Role of Gonadotropin-Releasing Hormone and Human Chorionic Gonadotropin Stimulation Tests in Differentiating Patients with Hypogonadotropic Hypogonadism from Those with Constitutional Delay of Growth and Puberty

Terry Y. Segal, Ameeta Mehta, Antoinette Anazodo, Peter C. Hindmarsh, and Mehul T. Dattani

London Centre for Paediatric Endocrinology at Great Ormond Street Hospital for Children and University College London Hospitals (T.Y.S., A.A., P.C.H., M.T.D.), London WC1N 3JH, United Kingdom; and Developmental Endocrinology Research Group (A.M., P.C.H., M.T.D.), Institute of Child Health, University College London, London WC1N 1EH, United Kingdom

Background: Delayed puberty can be due to either constitutional delay of growth and puberty (CDGP) or hypogonadotropic hypogonadism (HH). Differentiating between the two using current testing can be difficult. We assessed the utility of a GnRH test in combination with a 3-d and 19-d human chorionic gonadotropin (HCG) test to discriminate between the two conditions.

Methods: We performed a retrospective analysis of 43 boys with pubertal delay who required pubertal induction with testosterone. All were followed through puberty; 29 were subsequently diagnosed with CDGP and 14 with HH. A standard GnRH test (2.5 μg/kg) was undertaken and was followed by a short [3 d; n = 38 (13 HH, 25 CDGP)] or extended [19 d; n = 31 (12 HH, 19 CDGP)] HCG stimulation test, or both [n = 27 (11 HH, 16 CDGP)]. Receiver operating characteristic analysis was performed to assess the performance of the tests.

Results: Peak testosterone concentrations to both 3-d and 19-d HCG tests were significantly lower in patients with HH compared with CDGP. The 19-d test performed better than the 3-d test, and a combination of the LHRH, 3-d and 19 d HCG test [peak LH cutoff, 2.8 U/liter; peak 3-d testosterone cutoff, 1.04 μg/liter (3.6 nmol/liter); peak 19-d testosterone cutoff, 2.75 μg/liter (9.5 nmol/liter)] gave a sensitivity and a specificity of 100%.

Conclusions: Our data suggest that a GnRH test in combination with both a 3-d and 19-d HCG test may aid in differentiating between CDGP and HH. (***J Clin Endocrinol Metab* 94: 780–785, 2009**)

Delayed puberty in boys is one of the commonest causes for referral to a pediatric endocrinologist. The prevalence is approximately 5% at 14 yr of age, with 0.1% remaining prepubertal 3 yr later (1). The differential diagnosis lies between constitutional delay of growth and puberty (CDGP), which is common, and hypogonadotropic hypogonadism (HH), which is rare (prevalence 0.025%) (2). The commonest cause of HH is Kallmann syndrome (1 in 10,000 males). Other causes include isolated HH, tumors of the hypothalamus and pituitary, syndromes such as Bardet-Biedl and Prader-Willi, and mutations in genes that are implicated in pituitary development (*e.g. HESX1*, *SOX2*, *SOX3*, *PROP1*, *LHX3*), as well as mutations in leptin and the leptin receptor. Monogenic causes have been extended further with the identification of mutations in a number of genes in the hypothalamo-pituitary-gonadal (HPG) axis such as *LH*β, *FSH*β, *GnRHR*, *KAL-1*, *Kisspeptin*, *GPR54*, *FGFR1*, *NELF*, *prokineticin 2*, and *prokineticin receptor 2* (3).

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Abbreviations: CDGP, Constitutional delay of growth and puberty; HCG, human chorionic gonadotropin; HH, hypogonadotropic hypogonadism; HPG, hypothalamo-pituitary-gonadal; ROC, receiver operating characteristic.

At the time of referral, it is often difficult to distinguish boys with CDGP from HH because they may share similar clinical and hormonal features. Differentiation is not possible on unstimulated serum testosterone and gonadotropin concentrations because there is considerable overlap. As a result, a variety of physiological and stimulation tests have been proposed, such as nocturnal LH sampling (4), prolactin response to TRH, daily urine excretion of FSH (5) and GnRH and human chorionic gonadotropin (HCG) stimulation tests (6). Despite the variety of tests reported, no single test has been shown to differentiate between the two conditions with 100% sensitivity and specificity. Only the demonstration of a complete and spontaneous recovery can distinguish CDGP from HH, and few studies have verified outcomes in adulthood or at the end of pubertal induction. Recent studies have, however, shown reversibility of gonadotropin secretion in 10% of a cohort of young men with HH, 20% of whom had evidence of genetic mutations in *FGFR1* and *GnRHR* (7).

