Clinical Outcome, Hormonal Status, Gonadotrope Axis, and Testicular Function in 219 Adult Men Born With Classic 21-Hydroxylase Deficiency. A French National Survey

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Context: Outcomes of congenital adrenal hyperplasia due to classic 21-hydroxylase deficiency (21OHD) have been widely studied in children and women, but less so in men.

Objective: The objective was to analyze data from a network of metropolitan French teaching hospitals on the clinical outcome of classic 21OHD in a large sample of congenital adrenal hyperplasia/21OHD-genotyped adult men, and particularly the impact of 21OHD on the gonadotrope axis, testicular function, and fertility.

Methods: From April 2011 to June 2014, tertiary endocrinology departments provided data for 219 men with 21OHD (ages, 18–70 y; 73.6% salt wasters, 26.4% simple virilizers). Testicular sonography was performed in 164 men, and sperm analysis was performed in 71 men.

Results: Mean final height was 7.8 cm lower than in a reference population. Obesity was more common, and mean blood pressure was lower than in the reference population. None of the patients were diabetic, and lipid status was generally normal. Blood electrolyte status was normal in the vast majority of men, despite markedly elevated ACTH and renin levels. Serum progesterone, 17-hydroxyprogesterone, and androstenedione levels were above normal in the vast majority of cases. Hormonal profiling variously showed a normal gonadotrope-testicular axis, gonadotropin deficiency, or primary testicular insufficiency. Testicular sonography revealed testicular adrenal rest tumors (TARTs) in 34% of 164 men. Serum inhibin B and FSH levels were significantly lower and higher, respectively, in patients with TARTs. Severe oligospermia or azoospermia was found in 42% of patients and was significantly more prevalent in men with TARTs (70%) than in men with normal testes (3.6%; $P < .0001$). Among men living with female partners, TARTs were significantly more prevalent in those who had not fathered children.

Conclusion: We report the spectrum of testicular/gonadotrope axis impairment in the largest cohort of 21OHD men studied to date. Our results suggest that French men with 21OHD managed in specialized centers frequently have impaired exocrine testicular function but that its reproductive implications are often overlooked. **(*J Clin Endocrinol Metab* 100: 2303–2313, 2015)**

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Abbreviations: ADIONE, Δ4-androstenedione; AR, active renin; BMI, body mass index; LLN, lower limit of normal; 21OHD, 21-hydroxylase deficiency; 17OHPROG, 17-hydroxyprogesterone; PROG, progesterone; SV, simple virilizing; SW, salt-wasting; TART, testicular adrenal rest tumor; ULN, upper limit of normal.

Congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21OHD) is a rare autosomal recessive disease characterized by variable impairment of cortisol and aldosterone synthesis by the adrenal cortex (1). 21OHD is caused by loss-of-function mutations in *CYP21A2*, the gene encoding the adrenal enzyme 21-hydroxylase (2). Its incidence is estimated at 1:12 000 to 1:20 000 births worldwide (Refs. 3–5 and http://ghr.nlm.nih.gov/condition/21-hydroxylase). So-called classic 21OHD is subclassified into salt-wasting (SW) and simple virilizing (SV) forms, depending on whether or not a clinical episode of SW dehydration occurs during the neonatal period (1–6). Clinical manifestations of 21OHD are due to a combination of cortisol and aldosterone deficiency and accumulation of steroid precursors that are shunted into the androgen synthesis pathway (1, 3, 6), resulting in an androgen excess. In females, 21OHD causes prenatal masculinization of the external genitalia, resulting in more or less severe sexual ambiguity (1, 3, 6–11). After birth, female patients also develop chronic hyperandrogenism that can further affect their self-image and quality of life (7, 9–11). Because of its early diagnosis in the neonatal period or early childhood and its more obvious impact on female sexual development, the largest published series of classic 21OHD, addressing clinical outcomes, mainly concerns children and/or female patients (7–14). Data on the adult outcome of male patients born with this disease, including substantial clinical, hormonal, morphological, testicular, and sperm evaluation, are only available for a few dozen men (12, 13, 15–19). Indeed, even series that include male patients describe mainly children and adolescents (13, 20–24). The aim of the present study was therefore to describe anthropometric features, treatment, and hormonal control, especially with respect to the gonadotropic axis, testicular function, and fertility, in a large series of adult men with classic 21OHD managed in "adult" endocrinology departments of French teaching hospitals.

Patients and Methods

Patients

The study was funded by the French Health Ministry (Programme Hospitalier de Recherche Clinique; PHRC NI08013), and approved by the Bicêtre ethics committee. All of the men gave their written informed consent. The diagnosis and phenotypic classification of 21OHD was based on the clinical history, current clinical status, and hormonal and genetic criteria (Table 1). Clinical examinations and anthropometric measurements were performed by experienced endocrinologists in each center.

Clinical evaluation

Height, weight, and body mass index (BMI) were determined during medical consultations between April 2011 and June 2014 by referring endocrinologists in each center. When patients had had several clinical examinations, we considered only the most recent results.

Molecular analysis of *CYP21A2*

DNA was available in 209 cases (95%) for mutational analysis of the *CYP21A2* gene. *CYP21A2* molecular analysis was prescribed by the referring endocrinologist and performed (by Y.M. and V.T.-G.) in the Molecular Laboratory for Rare Endocrine Disorders (Lyon, France), as previously reported (8, 25, 26) Supplemental Table 1.

