Furthermore, it is also obvious, from the presence of a population of circulating red cells (group O in our patient) which are not modified by transferase present in plasma (A-transferase in our patient), that the final step in the formation of ABH-active sites on the red cell surface does not occur in the external environment of the cells (Race and Watkins, 1972), and is therefore mediated in the bone-marrow by a process yet to be elucidated.

We gratefully acknowledge the keen interest and valuable advice of Dr Ruth Sanger and Mrs Marie Crookston.

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REFERENCES


Gundolf, F. (1973). Anti-A_{1}Le\textsuperscript{b} in serum of a person of blood group A\textsubscript{1}h. Vox Sanguini, 25, 411–419.


A case of hypogonadotropic hypogonadism with anosmia (Kallmann’s syndrome) in a male, with familial incidence of a small metacentric chromosome (47,XY,mat?+)

Summary. A case of Kallmann’s syndrome in a male is reported. Besides the classical picture of hypogonadotropic hypogonadism (demonstrated both by endocrine investigation and a testicular biopsy) with anosmia, a number of other unusual features are present including gynaecomastia, agenesis of the anterior brachial muscles, some dental abnormalities, and dyschromatopsia. The karyotype, studied on peripheral lymphocytes, shows, in the propositus as well as in his mother, the presence in all mitoses of an extra small metacentric chromosome; its derivation is uncertain.

The association of anosmia with hypogonadotropic hypogonadism is a rare, but now well-recognized condition, also known as Kallmann’s syndrome (Kallmann et al., 1944) or olfactory-genital dysplasia (de Morsier, 1954). The condition appears to be heterogeneous, both because of the different patterns of inheritance, and also with respect to response to clomiphene. The syndrome has been described in both sexes, and, as several members of a kinship can be affected, it has been suggested that it is genetically determined. However, the mode of inheritance is still uncertain; in fact, behaviour consistent with X-linked dominant inheritance, X-linked recessive inheritance, and autosomal dominant inheritance have all been reported (McKusick, 1971). Santen and Paulsen (1973) reported a clinical study of six families which suggests an autosomal dominant pattern of inheritance with variability in expressivity, but the authors did not exclude a genetic heterogeneity.

Whereas most investigators report no response to short- or long-term administration of clomiphene in Kallmann’s syndrome, Hamilton et al (1973) obtained a different response according to the severity of anosmia: in Type I anosmia (no response to vapours at the primary olfactory area) clomiphene was ineffective, whereas some subjects with Type II anosmia (subnormal response to vapours at the primary olfactory area; olfactory responses can be made in an attenuated manner) responded adequately to prolonged treatment. In the view of the authors, the two types of anosmia imply a more or less severe defect of the olfactory lobe; this, in turn, is associated with a different degree of ‘maturation’ of the hypothalamus, which could explain the positive or negative response to clomiphene. No chromosomal abnormality has so far been described in this syndrome. We therefore report a case where, in addition to the typical features of hypogonadotropic hypogonadism with anosmia, other abnormalities and an extra small chromosome have been observed; the latter was also present in the maternal karyotype.
**TABLE**

<table>
<thead>
<tr>
<th>LH–RH stimulation test (200 μg, iv)</th>
<th>Normal Adult Male Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values in Present Case</td>
<td>Basal: 4–20 mIU/l</td>
</tr>
<tr>
<td>At 0 s</td>
<td></td>
</tr>
<tr>
<td>FSH (mIU/l)</td>
<td>1.25</td>
</tr>
<tr>
<td>LH (mIU/l)</td>
<td>1.25</td>
</tr>
<tr>
<td>At 15 s</td>
<td></td>
</tr>
<tr>
<td>FSH (mIU/l)</td>
<td>1.50</td>
</tr>
<tr>
<td>LH (mIU/l)</td>
<td>2.00</td>
</tr>
<tr>
<td>At 30 s</td>
<td></td>
</tr>
<tr>
<td>FSH (mIU/l)</td>
<td>1.50</td>
</tr>
<tr>
<td>LH (mIU/l)</td>
<td>3.50</td>
</tr>
<tr>
<td>At 45 s</td>
<td></td>
</tr>
<tr>
<td>FSH (mIU/l)</td>
<td>2.00</td>
</tr>
<tr>
<td>LH (mIU/l)</td>
<td>5.90</td>
</tr>
<tr>
<td>At 60 s</td>
<td></td>
</tr>
<tr>
<td>FSH (mIU/l)</td>
<td>1.75</td>
</tr>
<tr>
<td>LH (mIU/l)</td>
<td>6.20</td>
</tr>
</tbody>
</table>

FSH values vary widely. LH levels should show at least a four-fold increase over basal values

<table>
<thead>
<tr>
<th>Serum thyroxine</th>
<th>9.5 μg%</th>
<th>3.5–11.0 μg%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma testosterone</td>
<td>104.0 ng%</td>
<td>200–600 ng%</td>
</tr>
<tr>
<td>Urinary 17-hydroxysteroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before metyrapone*</td>
<td>4.03 mg/24 h</td>
<td>Basal: 2–7 mg/24 h</td>
</tr>
<tr>
<td>After metyrapone*</td>
<td>25.04 mg/24 h</td>
<td>Usually more than 100% above basal values</td>
</tr>
</tbody>
</table>

* 750 mg, po, six doses every 6 h.

