

# Identical twins discordant for Kallmann's syndrome

L J Hipkin, I F Casson, J C Davis

## Abstract

A 20 year old male patient presented with lack of sexual development. On examination he was eunuchoidal and hypogonadal, and olfactory function testing showed he was anosmic. Biochemical investigations proved he was hypogonadotrophic. Kallmann's syndrome was therefore diagnosed. His appearance was very different from his alleged identical twin who had undergone a normal puberty and had normal plasma testosterone and gonadotrophin levels. However, the twin was hyposmic. Genetic fingerprinting confirmed the twins were identical. Why Kallman's syndrome was incompletely expressed in one of them is unexplained. The parents and a normally menstruating sister had normal olfactory function.

The association of hypogonadism and disturbances of olfactory function was first reported over a century ago. Later it was recognised that other somatic abnormalities, particularly midline cranial and intracranial defects, were present in some patients and the whole subject has been well reviewed by Borghi *et al.*<sup>1</sup> Kallmann *et al.*<sup>2</sup> were the first to report the familial transmission of the disorder, favouring an X chromosome aberration rather than an X linked recessive or sex limited autosomal dominant inheritance, which they also considered. A review of published reports since then makes genetic heterogeneity seem likely, with X linked and autosomal dominant and recessive modes of inheritance all being reported.<sup>3</sup> Another feature is that the genetic abnormality may be incompletely expressed so that relatives of patients with Kallmann's syndrome may only suffer from hypogonadotrophic hypogonadism, hyposmia, or anosmia.<sup>4</sup> We report identical twin brothers, one with fully expressed Kallmann's

syndrome and the other with normal gonadal function and hyposmia. Similar discordance was reported in identical twin sisters by Hermanussen and Sippell.<sup>5</sup>

## Case reports

The patient, a 20 year old male, was referred because of lack of sexual development (fig 1). His voice had not broken and he did not shave. On questioning he reported a poor sense of smell. Examination showed that he was 183 cm tall with eunuchoidal proportions (span 191 cm, ground to pubis 101 cm, pubis to crown 82 cm). Genital development was at Tanner stage 1 but pubic hair was at stage 3. There were no other somatic defects on clinical examination.

Levels of plasma follicle stimulating hormone (FSH) and luteinising hormone (LH) were subnormal being 0.6 and 0.8 U/l respectively (reference range 1.2 to 5.0 U/l for FSH and 2.5 to 10.0 U/l for LH). There was an adequate but delayed response to IV injection

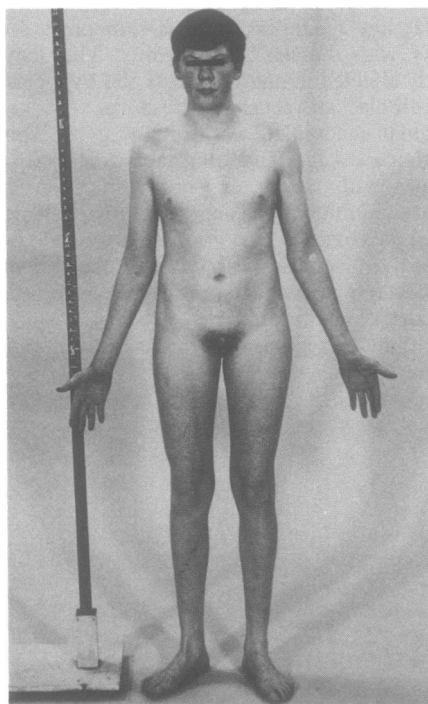


Figure 1 Eunuchoidism and hypogonadism in the patient with Kallman's syndrome.

Sub-Department of Endocrine Pathology, Alder Hey Hospital, Eaton Road, Liverpool L12 2AP.  
L J Hipkin, J C Davis

Royal Liverpool Hospital, Prescot Street, Liverpool L7 8XP.  
I F Casson

Correspondence to Dr Hipkin.

Received for publication 12 May 1989.  
Accepted for publication 4 September 1989.

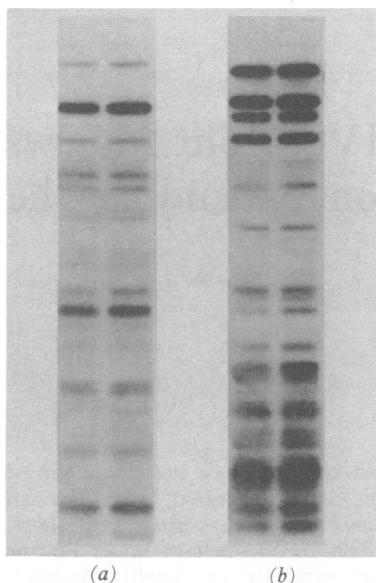


Figure 2 DNA fingerprints obtained from the patient and his twin using two different probes (a and b). The matching band patterns indicate monozygosity.

of 200 µg of gonadotrophin releasing hormone (5.2 U/l at 90 minutes for FSH; 5.5 U/l at 60 minutes for LH). Plasma testosterone was also subnormal being less than 2.6 nmol/l (reference range 8.5 to 32 nmol/l). Olfactory function testing was performed using the Smell Identification Test<sup>TM</sup> (Sensonics Inc). The patient correctly identified seven odours out of a total of 40, which is in the total anosmia range (6 to 19).

