Approach to the Male Patient with Congenital Hypogonadotropic Hypogonadism

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The term "congenital hypogonadotropic hypogonadism" (CHH) refers to a group of disorders featuring complete or partial pubertal failure due to insufficient secretion of the pituitary gonadotropins LH and FSH. Many boys (or their parents) will seek medical consultation because of partial or absent virilization after 14 yr of age. Small testes are very frequent, but height is generally normal. Laboratory diagnosis of hypogonadotropic hypogonadism is relatively simple, with very low circulating total testosterone and low to low-normal gonadotropin and inhibin B levels. This hormone profile rules out a primary testicular disorder. Before diagnosing CHH, however, it is necessary to rule out a pituitary tumor or pituitary infiltration by imaging studies, juvenile hemochromatosis, and a systemic disorder that, by undermining nutritional status, could affect gonadotropin secretion and pubertal development. Anterior pituitary function must be thoroughly investigated to rule out a more complex endocrine disorder with multiple hormone deficiencies and thus to conclude that the hypogonadotropic hypogonadism is isolated. The most likely differential diagnosis before age 18 yr is constitutional delay of puberty. Apart from non-Kallmann syndromic forms, which are often diagnosed during childhood, the two main forms of CHH seen by endocrinologists are Kallmann syndrome, in which CHH is associated with impaired sense of smell, and isolated CHH with normal olfaction. Anosmia can be easily diagnosed by questioning the patient, whereas olfactometry is necessary to determine reliably whether olfaction is normal or partially defective. This step is important before embarking on a search for genetic mutations, which will also be useful for genetic counseling. The choice of a particular hormone replacement therapy protocol aimed at virilizing the patient will depend on age at diagnosis and local practices. (***J Clin Endocrinol Metab* 97: 707–718, 2012**)

The Case

A 17-yr-old boy was referred to our unit for late puberty. He had a high-pitched voice, and physical examination showed a hypogonadal aspect with absent facial hair, sparse pubic hair (Tanner stage 2), and a 3-cm penis [normal stretched length for age, 13 ± 1.9 cm (mean ± SD)]. His height was 181 cm, his weight was 82

Abbreviations: CDP, Constitutional delay of puberty; CHH, congenital hypogonadotropic hypogonadism; MRI, magnetic resonance imaging.

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- Select hormonal measures for the positive diagnosis of hypogonadotropic hypogonadism and to exclude the need for a differential diagnosis.
- Design personalized step by step strategies for the molecular analysis of patients with congenital hypogonadotropic hypogonadism (CHH).
- Develop individualized pharmacologic regimens to achieve optimal virilization and to correct infertility in male CHH patients.

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kg, and his arm span was 183 cm. He had bilateral scrotal testes with volumes of 2 and 3 ml (normal for age, 15 to 30 ml). Gynecomastia was absent.

His serum testosterone concentration was 0.3 ng/ml [normal range, 2.60 to 6.90 ng/ml (9 to 24 nmol/liter)], and his basal serum LH and FSH concentrations were 0.3 (normal range, 2.3–6.6) and 0.8 (normal range, 2.1–6.8) IU/liter, respectively.

Background

Congenital hypogonadotropic hypogonadism (CHH), or idiopathic hypogonadotropic hypogonadism, is a classic cause of pubertal failure in boys (1–3). CHH is usually due to insufficient secretion of the two pituitary gonadotropins, LH and FSH, precluding normal testicular endocrine functions during the antenatal and postnatal periods of physiological activation of the gonadotropic axis and fertility after the age of puberty. CHH can be due to defective GnRH release by the hypothalamus or to primary gonadotrope cell dysfunction in the pituitary (2, 3, 5). The underlying neuroendocrine abnormalities can be divided into two main groups: molecular abnormalities of the gonadotrope cascade, and developmental abnormalities affecting the hypothalamic location of GnRH neurons (2–5). Clinically, there are three main categories of patients, raising different therapeutic and diagnostic issues (Table 1): isolated CHH with normal olfaction, Kallmann syndrome, and more complex non-Kallmann syndromic forms (3).

The prevalence of CHH, as with other causes of hypogonadism (6), is probably underestimated in the general population. Estimates based on civilian and military hospital series have given a prevalence of 1/4,000 to 1/10,000 in males (5, 7, 8).

TABLE 1. Main characteristics of the 402 patients with CHH referred, evaluated, and followed at the Endocrinology and Reproductive Diseases Department at Bicêtre Hospital, Paris-Sud University, France, from January 1993 to October 2011

Men = 330 (82.1%)
Women = 72 (17.9%)
Normosmic nonsyndromic CHH = 206 (51.2%)
Kallmann syndrome = 156 (38.8%)
Non-Kallmann syndromic = 40 (10.0%)
CHH and adrenal hypoplasia associated with DAX1 mutations = 9
CHH multiple pituitary deficiencies associated with PROP1 mutations = 7
CHARGE syndrome = 4
CHH with cerebral ataxia (Gordon Holmes syndrome) = 3
Bardet-Biedl syndrome = 2
Prader-Willi syndrome = 3
Not yet classified = 12

Isolated or apparently isolated CHH (*i.e.* in a patient with Kallmann syndrome who does not complain of an absent or diminished sense of smell) is usually diagnosed in teenagers or young men who present with pubertal failure. Such patients account for most cases of CHH seen by endocrinologists in teenage and adult healthcare institutions (Table 1). In contrast, this cause of defective pubertal development represents less than 20% of cases seen in pediatric endocrinology units (1), whereas functional gonadotropin deficiency accounts for most cases seen during early adolescence. Pediatric endocrinology units also diagnose the bulk of non-Kallmann syndromic forms, which are often symptomatic before the age of puberty, with growth retardation, adrenal failure, obesity, neurological disorders, or malformations (9–14). This is why most cases of isolated gonadotropin deficiency are seen by adult endocrinologists, among patients consulting for pubertal failure and severe hypogonadism.