Routine biochemistry

Fasting blood glucose, cholesterol, and triglyceride levels and plasma sodium and potassium levels were measured in the morning (8 to 9:30 AM) by the biochemistry laboratory of each center. When patients had had several routine laboratory tests, we considered only the most recent results.

Hormonal evaluation

Hormone concentrations were measured in the morning (8 to 9:30 AM) by the accredited (COFRAC; www.cofrac.fr) clinical endocrinology laboratory in each center, all of which participate in the French national quality control program for steroid and peptide hormone immunoassays (ProBioQual; www.probioqual.com). The main characteristics of the assays used by the laboratories are shown in Supplemental Table 2.

When patients had had several hormonal evaluations, we considered only the most recent results for each hormone measured.

Steroid precursor and androgen assays

Various RIAs or liquid chromatography-mass spectrometry assays were used in the different centers to measure serum progesterone (PROG), 17-hydroxyprogesterone (17OHPROG), Δ4-androstenedione (ADIONE), and total T. In these laboratories, the upper limits of normal (ULNs) for adult men were be-

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Table 1. Main Characteristics of the 21OHD Men Included

	21OHD	Normal Range
n	219	
Age, y (see Figure 1B)	32.1 ± 10.2 (18–79)	
Clinic presentation		
Salt wasters, %	73.6	
Simple virilizers, %	26.4	
Replacement therapy[a]		
SW		
HC (% patients/mg/d)	96.8%/27.7 ± 0.5	
9αF (% patients/μg/d)	93.6%/112.1 ± 3.6	
DXM (% patients/μg/d)	21.5%/0.41 ± 0.29	
Prednisone (%)	1.89%/NA	
SV		
HC (% patients/mg/d)	80%/21.76 ± 1.07	
9αF (% patients/μg/d)	46.9%/72.1 ± 2.4	
Height, cm (n = 211) (see Figure 1B)	167.8 (144–190)[a]	175.6 (162–188)[b]
BMI, kg/m^2 (n = 211) (see Figure 1C)	26.5 ± 5.6 (17.8–52.5)	(22–25)[b] (15–43)
Systolic blood pressure, mm Hg (n = 101)	124.5 (100–154)	129 ± 6.2 (110–125)[c]
Diastolic blood pressure, mm Hg (n = 101)	73.5 (50–95)	79 ± 4.9 (60–90)[c]
Fasting glycemia, mmol/L	4.78 ± 0.58 (3.6–6.7)	(4.5–5.5)[d]
Total cholesterol, mmol/L (n = 126)	4.7 ± 1.1 (2.7–7.7)	(4.63–5.90)[d]
Triglycerides, mmol/L (n = 126)	1.05 ± 0.64 (0.27–4.5)	(0.6–2.0)[d]
Plasma sodium, mmol/L (n = 107)	140.0 ± 2.73 (131–147)	(137–143)
Plasma potassium, mmol/L (n = 110)	3.96 ± 0.35 (3.2–5.3)	(3.5–5.1)

Abbreviations: DXM, dexamethasone; HC, hydrocortisone; NA, not available; 9αF, 9α-fludrocortisone. Data are expressed as mean ± SD (range).

[a] At the time the survey was conducted (April 2011 and June 2014).

[b] Reference data for height and BMI were obtained from the French l'IFM-Ctcoe (economic department of the Fashion French Institute; www.ifth.org); see also Statistical Analysis. For height in reference population, third-97th percentiles are indicated.

[c] Normal range of blood pressure was established from the ENNS survey. It consisted of a cross-sectional survey conducted in continental France in 2006–2007 in which blood pressure was measured in a national sample of 2407 men (age, 18–74 y).

[d] Range established in 734 men (age, 18–74 y): French Metropolitan National Nutrition and Health Study (ENNS) during the 2006–2007 period.

tween 0.6 and 1.2 ng/mL for PROG, 1.9 and 2.6 ng/mL for 17OHPROG, 1.6 and 2.4 ng/mL for ADIONE, and 7.1 and 9.9 ng/mL for T. The lower limit of normal (LLN) T values were between 2.6 and 3.4 ng/mL (Supplemental Table 2).

ACTH assay

Morning serum ACTH levels were measured using one of five sandwich immunoassays (immunoradiometric assay, enzyme immunoassay) available in France, for which the morning ULN was between 57 and 73 pg/mL (Supplemental Table 2).

Active renin

Serum supine active renin (AR) levels were determined in each center, using either a commercial electrochemiluminescence immunoassay (LIAISON; Diasorin) or a commercial RIA (Cis-Bio), with ULN values between 29 and 34 pg/mL (Supplemental Table 2).

Gonadotropin assay: LH and FSH

Various RIA, immunoradiometric assay, electrochemiluminescence immunoassay, and immunofluorometric assay methods were used in the different centers to measure serum FSH and LH levels. The main characteristics of these assays were similar, and the ULN values were between 5.9 and 8.2 IU/L for FSH and between 6.2 and 8.4 IU/L for LH. The LLN values were between 1.9 and 3.1 for FSH and between 1.8 and 3.3 for LH (Supplemental Table 2).

Inhibin B

Serum inhibin B levels were measured in each center using one of two commercial ELISA methods available in France: the GEN II assay by Beckman Coulter, or the assay from Oxford Bio-Innovation Reagents/Serotec. The inhibin B LLNs were between 80 and 92 pg/mL in the different laboratories (Supplemental Table 2).