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**Case report**

The propositus is a 29-year-old male who was born at term of non-consanguineous parents. His physical and mental development were normal. He reached puberty at 15 and thereafter his libido and sexual activity were reported as normal. During a routine examination at 19 years, small testes and a moderate degree of gynaecomastia were found and the diagnosis of Klinefelter's syndrome was proposed. He married at age 26; two years later, investigation for infertility showed azospernia, and the patient was therefore referred to us.

At this time physical examination showed a white male with eunuchoid appearance, 177 cm tall, weighing 77 kg. He had a scanty beard, normal pubic and axillary hair, minimal gynaecomastia, and hypoplastic nipples. The penis was of normal size; both testes were small (1 × 1.5 × 2 cm), soft, with a regular surface; no varicocele was present. The skeletal system showed no abnormalities. The muscular system showed agenesis of the anterior brachial muscles (as a consequence of which, some movements are hard for the patient to accomplish). Neurological examination was otherwise negative. Teeth: osseous inclusion of 3/3: persistence of III/III; agenesis of 8/8.

Special tests revealed: normal sensitivity to taste; dyschromatopsia for blue (right eye) and red (left eye); complete anosmia (including testing with ether, acetic acid, and pyridine). The EEG was normal and blood grouping showed: O, Rh+.

Endocrine investigation included: serum thyroxine assay, plasma testosterone, plasma-follicle stimulating hormone (FSH) and luteinizing hormone (LH) before and after intravenous administration of 200 μg synthetic LH-releasing hormone (LH–RH), and a Metyrapone test. Data are summarized in the Table.

The metyrapone test was positive and the serum thyroxine was normal: these results imply a normal release of adrenocorticotropic hormone (ACTH) and thyroid-stimulating hormone (TSH) and normal end-organ responses. Plasma testosterone was low for an adult male and plasma gonadotrophins were below the sensitivity of the radioimmunoassays (1.25 IU/l); intravenous injection of LH–RH evoked a significant increase (more than four-fold over baseline values) of LH, whereas FSH became barely detectable. Our results, in agreement with some recent data obtained by others (Zarate et al, 1973) point to a defective hypothalamic production of LH–RH as the cause of the lack of circulating gonadotrophins; once adequately stimulated the pituitary appears to be capable per se of synthesizing and releasing hormones. A clomiphene stimulation test has not been carried out; however, in view of the complete anosmia presented by our patient (Type I according to Hamilton et al (1973)) no response could have been anticipated.

In addition to routine stains for testicular biopsy, the Mallory–Vannucci, Caja1-Gallego, and Toluidine blue staining techniques were used. At low magnification (see Fig. 1) the overall picture is characterized by seminiferous tubules widely differing in size, and by marked hypoplasia of the germinal epithelium. The basal membrane in the tubules is somewhat thickened, homogeneous, and slightly metachromatic with toluidine blue; the stroma is loose and only small, scattered clusters of Leydig cells are occasionally seen. At higher magnification, Sertoli cells and spermatagonia are seen in great numbers. Few primary and secondary spermatocytes are present and only occasional tubule shows rare spermatids.

**Cytogenetics**

Sex chromatin (buccal smear) were negative. Karyotype (peripheral lymphocytes) showed an extra metacentric chromosome, smaller than groups 19–20, which was identified in all mitoses; the features of all groups were normal (see Figs. 2 and 3). An identical abnormality was found in the mother’s karyotype.

**Dermatoglyphics**

The results of the study performed on the patient and his family showed an unusual incidence of arches in the kinship. Such a configuration is present in less than 5% of the general population.

**Discussion**

Our patient exhibits, in addition to the classical findings of hypogonadotropic hypogonadism and anosmia, a number of other abnormal features; some, such as gynaecomastia, have already, though
Fig. 1. Marked hypoplasia of germinal epithelium. (H & E × 100.)

Fig. 2. Trypsin-Giemsa banded karyotype of the propositus showing extra small chromosome (arrow).
propositus showing the small to interesting not to compared with F-group chromosomes.

Moreover, karyotype, normal testicular defect has been seen elsewhere in mind.

The possibility that a primary testicular defect is present, whether related or not to the chromosomal abnormality, must be borne in mind.

Finally, the finding of a small extra metacentric chromosome, inherited through the mother and not seen elsewhere in the kinship is most unusual. It is interesting to know that a maternal uncle, with a normal karyotype, has two sons, one of whom is at present 20 and has been labelled as 'hypogonadal' by a family physician; unfortunately, he refused to be evaluated by us. In addition a sister of the patient, who also has a normal karyotype, has had three miscarriages, and no term pregnancies (Fig.4).