Assessment

Clinical features

It is first necessary to confirm that puberty is indeed delayed with respect to chronological age, *i.e.* to demonstrate a lack of pubertal development after age 14 yr. Because the first sign of male puberty is an increase in testicular volume (testicular volume of less than 4 ml indicates prepubertal status), careful assessment, preferably using a Prader orchidometer, is necessary to demonstrate testicular hypotrophy (Fig. 1A). The penis and testicles are also examined to detect cryptorchidism (inguinal scars may be a sign of corrective surgery) and micropenis (Fig. 1B). Weight and height must be evaluated, by comparison with the parental values, to distinguish isolated pubertal delay from statural-pubertal delay. Low patient height relative to the parent's height suggests statural-puberty delay due to constitutional delay of puberty (CDP) or multiple pituitary deficiencies, but not isolated CHH (1, 13, 14). The determination of body mass index may reveal underweight and subnormal fat mass, which might result from a systemic disorder leading to pubertal delay due to functional gonadotropin deficiency (1). Likewise, systemic diseases and treatments capable of causing hypogonadotropic hypogonadism must be ruled out, such as chronic corticosteroid therapy, Cushing's syndrome, and hematological disorders requiring repeated transfusions that may cause hemosiderosis. Recreational chronic opioid use should also be sought.

Because anabolic steroid abuse may result in hormonal changes similar to those seen in CHH, the clinician should

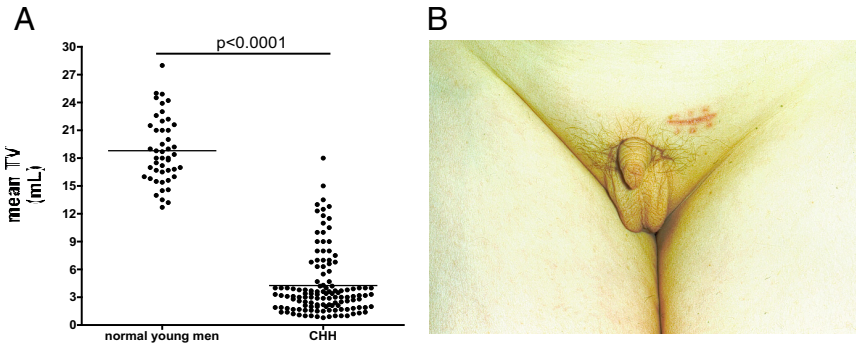

FIG. 1. A, Individual mean testicular volume (TV) at diagnosis in untreated men with CHH (n = 126; age range, 17–29 yr) evaluated at the Endocrinology and Reproductive Diseases Department, Bicêtre Teaching Hospital, France, compared to age-matched normal young men (n = 47; age range, 17–28). B, Genital aspect in a 17-yr-old man with Kallmann syndrome, surgically cured cryptorchidism (left inguinal scar), and a 2.5-cm micropenis [normal stretched length for age, 13 ± 1.9 cm (mean ± SD)].

thus inquire carefully about use of these steroids. Clinically, however, anabolic steroid users often have a well-virilized aspect and sometimes muscle hypertrophy, in stark contrast to the testicular hypotrophy and oligo- or azoospermia often caused by the gonadotropin suppression induced by these drugs.

Before treatment, gynecomastia is found in only a minority of nonobese men with complete CHH (Young, J., unpublished observations). In obese CHH patients, the prevalence of gynecomastia seems to be lower when assessed by mammography than by physical examination, owing to the high frequency of adipomasty (15). Some authors, however, consider that careful examination with the "pinch technique" can distinguish adipose tissue from breast tissue and obviate the need for ultrasound or mammography (15).

Accurate evaluation of sense of smell is an important step in the assessment of CHH patients. Total loss of olfaction (anosmia) or severe hyposmia can reliably be detected by interview, but olfactometry is necessary when the patient declares normal sense of smell because in our experience simple interview is not reliable enough to detect partial olfactory defects in patients with Kallmann syndrome (see below).

Show That the Hypogonadism Is Hypogonadotropic

In CHH, circulating total testosterone assay, performed in the morning, usually confirms the hypogonadism by showing very low levels relative to adolescents and young men with normal pubertal development (Fig. 2A). Basal serum total testosterone can be measured with routine immunoassays because levels of this steroid in these patients with severe hypogonadism are clearly lower than normal (16) (Fig. 2A). Although total testosterone immunoassays have been criticized for their lack of precision in the lower range of values (17, 18), they are nonetheless adequate to confirm severe hypogonadism in this setting. Measurement or calculation of bioavailable testosterone, free testosterone index has no added diagnostic value in this pathological setting (16). In the same way, no diagnostic advantages have been reported with reference techniques for total testosterone assay, such as gas chromatography/mass spectrometry and liquid chromatography/mass spectrometry, which may be more precise but are also more expensive. Pending comparative studies, these reference methods are best reserved for clinical research purposes.