Testicular sonography

Testicular morphology was studied between April 2011 and June 2014 in 164 (74.9%) of the 219 patients (43 with SV and 121 with SW) by experienced radiologists or urologists in each academic center, using high-spatial-resolution ultrasound transducers designed for soft tissues (7–15 MHz).

Sperm analysis

Sperm analysis was performed in 71 patients (32.4%) between April 2011 and June 2014 by accredited laboratories (COFRAC) in each center, after 3 to 7 days of sexual abstinence. When patients had had several sperm evaluations, we considered only the most recent results. Sperm status was classified, as recommended by the World Health Organization (WHO) in 2010 (27), as normal ($>15 \times 10^6$ sperm/mm^3), oligospermic ($<15 \times 10^6$ sperm/mm^3), severely oligospermic ($<5 \times 10^6$ sperm/mm^3), or azoospermic (Table 2).

Table 2. Sperm Parameters in 21OHD Patients

	Parameter	WHO (2010)[a]
No. of patients analyzed	71	
Volume, mL	2.8 ± 1.3 (0.8–7.9)	>1.5
Sperm count (sperm × 10^6/mm^3)	24 ± 12.0 (0–132)	>15 × 10^6/mm^3
Normal (>15 × 10^6/mm^3)	34%	
Moderate oligospermia (>5 to <15 × 10^6/mm^3)	24%	
Severe oligospermia (<5 × 10^6/mm^3)	30%	
Azoospermia	12%	
Vitality, %	62.8 ± 27.6 (0–95)	>58
Motility, %	39.9 ± 22.3 (0–89)	>40
No. of sperm cryopreservations performed	42	

Data are expressed as mean ± SD (range), unless specified otherwise.

[a] From the World Health Organization. *WHO Laboratory Manual for the Examination and Processing of Human Semen*. 5th ed. http://www.who.int/reproductivehealth/publications/infertility/9789241547789/en/index.html.

Statistical analysis

Data from anonymized clinical case report forms were entered into a central database. Subgroups were compared by using *t* tests for mean values of continuous variables and χ^2 tests for categorical variables. Anthropometric and blood pressure data were analyzed by comparison with a reference French adult male population. Reference data for BMI and height were obtained from IFM-Ctcoe (the economic department of the French Fashion Institute) and were established during a French national measurement campaign conducted during the period 2003–2006, using three-dimensional body scanning based on Lectra technology (www.ifth.org). This method yields body volume and automatically extracts 85 precise measurements, including height. The campaign involved 11 562 individuals aged 5 to 70 years at 37 representative sites in France. Using the public part of the IFM-Ctcoe database, we selected BMI data for men aged 18 to 75 years for comparison with the 21OHD patients. We used the mean and the third to 97th percentiles from this database to analyze the patients' heights. Data from the French Metropolitan National Nutrition and Health Study (ENNS) cross-sectional survey conducted in France in 2006–2007 in a national sample of healthy adults aged 18 to 74 years, including 2407 men, were used for blood pressure analysis as well as for glycemia and circulating lipids.

Analyses were performed using Graph Pad PRISM software (GraphPad Software, Inc) or Stata version 10 (StataCorp). Statistical significance was assumed at $P < .05$.

Results

Participating centers and geographic distribution

Supplemental Figure 1A shows the geographic locations of the 27 participating endocrinology departments. The number of patients enrolled by each center are shown in Supplemental Figure 1B.

Recruitment of men with 21OHD and theoretical prevalence of the disease

A total of 219 men with 21OHD were included in this study. Based on the presumed prevalence and incidence of the disease in France (5) (approximately one per 15 900, or 25 males born each year), we would expect there to be 1250 men (ages, 18 to 70 y) with 21OHD living in France. Thus, the patients included in this study represent less than 20% of this theoretical number, as also reported in a recent British survey (12).

Age, height, and BMI

The age distribution at inclusion is shown in Figure 1A. Mean ± SD age was 32.1 ± 10.2 years (range, 18–70 y). Average final height ± SD was 167.8 ± 8.36 cm (range, 144 to 190 cm), 7.8 cm less than the average height of healthy French men (175.6 cm) aged 18 to 70 years (Figure 1B). Thus, 76.7% (155 of 202) of the men with 21OHD were between the third and 97th height percentiles for the adult male population, whereas 22.8% (46 of 202) were below the third percentile. Parental height was available for 61 patients. As expected (12), the patients were significantly shorter than predicted, by an average of 8.7 cm (final height, 167.6 ± 8.9 cm, vs 176.3 ± 4.9 cm predicted by the Bayley-Pinneau method; $P < .0001$) (Supplemental Figure 2). Mean height did not differ between patients older than 30 years (167.9 ± 8.3 cm) and those younger than 30 years (169.9 ± 8.9 cm).

Mean BMI ± SD was 26.5 ± 5.6 kg/m^2. Thirty percent of patients were overweight (25 to 29.9 kg/m^2), and 22% were obese (BMI > 30 kg/m^2). Figure 1C shows the patients' BMI distribution, as compared to the normal adult male population.

Patients taking dexamethasone (n = 44; see "Replacement therapy" below and Table 1) had a significantly higher BMI (28.3 ± 6.9 kg/m^2) than patients (n = 156) taking only hydrocortisone as glucocorticoid replacement therapy (26.1 ± 5.1 kg/m^2) ($P = .02$).

