

Kallmann's syndrome: is it always for life?

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Summary

OBJECTIVE Kallmann's syndrome (KS) is defined by the association of olfactory deficit with irreversible, congenital gonadotrophin deficiency (IHH). We present evidence for the existence of a variant form of KS, in which endogenous gonadotrophin secretion recovers spontaneously in later life.

DESIGN Longitudinal clinical study.

PATIENTS Five men with anosmia or severe hyposmia, who originally presented in their late teens or early twenties as a result of severe pubertal delay and were thus presumed to have KS.

RESULTS Spontaneous onset of endogenous gonadotrophin secretion, evidenced by progressive normalization of testicular volume and of serum testosterone concentration, occurred in these men over a period of years following the initial diagnosis.

CONCLUSIONS This variant form of Kallman's syndrome is not well recognized and may well be underdiagnosed. Once full virilization has been induced, males with congenital gonadotrophin deficiency whose testes have significantly increased in size should be reassessed, off androgen replacement therapy, to identify those who no longer require treatment.

The prevalence of isolated hypogonadotrophic hypogonadism (IHH) in males has been estimated at 0.025% (Fromantin *et al.*, 1972), with a 5–1 male-female excess (Jones & Kemmann, 1976). Anosmia or severe hyposmia occurs in about half of all IHH cases (Waldstreicher *et al.*, 1996; Quinton *et al.*, 1998) and this association defines Kallmann's syndrome (KS). Olfactory acuity is readily assessed with simple odourants, e.g. coffee,

peppermint, oil of cloves, etc., although commercial kits can discriminate degrees of olfactory deficit. Results of the forced multiple-choice University of Pennsylvania Smell Identification Test (SIT[®]) are scored from 1 to 40, with 10/40 being the mean score obtainable by guesswork (Doty, 1995). In KS, anosmia is usually associated with abnormalities, or even complete absence, of the olfactory bulbs and sulci on magnetic resonance imaging (MRI) (Quinton *et al.*, 1996).

Gonadotrophin deficiency in KS is secondary to hypothalamic GnRH apulsatility. The pathophysiology underlying the X-linked form of KS appears to be an extracranial migration-arrest of GnRH neurones, consequent upon developmental failure of the olfactory and associated nerves to establish synaptic contacts within the forebrain (Schwanzel-Fukuda *et al.*, 1989). This aetiology has not been confirmed for autosomal or sporadic forms of KS. Unless exposed to physiological levels of gonadal steroids, KS patients cannot complete puberty and require lifelong replacement therapy to achieve and maintain secondary sexual characteristics and bone mineral density. Without therapy with GnRH or gonadotrophins, females are anovulatory and males azoospermic or severely oligozoospermic. We present five cases of KS, details of which are given below and in Table 1, in whom the gonadotrophin-deficiency appears not to have been permanent.

Case 1

A 22-year-old male presented with pubertal delay. He was found to be anosmic, with poorly developed secondary sexual characteristics and a bone age of 14 years. Serum biochemistry was consistent with IHH and a diagnosis of KS was therefore made. The patient was treated for one year with hCG 1000IU by twice weekly subcutaneous injection. This promoted full development of secondary sexual characteristics and testicular enlargement to 10 ml. Treatment was then changed to three-weekly testosterone enanthate 250 mg by intramuscular injection. This was continued for five years until, having entered a full sexual relationship, he sought a tertiary referral for advice on fertility and need for contraception. Because of an unexpected increase in testicular volume, treatment was discontinued and he was twice reassessed over the next six months. He appeared entirely eugonadal on both occasions and was advised of the need to take contraceptive precautions in the future.

Case 2

A 23-year-old male presented with pubertal delay. He was

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found to be completely anosmic with prepubertal genital development and body hair distribution and was presumed to have KS. Treatment with oral testosterone undecanoate 80 mg thrice-daily resulted in fully virilization. Aged 32 he successfully impregnated his wife during gonadotrophin therapy,

testicular volume having increased to 20 ml. Four years later, he discontinued androgen replacement therapy noticing no difference in himself. Subsequent reassessment confirmed that he was now clinically and biochemically eugonadal and he has remained so throughout 12 years of follow-up.