Once hypogonadism has been confirmed by hormone assays, it is then necessary to show that the pubertal delay is not secondary to a primary testicular disorder such as Klinefelter's syndrome (19, 20) by serum assay of FSH and LH. The rise in basal gonadotropin levels in patients with primary testicular insufficiency leading to pubertal delay is usually very marked, making this disorder easy to distinguish from pubertal delay due to decreased gonadotropin secretion (Fig. 2B) (16, 19, 20). The GnRH challenge test, introduced 40 yr ago (21) to differentiate these two types of hypogonadism, has no diagnostic advantages over evaluation of basal levels with modern gonadotropin assays.

In the vast majority of patients with CHH, levels of the two gonadotropins are very low or low to normal (Fig. 2B). One exception to this rule is the very rare case of mutations of the LH-and FSH-specific β-subunit genes (22, 23), in which the mutated hormone is usually undetectable whereas the concentration of the other gonadotropin is high. It is important to recall here that the response to the GnRH test in CHH patients is highly variable and depends on the severity of the gonadotropin deficiency, which is often yet clinically reflected by the degree of testicular atrophy (3, 21) and by basal gonadotropin levels if serum LH and FSH are measured by sensitive assays (Fig. 2B). In addition, this time-consuming challenge test cannot show whether the gonadotropin deficiency is hypothalamic or pituitary in origin because the results can be completely blunted in CHH patients with profound gonadotropin deficiency of both hypothalamic or pituitary origin (3, 24–26) and positive or even excessive in those with partial pituitary or hypothalamic gonadotropin deficiency (3, 24–27).

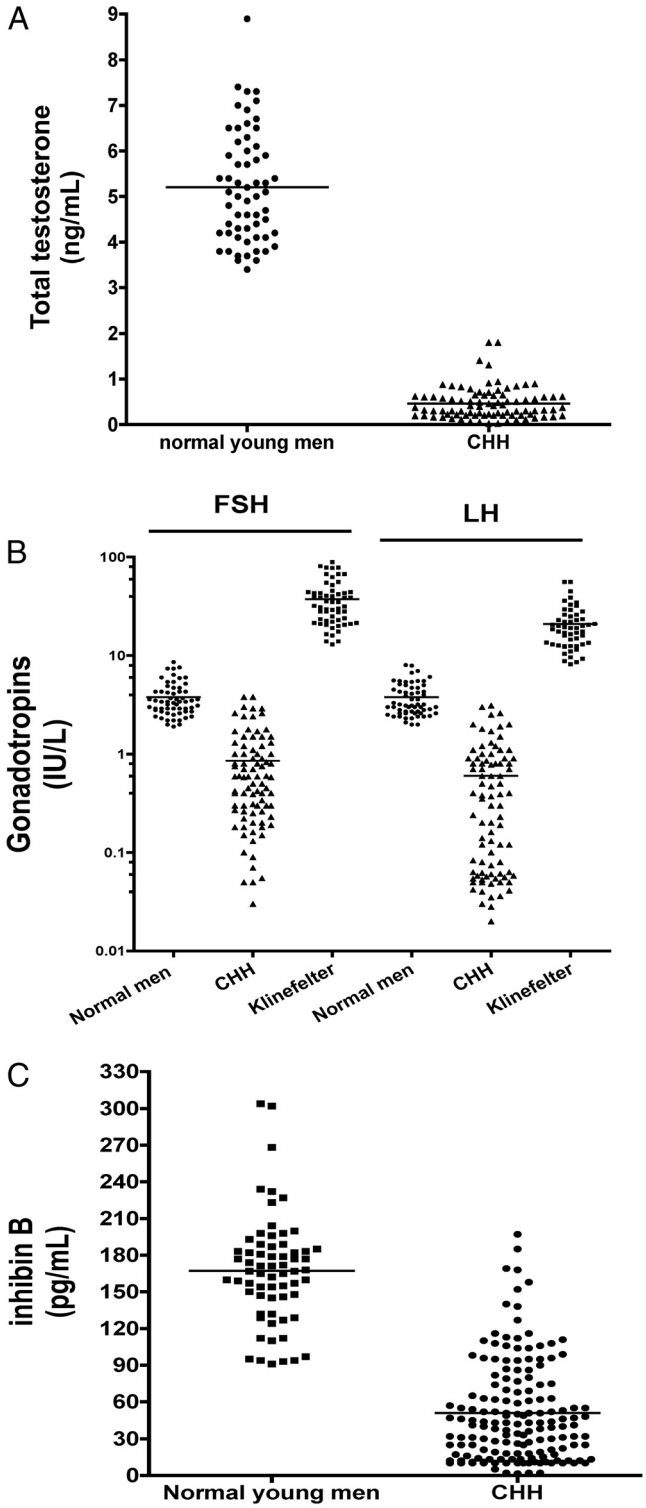

FIG. 2. Hormonal evaluation of the gonadotropic axis in male patients with CHH. A, Serum total testosterone levels in normal young men (16–25 yr old; n = 60) and patients with CHH (17–26 yr old; n = 86). (To convert the values for testosterone to nanomoles per liter, multiply by 3.467.) B, Serum pituitary gonadotropin levels in normal young men (n = 60), in CHH patients (n = 86), or those with Klinefelter syndrome (15–23 yr old, n = 54) measured with the same FSH and LH assays. Note the log scale. C, Serum inhibin B levels in normal males (16–25 yr old; n = 65) and in untreated CHH patients (17–29 yr old; n = 161). Hormonal assays used for the measures of serum testosterone, FSH, LH, and inhibin B were described in Refs. 18 and 20–22.