Replacement therapy

Specific information on daily oral replacement therapy could be collected in 193 cases, during interviews and/or

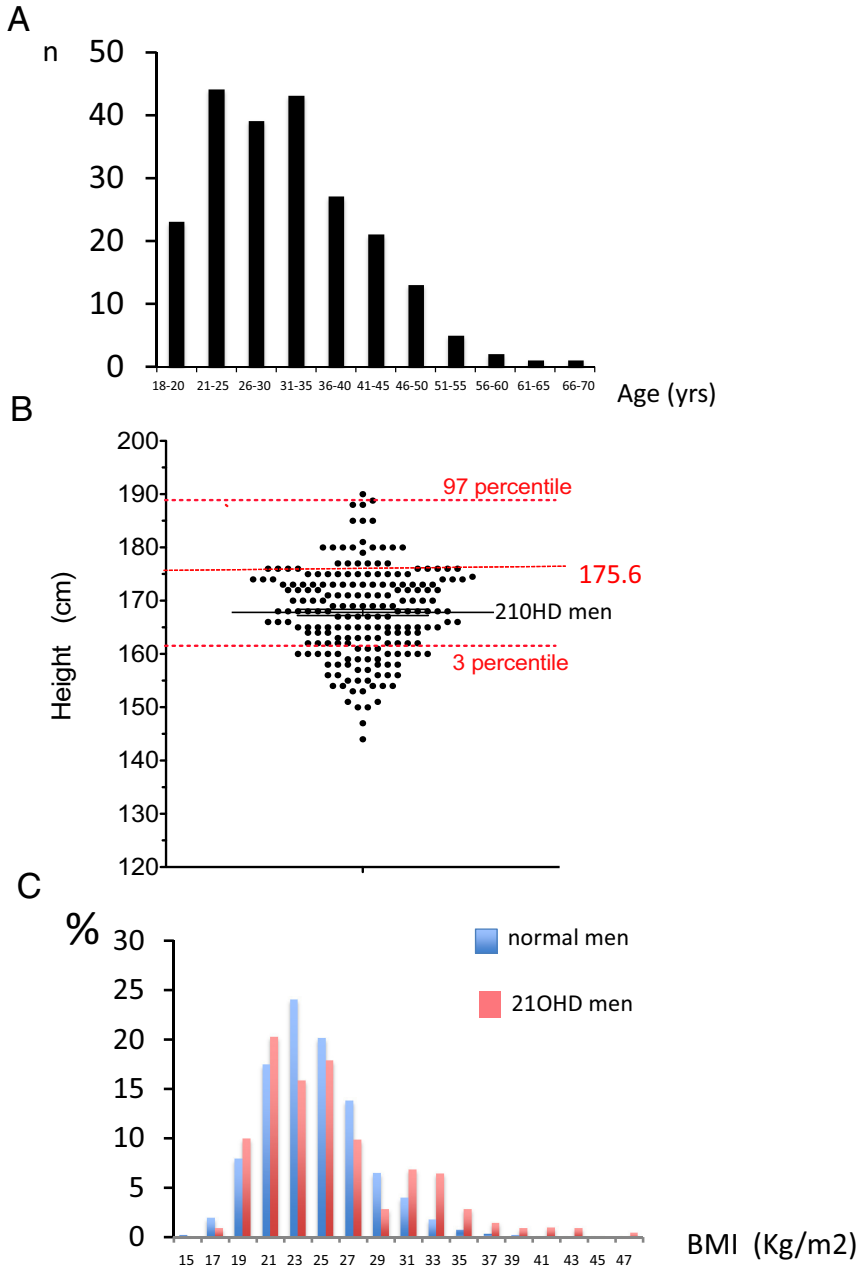

Figure 1. Clinical characteristics of the patients. A, Age distribution. B, Individual heights. The dotted red lines indicate the third and 97th percentiles and the mean height of a representative population of healthy French men. C, Body Mass Index (BMI) distribution of the patients compared to a population of healthy French men. See also Table 1.

from the patients' records. When patients were seen on several occasions, only the treatment taken at the most recent visit is reported.

Respectively, 96.8 and 93.6% of patients with the SW form were taking hydrocortisone and 9α-fludrocortisone (Table 1), compared to only 80 and 46.9% of patients with the SV form. It is noteworthy that 21.5% of patients with the SW form were taking dexamethasone (Table 1).

Table 1 also shows the average doses of glucocorticoids (hydrocortisone, 9α-fludrocortisone, prednisone, or dexamethasone) taken by the patients in the two subgroups. The average daily dose of hydrocortisone did not differ significantly according to BMI (<25, 25–30, or > 30 kg/m^2).

The mean doses of 9α-fludrocortisone taken by patients with the two clinical forms are shown in Table 1. Like the average dose, the percentage of patients receiving this synthetic mineralocorticoid was significantly lower in the SV subgroup than in the SW subgroup.

Blood pressure and routine biochemical parameters

When several values were obtained during follow-up, only the most recent values were reported here. A recent blood pressure measurement was available for 101 patients (Table 1). Average ± SD systolic blood pressure was 124.5 ± 10.9 mm Hg, and average diastolic blood pressure was 73.5 ± 9.4 mm Hg. These average values were significantly lower than those established between 2006 and 2007 in a population of 2407 healthy French men aged 18 to 74 years (Table 1; $P < .001$).