It is not possible to decide whether the association of the hypogonadotrophism and anosmia with the small extra metacentric chromosome is only a coincidence. It is well known that an extra metacentric, having the same appearance, if not the same origin, can be seen in a number of different diseases (Finley et al, 1971), and sometimes even in normal individuals (Ventruto et al, 1973). On the other hand, a similar chromosomal abnormality has been found in cases of oligospermia (Smith et al, 1965; Hulten et al, 1966; Chandley, 1970). In the case reported by Smith et al (1965) as in ours, the patient’s mother also carried an extra metacentric; no impairment of fertility from the chromosomal abnormality must therefore be implied, at least in females.

With the availability of human gonadotrophins (human chorionic gonadotrophin,—HCG, and human menopausal gonadotrophin—HMG) the prognosis of Kallmann’s syndrome, as far as fertility is concerned, has improved a great deal. Induction of ovulation, proved by pregnancy, has been reported in some female subjects (Naftolin et al, 1971). As for males, fertility could be restored by adequate replacement with exogenous gonadotrophins, provided the testes have not suffered an irreversible damage. We know of more than one unpublished case where normal spermatogenesis has been achieved and pregnancy ensued.

In our case a more profound, and possibly irreversible, testicular damage might be implied on the basis of the histological findings. The prognosis is therefore more obscure than in the typical instance of Kallmann’s syndrome; a trial of HCG plus HMG is under way and the results will be dealt with elsewhere.

Fig. 3. Partial karyotype of two Giemsa-stained cells from the propositus showing the small extra metacentric chromosome (right) compared with F-group chromosomes.

**Case reports**

exceptionally, been seen in cases of Kallmann’s syndrome (Carfagna et al, 1968); others, such as hypoplastic nipples, agenesis of anterior brachial muscles, dental abnormalities, dyschromatopsy, have never, till now, been described in such cases. Moreover, the histology of the testes shows more profound damage to the germinal epithelium than expected on the basis of a mere lack of gonadotrophic stimulation: as seen, for example, in the wide difference in size of the tubules, the paucity of primary and secondary spermatocytes, and the virtual absence of spermatids. The possibility that a primary testicular defect is present, whether related or not to the chromosomal abnormality, must be borne in mind.

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**References**
A probable case of mutation in Huntington's disease*

**Summary.** A patient is described in whom Huntington's disease was diagnosed at the age of 34 years. No evidence of the disorder was found in either parent. Their parentage of the alleged mutant could not be excluded from a study of the inheritance of 25 genetic markers.

It is rare for signs of Huntington's disease to appear in offspring before it manifests itself in one of the living parents. When such a case occurs, it is reasonable to suspect a mutation. Because of the possibility of very late onset of symptoms, few cases have been reported in which the parents of the alleged mutant are both alive. For such reasons, Reed and Neel (1959) do not believe that specific instances of mutation in the disorder can be demonstrated. It follows that an accurate estimate of the very low mutation rate is impossible until present diagnostic techniques improve. Palm (1973) has briefly reviewed the evidence against the gene being maintained in the population by new mutations.

We wish to describe a probable mutant who came to light in the course of an ascertainment of families affected with Huntington's disease in the state of Victoria.

**Case report**

The propositus was born in a village in Calabria, Italy, in 1935. At the age of 34 years, he began to develop involuntary movements. He was at that time a successful restaurant and store owner and was a highly respected migrant in a small town near Melbourne. The movements began first in his right leg and later spread to his abdomen, right arm, head, neck, and shoulders. These symptoms were followed by increasing deficits in memory and inability to carry on the conduct of his business. He took up employment in a real estate agency and over a period of some 14 months deteriorated to a packer in a vegetable market. For 12 months before presentation early in 1973, he was unemployed.

By the time of referral for investigation, his choreiform movements and demyelinating process were pronounced. The diagnosis of Huntington's chorea was made by two independent neurological opinions, and pneumoencephalographic examination confirmed atrophy of the caudate nucleus and associated apparent dilatation of the third ventricles with generalized cortical atrophy (Figs. 1 and 2).

There is no family history of Huntington's disease. His father was born in 1911 and his mother was born in 1913, both being of Calabrian descent. The propositus has four sibs, being younger sisters born in 1936, 1937, 1942, and 1947. Inquiries were made into the extended family and in the village. Within living memory, there was no recollection of anyone with similar symptoms part from a female second cousin who, at the age of 12 years, developed rheumatic fever and subsequently suffered from Sydenham's chorea, but had had no recurrence of choreiform symptoms.

Examination of the parents in Melbourne produced no evidence of Huntington's disease. The father was working as an orderly in a geriatric hospital and had been a professional soldier, being home only for short periods during the second World War. The question of the biological parentage of the propositus was investigated by the use of 25 genetic markers in saliva, red blood cells, and plasma (Table). No hereditary incompatibility was detected.

**Discussion**

For a mutation to be acceptable, Stevens and Parsons (1969) have laid down four criteria:

(i) The disease being investigated must have the cardinal features of Huntington's disease—namely,