How to Show That Hypogonadotropic Hypogonadism Is Isolated?

First, serum prolactin must be assayed to rule out hyperprolactinemia, secondary to a prolactinoma or another hypothalamo-pituitary tumor causing increased prolactin levels by compression of the pituitary stalk, which could impede pubertal activation of gonadotropin secretion (28). Thorough pituitary, adrenal, and thyroid hormonal secretion studies are also important to rule out associated endocrine deficiencies that may require specific treatment, such as adrenal failure and TSH or GH deficiencies. Careful investigation of the somatotrope axis is chiefly warranted when the pubertal delay is accompanied by statural retardation. Indeed, diagnosis of an associated endocrinopathy of this type will radically reorient the etiological diagnosis toward a specific lesional or genetic disorder (9–14, 29). In the same way, magnetic resonance imaging (MRI) of the pituitary region is desirable before making a firm diagnosis of CHH (3, 28, 29) to exclude a tumoral, infiltrative, or malformative disorder affecting the hypothalamo-pituitary region that could damage GnRH neurons, the pituitary stalk, or pituitary gonadotrope cells and thereby prevent pubertal development (29). Similarly, nutritional status must be carefully assessed because nutrient deficiency seems to be a more frequent cause of gonadotropin deficiency and pubertal delay than CHH in teenagers (1). If clinical or biological signs of nutrient deficiency are found, then the patient should be thoroughly investigated for a paucisymptomatic general condition such as celiac disease (30), an eating disorder, or excessive physical activity (31). Finally, it must be borne in mind that juvenile hemochromatosis may, like isolated CHH, lead to pubertal delay with low gonadotropin levels (32).

The Main Differential Diagnosis of Isolated CHH Is Constitutional Delay of Growth and Puberty

After eliminating systemic causes in a young adolescent presenting with absent or inadequate pubertal development and low gonadotropin levels, the most likely diagnosis is CDP. This particular pattern of pubertal maturation has not been linked to a particular underlying disorder and is currently considered to represent one extreme of the normal spectrum of pubertal timing (1). Its diagnosis is based on the elimination of other potential causes, hence the need to search thoroughly for signs of CHH in the patient's personal or family history or phenotype. Statural delay is usually the main feature of CDP, whereas adolescents and young men with CHH tend to have normal or slightly excessive height, with a eunuch-

oidal aspect even in the absence of a spontaneous pubertal growth spurt (33). In addition, CDP is associated with a general delay in maturation, with retarded bone age. This radiological sign is thus considered by pediatric endocrinologists as a useful diagnostic sign below age 13 yr (Refs. 1 and 33 and references within these articles). However, bone age is not a specific discriminator at the individual level because retarded bone age can also be observed in CHH.

In pediatric endocrinology, the differential diagnosis is far more difficult because isolated CHH is rare whereas CDP is frequent (1). Extensive efforts have therefore been made (34–37) to identify serum hormone markers that could reliably distinguish CHH from CDP, but none have so far been found. Older candidate markets include serum dehydroepiandrosterone sulfate levels or testosterone measurements under human chorionic gonadotropin test (34, 35), whereas inhibin B assay and GnRH infusion challenge have been proposed more recently (36, 37). However, most studies of these diagnostic tools included only a handful of CHH patients (35–37), most of whom had severe forms, raising the possibility of a selection bias. The cutoff values proposed to differentiate the two entities must therefore be used with great care. In the case of serum inhibin B for example (36), Fig. 2C shows serum inhibin B values obtained in unselected and untreated young CHH males of our population. The range of values is very broad, even overlapping values obtained in adolescents with normal pubertal development. In CHH, serum inhibin B values in fact correlate with testicular volume, so with the clinical severity of gonadotropin deficiency (24, 26, 38). This illustrates the difficulty of distinguishing CHH from CDP on the basis of a single hormone marker, especially in isolated partial CHH.

In view of these difficulties, classical clinical features distinguishing CHH from CDP are still of practical value, especially simply observing testicular volume over time, in patients receiving exogenous testosterone. In the male patient with pubertal delay and low gonadotropin levels, the presence of micropenis and/or cryptorchidism argues firmly in favor of CHH because they are rarely seen in CDP (1, 34). Signs of a particular etiology are also very useful in clinical practice. The archetypal example is the anosmia/hyposmia associated with Kallmann syndrome, but other signs (Fig. 3, *legend*) may also point to this (39) or another syndrome (12). It is equally important to search for these associated signs in the patient's family members because sometimes the propositus appears to have isolated CHH whereas the parents are found to have clinical signs of Kallmann (4, 5, 26, 40–42) or another syndrome. Endocrinologists working in units where most patients are older adolescents (from age 16 yr onward) or young adults have a higher likelihood of encountering CHH rather than CDP because a large fraction of CDP patients will already have consulted a pediatrician or undergone spontaneous puberty by this age. For these practitioners, the main challenge is therefore to differentiate normosmic nonsyndromic CHH patients from patients with Kallmann syndrome (Fig. 3) and non-Kallmann syndromic CHH, particularly those with the milder forms.

