PRACTICE

A PATIENT'S JOURNEY

Kallmann syndrome

The patient was diagnosed with Kallmann syndrome at the age of 22 years. Here he describes the consequences of that late diagnosis

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This is one of a series of occasional articles by patients about their experiences that offer lessons to doctors. The *BMJ* welcomes contributions to the series. Please contact Peter Lapsley (plapsley@bmj.com) for guidance

My early childhood was fairly uneventful medically apart from 70% hearing loss in one ear and no sense of smell. I reached what I now know to be the normal pre-puberty Tanner stages, and up to the age of 12 years nothing seemed to be amiss. Going through my early teenage years it was a case of waking up each day and hoping something was going to start to develop. I knew it was getting late to start puberty, but I assumed it would all start soon enough. Eventually I was the only one in my year group not to show any development, and this was certainly noticed by the rest of the year group.

A routine health inspection by the school nurse as part of the health screen for a permit to work on a newspaper delivery round led to a referral to a general practitioner at the age of 15 years. At that stage the GP said I was just late starting, that I should wait and see, and I was sent on my way.

Teenage years

Up to the age of 14, I was a normal enough schoolboy I think. I was in the Scouts and was involved in my local cricket club. I gradually got left out of social events as I lacked the confidence to go and had no sexual drive at all. I knew the basics from a purely physical point of view but had no libido or interest in any sort of teenage activities. I made up excuses not to go to social events, and eventually I stopped being invited.

By the age of 17, it was clear that nothing was starting so I was referred by my GP to my local general hospital, first to a general medicine consultant and then to a urologist. I was put on low dose injectable testosterone (Sustanon) monthly but not offered any follow-up assessment; it was just assumed everything would all start naturally.

By the time I went to university, something was obviously wrong, but I did not have the drive to do anything about it. I

even stopped taking the Sustanon for a time as it seemed to be having no effect on me apart from a slight growth spurt. Looking back now, there were opportunities for me at university, but, without the drive and the knowledge of the condition, I did not have the interest or confidence to notice them, let alone follow them up.

Diagnosis

The first time I saw an endocrinologist was when I started my first job, as a biomedical scientist at the Royal Free Hospital in London. I had studied endocrinology and haematology as part of my biomedical science degree and had a bit of an understanding on how puberty was supposed to work. Choosing the endocrinology pathway for my biomedical science degree was partly driven by the wish to know more about my own situation. When I started work at the Royal Free I was determined to talk to an endocrinologist even though my GP still had not referred me. Under my own volition, I contacted Richard Quinton, at the time a senior registrar in endocrinology under Pierre-Marc Bouloux. One of the first questions he asked was, "Do you have a sense of smell?" It was the first time any doctor had asked me that question. It was also the first time any doctor had mentioned Kallmann syndrome to me.

The correct diagnosis soon followed, and I was prescribed a suitable dose of testosterone, first in the form of Testogel and then later Nebido. The delay in suitable treatment from the age of 16 to 22 meant I went six years with a very low testosterone level, with the subsequent delay in secondary sexual development and bone strength.

Blood tests confirmed the low levels of follicle stimulating hormone (FSH) and luteinising hormone (LH) that, combined with the anosmia, confirmed the diagnosis. Magnetic resonance imaging showed the absence of the olfactory bulbs, and a bone density (DEXA) scan showed osteopenia. At the time of diagnosis, I probably looked 10 years younger than I was and had never shaved.

Delay of diagnosis

On a physical level the late diagnosis has left me with osteopenia, which is still present but at least not deteriorating. Recently, I have also been found to have severe vitamin D deficiency, which is probably contributing to the osteopenia, for which I am prescribed a 1000 IU vitamin D supplement. The lack of gonadotrophins and hence androgens in my teenage years also resulted in a delay in the development of secondary sexual characteristics. The lack of testicular development will always be present. The relative lack of penile growth remains a constant frustration. There will always be the question of what would have happened if testosterone treatment had been started earlier and at the physiologically correct dose.