Analysis of test performance requires a gold standard for comparison. To date, no single test fulfills the criteria required to make a diagnosis of HH, although advances in the understanding of the genetic basis of pubertal development offer the possibility of a more refined diagnostic process and a gold standard with which to compare endocrine tests (8). At present, genetic disorders of pubertal development only account for approximately 10% of cases (9), so assessment will continue to rely on clinical evaluation, often postpubertal induction. In this study, we have reevaluated the role of GnRH and HCG testing in the diagnosis of HH by comparing responses to testing with long-term clinical outcomes. In addition, we have considered the performance of the HCG test when extended from its more conventional 3-d duration to that of 19 d. We have also recorded pretest testicular volumes as well as those at diagnostic follow-up.

Patients and Methods

Patients

We audited the clinical outcome data in 43 males who presented with delayed puberty and had been treated with testosterone with assessments made of the HPG axis some 3–5 yr previously. All patients had presented to the London Centre for Pediatric Endocrinology at Great Ormond Street Hospital for Children and University College London Hospitals. Ethical Committee approval for the retrospective review was obtained at both hospitals. A diagnosis of HH was made in those that had undergone no spontaneous pubertal development by 15 yr of age, had required testosterone therapy for initiation and completion of pubertal development, and who required subsequent therapy after reevaluation as adults to maintain secondary sexual characteristics. CDGP was diagnosed in those who were treated with testosterone for pubertal induction but progressed through puberty and attained adult secondary sexual characteristics, not requiring testosterone as adults, or in those who progressed spontaneously through puberty. Additionally, 35 patients also underwent an LHRH stimulation test, allowing a comparison of the serum gonadotropin responses between the two groups.

Testicular volumes were recorded in both groups at the time of testing as well as at the final follow-up visit.

Endocrine assessment of the HPG axis was undertaken using an iv bolus of 2.5 μg/kg GnRH (HRS; Intrapharm, Maidstone, Kent, UK) in 35 of 43 patients (10 HH, 25 CDGP) with blood samples drawn at 0, 20, and 60 min after GnRH administration for the measurement of serum LH and FSH concentrations. This was followed by a short [3 d; n = 38 (13 HH, 25 CDGP)] or extended HCG stimulation test [19 d; n = 31 (12 HH, 19 CDGP)], or both [n = 27 (11 HH, 16 CDGP)]. HCG [Pregnyl; Organon Laboratories Ltd., Cambridge, UK] was administered im at a dose of 1500 U after the completion of the GnRH test, again on d 2 and 3 for the short (3 d) test, and on d 8, 11, 15, and 18 for the extended (19 d) test. A blood sample for the measurement of serum testosterone concentration was drawn before the GnRH test (d 0) and then 24 h after the d 3 (d 4) and d 18 (d 19) HCG injections.

Hormone assays

LH, FSH, and testosterone were measured using the Abbott Architect assay (Abbott Diagnostics, Abbott Park, IL).

Statistical analysis

All data are expressed as means and SD. Between-group comparisons were performed using Student's *t* test. The χ^2 test was used to compare frequencies of occurrences. Correlation analysis was performed using Pearson's correlation coefficient. Test performance was assessed using principles outlined by Sox (10). The groups were also compared to assess the positive predictive value at various cutoffs of rise in testosterone. The receiver operating characteristic (ROC) curve was used to depict and determine the trade-off between the true- and false-positive rates for the tests studied (11). The area under the ROC curve for each test was used to compare tests using the principle that the test with the greatest area under its ROC curve is the better test (12).

We analyzed the peak LH response at 20 min because it was significantly greater than that at 60 min ($P = 0.003$). We also used the peak FSH response at 20 min because there was no statistical difference between the 20- and 60-min concentrations ($P = 0.88$), and the 20-min sample reflects secretion of LH and FSH in response to GnRH, whereas the 60-min sample might reflect a combination of synthesis and secretion (13).