Other Investigations

Ultrasound examination of the testicles and internal genital organs by an experienced radiologist is a very useful complement to physical examination for determining and monitoring (during hormone therapy) precise testicular volume, which is an important prognostic factor for future fertility (43) and for detecting associated abnormalities of the genital tract that could worsen reproductive function (44). The same examination will show the inguinal or intraabdominal position of one or both testicles in case of ectopy, and this may help guide the therapeutic approach (medical or surgical) in case of cryptorchidism (45).

Total (anosmia) or severe partial loss of olfaction can reliably be detected by interview in patients with Kallmann syndrome, but olfactometry is necessary when the patient declares normal sense of smell. Several qualitative and semiquantitative methods are available (26).

Renal ultrasound is also useful to detect kidney agenesis (44, 46) or malformations suggestive of X-linked Kallmann syndrome (4, 5, 44). Likewise, panoramic dental x-ray examination and cranial computed tomography can be useful second-line investigations in subjects with Kallmann syndrome to detect dental or skull dysgenesis or malformations suggestive of *FGFR1* mutations (47–49).

The Search for a Genetic Cause (Fig. 3)

Identification of a genetic cause in patients with CHH is not only useful for pathophysiological purposes (2–5) but will also confirm the likely mode of transmission within the family. Once virilized, these patients often seek treatment for their infertility and raise questions as to the risk of transmitting the condition to their offspring. Given the high cost of genetic analyses, patients should be prioritized according to their clinical presentation and family history (4). The main feature guiding genetic analysis is the presence of anosmia or hyposmia in the propositus and/or his family (4). Indeed, marked phenotypic heterogeneity may exist within Kallmann families, some members having isolated anosmia, others normosmic CHH, and still others full-blown Kallmann syndrome (4, 5, 24, 26, 40–42).