The mean value for fasting glycemia was 4.77 ± 0.59 mmol/L (range, 3.6–6.7; normal range, 3.9–5.5 mmol/L). Nine (9.8%) of 92 patients had moderate fasting hyperglycemia (>5.5 mmol/L), but none was diabetic (>7 mmol/L) according to American Diabetes Association (ADA) criteria (http://www.ndei.org/treatmentguidelines.aspx).

Fasting cholesterol and triglyceride values are shown in Table 1. The mean total cholesterol level was 4.7 ± 1.1 mmol/L.

The mean plasma sodium concentration, determined in 107 patients (48.8%), was 140.9 ± 2.7 mmol/L (range, 131–146). Eight of these patients (7%) had moderate hyponatremia (135–131 mmol/L).

The mean plasma potassium concentration, determined in 110 patients, was 3.96 (± 0.35) mmol/L (range, 3.2–5.3; normal range, 3.5–4.5). Eight patients (7.3%) had below-normal values, four (3.6%) had moderate hyperkalemia, and one subject had a value above 5 mmol/L.

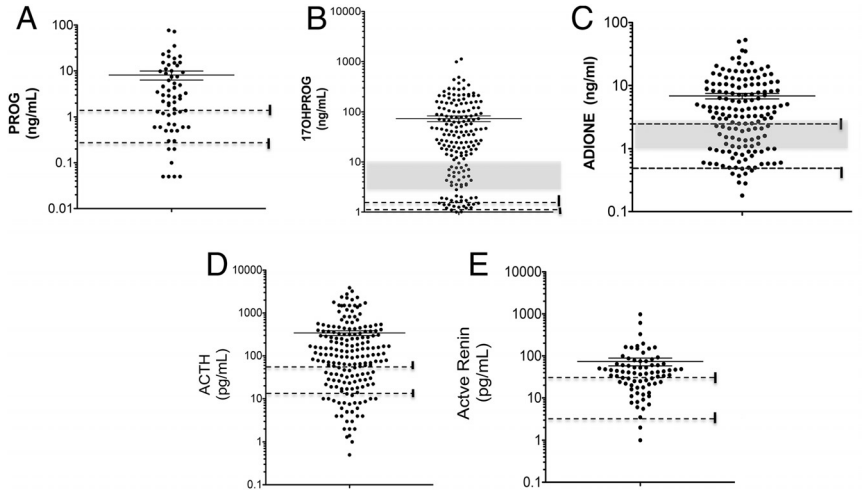

Figure 2. Hormonal profiles reflecting therapeutic efficacy. A–C, Serum levels of the adrenal steroid precursors PROG (A) and 17OHPROG (B) and the androgen precursor ADIONE (C) in 21OHD men sampled in the morning after intake of the usual glucocorticoid morning dose. For 17OHPROG and ADIONE, the shaded areas represent the recommended target ranges (1, 12). To convert nanograms per milliliter to nanomoles per liter, multiply by 3.18 for PROG, by 3.026 for 17OHPROG, and by 3.491 for ADIONE. D and E, Serum levels of the peptide hormones ACTH (D) and AR (E) in 21OHD men sampled in the morning after intake of the usual glucocorticoid and mineralocorticoid morning doses. Dotted lines indicate the mean values (range, vertical line) of the ULN and LLN for the different assays used (see also Patients and Methods and Supplemental Table 2). Note the logarithmic scale used to represent serum hormone concentrations.

Hormonal evaluation

When several hormonal values were obtained during follow-up, only the most recent values were reported here.

Adrenal steroid precursors

During the study period, the adrenal C21 steroid precursors 17OHPROG and PROG were measured in 199 and 62 patients, respectively. Individual values of these two steroids are shown in Figure 2, A and B. The mean ± SD 17OHPROG serum level was 73.5 ± 134 ng/mL (range, undetectable to 1123 ng/mL; median, 26.3 ng/mL). 17OHPROG levels were above the ULN in 81.9% of cases. The mean serum PROG level was 8.1 ± 14.4 ng/mL (range, 0.05–77; median, 2.8 ng/mL). PROG levels were above the ULN in 72.6% of cases.

Serum ADIONE levels were measured in 154 patients (Figure 2C). The mean ± SD value was 6.89 ± 8.62 ng/mL (range, 0.18 to 53 ng/mL; median, 3.75 ng/mL). ADIONE levels were above the ULN in 62.3% of patients.

As shown in Figure 2, B and C, both serum 17OHPROG and ADIONE levels were outside previously proposed target ranges in most patients (1, 6, 12).

ACTH and AR

Serum ACTH and AR were measured in 188 and 76 patients, respectively (Figure 2, D and E). The mean ACTH level was 342 ± 603 pg/mL (range, 0.5–3882; median, 106.3). ACTH levels were normal in 27.7% of patients, above the ULN in 54.3%, and below the LLN in 14.4%.

The mean AR level was 73.3 ± 134 pg/mL (range, 1.0–975; median, 40.3). The AR level was normal in 31.6% of patients, above the ULN in 65.8%, and below the LLN in 2.6%.

Pituitary gonadotropins, total T, and inhibin B

When several values were obtained during follow-up, only the most recent were reported here. Among the patients who had testicular ultrasound examination (see below), the reported gonadotropin, T, and inhibin B values are those obtained closest to the date of testicular ultrasound.

Serum LH and FSH, total T, and inhibin B levels were measured in 185, 146, and 93 patients, respectively (Figure 3).