Table 1 Details of five cases of Kallman's syndrome

Case	1	2	3	4	5
Olfaction (SIT [®])	Anosmia	Anosmia(7/40) (Quinton <i>et al.</i> , 1996)	Anosmia	Severe hyposmia (23/40)	Anosmia
Imaging: pituitary & hypothalamus	Normal (high res. CT)	Normal (MRI)	Normal (MRI)	Normal (MRI)	Normal (MRI)
Imaging: olfactory bulbs & sulci	–	Absent bulbs (Quinton <i>et al.</i> , 1996)	–	Normal	Absent bulbs asymmetric sulci
Family history of Kallman's syndrome	No	No	No	mother IHH; maternal uncle KS (Quinton <i>et al.</i> , 1996)	No
Cryptorchid?	No	No	No	No	No
Other endocrinopathy?	No	No	No	No	No
At presentation:					
Age (years)	22.0	23.0	16.5	17.7	19.4
Testicular volume (ml)	6.0	2.0	2.0	4.0	1.0
Height centile	68th	97th	3rd (mid parent = 30th)	75th	25th
LH (mIU/l)	1.0	Urine gonadotrophins:	–	1.6	2.3
FSH (mIU/l)	1.0	4.7 mg/24 h (NR 5–40)	–	< 1.0	1.1
Testosterone (nmol/l)	2.2	1.5	–	2.0	1.6
1st reassessment:					
Age (years)	28.0	36.3	18.2	19.0	30.0
Months since last Rx	1.4	3.0	9.0	1.4	0.5
Testicular volume (ml)	16.0	20.0	4.0	25.0	8.0
Height centile	–	–	35th	–	70th
LH (mIU/l)	1.2	5.8	1.9	2.8	1.6
FSH (mIU/l)	2.7	3.7	1.0	1.8	4.4
Testosterone (nmol/l)	33.4	15.5	1.9	7.6	8.2
SHBG (NR 18–50)	–	–	–	23.0	–
Sperm density (x10 ⁶ /ml)	37.0	38.0	–	–	8.0
2nd reassessment:					
Age (years)	28.6	46.5	20.0	19.3	30.1
Months since last Rx	6.4	122.5	21.6	3.4	1.4
Testicular volume (ml)	16.0	20.0	4.0	25.0	10.0
LH (mIU/l)	4.5	6.5	2.3	2.9	5.4
FSH (mIU/l)	5.0	3.7	2.2	1.5	9.4
Testosterone (nmol/l)	25.0	17.0	3.8	8.7	10.4
SHBG (nmol/l)	–	–	–	17.0	–
Sperm density (x10 ⁶ /ml)	26.0	–	–	–	58.0
3rd reassessment:					
Age (years)	–	–	22.0	20.0	30.4
Months since last Rx	–	–	6.0	8.6	4.4
Testicular volume (ml)	–	–	15.0	25.0	12.0
LH (mIU/l)	–	–	–	3.0	7.1
FSH (mIU/l)	–	–	–	1.7	12.3
Testosterone (nmol/l)	–	–	15.0	11.4	10.4
Sperm density (x10 ⁶ /ml)	–	–	13.0	–	–

Case 3

A 16.5-year-old boy was referred with delayed puberty. He was found to be anosmic with prepubertal pattern genital development and body hair and bone age delayed by two years. He was started on intramuscular testosterone enanthate 50 mg monthly, building up to 100 mg every three weeks, and continued on this therapy for 12 months. Pubertal development was initiated, growth rate accelerated and testicular volume increased from 2 to 4 ml. After discontinuation of treatment linear growth continued to be satisfactory, but bone age was still delayed by 2.4 years and biochemistry was consistent with IHH. He was thus thought to have KS rather than simple constitutional delay, but was lost to follow-up before therapy could be reinstated. There remained clear biochemical evidence of IHH when he re-presented aged 20 years. He was restarted on three-weekly testosterone enanthate 250 mg and continued on this for a further 1.5 years. During this period his girlfriend became pregnant, with some family members harbouring doubts about the child's paternity. However, it was subsequently demonstrated that testicular volume, sperm density and serum testosterone concentration had all normalized.

Case 4

An 17.7-year-old male presented with arrested puberty. Genital development and body hair distribution were early pubertal and bone age was delayed by 2.2 years. His mother was a known IHH patient who had conceived as a result of ovulation-induction therapy; her sense of smell was normal with a score of 34/40 on SIT[®] and MRI had demonstrated normal olfactory bulbs and sulci. His maternal uncle had KS, being completely anosmic (SIT[®] score 11/40), with asymmetric olfactory sulci at MRI as reported by Quinton *et al.* (1996). The patient's olfactory acuity was intermediate, with SIT[®] demonstrating severe hyposmia (score 23/40) and biochemistry was consistent with IHH. In view of the strong family history, a presumptive diagnosis of KS was made and he was started on transdermal testosterone (Andropatch, Smithkline Beecham). He was reviewed 15 months later, having discontinued Andropatch shortly beforehand. Although serum testosterone concentration remained slightly subnormal, pubertal development was complete and testicular volume was 25 ml. Reviewed on two further occasions over the following seven months, he was clearly both clinically and biochemically eugonadal.