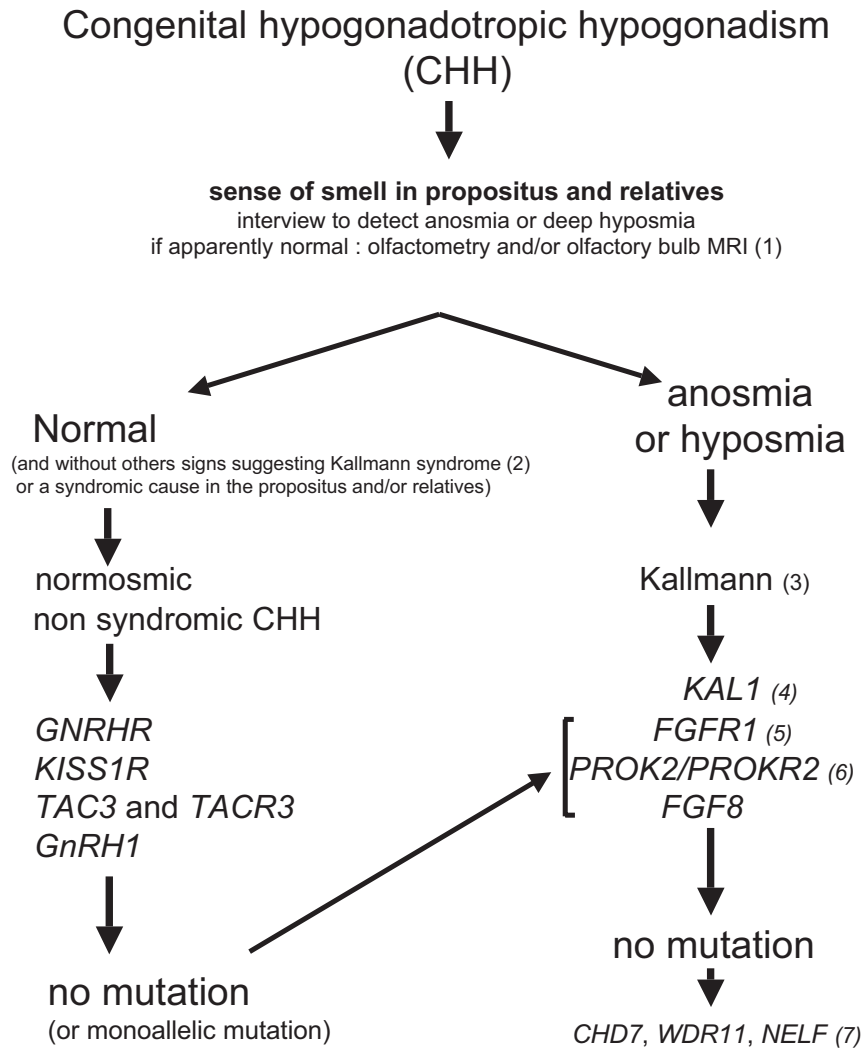

FIG. 3. Molecular studies performed in male patients with CHH categorized on the basis of sense of smell at the Endocrinology and Reproductive Diseases Department, Bicêtre and Paris-Sud University Teaching Hospital, France. 1) MRI. 2) Bimanual synkinesis, tooth agenesis, hearing impairment, renal agenesis, cleft lip/palate, high-arched palate, pes cavus, ptosis, absent nasal cartilage, hand/foot skeletal anomalies, and iris coloboma. 3) Our step-by-step strategy is based on familial history and putative mode of disease inheritance (pedigree), and the presence of additional clinical anomalies (see *item 2* and text) that may direct the geneticist toward a particular Kallmann gene. 4 and 5) For instance, 4) *KAL1* is analyzed especially in Kallmann men with mirror movements (bimanual synkinesis) and/or kidney agenesis and/or when the pedigree suggests an X-linked mode of inheritance; whereas 5) in subjects displaying cleft lip/palate, *FGFR1* mutations are searched in first line whatever the apparent mode of inheritance. 6) In subjects with monoallelic *PROK2* or *PROKR2* mutations, we search for mutations in other CHH genes to demonstrate a digenic or oligogenic mode of inheritance. 7) Analysis of these large genes (see below) will be performed in second line given their lower or unknown prevalence among normosmic CHH and Kallmann men. Sizes of the genes currently sequenced in CHH patients: *GNRH1*, three exons; *GNRHR*, three exons; *KISS1R*, five exons; *TAC3*, six exons; *TACR3*, five exons; *KAL1*, 14 exons; *FGF8*, six exons; *FGFR1*, 18 exons; *PROKR2*, two exons; *PROK2*, four exons; *CHD7*, 38 exons; *WDR11*, 29 exons; *NELF*, 16 exons.

Anosmia can be easily diagnosed by questioning the patient, whereas olfactometry is necessary to determine whether olfaction is normal or partially defective. MRI of the olfactory bulbs can show unilateral or bilateral atrophy or hypoplasia and abnormalities of the olfactory furrows (50). Although the diagnostic performance of this examination has not been evaluated in a large number of patients comparatively to olfactometry, it appears to be useful when fine assessment of olfaction is not locally available.

In case of abnormal olfaction and/or olfactory bulb defects and/or associated signs suggesting Kallmann syndrome (Fig. 3), first-line genetic analysis should focus on gene defects responsible for Kallmann syndrome (4). In the absence of an internationally validated algorithm, we use here a pragmatic step-by-step strategy based on familial history and putative mode of disease inheritance (pedigree) and the presence of additional clinical anomalies that may direct the geneticist toward a particular Kallmann gene. For instance, mutations in the *KAL1* gene, responsible for the X-linked form, will be searched for in the first line of the family genealogical tree (Kallmann syndrome only affecting men), suggesting transmission via the X chromosome. However, it must be recalled here that male patients with apparent X-linked Kallmann syndrome may have either a *KAL1* or a *FGFR1* mutation (4, 40). Searching for *KAL1* mutations will also be a priority in Kallmann men with renal agenesis (so far not reported in patients with *FGFR1*, *FGF8*, *PROKR2*, or *PROK2* mutations), and/or mirror movements (also called bimanual synkinesis, present in almost 75% of the reported Kallmann cases with documented *KAL1* mutations and rare in other genetic forms) (4, 5, 26, 40).

If the family includes female members with full Kallmann syndrome, normosmic CHH, pubertal delay, or isolated impaired sense of smell, the search will first focus on gene defects with autosomal transmission (4, 5), and especially *FGFR1* mutations (4, 40); indeed, identification of an autosomal dominant form likely to be transmitted to the offspring is crucial for genetic counseling. Signs of *FGFR1* mutations must be sought, including midline abnormalities and dental agenesis (4, 5, 40), regardless of the apparent mode of transmission (cleft lip and/or palate may occur in as many as 25–30% of the *FGFR1* mutated cases, and skeletal anomalies of the hands or feet have only been reported in *FGFR1* mutated patients), because in some

families with this genetic form only boys develop the Kallmann phenotype, either by chance or owing to higher penetrance in males (4, 40). Finally, as many as 30% of the *FGFR1* mutations found in the patients could be *de novo* mutations (4); searching for these mutations will also be undertaken in sporadic Kallmann cases.

Attention will then turn to *PROK2* and *PROKR2* and *FGF8* which, being smaller genes (Fig. 3) and seen frequently enough (about 10% of reported cases) (4) involved in the Kallmann phenotype, can be analyzed more rapidly and less expensively (26, 41, 42, 51). Other genes known to be associated with the Kallmann phenotype, such as *CHD7* (52, 53) and *WDR11*, are currently analyzed in second line in our department, given their lower or unknown prevalence and/or very large size (Fig. 3) (52, 54).

However, the *CHD7* gene should be analyzed earlier if the propositus or other family members have signs of the CHARGE syndrome (12, 52, 53) or evocative phenotypic abnormalities (outer ear defects, or hearing loss associated with semicircular canal defects on computed tomography scan) (12, 53).