The mean ± SD FSH level was 6.3 ± 10.2 IU/L (range, 0.05–74.5; median, 3.15). FSH levels were above the ULN in 14.3% of patients and below the LLN in 37.7%. The mean ± SD LH level (Figure 3A) was 4.2 ± 6.4 IU/L (range, 0.02–57.5; median, 2.7). LH levels were above the ULN in 10.9% of patients and below the LLN in 36.9%. Individual values of the two pituitary gonadotropins are shown in Figure 3A.

The mean total T concentration (Figure 3B) was 4.97 ± 2.21 ng/mL (range, 0.2–14.4; median, 4.6). T values were normal in 77.8% of patients and below the LLN in 20.5%.

The mean serum inhibin B level (Figure 3C) was 110.4 ± 77.1 pg/mL (range, 3.0–286; median, 110). Inhibin B levels were normal in 57% of patients and below the LLN in 43%.

Semen analysis

Only 71 men (32.4%) had an available sperm count (Table 2). According to the 2010 updated WHO criteria, the sperm count was normal in 34% of cases, whereas 24 and 30% of men, respectively, had moderate (>5 to <15 × 10^6 sperm/mm^3) and severe (<5 × 10^6 sperm/mm^3) oligospermia, and 12% had azoospermia. A semen sample was cryopreserved in 42 cases (59.2%).

Testicular morphology

Testicular ultrasound findings were available for 164 patients (74.9%) (Table 3). The testicular echostructure and volume were normal in 57% of cases, whereas testicular adrenal rest tumors (TARTs) (median volume, 1.2

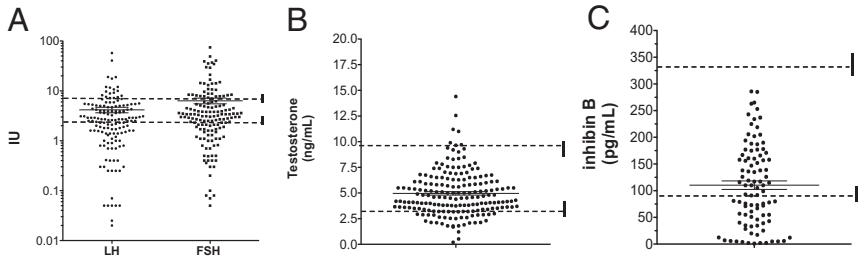

Figure 3. Pituitary gonadotropin and testicular hormone levels. A, Individual serum LH and FSH values. Dotted lines indicate the mean values (range, vertical line) of the ULN and LLN for the different gonadotropin assays used (see also Patients and Methods and Supplemental Table 2). Note the logarithmic scale used to represent serum gonadotropin concentrations. B, Individual serum total T values. Dotted lines indicate the mean values (range, vertical line) of the ULN and LLN for the different T assays used (see also Patients and Methods and Supplemental Table 2). To convert nanograms per milliliter to nanomoles per liter, multiply by 3.467 for T. C, Individual serum inhibin B values. Dotted lines indicate the mean values (range, vertical line) of the ULN and LLN in the different participating laboratories for inhibin assays available in France (see also Methods and Supplemental Table 2).

mL; range, 0.3–68 mL) were found in 56 cases (34%) and were bilateral in 79% of these 56 patients. Interestingly, scrotal ultrasound revealed TARTs in 39 patients (69.6%) in whom TARTs had not previously been detected, either because they were impalpable (19) or because scrotal palpation had not been performed. Testicular hypotrophy (testicular volume < 12 mL) was detected in 8% of the 164 men who underwent testicular ultrasound.

Gonadotropins, testicular hormones, and sperm analysis in 21OHD men who underwent testicular ultrasound (Table 3)

The relationships between testicular ultrasound findings and hormonal and sperm parameters are shown in Table 3. Patients with TARTs had a significantly higher mean FSH concentration than patients with normal ultrasound findings. Similarly, in men with TARTs, circulating inhibin B levels were markedly lower, the average sperm count was markedly lower, and severe oligospermia or azoospermia was markedly more frequent. Patients with testicular hypotrophy also had markedly lower sperm counts than those with normal testicular volume.

Fertility

The 219 patients received a questionnaire on marital status and fatherhood, either during a consultation or by post, and 159 responded. Of these, 104 men (65%) (compared to 61.8% of men in the INSEE French population survey no. 1482, January 2014; www.insee.fr and www.ined.fr) stated that they were living or had lived with a female partner, whereas 55 men (35%) reported no current or past cohabitation (compared to 31% of the French male population). Fifty-two (51%) of the 104 men who reported cohabitation stated that they had at least one child, naturally in 89% of cases (47 of 52) and after in vitro fertilization in five cases (11%). This fertility rate is lower than in the French reference population where 79% of adult males (age, 18–50 y) had fathered a child (INSEE French population survey, 2013, www.insee.fr).

Among the men who reported having fathered a child, TARTs were found in 28% of those who underwent testicular ultrasound examination, including four of the five men who had had recourse to in vitro fertilization. TARTs were significantly more frequent among the men who reported cohabitation but who had no children (48%; $P < .01$).