Results

General

All patients with HH, having failed to develop spontaneous puberty, received pubertal induction with testosterone therapy and are currently postpubertal and requiring long-term testosterone supplementation to maintain normal adult serum testosterone concentrations. The CDGP group attained spontaneous puberty or required testosterone treatment for pubertal induction; all subsequently progressed through puberty with increasing testicular volumes and pubertal staging. They maintained adult pubertal staging with serum testosterone concentrations within the normal adult range, and none require exogenous testosterone.

Unstimulated hormone concentrations

Table 1 details the unstimulated hormone concentrations in the two groups. The unstimulated serum testosterone concentrations were not significantly different between patients with HH [mean, 0.3 (0.17) μg/liter; or 1.0 (0.6) nmol/liter] and CDGP [mean, 0.4 (0.3) μg/liter; or 1.5 (1.1) nmol/liter] ($P = 0.08$) (Table 2). The area under the ROC for unstimulated testosterone was 0.63 (0.16) (Fig. 1). The estimated concentration with the best discrimination was 0.14 μg/liter (0.5 nmol/liter) (sensitivity, 93%; specificity, 100%), which was below the sensitivity of the assay. The unstimulated serum FSH concentration was signifi-

TABLE 1. Serum testosterone, FSH, and LH concentrations in patients with HH (patients 1–14) and CDGP (patients 15–43)

					Serum testosterone (μg/liter)								
	Investigation		Discharge/ diagnosis			Post HCG stimulation		Serum FSH (U/liter)			Serum LH (U/liter)		
Patient no.	Age (yr)	Testicular volume [mls (R/L)]	Age (yr)	Testicular volume [mls (R/L)]	Day 0	Day 4	Day 19	0 min	20 min	60 min	0 min	20 min	60 min
1	10.6	1/2	15.4	2/4	0.2	0.29	1.04	0.5	2.7	3.6	0.7	1.7	1.1
2	11.2	1/1	18.0	4/4	0.2	0.2	1.15						
3	10.3	1/1	16.3	3/5	0.2	0.2	1.6	2.0	3.0	3.6	0.7	2.4	2.1
4	12.0	0/1	17.4	0/1	0.2	0.2	0.6	0.2	0.2	0.2	0.7	0.7	0.7
5	11.6	1/1	17.8	1/1	0.2	0.45	0.29	0.3	0.7	1.4	0.7	1.2	1.0
6	15.8	1/1	18.6	1/1	0.61	0.84	1.13	0.2	1.6	3.0	0.1	0.8	1.0