By contrast to kidney abnormalities, synkinesia, or cleft lip or palate discussed above, hearing impairment or high-arched palate are not specific enough to direct the molecular genetic research because these associated signs are seen in several genetic forms of Kallmann syndrome (4, 26). In men with apparently sporadic and isolated (*i.e.* without associated signs) Kallmann syndrome, we usually analyze *KAL1*, *FGFR1*, *PROK2*, and *PROKR2* genes without established hierarchy, given the similar prevalence of these genetic forms (4).

When a deleterious mutation of *KAL1*, *FGFR1*, or *CHD7* is found in a propositus, the other family members should be invited to undergo clinical and genetic studies to detect asymptomatic or slightly symptomatic mutation carriers that are also capable of being transmitted to the offspring, especially because the phenotypic severity of a given mutation can vary, even within a family (4).

When the results of the patient's physical examination (showing normal sense of smell at olfactometry and no associated signs) and familial studies point to a sporadic or autosomal recessive form of isolated CHH, it is logical to begin genetic investigations with an analysis of smaller genes (Fig. 3) known to be involved in isolated (*i.e.* nonsyndromic) forms (2, 3). These include the *GNRHR* gene coding for the GnRH receptor (3, 27), the *KISS1R* gene (formerly GPR54) coding for the kisspeptin receptor (Ref. 55 and references therein), and more recently identified responsible genes such as *TAC3* and *TACR3*, responsible for abnormalities of neurokinin B and its receptor NK3R (56–58). *TAC3* and *TACR3* defects are especially likely when the FSH/LH ratio is elevated before treatment (57, 58). If these genes are normal in the patient with isolated CHH, it will also be necessary to analyze in second line (Fig. 3) the genes responsible for autosomal Kallmann syndrome or non-Kallmann syndromic forms of CHH because attenuated forms mimicking isolated normosmic CHH have been described (4, 5, 24, 26, 59). Genetic investigations are less straightforward in the case of men with CHH or Kallmann syndrome who are found to have a monoallelic mutation of a gene (*PROK2*, *PROKR2*, *GNRH1*, *GNRHR1*, *KISS1R*, *TAC3*, or *TACR3*, for instance) that cannot fully explain their phenotype. In this case, it may be of interest to seek one or more further mutations that may be present in a context of digenism or oligogenism (2, 4, 5, 26). These sometimes complex investigations can also be useful for establishing the mode of transmission, which is crucial for genetic counseling when the issue of parenthood arises.

Treatment

The initial treatment goal for adolescents and young men with CHH is to induce physical and behavioral development matching that of healthy subjects of the same age. This includes an increase in penis size, voice masculinization, development of muscle mass, and pubic and axillary hair growth. Other aims are to enhance libido, modify sexual behavior, and correct the delay in bone maturation and deficient bone mineralization (60–67). In our experience, effective testosterone replacement treatment can lead to a spectacular improvement in quality of life, clearly demonstrating the causal relationship between these young patients' symptoms and their testosterone deficiency.

Theoretically, such benefits can also be achieved with pulsatile GnRH administration (63) if the CHH is of hypothalamic origin or with combined gonadotropin therapy (human chorionic gonadotropin and FSH) (16, 68), both therapies effectively inducing testicular growth and secretion of testosterone and estradiol (16). In practice, however, testosterone therapy (as injectable esters) is generally preferred for reasons of convenience and cost. Contrary to dihydrotestosterone, which cannot be aromatized into estradiol (16), testosterone therapy corrects both the androgen and estrogen deficiencies (16) and thus meets the above-mentioned clinical objectives. Testosterone esters (60–67) have been used for decades as first-line treatment, given their low cost, convenience of use, and prolonged effect, promoting good adherence to what is almost always a very long-term treatment.

Testosterone enanthate for example, which is one of the cheaper preparations on the international market, can be injected once every 2 or 3 wk at usual doses (200–250 mg) (65). Injectable testosterone undecanoate is also an interesting compound to treat chronic severe hypogonadism in this setting because it allows the im injections to be spaced out to once every 2 or 3 months. Regrettably, this testosterone preparation is very expensive when compared with testosterone enanthate, thus limiting its use. Virilization of CHH patients can also be achieved by percutaneous testosterone administration in gel or patch form. However, these alternatives are costly and require daily administration, raising problems of adherence; in practice, they are only a second-line option in this setting.

The dose of testosterone esters prescribed to CHH patients will depend on age at diagnosis and local practices. Pediatric endocrinologists, who see these patients at a younger age, prescribe low doses initially and increase them very gradually (62, 66, 67), for fear of inducing abrupt virilization and bone maturation that could respectively lead to relational problems for the patient and his family and also to compromise final height by inducing early cartilage fusion. Endocrinologists see adult CHH patients at a later stage, when their main complaint is symptoms and signs due to their severe hypogonadism. These patients generally receive full-dose treatment from the outset. However, these two therapeutic approaches have not been compared head-to-head in clinical studies, and excessively dogmatic attitudes should therefore be avoided.

Whatever the approach used, it is crucial to explain to the patient that he will probably need several decades of androgen therapy and that this treatment will not increase testicular volume or induce spermatogenesis (69). Once full virilization has been induced by exogenous testosterone, males with congenital gonadotropin deficiency whose testes have significantly increased in size (less of 5% of CHH cases evaluated in our department) should be reassessed, off androgen replacement therapy, to identify those with reversible forms (70, 71) who sometimes no longer require treatment.