I did achieve a certain amount of testicular development and limited sperm development while on a gonadotrophin clinical trial. This lasted for only as long as the trial lasted, but it does give me hope for future fertility, and the increase in testicular size did bring a certain degree of reassurance and better self confidence.

It is on the psychological level that my delayed diagnosis has had the biggest impact in my view. Judging by my own experiences and those of fellow patients I have met and talked to, this is an area that is often overlooked.

With puberty and adolescence being so closely linked, if a patient does not enter puberty at almost the same stage as his peer group, he risks being left behind socially and emotionally, as well as physically. I feel that this emotional development of social interaction is difficult to catch up on and is often a result of feeling socially isolated when puberty fails to start.

I have not married, never had any serious girlfriends, and have very limited sexual experience. I think this is a direct result of my lack of emotional and physical development while a teenager and young adult. Although a lot of fellow patients I talk to do get married and have relationships, my experiences are by no means unique. I think early diagnosis plays a key part in being able to build the confidence to develop relationships, and the later you start the harder it is to catch up. From my experience with fellow patients, it is those who are diagnosed and treated early who cope with the condition better. For many, the very fact they can put a name to the condition and realise that they

are not the only person in the world not going through puberty is a big step in being able to cope with the condition.

Treatments available

Once I was diagnosed the variation in possible testosterone treatments available became apparent, as did possible fertility treatments. Up to the point of diagnosis, I was not taking the most appropriate dose of testosterone, which affected my energy levels and sex drive. There are several different forms of testosterone replacement methods, which suit different people at different times. Since being diagnosed, I have tried a few, including the gonadotrophin injections, which I found to be particularly beneficial to me as they induce a certain level of fertility and allow for limited testicular growth.

The most important treatment is possibly the diagnosis itself. Being labelled as a “late starter” or “late bloomer” when in your early 20s can be very humiliating. The ability to put a label to your condition and the knowledge that it is a recognised condition are the first steps in coming to terms with a condition that is difficult to describe to others. The use of patient support groups on Yahoo and Facebook also play a big part in being able to talk about the condition, but this is possible only once the correct diagnosis has been made.

The patient is happy to be contacted by any patient with Kallmann syndrome wishing to talk to another patient (email: neilsmith38@hotmail.com).

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A clinician's perspective

Congenital hypogonadotrophic hypogonadism (CHH), also known as isolated gonadotrophin deficiency, occurs in around 1 in 4000 men, over 60% of whom exhibit a non-reproductive defect, most commonly anosmia (lack of sense of smell). It is defined by serum testosterone <6 nmol/L, with low or "inappropriately normal" serum gonadotrophins (LH and FSH). It is three to five times less common in women. The combination of CHH with anosmia defines Kallmann syndrome. Anosmia is 100% ascertainable without formal testing by simply asking the patient: "Do you have a sense of smell? Can you smell coffee being brewed or food being cooked?" Unlike "medicolegal malingerers," anosmic patients will identify volatile irritants such as vinegar and bleach through their trigeminal chemosensory system.

The 1000-2000 gonadotrophin releasing hormone (GnRH) neurones that regulate human reproduction arise, remarkably, in the embryonic nasal placode and then migrate to the hypothalamus (where they eventually form a synchronised network). A genetic insult during intrauterine development leads to neural disconnection between the nose and brain, with GnRH neurones left stranded beneath the cribriform plate. Hence, congenital anosmia and GnRH deficiency.

Mutations in 19 different genes have thus far been found in CHH, of which 11 are specifically linked with Kallmann syndrome, yet the genetic basis of over half of CHH cases remains to be elucidated. Broadly speaking, products of the "Kallmann syndrome genes" have a role in olfactory nerve development, whereas those of "pure CHH genes" regulate GnRH neurosecretory function. Patients harbouring heterozygous (mono-allelic) mutations of two or more different CHH genes are increasingly being identified (oligogenic inheritance).