Case 5

A 19.4-year-old male presented with pubertal delay. He was completely anosmic, genital development and body hair distribution were prepubertal and serum biochemistry indicated IHH. He was started on intramuscular testosterone enanthate,

building up to 250 mg three-weekly, which was continued for 10 years, during which he became fully virilized and fathered two children. At 30 years of age, testicular volume was found to have increased to 8 ml and seminal fluid analysis revealed 8×10^6 /ml sperm density and he was therefore asked to discontinue replacement therapy. He was reviewed twice in the following four months and was found to be clinically and biochemically eugonadal with a normal sperm density.

Discussion

In these five cases the association of anosmia or severe hyposmia with pubertal delay led to the diagnosis of KS, implying a permanent gonadotrophin-deficiency requiring lifelong androgen replacement therapy. In case 4 there was even a strong family history of IHH, albeit an intriguing discordance in olfaction. Nevertheless, longitudinal follow-up revealed that all five men eventually became eugonadal. Congenital anosmia is described as an isolated phenomenon and the cases presented here could conceivably represent a chance association of olfactory deficit with constitutionally delayed puberty. Indeed, although the prevalence of cryptorchidism in KS is 70% (Quinton *et al.*, 1998), none of these patients had a history of testicular maldescent. However, unlike the five cases presented here, boys with simple pubertal delay are typically of short stature and rarely older than 17 years at presentation; endogenous puberty being usually triggered by six months low-dose androgen therapy (Albanese *et al.*, 1994).

Rezvani *et al.* (1975) and Bauman (1986) each described a single similar 'variant' case of KS. Both patients were anosmic, presented with delayed puberty and were started on androgen replacement therapy. Spontaneous puberty (i.e. onset of endogenous gonadotrophin secretion), subsequently occurred at ages 20.75 and 27 years, respectively. Cases 2–5 derive from a series of 76 KS men aged 23 years or older (Royal Free and Middlesex Hospitals, London), giving an estimated prevalence of 5%. However, this may be an underestimate as KS patients are not routinely reassessed off replacement therapy. Men with 'variant' KS may unwittingly continue on long-term treatment; indeed, Kadva *et al.* (1996) identified one case during a study of gonadotrophin pulsatility in IHH. Other patients may simply discontinue treatment therapy, realising that it is no longer necessary, and drop out of specialist follow-up.

Spontaneous impregnations have been reported for IHH males (Pasqualini & Bur, 1950; Bagatell *et al.*, 1994; Wortsman & Hughes, 1996) in whom severe oligozoospermia does not preclude fertility (Burriss *et al.*, 1988; Quinton *et al.*, 1994). The occurrence of both Pasqualini and undiagnosed Bauman variant cases in the IHH male population should therefore prompt any physician to arrange seminal fluid analysis before advising an IHH man that he need not take contraceptive precautions.

Should the partner of an IHH male fall spontaneously pregnant, great sensitivity is required as paternity may not necessarily lie elsewhere.

Although this variant form of KS challenges current assumptions on the all-or-nothing nature of GnRH neuronal migration, a number of potential pathophysiological explanations do exist. First, migration of an abnormally small contingent of GnRH neurones to the medial-basal hypothalamus, might be associated with delayed maturation of the GnRH pulse generator. In genetic arhinencephalic mice, GnRH cell migration, although disrupted, is not completely arrested despite agenesis of the primary migration pathway (Naruse et al., 1994). Second, there are several pools of GnRH neurones within the central nervous system, not all of which are derived from the olfactory placode (Norgren & Gao, 1994; Quanbeck et al., 1997). The primate hypothalamus also contains neurones synthesising GnRH-II, a distinct isoform of unknown biological function encoded by a separate gene at 20p13 (Lescheid et al., 1997). Third, cell renewal in the olfactory epithelium continues throughout life (Graziadei & Monti-Graziadei, 1978) and both mature olfactory- (Rawson et al., 1995) and GnRH-synthesising-neurones (Quinton et al., 1997) have been demonstrated in the nasal epithelium of adult human KS subjects. It is thus conceivable that migration of GnRH neurones might occur postnatally. Gonadotrophin pulsatility and menstrual cyclicality is restored in female rhesus monkeys, lesioned at the medial-basal hypothalamus, following transplantation of foetal olfactory placode into the third ventricle, as a result of migration of foetal GnRH neurones to the median eminence (Saitoh et al., 1995). Given the critical importance of GnRH secretion for reproductive success, it would be surprising if there were no inbuilt evolutionary redundancy.

In conclusion, male patients with isolated gonadotrophin deficiency, with or without associated anosmia, should be carefully re-examined after they have attained full virilization. Seminal fluid analysis should be undertaken for those patients enquiring about the need for contraception. Patients whose mean testicular volume is greater than 6 ml should undergo biochemical reassessment in order to identify variant cases who may no longer require androgen replacement therapy. Based on our series of five patients and on the three cases previously reported, we suggest this be performed shortly before 30 years of age. Reassessment should be performed sooner in cases where, without therapy with GnRH or gonadotrophins, testicular volume has grown beyond 8 ml or a female partner has been impregnated.

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