Discussion

We describe what is, to our knowledge, the largest reported series of well-genotyped adult men born with classic 21OHD who underwent substantial clinical, hormonal, morphological, testicular, and sperm evaluation. However, despite participation by most metropolitan French

Table 3. Gonadotropins, Testicular Hormones, and Sperm Analysis in 164 21OHD Men Who Underwent Testicular Ultrasound

Testicular Sonography	Normal	TART	Testicular Hypotrophy
n	94	56	14
FSH, IU/L	4.2 ± 2.7 (0.7–8.4) (n = 71)	9.2 ± 13 (0.03–74) (n = 46)[b]	2.9 ± 3.3 (0.4–16.8) (n = 10)[a]
LH, IU/L	4.9 ± 2.8 (0.8–7.8) (n = 70)	5.6 ± 9.8 (0.05–57) (n = 47)	3.9 ± 3.7 (0.02–9.2) (n = 11)
Serum T, ng/mL	4.9 ± 2.1 (0.5–14) (n = 82)	5.1 ± 2.9 (0.2–11) (n = 51)	4.3 ± 3.1 (1.2–9.2) (n = 10)
Serum inhibin, pg/mL	142 ± 29 (49–286) (n = 42)	87 ± 53 (1.0–202) (n = 39)[c]	73 ± 37 (22–135) (n = 8)[a]
Sperm count (sperm × 10^6/mm^3)	32 ± 24 (3.1–132) (n = 28)[a]	14.5 ± 13.9 (0–51) (n = 33)[b]	9.6 ± 3.1 (0.2–19.2) (n = 10)[a]
Severe oligospermia or azoospermia	3.6% (1/28)	70% (23/33)[d]	20% (2/10)[a]

Data are expressed as means ± SD (range). To convert T values in ng/mL to nmol/L, multiply by 3.467; to convert to ng/dL, multiply by 100.

[a] $P < .05$ vs normal; [b] $P < .01$ vs normal; [c] $P < .001$ vs normal; [d] $P < .0001$ vs normal (χ^2 test).

university hospitals, the number of men recruited to this study was far lower than would be expected given the estimated prevalence of the disease in France. Arlt et al (12) recently reported a similar situation in the United Kingdom. The difference between the actual and theoretical number of 21OHD men found in our study could be explained in part by at least three factors: 1) excess neonatal mortality, because the patients included in this study were older than 18 years and were born before the introduction of routine screening for the disease in France (5); 2) premature death could have reduced the number of patients in the >50-year age group: and 3) 21OHD men may be increasingly managed by general practitioners rather than in teaching hospitals. Further studies are needed to determine the respective roles of these possible factors. For example, it would be interesting to compare the prevalence of the different 21OHD genotypes between patients born before and after the introduction of routine neonatal screening.

The possibility that the men studied here may not be representative of the general population of men with 21OHD must be kept in mind when interpreting our findings.

Average final height was about 8 cm lower than that of healthy men of similar age. Based on parental heights in a subgroup of patients, the average shortfall was closer to 9 cm. These results are similar to those reported by Arlt et al (12) and Finkielstain et al (13) who studied 65 and 21 men with 21OHD, respectively, in the United Kingdom and the United States.

The prevalence of overweight in our patients was similar to that of French population-based controls, but obesity was more frequent. The overall prevalence of obesity and overweight was lower than reported among the 65 men studied in the United Kingdom (12), possibly owing in part to the more frequent prescription of potent glucocorticoids in the United Kingdom (see below).

Systolic and diastolic blood pressure values were both significantly lower in our patients than in healthy French men. Arlt et al (12) reported similar findings in the United Kingdom, whereas Finkielstain et al (13) found that hypertension was more frequent in adults with classic 21OHD than in the healthy US population. Two factors could contribute to low blood pressure in this setting. The first is possible chronic underdosing of both glucocorticoid and mineralocorticoid replacement therapy, as suggested by the markedly elevated levels of ACTH and renin found in most of our patients. Second, glucocorticoid and mineralocorticoid therapy might potentially lead to reduced sodium intake by the patients and/or their physicians, as reported by some of the men managed in participating centers. To test this hypothesis, it would be interesting to measure natriuresis (28). This moderately low blood pressure might protect these men from vascular complications (28).

Hydrocortisone, a glucocorticoid, was the drug most widely used in our patients to treat cortisol deficiency and was generally used as monotherapy. In contrast, a 2010 survey conducted in the United Kingdom showed that only 39% of male 21OHD patients received hydrocortisone, whereas the majority received either prednisone or dexamethasone (12). In France, as in the United Kingdom, dexamethasone is used less frequently, possibly because of the high potency of this glucocorticoid and a fear of overdose.

Sodium and potassium assays yielded interesting results. In over 90% of cases the serum sodium level was normal, suggesting that, despite the frequent and marked elevation of ACTH and circulating renin, latent decompensated adrenal insufficiency is infrequent. Similarly, potassium levels were normal in 99% of cases, suggesting acceptable mineralocorticoid impregnation despite often high renin levels. A minority of patients had subnormal potassium levels suggestive of mineralocorticoid overdosing.

Fasting plasma glucose levels were above 5.5 mmol/L in 9.8% of patients. This is higher than the 6% reported in a UK series of 65 men with 21OHD (12). The reason for this difference is unclear. It does not seem to be due to glucocorticoid overdosing because hydrocortisone doses were lower in our series than in the UK series. However, none of our patients had ADA-defined diabetes (fasting glycemia > 7.0 mmol/L).