7	12.7	1/1	16.2	4/4	0.23	1.01	2.7	1.3	3.7	6.3	0.1	1.4	1.8
8	14.3	2/2	17.5	5/6	0.35	0.78	2.14	0.6	1.4	1.5	0.1	0.1	0.1
9	16.9	3/0	20.4	4/5	0.78	3.01	2.42	2.6			2.5		
10	11.6	2/2	18.9	10/8	0.2	0.35	3.03						
11	10.3	1/2	14.3	5/5	0.2	0.2	2.02	1.5	4.2	6.8	0.7	1.8	1.9
12	14.3	2/2	18.5	4/4	0.2	0.5	1.33	0.1	0.6	0.6	0.1	0.8	0.6
13	14.0	1/1	19.6	2/2	0.4	0.64		0.6	2.8	4.2	0.7	6.1	5.3
14	11.8	2/2	17.5	4/4	0.2		2.02						
15	10.7	1/2	16.2	12/12	0.2	0.69	7.43	1.4	3.4	6.0	0.7	3.8	3.5
16	13.8	3/1	17.9	15/15	0.69	3.32	4.33	4.6	8.4	9.9	1.0	24.4	19.7
17	15.8	2/2	19.4	12/12	0.84	5.6	7.43	3.0	5.3	4.2	3.7	19.7	15.8
18	12.3	2/2	18.1	10/12	0.2	2.08	2.77	1.0	2.7	3.2	0.7	19.7	12.8
19	13.7	1/1	16.5	8/10	0.43	2.02	4.24	2.5	5.6	6.1	0.3	6.2	5.6
20	13.4	3/3	16.8	15/15	0.26	1.07	5.52	4.5	8.0	10.3	0.1	2.3	2.0
21	10.1	2/2	15.3	10/12	0.52	3.41	6.32	2.2	6.8	9.8	0.7	5.7	3.8
22	13.5	3/2	17.7	10/12	0.69	3.58	8.18	3.6	6.0	7.1	0.5	10.5	9.3
23	14.0	3/4	19.4	20/25	0.69	6.06	6.82	4.8	6.4	8.2	1.4	15.1	15.7
24	16.7	2/2	20.3	10/12	0.06	1.73	3.32	2.2	2.9	3.4	0.1	1.0	1.3
25	16.0	2/2	19.8	15/15	0.26	2.63	5.38	3.5	6.4	8.3	0.2	2.0	2.0
26	12.4	2/2	17.1	18/18	0.2	0.49	4.39	0.9	2.8	3.8	0.2	8.3	6.4
27	16.8	4/4	19.5	14/16	0.52	15.1	13.8	0.1	16.9	18.4	1.3	3.2	3.9
28	11.2	2/2	18.0	20/20	0.2	1.79	4.31	3.1	8.1	13.6	0.7	3.1	3.0
29	14.7	2/2	19.4	12/15	1.18	4.91	4.19	1.9	3.0	3.0	2.7	18.2	14.6
30	11.1	2/2	15.2	12/10	0.2	1.73	4.82	1.1	6.2	6.7	0.7	8.9	3.6
31	11.9	4/5	17.6	15/15	0.31	1.39		3.5	6.5	8.8	0.1	3.9	3.2
32	13.1	2/2	18.9	15/15	0.2	6.27		1.1	1.4	1.8	0.7	10.4	8.9
33	15.7	3/3	18.2	15/15	0.92	6.0		1.1	1.4	1.5	2.2	9.6	8.2
34	16.9	3/2	19.1	12/12	0.23	7.4		2.9	3.6	5.0	0.6	5.6	8.2
35	15.4	2/3	18.8	15/15	0.1	1.62		2.1	3.3	4.7	0.1	6.0	6.0
36	11.4	1/2	18.5	8/10	0.2	1.27							
37	12.7	2/3	17.3	12/12	0.2	1.13		1.0					
38	11.3	2/2	17.9	10/10	0.46	4.28		1.5					
39	14.6	2/3	19.2	12/12	0.2	2.89		0.8	1.4	1.9	0.7	9.2	7.6
40	11.4	2/2	16.5	10/12	0.29		2.45	1.5	2.8	4.9	0.1	0.3	0.6
41	15.2	1/2	19.6	10/12	0.46		3.64	3.1	4.8	5.6	1.1	9.4	7.8
42	16.5	4/4	19.1	8/10	1.13		4.77	1.5	2.3	2.5	2.7	16.0	15.2
43	10.6	2/4	17.4	8/8	0.61			1.1			0.1		

