose which is in great excess of the amount usually employed in hypopituitarism, failed to initiate spermatogenesis in a patient with Kallman's syndrome.

This case demonstrates that when separating patients with Kallman's syndrome into groups according to their gonadotropin response in addition to the two previously described groups [(1) both Leydig cells and germinal epithelium gonadotropin responsive; (2) resistance to gonadotropins] a third group should be added—(3) Leydig cell-responsive but germinal epithelium-resistant. Thus, in the hypogonadotropic hypogonad patient with anosmia seeking to improve fertility, HCG responsiveness does not ensure that fertility can be restored even despite therapy with prolonged expensive therapy.

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