Analysis of the hormonal profile also provided useful information on therapeutic control. It showed that most patients had concentrations of ACTH, PROG, 17OHPROG, and ADIONE well above the ULN of the relevant assays. Likewise, the vast majority of these men had 17OHPROG and ADIONE concentrations far higher than the therapeutic targets recommended by some authors (1, 3, 6, 12). These findings point to chronic glucocorticoid underdosing. AR concentrations measured in supine blood samples in a minority of patients were also above-normal in most cases, indicating underdosing and/or salt restriction in most patients.

Analysis of the gonadotrope-testicular axis showed various profiles, as reported in smaller series (18, 19). Circulating T levels were normal in most patients and low in a minority. However, concomitant analysis of circulating pituitary gonadotropins showed three different patterns: patients with normal gonadotropin and T levels (eugonadal subjects); patients with below-normal gonadotropin values reflecting hypogonadotropic hypogonadism; and patients with high FSH levels indicating primary testicular failure (17, 18, 29). In most patients with low go-

nadotropin levels, 17OHPROG, PROG, and ADIONE levels were very high, suggesting that the below-normal gonadotropin levels might be linked to the synergistic antigonadotropic effect of the elevated levels of these progestogens and T precursors (18, 29, 30). Knowledge of this gonadotropin profile may have therapeutic implications. Indeed, the gonadotropin inhibition linked to elevated 17OHPROG, PROG, and ADIONE levels might itself be responsible for azoospermia. If so, this cause of infertility might be treated by increasing the doses of glucocorticoids, which can lead to a decrease in these adrenal precursors, normalize gonadotropin levels, and improve the sperm count (31–34).

High gonadotropin levels were observed in a significant number of patients, pointing to primary testicular failure. In addition, FSH levels were significantly higher in men with TARTs, indicating that these tumors may lead to destruction of normal testicular tissue (29, 34) and thereby affect endocrine and exocrine testicular functions, particularly the secretion of hormones involved in FSH feedback control, such as inhibin B. This is further supported by the observed levels of this sertolian peptide. Inhibin B levels were indeed low or very low in more than one-third of patients, and the prevalence of TARTS was significantly higher in these patients than in those with normal inhibin B levels.

Testicular ultrasound examination was performed in most of our patients, making this the largest series of testicular sonography in men with 21OHD (12, 13, 15–19). French specialists thus appear to understand the importance of this morphological examination, which can detect TARTs before they become palpable. Our data may be less biased than those of other, smaller series (15–19) such as the study by Falhammar et al (19), in which the estimated prevalence of TARTs was 86% among 21 men with 21OHD who had testicular ultrasound examination.

Surprisingly, less than one-third of the men in this study had a sperm count. Yet, for more than a decade, concordant studies have shown that, contrary to the reassuring situation described in the princeps paper by Urban et al (35), men born with 21OHD have a significant risk of infertility (1, 6, 12, 15–19, 29). Therefore, it appears that the fertility status of these men is not sufficiently taken into account by French endocrinologists. We found that more than 40% of patients had extreme oligospermia or azoospermia and that the presence of TARTs was a major risk factor indicating severe degradation of spermatogenesis. We therefore recommend that a sperm count be done as early as possible in adolescence, particularly in postpubertal males with TARTs. We also agree with the proposition by Claahsen-van der Grinten et al (29) that sperm cryopreservation should be considered as soon as possible. In this respect, it was interesting to note that cryopreservation was performed for over half of the patients in our series who had a sperm count. Analysis of the patients' partner status showed that the frequency of cohabitation did not differ from that of the French general population of adult men. Congenital adrenal hyperplasia due to 21OHD does not therefore seem to affect men's intimate relationships, whereas sexuality is severely affected in women with this disease, who are markedly less likely to live with a partner (1, 3, 6, 7, 9). It is also interesting to note that more than half of the men with partners in our study had at least one child, although this is a smaller proportion than in the French reference population over 18 years of age. In agreement, a reduced fertility rate in 21OHD men has also been reported in a smaller series of Swedish patients (19). When we analyzed the fertility of cohabiting patients who had testicular ultrasound evaluation, we found that those with TARTs were significantly less likely to have had children. This further supports a role of TARTs in these patients' infertility (18, 19, 29). We also show that testicular hypotrophy, associated with lower sperm counts, may be a contributory factor.

One weakness of our study compared to that of Arlt et al (12) stems from its retrospective nature. Indeed, some study parameters were not available for all the patients, and not all parameters were collected at the same time. PROG and AR levels, for example, were less frequently available than other parameters. In addition, as indicated above, semen analysis was only done in a minority of cases. However, despite its limitations, this is the largest series with sonographic studies and semen analysis reported to date in this type of patient. Our data therefore probably give a less biased view of the impact of 21OHD on the sperm count and testicular status than previous, smaller studies (12, 13–19).

Conclusions

We report clinical features, laboratory findings, and testicular morphology in the largest series of genotyped and phenotyped adult men born with classic 21OHD reported to date. As in other European countries, only a minority of such patients are managed in specialized tertiary care centers, indicating poor transition from pediatric to adult management. Final height was frequently subnormal in our patients, suggesting that treatments used in childhood, or adherence to therapy, are still not optimal. Blood pressure tended to be low, and metabolic disorders were relatively infrequent. Episodes of overt acute adrenal decompensation need to be further studied (36), even if water-electrolyte control seemed adequate in most of our patients, despite a hormonal profile indicating very frequent underdosing of replacement therapy. We found fre-

quent alterations of the gonadotropin-testicular axis and a high prevalence of TARTs. Finally, routine semen analysis seems advisable, given the significant risk of infertility in these men.

Acknowledgments

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