He was treated with androgens (Sustanon 250, IM every two weeks) with a marked virilising effect.

An alleged identical twin was interviewed. He was a completely virilised, normal adult. Plasma gonadotrophin levels were normal (FSH 5.0 U/l, LH 5.8 U/l) as was the testosterone (21 nmol/l). Olfactory function testing was performed on two occasions with a seven month interval. Scores of 28 and 25 were obtained, which are both in the hyposmic (or microsmic) range of 20 to 33. He was so different in appearance from his hypogonadal brother, even after the latter had been treated with androgens, that Cellmark Diagnostics were requested to carry out genetic fingerprinting. This confirmed they were identical twins (fig 2).

Their mother and a sister (who menstruated normally) had normal olfactory function, each scoring 35 in the Smell Identification Test<sup>TM</sup> (reference range 35 to 40) as did the father who scored 36 (reference range 34 to 40).

## Discussion

There has been much debate about the genetics of hypogonadotrophic hypogonadism with anosmia or Kallmann's syndrome. There are several problems

with such studies. Gene frequency is low and without therapy the hypogonadism causes infertility. Not all patients with hypogonadotrophic hypogonadism or relatives of probands with the disorder are questioned or tested for olfactory function. Furthermore, it is not clear whether there are separate heritable forms of anosmia or hypogonadotrophic hypogonadism, although it has been pointed out that sporadic cases of Kallmann's syndrome have only appeared in families in which isolated anosmia is present.<sup>5</sup> Thus, variability of genetic expression is a frequent comment in published reports.

There is no doubt that the patient described here had Kallmann's syndrome and that his proven 'identical' twin brother had normal gonadal function but with hyposmia. There are few reports of hypogonadotrophic hypogonadism or anosmia or both in identical twins. Chang *et al*<sup>6</sup> reported twin girls with primary amenorrhoea and lack of secondary sex characteristics owing to gonadotrophin deficiency. They also had retinitis pigmentosa. Identical twin brothers with schizophrenia were noted to have hypogonadotrophic hypogonadism by Genz *et al*,<sup>7</sup> while Kissel and Andre<sup>8</sup> found Parkinson's disease and anosmia in monozygotic twin sisters.

The only comparable report to the twins described here occurred in the second family investigated by Hermanussen and Sippell.<sup>5</sup> A 16 year old girl with retarded pubertal development was found to be totally anosmic. Her twin sister, proved to be monozygotic by blood grouping and HLA typing, had undergone a normal menarche but there was concordance for total anosmia. The authors speculated that there could be an acquired hypothalamic deficiency of GnRH on the basis of pre-existing anosmia. Our study supports this. However, in the six families reported by Santen and Paulsen,<sup>4</sup> there were as many patients with hypogonadotrophic hypogonadism alone as with total anosmia alone. It is therefore tempting to argue that anosmia or gonadotrophin deficiency or both may be acquired in those genetically predisposed.

- Borghi A, Giusti G, Bigozzi U. La 'displasia olfatto-genitale' di de Morsier. *Acta Med Auxol* 1970;2:83-116.
- Kallmann FJ, Schoenfeld WA, Barrera SE. The genetic aspects of primary eunuchoidism. *Am J Ment Defic* 1944;48:203-36.
- McKusick VA. *Mendelian inheritance in man*. Baltimore: Johns Hopkins University Press, 1988: 440-1, 1022-3, 1332-3.
- Santen RJ, Paulsen CA. Hypogonadotrophic eunuchoidism. I. Clinical study of the mode of inheritance. *J Clin Endocrinol Metab* 1973;36:47-54.
- Hermanussen M, Sippell WG. Heterogeneity of Kallmann's syndrome. *Clin Genet* 1985;28:106-11.
- Chang RJ, Davidson BJ, Carlson HE, Lu JKH, Judd HL. Hypogonadotrophic hypogonadism associated with retinitis pigmentosa in a female sibship: evidence for gonadotropin deficiency. *J Clin Endocrinol Metab* 1981;53:1179-85.
- Genz A, Lössner C, Krüger E. Eineiiges Zwillingspaar mit schizoforner Psychose und hypothalamisch bedingtem hypogonadotropen Hypogonadismus. *Psychiatr Neurol Med Psychol (Leipzig)* 1987;39:209-15.
- Kissel P, Andre JM. Maladie de Parkinson et anosmie chez deux jumelles monozygotiques. *J Genet Hum* 1976;24:113-7.