The physiological consequences of absent GnRH action are profound. Around 30% of affected males are born with one or both testes undescended, and 5-10% have micropenis or hypoplastic scrotum, or both. Indeed, it is possible to diagnose CHH up to six months after birth by demonstrating lack of "mini-puberty" (normal male neonates exhibit levels of testosterone, LH, and FSH that are not far off the adult male reference range). Nevertheless, these boys typically only get surgical review in the UK without paediatric endocrine input, and therefore the opportunity to make an early diagnosis is lost.

Otherwise, the typical presentation in males is with delayed or absent puberty, which may not always be immediately distinguishable from "constitutional" delay. However, if the boy is anosmic or has a history of undescended testes, neonatal micropenis, cleft lip/palate, or deafness, then the pre-test probability of CHH increases exponentially. Reassurance or "wait and see" approaches, however well meant, can have devastating long term psychological consequences, and the overwhelming preference expressed by males with pubertal delay is to receive androgen replacement therapy, so as to enable them to undergo puberty alongside their peer group. Those whose endogenous puberty is "triggered" by androgen replacement (evidenced by increasing size of testes) can simply be reassessed later off therapy.

However, many UK doctors seem culturally reluctant to initiate a conversation about hypogonadism, waiting instead for patients to bring up the problem. If we physicians find it such a tricky subject to bring up, we can barely imagine just how hard it must be for patients to pluck up the courage and speak up. The Newcastle upon Tyne Endocrine Unit finds itself having to induce puberty in previously untreated CHH males aged over 40 years almost on an annual basis.

Timely sex hormone replacement therapy will result in a normal appearing and normally functioning man (or woman) indistinguishable from normal phenotype, but delayed initiation or inadequate dose greatly increases the risk of osteoporosis and psychosocial maladjustment. However, induction of fertility requires exposure to gonadotrophins so as to stimulate endogenous gonadal function. Reassuringly, there have only been a handful of reported cases of CHH having been inherited after successful fertility treatment.

Fertility treatment can be elegantly achieved through pulsatile subcutaneous infusion of GnRH via minipump (which physiologically reverses the underlying neurosecretory deficit), but this is not widely available outside a handful of specialist centres worldwide. Most commonly, fertility is achieved through subcutaneous gonadotrophin injections (FSH and human chorionic gonadotropin). Women with CHH can be often induced to ovulate after just a week of treatment, though commercial providers may offer (much more expensive) in vitro fertilisation, instead. However, CHH men may require up to two years of continuous gonadotrophin treatment to achieve adequate spermatogenesis. Nevertheless, the treatment is quite successful, with around a 40% chance of spontaneous impregnation of their partner, plus another 20-30% chance if the couple proceeds to in vitro fertilisation (less if there is a history of cryptorchidism).

The obstacles to CHH males accessing treatment are threefold. Firstly, they and their doctors may not even be aware that normal fertility can be achieved, instead assuming that they are irrevocably infertile. Secondly, there is no specific funding stream for gonadotrophin treatment of male infertility in the NHS, so that even informed, motivated patients can face years of dispiriting "buck passing" between primary and secondary healthcare providers. Finally, only a few endocrinologists and reproductive gynaecologists have experience of spermatogenesis induction with gonadotrophins.

Richard Quinton

Useful resources for patients and health professionals

- UK Pituitary Foundation (www.pituitary.org.uk)
- Endocrinology Society (www.endocrinology.org)
- Kallmanns.org website for the Kallmann Syndrome Organisation (www.kallmanns.org)
- Kallmann syndrome blog site (www.kallmannsyndrome.wordpress.com)
- Yahoo based patient forum (<http://health.groups.yahoo.com/group/kallmanns-syndrome>)
- Facebook based patient groups: Kallmann Syndrome Links & Help or Kallmann's syndromers. There is also a hidden "secret" group that remains hidden from other friends on your Facebook list
- Wikipedia page for Kallmann syndrome (http://en.wikipedia.org/wiki/Kallmann_syndrome)—A good source of information on the syndrome