To convert testosterone from μg/liter to nmol/liter, multiply by 3.46. L, Left; R, right.

cantly lower in HH [mean, 0.9 (0.8) U/liter] compared with CDGP [mean, 2.2 (1.3) U/liter] ($P = 0.007$). The unstimulated serum LH concentration was not significantly different between the groups [HH mean, 0.7 (0.7) U/liter; CDGP mean, 0.9 (0.9) U/liter; $P = 0.47$] (Table 2). The ROC for LH was 0.53 (0.11) and for FSH 0.76 (0.09). However, no valid LH cutoff could be established, and the best derived for FSH was 0.9 U/liter (sensitivity, 88.5%; specificity, 55%).

3-d (short) HCG stimulation

Short HCG stimulation was performed in 38 of 43 patients. Patients with HH had significantly lower d 4 serum testosterone concentrations as compared with patients with CDGP (Table 2). An absolute serum testosterone concentration on d 4 of 1.04 μg/liter (3.6 nmol/liter) offered the best sensitivity (92%) and specificity (92%) for the diagnosis of HH (Fig. 2A). The positive predictive value of this cutoff was 86%.

TABLE 2. Serum testosterone, FSH, and LH concentrations in patients with HH and CDGP

	HH	CDGP	*P*
Serum testosterone (μg/liter)			
Day 0	0.29 (0.17) (n=14)	0.43 (032) (n =29)	0.08
Day 4	0.75 (0.75) (n=13)	3.53 (3.12) (n=25)	<0.00001
Day 19	1.9 (0.8) (n =12)	5.49 (2.6) (n =19)	0.00001
Serum FSH (U/liter)			
Unstimulated	0.9 (0.8) (n =11)	2.2 (1.3) (n =28)	0.007
Peak (20 min)	2.2 (1.5)	5.1 (3.3)	<0.001
Serum LH (U/liter)			
Unstimulated	0.7 (0.7) (n =11)	0.9 (0.9) (n =26)	0.47
Peak (20 min)	1.7 (1.7)	8.9 (6.6)	<0.001

To convert testosterone from μg/liter to nmol/liter, multiply by 3.46.

19-d (extended) HCG stimulation

Thirty-one patients underwent extended HCG stimulation. The d 19 serum testosterone concentrations were significantly lower in HH patients compared with those with CDGP (Table 2). An absolute serum testosterone concentration on d 19 of 2.75 μg/liter (9.5 nmol/liter) provided optimal sensitivity (92%) and specificity (95%) for the diagnosis of HH (Fig. 2B). The positive predictive value for this cutoff was 92%.

Combination of short and extended HCG stimulation

Eleven patients with HH and 16 with CDGP underwent both 3-d and 19-d HCG stimulation. The area under the ROC was 0.92 (0.05) for the 3-d HCG stimulation and 0.98 (0.02) for the 19-d study (Fig. 1). Given the moderately greater area for the 19-d study, it would seem preferable to use this to define gonadal responsivity. No patient with HH had both 4-d and 19-d testosterone values that were above the respective cutoffs. Additionally, no patient with CDGP had both 4-d and 19-d testosterone values that were below the respective cutoffs.

GnRH stimulation test

The peak serum LH and FSH response to GnRH stimulation was significantly lower in the patients with HH ($P < 0.001$) (Table 2). The area under the ROC was greater for LH [0.88 (0.06)] than FSH [0.70 (0.10)] and yielded an optimal peak response cutoff point of 2.8 U/liter for LH (sensitivity, 90%; specificity, 84%; positive predictive value, 69%) (Fig. 2C) and 3.7 U/liter for FSH (sensitivity, 90%; specificity, 52%; positive predictive value, 41%). There was no difference between the groups in terms of the time of the FSH (χ^2 0.48; $P = 0.41$) and LH (χ^2 0.41; $P = 0.66$) peak responses.

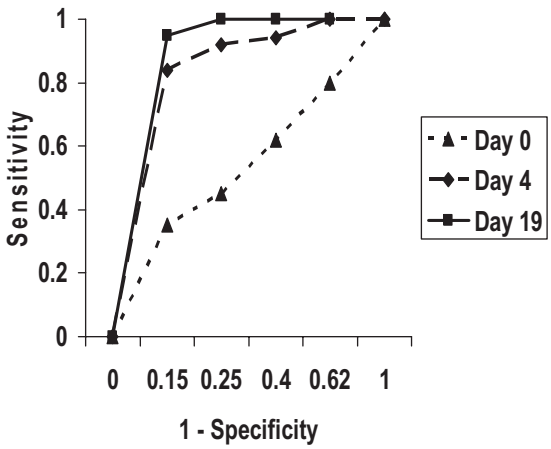

FIG. 1. Receiver operator characteristics for d 0 and d 4 and 19 post-HCG stimulation serum testosterone concentrations in 43 patients presenting with delayed puberty.

Approach to diagnosis

Using the "rule-in" approach to diagnose HH with an absolute d-4 serum testosterone cutoff, an absolute d-19 serum testosterone cutoff, and a peak serum LH cutoff of 1.04 μg/liter (3.6 nmol/liter), 2.75 μg/liter (9.5 nmol/liter), and 2.8 U/liter, respectively, resulted in a sensitivity of 100% and a specificity of 100% because 9 of 9 patients with HH who underwent all three tests did not achieve these cutoffs, and none with CDGP (n = 16) failed all three tests. If only the 3-d HCG and the LH response to GnRH test were used, the sensitivity decreased to 90%, although the specificity remained unchanged at 100%. On the other hand, if only the 3-d and 19-d tests are used with cutoffs as above, the sensitivity decreases to 83%, although the specificity remains at 100%, with a positive predictive value of 100%.

