Identical twins discordant for Kallmann’s syndrome

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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 hypogonadotropic. 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. Kallmann et al 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. 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. We report identical twin brothers, one with fully expressed Kallman’s syndrome and the other with normal gonadal function and hyposmia. Similar discordance was reported in identical twin sisters by Hermanussen and Sippell.

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 of hCG (human chorionic gonadotrophin).

Figure 1. Eunuchoidism and hypogonadism in the patient with Kallman’s syndrome.
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. 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. 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., while Kissel and Andre 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 Hermanus sen and Sippell. 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, 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.