HYPERGONADOTROPHIC HYPOGONADISM
WITH ANOSMIA

By

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ABSTRACT

A 58 year old male with anosmia and primary testicular failure is described. The presence of anosmia did not preclude the secretion of elevated levels of gonadotrophin suggesting that in hypogonadotrophic hypogonadism with anosmia (Kallmann's syndrome) the hypogonadotrophism is not the result of anosmia alone, but that other, probably hypothalamic, factors are involved. The patient described phenotypically resembled Klinefelter's syndrome, but no chromosomal abnormality was detected. To our knowledge, hypergonadotrophic hypogonadism associated with anosmia has not previously been reported, and thus may represent a heretofore unrecognized clinical entity.

A definite, yet poorly understood relationship exists between the sense of smell and sexual function. In animals, olfactory deprivation may alter mating behaviour (Parkes & Bruce 1961) and destruction of the olfactory tracts leads to a change in hypothalamic-pituitary-gonadal function, presumably by altering gonadotrophin secretion (Martini 1970; Signoret & Mauleon 1962). In man, a syndrome of anosmia and hypogonadotrophic hypogonadism is recognized.

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Photograph taken after testicular biopsy and surgical preparation (shaving) of pubis and perineum.

(Kallmann et al. 1944; Sparkes et al. 1968). The lack of smell sensation in hypogonadotrophic hypogonadism with anosmia (Kallmann’s syndrome) appears to be on the basis of absence of the olfactory bulbs and an incomplete development of the hypothalamus (De Morsier & Gauthier 1963) but the direct relationship of the anosmia to hypogonadotrophism is obscure. The anatomical studies by De Morsier and Gauthier suggest that abnormal hypothalamic structure may be the central defect in this syndrome, and that absence of the olfactory bulbs is a co-existing lesion, with anosmia serving as one of the main clinical clues for the detection of the condition.

The following case report is unique in that anosmia was demonstrated in a hypogonadal patient who had elevated gonadotrophin levels.
CASE REPORT

The patient was a 58 year old unmarried white male who was admitted to the hospital for evaluation of hypogonadism. He had failed to experience normal puberty. He denied having had mumps. He had no pubertal growth spurt, deepening of his voice or the development of a masculine physique. His libido was always decreased; he had no spontaneous erections and had never had an ejaculation. He shaved once or twice weekly. An inability to detect odours had been present for life. The parents were in good health and had no abnormality of the sense of smell. Physical examination revealed a short, obese man with eunuchoidal proportions (Fig. 1). He measured 165 cm in height with an arm span of 177 cm and a pubis to floor measurement of 84 cm. The blood pressure was 130/80 mm Hg; pulse 80 beats per minute. External strabismus and an early cataract were present in the left eye. The visual fields, retinal fundi and optic discs were normal. Slight dorsal kyphosis was present and inwardly curved fifth fingers were observed bilaterally. The breasts were large and obese, although definite glandular tissue could not be palpated. No temporal hair recession was evident, axillary hair was scant, and the escutcheon was gynaeccoid. The prostate was not palpable. The phallus measured 10 cm when stretched. The right testis was 3.4 × 2 cm in size; the left was cryptorchid and measured 0.5 × 0.5 cm. Except for anosmia, the neurological examination was normal.

Fig. 2.
Photomicrograph of testicular biopsy specimen. Zenker's fixative, haematoxylin and PAS stain, × 100.
Table 1.
Olfactory responses to various odours: + = odour perceived; B = burning irritation; 0 = no sensation.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Test Odours</th>
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<tr>
<td></td>
<td>Ammonia</td>
</tr>
<tr>
<td>Normal</td>
<td>+, B</td>
</tr>
<tr>
<td>Hysteric</td>
<td>0, 0</td>
</tr>
<tr>
<td>Anosmic</td>
<td>0, B</td>
</tr>
<tr>
<td>Patient</td>
<td>0, B</td>
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LABORATORY STUDIES

X-rays of the hands, wrists, skull and sella turcica were normal. No chromatin bodies were seen on repeated buccal smear examination; the lymphocyte karyotype was 46 XY. Protein bound iodine was 5.8 µg/100 ml, serum cortisol 8.3 µg/100 ml, rising to 23 µg/100 ml after metyrapone blockade. Plasma growth hormone concentrations rose normally following insulin induced hypoglycaemia (2 ng to 8 ng/ml). Serum testosterone concentration was 150 ng/100 ml1) and the urinary pituitary gonadotrophin level was greater than 100 mouse uterine units per 24 hours. A biopsy of the right testis showed absence of germinal epithelium, marked peritubular fibrosis and »clumping« of the Leydig cells (Fig. 2).

Although the nasal septum was partially deviated to the right, the nasal passages were patent. The patient was unable to detect the aroma of freshly ground coffee or other common odours (Table 1), but perceived a burning sensation from the odour of ammonia. This response is typical of true anosmia with preserved trigeminal innervation of the nasal mucosa.

DISCUSSION

The findings observed in this patient strongly indicate that anosmia itself does not preclude the production and secretion of pituitary gonadotrophin. The patient described here shares characteristics common to two different groups of hypogonadal patients. Although hypogonadism and anosmia are present, the patient differs from the classical description of Kallmann's syndrome by virtue of

1) Bioscience Laboratories, Van Nuys, California. Serum testosterone is measured by competitive protein binding. Normal values for adult males are 400–1200 ng/100 ml.
of the high urinary gonadotrophin levels. Hypogonadotrophism, usually clomiphene resistant, has been regularly documented in Kallmann's syndrome (Bardin et al. 1969; Schroffner & Furth 1970; Nankin et al. 1970), although hypogonadism, anosmia and normal gonadotrophin levels have been observed (Müller 1964; Boyar 1969), and Boyar (1969) observed a rise in plasma LH and FSH following clomiphene administration. Hypogonadotrophism and anosmia may be familial in some instances, and a divergence in these two markers may also be observed. Some family members may have both hypogonadotrophism and anosmia, others may have anosmia but normal gonadal function, and other members may be entirely normal (Nowakowski & Lenz 1961).

While it is most likely that patients with Kallmann's syndrome have a central defect in gonadotrophin secretion and regulation, our patient had primary testicular dysfunction as indicated by the low testosterone and high gonadotrophin levels and by the diffusely abnormal testicular biopsy. In this regard, the disorder phenotypically resembles Klinefelter's syndrome and could be classified as one of the types of so-called »chromatin-negative« Klinefelter's syndrome. The fibrosis of the spermatid tubules, the absence of spermatogenesis and the Leydig cell »clumping« found in this patient are indistinguishable from the testicular lesions of several forms of primary testicular disease including Klinefelter's and Reifenstein's syndrome (Bowen et al. 1965). The possibility of XY/XXY chromosomal pattern with 47/XXY of the testicular cells cannot be excluded on the basis of our studies, although the buccal mucosa and peripheral lymphocyte cells appeared to contain the normal compliment of chromatin and chromosomes. Total urinary bioassayable gonadotrophin, as was performed in this patient, does not distinguish between LH and FSH. However, the testicular dysfunction in this man involved both germinal and interstitial elements, and it would seem likely that elevated levels of both LH and FSH would be found.

The findings in this patient may represent the observation of a coincidence of clinical »markers«, namely, hypogonadism due to testicular failure and anosmia, but it is also possible that this association may be found in other subjects as more and more attention is given to the detection of anosmia in hypogonadal patients.

ACKNOWLEDGMENTS

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