Testicular volumes

The testicular volumes were documented at the time of testing in both groups as well as at the final follow-up visit. The mean age of testing in the HH group was 12.6 yr (SD 2.4), whereas that in the CDGP group was 13.4 yr (1.6). The mean age at the final follow-up visit was 17.6 yr (3.1) in the HH group, compared with 18.1 yr (1.4) in the CDGP group. The initial mean testicular volume in the HH group was 1.3 ml (0.5), compared with a mean initial testicular volume in the CDGP group of 2.4 ml (0.8) (unpaired *t* test, $P < 0.001$). At the time of the final follow-up visit, the mean testicular volume in the HH group was 3.7 ml (2.2), whereas that in the CDGP group was 13.1 ml (3.3) ($P < 0.001$). There was a significant increase in testicular volumes in both the HH and CDGP groups (paired *t* test, $P < 0.001$).

Using a cutoff testicular volume of 3 ml for the diagnosis of HH in isolation, we achieved a sensitivity of 93% with a specificity of 45%.

Using a combination of testicular volumes less than 3 ml and a 3-d HCG peak testosterone less than 1.04 μg/liter for a diagnosis of HH, the sensitivity was 92% with a specificity of 92%. Using the "rule-out" approach to exclude HH (testicular vol-

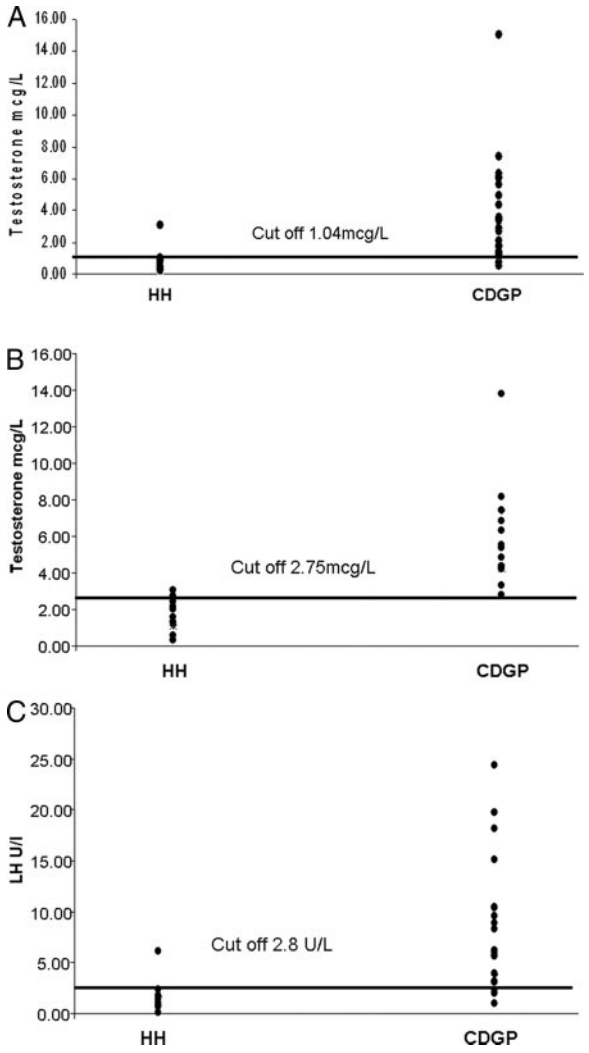

FIG. 2. Scatter plots showing 3-d plasma testosterone (μg/liter) in HH and CDGP (A); 19-d plasma testosterone (μg/liter) in HH and CDGP (B); and peak LH (IU/liter) in HH and CDGP (C).

umes >3 ml and testosterone >1.04 μg/liter), the sensitivity is 92% with 87% specificity.

Discussion

Presentation of adolescents in the peripubertal period with pubertal delay can be diagnostically challenging. In practice, a decision is often made to treat these adolescents with testosterone to optimize their growth and pubertal progress in a timely fashion and reassess later in terms of diagnosis. However, a definitive diagnosis would be desirable from the viewpoint of long-term prognosis for fertility and to alleviate anxiety in adolescents with CDGP. A number of tests have been evaluated for their potential to differentiate between HH and CDGP. Of these, use of HCG and GnRH appear to be most widely used but, when used in isolation, demonstrate poor discrimination between the two conditions (14–16). Other options include overnight sampling for LH secretion and the use of the pulsatile administration of GnRH, both of which are time-consuming, expensive, and difficult to perform on an ambulatory basis (17), as well as the prolactin response to TRH stimulation (18), estimation of daily excretion of urinary FSH (19), free α-subunit measurement (20), and the use of Gonadotropin-releasing hormone analog (21–24). All of these tests have relatively poor specificity due to overlap between the two groups.