Except for this infrequent context, patients who wish to obtain an increase in testicle volume or fertility can be offered gonadotropin combination therapy (68) or pulsatile GnRH (63). However, patients with severe CHH must be warned of the following. First, the sperm count rarely normalizes (based on World Health Organization criteria) despite long-term pulsatile GnRH or gonadotropin combined therapy. Second, the rise in testicular volume and sperm count occurs far later in men with complete CHH than in men with hypogonadotropic hypogonadism of postpubertal onset. Third, pretherapeutic testicular volume is an important factor in treatment outcome: the smaller the testicular volume (which is generally very low in those with complete CHH), the more difficult it is to achieve a testicular volume increase, to normalize the sperm count, and to achieve a pregnancy. Finally, several studies of patients with CHH indicate that cryptorchidism is the main risk marker of poor prognosis.

Controversies and Areas of Uncertainty

There is good consensus on many aspects of the diagnosis, assessment, and first-line treatment of men with CHH.

In contrast, more data are needed on the differential diagnosis, pathophysiological relationship, and frontiers between reversible forms of CHH and CDP.

More clear-cut criteria are needed to distinguish truly isolated nonsyndromic CHH from Kallmann syndrome and paucisymptomatic non-Kallmann syndromic forms that can mimic the phenotype of both Kallmann syndrome and isolated CHH (2–5). Rapid ongoing progress in the identification of genetic causes of CHH will facilitate this process and will also help to specify the mode of transmission—autosomal dominant, autosomal recessive, X-linked, digenic, or oligogenic (2–5, 26, 41, 72)—in each individual case, thereby assisting with genetic counseling.

Regarding treatment, the main problem is currently the lack of systematic studies of the impact of different hormone replacement therapy protocols on the quality of life of these adolescents and young men as well as their the long-term safety (73). For example, more data are needed on the sexuality and intimate relations of men with severe CHH accompanied by cryptorchidism and micropenis (74). Given the negative prognostic value of cryptorchidism and low testicular volume for the future fertility of patients with severe CHH, there is a possibility that earlier gonadotropin combination therapy, during the neonatal or normal pubertal period, might be beneficial (74–79), not only with respect to the psychological consequences of testicular hypotrophy but also in terms of future fertility (74–78). These and other questions will only be settled by intervention studies which, given the rarity of CHH, will require reinforced international collaboration between pediatric and "adult" endocrinologists managing CHH patients (74).

Another controversial point is the diagnosis and treatment of low bone mass. Male CHH patients have an increased risk of osteopenia and osteoporosis (16, 79), but whether or not this increases the risk of fracture in this young population is unclear. Currently, therefore, routine osteodensitometry does not appear to be recommended. Likewise, there is no firm evidence that routine

vitamin D supplementation and/or treatment with antiosteoporotic drugs is warranted for male CHH patients with osteoporosis.

Returning to the Case

This 17-yr-old patient presented with apparently isolated pubertal delay, and hormone assays pointed to a gonadotropin deficiency (low-for-age serum testosterone and gonadotropin levels). He had no signs of statural retardation or clinical signs of another anterior pituitary disorder. Simple interview would have been sufficient to detect anosmia, in which case a diagnosis of Kallmann syndrome could have been made with a high degree of confidence, without the need for further tests. However, his sense of smell was apparently normal and was subsequently confirmed by olfactometry. A blood sample was collected during the visit for prolactin assay to rule out hyperprolactinemia, which could have been responsible for the gonadotropin deficiency, even in the absence of specific clinical signs. The same sample was used to rule out severe corticotropin deficiency, based on serum assays of basal cortisol, ACTH (in the morning, before 0900 h), and dehydroepiandrosterone sulfate. TSH deficiency was eliminated by normal free T_4 and TSH levels, and severe somatotropin deficiency (unlikely, given the patient's height) was ruled out by normal IGF-I serum concentration. Despite the absence of clinical signs of iron overload (normal skin pigmentation), we also ruled out juvenile hemochromatosis by serum iron assay and by determining the transferrin saturation coefficient because this diagnosis would have had important therapeutic implications. Four blood samples in EDTA tubes were also collected to extract the DNA necessary for genetic analyses. MRI of the encephalon and the hypothalamo-pituitary region ruled out a lesion of the hypothalamo-pituitary region and showed two normal olfactory bulbs and furrows.

Treatment started with testosterone enanthate at a dose of one 250-mg vial by im injection every 3 wk. When seen again 6 months later, he was very cheerful. During the interview he described how his life at school had improved markedly after his voice had become deeper, he had gained 10 cm in height, and his musculature and body hair had developed. He now actively participated in sports activities, which were made easier by his increased muscle strength, and he was no longer embarrassed to be seen in swimming trunks. His relationship with the young girls in his class had vastly improved, and he had begun to date one of them. When interviewed without his parents (an important step in the clinical evaluation of CHH teenagers), he said he had erotic thoughts and masturbated, as is normal at his age. Physical examination showed that his testicular volume was still low, although he did not consider this a major problem for the moment; in addition, his pubic hair was abundant and his penis now measured 9 cm. The same treatment was pursued and an appointment was made for 6 months later. Bone densitometry showed osteopenia predominating in the vertebral bone (79).

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