It has been suggested that the GnRH test be used in conjunction with the HCG test to differentiate between CDGP and HH (15). Our data suggest that this may be a useful approach to the diagnostic question because the peak serum testosterone response to either 3-d or 19-d HCG stimulation was significantly lower in those with HH. ROC analysis revealed that unstimulated serum testosterone was unhelpful in diagnosis but generated cutoff points for d-4 and d-19 serum testosterone concentrations of 1.04 and 2.75 μg/liter (3.6 and 9.5 nmol/liter), respectively. Individually, this translates into positive predictive values for HH of 86% for the d-4 test and 92% for the d-19 study.

Historically, the extended HCG test has been used in children with undescended testes to assess the testicular response to long-term HCG, in addition to enabling testicular descent (24). Although the extended test has been evaluated in children with either a micropenis or cryptorchidism, Adiyaman *et al.* (25) did not formally compare the two tests. Additionally, to the best of our knowledge, the 19-d HCG test has not been evaluated in children with significant pubertal delay. Although the 19-d HCG test does prolong the evaluation of the patient, given the better test performance, we believe that the test is justified, although a good response on d 4 after the 3-d test could lead to termination of the extended test if results were available rapidly.

Our data also suggest that information from GnRH testing can be of value, particularly when combined with HCG testing. Unstimulated serum FSH concentrations were significantly lower in patients with HH, as were peak serum FSH concentrations in response to GnRH stimulation. In contrast, unstimulated LH concentrations were not different between the groups, whereas the peak serum LH concentration was again significantly lower in the patients with HH. ROC analysis suggested that the peak serum LH performed better than the peak FSH response, with an optimal cutoff value of 2.8 IU/liter (positive predictive value, 69%) for serum LH concentration at 20 min. Combining the GnRH and the two HCG tests led to a sensitivity and specificity of 100%. If only the 3-d HCG test and the LH response to GnRH are used, the sensitivity decreases to 90%, although the specificity remains at 100%. These observations on the limitation of the 3-d HCG test support the observations of Degros *et al.* (16) who derived similar cutoff points to ours and noted that some 29% of children lay in the borderline area of the HCG test between a clear diagnosis of HH or CDGP, a finding echoed by Kauschansky *et al.* (15).

Although we found that prepubertal testicular volumes in those with HH were slightly lower than those with CDGP [1.3 (SD 0.5) *vs.* 2.4 (SD 0.8) ml], the wide range would lead to considerable overlap in testicular sizes between the two groups, and hence testicular volumes could not on their own differentiate between the two groups. Testicular volumes of less than 3 ml on presentation identified patients with HH with a sensitivity of 93%, but 16 of 29 CDGP children also had testes less than 3 ml

at presentation. The use of initial testicular volumes in combination with the peak testosterone response to the 3-d HCG did not lead to improved diagnosis of HH.

The testicular volumes at the last follow-up visit were clearly larger in the CDGP group, as would be expected. Nevertheless, it is important to note that the HH group increased their testicular volumes to a mean of 3.7 (SD 2.2) ml.

Although observation over time may resolve the diagnosis itself, other issues such as growth, psychological consequences, and societal pressures with respect to delay/lack of pubertal development may necessitate earlier investigation. Confirmation of the diagnosis may also be required to alert the physician to the possibility of other hormonal deficiencies as well as a progressive underlying lesion such as a tumor, and the patient may also benefit from understanding the diagnosis and implications for future fertility. The data that we present suggest that combining a 19-d HCG test with a conventional GnRH test may be of benefit in the differentiation of HH from CDGP.

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Address all correspondence and requests for reprints to: Professor Mehul T. Dattani, Professor of Pediatric Endocrinology, Developmental Endocrinology Research Group, Institute of Child Health, University College London, 30 Guilford Street, London WC1N 1EH, United Kingdom. E-mail: m.dattani@ich.ucl.ac.uk.

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